The effects of small molecule analogues of the anti-inflammatory parasitic worm product ES-62 on the metabolome of mouse bone marrow-derived macrophages

By

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Declaration

‘I declare that, except where specifically indicated, all the work presented in this report is my own and I am the sole author of all parts.’

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Date: _____

Abstract

Lipopolysaccharide (LPS) and Cytosine-phosphate-guanosine oligodeoxynucleotides (CpG ODNs) cause macrophages to produce the proinflammatory cytokines IL-12, IL-6 and TNF-α. Pre-treatment of the macrophages with ES-62, an anti-inflammatory glycoprotein secreted by the parasitic filarial nematode *Acanthocheilonema viteae* suppresses the production of these cytokines. Although able to prevent disease development in mouse models of allergy and autoimmunity, ES-62 is not suitable for drug therapy due to its potential immunogenicity. A library of small molecule analogues (SMAs) therefore was designed and tested for the previously mentioned inhibitory effects. SMAs 11a and 12b among library members were found to mimic ES-62's anti-inflammatory effects. These findings rationalised further testing in order to determine their mechanism of action based on their effects on the metabolome of primary macrophages.

From analysis of cellular extracts using hydrophilic interaction chromatography in combination with high resolution mass spectrometry it could be seen that stimulation of macrophages with either LPS or CpG produced metabolic changes in various pathways. Stimulation of macrophages with LPS or CpG in the presence of SMAs 11a and 12b revealed that many of the metabolic shifts were the same as observed with LPS and CpG alone. However, there were clear effects of the SMAs in producing downregulation in creatine metabolism/uptake and upregulation in glutathione biosynthesis.

By downregulating creatine metabolism/uptake, the SMAs may be controlling the availability of creatine for transporting high energy phosphate from the mitochondria to where it is required for biological functions including cell signalling, phagocytosis and motility. By causing an upregulation of the glutathione biosynthesis pathway the SMAs may be protecting the cells from oxidative stress and of note SMA12b has been previously linked to increased activity of the Nrf2/ARE/HO-1 anti-oxidant pathway. The

SMAs may be downregulating the availability of the energy produced by oxidative phosphorylation in general without targeting the TCA cycle directly since they do not affect NADH levels in comparison with LPS or CpG stimulation alone. Finally, in the process of examining the response of the cells to LPS and CpG additional potential anti-inflammatory targets were revealed.

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List of Abbreviations

IFN regulatory factor 3	IRF3
5'—C—phosphate—G—3'	CpG
Acetyl CoA carboxylase	ACC
Adenosine diphosphate	ADP
Adenosine monophosphate	AMP
Adenosine Tiphosphate	ATP
Alanine, serine, cysteine-preferring transporter 2	ASCT2
Alternatively activated macrophages	AAMΦ
Alternatively activated macrophages	M2
Antigen-presenting cells	APCs
Area Under the ROC Curve	AUROCC
Aryl hydrocarbon receptor	AHR
B cell receptor	BCR
B lymphocytes	B cells
Bacille Calmette-Guérin	BCG
Bacterial lipoprotein	BLP
Bone marrow derived macrophages	BDMMs
Bovine Serum Albumin	BSA
Capillary electrophoresis	CE
Carbohydrate kinase-like protein	CARKL
c-Jun N-terminal kinase	JNK
Classically activated macrophages	CAMΦ
Classically activated macrophages	M1
Cluster of differentiation	CD80
Collagen-induced arthritis	CIA
Common DC antecedents	CDPs
Common lymphoid progenitor	CLP
Cross-validated ANOVA	CV-ANOVA
Cross-validation	CV
Cyclic adenosine monophosphate	cAMP
Cytosine-phosphate-guanosine oligodeoxynucleotides	CpG ODNs
Damage-associated molecular pattern molecules	DAMPs
Dendritic cells	DCs
Deoxyribonucleic acid	DNA
Double stranded RNA	dsRNA
Dulbecco's Modified Eagle Medium	DMEM
Enzyme-linked immunosorbent assays	ELISAs
Eosinophil-derived neurotoxin	EDN
Escherichia coli	E.coli
Excreted-secreted	ES
Excretory secretory product 62	ES-62
Extracellular Signal-regulated Kinase-1	ERK

False discovery rate	FDR
Fatty acid synthase	FASN
Fetal Bovine Serum	FBS
Fetal calf Serum	FCS
Flavin adenine dinucleotide	FADH
Fluorescence Minus One	FMO
Fluorescence-activated cell sorting	FACS
Fusion	F
Glutathione	GSH
Glutathione disulfide	GSSG
Glyceraldehyde 3-phosphate dehydrogenase	GAPDH
Glyceraldehyde 3-phosphate dehydrogenase	GAPDH
Glycoinositol-phospholipids	GIPLs
Glycosylphosphatidyl-inositol anchors	GPI-anchor
Goodness of fit	R2
Goodness of prediction	Q2
Granulocyte/macrophage progenitors	GMPs
Granulocyte-macrophage colony-stimulating factor	GM-CSF
Hematopoietic stem cell	HSC
Hierarchical clustering analysis	HCA
Hypoxia-inducible factor 1α	HIF1α
Indoleamine-2, 3-dioxygenase	IDO
Inflammatory bowel disease	IBD
Innate lymphoid cells	ILCS
Interferon-β	IFN-β
Interferon-γ	IFN-γ
Interleukin-	IL-
Interleukin-10	IL-10
knockout	KO
larva 3	L3
leucine rich repeats	LRR
lipopolysaccharide	LPS
Lipopolysaccharide binding protein	LBP
liquid chromatography	LC
Liquid chromatography/mass spectroscopy	LCMS
Liquid chromatography–mass spectrometry	LC-MS
Macrophage colony-stimulating factor	M-CSF
Macrophage/dendritic cell progenitors	MDPs
Mammalian target of rapamycin	mTOR
Mammary tumour virus envelope protein	MMTV
Megakaryocyte/erythrocyte progenitors	MEPs
MHC class II	MCHII
Mitochondrial uncoupling protein 2	UCP2
Mitochondria membrane potential/polarisation	MMP
Mitogen-activated protein kinase	MAPKs

Multivariate analysis	MVA
Myeloid differentiation primary response 88	MyD88
NACHT, LRR and PYD domains-containing protein 3	NLRP3
Natural killer cells	NK
Nicotinamide adenine dinucleotide phosphate	NADPH
Nicotinamide adenine dinucleotide (Oxidised form)	NAD+
Nicotinamide adenine dinucleotide (Reduced form)	NADH
Nitric oxide	NO
Nuclear magnetic resonance spectroscopy	NMR
Nuclear transcription factor κB pathway	NF-κB
Nucleotide-binding oligomerization domain-containing protein	NOD
Orthogonal partial least squares - discriminant analysis	OPLS-DA
Ovalbumin	OVA
Partial least squares-discriminant analysis	PLS-DA
Pathogen-associated molecular patterns	PAMPs
Pattern recognition receptors	PRRs
Peroxisome proliferator-activated receptor-γ	PPAR-γ
Phosphate-buffered saline	PBS
Phosphatidylinositol 3-kinase	PI3K
Phosphatidylinositol 3-kinase	PI3K
Phosphorylcholine	PC
plasmacytoid dendritic cells	pDCs
Polyunsaturated¬fatty acids	PUFAs
PPARγ-co-activator 1β	PGC1β
Principle component analysis	PCA
Programmed death 1	PD1
Pyrroline-5-carboxylate	P5C
Pyruvate dehydrogenase kinase 1	PDK1
Pyruvate kinase isoenzyme M2	PKM2
RAR-related orphan receptor gamma	RORγ
Reactive oxygen species	ROS
Receiver Operator Characteristic	ROC
Regulatory T cells	Treg
Respiratory syncytial virus	RSV
Roswell Park Memorial Institute medium,	RPMI
Salmonella enterica subspecies	Sal.
Signal transducer and activator of transcription	STAT
Small molecule analogues	SMAs
Soft-Independent Modelling of Class Analogy	SMICA
Sterol regulatory element binding protein	SREBP
Sterol regulatory element-binding transcription factor 1c	SREBP1c
Systemic lupus erythematosus	SLE
T helper	Th
T lymphocytes	T cells
TANK-binding kinase 1	TBK1

Toll like receptors	TLRS
Toll-IL-1 receptor domain	TIR
Tricarboxylic acid	TCA
Tumor necrosis factor	TNF
Type 1 diabetes	T1D

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Chapter 1. General introduction

1.1 Introduction to the immune system

1.1.1 Innate and adaptive immune systems

The immune system brings into play, various mechanisms to protect against a variety of pathogens and allergenic substances (Chaplin, 2010a). The implemented mechanisms can be divided into two lines of defence, innate and adaptive immunity. The two immunity arms have the same ability to differentiate between self and non-self-antigens but they are different in the way they do this. Innate immunity has the ability to recognise a series of conserved molecular structures of microorganisms via a limited number of receptors and secretory proteins encoded in the germline. However, adaptive immunity uses a process of somatic cell gene rearrangement to generate an enormous group of antigen receptors that are capable of distinguishing closely related molecules.

The innate immune defence recognition system is initiated via host recognition of conserved molecular structures known as pathogen-associated molecular patterns (PAMPs) (Janeway and Medzhitov, 2002). These PAMPs are sensed by the host's genome encoded pattern recognition receptors (PRRs), which are expressed on innate immune system cells such as dendritic cells, macrophages and neutrophils (Blasius and Beutler, 2010, Medzhitov, 2007, Takeuchi and Akira, 2010, Kawai and Akira, 2010a) . However, although the innate immune system provides immediate recognition and initiates a rapid response against infection, it has been characterised as a temporary system that often cannot compete with the demands for complete eradication of the microbes (Gonzalez et al., 2011).

The adaptive immune system is a second line of defence, which is usually triggered by antigens or the recognition of their fragments in order to mount stronger and long-lasting attacks against microbes (Gonzalez et al., 2011). The

adaptive immune response is dependent on antigen-specific receptors expressed on T and B lymphocytes. An important feature of the adaptive response is immune memory that is possible due to the long-life span of B and T cells allowing them to persist in a dormant state, but they can be re-activated when they encounter a specific antigen for a second time (Chaplin, 2010b).

1.1.2 Cellular elements of the immune response

An effective immune response entails a combination of different subsets of leukocytes. Each subset has a specific job to detect or clear the pathogen. This starts with hematopoietic stem cells (HSC) from bone marrow, which are divided into common myeloid progenitor (CMP) cells or common lymphoid progenitor (CLP) cells (Kawamoto et al., 1997, Kondo et al., 1997). Lymphoid progenitor cells differentiate to give B cells, T cells, natural killer (NK) cells, NK-T cells and innate lymphoid cells (ILCS) (Chaplin, 2010b). ILCS are a relatively newly described group of of innate immune cells which are defined by absence of an antigen specific B or T cell receptor because of the lack of recombination activating genes (RAGs). ILCs also do not express myeloid or dendritic cell markers (Spits and Cupedo, 2012).

The myeloid progenitors are antecedents of many cell types, which include megakaryocyte/erythrocyte progenitors (MEPs) or granulocyte/macrophage progenitors (GMPs). MEPs are differentiated into platelets and erythrocytes (Akashi et al., 2000, Adolfsson et al., 2005). GMPs are also differentiated into monocytes, which give rise to macrophages or dendritic cells and varied types of granulocyte, for example basophils, neutrophils, eosinophils, and mast cells (Kumar and Jack, 2006b, Chaplin, 2010b). In addition, there is another subgroup that has been identified as a new subset of cells. This subgroup shares numerous features with myeloid progenitors and is known as macrophage/dendritic cell progenitors (MDPs) (Fogg et al., 2006). MDPs also

differentiate into monocytes and common DC antecedents (CDPs) (Varol et al., 2007). A summary of immune system cell development is shown in Figure 1.1.

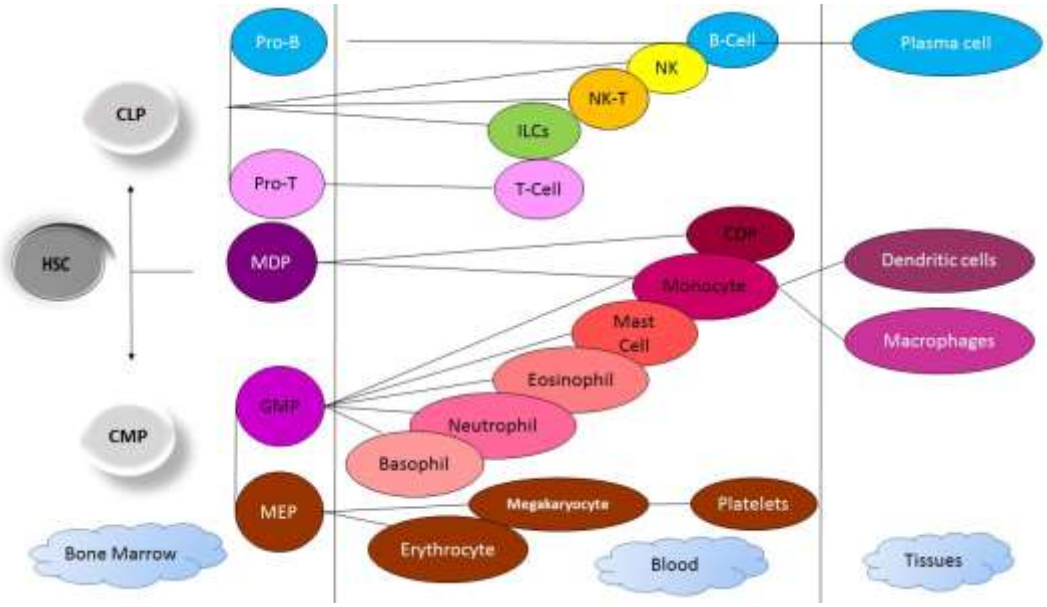

Figure 1.1: Immune system cell lineage

Hematopoietic stem cell (HSC) differentiation in bone marrow, blood and tissues: (CLPs) common lymphoid progenitors, (CMPs) common myeloid progenitor cells, (NK) natural killer cells, NK-T cells, (ILCs) innate lymphoid cells, Pro-B and Pro-T cells (which further transform into tissue B-cells and T-cells respectively), (GMPs) granulocyte/macrophage progenitors, (MEPs) megakaryocyte/erythrocyte progenitors, (CDPs) DC precursors.

1.1.3 Macrophages

Macrophages, which are phagocytic cells, are distinct from circulating monocytes. Blood distributes these cells to distinct tissues in a constant manner, or as a reaction to inflammation, creating types of tissue macrophage such as macrophages of the central nervous system (microglial cells), macrophages of the liver (kupffer cells), macrophages of the connective tissue (histiocytes), as well as the alveoli, spleen, gastrointestinal, and peritoneum macrophages (Kumar and Jack, 2006a).

Elie Metchnikoff 100 years ago, raised the idea of “stimulate the phagocytes” in which he explained the phagocytic process as a vital one for the immune response (Nathan, 2008b). Macrophages were then considered to be immune effector cells, in addition to being the first line of the host defence. Furthermore, they have crucial homeostatic functions that immunologists frequently disregard (Mosser and Edwards, 2008). Macrophages clear around 2×10^{11} erythrocytes to recycle around 3 kg of the iron and heamglobin for the host to be reused in this process (Kono and Rock, 2008a). In addition, macrophages eliminate dead cells and debris from tissue trauma (Kono and Rock, 2008a, Kumar and Jack, 2006a). These critical procedures are facilitated by scavenger receptors, thrombospondin and integrins and complement receptors (Erwig and Henson, 2007).

Moreover, it is observed that the physiology of macrophages significantly varies when necrotic cellular debris is engulfed. This involves changing surface-protein expression and cytokine production. The identification and elimination of necrotic cellular debris is unlike the clearance of apoptotic cells and tissue debris. It is usually mediated via Toll-like receptors which makes the process part of the innate immune response (Kono and Rock, 2008).

1.1.3.1 Activated macrophage phenotypes

At present, there is widespread acknowledgement that macrophages can exhibit incredible plasticity which allows them to alter their phenotype to respond efficiently to various environmental stimuli. This plasticity involves managing physiological modifications, regardless of whether they enhance the immune reaction or downgrade it, so as to prevent harmful outcomes. Several distinct macrophage activation states have been identified, such as innate activated macrophages, alternatively activated macrophages, classically activated macrophages and regulatory macrophages. These types are discussed below and displayed in figure 1.2.

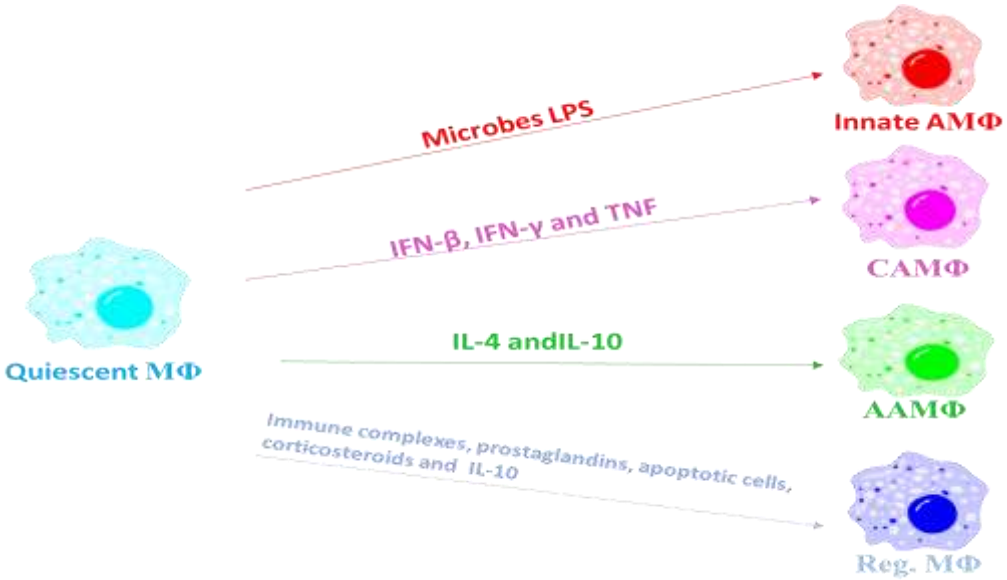

Figure 1.2: Macrophage phenotypes

Stimuli like microbial LPS induces innate activated macrophages whereas Interferon-β (IFN-β), interferon-γ (IFN-γ) and tumor necrosis factor (TNF), supplied either by innate immune or adaptive immune elements, stimulate macrophages towards a classical phenotype. Interleukin-4 (IL-4) and Interleukin-13 (IL-13) prime macrophages towards an alternative phenotype while various types of stimuli such as immune complexes, prostaglandins, apoptotic cells, corticosteroids and interleukin-10 (IL-10) are needed to activate regulatory macrophages.

1.1.3.2 Innate activated macrophages

The response of macrophages to microbial stimuli (when there is a lack of IFNγ or IL-4 or IL-23) has been explained as leading to the generation of "innate activated macrophages" (Forlenza *et al*., 2011). Nonetheless, these cells show similarity to classically activated cells in their phagocytic function and in their production of inflammatory cytokines, nitric oxide (NO) and reactive oxygen species (Forlenza et al., 2011, Gordon and Taylor, 2005, Zucchi et al., 1989). They differ in certain other aspects and most notably they express arginase (Menzies *et al*., 2011) and have marked but transient physiological changes upon stimulation (Mosser and Edwards, 2008). It is indicated that ligation of cell surface receptors such as Toll like receptors (TLRS) through lipopolysaccharide (LPS) is responsible for producing such macrophages (Forlenza *et al*., 2011).

1.1.3.3 Classically activated macrophages

Classically activated macrophages (CAMΦ) or type 1 macrophages indicate macrophages that are activated by interferon γ (IFN γ) and tumour necrosis factor (TNF) or TLR ligands (normally LPS). This phenotype increases microbicidal and tumoricidal capability and proinflammatory cytokine production (O'shea and Murray, 2008). The macrophages are transiently stimulated by NK cells, which constitute an initial source of IFN-γ, subsequently produced by Th1 cells, which provides constant macrophage activation to produce pro-inflammatory cytokines which in turn enhances immune function and provides better resistance against infections (Dale et al., 2008). Macrophages can be activated through MyD88-dependent TLR signalling which induces TNF release. IFN-γ and TNF both stimulate autocrine activation of macrophages (Mosser and Zhang, 2008). The activation of the TRIF-dependent pathway through IFN regulatory factor 3 (IRF3) releases interferon-β (IFN-β) which replaces IFN-γ in the form of the classically activated signal (Yamamoto et al.,

2003).It is crucial to regulate the classically activated macrophages as excessive cytokine production and synthesis of other immune mediators, can cause host tissue damage and autoimmune diseases (Szekanecz and Koch, 2007).

1.1.3.4 Alternatively activated macrophages

Alternatively activated macrophages (AAMΦ) are also called wound healing macrophages. IL-4 and IL-3 stimulation leads to the production of this kind of macrophage, which up-regulates expression of the mannose receptor (Stein et al., 1992a).These cells play a significant role by converting arginine into ornithine via the arginase enzyme. Ornithine is taken to be a precursor of collagen and polyamines which are important components of wound healing and tissue regeneration (evaluated by (Varin and Gordon, 2009).The over-stimulation of the IL-4 receptor is also linked to dysregulation or over-generation of the wound healing matrix, as witnessed for example with tissue fibrosis with schistosomiasis (Hesse et al., 2001). Macrophages which do not have the IL-4 receptor or have been subjected to a treatment which blocks the IL-4 receptor do not show this phenotype (Hesse et al., 2001)

1.3.1.5 Regulatory macrophages

This macrophage population is distinct from CAMΦ and AAMΦ. It is produced via varied stimuli and is actually not usually grouped as a single population. Nonetheless, all of the population's members have the similar capability to produce large amounts of IL-10 (examined by Mosser and Zhang, 2008). A combination of two signals is typically needed for generation of regulatory macrophages. The first signal is provided by immune complexes (Gerber and Mosser, 2001), prostaglandins (Strassmann et al., 1994), glucocorticoids, apoptotic cells (Erwig and Henson, 2007), adenine nucleotide (Haskó et al.,

2007) or IL-10 (Martinez et al., 2007) and is simultaneously imposed with the next signal, which is the TLR stimulus. A macrophage population that is created by these signals will have an effective anti-inflammatory response (evaluated by Mosser and Edwards, 2008) that relies on the inclusion of IL-10 and down regulation of IL-12 (Gerber and Mosser, 2001). Regulatory macrophages function as antigen presenting cells as they mostly express CD80 and CD86 co-stimulatory molecules (Edwards et al., 2006). There are certain bacteria, parasites and viruses that provide the appropriate signals to lead to the creation of regulatory macrophages and this supports the spread and survival of these microorganisms (Mosser and Edwards, 2008).

1.1.4 Toll like receptors (TLRs)

An important step in providing protection is the identification of non-self (microbes). After acknowledging a foreign body, the immune response is usually initiated (Beutler, 2009), but it needs to determine how to identify microbes. Several years of research were required to answer this question, leading to the identification of a distinct group of germ line-encoded receptors on various kinds of characteristic immune cells. These receptors were known as pattern recognition receptors (PRR) (Janeway, 2001), and consisted of various classes, each having a particular role, such as activation of the complement system, opsonisation, or phagocytosis (Pasare and Medzhitov, 2004). TLRs can be considered to be conserved receptors that signify the first line of defence against an extensive range of attacking microorganism, and represent an important part of the immune system (Doyle and O'Neill, 2006). Previously, these receptors were believed to be vital receptors for *Drosophila* defence against fungal infection via the innate immune response (Lemaitre et al., 1996). TLRs certainly identify several microbial structures that are found within microorganisms and not within mammals. These molecular structures are called

pathogen-associated molecular patterns (PAMPs). When various PAMPs are identified, several signalling pathways are activated, leading to inflammatory gene expression and the production of pro-inflammatory cytokines, type-1 interferons α/β and chemokines which facilitate the elimination of infectious agents (Kawai and Akira, 2005, Kopp and Medzhitov, 2003, Takeda and Akira, 2003). The production of these cytokines and chemokines can play a role in the stimulation of the adaptive immune system and in maturing dendritic cells (DCs) (Kawai and Akira, 2005, Takeda and Akira, 2003).

TLRs are type-1 membrane glycoproteins which comprise of an extracellular domain, consisting of leucine rich repeats (LRR) which are responsible for identifying distinct types of PAMPs, a transmembrane, spacing component and a cytoplasmic part which is identical to that of the interleukin-1 receptor (called Toll-IL-1 receptor domain or TIR (Takeda and Akira, 2003)). At present, it has been found that there are 13 members of TLRs in mammals (Uematsu and Akira, 2006).Humans and mice both have TLR1-9; TLR10 is found in humans, while TLR11-13 are only found in mice. It is not yet evident what role is played by TLR10 in humans and by TLR12 and TLR13 in mice (Kawai and Akira, 2010). There is expression of TLR 1, 2, 4, 5 and 6 on the plasma membrane at the cell surface. These receptors can identify molecules obtained from fungi, bacteria and protozoa, whereas TLR3, 7, 8 and 9 are found within the cell in the endocytic compartments, which play a role in detecting nucleic acids obtained from viruses or intracellular bacteria (Kawai and Akira, 2010b, Kumar et al., 2009).

1.1.5 TLRs and their ligands

Lipopolysaccharide LPS from Gram negative bacteria consists of lipid A, core oligosaccharide, and o-side chain, and the molecule is identified by TLR4 through detection of the lipid A moiety (Miller et al., 2005, Shimazu et al., 1999). It has been found that the fusion (F) protein of respiratory syncytial virus (RSV) and mouse mammary tumour virus envelope protein (MMTV) are identified by TLR4 (Kawai and Akira, 2009; Kumer *et al*., 2009a). TLR4 identifies the fungal element glucuronoxylomannan, while TLR4 and TLR2 identify the protozoan elements glycoinositol-phospholipids (GIPLs) and glycosylphosphatidyl-inositol anchors (GPI-anchor) obtained from *Trypanosoma (species), Plasmodium falciparium,* and *Toxoplasma gondii* (Kawai and Akira, 2009; Kumer *et al*., 2009a). TLR2 also identifies bacterial, fungal and viral elements. Triacyl lipopeptide can be identified through a TLR2 and TLR1 heterodimer, whereas diacyl lipopeptide structures on bacteria, mycobacteria, and mycoplasma can be identified through TLR2 and TLR6 dimers (Takeuchi *et al*., 2001; Takeuchi *et al*., 2002, Kumer *et al*., 2009b). It has been found that RSV induce cytokines and chemokine signalling with the help of TLR2 and TLR6 (Murawski et al., 2009). TLR3 can identify double stranded RNA (dsRNA) (Alexopoulou et al., 2001), while flagellin from bacteria can be identified through TLR5 (Kawai and Akira, 2010b, Kumar et al., 2009).

TLR7 and 8 can recognise viral RNA while genomic DNA of DNA viruses and other microorganisms are recognised by TLR9 (Takeda *et al*., 2003; Wagner, 2009). Mouse TLR11 identifies profilin from *T. gondii* (Kawai and Akira, 2009, Kumar et al., 2009). A summary of TLRs and their ligands is shown in table 1.1.

Table 1.1: TLRs and their Ligands (adapted from Kumar et al., 2009). TF, transcription factor; RSV, respiratory syncytial virus; MCMV, murine cytomegalovirus; HSV, herpes simplex virus; CPG, cytidine-phosphateguanosine.

TLR	Location of TLR	PAMPs recognized by TLR	Co-receptor (s)	Signaling adaptor	Transcri-ption factor(s)	Effector cytokines induced
TLR1/2	Plasma membrane (cell surface)	Triacyl lipopeptides (Bacteria and Mycobacteria)	Hetrodimer of TLR1/2 forms a functional receptor	TIRAP, MyD88	NFκB	Inflammatory cytokines (TNF-α, IL-6 etc.)
TLR2	Plasma membrane (cell surface)	Peptidoglycan (Gram-positive bacteria), LAM (Mycobacteria), Hemagglutinin (Measles virus, phospholipomannan (Candida), Glycosylphosphophatidyl inositol mucin (Trypanosoma)	CD36, RP105	TIRAP, MyD88	NFκB	Inflammatory cytokines (TNF-α, IL-6 etc.)
TLR3	Endosome	ssRNA virus (WNV, dsRNA virus (Reovirus, RSV, MCMV)		TRIF	NFκB, IRF3,7	Inflammatory cytokines (TNF-α, IL-6 etc.), type I IFNs
TLR4	Plasma membrane (cell surface)	LPS (Gram-negative bacteria), Mannan (De Rosa et al.), Glycoinositolphospholipids (Trypanosoma), Envelope proteins (RSV and MMTV)	MD2, CD14, LBP, RP105	TIRAP, MyD88, TRAM and TRIF	NFκB, IRF3,7	Inflammatory cytokines (TNF-α, IL-6 etc.), type I IFNs
TLR5	Plasma membrane (cell surface)	Flagellin (Flagellated bacteria)		MyD88	NFκB	Inflammatory cytokines (TNF-α, IL-6 etc.)
TLR6/2	Plasma membrane (cell surface)	Diacyl lipopeptides (Mycoplasma), LTA (Streptococcus), Zymosan (Saccharomyces)	Hetrodimer of TLR6/2 or dectin-1 forms a functional receptor(Kumar et al., 2009)	TIRAP, MyD88	NFκB	Inflammatory cytokines (TNF-α, IL-6 etc.)
TLR7	Endosome	ssRNA viruses (VSV,Influenza virus)		MyD88	NFκB, IRF7	Inflammatory cytokines (TNF-α, IL-6 etc.), type I IFNs
TLR8 (in human)	Endosome	ssRNA from RNA virus		MyD88	NFκB, IRF7	Inflammatory cytokines (TNF-α, IL-6 etc.), type I IFNs
TLR9	Endosome	dsDNA viruses (HSV, MCMV), CpG motifs from bacteria and viruses, Hemozoin (Plasmodium)		MyD88	NFκB, IRF7	Inflammatory cytokines (TNF-α, IL-6 etc.), type I IFNs
TLR11 (expressed in mouse)	Plasma membrane (cell surface)	Uropathogenic bacteria, profillin-like molecule (Toxoplasma gondii)		MyD88	NFκB	Inflammatory cytokines (TNF-α, IL-6 etc.)

1.2 The Hygiene Hypothesis:

The term “Hygiene Hypothesis” was coined in the 1980s and 1990s by both Strachan and Matricardi, together with their colleagues who noted that there is an inverse correlation between family size and hay fever incidence (Strachan, 1989). It was initially applied to the field of allergy and then later on it developed further to include application to the field of autoimmune diseases such as inflammatory bowel disease (IBD) and type 1 diabetes (T1D) (Bach, 2002). This hypothesis relates the decrease in communicable diseases in developed countries to the increase in allergic and autoimmune diseases. Taking the examples of the United Kingdom, Australia and New Zealand, the predominance of asthma was considered to increase by 15% in the last 15 years because of a rise in sanitation (Okada et al., 2010). The earliest explanation underlying the hypothesis was dependent on the idea that there was an imbalance between T helper 1 (Th1) and T helper 2 (Th2) responses. Disease such as allergy develops when the body responds inappropriately to an otherwise harmless substance and this inappropriate immune response is driven primarily by Th2 responses. Therefore, the imbalance theory relates the ability of pathogens to induce a Th1-mediated immune response, which would in turn lead to the over production of Th2 cells in order to maintain a well-regulated immune response (Yazdanbakhsh et al., 2002a, Matricardi and Bonini, 2000, Romagnani, 1992). However, this Th1/Th2 imbalance theory was considered unacceptable by 1989, as there was a simultaneous rise in Th1-mediated chronic inflammatory diseases experienced in the same countries as those showing the rise in allergic disorders (Rook et al., 2004). There is another argument that individuals infected with helminths, who develop Th2 responses, are less likely to have either allergic sensitization or allergic disorders, and that

treating people infected with the helminths with anthelminthics may lead to increased allergic sensitization (Yazdanbakhsh et al., 2002b).

The old friends' hypothesis (Rook, 2010, von Hertzen et al., 2011) relates protection from allergy and autoimmune diseases to continuous exposure to various types of organism, which are known to be a part of mammalian evolutionary history. Their continuous presence in the environment suggested that they must be tolerated by the immune system and examples are, environmental saprophytes, including mycobacteria and lactobacilli, and helminths. When these organisms interact with the host they cause a pattern of maturation of DCs, which in turn drives generation of Treg cells rather than Th1 or Th2 effector cells (Smits et al., 2005, van der Kleij et al., 2002a). This subsequently leads to two types of response in order to control inappropriate inflammation. Firstly, the presence of the Old Friends causes continuous background activation of regulatory DCs and of Treg cells specific for the Old Friends themselves, thereby resulting in constant background bystander suppression of inflammatory responses. Secondly, these regulatory DCs unavoidably sample self, gut contents and allergens, and therefore induce Treg cells specific for the target antigens of mentioned diseases. Figure 1.3 illustrates the mechanisms described in the text.

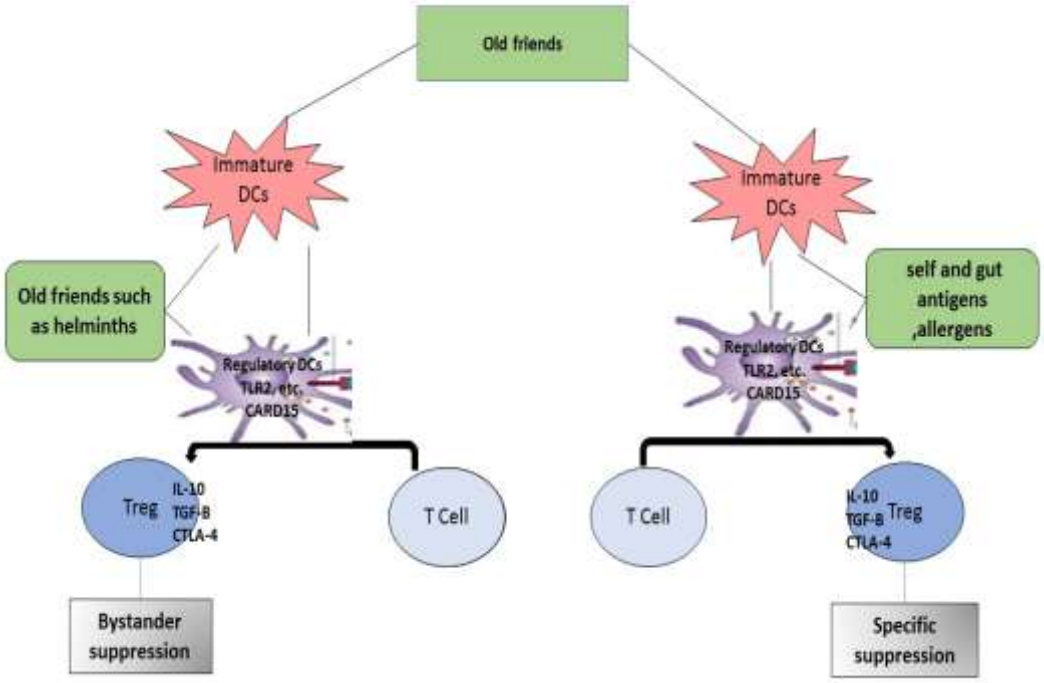

Figure 1.3: The hygiene hypothesis.

Both helminths and gut antigens on the two arms bind to DCs through PAMP receptors such as TLRs and drive their maturation to regulatory DCs. This in turn drives generation of Tregs and drives as well either bystander or specific suppression.

Finally, support for the hygiene hypothesis was provided by epidemiology data, animal models and a few clinical trials in humans. As mentioned earlier, it has been noted that in developing countries, allergy occurrence is low and the infection rate, with helminths, is high whereas allergy and autoimmune diseases are high in the developed world and are accompanied by a low infection rate (Cooper, 2009, Ruyssers et al., 2008). Several studies supported this correlation, for instance, infection with schistosomes has been shown to have protective properties against atopy in African children (van den Biggelaar et al., 2000). Moreover, abolition of helminth infections with anthelminthic treatment has been revealed to increase allergic disease (Lynch et al., 1993, Flohr et al., 2006).

1.2.1 Immunomodulation by helminths and helminth products

Helminths are capable of driving immunoregulation as was previously outlined and the organisms can be found in three unrelated phyla: the acanthocephalans (thorny-headed worms), the platyhelminths (tapeworms and flukes), and the nematodes (roundworms).

Helminths cause suppression of the host immune system because they need to share a long-term survival (Brooker et al., 2006, Subramanian et al., 2004). The parasitic organisms differ in their target tissue and organ-invading propensity, size, length of their life cycle, degree of pathogenicity and time required for maturation. A large number of parasites tend to cause chronic infections (Klion et al., 1991). Pathology caused by these helminths is limited since obvious symptoms in human populations are found to be relatively rare. However, adverse outcomes can be measurable, for example, in reduced growth or

cognitive development. The general limited level of pathogenicity is likely to be linked to adaptation by helminths. However, limited effects are not always the case, for example in the Philippines, in the years between 1967 and 1990, epidemics of an intestinal capillarid that usually infected fish-eating birds led to very serious disease and a 6% death rate (Cross, 1992).

Helminths cause immune system suppression or what we call "immunomodulation". As alluded to earlier, they can achieve this by promoting the delineation of DCs that cause Th cell polarization towards Th2 or Treg cell subsets. In addition to the DC differentiation occurring via live parasites, excreted-secreted (ES) helminth products interacting with PAMPs may also promote it. Worm PAMPs sometimes act via TLR family members and other times through additional classes of inborn receptor (Jenkins and Frohman, 2005, Perrigoue et al., 2008) such as C-type lectins, nucleotide-binding oligomerization domain-containing protein (Tripathi et al.) receptors or protease-activated receptors (Gieseler et al., 2013) .With respect to TLRs, the ES-62 molecule derived from the filarial nematode *Acanthocheilonema viteae* is known to mediate its immunomodulatory effects on macrophages (Goodridge et al., 2001a) and DCs (Whelan et al., 2000a) through a TLR4-dependent mechanism. The Lacto N-fucopentanose III product is another example of a helminth-derived secretory product that is known to exert its immunomodulatory effects through TLR4, producing Th2 polarizing DCs (Thomas et al., 2003). In addition, schistosome lyso-phosphatidylserine interacts with TLR2 producing Treg-polarizing DCs (Goodridge et al., 2005b, van der Kleij et al., 2002b).

It has however been argued that the interaction of ES-62 with TLR4 on mast cells, macrophages and DCs does not engage classical TLR signalling (Melendez et al., 2007b). What is more, the Th2-inducing effects of schistosome soluble egg antigen (Yin et al., 2015) on DCs have recently been discovered to

rely on MyD88, TLR2 and TLR4. Th2-inducing signals are found not to be necessarily mediated through classical TLRs but can be through PRRs on cell types apart from DCs such as *Intestinal epithelial cells,* basophils (Phillips et al., 2003, Sokol et al., 2008), mast cells (Melendez et al., 2007b) and eosinophils (Yang et al., 2008, Zaph et al., 2007) .The eosinophils, acting as an example of a cell type other than DCs, produce eosinophil-derived neurotoxin (EDN), which mediates TLR2/Myd88-dependent activation of DCs that drives *in vivo* antigen-specific adaptive responses towards a Th2 phenotype. Other examples of endogenous host molecules include alarmin molecules and cytokines that are found to be contributing to maturation of Th2-inducing DC phenotypes. In addition, it is argued that endogenous molecules, donated from damage-associated molecular pattern molecules (DAMPs), have been shown to interact with receptors of the TLR2, TLR3, TLR4, TLR7, TLR8 and TLR9 families, which in turn causes differentiation of immature DCs with tolerogenic properties favouring anti-inflammatory Th phenotypes (Wallet et al., 2005, Kim et al., 2004, Stuart et al., 2002, Steinman et al., 2000). Moreover, it even seems that endogenous molecules drive Treg activity in a worm infection (Kreider et al., 2007, Rodriguez-Sosa et al., 2002). In the case of anti-helminth Th2 responses, however, cross-talk between worm PAMPs and the innate immune system would be expected to be important, as many anti-helminth effectors (e.g. IgE and mast cells) are recruited that are apparently unconnected to wound healing (Jackson et al., 2009).

1.2.2 ES-62: structural, functional and immunomodulatory properties

A key ES protein of the rodent filarial nematode *Acanthocheilonema viteae* that was first isolated in 1989 by Harnett and colleagues, the 62kDa glycoprotein ES-62 is considered amongst the most thoroughly investigated helminth

products and constitutes more than 90% of the protein secreted by this class of worm (Harnett et al., 1989). ES-62 is most abundantly secreted by adult female worms (0.038-0.092 µg/hour) (Goodridge et al., 2001b). Detection of ES-62 in the blood circulation of *A. viteae*'s natural host, the jird, is possible four hours following release. ES-62 half-life is dependent on wither the jird is infected and duration of infection(Harnett et al., 1989).The detection of higher concentrations of ES-62 seems to be increased with the duration of host infection; for instance, the blood circulation of a jird with a 14-week infection will contain more ES-62 compared to that of a jird with 5- or 6-week infection. This difference in the production may be linked to the idea that the immune complexes comprising ES-62 and anti-ES-62 antibody are not the same size during infection and this can impact on removal from the circulation (Harnett et al., 1999, Harnett et al., 1989).ES-62 production is reported to be stage-specific as it is produced after L3 stages, however its mRNA presence can be detected at every life cycle stage (Stepek et al., 2004). The uncommon post-translational alteration of phosphorylcholine (Parry-Billings et al.) moieties bound through *N*-linked glycans is a defining feature of ES-62 (Houston et al., 1997). PC's presence on ES-62 was suggested after discovering that anti-PC antibodies were responsible for the recognition of ES-62 in serum samples from infected humans (Harnett et al., 1989). It was suggested, according to preliminary research, that PC moieties were present in carbohydrate containing molecules. Accordingly, [^{3}H] choline-labelled ES-62 was subjected to N-glycosidase F and this resulted in complete loss of radioactivity suggesting that the PC molecule was bound to the protein backbone through an *N*-type glycan (Harnett et al., 2003). The findings of additional inhibitor studies revealed that PC addition was a post ER event, since the treatment of *A. viteae* with Brefeldin A blocks protein secretion. Moreover, the dependence of PC addition on the formation of a

suitable substrate during the processing of oligosaccharides was proven by research employing agents that inhibited *N*-linked oligosaccharide processing. The research highlighted the transfer of PC within the medial golgi lumen and the indicated that the 3-linked branch of $Man_5GlcNAc_3$ or $Man_3GlcNAc_3$ was the choice of substrate (Houston et al., 1997). The substrate was validated to be $Man_3GlcNAc_3$ by fast atom bombardment mass spectroscopy, which also revealed the binding of PC to an N-glycan with a trimannosyl core and 1-4 *N*-acetlyglucosamine residues. Additionally, ES-62 was found to have two more glycans, namely, a glycan with complete trimming to the trimannosyl core and sub-stoichiometrically fucosylated and a glycan rich in mannose (Haslam et al., 1997). The structural analysis of ES-62 has revealed the presence of one to two PC residues in each glycan while ES-62 sequence analysis pointed to the existence of three *N*-linked glycosylation binding sites in the protein , meaning that up to six PC residues were present in every ES-62 molecule (Harnett et al., 1999, Haslam et al., 1997).

The ES of filarial nematodes *Brugia malayi* and *O. volvulus* that affect humans ,was observed to contain ES-62 homologues (Harnett et al., 2003) and the PC attachment to *N*-glycans that is likely to be conserved nature in filarial nematodes (Haslam et al., 1997). Numerous organisms contain PC as a conserved structural constituent and the most important of the wide range of functions it fulfils is regulation of the host immune response (Clark and Weiser, 2013). ES-62 can have interaction with immune response cells because it occurs in the blood of *A. viteae-i*nfected hosts. In fact, there is evidence based on a range of *in vitro* studies that ES-62 is a major regulator of the immune response to filarial infection. Several types of cells are targeted by ES-62, such as T and B lymphocytes, macrophages, DCs and mast cells (Pineda et al., 2014). Furthermore, a biased immune response toward a regulated TH2/anti-

inflammatory phenotype may be promoted by ES-62, leading to up-regulation of production of several cytokines (e.g. IL-4, IL-5 and IL-13), down-regulation in others (e.g. IL-12, IL-6 and TNF-α), as well as a distorted antibody response (Goodridge et al., 2007, Harnett and Harnett, 2010, Harnett and Harnett, 1993a).

1.2.3 ES-62 interaction with antigen presenting cells

An investigation was conducted to determine whether the inhibitory effect of ES-62 on T cells was caused by ES-62's modulation of macrophages and DCs (Whelan et al., 2000b, Goodridge et al., 2004).In fact at this point, the capability of polarising the immune response towards a TH2 phenotype via DC modulation had so far not been identified in any other helminth molecule apart from ES-62. Based on evidence of IFN-γ being produced by naïve CD4+T cells cultured alongside LPS-matured DCs, it was reported that a TH1 phenotype was promoted by these DCs, and at the same time, production of the defining TH2 cytokine, IL4, by T cells was encouraged by DCs matured with ES-62 (Whelan et al., 2000b). Additional investigation revealed that LPS stimulation causes DC maturation as showed by up-regulation of a number of co-stimulatory molecules (CD40, CD80, CD86 and CD54), however DCs treated with ES-62 did not exhibit this effect. Macrophage activity both *in vivo* and *in vitro* is regulated by ES-62, in addition to its priming of DCs toward a TH2 phenotype. LPS and IFN-γ, which usually stimulate macrophages, had diminished effects after these cells were treated with ES-62 in experiments conducted on cells *in vitro*. Consequently, the cells' production of TH1 cytokines IL-12, IL-6 and TNF-α was reduced, but their NO production was unaffected. Such inhibition occurred *in vivo* as well, as shown by mouse experiments employing osmotic pumps that released 0.05 µg ES-62 per hour to imitate natural filarial infection; by comparison to control mice, *ex vivo* LPS and IFN-γ stimulation of macrophages

from mice subjected to ES-62 treatment caused a decrease in these cells' production of IL-12 and TNF-α (Goodridge et al., 2007) . ES-62 actually induces a small transient amount of pro-inflammatory cytokine in macrophages prior to blockage of LPS-induced responses. Aborted signalling is a likely the cause of transient inflammatory cytokine release, leading, later on, to inhibition of cytokine production. Meanwhile, in addition to regulating macrophage and DC activity in the blood, ES-62 also seems to influence these cells' bone marrow precursors. These precursors will respond poorly to LPS stimulation if they are exposed to ES-62 beforehand. The mechanism underpinning this inadequate response seems to involve reduction in the levels of mRNA and protein of the IL-12 p40 and p35 subunits, which suppresses production of the cytokine (Goodridge et al., 2004)

When macrophages and DCs are pre-treated with PC alone or PC conjugated to OVA or BSA, followed by LPS stimulation there is subsequent suppression of full activation of DCs and macrophages. It is significant to note that neither macrophages nor DCs are affected by mock-conjugated OVA protein (Goodridge et al., 2007). An investigation was conducted to determine detection of ES-62 via TLRs, since PC is a common PAMP and therefore is targeted for immune cell detection. For that reason, mouse models with TLR4 and TLR2 knockout (KO) were employed to determine how ES-62 regulated macrophages and DCs. In the case of the mouse models employing TLR2 KO, macrophages and DCs exhibited low level production of IL-12 and TNF-α, identical to what was found with wild-type mice, as well as a subsequent cytokine inhibition suggesting that ES-62 regulated APCs without requiring TLR2. On the other hand, in the case of the mouse models employing TLR4 KO, ES-62 modulation was assessed using BLP, CpG and LPS, ligands of TLR2, TLR9 and TLR4 respectively: here ES-62 function was found to be dependent on TLR4 as after

IFN-γ/ BLP and IFN-γ/CpG stimulation the IL-12 and TNF-α production was inhibited by ES-62 pre-treatment in wild-type mice but not in TLR4 KO mouse models. However, further evidence indicated that the TLR4 receptor did not have to be fully active to support ES-62 effects, as deduced from C3H/HeJ mice that lacked LPS detection and responsiveness, due to a Pro712His point mutation in the TIR domain of TLR4. As with wild-type mice, IFN-γ/BLP stimulation led first to proliferation and then to inhibition of IL-12 and TNF-α by the macrophages and DCs of these mice (Goodridge et al., 2005a).

Cells treated with ES-62 did not show any changes in TLR-MD-2 surface expression, indicating that mouse peritoneal macrophages could detect LPS even in the presence of ES-62. This suggests that regulation of intracellular signalling pathways is important for mediation of ES-62 action in this context. After TLR4 is activated, downstream signalling required the adaptor MyD88, which seems to be essential for ES-62 to trigger low-level IL-12p40 in macrophages and DCs, since synthesis is not present in MyD88 KO cells (Goodridge et al., 2005a). A range of cells has been reported to be associated with down-regulation of MyD88 expression by ES-62, including macrophages (Ball et al., 2013b) ,mast cells (Ball et al., 2013b), TH17 cells during collagen-induced arthritis (CIA) (Pineda et al., 2012), as well as B cells and kidney cells in MRL/Lpr mice (Rodgers et al., 2015b). Although clarity is yet to be gained regarding the manner in which ES-62 acts on APCs, there is evidence that the activation of ERK, JNK and p38 MAPKs and NF-κB that are necessary for production of pro-inflammatory cytokines is regulated by the parasite molecule. The production of bioactive IL-12p70, IL-12p40 and IL-12p35 is dependent on two subunits that are modulated by ES-62 in a differential manner, through inhibition of LPS-based stimulation of p38 and JNK, without which p35, IL-6 and TNF-α cannot be produced. The activation of calcium ERK MAPK activation

was triggered by LPS which negatively decreased production of p40 (Goodridge et al., 2003, Goodridge et al., 2005a).

1.2.4 ES-62 synthetic Small Molecule Analogues (SMAs) 11a, 12b and their immunomodulatory properties

The helminth molecule ES-62 has been shown by research employing different animal models to be highly promising for the treatment of autoimmune and allergic conditions. However, it is not easy to develop into a medication because as a large foreign protein it is likely to be immunogenic. On the basis that the PC moiety of the molecule is the source of numerous immunomodulatory capabilities, Dr Abedawn Kalaf and Dr Judith Huggan, supervised by Professor Colin Suckling of the Department of Pure and Applied Chemistry at the University of Strathclyde, created a library of PC-based small molecule analogues (SMAs). *In vitro* examination of the immunomodulatory potential of the SMAs in macrophages revealed that the suppressing action of ES-62 on pro-inflammatory cytokines activated by TLR ligation was imitated by the sulfones 11a and 12b (Rzepecka et al., 2015, Al-Riyami et al., 2013c).

Further research indicated that the SMAs not only protected mice from CIA, but also down-regulated MyD88, the TLR adaptor protein, thus replicating the action mechanism of ES-62 (Rzepecka et al., 2015, Al-Riyami et al., 2013c). Moreover, the protection afforded by 11a inhibited IFN-γ and IL-17 responses, thus imitating ES-62 as well (Al-Riyami et al., 2013c).On the other hand, the protection afforded by 12b was related to immunomodulatory attributes less characterised with ES-62. Consequently, the therapeutic action of 12b resulted in marked down-regulation of several genes in macrophages involved in inflammasome modulation and IL-1β suppression *in vitro*. Additionally, *in vivo* research led to the same findings, as IL-1β levels in 12b-treated mice with CIA

were not as high as those in mice treated with PBS as a control (Rzepecka et al., 2015).

The two SMAs were also tested in MRL/lpr mice, a mouse model of systemic lupus erythematosus (SLE) and a decline in proteinuria and thus protection against kidney disease was observed. In addition, a reduction in the levels of anti-nuclear antibodies (ANA)and kidney MyD88 and IL-6 levels was observed with the SMAs and these data are likely to explain the protective effects against kidney disease (Rodgers et al., 2015a).

To find out how effective they were against allergic reactions, the SMAs were analysed with regard to effects on mast cell activation. When the cells were pre-treated with 11a or 12b, the production of pro-inflammatory cytokines induced by FcεR1-bound IgE cross-linking or LPS exposure was suppressed, while calcium mobilisation and degranulation were diminished, thus again replicating the effects of ES-62. The *in vitro* screening investigation was followed by assessment of the two sulfones in a model of airway inflammation triggered by ovalbumin (OVA) results showed that lung infiltration by eosinophils was suppressed by both 11a and 12b (Rzepecka et al., 2014a).Figure 1.4 illustrates the SMAs general effects on LPS/BLP- and CpG-stimulated macrophages .

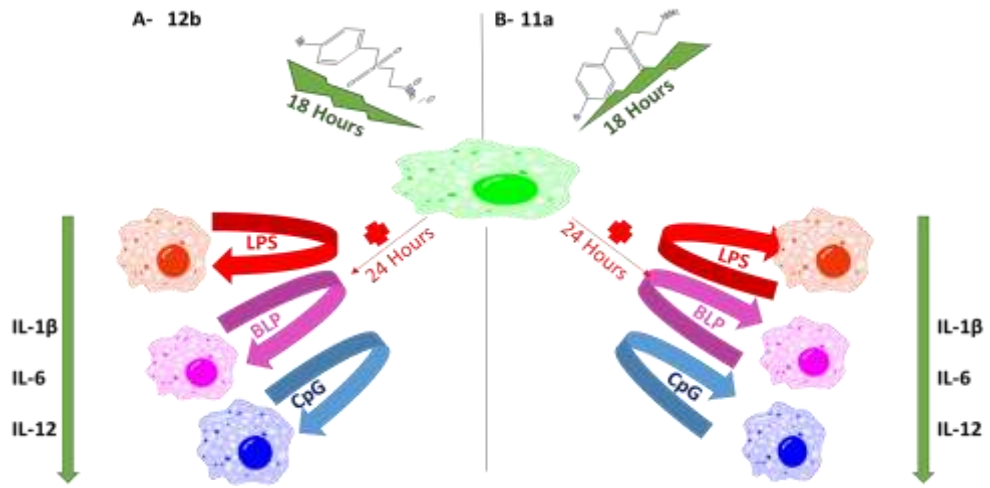

Figure 1.4: Illustration of SMAs general effects on LPS/BLP and CpG stimulated macrophages.

Adding 12b In A and 11a in B for 18 hours before stimulation with LPS/BLP and CpG decreases the production of the proinflammatory cytokines IL-1β, IL-6 and IL-12 which have been produced in response to LPS/BLP and CpG alone activation.

1.3 Introduction to immune metabolism

1.3.1 An overview of metabolic pathways

In order to link a cell's requirements to develop and survive with the metabolic system responsible for modulating the generation of the products essential for those requirements, metabolic pathway activities are controlled by cell intrinsic and extrinsic signals. However, the immune system is underpinned by particular metabolic pathway modifications that are aligned with immune effector functions, especially in the context of production of specific cytokines. To promote survival and to stimulate cells to develop and proliferate through production of various biosynthetic intermediates, a range of distinct metabolic pathways are employed by immune system cells fulfilling different roles to produce sufficient energy supplies. Despite yielding distinct end-products, these metabolic pathways are interconnected because they have the same fuel inputs and depend on the products of one pathway to promote alternative pathways as essential synthetic precursors. For instance, proliferation requires cell membranes and additional important structures with a lipid basis, which are generated through fatty acid synthesis, a process that illustrates the complexity of metabolic pathway interactions and is dependent on intermediate products of the cycle metabolism of the glycolytic pathway and tricarboxylic acid (TCA). Taking into account the close links between cellular metabolic pathways, six metabolic pathways of vital importance are illustrated in fig 1.5. These pathways are used for the production of products related to the development and survival of cells and are addressed in the following section. With singular cellular functions and controlled by cellular signalling pathways that establish correlations between their functions and the requirements of the cells, these six pathways are the glycolytic pathway, the TCA cycle pathway, the pentose

phosphate pathway, the fatty acid oxidation pathway, the fatty acid synthesis pathway and the amino acid pathway.

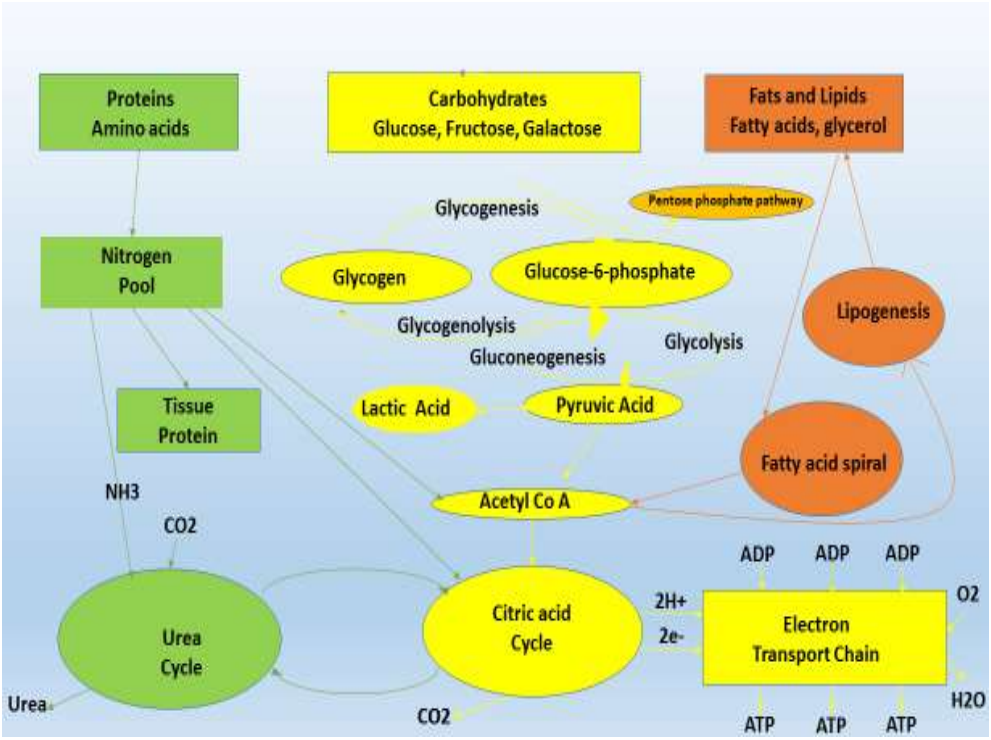

Figure 1.5: A simplified representation of the cell's main metabolomic pathways.

Carbohydrate metabolism is shown in yellow blocks, fatty acid synthesis and degradation pathways are illustrated as orange blocks while green blocks refer to protein /amino acids cooperation to cell metabolism. Arrows are indicating the direction of the metabolic flow.

1.3.1.1 The glycolytic metabolic pathway

Taking place in the cytosol of the cell outside the mitochondria, glycolysis begins with formation of pyruvate from glucose breakdown, resulting in two Adenosine triphosphate (ATP) molecules. This pathway enables the generation of 2 molecules of Nicotinamide adenine dinucleotide reduced form (NADH) from Nicotinamide adenine dinucleotide (Oxidised form) (NAD+), which serves as a cofactor for a number of enzymes and promotes development towards anabolic pathways. Pyruvate conversion to lactate through anaerobic glycolysis is essential to maintain the glycolysis flux, enabling in turn maintenance of the levels of NAD+ and reuse of NADH.

By triggering their metabolism through diversion of intermediate metabolites, the glycolytic pathway is essential for nucleotide, amino acid and fatty acid pathways. For example, the glycolytic pathway diverts glucose-6-phosphate to pentose phosphate, to 3‑phosphoglycerate for the serine biosynthetic pathway, while supply of pyruvate metabolites to the Krebs cycle can trigger fatty acids to generate citrate.

Cells with fast development derive their necessary energy from glycolysis. In recent times, this process has been afforded great significance because it supplies the energy required by a number of signalling pathways, including the phosphatidylinositol 3‑kinase (PI3K) pathway and the mitogen-activated protein kinase (MAPK) pathway.

1.3.1.2 Citric acid cycle (TCA, Krebs)

The primary pathway employed by quiescent cells and by cells without proliferation is the Krebs cycle, which occurs in the mitochondrial matrix. Ample

and long-lasting energy supplies are needed for the production of ATP in sufficient amounts. Thus, pyruvate or fatty acids are initially converted into acetyl CoA, which forms citrate by condensing with oxaloacetate. The TCA cycle produces 32 ATP molecules.

Similar to glycolysis, signalling pathways are supported by the TCA cycle through direction of its intermediates to either generate amino acids and lipids or to promote TCA metabolite production in what are respectively known as the processes of cataplerosis and anaplerosis.

1.3.1.3 The pentose phosphate pathway

To proliferate and survive, cells depend significantly on the pentose phosphate pathway, which occurs in the cell cytosol and consists of an oxidative and a non-oxidative phase, respectively involving Nicotinamide adenine dinucleotide phosphate (NADPH) production and 5-carbon sugar production. By diverting the metabolite glucose-6-phosphate from the glycolytic pathway, it promotes the generation of nucleotides and amino acid precursors.

1.3.1.4 Fatty acid oxidation

This pathway involves oxidation of fatty acids with long and short chains into acetyl-CoA so that they can enter the TCA cycle and produce energy as NADH, Flavin adenine dinucleotide (FADH2) and finally ATP.

Unlike fatty acids with short chains, which have no more than six carbons and therefore their diffusion into mitochondria is passive, fatty acids with medium and long chain are transported into mitochondria only after conjugation to carnitine. Within the mitochondria, the carnitine conjugated fatty acids undergo

conversion into acyl-CoA and finally acetyl-CoA, entering the TCA cycle and generating ATP in large proportions via the electron transport chain (a single palmitate molecule can generate 100 ATP molecules).

1.3.1.5 Fatty acid synthesis

To develop and proliferate, cells need lipids produced via the fatty acid synthesis pathway. The synthesis of fatty acids via malonyl CoA provides precursor metabolites for the other metabolomics pathways (e.g. citrate for the TCA cycle). On the other hand, elongation of fatty acids with branched chains employs branched amino acids (e.g. valine and leucine). The metabolite glycerol is a product of glycolysis that participates in the synthesis of major constituents of numerous cell wall structures, namely, triacylglycerols and phospholipids.

There is evidence that fatty acid synthesis is indirectly promoted by mTOR signalling via modulation of enzymes of the fatty acid pathway, such as stimulation of the cleavage and activation of the sterol regulatory element binding protein (SREBP), which in turn activates generation of endogenous ligands for PPAR-γ, peroxisome proliferator-activated receptor-γ, hence sustaining the transactivation activity of this nuclear receptor. Palmitate serves as an elongation substrate in the case of other enzymes, such as fatty acid synthase (FASN) and SREBP triggers acetyl CoA carboxylase (ACC).

1.3.1.6 Amino acid metabolic pathways

Cellular metabolic activities depend to a significant extent on amino acids that not only supply the key constituents of protein synthesis but also supply

substrates and manage the *de novo* synthesis of branched-chain fatty acid pathways. When cells are starving, the mTOR signalling pathway stimulates anabolic growth and reuses secondary cellular products via autophagy by increasing assimilation and synthesis of amino acids. Different amino acids fulfil different roles within central metabolomic pathways. For instance, ATP production and fatty acid synthesis are respectively promoted by glutamine by refuelling the TCA at α-ketoglutarate and at citrate. Meanwhile, aspartate is of importance for the *de novo* synthesis of purines and pyrimidines. Furthermore, the proliferation and anabolic growth of cells depends on amino acids such as arginine and tryptophan that undergo metabolism via different metabolic pathways.

1.3.2 Metabolism of immune cells

1.3.2.1 Glycolysis in immunity

Many immune system processes are underpinned by glycolysis. Research has revealed that macrophage and T cell stimulation causes glycolysis metabolites to accumulate, resulting in intensified glycolysis (Alonso and Nungester, 1956, Newsholme et al., 1986). Furthermore, the important function of glycolysis in the immune system has been highlighted by extensively the use of the glycolysis inhibitor, 2-deoxyglucose, which has been shown to hinder uptake of glucose and therefore stops macrophages from becoming activated (Hamilton et al., 1986, Michl et al., 1976).

Such findings are unexpected because glycolysis yields just two ATP molecules / glucose molecule, whereas oxidative phosphorylation yields about 36 ATP molecules per glucose molecule, which is a much larger amount of energy. Nevertheless, unlike the energy supply provided by oxidative phosphorylation,

which can be accessed with some difficulty due to a requirement for mitochondrial biogenesis, the energy supply of glycolysis, despite being less abundant, can be accessed much more quickly by cells needing energy to develop or for a particular immune activity. Furthermore, aside from the rate of the process, the ability to ensure the availability of metabolites required for cellular growth also makes glycolysis highly important.

The accumulation of glycolysis metabolites is promoted by many different cell types, including activated macrophages or DCs (Krawczyk et al., 2010, Rodríguez-Prados et al., 2010b), activated natural killer (NK) cells (Donnelly et al., 2014) , stimulated effector T cells (Michalek et al., 2011) such as T helper 17 (TH17) cells (Shi et al., 2011) , TH1 and TH2 cells (Michalek et al., 2011), activated effector CD8+T cells (Gubser et al., 2013), and activated B cells (Doughty et al., 2006). Stimulation of glycolysis will ensure that the immune cells will have enough ATP supplies and biosynthetic glycolysis intermediates to conduct specific effector activities, like phagocytosis and generation of inflammatory cytokines in the case of macrophages and of DCs , and effector cytokine production (e.g. IL-17) in the case of T cells such as TH17 cells (Shi et al., 2011).

It has been observed that the glycolysis pathway is significantly stimulated when more than one signalling pathway is activated. For instance, a rise in glycolysis has been related to activation in the mTOR pathway in effector T cell subsets (Wei et al., 2016, Huynh et al., 2015, Shrestha et al., 2015) as well as to the intensified activation of hypoxia-inducible factor 1α (HIF1α) as a result of LPS activation (Tannahill et al., 2013a) . Furthermore, LPS activation also triggers NF-κB, which has been associated with increased glycolysis as well, even in cells without HIF1α (Rodríguez-Prados et al., 2010b).

In DCs, glycolysis enhancement is achieved by inducing TANK-binding kinase 1 (TBK1) alongside or without suppression of NF-κB kinase ε (IKKε) and hexokinase 2 without dependence on HIF1α (Huynh et al., 2015). By contrast, in macrophages exposed to LPS, it is the activation of pyruvate kinase isoenzyme M2 (PKM2) that enhances glycolysis (Palsson-McDermott et al., 2015). Glycolytic flux reduction occurs with the involvement of PKM2 regulation via redirection of glycolytic intermediates toward biosynthetic pathways. Furthermore, besides glycolysis, PKM2 is also involved in stimulating the expression of HIF1α-dependent genes (Luo et al., 2011, Palsson-McDermott et al., 2015) and especially IL-1β via interaction with HIF1α following its translocation into the nucleus. Additionally, it is worth noting that, in order to encourage glycolysis, PKM2 assumes a dimeric form within the nucleus and with application of the small molecules TEPP-46 or DASA-58, which can endow this enzyme with a tetrameric form thus hindering its access to the nucleus, macrophages can be re-programmed towards an M2 phenotype in their gene expression profile (Palsson-McDermott et al., 2015). This is consistent with the idea regarding HIF1α suppression, whereby the M1 phenotype of macrophages become M2 due to the external position of PKM2 in relation to the nucleus. Moreover, the involvement of glycolysis in inflammation has been confirmed by the fact that in human atherosclerotic-coronary artery disease, a pro-inflammatory effect was displayed by PKM2 present in activated monocytes and macrophages (Shirai et al., 2016a).

The significance of glycolysis for immune system activities is also highlighted by the fact that TH17 cells convert to Treg cells when they are treated with the glycolysis inhibitor 2-deoxyglucose (Shi et al., 2011). The mTOR pathway signalling may become hyperactive due to elevated glycolysis in Treg cells, with adverse implications for cell survival and lineage commitment (Wei et al., 2016,

Huynh et al., 2015, Shrestha et al., 2015). On the whole, there is evidence that, apart from human Treg cells that use glucose (De Rosa et al., 2015, Procaccini et al., 2016) , accumulation of glycolysis metabolites in cells can promote inflammation, whereas an anti-inflammatory phenotype can develop if glucose is assimilated, as in the case of oxidative phosphorylation.

The effects of glycolysis on TH1 cells have been revealed by glyceraldehyde 3 -phosphate dehydrogenase (GAPDH). Activation of glycolysis in these cells initiates detachment of GAPDH from IFN-beta mRNA (Chang et al., 2013, Mukhopadhyay et al., 2009), thus enabling it to be translated and promoting production of extra ATP. However, elevated glycolysis is believed to induce a reaction between hexokinase 1, another glycolytic enzyme of macrophages, and NLRP3, a key regulator of caspase 1 that produces IL-1β and active IL-18 on the external membrane of mitochondria, leading to its activation (Moon et al., 2015a) and involvement in ATP production.

1.3.2.2 The role of the pentose phosphate pathway within immune cells

The pentose phosphate pathway is considered important in immune cells as it contributes to the production of nucleotides and NADPH. In immune cells, during oxidative burst, ROS production is induced by NADPH through NADPH oxidase, and the production of glutathione and additional antioxidants is stimulated as well. The generated ROS are employed by macrophages and neutrophils to eliminate infectious agents, while antioxidants are subsequently activated to provide cells with protection against damage.

In DCs, endoplasmic reticulum synthesis underpinning DC activation and cytokine production is promoted by both NADPH and lipid synthesis (Everts et

al., 2014). Inhibition of carbohydrate kinase-like protein (CARKL or SHK) enhances the pentose phosphate pathway in LPS-activated macrophages, causing the latter to express an M1 phenotype. However, overexpression results in conversion to M2 phenotype (Haschemi et al., 2012).

There is still no comprehensive understanding as to why the levels of nucleotides are so high in M1 macrophages. One potential explanation is that the production of nucleotides in these macrophages is intended to support the generation of various RNA populations, microRNAs and long non-coding RNAs needed to regulate cell activities.

1.3.2.3 TCA cycle accompanying immune responses

Recent studies have addressed the functions played by the TCA cycle and oxidative phosphorylation in immune cells. They possess complete functionality in all T cells apart from effector T cells, where there is a minor inclination toward glycolysis (O'Sullivan et al., 2014, Michalek et al., 2011). There is evidence that, in M2 macrophages, the TCA cycle is whole and is associated with oxidative phosphorylation, enabling generation of glycan precursors (e.g. UDP-GlcNAc intermediates) that are crucial in glycosylating receptors related to M2, such as the mannose receptor (Jha et al., 2015a). By contrast, the TCA cycle is incomplete in macrophages with the M1 phenotype and in DCs, being disrupted after citrate and succinate (Jha et al., 2015a, Tannahill et al., 2013a, Everts et al., 2014). The post-citrate disruption causes citrate to accumulate and be removed from mitochondria to support generation of fatty acids, membrane synthesis, antigen presentation, production of nitric oxide and prostaglandins, and production of itaconic acid with respect to two *Salmonella enterica* subspecies (i.e. *Enterica serovar typhimurium)* and *Mycobacterium*

tuberculosis, which is believed to target bacteria directly (Michelucci et al., 2013). Meanwhile, the post-succinate disruption causes accumulation of succinate, which stabilises HIF1α and supports IL-1β21 generation in both normoxia and hypoxia, owing to prolyl hydroxylase suppression.

Accumulation of TCA metabolites in mitochondria benefits the immunity-related activities of macrophages, including generation of nitric oxide, which disrupts the electron transport chain in these cells (Clementi et al., 1998).

1.3.2.4 Oxidation of fatty acids and immune function

The regulatory capability of immune cells, particularly those with an anti-inflammatory phenotype (e.g. M2 macrophages, memory T cells, and Treg cells) is supported by fatty acid oxidation. Activated macrophages elicit the accumulation of unsaturated fatty acid metabolites (e.g. oleic acid, linoleic acid and arachidonic acid), thereby regulating fatty acid oxidation. This triggers foam cells to produce IL-1α, leading to intensified inflammation (Feingold et al., 2012b). Hence, it is likely that enhanced inflammation in foam cells is related to the accumulation of fatty acids and their derivatives (Shoelson et al., 2006, Lusis, 2000, Carpenter et al., 1995). It is worth noting that fatty acid oxidation is intensified while cytokine production is diminished when macrophage long-chain fatty acids are transported to mitochondria via CPT1A (Malandrino et al., 2015).

Fatty acid oxidation seems to not only reduce the production of cytokines in macrophages, but also to promote an M2 phenotype. It has been observed that when macrophages are stimulated with the M2 phenotype promoter, IL-4, the transcription factor STAT6 and PPARγ-co-activator 1β (PGC1β) are stimulated as well (Huang et al., 2014, Vats et al., 2006). Nevertheless, M2 polarisation is

unaffected by Cpt2 deletion (Nomura et al., 2016), which means that it may be involved in cellular activities other than the transport of fatty acids or macrophage differentiation, therefore increasing the challenge of determining its function within the macrophage metabolome.

In the case of T cells, fatty acid oxidation ensures that T effectors and suppressive Treg cells are balanced, thus ensuring that memory T cells are activated and that immune function is maintained. To trigger the production of Treg cells and prevent T effectors from differentiating, the achievement of equilibrium between the two types of cells requires increasing the Treg fatty acid oxidation in relation to TH1, Th2 and Th17 cells (Michalek et al., 2011). Consistency exists between Treg-based enhancement of fatty acid oxidation metabolites and enhancement of fatty acid gene expression (e.g. Cpt1a) compared to Th17 cells (Gerriets et al., 2015). It is worth noting that the genes of molecules involved in fatty acid oxidation are down-regulated by effector T cells (Wang et al., 2011). On the whole, effector T cells promote Cpt1a expression and stimulate the fatty acid oxidation pathway by reducing fatty acid metabolites and hence causing expression of the inhibitory programmed death 1 (PD1) receptor to ligate on T cells (Patsoukis et al., 2015).

A close correlation has been established between the development and survival of memory CD8+T cells and fatty acid metabolic activities. Fatty acid oxidation appears to be essential for the ability of these cells to react to antigens they encounter and this reaction is time-dependent (van der Windt et al., 2013). Memory CD8+T cells express more Cpt1a as a result of IL-15 stimulation, enhancing fatty acid oxidation and ensuring the cells' ability to survive (van der Windt et al., 2012). However, *de novo* synthesis may be necessary to provide an additional fatty acid supply to support their activities, given that these cells depend on fatty acid oxidation to such a great extent (O'Sullivan et al., 2014).

1.3.2.5 Fatty acid synthesis in the immune system

It has been proposed that pro-inflammatory immune cells are associated with fatty acid synthesis while non-inflammatory immune cells are known to be associated with by fatty acid oxidation.

Addition of the macrophage colony-stimulating factor (M-CSF) in the process in which monocytes differentiate into macrophages was discovered to stimulate the sterol regulatory element-binding transcription factor 1c (SREBP1c), which intensified expression of target genes associated with fatty acid synthesis (e.g. FASN) and lipid synthesis. In turn, both macrophages and fatty acid synthesis were stimulated by LPS (Posokhova et al., 2008, Ecker et al., 2010, Feingold et al., 2012b). Furthermore, fatty acid synthesis in macrophages and inflammation via activation of the NLRP3 inflammasome has also been reported to be promoted by the mitochondrial uncoupling protein 2 (UCP2) (Moon et al., 2015b).

In the case of DCs, TLR stimulation promoted fatty acid synthesis, triggering these cells to become activated, which in turn stimulated CD8+T cells (Everts et al., 2014). Fatty acid synthesis has been shown to be necessary for T and B cell activation (Dufort et al., 2014, Chen et al., 1975). According to the findings reported by one study, the efficiency of T cells was negatively affected when the acetyl-CoA carboxylase 1 (ACC1) was deleted, while addition of exogenous fatty acids corrected this (Lee et al., 2014).

The essential function of fatty acid synthesis in encouraging TH17 cells to differentiate has been emphasised by the genetic or deliberate deletion of ACC1 in CD4+T cell subsets and at the same time fatty acid synthesis has been demonstrated to balance effector and regulatory T cells (Berod et al., 2014). One study notably reported that IL-17 and IL-10 production was diminished

when the CD5 antigen-like (CD5L) was expressed in non-pathogenic TH17 cells (Wang et al., 2015). These cells stimulate the epithelial barrier function to prevent microbiota attacks in mouse gut (Guglani and Khader, 2010), whereas in humans they demonstrated a protective effect against *Staphylococcus aureus* (Zielinski et al., 2012). Two theories have been formulated regarding the fatty acid types regulating particular cytokines in TH17 cells. According to one theory, the binding of polyunsaturated¬fatty acids (PUFAs) to fatty acid synthase is encouraged in non-pathogenic TH17 cells by CD5L, thus supplying a transcription factor for these cells as well as cholesterol-derived ligands for RORγt, improving IL-10 production and restricting IL-23 and IL-17. By contrast, according to the other theory, the binding of saturated fatty acids to fatty acid synthase in pathogenic TH17 cells is promoted by CD5L, resulting in ligands for RORγt, which is beneficial for production of IL-23 and IL-17 but detrimental to IL-10 production. Thus, it was concluded that anti-inflammatory cytokines (e.g. IL-10) are promoted by PUFAs, whereas IL-10 production is limited by saturated fatty acids.

To summarise, in M2 macrophages, Treg cells and memory cells, fatty acid oxidation promotes anti-inflammatory responses and oxidises lipids for ATP production, while in effector immune cells, fatty acid synthesis fosters inflammatory responses and supplies lipids for biosynthesis and fast growth (Maceyka and Spiegel, 2014, Fessler, 2015).

1.3.3 Amino acid metabolism associated with the immune functions

Immune system cells are regulated with the participation of amino acid metabolism. When the cells are starved, the availability of amino acids plays a crucial role in regulating not only the mTOR pathway but also the development

and proliferation of cells. The metabolic activities of the amino acids glutamine, arginine and tryptophan are particularly important for the functioning of immune cells. These amino acids are addressed in the following part and additional amino acids with essential involvement in immunity are also discussed to gain a comprehensive understanding of the significance of amino acids for the metabolism of the immune system.

1.3.3.1 Glutamine metabolism

Plasma, skeletal muscle, foetal fluid and milk are all high in glutamine, an amino acid that in the case of immune system cells serves as an energy substrate. Glutamine is catabolised via glutaminolysis, generating mainly glutamate, aspartate, alanine, lactate, pyruvate and carbon dioxide.

Glutathione is a tripeptide with an essential role in preventing oxidative stress from damaging immune system cells and is synthesised with the participation of glutamate. To react to antigen receptor stimulation, glutamine assimilation is enhanced in T and B cells when these cells become activated (Crawford and Cohen, 1985, van der Windt et al., 2013, Wang et al., 2011). Meanwhile, glutaminase is involved in ROS stress regulation, since its knockout leads to an increase in ROS, which is particularly pronounced in hypoxic conditions (Le et al., 2012). Additionally, glutamine is considered as a key precursor of purine and pyrimidine nucleotides and therefore is important for the proliferation of lymphocytes.

Glutamine feeds the arginine pathway (MURPHY and NEWSHOLME, 1998) to support the antimicrobial effects of macrophages and its withdrawal from culture medium has been reported to lead to a reduction in the levels of nitric oxide produced by macrophages activated by Bacille Calmette-Guérin (BCG) (Bellows and Jaffe, 1999, MURPHY and NEWSHOLME, 1998). Furthermore, in

the case of macrophages exposed to IL-4 stimulation, they undergo polarisation to an M2 phenotype when the TCA cycle and hexosamine pathway are fed by glutamine. By contrast, the growth of macrophages with the M1 phenotype does not depend on glutamine (Jha et al., 2015a), although this amino acid remains necessary for IL-1 and TNF-a production via LPS stimulation (Wallace and Keast, 1992) and for IL-6 and IL-8 generation by human monocytes (Field et al., 2002).

The deletion of the alanine, serine, cysteine-preferring transporter 2 (ASCT2) can impair the activity of TH1 and TH17 cells but not Treg cells. This transporter is involved in the assimilation of neutral amino acids (e.g. glutamine and leucine) and its deletion in effector T cells results in a decrease in mTORC1, which is damaging to the cells (Nakaya et al., 2014).

1.3.3.2 Arginine metabolism

Arginine is a key amino acid for which ample knowledge has been accumulated, particularly with regard to its role in macrophages (Rath et al., 2014). It is catabolised by macrophages to generate two distinct products that determine the phenotype of these cells. Thus, one product derived from arginine through citrulline is nitric oxide, whose generation is controlled by iNOS expression (MacMicking et al., 1997a) and is associated with inflammatory macrophages or macrophages with the M1 phenotype. Research conducted on mice without iNOS revealed that macrophages exhibited dysfunctional killing action *in vitro*. In contrast ,if the arginine enters via the arginase pathway, this will endow macrophages with an M2 phenotype related to wound repair (Albina et al., 1988), but also reduces the potency of the inflammatory response triggered by effector T cells (Pesce et al., 2009) in visceral leishmaniasis and HIV infection

(Takele et al., 2013). Meanwhile, in the case of T cells, their proliferation is promoted by arginase (Rodriguez et al., 2007), which additionally stimulates expression of T cell receptor constituents (Rodriguez et al., 2002). Furthermore, arginine may be involved in mTORC1 regulation because an *in vitro* study found that mTORC1 activity diminished in the absence of arginine (Cobbold et al., 2009).

1.3.3.3 Tryptophan metabolism

Immune system cells also rely on tryptophan metabolism. Studies revealed that treating an animal with a higher doses of extracellular tryptophan resulted in development of an autoimmune phenotype characterised by aberrant eosinophil function (Stahl et al., 2001, Silver et al., 1990).

The enzyme indoleamine-2, 3-dioxygenase (IDO), which acts as a restrictive agent of tryptophan catabolism, has been examined by many studies concerned with the significance of tryptophan metabolism. Some studies reported that elevated levels of this enzyme were found in cells which responded to LPS exposure and IFNγ treatment (Werner et al., 1989, Yoshida and Hayaishi, 1978). The essential role played by tryptophan in immunity has been highlighted by findings that bacterial development and parasite intrusion were hindered by tryptophan metabolites in host cells (Schroten et al., 2001, Pfefferkorn, 1984). T cell stimulation was reduced by IDO expressed in antigen-presenting cells in an *in vitro* study, suggesting that tryptophan metabolism was important for cell proliferation (Munn et al., 1999, Lee et al., 2002). By contrast, levels of charged tRNAs increased and the unfolded protein response GCN2 was activated when tryptophan metabolism declined (Liu et al., 2014). Overall, these studies indicate that immune cell functionality depends on tryptophan and that the immune cells may even compete with each other to obtain this amino acid. Furthermore, the significance of tryptophan metabolites for target function was

confirmed by additional studies. For example, immune system cell functionality is supported by kynurenine via stimulation of a ligand-induced transcription factor, aryl hydrocarbon receptor (Berod et al.) (Bessede et al., 2014a). Moreover, IDO was found to be expressed in high levels in tumour cells and stromal cells related to tumours (Weinlich et al., 2007, Munn et al., 2004, Okamoto et al., 2005, Uyttenhove et al., 2003), diminishing T cell anti-tumour action, an effect which was reversed by using 1-methyltryptophan to suppress IDO (Holmgaard et al., 2013). Nevertheless, further research is needed to clarify its mechanisms in non-tumorous immune cells.

1.3.3.4 Glycine metabolism

Alone, glycine has good antioxidant properties and can detect free radicals (Fang et al., 2002). Key metabolites (e.g. purine nucleotides, glutathione and haem metabolites) are synthesised with glycine participation (Kim et al., 2007). Additionally, leucocytes rely on glycine to proliferate and fulfil their defensive function. When activated, a glycine-gated chloride channel in leucocytes has a diminishing effect on the agonist, which signals the L-type calcium channels with voltage dependence to open (Froh et al., 2002), lowering the levels of intracellular calcium ions. Cytokine production can be regulated by immune system cells via this mechanism (Zhong et al., 2003). In macrophages, monocytes, lymphocytes and neutrophils, the glycine-gated chloride channel is activated and the plasma membrane is polarised at 0.1-1 mm concentration of extracellular glycine (Froh et al. 2002).

Wheeler and Thurman (1999) reported that the use of extracellular glycine to pre-treat LPS-activated macrophages had a negative impact on H_2O_2

production and levels of IL-1 and TNFα by reducing the Ca^{2+} flow and, implicitly, the intracellular accumulation of Ca^{2+} (Wheeler and Thurman, 1999) .

Although IL-2 production in T cells was unaffected when the T cells were stimulated by immobilised anti-CD3 antibody, the proliferation was inhibited through attenuating the level of intracellular calcium by glycine dosage in the range of 0.1-1 mm (Stachlewitz et al., 2000).In a different study, addition of 2 mm of extracellular glycine in the culture medium hindered apoptosis and enhanced production of antibodies by B lymphocytes (Duval et al., 1991a).

In their *in vivo* study, Konashi et al. (2000) found that inflammation and morbidity diminished when they added glycine to the diet given to animals with pathogenic infections (Konashi et al., 2000). Similarly, Ikejima et al. (1996) reported that plasma TNF decreased when rats infected with LPS were given a supplement of 5% glycine (Ikejima et al., 1996). Furthermore, in rats subjected to treatment with 2,4,6-trinitrobenzene sulphonic acid and dextran sulphate sodium, experimental colitis was halted by 5% glycine, which also reduced IL-1β and TNFα expression in the colon (Tsune et al., 2003).

All the above-mentioned studied confirmed that glycine possessed anti-inflammatory, immunomodulatory and cytoprotective properties.

1.3.3.5 Histidine metabolism

Various immune cell functions, including cell interaction, migration, and removal of apoptotic cells, were shown to involve the histidine anabolism and catabolism pathway (Jones et al., 2005). This pathway is significant primarily because it generates histamine, which crucially controls inflammation not just in stimulated mast cells and basophils (Tanaka and Ichikawa, 2006), but also in other immune cells such as macrophages, DCs and T lymphocytes (Dy and Schneider, 2004).

As explained by Tanaka and Ichikawa (2006), histamine is regulated via stimulation of its receptor, the histamine 4 receptor, on the target cells, inducing regulation of platelet aggregation and promotion of Th2 cells by lowering IL-12 production and enhancing IL-10 production (Dy and Schneider 2004).

Histidine metabolism is also important because it yields urocanic acid, which has several actions, including minimisation of the response of antigen-presenting cells, reduction of the ability of immune cells to proliferate in response to stimuli, as well as reduction of IL-2 and IFNγ production and increase of IL-10 production by these cells (Holáň et al., 1998).

However, the implications of the use of histidine as diet supplement in culture environments have been only superficially addressed. Using a 2mm dosage extracellularly , histidine was found to prevent apoptosis and promote cell development and antibody production in lymphocytes (Duval et al., 1991b), while the concentration of plasma proteins, comprising mostly glycoproteins abundant in histidine, decreased in the absence of histidine, with adverse consequences for immunity (Jones et al. 2005). Based on the results of the above studies, it can be argued that immune function benefits from histidine supplementation.

1.3.3.6 Lysine metabolism

The importance of lysine for protein synthesis by cells, lymphocyte proliferation and the immune response to infection and foreign agents was demonstrated by several studies that eliminated lysine from the diet of chickens (Kidd et al., 1997, Chen et al., 2003, Konashi et al., 2000). Meanwhile, addition of lysine in dosage of 0.3-2 mm reduces intracellular arginine and synthesis of nitric oxide in activated macrophages (Closs et al., 2000, Wu and Meininger, 2002).

Furthermore, Griffith et al. (1981) reported that 1 g of lysine enabled elimination of infection by the herpes simplex virus quicker, as well as reducing polyamines required for virus growth by suppressing arginase action (Griffith et al., 1981).

1.3.3.7 Phenylalanine and tyrosine metabolism

Leucocytes depend on phenylalanine to regulate NO synthesis due to its effect on GTP cyclohydrolase I, the enzyme in charge of the generation of tetrahydrobiopterin, a key NOS cofactor (Shi et al., 2004). Therefore, in stimulated macrophages and other leucocytes, sustained production of tetrahydrobiopterin necessitates a sufficient phenylalanine supply, which is itself dependent on iNOS-based NO synthesis (Wu and Meininger 2002).

A number of hormones, including epinephrine, norepinephrine, triiodothyronine, thyroxine, dopamine and melanin, are synthesised with tyrosine as direct precursor (Kim et al., 2007). Attaching to adrenergic receptors of B cells, norepinephrine and epinephrine promote generation of cAMP, which is responsible for activation of protein kinase A that in turn encourages Th1 cells and B cells to proliferate (Dorshkind and Horseman, 2000, Kin and Sanders, 2006). Meanwhile, in monocytes and macrophages, dopamine and melanin are believed to alleviate pro-inflammatory cytokines (e.g. TNFα, IL-1β, IL-6), and in neutrophils they underpin phagocytosis (Mohagheghpour et al., 2000, Basu and Dasgupta, 2000). Konashi et al. (2000) reported that the immune response in chicken was impaired by lack of tyrosine and phenylalanine from the diet, but supplementation corrected this.

1.3.3.8 Proline metabolism

According to Duval et al. (1991), the survival, development and antibody generation of immune cells are all supported by proline catabolism, the key metabolites of which are pyrroline-5-carboxylate (P5C) and H_2O_2 (Wu et al., 2005, Wu, 1997). With NADPH mediation, P5C is converted into proline via the proline-P5C cycle, which also helps generation of ROS and differentiation of lymphocytes (Phang, 1985). Proline is also important in wound healing and immunity damage repair because it is a key element of collagen (Abumrad and Barbul, 2003). Furthermore, Ha et al. (2005) provided evidence that gut immune function is impaired in the absence of proline catabolism.

The signalling molecule H_2O_2 metabolite (Shi et al. 2004) is essential for pathogen killing (Kim et al. 2007). Meanwhile, some studies on pig placenta and small intestine from piglets reported a protective effect as reflected in intensified proline oxidase activity (Wu et al. 2005; Wu 1997). Furthermore, compared to neonates not fed on maternal milk, those that were fed on maternal milk were less likely to have intestinal dysfunction, suggesting that proline oxidase which present in maternal milk may contribute to protection against bacteria and viruses (Field, 2005, Wu, 1996, Sun et al., 2002).

1.3.3.9 Serine metabolism

Serine is involved in various processes, including glucose synthesis in the liver and kidney as well as synthesis of glycine, ceramide and phosphatidylserine. The latter two are cell wall components and act as signalling molecules in T and B lymphocytes and other immune system cells (Jones et al., 1999, Kim et al., 2007). Furthermore, T lymphocytes are produced via IL-2 with mediation by phosphatidylserine in response to a stimulus (Pelassy et al., 1990).

Glucose is essential for the functionality of macrophages and lymphocytes (Newsholme et al., 1999) and a suitable supply of glucose requires serine (Wu et al., 2006). Several studies indicated that addition of 2 mM of serine in culture medium, which exceeds its plasma concentration, prevented the apoptosis of lymphocytes and promoted their development and antibody production (Franěk and Šrámková, 1996, Duval et al., 1991b). Furthermore, Konashi et al. (2000) reported that the immune response in chicken was impaired by serine deficiency, but this effect could be corrected by supplementing serine.

1.3.3.10 Sulphur-containing amino acids

Synthesis of proteins, particularly those involved in immunity, occurs with the participation of the key metabolites of methionine and cysteine (Grimble, 2006). Methionine supplies a methyl group that supports DNA and protein methylation, synthesis of spermidine and spermine, and control of gene expression (Wu et al. 2006). Furthermore, methionine also plays a role in the synthesis of choline, phosphatidylcholine and acetylcholine which is considered to be of significance in leucocytes (Kim et al. 2007). Meanwhile, cysteine is necessary for the synthesis of glutathione and H2S in animal cells and its metabolism is markedly altered in response to infection(Malmezat et al., 2000). The synthesis of glutathione is triggered when sulphur amino acids are available (Wu et al., 2004), which is why a positive correlation is believed to exist between transulphuration pathway activity and the level of glutathione in liver, spleen and muscle (Malmezat et al. 2000). According to Fratelli et al. (2005), during immunological challenges, cellular signalling pathways (e.g. nuclear transcription factor κB pathway) are crucially mediated by intracellular glutathione, targeting and eliminating free radicals and other ROS (Fratelli et al., 2005, Fang et al., 2002). If there is not enough cysteine or intracellular GSH,

CD4 cells decline in number, less IFNγ is produced, cytotoxic T cells diminish their activity, and lymphocytes proliferate dysfunctionally in the presence of mitogens (Obled et al. 2004). A direct connection has been established between intracellular glutathione unavailability and a number of diseases, including cancers, AIDS, and rheumatoid arthritis, whilst trauma, sepsis and injury enhance the demand for sulphur-containing amino acids (Obled et al. 2004; Grimble 2006).

Tsiagbe et al., (1987b) conducted a study on chicken presenting with infection with Newcastle disease and found that addition of methionine in the diet promoted T cell proliferation in the presence of a mitogen, elevated the plasma levels of immunoglobulin G, and stimulated migration and antibody titre. In a subsequent study, Tsiagbe et al., (1987a) obtained similar results when cysteine was added to the diet of chicken. However, the chicken's immune response was adversely affected by excessive supplementation (Tsiagbe et al., 1987a, Tsiagbe et al., 1987b) which was likely due to overproduction of homocysteine and sulphuric acid (Wu et al., 2000).

The amino acid of the highest prevalence in lymphocytes is taurine, which displays potent antioxidant effects (Fang et al. 2002). Taurine chloramine is generated when taurine reacts with hypochlorous acid present in activated monocytes and neutrophils (Wright et al., 1986) and has a restrictive effect on the generation of pro-inflammatory cytokines (i.e. IL-1, IL-6 and TNFα) and prostaglandin E2 (Chorazy et al., 2002, Weiss et al., 1982). Wojtecka-Lukasik et al. (2004) carried out research on rats induced with carrageenin and observed that the release of histamine in neutrophils was triggered by taurine chloramine. Meanwhile, in another study, bleomycin-induced lung inflammation in rats was found to be diminished when 1% taurine was added to drinking water (Wojtecka-Lukasik et al., 2004).

1.3.3.11 Threonine metabolism

Animal intestinal mucin and plasma γ-globulin have the amino acid threonine as a fundamental component (Kim et al. 2007). Cell survival and growth as well as production of antibodies in lymphocytes were supported by supplementation of culture medium with 2 mM of extracellular threonine in the work carried out by Duval et al. (1991). Elevated levels of serum antibodies were found to accompany the use of threonine as supplement in the diet (Defa et al., 1999), while Bhargava et al. (1971) similarly observed that chickens infected with Newcastle disease virus benefitted from addition of threonine to their diet (Bhargava et al., 1971). Furthermore, in a study on sows, (Cuaron et al., 1984) discovered that threonine supplement in the diet led to a rise in IgG serum levels.

Likewise, elevated serum levels of IgG were associated with diet supplementation with threonine in addition to IgG and IgA levels in the jejunal mucosa (Wang et al., 2006). By contrast, young pigs infected with *Escherichia coli* displayed decreased IL-6 levels in the jejunal mucosa. It is clear that, in animals, immunity depends significantly on threonine used as supplement in the diet and this may also be true in humans.

1.4 Introduction to metabolomics

The term “metabolism” from the Greek term for “change”, “metabole”, has given “metabolomics”, which refers to objective identification and measurement of the whole metabolome using a highly selective and sensitive analytical method under particular conditions (Dunn et al., 2005). Although metabolomics has been defined in various other ways, all definitions acknowledge that the purpose of metabolomics is the investigation of molecules with low molecular weight that support the biological metabolic activities (e.g. growth, maintenance) without which cells could not function effectively (Oliver et al., 1998, Harrigan and Goodacre, 2012).

Metabolomics can be traced back to 1971, when Linus Pauling et al. carried out the first untargeted metabolic profiling of human urine and breath vapor using gas-liquid partition chromatography which was capable of detecting 250 biological compounds (Pauling et al., 1971). This marked the beginning of metabolomic research.

Based on how the cells interact with their surrounding environment, such metabolites are the outcomes of cellular expression of genes and proteins (Fiehn, 2002). Metabolomics requires a multi-disciplinary approach to be comprehensively investigated and applied, drawing on organic and analytical chemistry, chemometrics, bioinformatics and bioscience (Fukusaki and Kobayashi, 2005). Medical diagnosis and treatment assessment, research on drug effects, microbiology, plant science, and food and plant nutrition are just some of the areas benefitting from metabolomics (Harrigan and Goodacre, 2012, Bundy et al., 2005, Al Zweiri et al., 2010, Kondo et al., 2011, Kim et al., 2013).

1.4.1 Approaches to metabolome analysis

Untargeted, semi-targeted and targeted metabolomics profiling are the three main methods that enable the examination of metabolic disruptions accompanying various diseases or treatments (Dunn, 2013). The differences between these methods stem from their absolute or relative quantitative potential, how accurate the experiments are, how complex the sample is depends on the metabolite count, and the research aim.

1.4.1.1 Targeted approach (hypothesis assessment)

The defining characteristic of targeted metabolomics is that it is a quantitative method concerned with ensuring accuracy and specificity for the targeted analytes based on already acquired knowledge of the identity of sample metabolites before analysis. Employing reliable approaches underpinned by genuine standards, this method evaluates the hypotheses formulated through the untargeted or semi-targeted methods. Once key metabolites are clearly identified, inferences can be made regarding how biologically relevant they are with regard to the hypothesis.

1.4.1.2 Untargeted approach (hypothesis formulation)

Untargeted or global metabolomics enables identification of countless metabolites with little or no knowledge regarding the expected profile of a sample of metabolites. The process involves sample analysis and processing of generated data with various instruments. The outcomes and observations derived from the data facilitate hypothesis formulation. Not all of the multitude of metabolites encompassed in this method can be identified and of those that

are identified not all can be validated due to the high cost and possible unavailability of the numerous different standards needed to do so.

The recently developed field of metabolomics is rooted in innovations in analytical approaches and informatics instruments that accelerate and facilitate examination of samples of great complexity, yielding ample data that can be subjected to analysis and modelling with a range of software and Internet tools. Recent applications of these techniques have included detection of new biomarkers and insight into potential biological processes associated with various treatments or genetic modifications in vegetal, environmental and animal systems (Dunn 2013).

1.4.2 Analytical platforms

Initially, cellular metabolites were quantified using enzyme-based assays and thin layer chromatography (IWATA and YAMASAKI, 1964). Later on, metabolomics was dependent on nuclear magnetic resonance spectroscopy (NMR), which has the shortcomings of poor resolution for each metabolite and detection of a limited number of analytes however, with the development of MS techniques ,in 1990s, mass spectrometry is employed for metabolomics more and more often (Zhen et al., 2007, Fardet et al., 2008, Van Ginneken et al., 2007, Beynon and Morgan, 1978).The introduction of the LTQ Orbitrap Fourier Transform mass spectrometer (FTMS) (Makarov et al., 2006) has been beneficial because it enables not only extreme and consistent mass precision, but also fast scanning that is necessary to be compatible with chromatographic systems (Kamleh et al., 2008).

No single analytical platform will be able to fully analyze the entire intracellular or extracellular metabolome, therefore three chromatographic techniques, MS-

based metabolomics, can be used to target specific analytes i.e. gas chromatography (Lee et al.), which suits volatile and derivatized non-volatile metabolites, liquid chromatography (LC), for polar and non-polar, ionic and neutral metabolites thats requires little to no derivatization, and capillary electrophoresis (CE) to target charged metabolites. MS techniques coupled with the innovation of analytical methods made it possible to obtain numerous metabolite peaks from a single sample. Furthermore, an effective and reliable multi- and uni-variate statistical approach is required to undertake the difficult task of observing and understanding metabolomics transformations and of detecting dependable biomarkers.

1.4.3 Multivariate analysis

The next ten years are expected to see better medical diagnostics thanks to the innovations made in high data-density analytical methods. Unparalleled insight into individual biological structures can be achieved not only through metabolomics, but also through genomics and proteomics. However, traditional multivariate statistics is an inadequate approach for establishing correspondences between vast amounts of data related to numerous individuals and their present and even future phenotype. The metabolomics method yields sets of data that are frequently at odds with the conditions of traditional multivariate analysis (MVA), like multiple regression, X-matrix comprehensiveness, K must be lower than N, and the K variables have to be without noise and correlations. By contrast, in MVA, N can be lower than K, the K variables can have multicollinearity, and the X-matrix can have noise and does not need to be comprehensive. MVA is a statistical approach created by Wold et al. (1938) as an alternative to traditional statistical methods, to address existing issues and improve medical diagnosis for different diseases (Wold et

al., 1983). As argued by Grainger (2003), this approach could facilitate the development of sophisticated systems capable not only of detecting more than one disease process at the same time, but also of anticipating the conditions that are likely to afflict an individual in the future (Grainger, 2003).

Multivariate analysis and univariate analysis are the two sequential stages of data analysis. There are two sub-stages in multivariate analysis, namely, general review of data to confirm absence of outliers by employing unsupervised methods to achieve pattern identification and confirmation of predictive capacity by identifying biomarkers and verifying model. However, data processing should be undertaken before proceeding to data visualisation and detection of biomarkers.

1.4.4 Pre-processing of data: Transformation and scaling

Metabolomic datasets are not entirely normal or homogenously distributed according to Vinaixa et al. who found a minor discrepancy (<4%) between parametric and non-parametric tests on four comprehensive LC-MS metabolomic datasets (Vinaixa et al., 2012) therefore ,if individual variables lack normal distribution, the data must be ensured to approach normality through the procedure of transformation (Eriksson et al., 2013). Transformation can be performed via various approaches, including log2, log10, inverse and neg log in order to position observations closest to straight line with an acceptable R2 value i.e > 0.9 (Eriksson et al., 2013g) though data transformation should be handled carefully as it may alter data integrity and hinder data interpretation.

Scaling is another important pre-processing step which deals with smaller metabolites that might have high biological importance but unfortunately have lower intensities (Xi et al., 2014). Scaling can be performed by different

parameters: Mean centring, which takes the average of each variable and subtracting it from the intensity of the variable in each row; Univariate scaling, i.e., that calculates standard deviation of each variable (column) and dividing it by the intensity of the variable in each row (sample); Auto scaling, which represents a combination of univariate scaling and mean centring; Pareto scaling which takes the square root of each variable in a column and divides it by the intensity of the variable per row .Among above mentioned scaling methods, Pareto scaling is recommended and more commonly used to reduce undesirable effects in spectroscopic data (Xi et al., 2014).

Transformation as well allows outlier removal (Eriksson et al., 2013).Outliers, on SMICA , are presented by Hotelling's T2 on the y-axis, namely, the warning limit and action limit, which are respectively the T2 Crit (95%) and T2 Crit (99%) denoted by the yellow and red dotted lines. On the x-axis, the red dotted line stands for DModX with the critical distance DCrit at 0.05 level. Observations must be above the action limit or above the warning limit together with the DModX critical limit to be deemed strong outliers.

1.4.5 Hierarchical clustering analysis (HCA)

Hierarchical clustering analysis, otherwise called a dendrogram, is designed to organise data into groups in such a way that observations are either highly similar or less similar between groups, being respectively indicative of low or high variability. This technique allows integration of the two groups or observations that are closest, followed by the integration of the next two closest groups or observations and so on until a super cluster is formed (Lozano et al., 2014). HCA, which performed on PCA model, is particularly useful in cases

where clustering is unknown and thus serves as a preliminary step towards supervised multivariate methods.

1.4.6 Unsupervised and supervised techniques

Although it affords a general picture of a set of data, principle component analysis (Meiser et al.,2016) unsupervised technique, cannot establish correlations between an individual's phenotype-disease state and measured parameters. A few latent variables are generated when PCA analysis is undertaken by partial least squares-discriminant analysis (PLS-DA) on the Y-matrix denoting observations and samples. This is followed by interpretation of the maximum variance in the latent variables based on the developed X-matrix (descriptors/variables/metabolites) latent variables.

Built on the PLS-DA model, orthogonal partial least squares - discriminant analysis (OPLS-DA),supervised technique, is more advantageous because it is capable of isolating variation in X corresponding to Y (horizontal) known as predictive variation as well as variation in X without Y correspondence (orthogonal) . No other method has greater efficiency than OPLS-DA in assessing inter-group distinctions(Kirwan et al., 2012) , detecting dependable biomarkers closely related to inter-group separation (Trygg et al., 2007) and establishing correlations between disease processes and metabolic pathway disruptions (Goodacre, 2007). Consequently, OPLS-DA can provide invaluable insight into pathophysiology as well as potential targets for therapy.

A supervised model's significance and quality can be measured with cross-validation methods via the quality parameters of goodness of fit (R2), goodness of prediction (Q2), and p-value (P CV-ANOVA) (Wheelock and Wheelock, 2013, Triba et al., 2015).

1.4.7 Model assessment

Validation of an applied model can be most effectively achieved based on the quality parameters R2 and Q2. Reflecting goodness of fit, R2 measures the fraction of y (observations) elucidated by variation in x (variables) to establish correlations between y and x. This parameter presents a major problem because, provided that the number of components is increased, it can be set at random near the highest value of one. The resulting unbalanced ratio of variables to observations can cause data over-fitting that could provide false positive outcomes. However, Q2 derived from cross-validation (CV) corrects this problem (Kirwan et al. 2012), applying a process to all the data involving exclusion of a predefined number of observations and readjustment of the model until all the data have been excluded just one time (Eriksson et al., 2013b). This is followed by a comparison between the average value of the Q2 and R2 of the readjusted model to determine how much better its predictive capacity is than chance.

One-seventh of the data is typically excluded by the SIMCA P software when performing CV. To determine how effective CV is, and hence to improve the R2 of the regression line, an observed plot is compared against a predicted plot using permutation plot provided by SMICA. Permutation plot is performed to determine the extent to which the clustering of observations in the two established classes is more effective compared to arbitrary clustering in two random classes (Westerhuis et al., 2008). This test involves comparison between the original and the permuted R2 and Q2 parameters and new quality parameters, whose values should not exceed those of the initial parameters can be obtained by repeating this procedure and the horizontal zero line should be crossed by the predictive model's regression line (Eriksson et al. 2013f). ANOVA of the cross-validated residuals (CV-ANOVA) enables assessment of

how significant the variation estimated by the supervised model is. After this procedure, the receiver operating characteristic (Kono and Rock) curve should be employed to measure how precise the model is in differentiating observations according to their metabolic profile.

1.4.8 Cross-validated ANOVA

Cross-validated ANOVA (CV-ANOVA) also permits assessment of how valid the supervised model is. As explained by Eriksson et al. (2008b), the principle underlying this process is evaluation of the variation anticipated by the model in relation to the H0 hypothesis of cross-validated predictive residuals with the same value around the mean.

1.4.9 Receiver operating characteristic

The ability of a supervised model to effectively differentiate samples or observations with identical and different metabolomics profile is indicated by the area under the ROC curve (AUROCC). This ability is stronger the greater the AUROCC is. Sensitivity and specificity are the two most important dimensions of the ROC curve. According to Bewick et al. (2004), in the context of metabolomics, biomarker sensitivity represents the number of individuals with a high biomarker and who have been accurately detected by the test, while specificity refers to the number of individuals with low biomarker and who have been accurately detected by the test (Bewick et al., 2004). Multiple sensitivity and specificity points make up the ROC curve with normalisation of AUROCC to 1 in order to enable evaluation of how predictable the classifier is: 0.9–1.0 = excellent; 0.8–0.9 = good; 0.7–0.8 = fair; 0.6–0.7 = poor; 0.5–0.6 = fail (Xia et al. 2013). In Figure 1.9, the classifier scores higher than 0.9 for every group,

confirming the model's ability to accurately (>90%) identify and estimate the metabolomic discrepancies among the three groups.

1.4.10 Recognition of biomarkers based on S-plot

In the context of a supervised model, biomarkers can be detected with the S-plot. Discrepancies among the assigned groups are closely correlated with the metabolites in the extreme upper right and lower left. However, selection of metabolites based on the S-plot does not involve clear cut-offs and it is not comprehensive enough, which means that important metabolites could be left out. Given this limitation, univariate analysis should be employed instead to ensure that all the metabolites are treated the same and thus making selection more objective and minimising the risk of overlooking possible biomarkers.

1.4.11 Corrected p-value

The p-value, usually of 0.05 level (i.e. the likelihood of the difference being random is less than 5%), is the sole measure of how statistically significant a variable is. When more than one variable exhibits difference, the likelihood of random difference is raised to 1-(0.95) k (Eriksson et al. 2013c), with k denoting the number of variables (e.g. for five variables, there is 22% likelihood of random difference). This likelihood can be reduced by applying the Bonferroni correction, whereby the 0.05 α is divided by k (e.g. k = 5 gives a 0.01 α significance level, meaning that only variables under 0.01 will have significance). There are hundreds of variables in metabolomics; for instance, for k = 100, the α level will be 0.0005, which is admissible when human cell lines serves as a matrix of metabolomics profiling with most conditions being controlled. However, there is significant variation between individuals belonging

to the same disease group or control group due to cellular output and differences in individuals' diet, with implications for the level of significance of the variables (Dunn et al., 2011). Owing to these considerations, biological samples from human subjects are usually analysed with a more flexible tool, like false discovery rate (FDR) (Benjamini and Hochberg, 1995).

1.5 Aims:

This study is aimed at further understanding the process of immunomodulation by Small Molecule Analogues (SMAs) of the parasitic worm product ES-62 in the context of the macrophage metabolome. The specific aims are:

1: To determine the effect of known immunomodulatory SMAs on the metabolome of mouse bone marrow-derived macrophages (BMMs)

2: To determine whether the SMAs can reverse changes in the BMM metabolome induced by LPS or CpG

3: To try and establish whether the effects of the SMAs on the BMM metabolome can help determine whether the SMA-macrophage fits with any known phenotype such as M2

4. To establish whether information gained from the metabolomics studies can be correlated with the SMAs known anti-inflammatory effects

Chapter 2. Materials and methods

2.1 Materials:

Table 2.1.1: Cell cultures /biology studies

Materials	Suppliers information
6-8-week old BALB/c mice	Strathclyde University animal house
L929 cells aliquots	European Collection of Authenticated Cell Cultures: ECACC
SMAs (11a, 12b, 19o)	Created by Dr Abedawn Kalaf and Dr Judith Huggan, supervised by Professor Colin Suckling of the Department of Pure and Applied Chemistry at the University of Strathclyde
Salmonella LPS	Lot# 046M4089V, Sigma-Aldrich
Escherichia coli LPS	L2880-10MG,Sigma-Aldrich
CpG-ODN1826	Cat#tlr1-1826-1,InvivoGen
DMEM media (1X)	Lot#1813354,Gipco
DMEM media (1X),Phenol red -free	Lot#1801726,Gipco
RPMI-1640	Cat#BE12-167F,Lonza
RPMI-1640	Lot#RNBF7737,Sigma
RPMI-1640	Lot#1838059,Gibco
RPMI-1640 glucose free	Lot#1789610,Gibco
RPMI-1640 L-cyctiene.2HCL free	Lot#RNBF7736,Sigma
Glutamine solution	Lot#RNBF3688,Lonza
Penicillin/ streptomycin solution	Lot#065M4794v,Lonza
Fetal Bovine Serum	Lot# 41F07444K.Gibco
PBS	Cat# be17-516F, Lonza
Cell scrapers	TPP, Switzerland
T75 cell culture flasks	REF#430720U,Corning
Triple layer flask	REF# 353143,CorningFalcon
Ethanol	Lot# STBG4076V, Sigma-Aldrich, Dorset UK
Cell strainers,40um	REF# 352340,CorningFalcon
Trypan blue stain	Lot#RNBC8659,Sigma, Dorset UK
Bacteriological petri dishes	Thermo Fisher Scientific
6 well cell culture plates	Cat#140685,Thermo Fisher Scientific
96 well cell culture plates	Lot# 20160594,TPP, Switzerland

Table 2.1.2: Flow Cytometry

Materials	Suppliers information
5 ml polystyrene tubes	Falcon, BD
Bovine Serum Albumin	Lot#SLBR0420V,Sigma-Aldrich
EDTA	Sigma-Aldrich
Anti-mouse CD16/CD32	Clone:93,Lot# E03558-1639,eBioscience
Alexa Fluor® 647 Rat Anti-Mouse CD11b	Clone:M1/70,Cat# 557688,BD Pharmingen
Anti-mouse F4/80,FITC	Clone:BM8,Lot# E00610-1638,eBioscience
Anti-mouse F4/80,PE,FITC	Clone:BM8,Lot# E01705-1637,eBioscience
MitoTracker Green(MTG)	Molecular Probes Cat# M7514; CAS: 201860-17-5
Tetramethylrhodamine methyl ester (TMRM)	Molecular Probes Cat# T668; CAS: 115532-50-8
Carbonyl cyanide m-chlorophenyl hydrazine	Sigma-Aldrich Cat# C2759; CAS: 555-60-2
Oligomycin A	Sigma-Aldrich Cat# 75351; CAS: 579-13-5
FACSDiva immunocytometry system	BD Pharmingen
FlowJo	https://www.flowjo.com/

Table 2.1.3: Untargeted metabolomics study

Materials	Suppliers information
Mouse IL-4 Recombinant protein	Lot# 4314738, eBioscience
IFN-γ	Lot# MFCD00131391,Sigma-Aldrich
Methanol	Lot#15A190510,VWR
Acetonitrile	Lot#14D028945,VWR
Amonium carbonate	Lot#BCBQ6156V,Sigma-Aldrich
HPLC grade water	Lot#1708940,Thermo Fisher Scientific
A ZICpHILIC column (150 × 4.6 mm × 5 µm)	Lot#P130326,Merck,Germany
Conical glass insert 200uL	Lot# 00219799,Thermo Fisher Scientific
Auto sampler vials	Lot# 44383092515DM,Thermo Fisher Scientific
Cell shaker	Thermomixer comfort,eppendorf,MTB
LC-MS	Orbitrap mass spectrometer ,Thermo Fisher Scientific , Germany
mzmatch	http://mzmatch.sourceforge.net/
MZmine-2.10 ans 2.17	http://mzmine.github.io/download.html
SIMCA	Version 14, Umetrics, Umeå, Sweden
Metaboanalyst 3.0	http://www.metaboanalyst.ca/
Thermo Xcalibur 2.2 SP1.48-August 12, 2011	Thermo Fisher Scientific
Thermo ToxID 2.1.2 SP2.17-September 9,2011	Thermo Fisher Scientific

Table 2.1.4: 13C-glucose label studies

Materials	Suppliers information
$^{13}C_6$ -glucose	Lot#PR-26833,Cambridge Isotope Laboratories,Inc.

Table 2.1.5: Mitochondria membrane potential study

Materials	Suppliers information
Coverslips-Round,13mm	13mm Diameter, Lot#29552819,VWR
Paraformaldehyde solution 4% in PBS	Lot# E2016, Chem Cruz
Confocal Leica SP5	Leica Microsystems CMS GmbH,Germany
DAPI,5mM Aqueous solution formulated	Lot# 060109, AAT Bioquest

Table 2.1.6: Migration studies

Materials	Suppliers information
ThinCerts for 24 well plate, translucent, 0.8µm,TC-treated	Cat# 662638 Greiner Bio-One
Calcein-AM	Cat# 65-0853-78, eBioscience
TrypLE™ Express Enzyme (1X), no phenol red	Cat# 12604013ThermoFisher Scientific
Black/clear flat bottom TC-treated 96 well plate	Cat# 10530753,ThermoFisher Scientific
PolarStar Omega ,fluorescence plate reader	BMG,Labtech
24 well cell culture plates	TPP, Switzerland

Table 2.1.7: Nitric oxide assay

Materials	Suppliers information
Sodium nitrite	BDH limited pool, Lot#10256,England
Sulfanilamide P-Aminobenzene sulphonamide	Cat# 5-9251, Sigma
N-(1-Naphthyl)-ethylendiamine	Cat# 22.248-8,Germany

Table 2.1.8: Cytokine stimulation assay and ELISA

Materials	Suppliers information
2-deoxyglucose	Sigma-Aldrich Cat# D3179; CAS: 154-17-6
Diethyl succinate	Sigma-Aldrich Cat# 112402; CAS: 123-25-1
Dimethyl malonate	Sigma-Aldrich Cat# 136441; CAS: 108-59-8
Dimethyl fumarate	Santa Cruz Biotechnology Cat# sc-239774; CAS: 624-49-7
Methyl pyruvate	Sigma-Aldrich Cat# 371173; CAS: 600-22-6
Triethyl citrate	Sigma-Aldrich Cat# 14849; CAS: 77-93-0
Alpha-ketoglutarate	Sigma-Aldrich Cat# 349631, CAS: 13192-04-6
Lactic acid	Sigma-Aldrich
Taurine	Cat#1372964 ;Sigma-Aldrich
L-Cysteine	Lot#BCBD3830V,Sigma-Aldrich
Phosphocholine chloride calcium salt tetrahydrate	Lot#SLBK5048V, Sigma-Aldrich
Interleukin-6	BD Pharmingin, Oxford, UK
Interleukin-1β	R&D Systems, Abingdon, UK
streptavidin horseradish peroxidase (SAvHRP)	R&D Systems, Abingdon, UK
TMB Substrate	Lot#10219040,KPL
2 $(NH_3)_2SO_4$	Lot#120669A,invitrogen
High binding 96 well ELISA plates	Greiner BioOne
Epoch microplate spectrophotometer ,Gen5	BioTek
Prism 7	https://www.graphpad.com/scientific-software/prism/

Table 2.1.9: Phenotype Microarray assay

Materials	Suppliers information
MC-0 Medium	Components list in 2.2.14
PM-M1 ,PM-M2 Plates	Technopath Distribution, Tipperary, Ireland
Biolog Redox Dye Mix MB	Technopath Distribution, Tipperary, Ireland
2% SDS	Cat# 073K00341,Sigma-Aldrich

2.2 Methods:

2.2.1 Generation of L-cell conditional medium

Macrophage-colony stimulating factor (M-CSF) was obtained from L929 cells (European Collection of Authenticated Cell Cultures: ECACC) gifted from by Professor Robin Plevin, UoS. The L929 cells aliquots were thawed first at 37°C and then centrifuged at 200g for 5 minutes. The pellet obtained was re-suspended in 10 ml of complete DMEM medium (DMEM medium from Gipco, 2mM glutamine (Lonza), 50 U/ml penicillin (Lonza), 50 µg/ml streptomycin (Lonza), 10% FCS (Gipco)) and then was cultured in a T25 cell culture flask (CorningFalcon) at 37°C in a humidified atmosphere of 5% (v/v) CO2 for 4 to 5 days to achieve confluent growing. To harvest the cells, medium was aspirated and replaced with 5ml cold PBS for 10 minutes incubation at 4°C. Cells were then scraped gently using a 30 cm cell scraper (TPP, Switzerland). The acquired cell suspension was centrifuged, at 200g for 5 minutes, and the pellet obtained re-suspended with fresh 10 ml complete DMEM medium. Suspended cells were then split into ten T75 cell culture flasks by adding 1ml of cell suspension to fresh 9 ml of complete DMEM medium and maintained in a CO_2 incubator at 37°C / 5% CO_2 until reaching the required 80-90% confluency. Cells were then harvested as above and re-suspended with fresh complete DMEM medium. A portion of the cell suspension (6 ml) was added to 44 ml of fresh complete DMEM medium and placed into one layer of triple layer flask, CorningFalcon. The total volume of the entire triple layer flask should not exceed 150 ml. Cells were then maintained in the incubator, at 37°C / 5% CO_2, until 90 % confluency which is approximately acquired in 7 days. The supernatants then were collected from the flasks, centrifuged at 3000g for 5 min, filtered, distributed in 50 ml tubes and stored at -20°C to be used for differentiating macrophages from bone marrow stem cells.

2.2.2 Generation of bone marrow-derived macrophages (BMMs)

Bone marrow was collected from the femur and tibia bones of 6-8-week old male or female BALB/c mice, bred in Strathclyde University, and killed by cervical dislocation. Bones were then dissected from adherent tissues and washed briefly with 70 % ethanol. In sterile conditions, under a tissue culture hood, the bone ends were cut to allow bone marrow elution through washing the bones with complete DMEM medium. The eluted bone marrow was then collected, filtered using a cell strainer, and centrifuged at 400g for 5 minutes. The supernatants were next aspirated and replaced with a known amount of fresh complete DMEM medium to count the obtained cells, using trypan blue stain in order to culture them at the required density. Cells then were plated and cultured on bacteriological Petri dishes at a density of 2×10^6 cells/ml in complete DMEM with 20% L929 cell supernatant and maintained at 37°C in a humidified atmosphere of 5% (v/v) CO_2. Fresh complete DMEM was added on day 4 to feed the macrophages. On day seven the cells were harvested by scraping them into 5 ml complete DMEM at 4°C to allow adherent cell detachment and they were then collected for further centrifugation at 400g for 5 minutes. The viability and number of cells was then checked using trypan blue stain followed by identification, by flow cytometry, and plating according to the desired experiments. Flow cytometry is described in 2.2.3.

2.2.3 Flow Cytometry

Re-suspended cells with a density of 0.5×10^6 / FACS tube were incubated with anti-mouse CD16/CD32 for 5 minutes to block subsequent nonspecific binding of immunoglobulin to the FC receptor. Cells were next incubated with antibodies specific for CD11b (BD Pharmingen) and F4/80 (ebioscience) along with the

fluorescence Minus One (FMO) controls (ebioscience and BD Pharmingen) and placed in a dark cool place for 25 minutes after which they were washed in FACS buffer, (2 % Bovine Serum Albumin (Sigma) in PBS (Lonza) with 2mM EDTA). The cells were then re-suspended in 300ul of FACS buffer to render them ready for flow cytometry analysis. Flow cytometry was carried out using a FACSDiva immunocytometry system (BD Pharmingen) to determine the cell population that expresses both CD11b and F4/80 surface markers. The cell population and confluency calculated numerically using FlowJo and the average macrophages obtained were 95% $CD11b^{+}$ $F4/80^{+}$. These were employed for different assays and the minimum percentage acquired was > 90 % $CD11b^{+}F4/80^{+}$ in initial macrophages metabolomics experiments.

2.2.4 Macrophage treatment conditions for untargeted metabolomics study/cytokines study

After identification by flow cytometry, the bone marrow-derived macrophages cells (BMMs) were plated at a concentration of 2 x 10^{6} cells/2 ml of complete RPMI medium (RPMI-1640 (Lonza), 2mM glutamine (Lonza), 50 U/ml penicillin (Lonza), 50 µg/ml streptomycin (Lonza), 10% FCS (Gipco)), in 6-well plate, with 5 to 6 replicates / each condition used, and then rested for 5 hours or overnight.

1- To study the effect of adding SMAs (11a, 12b, 19o) on the macrophage metabolome, SMAs were added at a concentration of 5 µg/ml along with an equivalent amount of medium only added to the control group. Treated BMMs were then incubated for 18 hours at 37°C in a humidified atmosphere of 5% (v/v) CO_2. BMMs were subsequently prepared for metabolite extraction to study the effects of adding SMAs alone in comparison to unstimulated macrophages.

2- To identify the effect of SMA pre-treatment on the macrophage metabolome in the presence of TLR ligands such as *Salmonella* LPS and CpG, SMAs were added to rested cells at a concentration of 5 µg/ml for 18 hours and the cells were maintained at 37°C in a humidified atmosphere of 5% (v/v) CO_2 with an equivalent volume of medium only added to the control groups. After 18 hours incubation, 100 ng/ml of LPS or 0.1 µM/ml of CpG was added to +ve control groups, samples pre-treated with SMAs for 24 hours and an equivalent volume of medium only added to the -ve control group. Treated cells then were extracted to study effects of pre-treatment of macrophages with SMAs in LPS- or CpG-activated macrophages.

3- To analyse the metabolomic profile caused by effects of different stimulants which were known for their pro-inflammatory and anti-inflammatory effects i.e. on cytokine production profiles, the different stimulants were added to rested macrophages for 24 hours with the exact concentration that was used previously (100 ng/ml *Salmonella* LPS, 100 U/ml IFN-γ, 100 U/ml IL-4, 100 ng/ml of LPS +100 U/ml IFN-γ and 100 ng/ml LPS +100 ng/ml IL-4) to induce/inhibit cytokine production by macrophages.

All extracts were stored at -80°C until analysed as detailed in section 2.2.7.

2.2.5 Conditions used to study metabolomic effects of SMA-treated macrophages condition using $^{13}C_6$-glucose tracer.

Bone marrow-derived macrophages cells (BMMs) were plated at a concentration of 2 x 10^6 cells/ 2 ml of complete RPMI in 6-well plate with 4 replicates for each condition used, and rested overnight. The complete RPMI medium then was aspirated and replaced by 1.5 ml of mixed medium; containing glucose free RPMI glucose free supplemented with 5.5 mM of $^{13}C_6$-

glucose and 5.5 mM of unlabelled glucose followed by incubation for 90 minutes. SMAs then were added, in the same medium, at a concentration of 5 µg/ml for 4, 8 and 18 hours, and maintained at 37°C in a humidified atmosphere of 5% (v/v) CO_2, with an equivalent volume of mixed medium only being added to the control group. In the case where CpG or LPS stimulation was used the cells were incubated in the growth medium containing the label for 18h before addition of LPS or CpG and incubation was carried out for a further 4h, 8h and 24 h in the presence of the stimulants. The extracts were stored at -80°C then run as described in section 2.2.7.

2.2.6 Cell metabolites extraction protocol

Cell extracts were prepared by washing the cells once with warm PBS before harvesting the cells in a chilled extraction solution (MeOH/MeCN/H2O, 50:30:20 v/v) with a concentration of 1 ml of extraction mix per 2×10^6 cells. Cell lysates were then collected and shaken at 1200 rpm for 20 minutes at 4 °C before being centrifuged at 0°C at 13000 rpm for 15 min. The supernatants then were collected and transferred into auto sampler vials for loading into the LC-MS autosampler or storage at -80°C until analysis.

2.2.7 Liquid chromatography/mass spectroscopy (LC/MS)

The chromatographic conditions were set as follows: A ZICpHILIC column (150 × 4.6 mm × 5 µm) was eluted with a linear gradient over 30 min between 20 mM (NH4)2CO3 (pH 9.2)/MeCN (20:80) at 0 min and 20 mM (NH4)2CO3 (pH 9.2)/MeCN (20:80) at 30 min with a flow rate of 0.3 mL/min, followed by washing with 20 mM (NH4)2CO3 MeCN (95:5) for 5 min and then re-equilibration with the starting conditions for 10 minutes. LC/MS was carried out by using an Dionex 3000 HPLC pump coupled to an Exactive (Orbitrap) mass spectrometer

from Thermo Fisher Scientific (Bremen, Germany). The spray voltage was 4.5 kV for positive mode and 4.0 kV for negative mode. The temperature of the ion transfer capillary was 275 °C and sheath and auxiliary gas were 50 and 17 arbitrary units, respectively. The full scan range was 75 to 1200 m/z for both positive and negative modes. The data were recorded using the Xcalibur 2.1.0 software package (Thermo Fisher Scientific). The signals of 83.0604 m/z (2xACN+H) and 91.0037 m/z (2 × formate-H) were selected as lock masses for the positive and negative modes, respectively, during each analytical run. The obtained raw data then were processed using several software discussed in 2.2.8. A summary of metabolomics workflow is showed in figure 2.2.7.1.

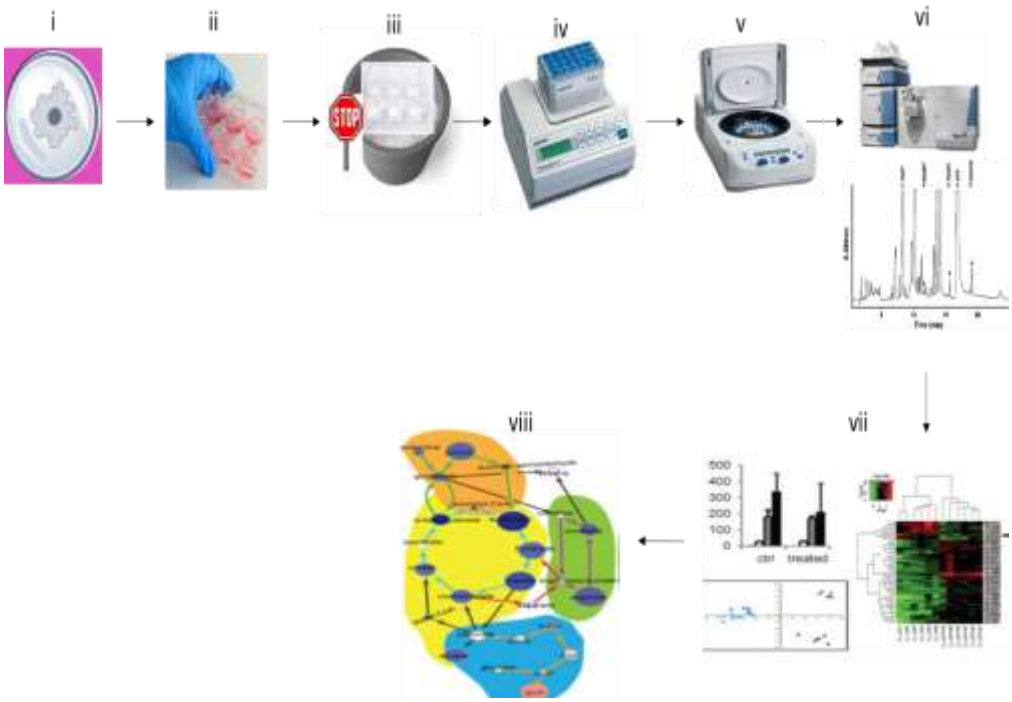

Figure 2.2.7.1 Metabolomic workflow. Cell metabolomics consists of eight sequential steps: (i) cell culture harvesting/ scraping (ii) Cell culture stimulation, (Wold et al.,1983) quenching metabolic activity and metabolite extraction (iii), (iv) shaking cell extracts for further extraction (v) centrifugation for extracts collection (vi) data acquisition using MS-based spectroscopy techniques to generate chromatograms and MS spectra, (vii) statistical and chemometric analysis including univariate and multivariate analyses, (vii) data interpretation linking metabolomics to biological process using metabolic network or identify biomarkers.

2.2.8 Metabolomic data analysis

Raw data ,from untargeted metabolomic studies, were putatively identified and processed using Mzmine (Pluskal et al., 2010) whereas Mzmatch (Scheltema et al., 2011) was used for putative metabolomic identification on targeted studies .Prior to further analysis, data were filtered in which metabolites of low intensities (<1000 peak height) and metabolites which did not show any significant fold changes were excluded in order to simplify the data for interpretation. Putatively identified metabolites were then further analysed and validated with SMICA 14.1 (version 14, Umetrics, Umeå, Sweden). Analysis involves univariate and multivariate analysis; clusters model creation using PCA, which provides a crude dataset overview and is used for initial exploratory analysis and OPLAS-DA, for class discrimination, which integrates orthogonal signal correction. Partitioning of predictor variables improves both model transparency and interpretability (Bylesjö et al., 2006, Trygg et al., 2007).
Using SIMCA as well will provide validity testing; outliers check, permutation, AUROC, regression analysis and cross validation (sensitivity and specificity of created OPLS-DA model).

Metabolite concentrations, in some of the treatments designed above, were log-transformed to account for non-normal distribution of metabolite data, mean-centred to improve interpretability of the models generated and scaled to unit variance to ensure all metabolites, both high range and low range, were given equal weight in analysis. However, all fold changes were calculated from original intensities and not from log transformed intensities. Metabolites of interest then checked by Xcalibur software / ToxID software to confirm existence of true peaks in comparison to standards. The standard mixtures used for retention time checking have been described in detail previously (Howe *et al*, 2018).

2.2.9 Mitochondria membrane potential study of SMA treatment effects and LPS/CpG addition effect on SMA pre-treated macrophages, using Confocal Microscopy and Flow Cytometry

2.2.9.1 Determination of mitochondrial membrane potential study using confocal microscopy

BMMs were seeded at 0.5 x10^6 cells/ml suspended in complete RPMI and rested on sterile 13mm cover slips for 2 hours at 37°C in a humidified atmosphere of 5% (v/v) CO_2 to allow adherence. After resting, 2ml of SMAs at a concentration of 5µg/ml were added on the top of cover slips and the samples were incubated for 18 hours. Complete RPMI medium was then aspirated and the glass slides were washed with PBS three times and then placed into a fresh 6-well plate with complete DMEM, phenol red-free, mixed with 20 nM TMRM and 50 nM MTG and incubated at 37°C in the dark for 30 minutes. Cells were then fixed, using 4% PFA, ChemCruz, by adding 500 µl to each well for 20 minutes and washed tice with PBS. Cells afterwards permealised in a PBS solution containing, 1% FBS, 0.5 % Triton X-100, and then washed three times with PBS containing 1% FBS. To stain cell nuclei, DAPI solution was used, at 1ug/ml, AAT Bioquest, and allowed to be incubated for 10 minutes at room temperature. Cells were then washed twice with PBS, water and left to air-dry briefly. Coverslips were then mounted with few drops of glycerol and imaged on a Leica SP5 confocal microscope with an excitation laser of 550 nm and detection set for 560-650 nM using a 40x oil-objective lens. A number of images were taken for each treatment.

In the LPS-treated macrophages, which were pre-treated with SMAs for 18 hours, LPS was added at concentration of 100 ng/ml and the samples were incubated at 37°C in a humidified atmosphere of 5% (v/v) CO_2 for 24 hours. Following stimulation, the medium was aspirated and coverslips were washed

with PBS three times and then the medium was replaced in the 6-well plate with fresh complete phenol red-free DMEM containing 20 nM TMRM and 50 nM MTG and the samples were incubated at 37°C in the dark for 30 minutes. The cells were then fixed and imaged as above.

2.2.9.2 Mitochondria membrane potential study using Flow cytometry

BMMs were plated and stimulated with SMAs only / SMAs pre-treatment followed by LPS activation as in section 2.2.4. Stimulated macrophages were next stained as in section 2.2.13.1. Cells were then analysed using FACS in which the cells were placed as 0.5 x 10^6 / FACS tube and stained with anti-mouse CD16/CD32 for 5 minutes to block nonspecific binding of immunoglobulin to FC receptors. Cells then were stained with a mix of anti-CD11b (BD Pharmingen), anti-F4/80 FITC (eBioscience) and anti-mouse F4/80, PE (eBioscience) along with Fluorescence Minus One (FMO) controls and placed in a dark cool place for 25 minutes after which they were washed in FACS buffer. Cells were then re-suspended in 300µl FACS buffer and readout using a FACSDiva immunocytometry system (BD Pharmingen) to determine the cell population that express both CD11b and F4/80 surface markers and mean fluorescent intensity of TMRM and MTG were analysed using FlowJo software.

2.2.10 Migration study of SMA treatment effect on BMMs and LPS/CpG addition effect on SMA pre-treated macrophages

BMMs, which were generated as in section 2.2.2 and identified as in section 2.2.3, were re-suspended in serum-free medium to a final concentration of 1x10^6/ml. Following the Boyden chamber assay (Boyden, 1962b, Chen, 2005), cell culture inserts, which were designed with 0.8µm polyethylene terephthalate

membranes with a size suitable for macrophages (Greiner Bio-One), were placed in a 24 well cell culture plate, thereby forming two compartments; the upper compartment of the insert and the lower compartment of the plate well. 550 µl of complete RPMI were added to the lower compartment of the insert and 200 µl of prepared cell suspension were loaded into upper compartment of cell culture insert and rested for 2-4 hours. After resting, 50 µl of SMAs at a concentration of 5µg/ml were added to the lower compartment with an equal amount of complete RPMI to the control groups and incubated for 18 hours at 37°C in a humidified atmosphere of 5% (v/v) CO_2. After 18 hours, the complete RPMI, in the lower compartment, was removed and replaced by 450 µl of fresh serum-free complete RPMI mixed with 8 µM Calcein-AM (eBioscience) and incubated in dark for 45 minutes at 37°C in a humidified atmosphere of 5% (v/v) CO_2 to allow staining of migratory cells. Cells, non-migrated on the upper compartment, were aspirated and the inserts were placed into a freshly prepared 24 well cell culture plate containing 500 µl/well of prewarmed TrypLE™ Express Enzyme (1X) (no phenol red) solution to allow detachment of stained migratory cells, and then incubated for 10 minutes at 37°C and 5 % CO_2, with agitation of the plate from time to time. Cell culture inserts were then discarded and 200 µl of the TrypLE™ solution was added to the lower compartment which now contained the migratory cells the samples were then transferred into a black flat bottom 96 well plate with an equal volume of TrypLE™ A added as a blank. Cells then were readout at an excitation wavelength of 485 nm and an emission wavelength of 520 nm.

2.2.11 Measurement of NO production in BMMs

BMMs were plated and stimulated with SMAs only / SMAs pre-treatment followed by LPS /CpG activation as in section 2.2.4. 50µL of cells supernatants then were collected and added into wells of a 96 well plate (in triplicate for each

condition). Greiss Reagents (A+B) were then mixed in a ratio of 1:1 [2% (w/v) sulphanilamide in 5% (v/v) H3PO4 and 0.2% (w/v) naphylethylenediamine HCl in water] and 50µL of the mix were added to the cell supernatants in each well. The 96 well plate was then incubated in the dark for 10 minutes. The absorbance was then read using a Polarstar Omega plate reader at 540 nm. Nitrite production was determined relative to a standard curve constructed with solutions of sodium nitrite ($NaNO_2$) as described by (Griess, 1879) from a 10 mM stock solution of $NaNO_2$ prepared in complete RPMI 1640 cell medium.

2.2.12 Cytokine stimulation assay

BMMs, generated as in section 2.2.2 and identified as in section 2.2.3, were plated in triplicate at a density of 1 x 10^5 cells/ml and rested for 5 hours in complete RPMI-1640. The complete RPMI was then aspirated and different conditions were set by adding 100 µl of:

- SMAs at concentration of 5 µg/ml
- Glycolysis cell culture permeable substrates at a concentration of 5 mM lactate; 5 mM pyruvate and 1mM 2-deoxy glucose as recommended by (Mills et al., 2016)
- TCA cell culture permeable substrates at a concentration of 10 mM citrate; 1 mM a-ketoglutarate; 10 mM dimethylmalonate; 25µM dimethylefumurate;1 and 5 mM succinate which as recommended by (Mills et al., 2016)
- Taurine was tested at a concentration of 20 mM which represents its concentration in leukocytes according to (Fukuda et al., 1982, Learn et al., 1990, Green et al., 1991) .

All above samples, were added to the cells and incubated at 37°C in a humidified atmosphere of 5% (v/v) CO_2, for 18 hours with an equal amount of complete RPMI to the control group. LPS (Salmonella and Escherichia coli), at a concentration of 100 ng/ml, was then added for 24 and 48 hours. Finally,

supernatants were collected to determine cytokine production/inhibition by ELISA.

2.2.13 ELISA

Interleukin-6 (BD Pharmingin, Oxford, UK) and IL-1β (R&D Systems, Abingdon, UK) production and inhibition were measured using enzyme-linked immunosorbent assays (ELISAs). ELISA was performed according to the supplied manufacturer's instructions. 96 well ELISA plates, High binding from Greiner BioOne, were prepared by adding 50 µl capture antibody diluted in specified coating buffer; 0.1 M sodium carbonate pH 9.5 for IL-6 and PBS with pH 7.2-7.4 for IL-1β for the coating step. Plates then were washed three times in wash buffer containing PBS with 0.05 % Tween 20 and dried by blotting. The plates then were blocked with 200 µl assay diluent (PBS with 10% FCS for IL-6; PBS with 2%BSA for IL-1β) and incubated at room temperature for 1 hour. After washing, as above, 50 µl samples were added to the plates either neat for IL-1β or diluted in assay diluent for IL-6. Standard cytokine samples that had been serially diluted were added, 50 µl, per well, to generate a standard curve and incubated at either room temperature for two hours or at 4°C overnight.

Plates were then washed five times in wash buffer, dried for addition of detection antibody, 50 µl per well. Detection buffer was diluted in assay diluent, at the concentration recommended by the manufacturer for both cytokines. For IL-6, the enzyme reagent, streptavidin-horseradish peroxidise conjugate, was diluted in the detection antibody [is this correct?] and the plates were incubated for an hour. For IL-1β, plates were incubated with detection antibody for two hours before washing and addition of the enzyme-streptavidin conjugate, diluted in assay diluent, for 20 minutes. After seven washes, with a 30-60 seconds-soak for each wash, 50 µl of TMB substrate solution was added to the plates. All reactions were stopped using 25 µl of 2 NH_2SO_4. Plates then were read at 450

nm on an Epoch microplate spectrophotometer (BioTek) and the data obtained analysed using Gen5 and Prism 7.

2.2.14 Phenotype Microarray assay of SMAs alone and LPS/CpG addition to SMAs pretreated macrophages

BMMs were resuspended, at concentration of 2 x 10^6/ml, in the MC-0 Medium, composed of IF-M1 (Technopath Distribution, Tipperary, Ireland) medium supplemented with 5.3% (v/v) dialysed foetal bovine serum (dFBS) (Gibco, Paisley, UK), 1.1% of 100x Pen/Strep solution (Gibco, Paisley, UK), and 0.16% (v/v) of 200 mM glutamine (final concentration 0.3 mM).

BMmMs then plated, in PM-M1 and PM-M2 plates (Technopath Distribution, Tipperary, Ireland), at a concentration of 0.04 x 10^6/ml in 20 µl and rested for 90 minutes -2 hours. After resting, BMMs were treated with 5 µg/ml SMAs in 30 µl, using MC-0 Medium, for 18 hours.

With LPS/CpG addition to SMA-pre-treated macrophages; SMAs were added in MC-0 Medium at the same concentration but in 20 µl volume for 18 hours and then LPS / CpG added at concentration of 100ng/ml and 100µM respectively in 10 µl volume and incubated at 37^{o}C in a humidified atmosphere with 95% Air-5% CO_2 for 24 hours.

Following incubation, the cells were stained with Biolog Redox Dye Mix MB, (Technopath Distribution, Tipperary, Ireland), by adding 10 µL of 6X per well. The plates then were sealed with tape to prevent off-gassing of CO_2 and incubated from 1 to 24 hours to allow optimum reduction of the tetrazolium dye. The reaction then was stopped by adding 2% SDS solution and endpoint read was performed at 590 nm with subtraction of a 750 nm reference reading (A590-750) which corrects for any background light scattering.

Results

Chapter 3. Application of untargeted metabolomics profiling to understand the mechanism of action of small molecule analogues (SMAs) of ES-62

3.1 Introduction

ES-62, a molecule secreted by the filarial nematode *Acanthocheilonema viteae*, has a range of immunomodulatory effects which includes rendering B lymphocytes hypo-responsive to crosslinking of the B cell receptor (BCR) for antigen recognition (Harnett and Harnett, 1993b), inhibiting FcεR1-induced activation of mast cells (Melendez et al., 2007a) and subverting TLR4 signalling following PAMP stimulation in macrophages and DCs (Goodridge et al., 2001a) . Its immunomodulatory effects have been linked to its post-translational glycosylation and subsequent esterification by phosphorylcholine (Harnett and Harnett, 2009). However, ES-62 is not suitable for drug therapy due to its potential immunogenicity and therefore a library of Small Molecule Analogues (SMAs) was designed based on phosphorylcholine moiety of ES-62 with the aim of mimicking its anti-inflammatory activities (Al-Riyami and Harnett, 2012, Al-Riyami et al., 2013a). Initially these SMAs were screened to investigate their effects on the production of the Th1/Th17- promoting inflammatory cytokines IL-12p40 and IL-6 by mouse bone marrow-derived macrophages by treating the cells with the SMAs for 18 hours and then stimulating them with TLR ligands – LPS (TLR4), BLP (TLR2) or CpG (TLR9) - for 24 hours. During the screening, it was found that some of the SMAs were indeed able to mimic the effects of ES-62 on PAMP-induced macrophage cytokine production, whereas some showed a selectivity for the cytokine being targeted plus, surprisingly, some increased pro-inflammatory cytokine production (Al-Riyami et al., 2013a), a result which had not previously been seen as an effect of ES-62.

The SMAs were also screened to check on their abilities to mimic ES-62 in inhibiting mast cell activation via suppression of calcium signalling (Ball et al., 2013a). In particular, among 65 screened SMAs, few were found to resemble ES-62 in its ability to affect FcεR1-mediated calcium mobilization. However, the

SMAs which resembled ES-62 in this assay were further tested for their ability to inhibit mast cell degranulation as well as the production of IL-6 and TNF-α after FcεRI -mediated IgE crosslinking (Rzepecka et al., 2014b). Only SMAs 11a and 12b were found to mimic ES-62 in its efficiency in inhibiting cytokine responses by macrophages, mast cells, and also dendritic cells (DCs). Low molecular weight sulfones, other than 11a and 12b, such as 11e, 11h, 11i and 11k were tested on DCs and were found to inhibit LPS-induced pro-inflammatory cytokines (Lumb et al., 2017). However, 11a and 12b, also resemble ES-62 in it its ability to protect against arthritis and asthma in mouse models, illustrating the potential of these compounds to be active against inflammatory diseases (Pineda et al., 2012) and suggesting the need for further testing to reveal the mechanism of action underlying their immunomodulatory effects.

3.2 Results

3.2.1 Bone marrow macrophages production

A study of the effect of SMAs on the metabolome, in this project, was conducted with the aid of bone marrow-derived macrophages (BMMs). BMMs were cultured from the femurs and tibias of 6-8 week-old BALB/c mice in DMEM medium supplemented with 20% L929 cell medium for 7 days to generate BMMs. The macrophages were then analysed to confirm their identity by using flow cytometry. A minimum of 92% and maximum of 98% of co-expression of $CD11b^+$ and MHC II^+ was recorded for the macrophages used for the metabolomics studies. Figure 3.1.1 describes the gating scheme used in phenotyping BMMs.

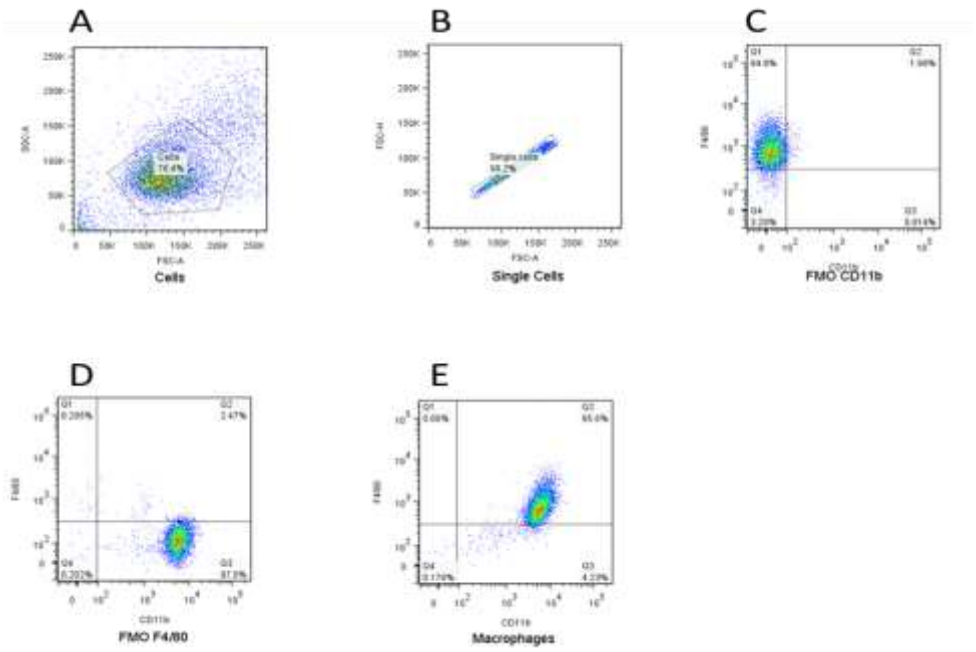

Figure 3.1: Macrophage phenotyping using flow cytometric analysis

The bone marrow-derived macrophage (BMM) phenotype was assessed by flow cytometric analysis of co-expression of CD11b and MHC II. To assess the population, size and granularity of BMMs, A: dot plot analysis of FFS versus SSC was used to give the size and granularity. B: gating on the single cell population, C: position and percentage of the single positive staining of F4/80-expressing cells population using fluorescence minus one (FMO) control system. D: position and percentage of the single positive staining of CD11b-expressing cells using fluorescence minus one (FMO) control system. E: double positive staining of CD11b and F4/80 on cells revealing macrophage population percentage.

3.2.2 Effect of SMAs on the BMM metabolome

The list of metabolites affected by the SMAs is shown in Table 3.1. Immunomodulatory SMAs 11a and 12b induced a number of changes whereas inactive 19o had very little effect. Oxidative stress can be observed through an increased production of glutathione disulphide and increased utilisation of L-cystine by SMAs 11a and 12b. Another main effect produced by 11a/12b SMA treatment is a significant decrease in taurine and hypotaurine levels. The active SMAs also decreased the levels of creatine phosphate and guandinoacetate and creatine in the creatine pathway as well as downregulating the levels of some acyl carnitines. The SMAs also decreased the levels of glycerophosphocholine in the cells which is interesting in view of their similarity to the structure of phosphocholine.

The SMAs 11a, 12b and 19o had almost no effect on either glycolysis or on TCA cycle metabolites, not showing an alteration in comparison to unstimulated macrophages. However, the SMAs decreased production of glycerol 3-phosphate. None of the changes are major, although as will be seen in subsequent chapters there is a consistent effect on the taurine, creatine and glutathione pathways and this gives an important directive for the interpretation of the results in the stimulated macrophages.

Table 3.1: The list of detected metabolites that have changed following SMA 11a, 12b or 19o treatment in comparison to untreated BMMs. DM refers to detection mood, m/z to mass to charge ratio, FC to fold change, RT to raw retention time and P to P-values (n=5).Metabolite pathways of interest highlighted in red. All the metabolites in table 3.1 are from a single experiment (n=5). Tables 14 and 15 in the appendix show data from additional experiments.

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
Oxidative stress									
+	613.200	17.8	Glutathione disulfide	<0.001	1.282	<0.001	4.143	0.289	1.152
+	336.100	14.9	S-Formylglutathione	0.007	0.808	<0.001	0.635	0.016	1.199
+	166.100	13.8	L-Methionine S-oxide	0.006	0.806	0.115	0.826	0.699	1.044
+	241.000	16.7	L-Cystine	0.01	0.638	<0.001	0.329	0.35	0.873
Taurine metabolism									
+	110.000	15.3	Hypotaurine	<0.001	0.538	<0.001	0.451	0.781	0.989
-	124.000	15.2	Taurine	<0.001	0.743	<0.001	0.679	0.471	0.983
+	126.000	15.2	Taurine	<0.001	0.687	<0.001	0.594	0.137	1.036
Choline metabolism									
+	184.100	15.4	Choline phosphate	0.005	1.143	0.119	1.104	0.649	1.034
+	258.100	14.9	sn-glycero-3-Phosphocholine	<0.001	0.644	<0.001	0.466	0.168	0.943
ATP and high energy phosphates									
-	210.000	15.5	Phosphocreatine	<0.001	0.579	<0.001	0.477	0.957	1.003
Carnitines and carnitine biosynthesis									
+	147.100	25.3	L-Lysine	0.04	0.855	0.484	0.914	0.536	1.075
+	146.100	13.7	4-Trimethylammoniobutanoate	<0.001	0.683	<0.001	0.358	0.478	0.977
+	162.100	13.7	L-Carnitine	<0.001	0.715	<0.001	0.531	0.297	1.066
+	204.100	11.2	O-Acetylcarnitine	<0.001	0.685	<0.001	0.414	0.023	0.915
+	232.200	9.0	O-Butanoylcarnitine	<0.001	0.84	0.014	0.821	0.451	0.944

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	372.300	4.9	Tetradecanoylcarnitine	<0.001	0.781	<0.001	0.675	0.56	1.018
Purine and pyrimidine metabolism									
+	228.100	10.8	Deoxycytidine	0.01	0.793	<0.001	0.455	0.611	0.966
+	263.100	8.2	Thiamine aldehyde	0.024	0.785	0.304	0.862	0.46	0.908
Aminosugar metabolism									
+	310.100	13.6	N-Acetylneuraminate	0.016	0.932	0.002	0.868	0.155	1.063
-	308.100	13.6	N-Acetylneuraminate	0.02	0.917	0.002	0.848	0.058	1.133
Glycolysis and TCA cycle and related metabolites									
-	179.100	17.4	D-Glucose	0.002	0.749	0.113	0.802	0.644	1.037
-	171.000	14.9	sn-Glycerol 3-phosphate	<0.001	0.621	<0.001	0.418	0.004	0.873
+	170.100	8.2	Pyridoxine	0.013	0.812	0.498	0.916	0.823	0.977
+	664.100	14.6	NAD+	0.004	1.073	<0.001	1.255	0.549	1.026
Creatine metabolism									
-	210.000	15.5	Phosphocreatine	<0.001	0.579	<0.001	0.477	0.957	1.003
-	210.000	15.5	Phosphocreatine	<0.001	0.579	<0.001	0.477	0.957	1.003
+	118.100	16.1	Guanidinoacetate	<0.001	0.801	<0.001	0.445	0.507	0.973
+	132.077	15.5	Creatine	0.014	0.482	<0.001	0.534	0.148	1.153
Miscellaneous									
+	205.100	12.1	L-Tryptophan	0.021	0.852	0.434	0.912	0.725	1.037
+	150.100	11.9	L-Methionine	0.022	0.845	0.477	0.921	0.868	1.017
+	175.100	13.9	N-Acetylornithine	0.017	0.83	0.499	0.916	0.884	1.018
-	145.100	25.3	L-Lysine	0.026	0.829	0.406	0.907	0.687	1.041
+	176.100	4.4	Indole-3-acetate	0.035	0.814	0.444	0.906	0.844	0.978
-	218.100	8.8	Pantothenate	0.011	0.805	0.423	0.897	0.902	0.986
-	181.100	14.2	D-Sorbitol	0.002	0.756	0.285	0.869	0.042	1.284
-	164.100	10.6	L-Phenylalanine	0.015	0.751	0.056	0.767	0.1	0.822

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
Phospholipids									
-	245.000	13.0	Glycerophosphoglycerol	<0.001	0.753	<0.001	0.759	0.295	1.076
+	247.100	12.9	Glycerophosphoglycerol	<0.001	0.781	<0.001	0.755	0.901	1.005
+	216.100	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	0.596	<0.001	0.501	0.289	0.959
-	214.000	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	0.583	<0.001	0.489	0.514	0.969
+	752.600	4.0	PE38:5	<0.001	1.215	0.08	1.083	0.167	0.928
+	766.600	4.2	PC36:4 ether	<0.001	1.178	0.073	0.941	0.706	1.015
-	437.300	3.9	[GP (18:0)] 1-octadecanoyl-2-sn-glycero-3-phosphate	0.004	1.168	0.237	1.071	0.659	1.04
-	838.600	3.8	1-22:1-2-18:3-phosphatidylserine	0.004	1.153	0.36	1.05	0.301	0.93
+	788.600	4.2	PC36:1	0.004	1.133	0.041	1.118	0.137	0.926
-	786.500	3.9	PS36:2	0.004	1.121	0.817	1.01	0.226	0.939
+	718.600	4.2	PC32:0 ether	0.001	1.112	<0.001	1.224	0.192	0.96
+	840.600	3.8	PS40:4	0.012	1.107	0.172	0.944	0.29	0.935
+	703.600	4.4	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.036	1.104	0.763	1.014	0.316	0.938
+	792.600	4.2	PC38:5 ether	0.025	1.084	0.845	0.993	0.964	1.002
-	746.500	4.1	PE38:7	0.007	1.069	0.047	0.94	0.957	0.999
+	482.300	4.7	Lyso PE 18:0	0.048	0.936	0.015	0.875	0.409	1.056
+	149.100	15.5	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.023	0.862	0.324	0.909	0.711	0.972
-	738.500	4.1	PE 36:4	<0.001	0.854	<0.001	0.893	0.449	1.02
-	498.300	4.4	[ST hydrox] N-(3alpha,7alpha-dihydroxy-5beta-cholan-24-oyl)-taurine	0.01	0.831	0.463	0.919	0.484	0.941

3.3 Discussion

As can be seen from table 3.1, treating macrophages with SMA 11a or 12b significantly induce some alterations to the metabolism of the macrophages. Starting with their first main effect, which is increasing the production of glutathione disulfide, it can be concluded that this is indicative of the metabolism of the macrophages being challenged by SMA uptake/presence in the culture medium. Up regulating glutathione disulfide production suggests that the SMAs are subjecting the cells to increasing oxidative stress by some unknown mechanism.

The SMAs also appear to affect creatine metabolism possibly through decreasing its precursor guandinoacetate and thus ultimately lead to decreasing phosphocreatine production. As will be seen in subsequent chapters, control of the formation of phosphocreatine could have far reaching effects on cell metabolism. It is not clear whether or not macrophages can make creatine and it is believed that most creatine is formed in the liver (Daly, 1985).Thus, the SMAs may be affecting creatine uptake from the culture medium where it is a component of the added FCS.

Another effect observed related to decreased uptake/biosynthesis of taurine as well as that of its precursor hypotaurine. Taurine is identified generally as an organic osmolyte (Romio et al., 2001) and the observed changes in taurine uptake might reflect a mechanism of action for the SMAs as taurine accumulation has been reported to be linked to cells being in a hyper-osmolality status (Warskulat et al., 1995, Zhang et al., 1996, Warskulat et al., 1997b, Warskulat et al., 1997a) as well as to macrophages stimulated with LPS or IFY gamma (Romio et al., 2001).

Generally, the SMAs do not show a clear effect on either glycolysis or TCA metabolism.

However, decreasing glycerol-3 phosphate, a metabolite that is involved in glycolysis, in the electron transport chain, in glycerophospholipid metabolism and the

hyperosmotic stress response was observed. This metabolite is reported as a promising target in tumor treatment (Lalle et al., 2015). The decrease in glycerol-3 phosphate was observed along with a decrease in diglycerol phosphate as well as sn-glycero-3-phosphoethanolamine and sn-glycero-3-phosphocholine which are major components of cellular membranes (Kennedy, 1956b, Kennedy, 1956a, Holub and Kuksis, 1978). Alteration in membrane glycolipids plays a critical role in signal transduction (Kojima and Hakomori, 1991, Boggs et al., 2000, Schnaar, 2004)

Several metabolites involved in carnitine metabolism were significantly decreased by 11a or 12b treatment. Among them was the carnitine precursor metabolite 4-Trimethylammoniobutanoate, which is hydroxylated to L-carnitine via oxidative decarboxylation of 2-ketoglutarate. Carnitine is essential for the transport of activated fatty acids across the mitochondrial membrane during mitochondrial beta-oxidation (Kompare and Rizzo, 2008).

In the next chapter, the above effects obtained from SMA-treatments, will be explored further through challenging macrophages with LPS or CpG stimulation to see if the effects produced by the SMAs alone are influencing their possible mechanism of action in countering the effects of macrophage activators.

Chapter 4

Metabolomic profiling of CpG-treated macrophages pre-exposed to ES-62 SMAs

4.1 Introduction

Cytosine-phosphate-guanosine oligodeoxynucleotides (CpG ODNs) are synthetic oligonucleotides that contain unmethylated CpG dinucleotides in particular sequence contexts (CpG motifs) (Krieg et al., 1995). These CpG motifs are present at a 20-fold greater frequency in bacterial DNA compared to mammalian DNA. CpG ODNs are comprised four classes of stimulatory CpG: classes A, B and C, and P which differ in their immune-stimulatory activities (Krug et al., 2001, Marshall et al., 2005).For example, CpG-A ODNs have been reported to activate NK cells and stimulate plasmacytoid dendritic cells (pDCs) and macrophages to produce high levels of interferon-α (Verthelyi and Zeuner, 2003, Lenert et al., 2003). In contrast, CpG-B ODNs were found primarily, to stimulate B cell proliferation and secretion of immunoglobulins, and the cytokines IL-6 and IL-10. In addition, CpG-B ODNs induce maturation and activation of pDCs and macrophages (Hartmann et al., 2003, Verthelyi and Zeuner, 2003), and protect B cells, pDCs and macrophages from apoptosis (Yi et al., 1998, Park et al., 2002, Sohn et al., 2006) . CpG-B ODNs additionally have been shown to induce macrophage migration via NF-κB activation and MMP-9 expression (Rhee et al., 2007). Class C oligos are claimed to combine the properties of Class A and B, and are characterized by their complete phosphorothioate (PS) backbone and palindromic CpG-containing motifs.

CpG ODNs are recognised by mouse TLR9 (Bauer et al., 2001) which initiates a signalling cascade leading to the production of pro-inflammatory cytokines and, as a result, the mounting of rapid responses to microbial pathogens (Hacker et al., 2000). The immune response to CpG ODNs is dependent on MyD88 activation (Schnare et al., 2000) and this response is completely lost in MyD88 knock out mice (Hoffmann et al., 1999, Takeuchi et al., 2000).

The SMAs were screened earlier *in vitro* using CpG-B ODNs to determine their effects on pro-inflammatory cytokines (Al-Riyami et al., 2013a) . 11a and 12b but not 19o were found to decrease the effect of CpG in promoting IL-6 and IL-12 release (Al-Riyami et al., 2013a). Therefore, in this study I tried to further understand the mechanism of action of the SMAs through observing their effects on the metabolome of CpG-activated macrophages. The results of a metabolomics study of the effect of CpG on macrophage response are thus reported for the first time and no literature has been found regarding metabolic profiling of the effects of CpG ODNs in macrophages or other immune system cells.

4.2 Results:

As shown from table 4.1, treating macrophages with CpG for 24 hours alters their metabolome in many pathways. This can be seen through an increase in the production of metabolites involved in oxidative stress, taurine metabolism, choline metabolism, ATP and high energy phosphates, carnitines and carnitine biosynthesis, purine and pyrimidine metabolism, amino sugar metabolism, arginine metabolism, glycolysis, TCA cycle, pentose phosphate pathway and creatine metabolism. The metabolites involved in fatty acid and phospholipid biosynthesis pathways show a variable pattern between increases in some instances and decreases in others.

In comparison, pre-treatment of the CpG activated macrophages with the SMAs has changed the CpG metabolome in comparison with CpG treatment alone (table 4.1) in only a few pathways. The main differences between the metabolomic response to treatment with CpG alone and CpG in the presence of the the SMAs are in the creatine metabolism and glutathione biosynthesis pathways. The metabolites involved in the creatine pathway include glycine, arginine, guandinoacetate, creatine and phosphocreatine whereas the metabolites included in the glutathione biosynthesis pathway are L-cysteine, L-phospho-L-serine, L-cystine, gamma-L-Glutamyl-L-cysteine, glutathione, S-glutathionyl-L-cysteine and glutathione disulphide. There were some differences between the two active SMAs but there were also marked changes produced by 19o in comparison to CpG treatment alone in some cases. Thus, to simplify discussion changes that were consistent with the effect of the two active SMAs and were > 1.5 or < 0.66-fold relative to CpG treatment alone have been highlighted in red in table 4.1 for more detailed discussion.

Some isolated metabolites in various pathways showed significant variations in fold change in comparison to changes induced by CpG treatment alone. These include

choline phosphate, sn-glycero-3-Phosphocholine, UDP, UDP-glucose, UDP-glucuronate, GDP-mannose, UDP-N-acetyl-D-glucosamine, D-Ribose 5-phosphate, phosphoribosylglycinamide, sedoheptulose 7-phosphate, 3-Phospho-D-glycerate, inosine monophosphate, D-glucosamine and 5'-methylthioadenosine. In order to simplify discussion and attempt to develop a hypothesis for a mechanism of action for the SMAs it can be suggested that many of these metabolites depend on ATP supply.

All metabolites detected and listed in table 4.1, which is from one run with 5 replicates of each treatment were also consistent in the pattern of change in at least 2/3 metabolomic runs (the majority of the changes occurred in all 3 replicates with 5/6 incubations in each run). Table 4.1 includes the detection mode, mass to charge ratio, retention time, p-value (P) and fold change (F) which is calculated in comparison to unstimulated macrophages. The other two runs tables are listed in appendices 11 and 12.

Tables 4.2-4.4 show the data obtained from labelling experiments where $^{13}C_6$-glucose was added to the culture medium of the macrophages and then stimulation with CpG or CpG + SMAs was carried out. The incubation was allowed to continue for 4, 8 or 24h. The labelling studies gave an indication or the rate of flux through glycolysis or the TCA cycle which were increased in all treatments in comparison to the control.

Table 4.1: The list of detected metabolites that have changed following CpG treatment, CpG +11a (C11a), 12b (C12b) or 19o (C19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, FC to fold change, RT to raw retention time and p to P-value (n=5). * Indicates retention time corresponding to analytical standard. (PC= phosphatidylcholine, PE= phosphatidylethanolamine, PS = phosphatidylserine, PI= phsophatidyl inositol, PG = phosphatidyl glycerol, SM = sphingomyelin, SP = sphingosine). Metabolites are highlighted in red where the change in level for one of more SMA treatments is both significant (P value <0.05) and has fold change >1.5 of <0.66 relative to CpG treatment alone.

All metabolites detected and listed in table 4.1 are from a single experiment with 5 independent replicates for each treatment. Tables 16 and 17 in the appendix show the metabolite changes induced by a subsequent independent experiment.

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
Oxidative stress											
+	76.039	16	*Glycine	<0.001	1.583	0.021	1.336	0.004	1.501	<0.001	6.901
-	120.012	16.6	*L-Cysteine	0.007	0.744	<0.001	0.551	<0.001	0.321	<0.001	5.49
+	148.06	14.9	*L-Glutamate	<0.001	2.248	<0.001	2.653	<0.001	3.174	<0.001	4.265
-	167.021	12.7	*Urate	0.007	1.277	<0.001	1.669	0.001	1.567	<0.001	5.67
+	168.052	15.1	8-Hydroxyguanine	<0.001	5.199	<0.001	5.787	<0.001	6.198	<0.001	6.426
-	184.002	3.9	O-Phospho-L-serine	0.008	0.089	0.007	0.059	0.007	0.048	0.007	0.057
+	241.031	16.6	*L-Cystine	0.008	0.75	<0.001	0.637	<0.001	0.379	<0.001	4.323
+	251.07	14.4	gamma-L-Glutamyl-L-cysteine	0.007	9.347	<0.001	302.333	<0.001	200.176	0.004	16.718
+	308.091	14.6	*Glutathione	<0.001	2.17	<0.001	3.944	<0.001	4.753	0.003	0.531
+	427.095	16.9	S-glutathionyl-L-cysteine	<0.001	3.242	<0.001	4.157	<0.001	3.829	<0.001	14.382
+	613.16	17.6	*Glutathione disulfide	<0.001	4.79	<0.001	8.001	<0.001	6.219	<0.001	2.923
+	744.083	17.1	*NADP+	<0.001	9.896	<0.001	11.664	<0.001	13.559	<0.001	8.324
+	746.099	17.5	*NADPH	<0.001	3.402	<0.001	3.305	<0.001	5.035	<0.001	3.669
Taurine metabolism											
+	110.027	15.3	Hypotaurine	<0.001	11.296	<0.001	12.86	<0.001	15.323	<0.001	11.654
+	126.022	15.1	*Taurine	<0.001	3.923	<0.001	4.685	<0.001	4.907	<0.001	4.744
+	168.044	15.9	Taurocyamine	<0.001	6.188	<0.001	8.081	<0.001	9.373	<0.001	7.925

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
-	167.997	15.1	L-Cysteate	<0.001	7.006	0.003	4.939	0.001	8.734	0.001	15.831
+	255.065	15.7	5-L-Glutamyl-taurine	<0.001	8.684	<0.001	6.293	<0.001	20.393	<0.001	10.882
Choline metabolism											
+	104.107	20.8	*Choline	<0.001	1.567	<0.001	1.756	0.008	1.255	<0.001	5.598
+	184.073	15.3	*Choline phosphate	<0.001	2.338	<0.001	5.642	<0.001	7.188	<0.001	3.038
+	258.110	14.8	*sn-glycero-3-Phosphocholine	<0.001	1.602	0.002	0.843	0.547	1.033	<0.001	2.342
ATP and high energy phosphates											
+	212.043	15.4	*Phosphocreatine	<0.001	3.667	<0.001	2.102	<0.001	2.279	<0.001	3.959
+	324.059	15.5	CMP	0.012	2.712	0.003	3.425	0.002	2.676	0.001	2.993
-	323.029	15.4	UMP	<0.001	3.150	<0.001	4.411	<0.001	4.040	0.104	1.557
+	348.070	14	AMP	0.001	3.295	<0.001	3.789	<0.001	4.632	0.017	1.300
-	402.995	16.8	UDP	<0.001	17.538	<0.001	21.861	<0.001	27.511	<0.001	15.669
+	428.037	15.5	*ADP	<0.001	3.235	<0.001	3.707	<0.001	4.757	0.003	2.475
-	429.058	15.6	CMP-2-aminoethylphosphonate	<0.001	6.575	<0.001	6.103	<0.001	7.717	<0.001	8.029
+	447.068	16.6	CDP-ethanolamine	<0.001	6.165	<0.001	6.227	<0.001	7.468	<0.001	6.798
-	481.977	18.9	CTP	<0.001	40.084	<0.001	38.149	<0.001	48.354	0.007	14.696
-	482.961	18.3	UTP	<0.001	20.169	<0.001	20.628	<0.001	22.792	<0.001	12.664
+	508.003	17	*ATP	<0.001	4.322	<0.001	4.561	<0.001	4.891	<0.001	2.463
-	521.983	19.9	*GTP	0.002	29.142	0.026	13.338	0.001	31.176	0.026	3.539
-	565.047	16.6	UDP-glucose	<0.001	4.917	<0.001	6.103	<0.001	5.977	<0.001	6.253
-	572.080	12.9	GDP-3,6-dideoxy-D-galactose	0.001	3.056	0.001	3.277	0.001	3.303	<0.001	5.107
+	574.095	12.9	GDP-3,6-dideoxy-D-galactose	0.002	4.006	0.002	3.782	0.001	4.753	0.001	7.624
-	579.027	19.3	UDP-glucuronate	<0.001	7.065	<0.001	8.102	<0.001	9.249	<0.001	9.214
-	604.070	18.5	GDP-mannose	<0.001	3.358	<0.001	14.739	<0.001	7.165	0.002	5.502
+	608.089	15.3	*UDP-N-acetyl-D-glucosamine	<0.001	8.677	<0.001	10.376	<0.001	10.008	0.005	5.992
+	615.155	15.5	CMP-N-acetylneuraminate	<0.001	3.125	<0.001	3.215	<0.001	3.082	<0.001	3.845
Carnitines and carnitine biosynthesis											
+	146.118	13.6	4-Trimethylammoniobutanoate	<0.001	1.568	<0.001	1.530	<0.001	1.499	<0.001	2.896

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	162.113	13.6	*L-Carnitine	<0.001	1.351	<0.001	1.305	0.926	0.996	<0.001	3.268
+	189.160	22.8	*N6,N6,N6-Trimethyl-L-lysine	0.003	2.110	<0.001	2.482	<0.001	2.625	<0.001	15.754
+	204.123	11.3	*O-Acetylcarnitine	<0.001	2.784	<0.001	2.773	<0.001	3.264	<0.001	4.375
+	218.139	10	O-Propanoylcarnitine	<0.001	1.811	<0.001	1.582	<0.001	1.372	<0.001	2.664
+	232.154	9	O-Butanoylcarnitine	<0.001	1.703	<0.001	1.667	<0.001	1.570	<0.001	5.022
+	248.149	11.6	Hydroxybutyrylcarnitine	<0.001	4.932	<0.001	4.284	<0.001	5.455	0.034	3.016
+	288.217	7.6	L-Octanoylcarnitine	0.037	1.580	0.037	1.528	0.014	1.645	0.024	6.487
+	372.311	4.9	Tetradecanoylcarnitine	<0.001	3.079	<0.001	3.315	<0.001	5.143	<0.001	3.362
+	374.254	4.2	Dodecanedioylcarnitine	0.011	0.278	0.004	0.176	0.003	0.111	0.003	0.127
+	398.327	4.8	trans-Hexadec-2-enoylcarnitine	<0.001	3.489	<0.001	3.618	<0.001	6.497	<0.001	4.671
+	400.342	7.5	O-Palmitoyl-R-carnitine	<0.001	2.706	<0.001	3.169	<0.001	5.895	<0.001	3.556
+	400.342	4.7	O-Palmitoyl-R-carnitine	<0.001	2.945	<0.001	3.396	<0.001	5.196	<0.001	3.724
+	414.358	4.1	Heptadecanoylcarnitine	0.023	0.507	0.016	0.470	0.015	0.463	0.015	0.457
+	424.342	4.7	Linoelaidylcarnitine	<0.001	6.716	0.001	6.973	<0.001	13.383	0.001	9.169
+	426.358	4.7	Elaidiccarnitine	<0.001	3.489	<0.001	3.970	<0.001	6.577	<0.001	5.034
+	428.374	4.6	Stearoylcarnitine	<0.001	1.668	<0.001	1.77	<0.001	1.654	<0.001	2.220
Purine and pyrimidine metabolism											
-	111.020	8.6	*Uracil	<0.001	2.150	0.017	1.439	0.015	1.791	<0.001	20.342
+	136.062	9.8	*Adenine	0.034	2.455	0.300	1.466	0.008	2.561	0.037	2.076
+	137.046	10.4	*Hypoxanthine	<0.001	0.17	<0.001	0.184	<0.001	0.306	<0.001	0.534
-	151.026	11.4	*Xanthine	<0.001	0.611	<0.001	0.558	0.001	0.526	<0.001	4.26
+	166.072	13.1	3-Methylguanine	<0.001	178.727	<0.001	208.408	<0.001	265.45	<0.001	255.799
-	229.012	16.0	D-Ribose 5-phosphate	0.001	113.44	0.001	81.766	0.002	43.493	<0.001	33.046
+	242.114	9.7	5-Methyl-2'-deoxycytidine	0.033	1.241	0.017	1.279	0.286	1.128	<0.001	7.643
-	243.062	10	*Uridine	<0.001	0.691	0.003	0.835	<0.001	0.636	<0.001	2.436
-	243.062	12.2	pseudouridine	0.020	1.258	<0.001	1.377	<0.001	1.407	<0.001	6.286
-	289.033	16.6	Sedoheptulose 7-phosphate	<0.001	17.617	<0.001	12.283	<0.001	9.978	<0.001	14.115

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	287.064	16.7	5'-Phosphoribosylglycinamide	<0.001	1377.671	<0.001	1179.108	<0.001	1256.043	<0.001	1409.851
-	347.040	15.7	*Inosine monophosphate	<0.001	3.680	0.001	7.025	<0.001	30.828	0.002	2.491
+	446.179	3.9	Tetrahydrofolate	0.001	#DIV/0!	0.001	#DIV/0!	0.004	#DIV/0!	<0.001	#DIV/0!
Aminosugar metabolism											
+	180.087	15.2	*D-Glucosamine	0.006	23.432	0.001	32.438	<0.001	33.791	0.005	178.047
+	260.053	15.6	D-Glucosamine 6-phosphate	<0.001	2.870	0.002	2.850	<0.001	4.166	<0.001	4.057
+	310.113	13.5	N-Acetylneuraminate	<0.001	1.983	<0.001	1.857	<0.001	1.980	<0.001	2.422
+	326.108	14.6	N-Glycoloyl-neuraminate	<0.001	2.765	<0.001	2.713	<0.001	2.833	<0.001	4.180
Arginine metabolism											
+	146.092	15.5	4-Guanidinobutanoate	0.012	1.164	0.003	1.21	<0.001	1.381	<0.001	2.308
+	174.087	14.9	5-Guanidino-2-oxopentanoate	0.049	0.273	0.422	0.73	0.325	0.689	0.007	2.308
+	174.087	15.6	5-Guanidino-2-oxopentanoate	0.050	1.525	0.073	1.537	0.027	2.003	<0.001	18.078
+	175.119	26.9	*L-Arginine	0.020	1.272	0.001	1.478	0.001	1.487	<0.001	6.541
+	203.150	22.3	NG,NG-Dimethyl-L-arginine	0.005	1.729	<0.001	2.038	<0.001	2.099	<0.001	12.173
+	291.130	17.1	N-(L-Arginino)succinate	<0.001	3.467	<0.001	3.673	<0.001	5.593	<0.001	10.469
+	247.140	14.5	N2-(D-1-Carboxyethyl)-L-arginine	0.001	1.337	<0.001	1.52	<0.001	1.634	<0.001	6.590
Histidine metabolism											
+	139.050	10.8	*Urocanate	0.011	0.576	0.053	0.716	0.07	0.742	0.036	2.199
+	141.066	10.5	Methylimidazoleacetic acid	<0.001	2.491	0.001	1.681	<0.001	2.525	<0.001	7.040
+	141.066	9.5	Methylimidazoleacetic acid	0.001	1.405	0.002	1.417	0.002	1.361	<0.001	6.685
+	156.077	14.9	*L-Histidine	<0.001	1.417	<0.001	1.465	<0.001	1.511	<0.001	4.370
+	227.114	16	Carnosine	0.030	1.466	0.078	1.350	0.039	1.430	<0.001	6.301
Glycolysis and TCA cycle and related metabolites											
-	89.024	9.4	*(R)-Lactate	<0.001	2.498	<0.001	2.177	<0.001	2.603	<0.001	12.958
+	810.133	12.6	Acetyl CoA	<0.001	7.849	<0.001	9.805	<0.001	11.710	<0.001	9.450
-	115.004	16.2	*Fumarate	<0.001	2.742	<0.001	2.971	<0.001	4.854	<0.001	5.354
-	117.019	15.3	*Succinate	<0.001	2.038	0.001	2.052	<0.001	2.401	<0.001	5.567
-	129.019	15.2	*itaconate	<0.001	4.720	<0.001	4.766	<0.001	6.082	<0.001	8.286

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
-	133.014	16.2	*(S)-Malate	<0.001	2.736	<0.001	2.93	<0.001	4.772	<0.001	5.018
+	168.066	8.1	Pyridoxal	0.012	1.226	0.183	1.282	0.601	1.041	<0.001	4.524
-	145.014	15.7	*2-Oxoglutarate	<0.001	4.484	<0.001	5.430	<0.001	8.496	<0.001	14.098
-	147.030	18.4	2-Hydroxyglutarate	0.006	1.841	0.005	2.257	<0.001	2.522	<0.001	19.140
-	171.006	14.8	sn-Glycerol 3-phosphate	<0.001	1.570	<0.001	0.807	0.049	0.933	<0.001	1.967
-	173.009	18.5	*cis-Aconitate	<0.001	2.306	<0.001	2.764	0.010	5.032	<0.001	17.321
-	179.056	17.4	D-Glucose	0.007	1.340	0.037	1.417	0.020	1.345	<0.001	6.356
-	179.056	13.7	D-Glucose	<0.001	2.068	0.001	2.268	0.002	2.227	0.001	8.219
-	184.986	17.3	*3-Phospho-D-glycerate	<0.001	30.158	<0.001	51.56	<0.001	94.34	<0.001	89.925
-	191.020	18.4	*Citrate	<0.001	1.776	<0.001	2.239	<0.001	2.742	<0.001	5.749
+	170.081	8.2	*Pyridoxine	0.012	1.282	0.004	1.323	0.034	1.215	<0.001	6.888
-	259.022	17.1	*Glucose 6-phosphate	<0.001	2.330	<0.001	2.125	<0.001	1.756	<0.001	3.212
+	664.117	14.4	*NAD+	<0.001	3.73	<0.001	5.042	<0.001	5.427	<0.001	4.716
+	666.132	13.6	*NADH	<0.001	3.715	<0.001	3.913	<0.001	5.663	<0.001	5.184
Fatty acids											
-	253.217	3.9	Hexadecenoic acid	0.028	0.484	0.054	0.573	0.070	0.603	0.346	0.822
-	255.233	3.9	Hexadecanoic acid	0.010	0.489	0.010	0.508	0.006	0.428	0.012	0.526
-	271.228	3.9	16-hydroxypalmitate	0.010	0.868	0.007	0.860	0.033	0.888	<0.001	1.256
-	281.249	3.9	Octadecenoic acid	0.034	0.677	0.024	0.644	0.018	0.620	0.671	1.052
-	283.264	3.9	Octadecanoic acid	0.008	0.459	0.005	0.397	0.003	0.330	0.004	0.360
-	297.243	3.9	Oxooctadecanoic acid	0.028	0.856	0.007	0.804	0.009	0.812	0.032	0.860
-	299.259	4.0	Hydroxy-octadecanoic acid	0.024	0.857	0.002	0.760	0.003	0.777	0.005	0.793
-	301.217	3.9	Eicosapentaenoic acid	0.022	1.658	<0.001	1.603	0.004	1.548	<0.001	3.130
-	309.28	3.9	Eicosenoic acid	0.026	0.638	0.021	0.620	0.017	0.601	0.884	0.982
-	311.223	4.0	Hydroperoxy-octadecadienoic acid	0.039	1.343	0.359	1.202	0.002	1.487	0.005	1.575
-	311.296	3.9	Eicosanoic acid	0.009	0.433	0.005	0.369	0.004	0.332	0.004	0.315
-	312.172	3.8	Oxo-retinoate	0.008	0.325	0.006	0.265	0.005	0.234	0.005	0.230

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
-	319.228	4.0	Hydroxyeicosatetraenoic acid	0.031	1.837	0.051	2.582	0.004	3.512	0.006	9.947
-	327.29	3.9	Hydroxyphytanate	0.002	1.428	0.791	0.966	0.093	1.575	0.016	2.502
-	333.28	3.9	Docosatrienoic acid	0.023	1.999	0.010	2.297	<0.001	2.022	<0.001	4.323
-	337.311	3.9	Docosenoic acid	0.015	0.469	0.033	0.502	0.006	0.354	0.011	0.434
-	339.327	3.9	Docosanoic acid	0.005	0.418	0.002	0.334	0.003	0.361	0.002	0.334
-	341.196	3.8	Eicosanedioic acid	0.009	0.872	0.001	0.795	0.002	0.825	0.002	0.823
Creatine metabolism											
+	76.039	16	Glycine	<0.001	1.583	0.021	1.336	0.004	1.501	<0.001	6.901
+	114.066	9.9	*Creatinine	0.005	1.242	0.001	1.403	0.004	1.337	<0.001	5.597
+	118.061	16	Guanidinoacetate	<0.001	2.923	0.002	0.694	<0.001	1.578	<0.001	5.921
+	132.077	15	*Creatine	<0.001	2.499	<0.001	1.531	<0.001	1.563	<0.001	4.334
+	133.097	23.8	*L-Ornithine	0.007	1.226	0.005	1.432	<0.001	1.592	<0.001	5.675
+	150.058	11.8	L-Methionine	0.006	1.299	<0.001	1.417	0.001	1.379	<0.001	7.169
+	175.119	26.9	L-Arginine	0.020	1.272	0.001	1.478	0.001	1.487	<0.001	6.541
+	212.043	15.4	*Phosphocreatine	<0.001	3.667	<0.001	2.102	<0.001	2.279	<0.001	3.959
Miscellaneous											
+	90.055	15.6	*L-Alanine	<0.001	8.544	<0.001	9.366	<0.001	11.156	<0.001	10.822
+	104.071	5.4	Aminobutanoate isomer	0.024	0.329	0.263	0.682	0.146	0.541	0.115	0.571
+	118.086	11.5	*L-Valine	<0.001	1.358	<0.001	1.565	<0.001	1.374	<0.001	3.575
+	123.055	7.6	*Nicotinamide	<0.001	2.03	<0.001	2.263	<0.001	2.167	<0.001	6.885
+	128.071	13.5	2,3,4,5-Tetrahydropyridine-2-carboxylate	0.038	2.098	0.192	1.832	0.001	2.624	0.004	16.941
+	130.05	15.4	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.001	1.286	<0.001	1.469	<0.001	1.355	<0.001	4.203
+	132.065	14.8	L-Glutamate 5-semialdehyde	0.024	1.288	<0.001	1.565	<0.001	1.527	<0.001	5.381
+	134.045	15.2	*L-Aspartate	<0.001	1.297	<0.001	1.524	<0.001	1.804	<0.001	3.861
+	134.06	8.2	Indoxyl	0.020	1.249	0.003	1.396	0.054	1.230	<0.001	7.296
+	142.026	16.2	Ethanolamine phosphate	<0.001	1.798	<0.001	1.798	<0.001	1.988	<0.001	2.163

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	146.081	9	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.002	1.566	0.129	1.595	0.02	1.762	0.001	6.676
+	147.076	15.4	*L-Glutamine	0.003	1.263	0.001	1.315	0.003	1.266	<0.001	4.447
+	147.113	25.4	*L-Lysine	0.029	1.225	0.002	1.367	<0.001	1.391	<0.001	8.210
+	160.133	13.6	DL-2-Aminooctanoicacid	<0.001	1.902	<0.001	1.762	<0.001	1.959	<0.001	4.054
+	161.129	24.3	N6-Methyl-L-lysine	<0.001	2.923	<0.001	3.151	<0.001	3.513	<0.001	7.983
+	162.076	15.1	Aminoadipate	0.043	2.681	0.036	2.934	0.051	2.617	0.024	23.133
+	162.076	11.3	Aminoadipate	0.006	6.898	<0.001	6.486	0.002	13.353	<0.001	21.507
+	166.086	10.5	*Phenylalanine	0.010	1.270	0.002	1.369	0.001	1.342	<0.001	6.788
+	174.113	5	N-Acetyl-L-leucine	0.011	0.170	0.021	0.287	0.009	0.119	0.010	0.160
+	175.108	13.8	N-Acetylornithine	0.007	1.355	0.001	1.609	0.001	1.625	<0.001	12.134
+	177.112	5	[FA hydroxy(8:0)] 6,8-dihydroxy-octanoic acid	0.026	0.277	0.046	0.382	0.022	0.243	0.015	0.158
+	178.086	7.5	5-Hydroxytryptophol	0.026	1.288	0.041	1.316	0.165	1.741	0.114	2.523
+	180.066	7.5	Hippurate	0.037	1.351	0.004	1.512	0.013	1.44	0.018	15.885
+	184.061	4.8	4-Pyridoxate	0.045	1.233	0.145	1.270	0.166	1.228	<0.001	7.348
+	188.103	15.4	5-guanidino-3-methyl-2-oxo-pentanoate	<0.001	2.182	0.003	1.828	0.027	1.901	<0.001	17.924
+	189.087	11.2	N-Acetylglutamine	0.051	0.175	0.101	0.347	0.047	0.157	0.049	0.168
+	189.087	14.9	N-Acetylglutamine	<0.001	4.232	<0.001	3.546	<0.001	5.533	<0.001	9.505
+	190.05	4.1	Kynurenate	0.023	1.142	0.402	0.938	0.016	0.779	0.232	0.866
+	190.086	10.5	Indolepropionicacid	0.013	1.349	0.003	1.432	0.11	1.276	<0.001	8.542
+	198.087	6.3	N-Acetyl-L-histidine	0.027	0.569	0.006	1.309	0.766	0.972	0.001	5.144
+	198.087	8.9	N-Acetyl-L-histidine	0.002	1.506	0.002	1.374	0.007	1.339	<0.001	8.122
+	203.04	14.6	5-Hydroxy-2-oxo-4-ureido-2,5-dihydro-1H-imidazole-5-carboxylate	0.007	0.490	0.003	0.436	0.008	0.490	0.436	1.511
+	205.097	12	*Tryptophan	0.011	1.254	0.001	1.391	0.002	1.328	<0.001	6.936
+	205.119	14.6	N6-Acetyl-N6-hydroxy-L-lysine	0.003	2.009	0.002	2.523	0.003	2.542	<0.001	16.052
+	215.139	10.2	Dethiobiotin	0.005	1.855	0.02	2.083	0.007	2.236	0.009	9.252

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	216.063	15.9	sn-glycero-3-Phosphoethanolamine	0.008	1.197	<0.001	0.548	<0.001	0.782	<0.001	1.617
+	217.129	15.1	N-acetyl-(L)-arginine	0.043	0.212	0.077	0.343	0.071	0.328	0.915	0.966
+	220.118	8.6	Pantothenate	0.002	1.477	0.002	1.446	0.007	1.355	<0.001	7.877
+	220.118	6.0	Pantothenate	0.034	0.484	0.003	1.360	0.704	0.921	<0.001	6.219
+	230.248	4.9	[SP (14:0)] 1-deoxy-tetradecasphinganine	0.019	0.510	0.04	0.567	0.019	0.509	0.065	0.532
+	240.109	12.9	Dihydrobiopterin	0.001	129.082	0.001	179.461	<0.001	239.83	<0.001	402.62
+	243.027	16.6	D-myo-Inositol 1,2-cyclic phosphate	0.024	0.729	0.001	0.552	<0.001	0.268	<0.001	4.870
+	245.096	8.8	Biotin	0.045	1.453	0.008	1.584	0.005	1.508	<0.001	10.595
+	253.144	7.5	ubiquinol-1	0.017	1.754	0.611	1.197	0.070	1.746	0.611	1.109
+	265.112	21.4	Thiamine	0.010	1.342	0.001	1.517	0.003	1.465	<0.001	8.502
+	276.155	17.1	glutamyl-L-Lysine	<0.001	0.551	<0.001	0.470	<0.001	0.572	0.883	1.015
+	282.279	7.5	Octadecenamide	<0.001	0.326	<0.001	0.269	<0.001	0.330	<0.001	0.347
+	298.097	7.6	5'-Methylthioadenosine	<0.001	6.515	<0.001	11.770	<0.001	23.433	<0.001	19.939
+	300.29	7.5	Dehydrosphinganine	<0.001	0.331	<0.001	0.262	<0.001	0.326	<0.001	0.350
+	314.269	4.2	N-hexadecanoyl-glycine	0.008	0.489	0.014	0.558	0.002	0.363	0.003	0.390
+	345.185	4.3	Tetracosahexanoic acid	0.026	0.262	0.015	0.131	0.013	0.113	0.022	0.226
+	350.305	4.3	Eicosatrienoyl ethanolamine	0.049	0.072	0.133	0.35	0.053	0.093	0.054	0.096
+	354.337	4.2	Eicosaenoyl ethanolamine	0.041	0.152	0.095	0.357	0.080	0.316	0.046	0.177
+	377.146	8.8	Riboflavin	0.019	1.849	0.600	1.103	0.805	0.950	<0.001	11.076
Phospholipids											
+	452.314	4.7	Lyso PC 14:1	<0.001	0.661	0.865	0.978	0.882	1.023	0.927	1.018
+	454.293	4.8	Lyso PE 16:0	<0.001	2.257	<0.001	2.375	<0.001	2.91	<0.001	3.072
+	480.308	4.7	Lyso PE18:1	<0.001	2.603	0.023	1.855	0.001	2.603	<0.001	3.033
+	482.324	4.7	Lyso PE 18:0	<0.001	1.277	<0.001	1.266	<0.001	1.392	<0.001	1.808
+	482.361	4.9	Lyso PC 16:1 ether	0.010	0.871	0.105	0.935	0.157	0.938	0.211	1.096
+	496.34	7.5	Lyso PC 16:0	0.004	0.828	0.084	0.899	0.001	1.227	0.002	1.289
+	502.291	7.5	Lyso PE 20:4	<0.001	2.128	0.735	0.956	0.010	1.422	0.255	1.149

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	502.293	4.7	Lyso PE 20:4	<0.001	2.249	0.452	1.076	0.055	1.239	0.763	1.032
+	508.376	4.8	Lyso PC 18:1 ether	<0.001	0.576	0.001	0.611	0.004	0.601	0.001	0.760
+	522.355	7.5	Lyso PC 18:1	<0.001	0.667	0.001	0.704	0.167	1.101	0.003	1.290
+	524.371	4.7	Lyso PC 18:0	0.002	0.861	0.003	0.876	0.019	0.895	0.897	0.992
+	526.293	4.6	LysoPE 22:6	<0.001	3.681	0.026	1.515	<0.001	2.114	<0.001	1.882
+	526.313	4.3	LPS 18:0	<0.001	0.406	<0.001	0.384	<0.001	0.341	<0.001	0.433
+	528.309	4.6	LysoPE 22:5	<0.001	3.304	<0.001	1.665	0.004	2.008	0.077	1.430
+	530.324	4.6	Lyso PE 22:4	<0.001	3.453	0.056	1.451	0.044	1.774	0.342	1.227
+	538.519	4	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine	<0.001	0.263	<0.001	0.203	<0.001	0.230	<0.001	0.308
+	544.34	4.7	LysoPC 20:4	0.035	0.680	0.055	0.704	0.812	1.031	0.033	1.459
+	552.402	4.6	Lyso PC 20:0	0.028	1.506	0.537	1.170	0.577	1.126	0.036	1.595
+	675.544	4.5	SM32:1	<0.001	1.704	<0.001	1.676	<0.001	1.691	<0.001	1.626
+	689.56	4.5	[SP (18:0/14:0)] N-(octadecanoyl)-tetradecasphing-4-enine-1-phosphoethanolamine	<0.001	1.358	<0.001	1.311	<0.001	1.506	<0.001	1.426
+	692.56	4.2	PC30:2	0.016	0.414	0.011	0.359	0.030	0.474	0.018	0.429
+	703.575	7.5	SP16:0	0.020	0.753	0.002	0.734	0.005	1.234	0.695	0.973
+	703.575	4.4	SP16:0	<0.001	1.365	<0.001	1.439	<0.001	2.062	<0.001	1.786
+	704.523	4.2	PC32:1	<0.001	20.619	0.003	22.385	<0.001	45.042	<0.001	26.967
+	705.581	4.4	[ST (20:4)] cholest-5-en-3beta-yl (15S-hydroperoxy-5Z,8Z,12E,14Z-eicosatetraenoate)	0.001	1.329	<0.001	1.436	<0.001	2.065	<0.001	1.812
+	706.539	4.2	PC30:0	<0.001	4.944	<0.001	6.21	<0.001	8.691	<0.001	6.152
+	716.523	4.2	PE34:2	0.001	80.073	0.006	224.128	<0.001	434.22	<0.001	89.618
+	718.539	4.2	PE34:1	<0.001	8.414	<0.001	9.863	<0.001	12.60	<0.001	8.993
+	718.575	4.2	PC32:0 ether	0.007	0.896	0.009	1.088	<0.001	1.190	0.545	1.018
+	719.579	4.2	menaquinol-8	0.010	0.770	0.138	0.720	0.003	1.164	0.053	0.728
+	720.555	4.2	PE34:0	<0.001	2.140	<0.001	2.417	<0.001	2.812	<0.001	2.291
+	720.592	4.2	PC32:2	<0.001	0.420	<0.001	0.377	<0.001	0.469	<0.001	0.253

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	722.513	4.1	PE36:5 ether	0.003	4.012	<0.001	3.805	<0.001	3.755	0.001	3.950
+	724.528	4.1	PE36:4 ether	0.025	1.093	<0.001	1.165	<0.001	1.179	0.003	1.121
+	728.523	4.2	PC32:3	<0.001	32.232	<0.001	41.141	<0.001	43.783	<0.001	34.838
+	730.539	4.2	PC32:2	<0.001	11.324	<0.001	14.049	<0.001	16.884	<0.001	12.529
+	732.554	4.2	PC32:1	<0.001	4.368	<0.001	5.003	<0.001	6.069	<0.001	4.699
+	732.589	4.2	PE36:0 ether	0.008	0.259	0.105	2.755	0.223	2.217	0.451	0.690
+	734.497	3.9	PS32:1	<0.001	21.108	0.002	20.926	<0.001	42.404	<0.001	15.798
+	734.57	4.2	PC32:0	0.002	1.414	<0.001	1.479	<0.001	1.654	<0.001	1.511
+	738.544	4.1	PC34:4 ether	0.001	0.802	0.001	0.845	0.004	0.872	<0.001	0.805
+	740.523	4.1	PE36:4	<0.001	7.660	<0.001	7.840	<0.001	9.427	<0.001	7.568
+	744.554	4.2	PE36:2	<0.001	15.954	<0.001	17.574	<0.001	22.521	<0.001	15.837
+	746.57	4.2	PE36:1	<0.001	3.797	<0.001	4.086	<0.001	4.889	<0.001	4.083
+	746.607	4.2	PC34:0 ether	<0.001	1.407	<0.001	1.532	<0.001	1.818	<0.001	1.604
+	748.528	4.1	PE38:7	<0.001	1.824	<0.001	1.797	<0.001	1.908	<0.001	1.859
+	749.532	4.1	PG34:1	<0.001	1.886	<0.001	1.859	<0.001	2.062	<0.001	1.970
+	750.544	4.1	PE38:5 ether	<0.001	1.228	<0.001	1.372	<0.001	1.413	<0.001	1.219
+	751.548	4.1	PG34:0	<0.001	1.220	<0.001	1.385	<0.001	1.432	<0.001	1.248
+	754.54	4.2	PC34:4	<0.001	16.846	<0.001	19.413	<0.001	22.591	0.001	17.305
+	756.555	4.2	PC34:3	<0.001	9.655	<0.001	11.816	<0.001	14.506	<0.001	10.582
+	758.57	4.2	PC34:2	<0.001	5.430	<0.001	6.334	<0.001	7.385	<0.001	5.983
+	760.513	3.9	PS34:2	0.002	7.380	0.001	8.424	<0.001	15.256	0.005	6.719
+	760.586	4.2	PC34:1	<0.001	3.320	<0.001	3.558	<0.001	3.998	<0.001	3.676
+	762.529	3.9	PS34:1	<0.001	2.360	<0.001	2.246	<0.001	3.040	<0.001	1.944
+	762.6	4.1	PC34:0	0.002	<0.001	0.002	<0.001	0.002	<0.001	0.002	<0.001
+	764.524	4.1	PE38:6	<0.001	12.659	<0.001	12.657	<0.001	14.559	<0.001	13.304
+	764.544	3.8	PS34:0	0.018	2.229	0.045	3.916	0.056	3.128	0.035	3.800
+	766.54	4.1	PE38:5	<0.001	13.705	<0.001	13.526	0.001	17.331	0.003	14.294
+	766.575	4.2	PE36:4 ether	<0.001	0.472	<0.001	0.616	<0.001	0.509	<0.001	0.543

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	768.555	4.1	PE38:4	<0.001	2.268	<0.001	2.147	<0.001	2.365	<0.001	2.282
+	771.61	4.2	demethylmenaquinone-9	0.001	6.309	0.012	9.366	0.034	18.615	0.006	7.707
+	772.586	4.2	PE38:2	0.006	8.651	<0.001	13.927	<0.001	16.609	<0.001	14.656
+	774.544	4.1	PE40:7 ether	<0.001	1.903	<0.001	1.93	<0.001	2.136	<0.001	1.927
+	774.602	4.2	PE38:1	<0.001	2.450	<0.001	2.643	<0.001	2.764	<0.001	2.825
+	775.547	4.1	PG36:2	0.001	1.914	0.001	2.139	<0.001	2.510	0.002	1.964
+	776.56	4.1	PE40:7	0.001	1.499	<0.001	1.628	<0.001	1.733	0.001	1.505
+	778.539	4.2	PC36:6	0.001	29.861	0.002	26.615	0.002	39.196	<0.001	37.269
+	778.576	4.1	PE40:5 ether	0.006	1.169	<0.001	1.287	<0.001	1.440	0.001	1.170
+	779.579	4.1	PG36:0	0.046	1.409	0.012	1.588	0.005	1.727	0.373	1.230
+	780.555	4.2	PC36:5	<0.001	4.901	<0.001	5.439	<0.001	5.991	<0.001	5.492
+	780.591	4.2	PE40:4 ether	<0.001	0.868	0.001	0.886	0.006	0.901	0.063	0.938
+	782.57	4.2	PC36:4	<0.001	2.701	<0.001	2.812	<0.001	2.759	<0.001	3.084
+	784.513	3.8	PS36:4	<0.001	6.632	<0.001	6.729	<0.001	8.039	<0.001	6.20
+	784.586	4.2	PC36:3	<0.001	4.725	<0.001	5.278	<0.001	5.992	<0.001	5.321
+	786.529	3.9	PS36:3	<0.001	10.313	<0.001	11.998	0.005	12.668	0.001	8.687
+	786.602	4.2	PC36:2	<0.001	4.253	<0.001	4.547	<0.001	5.372	<0.001	4.788
+	788.544	3.8	PS36:2	<0.001	1.644	0.001	1.542	<0.001	1.987	0.003	1.319
+	790.56	3.9	PS36:1	0.001	0.567	<0.001	0.525	0.001	0.643	<0.001	0.462
+	792.554	4.1	PE40:6	<0.001	3.914	<0.001	3.504	<0.001	3.849	<0.001	3.925
+	792.591	4.2	PC38:5 ether	<0.001	1.153	<0.001	1.192	<0.001	1.215	<0.001	1.333
+	793.558	4.1	acyl phosphatidylglycerol (n-C12:0)	<0.001	4.855	<0.001	4.421	<0.001	4.836	<0.001	4.912
+	794.571	4.1	PE40:6	<0.001	6.982	<0.001	6.652	<0.001	7.578	0.005	6.110
+	796.588	4.1	PE40:4	0.004	21.543	<0.001	22.524	0.003	18.566	0.001	22.926
+	800.617	4.2	PE40:2	0.001	4.193	0.001	4.581	0.010	12.437	<0.001	4.808
+	804.554	4.2	PC38:7	<0.001	12.815	<0.001	14.608	<0.001	16.782	<0.001	14.313
+	806.57	4.2	PC38:6	<0.001	3.835	<0.001	4.185	<0.001	4.294	<0.001	4.505

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	808.513	3.8	PS38:6	<0.001	16.349	<0.001	17.726	<0.001	22.463	<0.001	15.017
+	808.586	4.2	PC38:5	<0.001	3.612	<0.001	3.683	<0.001	3.877	<0.001	4.15
+	809.517	3.8	PI32:2	<0.001	20.365	<0.001	21.434	0.001	27.415	<0.001	20.012
+	810.529	3.8	1-20:2-2-18:3-phosphatidylserine	<0.001	6.172	<0.001	5.324	<0.001	7.811	<0.001	5.862
+	810.602	4.2	PC38:4	<0.001	1.696	<0.001	1.680	<0.001	1.589	<0.001	1.974
+	811.532	3.8	PI32:0	0.001	6.252	<0.001	7.000	<0.001	9.178	<0.001	6.357
+	812.544	3.8	PS38:4	0.017	1.168	0.855	1.011	0.027	1.118	0.875	0.991
+	813.685	7.4	SM42:2	0.001	0.465	0.001	0.59	0.023	0.746	0.007	0.565
+	813.685	4.4	SM42:2	0.009	0.475	0.011	0.619	0.034	0.585	0.049	0.585
+	818.607	4.1	PC40:7	<0.001	1.651	<0.001	1.602	<0.001	1.678	<0.001	1.908
+	819.518	3.7	PG40:8	0.008	1.528	0.901	0.983	0.084	0.713	0.195	1.317
+	820.622	4.1	PC40:5 ether	<0.001	1.439	<0.001	1.440	<0.001	1.541	<0.001	1.643
+	822.638	4.2	PC40:4 ether	<0.001	1.216	<0.001	1.253	<0.001	1.368	<0.001	1.329
+	824.653	4.1	PC40:3 ether	<0.001	0.122	<0.001	0.163	0.003	0.410	<0.001	0.194
+	828.555	4.2	PC40:7	0.003	6.93	0.023	5.474	0.072	9.471	0.001	8.489
+	830.57	4.2	PC40:8	<0.001	2.152	<0.001	2.126	<0.001	2.262	<0.001	2.458
+	832.586	4.1	PC40:7	<0.001	4.718	<0.001	5.026	<0.001	5.596	<0.001	5.390
+	834.529	3.8	PS40:7	<0.001	2.931	<0.001	2.466	<0.001	2.855	<0.001	2.942
+	834.602	4.1	PC40:6	<0.001	2.771	<0.001	2.832	<0.001	2.951	<0.001	3.419
+	835.532	3.8	PI34:2	<0.001	4.787	0.001	4.039	<0.001	4.483	<0.001	5.011
+	836.545	3.8	PS40:6	<0.001	1.672	<0.001	1.378	<0.001	1.592	<0.001	1.539
+	836.618	4.1	PC40:5	<0.001	2.173	<0.001	2.186	<0.001	2.266	<0.001	2.642
+	837.548	3.8	PI34:1	<0.001	1.681	<0.001	1.399	<0.001	1.596	<0.001	1.558
+	838.56	3.8	PS40:5	<0.001	1.688	<0.001	1.509	<0.001	1.809	<0.001	1.514
+	838.633	4.1	PC40:4	<0.001	1.616	<0.001	1.699	<0.001	1.716	<0.001	1.840
+	839.564	3.8	PI34:0	<0.001	1.706	<0.001	1.517	<0.001	1.818	<0.001	1.511
+	854.57	4.1	PC42:10	<0.001	5.291	<0.001	4.990	<0.001	5.299	<0.001	5.897
+	856.586	4.1	PC42:9	<0.001	3.356	<0.001	3.097	<0.001	3.357	<0.001	3.836

DM	m/z	RT	Name	CpG P	CpG FC	C11aP	C11a FC	C12bP	C12bFC	C19oP	C19oFC
+	858.529	3.7	PS42:9	<0.001	3.718	<0.001	3.407	<0.001	3.622	<0.001	3.926
+	858.602	4.1	PC42:8	<0.001	2.970	<0.001	2.576	<0.001	2.586	<0.001	3.255
+	859.533	3.7	PI36:4	<0.001	4.644	<0.001	4.365	<0.001	4.614	<0.001	4.905
+	860.617	4.1	PC42:7	0.003	10.334	<0.001	11.496	0.004	10.441	<0.001	14.38
+	861.548	3.7	PI36:3	<0.001	1.677	<0.001	1.435	<0.001	1.342	<0.001	1.771
+	862.633	4.1	PC42:6	<0.001	15.191	<0.001	15.307	0.001	15.987	<0.001	17.281
+	880.587	4.1	PC44:11	<0.001	18.598	0.007	14.153	0.008	16.079	<0.001	19.838
+	882.602	4.1	PC44:10	<0.001	10.910	<0.001	9.402	<0.001	10.557	<0.001	11.836
+	884.617	4.1	PC44:9	<0.001	9.615	<0.001	8.051	<0.001	7.936	<0.001	10.571
+	885.548	3.7	PI 38:5	<0.001	2.817	<0.001	3.178	<0.001	3.174	<0.001	3.049
+	886.633	4.1	PC 44:8	0.001	10.089	0.003	7.746	0.01	9.098	0.010	9.265
+	887.564	3.7	PI 38:4	<0.001	1.795	<0.001	1.884	<0.001	1.852	<0.001	1.934
+	889.579	3.7	PI 38:3	<0.001	1.433	<0.001	1.408	<0.001	1.299	<0.001	1.554

Table 4.2: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in CpG treated macrophages relative to unlabeled metabolite after 4h.

	M1	M2	M3	M4	CpG1	CpG2	CpG3	C11a1	C11a2	C11a3	C12b1	C12b2	C12b3	C19o1	C19o2	C19o3
^{13}Clac/lac	10.3	11.1	10.2	8.6	38.0	37.4	22.4	20.9	23.8	16.9	32.1	21.9	27.9	35.9	28.4	29.5
^{13}CItacon/itacon	1.6	0.7	0.4	0.9	4.4	4.8	1.8	4.1	6.2	2.6	5.1	6.0	7.0	5.7	7.3	7.1
^{13}Cmal/mal	0.6	1.5	0.6	1.2	6.6	5.4	3.8	3.8	4.0	1.5	6.8	7.7	8.3	4.1	7.2	7.8
^{13}Ccit/cit	2.5	3.1	1.7	2.4	8.5	5.9	6.2	5.8	6.0	3.1	5.6	6.1	11.1	6.2	3.9	7.2

Table 4.3: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in CpG treated macrophages relative to unlabeled metabolite after 8h.

	M1	M2	M3	M4	CpG1	CpG2	CpG3	C11a1	C11a2	C11a3	C11a4	C12b1	C12b2	C19o1	C19o2	C19o3	C19o4
^{13}Clac/lac	10.1	10.6	9.9	9.8	28.1	30.1	27.1	28.0	27.7	26.7	28.2	29.1	31.3	35.6	37.1	41.2	40.9
^{13}CItacon/itacon	0.5	1.0	0.5	0.8	6.8	6.7	6.5	7.0	6.2	6.1	6.8	8.7	9.7	9.6	9.1	10.0	9.1
^{13}Cmal/mal	0.6	0.6	0.9	0.8	5.9	6.1	4.6	6.7	5.6	6.5	3.8	8.8	8.8	5.5	7.6	6.3	5.2
^{13}Ccit/cit	2.0	2.6	2.1	2.7	4.9	4.2	4.2	7.8	7.9	8.0	7.0	9.6	8.9	7.8	7.8	8.4	8.9

Table 4.4: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in CpG treated macrophages relative to unlabeled metabolite after 24 h.

	M1	M2	M3	M4	CpG1	CpG2	CpG3	CpG4	C11a1	C11a2	C11a3	C11a4	C12b1	C12b2	C12b3	C12b4	C19o1	C19o2	C19o3	C19o4
^{13}Clac/lac	10.4	7.7	9.2	7.6	52.5	49.2	56.6	41.3	38.0	29.9	34.8	35.8	43.8	41.1	31.9	41.5	53.5	48.6	50.5	53.5
^{13}CItacon/itacon	1.2	0.0	0.0	0.0	11.8	12.0	12.4	13.7	7.3	11.6	11.6	10.5	12.5	12.1	10.4	10.8	13.2	12.6	11.6	11.9
^{13}Cmal/mal	0.0	0.0	0.0	0.0	7.6	7.1	7.5	7.6	7.9	7.4	3.0	5.3	5.5	5.7	6.5	6.5	4.5	8.3	7.2	8.1
^{13}Ccit/cit	1.6	0.4	1.1	1.2	13.5	14.2	14.1	14.0	11.0	14.2	11.7	12.1	17.6	18.4	17.2	17.7	12.4	13.6	11.2	12.5

4.3 Discussion

The main effects of 11a and 12b on CpG-activated macrophages were found to be in downregulating the creatine pathway and upregulating the glutathione biosynthesis pathway. Down regulation of the creatine pathway was observed even at the outset in the macrophages treated with SMAs alone. Thus, the SMAs may be decreasing the amount of energy produced by oxidative phosphorylation without targeting the TCA cycle directly as explained below. As the metabolomics experiments were carried out they suggested various biological experiments to underpin the metabolomics observations. These are described in chapter 7 but since they are directly relevant to the metabolomics data the discussion below draws on them to support the hypotheses arising from the metabolomics data.

The uptake of creatine by macrophages is rapid and it has been proposed the macrophages have a high requirement for creatine in order to form creatine phosphate which is required for phagocytosis (Loike et al., 1986). A previous study measured creatine uptake in macrophages using a medium that substituted Na^+ buffer with choline chloride buffer, demonstrating the Na^+ dependence of creatine uptake. Creatine is generally synthesised by the liver rather than the tissues that utilise it so has to be taken up from the blood stream. The creatine transporter has similar homology to the transporters for various neurotransmitters and for taurine (Snow and Murphy, 2001). Inhibitors of creatine transport include guanidino propionate, which has a strongly inhibitory effect, guanidino butyrate and arginine (Moller and Hamprecht, 1989). Taurine has a weakly inhibitory effect suggesting some commonality between the transporter for creatine and the transporter for taurine. The SMAs have some similarities to the structure of taurine and might thus affect creatine transport in this way. The immunosuppressant molecule cyclosporin

A has been found to alter the availability of the creatine transporter and thus have an effect on creatine uptake (Tran et al., 2000) .

Given that creatine tends to be formed in the liver it is likely that uptake of creatine is being affected by the SMAs rather than its biosynthesis. Guanidino acetate can be used to biosynthesise creatine but it is not clear if macrophages have the ability to undertake the single biosynthetic step required for converting guanidino acetate to creatine. However, guanidino acetate levels are lower in the SMA-treated macrophages and this could be either due to decreased uptake or increased biosynthesis of creatine from guanidino acetate within the cells to compensate for reduced uptake of creatine. The major role of creatine is in the transport of high energy phosphate from mitochondria to the cytosol. Creatine does this indirectly through accepting a phosphate group from ATP in mitochondrial intermembrane space in order to continually regenerate ADP which is then converted once again to ATP by the mitochondrion (Guimbal and Kilimann, 1993, Wyss and Kaddurah-Daouk, 2000) . The phosphocreatine molecule has a diffusion rate about 3X that of ATP so it can rapidly export phosphate to wherever regeneration of ATP from ADP is required (Brown, 1992, Jacobus, 1985) . In addition, creatine has a diffusion rate around 3 orders of magnitude higher than that of ADP so that supplies can move rapidly to maintain the ADP/ATP ratio if the rate of ATP production by the mitochondria is increased (Jacobus, 1985). Previous work has suggested that the TCA cycle is disrupted during the inflammatory response in macrophages and there is a switch towards anaerobic glycolysis (O'Neill, 2015). However, in the current work it would appear that all the intermediates in the TCA cycle are elevated and that there is an increase in NADH levels compared with the control. The NADH/NAD+ ratio is not greatly changed in the treated versus control cells and is between 35 and 50. It has

been estimated that the NADH/NAD+ ratio in the cytosol is between 300 and 700 while the ratio in mitochondria is around 7 (Williamson et al., 1967). Thus, it would seem that the increased levels of NADH originate from mitochondria and thus from the TCA cycle rather than glycolysis because the ratio of < 50:1 NADH/NAD+ is well below >300:1 ratio available from glycolysis. Glycolysis can produce two moles of NADH for each molecule of glucose reaching the TCA cycle assuming that some of the NADH is not consumed in the production of lactate. The TCA cycle produces 6 moles of NADH and 2 moles of $FADH_2$ for each molecule of glucose consumed and each mole of NADH yields 3 moles of ATP (2 from $FADH_2$). Thus, energy generation from the TCA cycle is much more efficient than from glycolysis. In order to determine the flux through the TCA cycle and glycolysis $^{13}C_6$-glucose labelling was used. The first thing which was obvious was that much of the label accumulated in lactate and all the CpG treatments produced labelled lactate at about 20-30% of the unlabelled lactate in comparison to around 10% incorporation for the control. This indicated that glycolysis was indeed increased by the treatments. Labelling at the $^{13}C_2$ level was also observed in itaconate, citrate and malate (table 4.2). The labelling for citrate was around 6-10% for the CpG control and in the SMA treated cells thus lower than in lactate but given that ATP production is higher from the TCA cycle this still indicates appreciable energy generation from this source. There was no strong evidence for a disrupted TCA cycle as judged from the labelling with malate which incorporated around 6% of label in comparison to around 1% in the control. Malate is almost at the end of a complete cycle so the label has passed the reported break in the cycle at succinate (O'Neill, 2015). In addition, the generation of large amounts of labelled lactate suggests much of the NADH derived from glycolysis is being used to form lactate. Thus, it is reasonable to assume that most of the additional NADH in the cells is formed by the TCA cycle and that thus, creatine is required for export of the high energy phosphate, generated from NADH, from the mitochondria in the form of

phosphocreatine. Motility and phagocytosis consume a lot of ATP and are thus dependent of phosphocreatine to maintain ATP supplies. The behaviour of macrophages could be considered to be analogous to that of other high energy cells such as muscle cells. The depletion of phosphocreatine (PCr) and ATP is linked to the high levels of IMP formation in muscle cells (Dobson and Hochachka, 1987) which occurs when the regeneration rate for ATP falls below requirement and some of the "endogenous pool" of ATP in muscle cells is consumed and this can lead to some of the ATP pool entering the oxypurine cycle via formation of IMP from AMP (L Ipata and Balestri, 2014) . From table 4.1 it can be seen that the SMAs deplete PCr and this is associated with increased production of IMP. This is also true for the CpG alone but in this data set the IMP levels are higher for the SMA treated samples. This suggests a fall in the supply of phosphocreatine resulting in some AMP being lost to the oxypurine cycle. Overall the ATP pool levels in the cells treated with SMAs are similar to those treated with CpG alone so the effect of the SMAs is not on ATP levels *per se* but rather on the rate of supply to ATP to where it is needed. A biological observation supporting the effect of reduced rate of supply to ATP where it is required is the effect of the SMAs in reducing macrophage motility (chapter 7).

A secondary effect of the SMAs on the macrophages was in upregulation of metabolites indicative of oxidative stress in the cells. As can be seen, pre-treating BMMs with 11a and 12b but not 19o, the negative control, upregulates metabolites involved in glutathione production resulting in significant increase in glutathione biosynthesis by SMA pre-treatment in comparison to treatment with CpG alone. Gamma-L-Glutamyl-L-cysteine, a glutathione precursor, was the most increased metabolite in this pathway when the cells were pre-treated with 11a and 12b but not 19o. This is possibly due to its role in as an intermediate in glutathione production.

However, additional functions of γ-glutamylcysteine have been reported (Sullivan et al., 2013, Quintana-Cabrera and Bolanos, 2013). A study by Quintana et.al reported that mitochondrial γ-glutamylcysteine was shown to be sufficient to respond to oxidative stress irrespective of the cytosolic glutathione concentration (Quintana-Cabrera and Bolanos, 2013). Specifically, γ-glutamylcysteine was shown to be an enzymatic cofactor for glutathione peroxidase 1, and this system was able to control mitochondrial H_2O_2 concentrations to limit cellular damage. However, it is unclear how γ-glutamylcysteine is partitioned between detoxification and glutathione synthesis pathways and how oxidized γ-glutamylcysteine is reduced, as this process is not likely to be mediated by glutathione reductase. GSH, GSSG and γ-glutamylcysteine upregulation was reported to be linked to increasing expression of the Nrf2/ARE/HO-1 pathway and endogenous antioxidants (Gupta et al., 2012). Interstingly SMA12b has been previously linked to increased activity of the Nrf2/ARE/HO-1 anti-oxidant pathway (Suckling et al., 2018).The effects of the SMAs in increasing oxidative stress might stem from their effect on creatine uptake with the consequent effect on ATP transport out of the mitochondria. A major source of oxidative stress arises from ROS species escaping from the mitochondria and this depends on mitochondrial permeability. In chapter 7 the polarisation of the mitochondrial membrane was explored by using dye staining and it was apparent that treatment with the SMAs decreased the polarisation of the mitochondrial membrane in comparison with LPS treatment alone suggesting that the mitochondrial membrane might be more permeable (as will be discussed in chapter 5, the effects of LPS are similar but not identical to those of CpG). A reduction in membrane potential reduces the ability of mitochondria to generate ATP (Zoratti and Szabò, 1995, Hüttemann et al., 2008). ADP is a major inhibitor of mitochondrial membrane permeability and the increased permeability of the mitochondria fits with the hypothesis that lowered availability of creatine results in lower levels of ADP. The Biolog microarray data are

difficult to explain since CpG-treated macrophages produce much greater reduction of the tetrazolium dye with most of the carbon sources in comparison with cells treated with CpG + SMAs. However, considering that tetraethyl rhodamine methyl, used to test mitochondrial permeability, is not strongly retained in the mitochondria of LPS/SMA-treated macrophages it might be that the tetrazolium dye used in the Biolog assay is not strongly localised in the mitochondria of LPS/SMA-treated macrophages. This would result in less efficient reduction of the dye since it largely depends on NADH (Berridge et al., 2005) and most of the NADH is localised in the mitochondria. Thus the Biolog assay may be largely measuring the degree of mitochondrial polarisation with high values being returned where the mitochondria are highly polarized and the cationic tetrazolium dye becomes localised within the mitochondria.

The SMAs did not change the enhanced glycolysis rate resulting from CpG activation as this is indicated by the similarity in the lactate production between CpG and the CpG + SMA incubations. Lactate being a marker for the glycolytic rate exceeding the TCA cycle rate. This is also supported by the incorporation of the ^{13}C-label into lactate which is higher than control for both CpG ad CpG+ SMA treatments. While there are differences in the label incorporation between individual runs the variability makes it difficult to be confident that the SMAs are affecting incorporation of the label into lactate. It is clear that the rate of incorporation of label in all treated cells is about 4 x that of the control, but the rate of increase of incorporation of the label after the first 4 hours in slow and assuming that a steady state would be indicated by equal amounts of labelled/unlabeled lactate there is still some way to go at 24 h for the pool of unlabeled glucose in the cells to be replaced by labelled glucose.

CpG activation increases ribose 5-phosphate production and sedoheptulose 7-phosphate production greatly in comparison with controls and the pentose phosphate

pathway enters the biosynthetic pathway for nucleotides in the form of phosphoribosylglycinamide which is also hugely elevated. This is in line with the increased demand for high energy phosphates such as UTP, CTP and ATP. A side effect of enhanced flux through the pentose phosphate pathway is increased production of NADPH which is required to combat oxidative stress through reducing GSSG back to GSH. The SMAs have some effect on the pentose phosphate pathway but the increases in these metabolites are still high in the SMA+ CpG treated cells compared to control. A decrease in sedoheptulose 7-phosphate production could be the result of high expression of carbohydrate kinase-like protein (CARKL) which is known to be highly expressed in M2-like macrophages and suppressing it is a marker of M1-like macrophages (Haschemi et al., 2012). Even though the SMAs decreased production of ribose 5-phosphate and sedoheptulose 7-phosphate, this did not affect NADPH production.

Glycerol 3-phosphate phosphate is decreased by the SMA + CpG treatments in comparison to CpG treatment alone. This is possibly due to the SMAs affecting oxidative phosphorylation through decreasing production of glycerol 3-phosphate so less NADH that is formed by glycolysis in the cytosol will be shuttled via the glycerol 3-phosphate shuttle into the mitochondria in order to generate ATP through oxidative phosphorylation. This might occur via a feedback mechanism where the mitochondria in the SMA-treated cells are already overloaded with regard to their ability to export ATP back into the cytosol.

The TCA cycle in all treatments seemed be more activated than in the control as judged from the incorporation of the ^{13}C-label or from the levels of the intermediates in the TCA cycle, in particular malate. The levels of NADH were higher in all

treatments than in the control. Thus, the SMAs do not seem to control the TCA cycle directly through decreasing NADH production in comparison to CpG as CpG as well as the SMAs have both produced similar levels of NADH. Although, at 24 h the label incorporation into malate is on average lower with the 11a and 12 b treatments, with the level of label being so variable it is difficult to tell if this is significant. Once again, it should be highlighted that there is no strong evidence for a broken TCA cycle and it seems both glycolysis and the TCA cycle rates increase in response to CpG treatments although the increase in the glycolysis rate is faster than the increase in the rate of the TCA cycle.

SMA-treated cells revealed increased production of NG-Dimethyl-L-arginine in comparison to cells activated with CpG alone. NG, NG-Dimethyl-L-arginine (ADMA) is an endogenous inhibitor of nitric oxide synthase. The elevation of ADMA has been reported to be associated with reduced NO production (Vallance et al., 1992).

SMA-treatment slightly increased production of UDP, UDP –glucose and UDP-glucuronate and uridine diphosphate-N-acetyl-alpha-d-glucosamine (UDP-GlcNAc), a marker for M2 macrophages. GDP-mannose was also increased. GDP-mannose is produced by the catalysis of the reaction between mannose1-phosphate and GTP by GDP-mannose pyrophosphorylase (GDP-MP). UDP-GlcNAc production is required for the N-glycosylation of proteins, including mannose and lectin receptors to promote the function of M2-like macrophages (Jha et al., 2015b).

As can be seen in table 4.1 the CpG treatment changed the levels of a huge number of phospholipids in particular phosphatidylcholine-type lipids containing highly unsaturated long chain fatty acids. It would seem likely that these changes would be

associated with an increase in membrane fluidity. However, these changes were not significantly affected by the SMA treatments.

Altogether, CpG activation of macrophages induced a M1 like macrophage phenotype with an increased rate of glycolysis and increased levels of high energy phosphates. The CpG + SMA treated macrophages were metabolically similar in many respects. However, there were some differences and it was concluded that SMA-pre-treatment of CpG activated macrophages might act via inhibiting creatine uptake with a knock on effect on the export of ATP from the mitochondria into the cytosol. Reducing the availability of ATP at its site of action, via reducing phosphocreatine levels, might reduce M1 macrophage function without phenotyping the macrophages to M2.

Chapter 5

Metabolomic profiling of the effect of SMA pre-treatment in LPS- treated macrophages

5.1 introduction

Pathogens are recognized by pattern recognition receptors and are capable of inducing innate immunity (Medzhitov and Janeway, 2000, Akira et al., 2006). Innate activation can be triggered by lipopolysaccharide (LPS) which is an outer membrane component of Gram negative bacteria. LPS is used as potent activator of monocytes and macrophages and is recognised by TLR4 (Kayagaki et al., 2013) although recent evidence indicates that recognition can be through TLR4-independent mechanisms (Hagar et al., 2013). TLR4 activation induces MyD88 and MaL/Tirap (Toll-interleukin 1 receptor domain containing adaptor protein)-dependent pathways which cause pro-inflammatory changes, e.g., in cytokines (e.g. IFN-β, IL-12, TNF, IL-6, and IL-1β), chemokines (e.g. chemokine [C-C motif] ligand 2 CCL2, chemokine [C-X-C motif] ligand 10 [CXCL10], and CXCL11) and antigen presentation molecules, such as MHC members, co-stimulatory molecules, and antigen-processing peptidases. These profiles are controlled by nuclear factor of kappa light polypeptide gene enhancer (NF-κB), activator protein 1 (AP-1), IRFs, STAT1, and EGR (early growth response) family members, many of which participate in IFN responses (Hu and Ivashkiv, 2009).

LPS as well as IFN-γ and recently granulocyte macrophage colony-stimulating factor (GM-CSF) (Hansen et al., 2008) have been used to stimulate macrophages to yield an M1-like macrophage profile. LPS among other M1 stimulants is the best studied one in the immunological context (Martinez and Gordon, 2014) and recently in metabolomics.

The LPS metabolomic profile is mainly characterised by rapid activation of glycolysis (Kelly and O'Neill, 2015), a broken TCA cycle after citrate and after succinate (O'Neill, 2015), an elevated pentose phosphate pathway (Tannahill et al., 2013b) , as well as

upregulation of fatty acid biosynthesis (Posokhova et al., 2008, Feingold et al., 2012a). In their amino acid profile, M1 macrophages are known for their requirement for an adequate supply of glutamine, for directing arginine for nitric oxide production with formation of citrulline as a result, as well as stimulating tryptophan catabolism through the high expression of indoleamine‑2,3‑dioxygenase (IDO) and increasing production of kynurenine metabolites which are claimed to activate the aryl hydrocarbon receptor(AHR), which is a ligand-activated transcription factor (Bessede et al., 2014b).

Pre-treatment of LPS-activated macrophages by ES-62 SMAs 11a and 12b was found to down- regulate LPS-induced IL-6, IL-12 and IL-1β secretion significantly (Al-Riyami and Harnett, 2012, Al-Riyami et al., 2013a, Rzepecka et al., 2014b, Rodgers et al., 2015c) and thus the SMAs would be predicted to have effects on the LPS-induced metabolic profile. Through applying the exact conditions carried out previously for the cytokine studys this was investigated in the current project.

5.2 Results:

The SMA 19o was included as a negative control in this experiment since it does not exert immunomodulatory effects and thus most of the effects of interest are observed in treatment with 11a and 12b. Stimulating macrophages with *Salmonella* LPS upregulates several metabolic pathways in comparison to unstimulated ones. This can be characterised by increases in the production of metabolites involved in oxidative stress, taurine metabolism, ATP and high energy phosphates, carnitines and carnitine biosynthesis, purine and pyrimidine metabolism, amino sugar metabolism, arginine metabolism, glycolysis ,TCA cycle ,pentose phosphate pathway, creatine metabolism and phospholipid biosynthesis whereas the detected metabolites involved in fatty acid pathways are showing a variable pattern between increases in some and decreases in others as shown in Table 5.1. As discussed in the previous chapter, although there were some differences in the effects of the active SMAs the changes which are highlighted in the discussion are those where there are consistent effects for the two SMAs. 19o also had some strong effects on selected metabolites but is is presumed that these are off target.

In comparison, pre-treating BMMs with SMAs for 18 hours and then stimulating them with LPS for 24 hours changes the metabolome profile of LPS stimulated macrophages to some extent but many changes remain broadly the same as those for LPS stimulation alone. The main differences from LPS treatment alone involve further upregulation of glutathione biosynthesis, significant downregulation of creatine synthesis/uptake, increasing taurine uptake and a decrease in ATP and many high energy phosphate metabolites. To simplify discussion changes that were consistent with the effect of the two active SMAs and were > 1.5 or < 0.66-fold relative

to LPS treatment alone have been highlighted in red in table 5.1 for more detailed discussion.

Upregulation of the glutathione pathway is indicated with the high production of metabolites such as gamma-L-Glutamyl-L-cysteine, glutathione, S-glutathionyl-L-cysteine glutathione disulphide, prenyl-L-cysteine, S-allyl cysteine and glutamate. An increase in NADPH might indicate increased recycling of GSSG back to GSH.

Inhibiting creatine uptake is indicated by downregulation of the metabolites involved in the creatine pathway including guandinoacetate, creatine and phosphocreatine. It is likely that the macrophages are creatine-dependent thus need to take it up from the growth because within the body most creatine is produced in the liver. Thus, the lower levels in creatine and phosphocreatine in the SMA-treated macrophages might imply impaired uptake of creatine.

SMA pre-treatment decreases taurine uptake in comparison to LPS-activated macrophages. It is not clear whether or not the macrophages are taurine-dependent so this decrease might be due to decreased taurine uptake, there is some degree of homology between the taurine transporter protein and the creatine transporter (Snow and Murphy, 2001).

Other changes induced by SMA-pretreatment include a decrease in metabolites that are involved in the N/O-glycosylation of proteins such as UDP-glucose, UDP-glucuronate, UDP-N-acetyl-D-glucosamine, CMP-N-acetylneuraminate and N-acetylneuraminate. Some of this might be attributed to reduced availability of ATP which is required to make many other high energy phosphates. These metabolites

were slightly increased by the SMA plus CpG treatment thus the interaction between LPS and the SMAs is not entirely equivalent to the interaction with CpG.

The LPS appears to have a large impact on glycolysis with very large amounts of lactate accumulating even more than in the case of CpG treatment. However, there is no indication of the TCA cycle shutting down particularly with regards to the large amount of ketoglutarate accumulating. The SMAs exert a variable control in this experiment. The labelling with $^{13}C_6$-glucose again confirmed an increased rate of glycolysis was stimulated by LPS although the incorporation of the label appeared to be a bit lower than in the CpG treatment (tables 5.2-5.4). Itaconate, citrate and malate were also labelled but the label incorporation into malate and itaconate was not as high as in the CpG treatment. This might suggest that the LPS treatment does not stimulate glycolysis and TCA cycle metabolism to the same extent as the CpG treatment and that the onset of the effect of LPS is slower than that of CpG.

Table 5.1: The list of detected metabolites that have changed following LPS treatment, LPS+11a (L11a), 12b (L12b) and 19o (L19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, FC to fold change RT to raw retention time and P to p-value (n=5). Metabolites are highlighted in red where the change in level for one of more SMA treatments is both significant (P value <0.05) and has fold change >1.5 of <0.66 relative to CpG treatment alone for at least one of the active SMA treatments. All metabolites detected and listed in table 5.1 are from a single experiment with 5 independent replicates for each treatment. Tables 18 and 19 in the appendix shows the metabolite changes induced by a subsequent independent experiment.

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
Oxidative stress											
+	76.039	16.2	Glycine	0.004	0.728	0.219	0.874	0.051	0.845	0.017	0.746
+	148.060	15.1	L-Glutamate	<0.001	1.516	0.844	1.02	0.069	1.216	0.002	1.434
+	168.052	15.4	8-Hydroxyguanine	<0.001	2.447	<0.001	1.306	<0.001	1.843	<0.001	2.214
+	241.031	16.8	L-Cystine	<0.001	0.337	<0.001	0.412	<0.001	0.384	<0.001	0.284
+	251.070	14.4	gamma-L-Glutamyl-L-cysteine	<0.001	25.018	<0.001	268.791	<0.001	278.948	<0.001	24.759
+	162.058	5	S-Allyl cysteine	<0.001	11.537	<0.001	15.969	<0.001	11.234	<0.001	7.9
+	162.058	7.6	S-Allyl cysteine	<0.001	14.345	<0.001	16.333	0.001	13.933	<0.001	9.444
+	190.090	4.8	Prenyl-L-cysteine	<0.001	13.774	<0.001	17.459	<0.001	12.646	0.001	8.719
+	308.091	14.6	Glutathione	0.019	9.947	0.004	12.751	<0.001	9.599	<0.001	7.785
+	427.095	17.1	S-glutathionyl-L-cysteine	<0.001	2.206	<0.001	2.367	<0.001	1.912	<0.001	1.891
+	613.160	17.6	Glutathione disulfide	<0.001	7.954	<0.001	16.225	<0.001	11.787	<0.001	8.345
+	462.093	15	3-Phosphoglycerol-glutathione	<0.001	1.895	<0.001	0.814	0.664	0.967	<0.001	2.391
+	744.083	17.2	NADP+	<0.001	3.714	<0.001	2.273	<0.001	2.607	0.002	2.419
+	746.099	17.4	NADPH	<0.001	2.731	<0.001	2.298	<0.001	2.391	<0.001	2.405
Taurine metabolism				<0.001							
-	108.012	15.6	Hypotaurine	<0.001	5.266	<0.001	1.743	<0.001	3.562	<0.001	5.197
+	126.022	15.3	Taurine	<0.001	2.306	0.027	1.189	<0.001	1.837	<0.001	2.548
-	167.997	15.4	L-Cysteate	<0.001	2.824	0.001	1.27	<0.001	2.025	<0.001	2.32

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
Choline metabolism											
+	104.107	20.5	Choline	<0.001	0.656	0.043	0.793	0.01	0.773	0.005	0.645
+	184.075	14	Choline phosphate	0.001	2.526	0.862	0.948	0.212	1.428	0.002	3.119
ATP and high energy phosphates											
-	210.029	15.4	Phosphocreatine	<0.001	2.312	<0.001	0.506	0.311	0.906	<0.001	2.742
-	346.056	14.4	AMP	<0.001	2.564	<0.001	1.99	<0.001	1.843	<0.001	2.197
-	402.995	16.8	UDP	<0.001	7.794	<0.001	3.072	<0.001	4.932	<0.001	4.476
-	426.023	16.9	ADP	<0.001	3.51	<0.001	1.768	<0.001	1.755	<0.001	2.708
-	429.058	15.9	CMP-2-aminoethylphosphonate	<0.001	4.121	0.021	1.452	<0.001	2.481	<0.001	3.404
-	481.977	18.6	CTP	<0.001	3.964	0.022	1.224	<0.001	1.891	<0.001	2.293
-	482.961	18.3	UTP	<0.001	5.626	<0.001	1.557	<0.001	2.778	<0.001	3.792
+	508.003	16.7	ATP	<0.001	2.007	0.247	1.12	<0.001	1.888	<0.001	3.205
-	521.983	19.5	GTP	<0.001	3.552	<0.001	1.443	0.023	1.273	<0.001	2.183
-	565.048	16.8	UDP-glucose	<0.001	3.244	<0.001	1.571	<0.001	2.76	<0.001	2.892
-	579.027	19.3	UDP-glucuronate	<0.001	4.443	<0.001	3.266	<0.001	3.546	<0.001	3.674
-	606.074	15.6	UDP-N-acetyl-D-glucosamine	<0.001	2.747	<0.001	1.533	<0.001	1.989	<0.001	2.578
+	615.155	15.5	CMP-N-acetylneuraminate	<0.001	1.649	0.429	1.026	0.099	0.943	<0.001	1.564
Carnitines and carnitine biosynthesis											
+	146.118	14	4-Trimethylammoniobutanoate	0.017	1.236	<0.001	0.727	0.001	0.799	0.457	1.052
+	162.113	13.9	L-Carnitine	0.465	0.921	0.04	0.75	0.003	0.621	0.76	0.969
+	189.160	22.5	N6,N6,N6-Trimethyl-L-lysine	<0.001	0.624	0.096	0.809	0.012	0.805	<0.001	0.527
+	204.123	11.5	O-Acetylcarnitine	0.776	1.027	0.001	0.6	0.002	0.604	0.024	1.253
+	232.154	9.2	O-Butanoylcarnitine	0.013	1.396	0.619	1.063	0.91	0.986	0.052	1.267
+	248.149	11.9	Hydroxybutyrylcarnitine	<0.001	2.808	0.294	1.246	0.083	1.387	0.003	2.36
+	372.311	4.8	Tetradecanoylcarnitine	<0.001	2.137	0.855	0.986	0.073	1.209	<0.001	2.406
+	398.327	4.7	trans-Hexadec-2-enoylcarnitine	<0.001	2.755	<0.001	1.517	<0.001	2.454	<0.001	2.871
+	400.342	4.6	[FA] O-Palmitoyl-R-carnitine	<0.001	1.956	0.193	1.114	0.001	1.556	<0.001	2.104
+	414.357	4.6	Heptadecanoylcarnitine	<0.001	2.981	0.002	1.533	<0.001	2.043	<0.001	2.874

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	424.342	4.6	Linoelaidylcarnitine	<0.001	5.777	<0.001	2.329	<0.001	3.891	<0.001	6.097
+	426.358	4.6	Elaidiccarnitine	<0.001	2.139	0.068	1.174	<0.001	1.709	<0.001	2.301
+	428.373	4.5	Stearoylcarnitine	0.001	1.458	0.162	0.862	0.834	0.979	<0.001	1.587
+	286.201	4.5	2-Octenoylcarnitine	0.018	0.38	0.303	0.76	0.989	1.004	0.212	0.63
Purine and pyrimidine metabolism											
-	111.020	8.6	Uracil	0.001	9.953	0.158	4.668	0.145	5.678	<0.001	10.145
-	287.052	12.7	Orotidine	0.004	3.995	<0.001	1.263	<0.001	2.085	<0.001	4.077
-	110.036	29.9	Cytosine	0.002	3.753	0.132	2.844	0.048	3.812	0.174	2.569
+	168.052	15.3	3-Methylguanine	<0.001	2.469	0.914	1.016	0.002	1.959	<0.001	3.446
+	151.062	12.2	D-Ribose	0.009	0.557	0.174	0.836	0.027	0.803	0.004	0.59
+	258.110	15.1	5-Methylcytidine	<0.001	1.759	0.018	0.717	0.018	0.706	<0.001	2.026
-	243.062	10.2	Uridine	<0.001	0.29	0.204	0.873	<0.001	0.591	<0.001	0.366
-	285.049	17	5'-Phosphoribosylglycinamide	<0.001	#DIV/0!	#DIV/0!	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
+	183.053	16.6	1-Methyluric acid	0.03	1.783	0.252	0.789	0.412	1.154	0.074	1.543
Aminosugar metabolism											
+	180.087	15.3	D-Glucosamine	0.671	1.253	0.08	2.074	0.632	1.274	0.362	0.616
-	308.099	13.8	N-Acetylneuraminate	0.027	0.854	<0.001	0.512	<0.001	0.527	0.352	1.056
Arginine metabolism											
+	146.092	15.8	4-Guanidinobutanoate	0.008	1.109	0.074	0.91	0.059	0.936	0.072	1.142
+	174.087	15.2	5-Guanidino-2-oxopentanoate	0.035	0.721	0.619	0.935	0.474	0.948	0.093	0.778
+	174.087	15.8	5-Guanidino-2-oxopentanoate	0.003	0.436	0.016	0.594	0.278	0.771	0.017	0.403
+	175.119	26.5	L-Arginine	0.001	0.696	0.189	0.874	0.052	0.872	0.001	0.613
+	203.150	22.6	NG,NG-Dimethyl-L-arginine	0.517	1.087	0.406	0.892	0.07	0.754	0.378	0.879
+	247.140	14.7	N2-(D-1-Carboxyethyl)-L-arginine	0.85	0.977	0.899	1.015	0.564	0.923	0.357	1.127
+	133.097	24	L-Ornithine	0.005	1.17	0.013	1.145	0.025	1.103	0.019	1.185
Histidine metabolism											
-	137.036	17.4	Urocanate	0.287	4.996	0.343	3.343	0.415	0.784	0.103	9.923

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	141.066	9.9	Methylimidazoleacetic acid	0.495	1.126	0.508	0.877	0.219	0.771	0.848	0.963
+	141.066	10.8	Methylimidazoleacetic acid	0.176	1.135	0.192	0.871	0.965	0.993	0.039	1.207
+	156.077	15.2	L-Histidine	0.025	1.291	0.954	0.994	0.379	0.903	0.135	1.172
Glycolysis and TCA cycle and related metabolites											
-	89.024	9.4	(R)-Lactate	0.053	11.999	0.05	12.923	<0.001	21.037	<0.001	22.801
-	338.989	18.5	D-Fructose 1,6-bisphosphate	<0.001	13.216	0.001	4.388	<0.001	12.499	<0.001	15.492
-	213.017	15.2	2-Deoxy-D-ribose 5-phosphate	<0.001	12.532	0.021	2.583	<0.001	11.521	<0.001	9.028
-	115.004	16.4	Fumarate	0.665	1.049	0.192	0.879	0.607	1.047	0.956	1.006
+	168.066	8.3	Pyridoxal	0.001	0.627	0.654	0.944	0.03	0.782	0.009	0.625
-	145.014	15.7	2-Oxoglutarate	<0.001	29.664	<0.001	38.784	0.001	22.715	0.001	16.463
-	147.030	18.5	(R)-2-Hydroxyglutarate	0.583	0.784	0.839	0.923	0.413	1.279	0.329	0.667
-	171.007	15.1	sn-Glycerol 3-phosphate	<0.001	1.712	<0.001	0.754	<0.001	0.689	<0.001	1.671
-	179.056	17.4	D-Glucose	0.005	0.749	0.185	0.911	0.237	0.887	0.159	0.857
-	191.020	18.5	Citrate	0.018	0.851	0.284	0.915	0.655	1.025	0.013	0.779
+	170.081	8.4	Pyridoxine	0.001	0.624	0.128	0.824	0.014	0.775	0.003	0.587
+	664.117	14.6	NAD+	<0.001	1.41	<0.001	1.462	0.002	1.429	<0.001	1.732
+	666.132	13.9	NADH	0.004	1.927	0.032	1.369	0.034	1.497	0.004	1.924
+	196.083	10.3	2-Amino-2-deoxy-D-gluconate	<0.001	11.75	<0.001	3.175	<0.001	5.146	<0.001	7.383
Fatty acids											
-	303.233	3.9	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	<0.001	0.51	0.134	0.865	0.002	0.719	0.001	0.518
-	365.343	3.8	[FA (24:0)] 15Z-tetracosenoic acid	0.013	0.653	0.001	0.434	0.003	0.555	0.021	0.645
+	174.041	14.8	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.217	<0.001	1.28	<0.001	1.683	<0.001	1.942
Creatine metabolism											
+	76.039	16.2	Glycine	0.005	0.728	0.22	0.874	0.052	0.846	0.017	0.746
-	112.052	10.1	Creatinine	0.035	0.658	0.636	0.948	0.039	0.851	0.014	0.729
+	118.061	16.5	Guanidinoacetate	<0.001	1.856	<0.001	0.618	<0.001	0.758	<0.001	1.539
+	132.077	15.3	Creatine	<0.001	1.895	0.012	0.723	0.017	0.754	<0.001	1.988

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	133.097	24	L-Ornithine	0.005	1.17	0.013	1.145	0.025	1.103	0.019	1.185
+	175.119	26.5	L-Arginine	0.001	0.696	0.189	0.874	0.052	0.872	0.001	0.613
+	210.029	15.4	Phosphocreatine	<0.001	2.312	<0.001	0.506	0.311	0.906	<0.001	2.742
Miscellaneous											
+	90.055	15.4	L-Alanine	0.079	1.236	0.231	0.853	0.533	0.932	0.012	1.363
-	130.051	25.2	L-Glutamate 5-semialdehyde	0.002	3.803	0.515	1.191	0.068	2.392	0.09	2.511
-	142.026	16.4	Ethanolamine phosphate	<0.001	2.308	0.001	1.131	<0.001	1.401	<0.001	2.104
+	188.103	15.6	5-guanidino-3-methyl-2-oxo-pentanoate	<0.001	0.497	0.01	0.674	0.001	0.653	0.001	0.407
+	188.103	14.5	5-guanidino-3-methyl-2-oxo-pentanoate	0.644	0.871	0.917	1.024	0.496	1.124	0.792	0.941
+	130.050	10.6	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.042	1.299	0.776	1.037	0.352	0.899	0.832	0.976
+	133.061	15.9	L-Asparagine	0.006	1.616	0.01	1.5	0.069	1.347	0.169	1.296
+	166.053	13.9	L-Methionine S-oxide	0.004	0.634	0.135	0.788	0.051	0.787	0.004	0.504
+	161.129	24.5	N6-Methyl-L-lysine	0.005	1.308	0.032	0.793	0.201	0.881	<0.001	1.625
-	96.960	16.2	Sulfate	<0.001	0.708	0.001	0.76	0.01	0.823	0.001	0.611
+	216.063	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	1.56	<0.001	0.504	0.002	0.63	<0.001	1.875
+	276.155	17.6	L-a-glutamyl-L-Lysine	<0.001	0.729	<0.001	0.366	<0.001	0.441	0.001	0.777
+	298.097	7.6	5'-Methylthioadenosine	<0.001	3.502	<0.001	1.72	<0.001	3.997	<0.001	4.715
Phospholipids											
+	544.340	4.6	LysoPC 20:4	0.011	1.377	0.228	0.824	0.914	1.014	0.022	1.491
+	794.571	3.9	PE40:5	<0.001	26.405	0.007	9.188	<0.001	21.718	<0.001	25.819
+	746.606	4.1	PC34:0 ether	0.022	1.63	0.215	1.148	0.003	1.534	0.03	1.341
+	784.585	4	PC36:3	<0.001	2.239	<0.001	1.434	<0.001	2.282	<0.001	2.478
+	738.544	4	PC34:4 ether	0.006	0.822	0.165	0.897	0.001	0.827	0.005	0.875
+	764.559	4.1	PC36:5 ether	<0.001	0.44	0.839	0.971	0.019	0.637	0.307	0.874
+	860.617	4	PC42:7	<0.001	3.627	0.774	1.114	0.002	2.608	<0.001	4.04
+	858.602	4	PC42:8	<0.001	1.446	0.025	0.621	0.011	1.223	<0.001	1.771
+	856.586	4	PC42:9	0.002	1.319	0.005	0.622	0.012	1.155	<0.001	1.714

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	796.589	3.9	PE40:4	0.022	23.692	0.042	10.293	0.019	18.389	0.113	14.537
+	766.540	3.9	PE38:5	<0.001	5.835	0.004	1.924	<0.001	5.267	<0.001	6.117
+	774.544	3.9	PE40:7 ether	<0.001	1.39	0.56	0.923	<0.001	1.334	<0.001	1.653
+	891.595	3.6	PI38:2	<0.001	0.353	<0.001	0.299	<0.001	0.358	<0.001	0.444
+	889.579	3.6	PI38:3	<0.001	0.485	<0.001	0.347	<0.001	0.451	<0.001	0.579
+	838.560	3.7	PS40:5	0.038	1.414	0.64	0.958	0.067	1.185	0.026	1.282
+	808.513	3.8	PS40:6	<0.001	6.341	<0.001	2.867	<0.001	6.293	<0.001	6.216
-	883.534	3.7	PI38:5	<0.001	2.155	<0.001	1.395	<0.001	2.215	<0.001	2.555
-	764.563	4.4	PC36:4 ether	0.038	1.085	0.033	0.858	0.524	1.025	0.035	1.086
-	762.507	4	PE36:6	<0.001	8.52	<0.001	2.757	<0.001	5.753	<0.001	7.799
-	478.294	4.7	Lyso PE18:0	<0.001	2.109	0.001	1.695	<0.001	1.837	<0.001	2.431
-	766.540	3.9	PE38:4	<0.001	1.718	0.599	1.039	<0.001	1.372	<0.001	1.798
-	790.539	3.9	PE38:6	0.001	8.138	0.004	3.538	0.003	4.296	<0.001	10.757
-	774.545	3.9	PE38:7	0.002	1.75	<0.001	1.61	<0.001	1.921	<0.001	1.82
-	500.279	4.6	Lyso PE20:4	<0.001	4.447	<0.001	2.896	<0.001	2.167	<0.001	4.155
-	747.517	3.7	PG34:1	<0.001	1.73	<0.001	1.581	<0.001	1.684	<0.001	1.773
-	821.534	3.6	PG38:6	0.048	0.869	<0.001	0.682	0.833	1.017	0.255	1.073
-	773.533	3.7	PG36:2	0.005	2.413	0.04	2.146	<0.001	4.089	<0.001	4.008
-	885.549	3.7	PI38:4	<0.001	1.421	0.004	1.347	<0.001	1.407	<0.001	1.441
-	760.513	3.8	PS34:1	0.005	2.388	0.075	1.392	0.001	2.068	0.009	1.821
-	804.576	4.1	PS40:0	0.043	2.586	0.599	1.205	0.105	2.892	0.117	2.344
-	834.529	3.7	PS40:6	0.004	1.92	0.165	1.17	0.008	1.458	0.001	1.755
-	786.529	3.7	PS36:2	0.007	2.095	0.055	1.331	<0.001	1.754	0.002	1.854
-	782.497	3.7	PS36:4	<0.001	4.072	0.001	2.459	<0.001	4.429	<0.001	4.463
-	616.471	4.3	SP16:0	0.009	3.902	0.027	2.416	0.345	1.504	0.057	2.842
+	732.554	4.1	PC32:1	<0.001	2.019	<0.001	1.449	<0.001	2.209	<0.001	2.171
+	730.539	4.1	PC32:2	<0.001	2.699	<0.001	1.5	<0.001	2.716	<0.001	3.58
+	728.523	4.1	PC32:3	0.002	3.023	0.561	0.759	0.152	2.428	0.006	9.174

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	754.540	4.1	PC34:4	<0.001	5.726	0.179	1.807	<0.001	4.995	<0.001	7.34
+	482.324	4.6	Lyso PE 18:0	0.007	1.456	0.327	0.902	0.777	1.03	0.011	1.38
+	706.539	4.1	PC30:0	<0.001	3.308	<0.001	1.984	<0.001	2.928	<0.001	3.156
+	720.554	4.1	PE34:0	0.004	2.518	0.002	1.648	<0.001	2.209	0.002	1.92
+	760.586	4.1	PC34:1	<0.001	2.605	<0.001	1.682	<0.001	2.446	<0.001	2.357
+	758.570	4.1	PC34:2	<0.001	2.505	<0.001	1.721	<0.001	2.73	<0.001	2.812
+	756.555	4.1	PC34:3	<0.001	2.749	0.075	1.356	<0.001	2.981	<0.001	3.462
+	782.570	4	PC36:4	<0.001	1.522	0.001	1.2	<0.001	1.514	<0.001	1.775
+	806.570	4	PC38:6	<0.001	1.507	0.415	1.041	<0.001	1.428	<0.001	1.742
+	780.554	4.1	PC36:5	<0.001	1.589	0.424	1.037	<0.001	1.693	<0.001	1.98
+	838.633	4	PC40:4	0.021	1.439	0.051	1.205	0.033	1.295	0.004	1.342
+	836.617	4	PC38:5	0.002	1.474	0.059	1.163	0.01	1.291	<0.001	1.481
+	508.376	4.7	Lyso PC18:1	0.005	0.702	0.002	0.63	0.005	0.693	0.01	0.502
+	772.621	4	PC36:1 ether	0.001	2.106	0.316	1.36	<0.001	2.637	0.014	2.006
+	786.602	4	PC36:2	<0.001	2.594	<0.001	1.702	<0.001	2.657	<0.001	2.798
+	810.601	4	PC38:4	0.021	1.242	0.863	1.01	0.374	1.063	0.001	1.298
+	808.586	4	PC38:5	<0.001	1.781	0.001	1.227	<0.001	1.703	<0.001	2.064
+	834.601	4	PC40:6	0.001	1.561	0.095	1.143	0.002	1.358	<0.001	1.608
+	832.586	4	PC40:7	<0.001	1.692	0.03	1.123	<0.001	1.661	<0.001	2.033
+	778.538	4	PC36:6	0.001	3.861	0.004	0.396	0.084	2.138	<0.001	5.98
+	862.633	3.9	PC42:6	<0.001	3.711	0.495	1.447	0.005	2.63	<0.001	4.46
+	454.293	4.7	Lyso PE16:0	<0.001	2.408	0.649	0.961	<0.001	1.86	<0.001	2.502
+	718.539	4.1	PE34:1	<0.001	4.486	<0.001	2.525	<0.001	4.152	<0.001	3.953
+	740.523	4	PE36:4	<0.001	3.662	0.141	1.59	<0.001	3.586	<0.001	3.836
+	774.601	4	PE38:1	0.003	2.211	0.004	1.438	<0.001	1.844	<0.001	1.888
+	764.523	4	PE36:6	<0.001	7.776	0.032	2.454	<0.001	5.943	<0.001	7.925
+	748.528	3.9	PE38:7	0.001	1.537	0.077	1.12	0.001	1.326	<0.001	1.682
+	480.308	4.6	Lyso PE18:0	<0.001	2.516	0.185	1.215	0.004	1.633	0.001	2.48

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L11a FC	L 12b P	L 12b FC	L 19o P	L19o FC
+	744.555	4.1	PE36:2	<0.001	7.698	0.031	2.929	<0.001	7.267	<0.001	7.492
+	772.586	4	PE38:2	<0.001	2.636	0.002	1.598	<0.001	2.812	<0.001	2.828
+	768.555	4	PE38:4	0.002	2.193	0.025	1.284	<0.001	1.711	<0.001	1.932
+	792.554	3.9	PE40:6	0.001	2.842	0.003	1.375	<0.001	1.951	<0.001	2.69
+	776.560	3.9	PE40:7	0.027	1.438	0.475	1.123	0.005	1.369	0.015	1.336
+	800.617	4	PE40:2	<0.001	9.797	0.067	3.166	0.025	4.614	<0.001	7.967
+	502.292	4.6	Lyso PE20:4	<0.001	3.063	0.623	1.085	0.001	1.856	0.001	3.278
+	766.560	3.7	PG34:0	0.004	2.156	<0.001	1.927	<0.001	2.119	<0.001	1.865
+	749.532	3.9	PG34:1	0.001	1.613	0.06	1.139	<0.001	1.417	<0.001	1.75
+	811.531	3.8	PI32:0	<0.001	2.836	0.826	1.045	<0.001	2.476	0.002	2.37
+	863.564	3.6	PI 36:0	<0.001	0.538	<0.001	0.357	<0.001	0.523	<0.001	0.594
+	762.528	3.8	PS34:1	0.008	2.333	0.036	1.438	0.001	1.962	0.007	1.712
+	788.544	3.8	PS36:2	0.008	1.881	0.353	1.133	0.003	1.566	0.008	1.581
+	784.512	3.8	PS36:4	<0.001	2.842	0.247	1.211	<0.001	2.692	<0.001	2.877
+	300.290	7.5	[SP] 3-dehydrosphinganine	<0.001	0.46	<0.001	0.333	<0.001	0.454	<0.001	0.562

Table 5.2: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in LPS stimulated macrophages at 4h.

	M1	M2	M3	M4	LPS1	LPS2	LPS3	LPS4	L11a1	L11a2	L11a3	L11a4	L12b1	L12b2	L12b3	L12b4	L19o1	L19o2	L19o3	L19o4
13lac/lac	10.3	11.1	10.2	8.6	31.7	27.5	25.7	26.8	21.2	28.4	24.4	23.8	30.6	32.2	26.1	18.9	36.5	27.1	35.8	27.2
13Itacon/itacon	1.6	0.7	0.4	0.9	6.1	4.8	5.1	5.5	6.1	5.5	5.8	5.7	7.2	8.6	8.5	2.9	5.8	6.8	6.1	5.9
13mal/mal	0.6	1.5	0.6	1.2	5.0	3.6	1.7	5.5	2.1	4.1	2.1	5.6	5.5	7.5	6.4	5.4	4.8	3.0	5.2	5.6
13cit/cit	2.5	3.1	1.7	2.4	5.0	6.0	5.6	7.4	5.2	5.1	4.8	5.9	8.4	10.8	5.7	6.8	6.0	4.8	5.5	5.9

Table 5.3: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in LPS stimulated macrophages second run 8 h incubation.

	M1	M2	M3	M4	LPS1	LPS2	LPS3	LPS4	L11a1	L11a2	L11a3	L11a4	L12b1	L12b2	L12b3	L19o1	L19o2	L19o3	L19o4
13lac/lac	10.1	10.6	9.9	9.8	35.5	31.3	31.6	30.2	25.6	27.9	32.8	27.5	30.4	17.6	20.4	43.1	27.0	29.3	42.9
13Itacon/itacon	0.5	1.0	0.5	0.8	7.9	8.4	8.2	8.6	5.7	7.9	7.2	6.2	10.2	8.0	8.1	9.8	3.5	8.1	11.0
13mal/mal	0.6	0.6	0.9	0.8	8.9	9.1	8.4	9.1	2.4	5.5	7.0	5.9	10.5	8.9	8.3	7.9	3.7	8.6	8.5
13cit/cit	2.0	2.6	2.1	2.7	9.4	8.9	9.9	9.7	7.2	9.9	9.6	9.4	13.5	11.9	12.4	5.9	1.5	7.7	7.5

Table 5.5: % incorporation of label from $^{13}C_6$ glucose into $^{13}C_2$ citrate, $^{13}C_2$ itaconate $^{13}C_2$ malate and $^{13}C_3$ lactate in LPS stimulated macrophages at 24h.

	M1	M2	M3	M4	LPS1	LPS2	LPS3	L11a1	L11a2	L11a3	L12b1	L12b2	L12b3	L19o1	L19o2	L19o3	L19o4
13lac/lac	10.3	11.1	10.2	8.6	39.7	17.1	34.2	32.8	30.9	33.2	35.3	49.6	42.9	38.2	45.7	38.5	15.3
13Itacon/itacon	1.2	0.0	0.0	0.0	11.8	3.4	11.6	10.8	9.2	9.0	7.2	13.6	12.5	12.2	12.0	11.1	6.2
13mal/mal	0.0	0.0	0.0	0.0	4.9	0.0	4.3	5.2	2.3	3.3	5.0	9.3	9.0	3.3	6.8	5.0	2.8
13cit/cit	1.6	0.4	1.1	1.2	6.6	2.1	2.6	5.2	5.0	5.9	8.3	11.2	6.1	9.9	7.7	8.8	10.1

5.3 Discussion

Pre-treating macrophages with either SMA 11a or 12b prior to treatment with LPS, was found to affect the metabolic changes induced in macrophages by LPS with respect to various pathways. Their main effects were exerted in downregulating/decreasing creatine and creatine phosphate in comparison with LPS. They also decreased taurine levels in the cells and upregulated glutathione biosynthesis. All of these effects were observed in the metabolome of macrophages treated with SMAs alone (chapter 3). Similarly, pre-treating CpG- activated macrophages with 11a or 12b had the same effects on creatine uptake as well as in glutathione production whereas their effect on taurine levels was very slight in the case of CpG treatment (chapter 4). The interactions between the SMAs and CpG and LPS are thus similar but not identical and indeed the effect of LPS on the macrophage metabolism was not the same as that of CpG.

By decreasing creatine uptake in the face of LPS treatment, the effect of the SMAs again points towards the importance of creatine metabolism in their mechanism of action in that this limits an energy supply in the form of ATP to where it is required thus producing the anti-inflammatory effects of the SMAs as discussed in chapter 4. The most obvious consequence of the loss of energy supply is the reduced motility of the macrophages resulting from the SMA treatments (chapter 7) which might also be correlated to reduced phagocytosis if the appropriate biological measurement were made. The levels of NADH are similar for the LPS- and LPS+ SMA-treated cells, the glycolytic flux is similarly increased in the various treatment groups, although labelling suggests not to the same extent as in the CpG treatment. As discussed in chapter 4, creatine is required to maintain ADP levels by accepting a phosphate group from ATP. In the SMA-treated cells the ADP levels are lower, as well as the creatine phosphate levels, in comparison with LPS treatment alone. This fits the

working hypothesis better than the effects observed with CpG treatment where ADP levels were slightly raised by the SMA treatments. ADP is one of the main factors protecting the mitochondria from depolarisation and thus impaired ability to convert NADH to ATP. Increased mitochondrial permeability results in increased oxidative stress and this is evidenced by an increase in GSSH levels. GSSG itself has been shown to increase mitochondrial permeability (Zoratti and Szabò, 1995). It seems that mitochondrial function is impaired to a greater extent by LPS treatment than by CpG treatment and that the effects of the SMAs are greater in the case of the LPS treatment.

The second main effect on the metabolome of SMAs in the presence of LPS activation is in the upregulation of metabolites reported to be involved in protecting against oxidative stress in the cells (table 5.1). The most increased metabolite promoted by 11a and 12b is the glutathione precursor gamma-L-glutamyl- L-cysteine which has been reported to be important in replenishing glutathione production to protect cells from oxidative stress. Other important functions by γ-glutamylcysteine were explained in chapter 4.

SMAs, 11a and 12b but not 19o, decreased the levels of metabolites involved in taurine metabolism, namely hypotaurine, taurine and cysteate. This effect was observed when the macrophages were treated with SMAs alone (chapter 3) although it was less marked in the CpG-activated macrophages (chapter 4). The fact that several metabolites in the pathway are affected suggests the effect is more likely to be on taurine biosynthesis rather than uptake. Nevertheless, the diet is the main source of taurine (Ward et al., 2011), so it is not known if macrophages have the capability of making enough intracellular taurine from cysteine and methionine. It is possible that the higher requirement for glutathione biosynthesis in the SMA- treated

cells diverts cysteine away from the taurine pathway resulting in lower levels of taurine.

Both CpG and LPS stimulants used alone were found to upregulate taurine metabolism suggesting taurine metabolism alteration could correspond to M1 activation or an M1 metabolic profile. A study by Romio et al reported that macrophages activated by LPS or IFN-γ under hypertonic conditions activated taurine transport, thereby increasing its intracellular concentration (Romio et al., 2001). The same study indicated that the effects of LPS on taurine transport in macrophages is mediated by the interaction of LPS with TLR4, as indicated by the lack of response of TLR4-defective macrophages (Romio et al., 2001). However, the effects of LPS in increasing intracellular taurine levels in the current study are much lower than those of CpG. Besides being an osmolyte, taurine is reported to have other functions such as protecting cells from oxidative stress (Raschke et al., 1995, Schuller-Levis et al., 1995, Trachtman et al., 1994), modulating intracellular Ca^{2+} concentration (Bkaily et al., 1997), and affecting K^+ channel activity (Han et al., 1994). Ca^{2+} is one of the major factors affecting mitochondrial permeability with increased levels of Ca^{2+} strongly promoting mitochondrial depolarisation.

SMAs, 11a and 12b seem to affect glycolysis in comparison to LPS treatment alone which is indicated by higher production of lactate in LPS + SMA incubations. Although LPS treatment produces more lactate over the 42h incubation than the CpG treatment the ^{13}C label incorporation into lactate is consistently slightly lower in the LPS-treated cells at 4, 8 and 24h. This might suggest that LPS has a slower onset of action than CpG and that the acceleration of glycolytic flux is slower such that less of the label is incorporated. This is also supported by the lower incorporation of label into TCA cycle metabolites in the LPS treatments compared to the CpG treatments. In addition, 11a

and to some extent 12b, produced significant decreases in the production of D-Fructose-1,6-bisphosphate. However, glycolysis remains high in all the treatments including LPS and it seems that this is not indicative of the anti-inflammatory mechanism of the SMAs.

There is some indication that the TCA cycle is activated by LPS and with all the treatments. The main indication of this was hugely increased production of 2-oxoglutarate and a modest increase in NADH plus the labelling studies show a slow accumulation of label in malate up to 8 h. However, at 24 h the label in malate is lower possibly indicating less flux through the TCA cycle.

SMA treatment decreased the production of glycerol 3-phosphate by BMMs. This effect is also observed in SMAs +CpG treatment as well in treatment with the SMAs alone (chapter 3 and 4). Again, this suggests possibly less requirement for glycerol phosphate shuttle for transporting NADH equivalents to the mitochondria.

Many phospholipids were upregulated by LPS as expected (table 5.1) and 11a and 12b downregulated phospholipid levels in comparison with LPS treatment alone, thus revealing an opposing effect to LPS. However, LPS did not produce the same very large shifts in long chain highly unsaturated phospholipids that were observed to increase greatly with the CpG treatments. This again points to a marked difference in the CpG- vs the LPS-activated macrophages. The effects of the SMAs in reducing the concentrations of many phospholipids might be an indirect one since ATP is also required in the formation of phospholipid head groups and in the case of the SMA+LPS combination there is a reduction in ATP levels in contrast to the CpG+SMA combination where there is no marked effect on ATP levels.

SMAs decreased the levels of UDP, UDP –glucose and UDP-glucuronate and uridine diphosphate-N-acetyl-alpha-d-glucosamine (UDP-GlcNAc) in comparison with LPS treatment alone (table 5.1). Again, the lowered levels correlate with lowered levels of ATP which would result in lower lowers of activated phosphates such as UTP which are required to form the activated UDP sugar conjugates.

In conclusion, we cannot determine whether or not the SMA treatment is resulting in macrophages with the M1 or M2 phenotype due to the difference in metabolic responses of LPS- and CpG-activated macrophages compared to controls.

Chapter 6

Untargeted metabolomics profiling of macrophages following stimulation with LPS, interferon-γ and interleukin 4

6.1 Introduction

Macrophages play a critical role in immune responses. They have a number of different forms (histiocytes, Kupffer cells, alveolar macrophages, microglia, and others) (Kumar and Jack, 2006a) and play a very important role in antigen presentation, which activates T lymphocytes, as well as in the phagocytosis of parasites and microbes (Nathan, 2008a). Macrophages need to be either classically activated (M1) or alternatively activated (M2) in order to exert their physiological effects.

Differentiation into the classically activated form of macrophages requires two signals, a priming signal in the form of IFN-gamma (IFN-γ) and a stimulus signal such as bacterial LPS (Nacy and Meltzer, 1991). LPS firstly will be bound by soluble LBP and this is followed by binding to soluble or membrane bound CD14 receptor, which will present LPS to the LPS recognition complex, TLR4 and MD-2. LPS-containing pathogens and their components will be then taken up by phagocytosis and delivered to lysosomes where degradation enzymes are located. The processed antigens are then loaded onto MHC class II molecules and presented to T cells (Harding et al., 2003). This process will change the morphology and secretory profile of the T cell to attract neutrophils, immature dendritic cells, natural killer cells, and activated T cells. This is followed further by release of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α as well as production of NO after iNOS upregulation (Nacy, 1984, MacMicking et al., 1997b).

Contrary to the classical activation form, the differentiation to alternatively activated macrophages does not require any priming since adding IL-4 and/or IL-13 would provide sufficient stimulus (Stein et al., 1992b, Doherty et al., 1993). In a manner similar to M1 cells, M2 cells will present antigen to T cells, as an antigen/MHCII

complex which will be followed by changes in their cellular morphology and secretory pattern, mainly by upregulating the enzyme Arginase I which lowers the levels of arginine in the cell and thus lowers NO production and which is involved in proline and polyamine biosynthesis (Modolell et al., 1995, Hesse et al., 2001, Wynn, 2004). Both activation forms, M1 and M2, are needed to determine the function of the macrophages as bacteriocides as the M1 form or for wound repair as the M2 form.

Since the two activated forms possess different morphology and cytokine profiles as well as different functions, it would be logical for them to have different metabolomic profiles that support the energy demands required for their regulatory function. The classical and alternative metabolomics profiles of macrophages have been studied by different groups mainly using young C57BL/6 mice (Rodríguez-Prados et al., 2010a, Freemerman et al., 2014, Jha et al., 2015b, Fei et al., 2016, Kerrinnes et al., 2017, Sorgi et al., 2017, Serbulea et al., 2018).

For the aforementioned reasons, as well as to assess if pre-treatment with the SMAs would result in BMMs with possibly either form of activation, the metabolome of macrophages exposed to molecules that help drive M1 or M2 polarisation was investigated.

6.2 Results

As can be seen from table 6.1, treating macrophages with different activators for 24 h changes the macrophage metabolome in comparison to unstimulated macrophages. The treatment for 24 h is more in line with previous work on LPS activation whereas for the treatment with SMAs 42 h incubations were used. The most important differences between treatments involving LPS or IFNγ and IL4 are highlighted in red in table 6.1.

Stimulating macrophages with either LPS or IFN-γ or both, to produce a response indicative of the M 1 phenotype, mainly upregulated the production of 5'-phosphoribosylglycinamide, citrulline, N-(L-Arginino)succinate, 4-Methylene-L-glutamine, propanoyl phosphate, glyceraldehyde 3-phosphate and deoxycytidine. The same stimulants as well induced general upregulation of metabolites linked to taurine biosynthesis, ATP and high energy phosphate metabolites, C5-Branched dibasic acid metabolism, glycolysis, the pentose phosphate pathway and TCA cycle and creatine metabolism. The changes in some instances were not as marked as those observed with the 42 h treatment with LPS. For instance, the increases in ATP were not as marked as with the 42 h incubation, however in contrast, the impact of the 24 h incubation with LPS was similar to that obtained with the 42 h incubation and indeed even more marked for some glycolytic intermediates.

On the contrary, treating macrophages with IL-4, mainly upregulated the production of L-ornithine which is considered as a marker of M2 macrophage phenotype. IL-4 treatment also increased production of 5'-phosphoribosylglycinamide, even doubling the increase obtained by either LPS or IFNγ or both, and also increases metabolites involved in creatine metabolism.

IL-4 activation increases glycolysis significantly however it did not significantly change metabolites involved in ATP and high energy phosphate production,

carnitines and carnitine biosynthesis, aminosugar metabolism, C5-Branched dibasic acid metabolism, pentose phosphate and TCA cycle and showed a variation in data relating to fatty acid synthesis and phospholipids.

Moreover the co-stimulation of macrophages with both LPS and IL-4 induces, mainly, a similar pattern of changes to those obtained by LPS or IFN-γ or both showing upregulation of metabolites linked to taurine biosynthesis, ATP and high energy phosphate metabolites, C5-branched dibasic acid metabolism, glycolysis ,pentose phosphate pathway, TCA cycle and creatine metabolism. There was no marked effect on fatty acid and phospholipid metabolism pathways as observed for the CpG and LPS treatments for 42 h and this suggests that observation of these changes requires a longer incubation time. All the metabolites detected and listed in table 6.1 are consistent in pattern of change in at least 2/3 metabolomic runs (the majority of the changes occurred in 3 replicates) with 5/6 incubations in each run. The tables include the detection mode, mass to charge ratio, retention time, p-value (P) and fold change (F) which is calculated in comparison to unstimulated macrophages. The other two runs tables are listed in tables 24 and 25 in the appendix.

Table 6.1: The list of detected metabolites that have changed following stimulating untreated macrophages with different activators: LPS, IFN-γ, IL-4, LPS+IFN-γ and LPS+IL-4. DM refers to detection mood, m/z to mass to ratio, RT to raw retention time and P to p-value. All metabolites detected and listed in table 5.1 are from a single experiment with 5 independent replicates for each treatment. Tables 24 and 25 in the appendix shows the metabolite changes induced by a subsequent independent experiment. P = P value, F = fold change in comparison with control. The most important differences between IL4 treatment and the treatments involving LPS or IFNγ are highlighted in red.

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
Oxidative stress													
-	146.046	11.1	L-Glutamate	<0.001	2.600	<0.001	2.585	0.047	0.717	<0.001	1.917	<0.001	2.407
-	166.018	9.0	Homocysteinesulfinicacid	<0.001	2.674	<0.001	2.596	0.216	1.241	<0.001	3.501	<0.001	2.578
-	465.982	17.9	Deoxy CTP	<0.001	3.460	<0.001	4.352	0.002	3.154	<0.001	7.969	<0.001	5.340
+	746.099	17.5	NADPH	0.714	1.051	0.002	1.511	0.040	1.517	0.504	0.920	0.008	1.407
+	664.117	14.6	NAD+	0.001	1.466	<0.001	1.951	0.020	1.536	<0.001	1.705	<0.001	1.557
+	666.132	13.8	NADH	<0.001	3.004	<0.001	3.042	0.958	0.992	<0.001	3.251	<0.001	2.937
-	249.055	14.6	gamma-L-Glutamyl-L-cysteine	<0.001	2.029	<0.001	2.097	0.084	0.573	<0.001	10.061	0.001	2.750
Taurine metabolism													
-	108.012	15.7	Hypotaurine	<0.001	2.171	<0.001	2.107	0.007	1.831	<0.001	2.662	<0.001	2.350
+	110.027	15.6	Hypotaurine	<0.001	1.938	<0.001	1.908	0.008	1.627	<0.001	2.238	<0.001	2.120
+	168.044	16.3	Taurocyamine	<0.001	1.568	<0.001	1.527	0.148	1.264	<0.001	1.640	<0.001	1.719
-	166.029	16.3	Taurocyamine	0.097	1.431	0.001	1.501	0.049	1.413	<0.001	1.680	<0.001	1.762
-	253.05	16.0	5-L-Glutamyl-taurine	<0.001	4.711	<0.001	8.642	0.744	0.893	<0.001	4.307	<0.001	4.305
-	167.997	15.6	L-Cysteate	0.028	1.271	0.005	1.295	0.876	0.977	0.002	1.457	0.005	1.340
-	124.007	15.6	Taurine	0.010	1.251	0.001	1.278	0.923	0.987	0.002	1.355	0.001	1.320
+	126.022	15.6	Taurine	0.015	1.237	0.004	1.263	0.955	0.993	0.002	1.373	0.004	1.317
Choline metabolism													
+	184.073	15.6	Choline phosphate	0.956	1.006	0.001	1.473	0.069	1.465	0.002	0.633	<0.001	1.562
+	258.11	15.1	sn-glycero-3-Phosphocholine	<0.001	0.611	<0.001	0.665	<0.001	0.237	0.404	1.070	<0.001	0.458
-	256.096	15.1	sn-glycero-3-Phosphocholine	<0.001	0.559	<0.001	0.630	<0.001	0.173	0.143	1.166	<0.001	0.421

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
ATP and high energy phosphates													
-	445.053	16.8	CDP-ethanolamine	0.005	1.333	<0.001	1.789	0.124	1.305	<0.001	3.546	<0.001	2.061
+	447.068	16.8	CDP-ethanolamine	0.006	1.311	<0.001	1.751	0.077	1.323	<0.001	3.662	<0.001	2.010
-	426.022	16.9	ADP	0.057	1.209	0.016	1.260	0.277	0.842	0.059	1.207	0.788	1.028
-	426.022	16.9	ADP	0.057	1.209	0.016	1.260	0.277	0.842	0.059	1.207	0.788	1.028
+	523.998	19.7	GTP	0.089	1.182	0.074	1.195	0.653	0.933	0.176	1.163	0.311	1.141
+	508.003	16.9	ATP	0.063	1.181	0.032	1.217	0.335	0.874	0.064	1.200	0.769	1.030
-	505.988	16.9	ATP	0.065	1.175	0.020	1.226	0.271	0.856	0.088	1.165	0.863	1.018
-	481.977	18.8	CTP	0.757	1.033	0.002	1.455	0.169	1.255	<0.001	1.968	0.001	1.665
+	483.992	18.8	CTP	0.920	0.989	0.004	1.376	0.178	1.256	<0.001	1.809	0.006	1.462
-	323.029	15.5	UMP	0.857	0.957	0.062	0.650	0.199	1.252	<0.001	0.273	0.155	0.743
-	402.995	16.9	UDP	0.325	0.876	0.018	0.740	0.062	1.409	0.010	0.695	0.081	1.354
-	565.047	16.8	UDP-glucose	0.008	0.737	0.002	0.720	0.164	1.261	0.206	0.891	0.842	1.017
-	210.029	15.6	Phosphocreatine	0.001	1.443	<0.001	1.448	0.002	2.100	0.001	1.415	<0.001	2.319
+	212.043	15.6	Phosphocreatine	0.001	1.413	<0.001	1.425	0.002	2.082	0.002	1.371	<0.001	2.294
-	784.149	11.8	FAD	0.003	1.337	<0.001	1.491	0.950	0.991	0.001	1.560	0.006	1.340
-	535.037	16.7	UDP-D-xylose	0.108	1.399	<0.001	1.990	0.146	1.640	0.012	1.770	0.006	2.219
-	402.011	17.5	CDP	0.043	1.397	0.001	1.535	0.567	1.113	<0.001	2.427	0.004	2.085
+	348.07	14.1	AMP	0.010	1.364	0.002	1.443	0.033	0.683	0.204	0.862	0.318	0.907
-	346.056	14.1	AMP	0.006	1.441	0.001	1.531	0.032	0.686	0.268	0.874	0.669	0.961
-	442.017	18.4	GDP	<0.001	1.522	0.011	1.235	0.202	0.773	0.024	1.294	0.019	1.376
-	362.051	17.1	GMP	<0.001	1.708	0.000	1.930	0.071	0.770	0.012	1.321	0.037	1.208
-	588.075	18.0	GDP-L-fucose	<0.001	1.678	0.003	1.342	0.138	0.790	0.001	1.565	0.003	1.361
+	590.09	18.0	GDP-L-fucose	<0.001	1.637	0.005	1.315	0.159	0.803	0.001	1.510	0.003	1.351
+	428.037	15.5	ADP	<0.001	1.592	0.004	1.261	0.209	0.864	0.001	1.458	0.005	1.298
-	426.022	15.6	ADP	<0.001	1.640	0.001	1.327	0.421	0.909	<0.001	1.549	0.005	1.297
-	604.07	18.7	GDP-mannose	<0.001	2.071	<0.001	2.605	0.453	0.900	<0.001	3.679	0.394	1.174
+	251.07	14.6	gamma-L-Glutamyl-L-cysteine	<0.001	2.125	<0.001	2.202	0.748	0.942	<0.001	9.544	<0.001	2.874

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	429.058	15.8	CMP-2-aminoethylphosphonate	<0.001	2.389	<0.001	1.972	0.055	1.420	<0.001	1.649	<0.001	1.816
+	431.073	15.8	CMP-2-aminoethylphosphonate	<0.001	2.488	<0.001	2.043	0.030	1.510	<0.001	1.688	<0.001	1.874
-	572.08	13.1	GDP-3,6-dideoxy-D-galactose	<0.001	4.894	<0.001	5.168	0.939	1.018	<0.001	6.036	0.006	3.785
+	574.095	13.1	GDP-3,6-dideoxy-D-galactose	<0.001	4.762	<0.001	4.918	0.625	1.118	<0.001	5.678	0.002	3.490
Carnitines and carnitine biosynthesis													
+	162.112	13.9	L-Carnitine	<0.001	0.448	0.001	0.664	0.306	1.187	0.417	0.922	<0.001	0.565
+	204.123	11.6	O-Acetylcarnitine	<0.001	1.907	<0.001	1.760	0.131	1.314	0.037	0.789	<0.001	2.099
-	202.109	11.6	O-Acetylcarnitine	<0.001	1.794	<0.001	1.707	0.139	1.292	0.124	0.855	<0.001	1.978
Inositol phosphate metabolism													
-	333.059	16.6	sn-glycero-3-Phospho-1-inositol	<0.001	4.694	<0.001	3.092	0.002	2.140	<0.001	4.057	<0.001	3.261
Propanoate metabolism													
-	152.996	11.8	Propanoyl phosphate	<0.001	11.827	<0.001	7.023	0.696	1.147	<0.001	15.509	0.001	5.510
C5-Branched dibasic acid metabolism													
-	152.996	11.8	Propanoyl phosphate	<0.001	11.827	<0.001	7.023	0.696	1.147	<0.001	15.509	0.001	5.510
+	159.076	16.6	4-Methylene-L-glutamine	<0.001	9.083	<0.001	12.743	0.600	1.036	<0.001	79.755	<0.001	8.048
-	173.009	18.3	cis-Aconitate	<0.001	3.071	<0.001	1.776	0.303	1.155	0.778	0.937	<0.001	3.542
-	129.019	15.5	Itaconate	<0.001	2.136	<0.001	1.618	0.776	1.043	<0.001	0.357	<0.001	2.468
Purine and pyrimidine metabolism													
+	112.051	11.0	Cytosine	0.002	0.532	<0.001	0.442	<0.001	0.359	0.106	0.783	0.004	0.597
-	242.078	12.5	Cytidine	0.011	0.687	<0.001	0.416	<0.001	0.140	0.003	0.609	<0.001	0.424
+	228.098	11.0	Deoxycytidine	0.023	0.621	0.001	0.483	0.001	0.421	0.184	0.785	0.003	0.574
+	112.051	12.5	Cytosine	0.174	0.823	0.001	0.509	<0.001	0.217	0.042	0.705	0.001	0.514
+	244.093	12.5	Cytidine	0.054	0.764	<0.001	0.457	<0.001	0.131	0.017	0.679	<0.001	0.462
+	115.05	15.3	5,6-Dihydrouracil	<0.001	1.668	<0.001	1.427	0.001	2.176	<0.001	1.905	<0.001	2.425
-	243.062	10.4	Uridine	<0.001	0.106	<0.001	0.015	<0.001	0.037	<0.001	0.040	<0.001	0.075
-	267.073	11.4	Inosine	<0.001	2.469	0.001	0.361	<0.001	0.051	<0.001	5.189	0.197	1.240
+	129.066	15.4	5,6-Dihydrothymine	<0.001	2.601	<0.001	2.150	<0.001	2.718	<0.001	3.091	<0.001	3.377

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	331.046	15.2	2'-Deoxyinosine 5'-phosphate	0.031	2.792	0.021	2.346	0.001	7.457	0.947	1.025	0.005	3.752
-	465.982	17.9	Dctp	<0.001	3.460	<0.001	4.352	0.002	3.154	<0.001	7.969	<0.001	5.340
+	228.098	10.1	Deoxycytidine	<0.001	18.515	<0.001	14.408	0.002	2.866	<0.001	23.022	<0.001	17.459
-	285.049	17.0	5'-Phosphoribosylglycinamide	<0.001	185.899	<0.001	104.952	<0.001	314.982	<0.001	64.515	<0.001	334.259
+	287.064	17.0	5'-Phosphoribosylglycinamide	<0.001	105.701	<0.001	67.499	<0.001	190.202	<0.001	48.502	<0.001	193.545
-	226.083	11.1	Deoxycytidine	0.042	0.500	0.001	0.254	0.002	0.217	0.165	0.680	0.034	0.553
Aminosugar/glycan metabolism													
-	588.075	18.0	GDP-L-fucose	<0.001	1.678	0.003	1.342	0.138	0.790	0.001	1.565	0.003	1.361
+	590.09	18.0	GDP-L-fucose	<0.001	1.637	0.005	1.315	0.159	0.803	0.001	1.510	0.003	1.351
-	604.07	18.7	GDP-mannose	<0.001	2.071	<0.001	2.605	0.453	0.900	<0.001	3.679	0.394	1.174
-	178.072	11.9	D-Glucosamine	0.094	1.125	0.002	0.817	0.001	1.659	0.005	0.765	<0.001	1.545
+	310.113	13.8	N-Acetylneuraminate	0.217	1.113	<0.001	0.550	<0.001	0.424	0.979	1.002	<0.001	0.516
-	308.099	13.8	N-Acetylneuraminate	0.119	1.192	0.001	0.549	<0.001	0.412	0.729	1.041	0.001	0.574
-	324.094	14.9	N-Glycoloyl-neuraminate	0.669	1.037	0.001	0.650	0.104	0.792	0.004	0.707	0.003	0.723
Arginine metabolism													
+	133.0971	24.7	L-Ornithine	0.643	1.050	0.046	0.861	<0.001	10.716	0.191	0.810	<0.001	14.866
+	146.092	15.8	4-Guanidinobutanoate	<0.001	2.610	<0.001	5.134	0.002	2.209	<0.001	8.646	<0.001	3.804
+	291.13	17.3	N-(L-Arginino)succinate	<0.001	5.325	<0.001	4.130	0.362	0.857	<0.001	30.243	<0.001	6.346
-	289.115	17.3	N-(L-Arginino)succinate	<0.001	6.056	<0.001	4.901	0.813	0.951	<0.001	35.746	<0.001	7.881
+	176.103	16.6	L-Citrulline	<0.001	10.300	<0.001	13.886	0.953	1.006	<0.001	84.755	<0.001	9.224
Histidine metabolism													
+	141.066	9.8	Methylimidazoleacetic acid	<0.001	3.170	<0.001	2.194	0.005	1.937	<0.001	3.375	<0.001	4.370
+	141.066	10.8	Methylimidazoleacetic acid	<0.001	6.621	<0.001	4.401	<0.001	3.673	<0.001	9.540	<0.001	7.217
Glycolysis and TCA cycle and related metabolites													
-	259.022	16.4	D-Glucose 6-phosphate	<0.001	4.565	<0.001	6.392	0.006	2.530	<0.001	6.980	<0.001	4.566
-	89.024	10.0	(R)-Lactate	<0.001	6.005	<0.001	4.571	0.060	1.263	<0.001	5.292	<0.001	4.191
-	338.989	18.6	D-Fructose 1,6-bisphosphate	<0.001	6.323	<0.001	4.607	0.150	1.369	<0.001	10.520	<0.001	6.034
-	168.991	15.8	dihydroxy acetone phosphate	<0.001	8.991	<0.001	6.316	0.709	1.062	<0.001	11.292	<0.001	5.229

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	168.991	16.6	DL-Glyceraldehyde 3-phosphate	<0.001	19.947	<0.001	15.927	0.001	2.425	<0.001	14.700	<0.001	19.725
-	184.986	17.4	3-Phospho-D-glycerate	<0.001	3.213	<0.001	3.417	0.642	1.119	<0.001	4.020	<0.001	3.13
+	666.132	13.8	NADH	<0.001	3.004	<0.001	3.042	0.958	0.992	<0.001	3.251	<0.001	2.937
-	664.117	13.8	NADH	<0.001	3.284	<0.001	3.002	0.653	0.925	<0.001	3.348	<0.001	3.306
-	289.033	16.7	Sedoheptulose 7-phosphate	<0.001	2.726	<0.001	3.294	0.213	1.187	<0.001	3.623	<0.001	2.148
-	259.022	17.3	D-Glucose 6-phosphate	<0.001	2.157	<0.001	3.575	0.012	1.888	<0.001	2.109	<0.001	2.588
+	810.134	12.7	Acetyl-CoA	<0.001	1.832	<0.001	1.782	0.002	2.166	<0.001	1.586	<0.001	2.227
	117.0193	15.6	Succinate	0.001	1.452	0.003	1.292	0.803	0.965	0.150	0.861	0.003	1.574
	129.0193	15.5	Itaconate	<0.001	2.128	<0.001	1.606	0.599	0.887	<0.001	0.387	<0.001	2.435
	133.0142	16.5	(S)-Malate	<0.001	1.564	0.218	1.076	0.904	0.981	<0.001	2.832	<0.001	1.509
	145.0142	16.0	2-Oxoglutarate	0.615	0.962	<0.001	0.602	0.764	1.071	0.009	1.275	0.404	1.086
	173.0091	18.3	cis-Aconitate	<0.001	3.164	<0.001	1.975	0.648	0.900	0.507	1.087	<0.001	3.484
-	229.012	16.0	D-Ribose 5-phosphate	<0.001	1.709	<0.001	2.524	0.337	0.867	<0.001	1.871	0.077	1.154
-	213.017	15.1	2-Deoxy-D-ribose 5-phosphate	0.004	1.668	<0.001	2.487	0.473	1.170	<0.001	2.583	<0.001	2.323
+	664.117	14.6	NAD+	0.001	1.466	<0.001	1.951	0.020	1.536	<0.001	1.705	<0.001	1.557
-	171.006	15.1	sn-Glycerol 3-phosphate	<0.001	0.667	0.001	0.717	<0.001	0.234	0.063	1.175	<0.001	0.493
-	179.056	15.0	D-Glucose	<0.001	0.452	<0.001	0.395	0.022	0.709	<0.001	0.336	<0.001	0.501
Fatty acids													
+	145.05	11.6	2,3-Dimethylmaleate	<0.001	1.959	<0.001	1.789	0.123	1.324	0.024	0.764	<0.001	2.134
-	158.119	11.6	DL-2-Aminooctanoicacid	<0.001	1.898	<0.001	1.803	0.101	1.350	0.017	0.77	<0.001	2.122
-	211.026	15.6	2-Hydroxy-6-ketononatrienedioate	0.124	1.911	0.001	2.595	0.004	4.486	<0.001	2.796	<0.001	5.145
-	174.041	15.0	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	<0.001	0.454	<0.001	0.435	0.001	0.556	<0.001	0.473	<0.001	0.547
-	172.134	10.3	[FA amino(9:0)] 9-amino-nonanoic acid	<0.001	0.120	0.001	0.579	0.005	1.728	0.454	1.050	<0.001	0.227
+	143.049	15.6	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	0.015	1.236	0.002	1.273	0.938	0.99	0.002	1.370	0.001	1.313
+	128.071	13.9	2,3,4,5-Tetrahydropyridine-2-carboxylate	0.664	0.972	0.063	0.865	0.450	0.931	0.229	0.919	0.417	0.949
+	128.071	16.1	2,3,4,5-Tetrahydropyridine-2-carboxylate	<0.001	1.748	<0.001	1.548	<0.001	1.975	<0.001	2.012	<0.001	2.346

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
+	144.066	13.9	Vinylacetylglycine	<0.001	0.509	0.005	0.683	0.273	1.214	0.408	0.910	0.001	0.600
Creatine metabolism													
+	118.061	16.5	Guanidinoacetate	<0.001	2.932	<0.001	2.226	0.021	1.743	<0.001	2.041	<0.001	5.297
+	132.077	15.3	Creatine	<0.001	1.696	<0.001	1.503	0.001	2.159	<0.001	2.014	<0.001	2.499
+	212.043	15.6	Phosphocreatine	0.001	1.413	<0.001	1.425	0.002	2.082	0.002	1.371	<0.001	2.294
Miscellaneous													
+	90.055	16.0	L-Alanine	<0.001	2.519	<0.001	2.493	0.001	2.316	<0.001	3.467	<0.001	2.86
+	240.109	13.2	Dihydrobiopterin	<0.001	2.223	<0.001	1.723	0.255	1.219	<0.001	2.277	<0.001	2.476
+	85.028	11.6	4-Hydroxy-2-butynal	<0.001	2.118	<0.001	1.895	0.111	1.373	0.022	0.75	<0.001	2.326
+	276.155	17.6	L-a-glutamyl-L-Lysine	<0.001	1.880	0.003	1.382	0.907	1.019	<0.001	2.217	<0.001	1.715
+	170.058	14.6	Phosphodimethylethanolamine	<0.001	1.868	<0.001	2.265	0.08	1.577	0.062	1.307	<0.001	2.017
-	187.072	11.0	N-Acetylglutamine	0.003	1.570	0.004	1.434	0.59	1.085	<0.001	1.992	<0.001	2.768
+	146.118	14.0	4-Trimethylammoniobutanoate	<0.001	0.520	<0.001	0.534	0.317	0.855	<0.001	0.434	<0.001	0.605
+	134.045	15.5	L-Aspartate	0.086	0.889	<0.001	0.732	0.007	0.789	0.002	0.749	0.006	0.765
+	156.042	15.5	N-Methylethanolamine phosphate	0.015	1.254	0.001	1.356	0.678	0.943	0.415	0.934	0.002	1.352
-	320.1	15.1	S-Glutaryldihydrolipoamide	<0.001	0.597	<0.001	0.668	<0.001	0.193	0.142	1.130	<0.001	0.437
Phospholipids													
-	245.043	13.1	Glycerophosphoglycerol	<0.001	2.546	<0.001	2.712	<0.001	2.941	<0.001	2.312	<0.001	2.873
+	247.058	13.1	Glycerophosphoglycerol	<0.001	2.494	<0.001	2.724	0.001	2.920	<0.001	2.193	<0.001	2.711
-	168.043	14.6	Phosphodimethylethanolamine	0.068	1.957	0.010	3.042	0.114	2.392	0.728	1.128	0.002	2.531
+	258.11	15.1	sn-glycero-3-Phosphocholine	<0.001	0.611	<0.001	0.665	<0.001	0.237	0.404	1.070	<0.001	0.458
-	256.096	15.1	sn-glycero-3-Phosphocholine	<0.001	0.559	<0.001	0.630	<0.001	0.173	0.143	1.166	<0.001	0.421
-	154.027	15.5	N-Methylethanolamine phosphate	0.020	1.223	<0.001	1.426	0.992	1.001	0.310	1.082	0.002	1.320

6.3 Discussion

6.3.1 Metabolomes of LPS-, IFN-γ- and LPS+ IFN-γ-treated macrophages

The main effects of LPS, IFN-γ and LPS+ IFN-γ on the metabolome are the upregulation of metabolites linked to glycolysis, the pentose phosphate pathway, TCA cycle, C5-Branched dibasic acid metabolism, taurine biosynthesis, ATP and high energy phosphate metabolites, oxidative stress and creatine metabolism. However, what is also noticeable is that the fold increase in ATP levels was less than that observed for the 42 h incubation exposure with LPS where the increase was twofold. However, the increase in NADH levels was greater than that observed with the 42 h incubation suggesting that perhaps there is less conversion of NADH into ATP with a shorter incubation time.

Increased glycolysis is observed with the accumulation of glucose-6-P, D-Fructose 1,6-bisphosphate, glyceraldehyde 3-phosphate, 3-Phospho-D-glycerate, glycerol-3-P and lactate, see table 6.1. Glycolysis upregulation has been reported to be associated with the M1 metabolome (Krawczyk et al., 2010, Rodriguez-Prados et al., 2010) as well as with rapidly proliferating cells or tumour cells. Increased glycolysis biosynthesis is associated with the upregulation of many signalling pathways including the phosphatidylinositol 3‑kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways (O'Neill et al., 2016). Studies in LPS-activated macrophages have reported an increase in glycolysis and emphasized its importance

in the regulation of phagocytosis, cytokine production, activation of hypoxia-inducible factor 1α (HIF1α) (Tannahill et al., 2013b), as well as NF-κB (Rodríguez-Prados et al., 2010b). It is also considered that the mechanism behind maintaining the upregulation of glycolysis metabolites is through regulating pyruvate kinase isoenzyme PKM2, which translocates to the nucleus to interact with HIF1α and promotes the expression of HIF1α-dependent genes (Luo et al., 2011, Palsson-McDermott et al., 2015), as well as through diversion of glycolytic intermediates to promotes biosynthesis of the pentose phosphate pathway, the serine pathway and the TCA cycle (O'Neill et al., 2016). PKM2 was found to be pro-inflammatory in human atherosclerotic-coronary artery disease according to Shirai et al (Shirai et al., 2016b). Moreover, upregulating glyceraldehyde 3-phosphate dehydrogenase (GAPDH) has been claimed to dissociate from IFN-γ mRNA allowing its translation. The presence of hexokinase 1 in the outer mitochondrial membrane was claimed to allow NLRP3 activation (Moon et al., 2015a).

In the pentose phosphate pathway 2-Deoxy-D-ribose 5-phosphate, ribose 5-phosphate, sedoheptulose 7-phosphate and NADPH were upregulated (table 6.1). This is important to note as the pentose phosphate pathway serves as the second important cytosolic pathway for cell proliferation and survival, firstly due to its production of nucleotide and amino acid precursors required for cell growth and proliferation through its non-oxidative branch (O'Neill et al., 2016) and secondly for the generation of reducing equivalents of NADPH which maintain redox balance and which are also important for fatty acid synthesis. During an infection, macrophages require NADPH-dependent functions such as rapid ROS production to kill pathogens as well as GSH and other antioxidants to prevent excessive tissue damage. Previous work has indicated that sedoheptulose kinase in M1 macrophages is down regulated but has high expression in M2-like macrophages, while the generation of nucleotides is still upregulated (Haschemi et al., 2012). In the current case there is no evidence for upregulation of the pentose phosphate in the IL-4 treatment but in the case of LPS and IFNγ treatments there is an increase in sedoheptulose phosphate and ribose phosphate as well as a very large increase in 5'-phosphoribosylglycinamide where the pentose phosphate cycle joins the pathway for nucleotide biosynthesis.

An increase in part of the TCA cycle was observed with high production of Acetyl-CoA, citrate, cis-Aconitate and itaconate (Table 6.1). The TCA cycle occurs in mitochondria and is commonly thought to be the source of energy in non-activated cells (O'Neill et al., 2016) . It represents the most efficient source of energy generation in the form of NADH and FADH2 to support oxidative phosphorylation which produces a much higher yield of ATP than glycolysis. Similar to glycolysis, TCA intermediates can be diverted to produce lipids and amino acids. In classically activated macrophages, the TCA cycle has been reported to be broken after citrate and after

succinate whereas in M2 cells it is claimed to be intact which will allow generation of UDP-GlcNAc intermediates, which are required for formation of the M2 receptor (e.g., mannose receptor) glycosylation (Jha et al., 2015a). There were no marked changes in malate, fumarate and succinate between the controls and treated cells apart from in the case of the IFN/LPS treatment where malate in particular was elevated. There was in fact a large increase in NADH suggesting that the TCA cycle was operating. Succinate accumulation in M1 cells is reported to stabilise HIF1α and to sustain the IL-1β production, which might lead to nitric oxide production that would inactivate mitochondria (Clementi et al., 1998, Tannahill et al., 2013b).

Consistent with TCA cycle activation, LPS, IFN-γ and LPS+ IFN-γ upregulate C5-Branched dibasic acid metabolism (Table 6.1) through increasing production of cis-aconitate, itaconate, propanoyl phosphate and 4-methylene-L-glutamine. Itaconate as well has been shown to drive a bactericidal effect against *Salmonella enterica* subsp (Michelucci et al., 2013). Interestingly a single treatment by either LPS or IFN-γ increases itaconate production while surprisingly co-stimulation with LPS + IFN-γ decreases it significantly.

The upregulation of glycolysis, pentose phosphate, TCA cycle and C5-Branched dibasic acid metabolism produces a large amount of energy and this can be seen by upregulation of ATP and other high energy phosphates metabolites (table 6.1).

L-Citrulline and N-(L-Arginino) succinate production was significantly high with LPS, IFN-γ and LPS+IFY treatments (table 6.1).This is not surprising as it is reported extensively that arginine via acting as a substrate for NO formation with the formation

of citrulline will promote M1 polarisation (MacMicking et al., 1997a) and the N-(L-Arginino) succinate shunt is important in maintaining NO production (Jha et al., 2015a).

6.3.2 Metabolome of IL-4 treated macrophages

IL-4 activation did not produce a significant increase, in comparison to unstimulated macrophages of any metabolites involved in ATP and high energy phosphate production, carnitines and carnitine biosynthesis, aminosugar metabolism, C5-Branched dibasic acid metabolism, the pentose phosphate pathway and TCA cycle.

It has been reported that the IL-4 treatment causes an upregulation of glycolysis and intact TCA cycle coupled to oxidative phosphorylation (Jha et al., 2015a) as this allows production of UDP-GlcNAc intermediate for the glycosylation of M2‑associated receptors, such as the mannose receptor (Jha et al., 2015a). IL-4 treatment did induce a slight upregulation of glycolysis since there is a small increase in lactate formation but not to the same extent as with the LPS and IFNγ treatments. The IL-4 treatment significantly increases production of acetylCoA but it does not increase the remainder of detected TCA cycle metabolites (table 6.1).

IL-4 treatment does not increase levels of N-L-arginino succinate or citrulline and thus IL-4 activation does not appear as would be expected to induce nitric oxide production and it mainly upregulates the production of ornithine (table 6.1) which is considered as a marker of M2 macrophage phenotype.

Interestingly, all treatments increased production of 5'-Phosphoribosylglycinamide, however IL-4 gave double the increase obtained with LPS or IFN-γ or both and there is also an increase when macrophages co-stimulated with both IL-4 and LPS which might suggest a upregulation of nucleotide biosynthesis.

6.3.3 Metabolomes of IFN-γ + IL-4 macrophages

Stimulating macrophages with IFN-γ +IL-4 indicated the strength of IFN-γ in exerting its effects in this co-stimulation situation such as upregulation of detected metabolites linked to cellular oxidative stress status, taurine biosynthesis, ATP and high energy phosphate metabolites, C5-Branched dibasic acid metabolism, glycolysis ,pentose phosphate pathway and TCA cycle and creatine metabolism and in their different pattern of change regarding fatty acid and phospholipid biosynthesis pathways as seen in table 6.1.

By upregulating levels of both L-ornithine and L-citrulline, this treatment condition emphasises the importance of arginine pathway in the phenotyping markers M1 and M2.

6.3.4 Conclusions

The main conclusion regarding the differences between the metabolome of M1 vs M2 macrophages were as follows:

1. There was a clear diversion in the M2 type away from NO biosynthesis resulting in metabolism of arginine into ornithine.

2. There was clearly a greater increase in glycolysis in the M1 phenotype but this did not result in the levels of ATP being much higher in the M1 than the M2 phenotype.
3. There was no strong indication of downregulation of the TCA cycle in either M1 or M2 macrophages and, if anything, the TCA cycle appeared to be upregulated as judged by NADH production and the increased levels of malate in the IFN-γ /LPS treated cells.

4. Succinate levels appeared to be similar across all treatments.

5. Itaconate increased in the LPS treatment and IFN-γ treatment but decreased in the combination treatment which when taken with the increase in malate in this treatment suggests greater flux through the TCA cycle.

6. Metabolising arginine into ornithine in M2 and to citrulline in M1 cells as well as the upregulation of glycolysis, the pentose phosphate pathway and TCA cycle obtained in this study is supporting the previously puplished data (O'neill and Hardie, 2013, O'Neill, 2015, O'Neill et al., 2016) however, the TCA cycle was intact here with detection of high production of malate (see table 6.1)

7. Comparing SMAs 11a and 12b with either profile shows a unique profilefor the former as they did not change the upregulation level of glycolysis by M1 /M2 cells and did not decrease TCA cycle activation as witnessed with IL-4 in this study.

Chapter 7

Investigating the metabolomic effects of ES-62 SMAs in a biological context

7.1 Introduction

Treating macrophages with SMA 11a or 12b significantly changes their metabolism as seen previously in chapters 3, 4 and 5. This is mainly through increasing glutathione biosynthesis and decreasing creatine/phosphocreatine and taurine metabolism. Additionally, the SMAs did not alter glycolysis or TCA cycle metabolism and even SMA-pretreatment of CpG/LPS-activated macrophages did not alter the upregulated level of glycolysis and TCA cycle induced by both stimulants (see chapters 3, 4 and 5). From these interesting findings, several hypotheses were generated suggesting a possible mechanism of action for the SMAs with respect to their effects on the macrophage metabolome.

As mentioned above, one of the main effects of the SMAs on the BMM metabolome is to increase metabolites related to glutathione. This upregulation was hypothesised to stem from their effect of creatine uptake with consequent effect on ATP transport out of the mitochondria (chapter 4). Oxidative stress can also result from ROS species escaping from the mitochondria due to increased mitochondrial permeability (Turrens, 2003).

Another hypothesis assumes that changes in creatine uptake induced by the SMAs, but not levels of ATP *per se*, affect the supply rate of ATP in relation to where it is required and thus possibly lead to a reduction in macrophage motility. Of note, it was found previously that addition of creatine to the growth medium of tumor cells reversed the motility inhibition induced by cyclocreatine (Mulvaney et al., 1998).

Moreover, SMA-pre-treatment of CpG/LPS activated macrophages did not disturb the upregulation of glycolysis or TCA cycle metabolism induced by both stimulants and therefore it was suggested that effects on these pathways are possibly not involved directly in producing the SMA –mediated immunomodulatory effects such as decreasing cytokine production, in particular IL-1β and IL-6.

Therefore, the above hypothesis was subjected to further biological investigations.

The SMAs first were tested for their effects on mitochondrial permeability using cationic permeable fluorescent dyes such as tetraethyl rhodamine methyl (TMRM) and mitotracker green (MTG). In addition, the SMAs were assessed for their possible effect on macrophage motility using an *in vitro* transwell migration assay. Furthermore, the effect of the SMAs on nitric oxide production, which is reported to be linked to high glycolysis and oxidative phosphorylation were tested by using the Griess assay. Moreover, to further investigate the effect of the SMAs on glycolysis, the TCA cycle and any possible involvement of these pathways in SMA-immunomodulatory effects, substrates affecting glycolysis and the TCA cycle, in particular dimethyl malonate and 2-deoxy glucose, were added exogenously. In addition, the exogenous addition of taurine was undertaken since the SMAs lowered it in both the treated and untreated macrophages. Cytokine production then was measured using enzyme-linked immunosorbent assay (ELISA) to test if the presence of the exogenous compounds altered the ability of the SMAs to decrease IL-1β and IL-6. Finally, the Biolog microarray assay was used to measure the effect of SMAs on output of NADH from various catabolic pathways affected by the SMAs alone and by SMAs+CpG/LPS in macrophages.

7.2 Results

7.2.1 Effects of the SMAs on mitochondrial membrane potential (MMP) as determined using FACS and confocal microscopy

Treating macrophages with SMAs on their own did not change the MMP in comparison to unstimulated macrophages (figure 7.1 A) whereas SMA 11a and 12b but not 19o pre-treatments, under normal glucose concentration, were found to reduce the MMP hyperpolarization produced by LPS treatment significantly (figure 7.1B) and decrease it but not significantly in glucose- and glutamine-deprived conditions (figure 7.1 C-D). 2-DG, 1L-4 and IL-10 were used as experimental controls since they are known to dissipate the MMP. Figures 7.2.1-7.2.9 represent qualitative assessment of effects of SMAs alone and SMAs+LPS in mitochondrial membrane polarization.

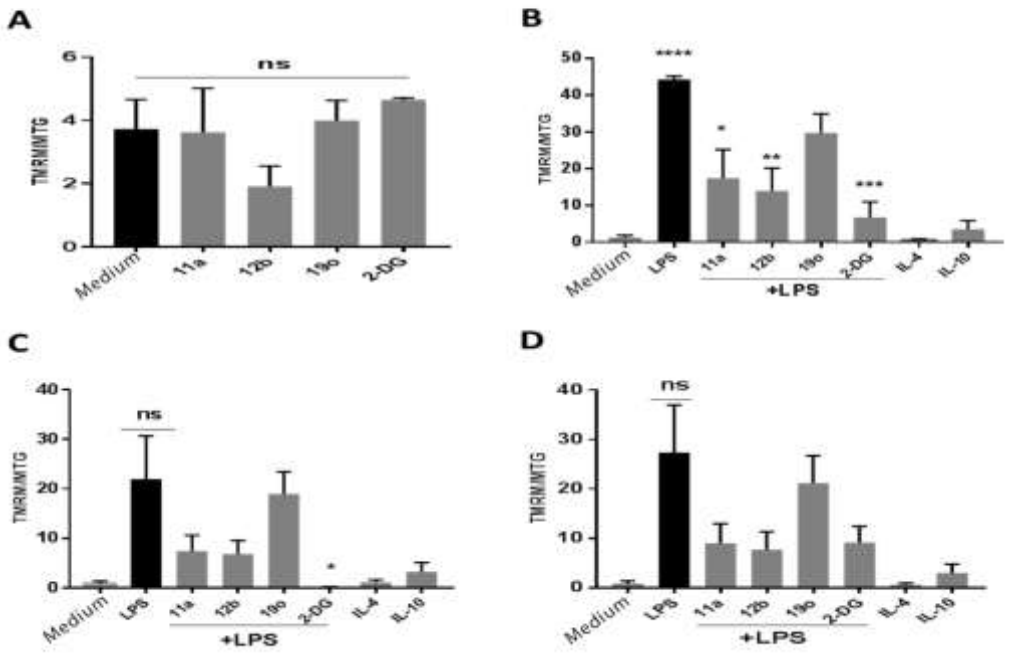

Figure 7.1: Effects of SMA-18 hours treatement /SMAs+LPS-42 hours treatment on mitochondrial membrane potential as determined by FACS

SMA pre-treatment on its own did not have an effect on MMP (A), however, LPS activation hyperpolarises the MMP of macrophages as seen in panels B, C and D. B, C and D refer to normal glucose stimulation, glucose deprived stimulation and glutamine deprived stimulation. SMAs 11a and 12b and 2DG pre-treatment, of LPS-activated macrophages, as well as IL-4 and IL-10 treatment dissipated the MMP, (B, C and D). SMAs 11a and 12b in addition to 2-DG reduced the effects of LPS further in the absence of glucose (C) whereas the 2-DG dissipating effect was non-significantly altered by the absence of glutamine (D). IL-4 and IL-10 were used as controls for anti-inflammatory phenotype form of MMP. Results are expressed as mean (of triplicate determinations) ± SEM and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001; ****p < <0.0001.

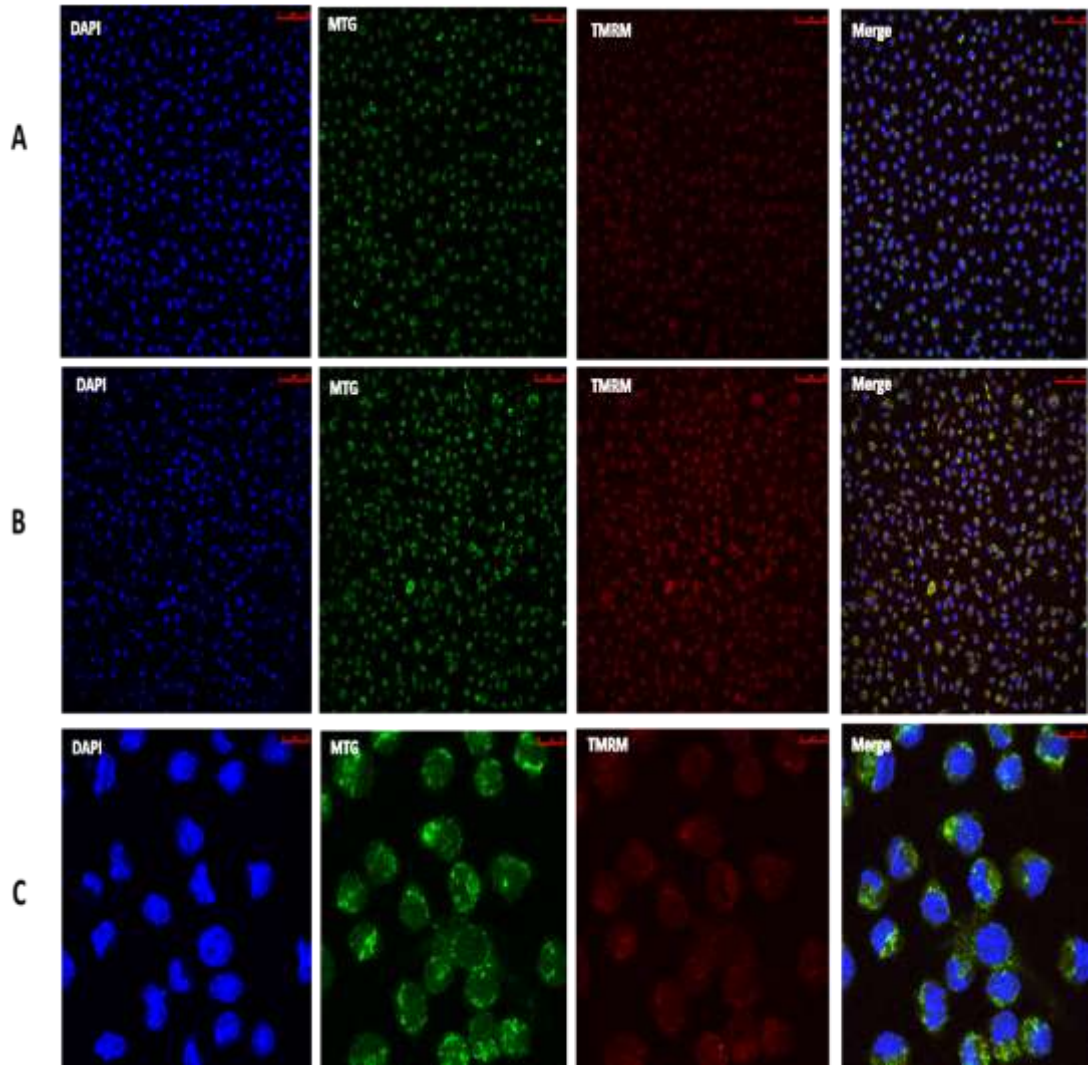

Figure 7.2.1: Mitochondrial membrane potential of the unstimulated macrophages following 18-hour incubation as determined using confocal microscopy and FACS

Qualitative assessment of mitochondrial membrane potential of 18 hours-maintained but unstimulated macrophages. (A) represents, from left to right, DAPI, MTG, TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field. Both (A) and (B) were taken at magnification X40 while (C) represents the third field with magnification X6. The quantitative analysis of relative fluorescence intensity was undertaken using FACS.

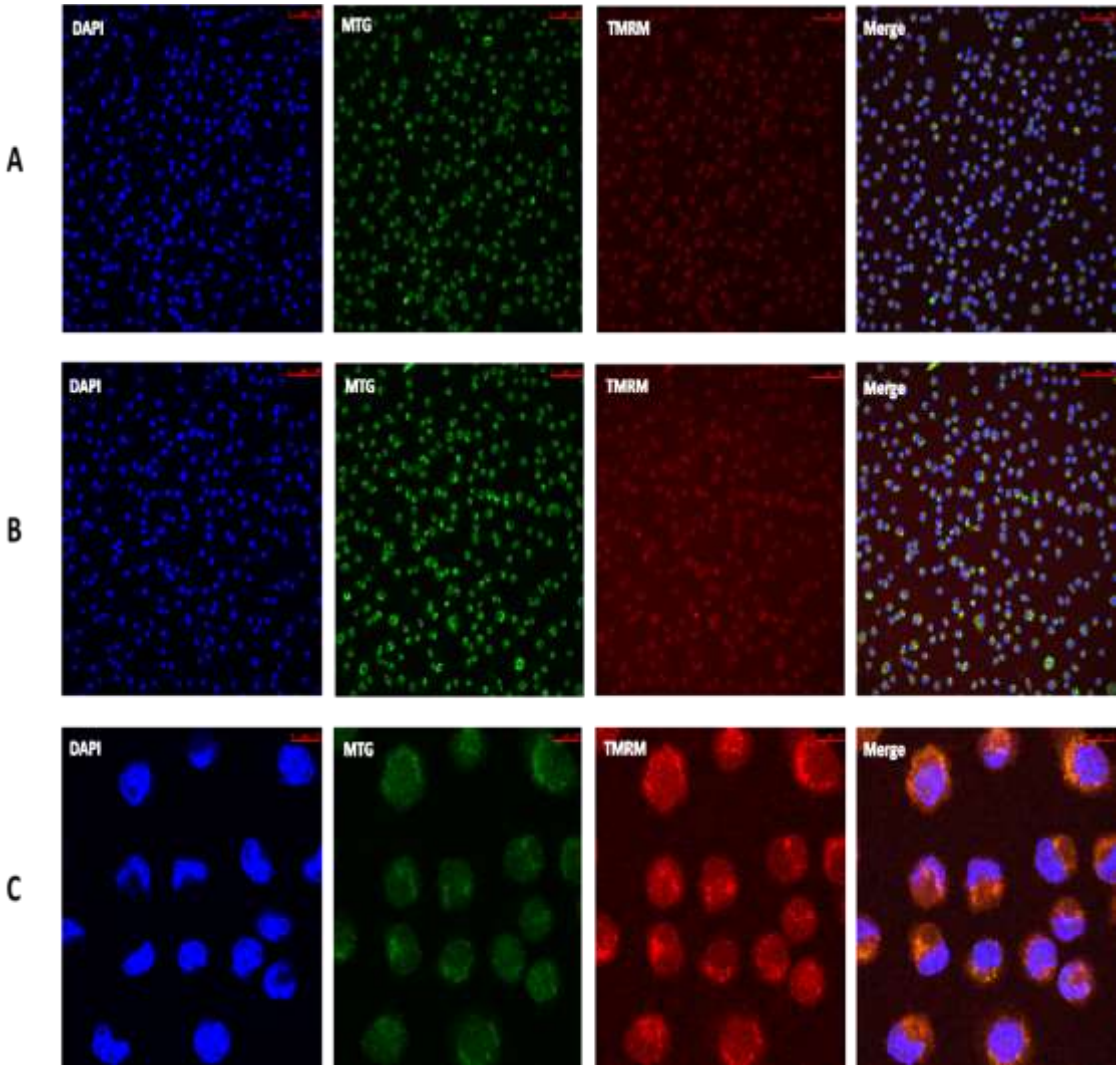

Figure 7.2.2: Mitochondrial membrane potential of 18-hour 11a-pre-treatment of LPS-activated macrophages as determined using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 11a-treatment of macrophages. (A) represents, from left to right, DAPI, MTG, TMRM stains and merged picture of the first field whereas (B) represents the above stains in a second field. Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X6. Although the images are not always that clear the quantitative analysis of relative fluorescence intensity was undertaken by using FACS.

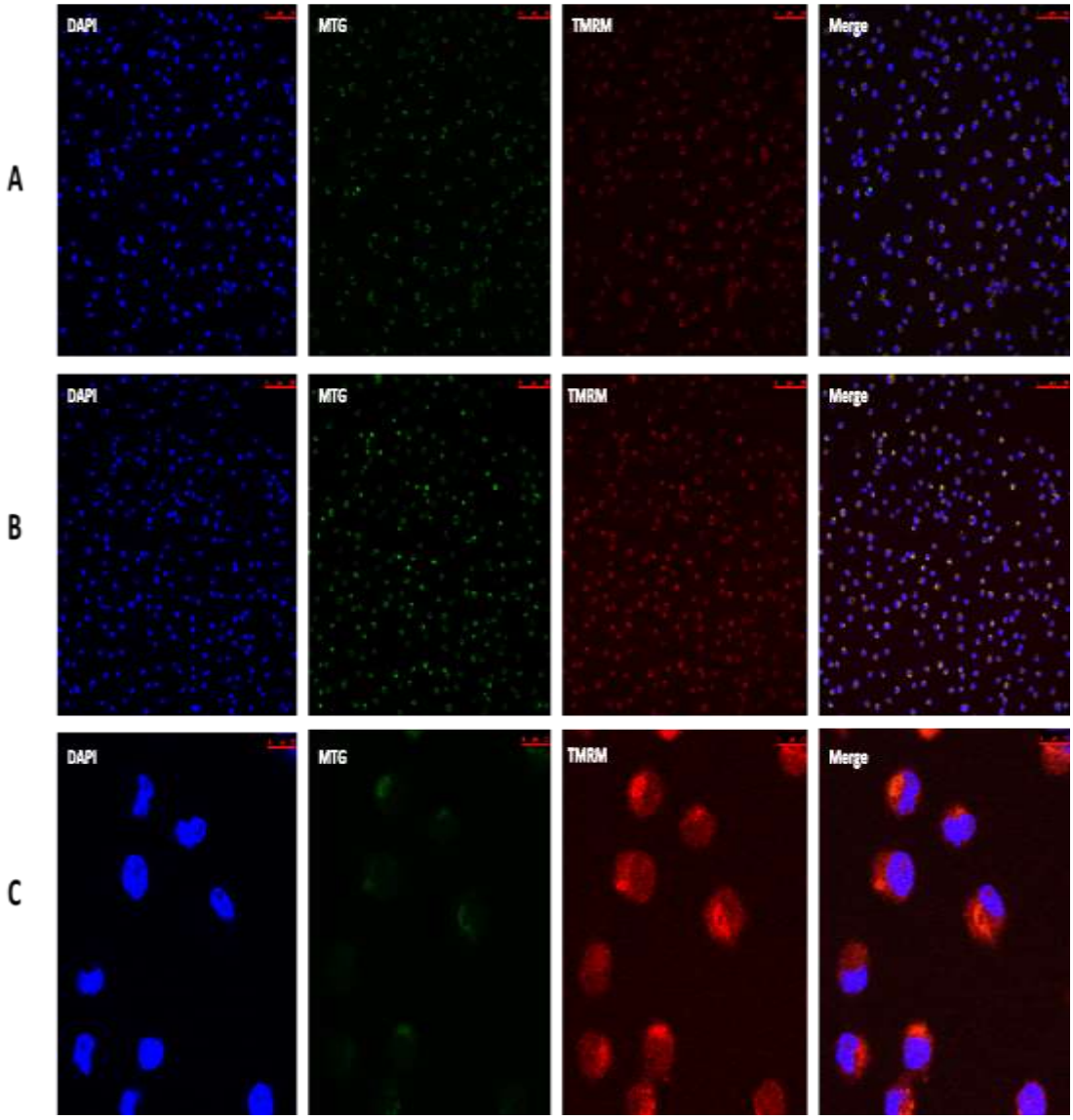

Figure 7.2.3: Mitochondrial membrane potential of 18-hour 12b pre-treatment on LPS-activated macrophages using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 12b-treatment but unstimulated macrophages. (A) represents, from left to right, DAPI, MTG, TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field. Both (A) and (B) were taken at magnification X40 while (C) represents the third field with magnification X6. The quantitative analysis of relative fluorescence intensity was undertaken using FACS.

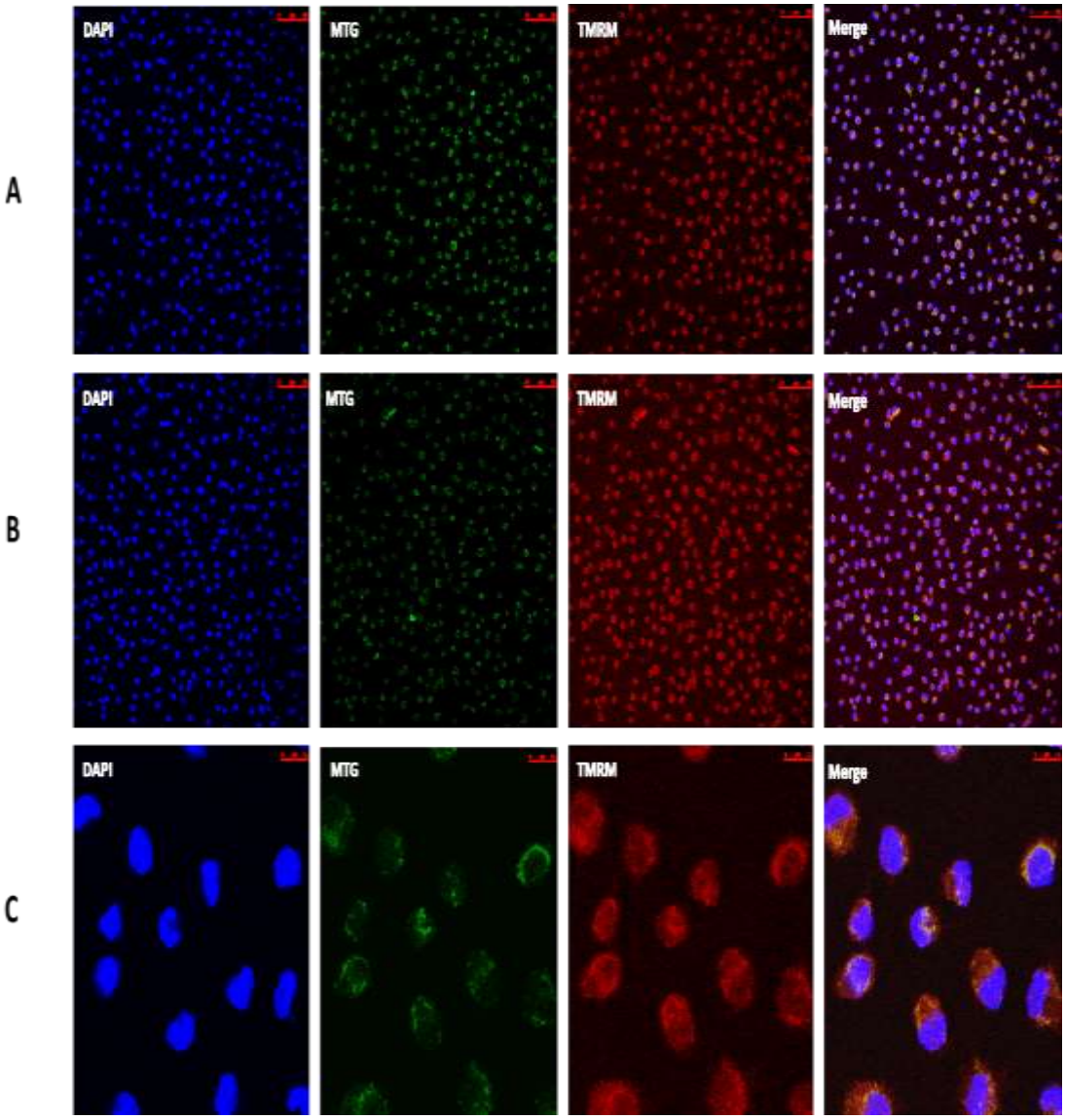

Figure 7.2.4: Mitochondrial membrane potential of 18-hour 19o pre-treatment on LPS-activated macrophages using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 19o-treatment but unstimulated macrophages. (A) represents, from left to right, DAPI, MTG, TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field. Both (A) and (B) were taken at magnification X40 while (C) represents the third field with magnification X6. The quantitative analysis of relative fluorescence intensity was undertaken using FACS.

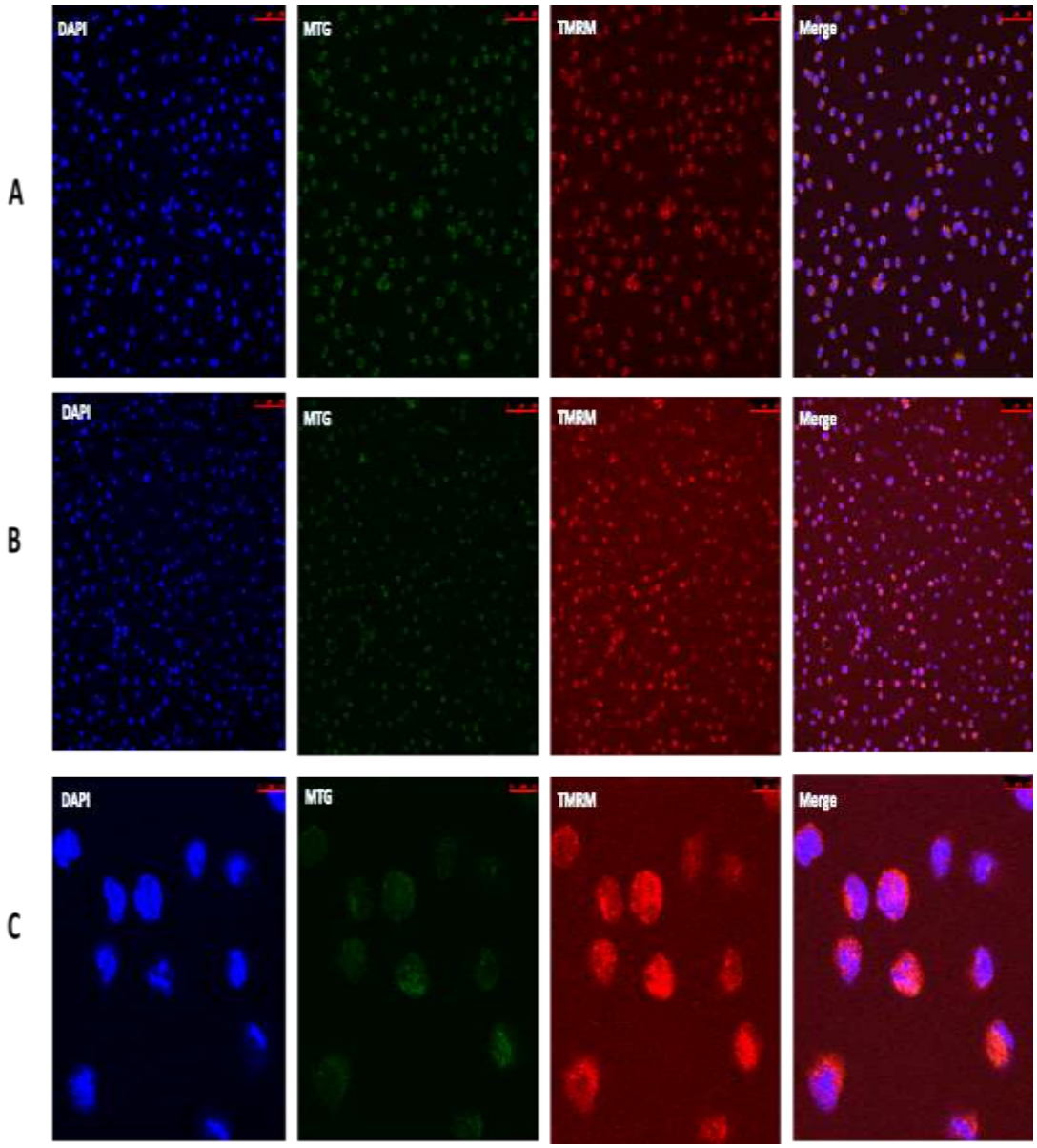

Figure 7.2.5: Mitochondrial membrane potential of 42-hour incubation of the unstimulated macrophages using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 42 hours incubation of unstimulated macrophages. **A** represents, from left to right ,DAPI ,MTG,TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field .Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X6 . The quantitative analysis of relative fluorescence intensity was done using FACS.

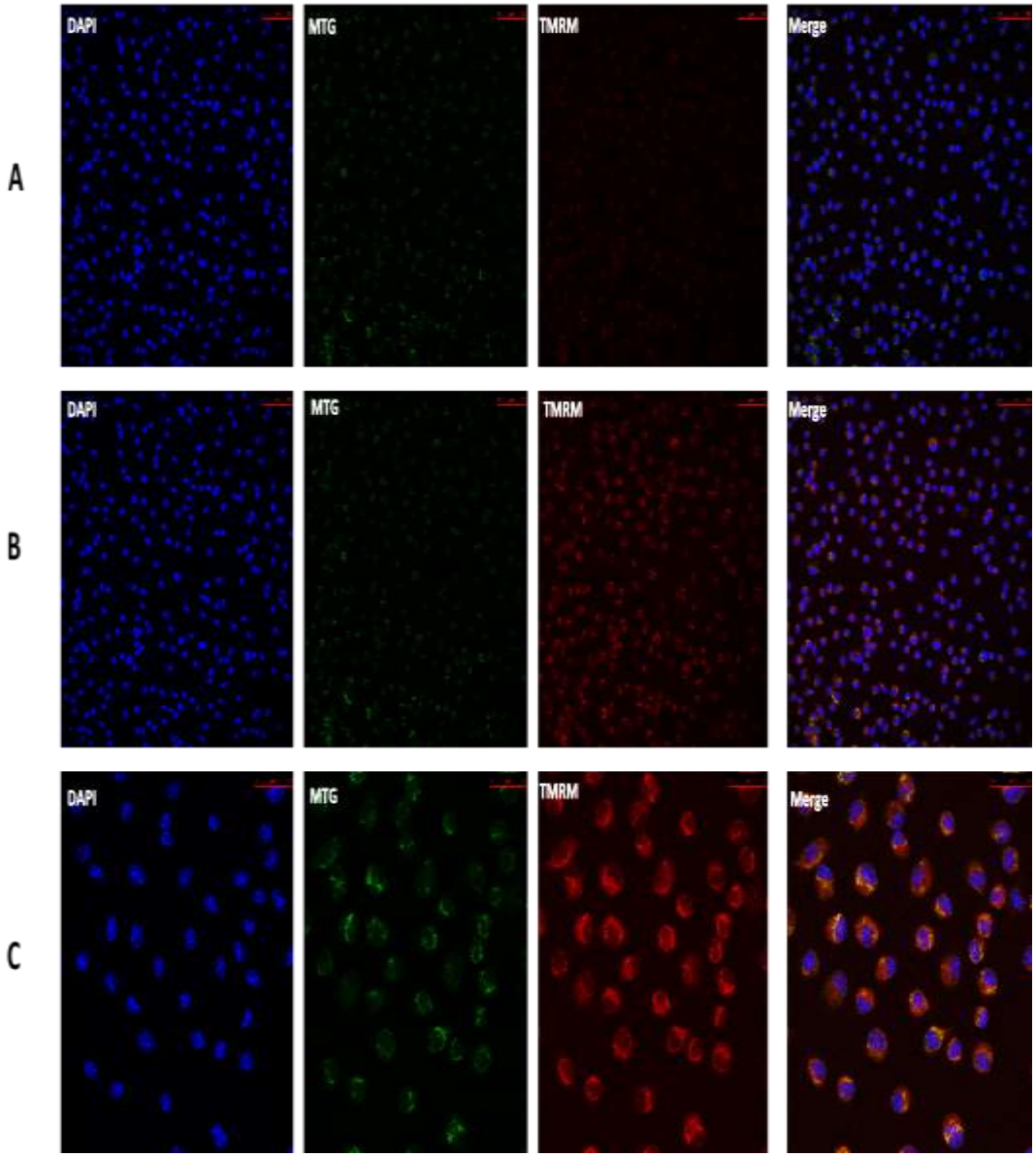

Figure 7.2.6: Mitochondrial membrane potential of 42 hours treatment with LPS on macrophages as determined using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 24 hours LPS activation of macrophages. **A** represents, from left to right ,DAPI ,MTG,TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field .Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X6 . The quantitative analysis of relative fluorescence intensity was done using FACS.

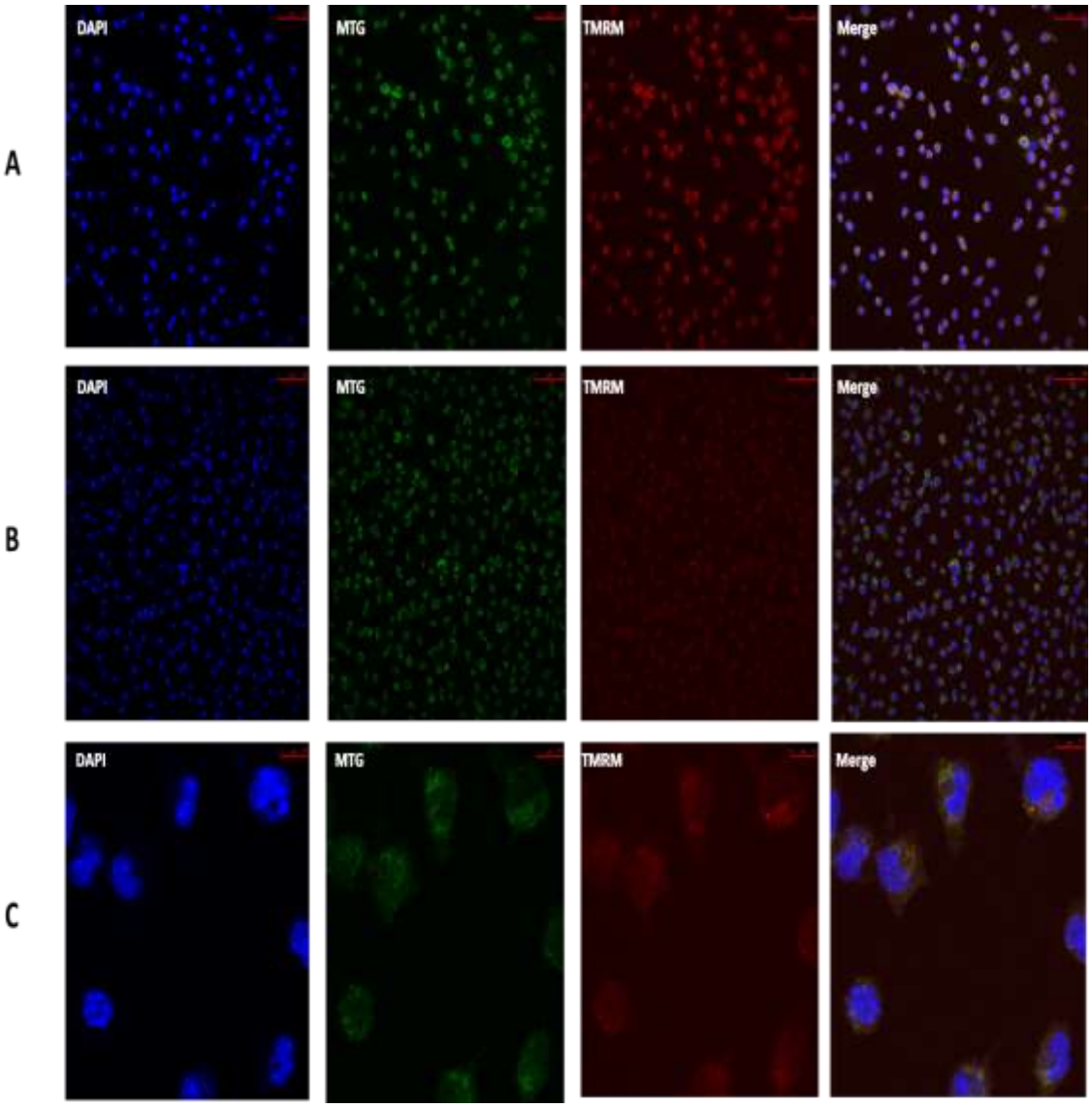

Figure 7.2.7: Mitochondrial membrane potential of 42 hour treatment with 11a + LPS-activated macrophages as determined using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 11a pre-treatment effect on 24 hours LPS activation. **A** represents ,from left to right ,DAPI ,MTG,TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field .Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X6 . The quantitative analysis of relative fluorescence intensity was done using FACS.

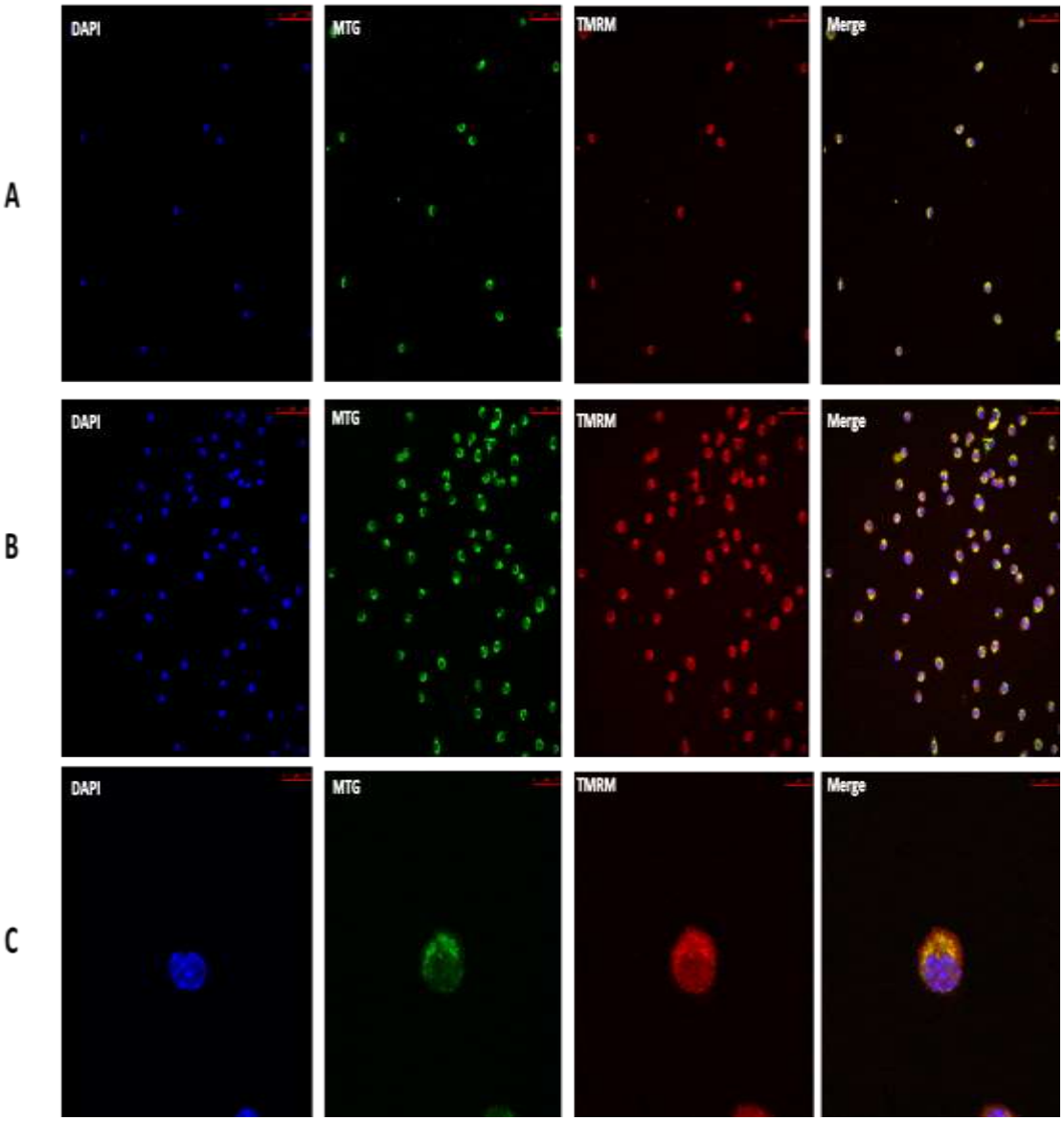

Figure 7.2.8: Mitochondrial membrane potential of 42 hour treatment with 12b + LPS activated macrophages as determined using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 12 pre-treatment effect on 24 hours LPS activation. **A** represents, from left to right ,DAPI ,MTG,TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field .Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X 2.5 . The quantitative analysis of relative fluorescence intensity was undertaken using FACS.

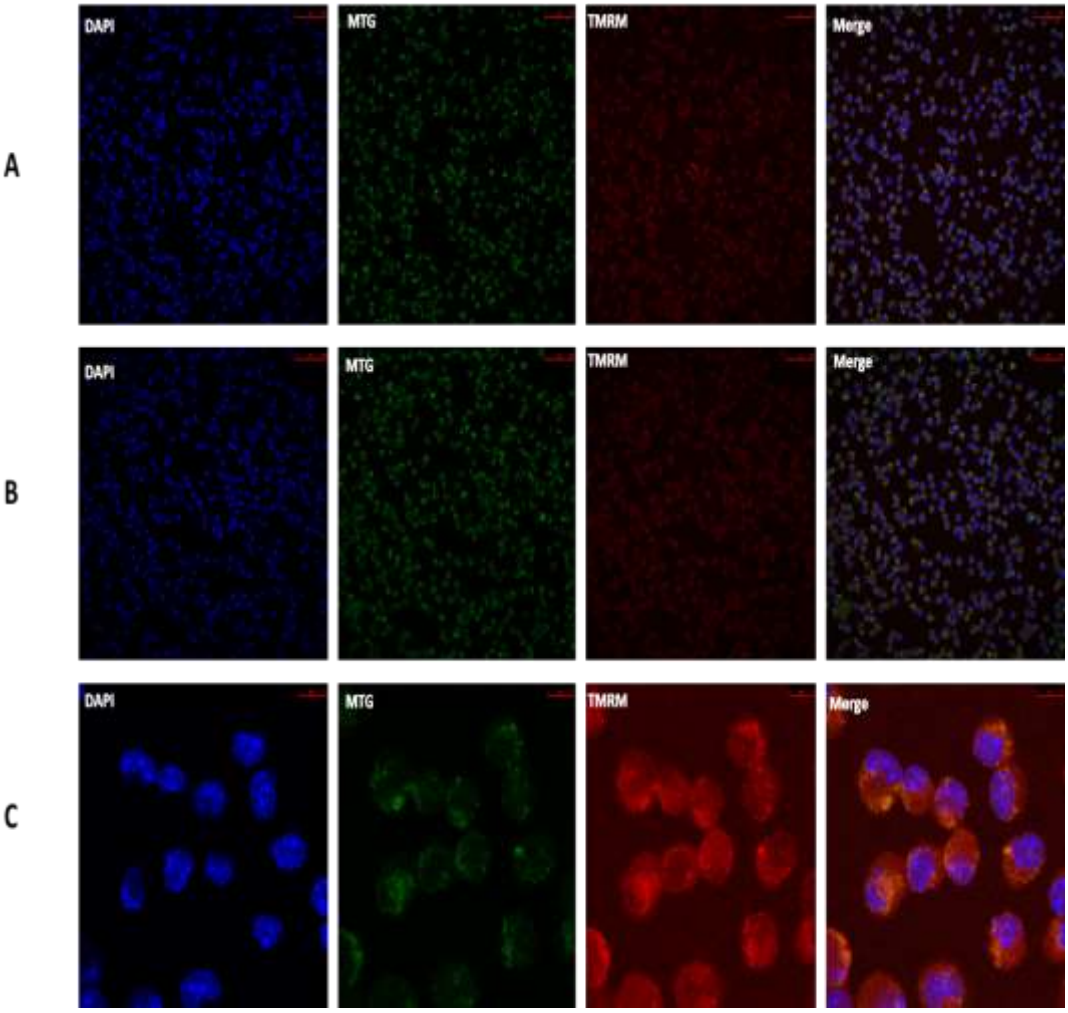

Figure 7.2.9: Mitochondrial membrane potential of 42 hour treatment with 19o + LPS activated macrophages as determined using confocal microscopy

Qualitative assessment of mitochondrial membrane potential of 18 hours 19o pre-treatment effect on 24 hours LPS activation. **A** represents, from left to right, DAPI ,MTG,TMRM stains and merge picture of the first field whereas (B) represents the above stains in a second field .Both (A) and (B) were taken on magnification X40 while (C) represents the third field with magnification X6 . The quantitative analysis of relative fluorescence intensity was undertaken using FACS.

7.2.2 Effects of SMAs on macrophage migration in the presence and absence of LPS or CpG stimulation

Since LPS induces glucose uptake to keep glycolysis turned on, thereby providing the energy requirements for macrophage activation (Vats et al., 2006, Tannahill et al., 2013), it was of interest to investigate if the SMAs as a pretreatment (which had no effect on glycolysis activation) by their ability to decrease creatine (Cr) and phosphocreatine (Cr-P) could control energy transduction in BMMs activated by CpG or LPS and thereby inhibiting their migration.

Adding SMAs alone (figure 7.3A) to “starving” macrophages (where no FCS to rule out its possible invovment in inducing motility at the starting point) did not affect significantly the migration of macrophages in relation to non-stimulated macrophages. However, LPS and CpG addition to the starved macrophages significantly induced cell migration in response to complete medium (complete medium has FSC which contains creatine) in comparison to unstimulated macrophages (figure 7.3B-C). IL-4 addition did not alter macrophage migration in comparison to unstimulated ones (figure 7.3 B-C). SMA (11a and 12b) pre-treatment inhibits cell migration towards the complete medium in response to LPS activation and only 11a with CpG stimulation and therefore are showing an interesting effect on movement responses (figure7.3 B-C).

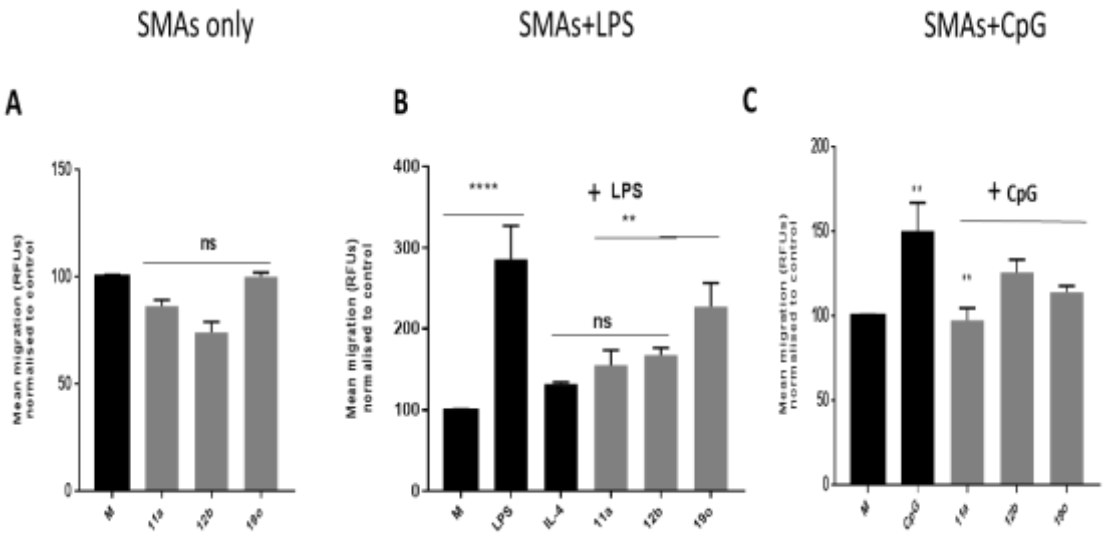

Figure 7.3: Effect of ES-62 SMAs on migration of starved macrophages

Pre-incubation of macrophages with SMAs 11a, 12b or 19o alone did not induce macrophage migration towards complete medium as shown in (A) whereas in (B), 11a and 12b inhibit the migration of the LPS-activated macrophages significantly. IL-4 alone in (B) did not induce migration of macrophages. 11a inhibits CpG-activated macrophages significantly while 12b and 19o show a non-significant decrease in migration (C). In Panel A SMAs were compared to the medium, in panel B, SMAs+LPS were compared with LPS while IL-4 and LPS were compared to the medium and in panel C, SMAs+CpG were compared to CpG. Results which were obtained from triplicate experiments are expressed as a mean (of triplicate determinations) ± SEM and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001; ****p < <0.0001

7.2.3 Effects of SMA-pre-treatment and SMAs+LPS/CpG on nitric oxide production in BMMs

Using the *in vitro* nitric oxide assay, the Griess test, SMAs were examined for their ability to produce/inhibit nitric oxide production indirectly via measurement of breakdown products (nitrite and nitrate) in cell culture supernatants. In particular, nitrite accumulation is used as an indicator of NO production (Green et al., 1982). SMAs on their own did not induce any changes to nitric oxide production (figure 7.3) however it was found that 18 hours pretreatment with SMAs, 11a and 12b but not 19o, significantly reduced nitrite production generated after 24 hours exposure to LPS or CpG (figure 7.3). IL-4 was used on its own in parallel to LPS and CpG, over 24 hours, and was found not to induce any significant changes (figure 7.3).

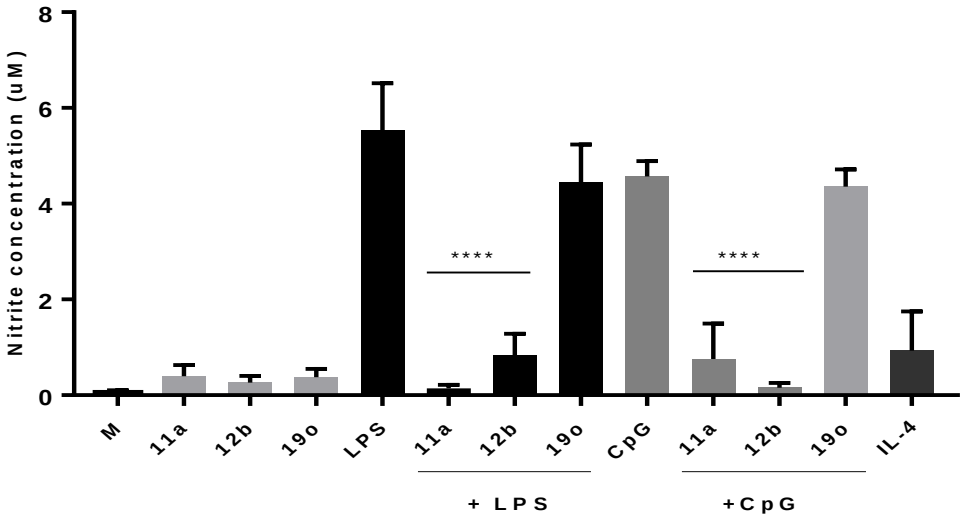

Figure 7.4: Measurement of effects of ES-62 SMAs on nitrite production

The effect of LPS- or CpG on nitrite production in macrophages. Nitrite production was determined relative to a standard curve constructed with solutions of sodium nitrite ($NaNO_2$) as described by (Griess, 1879) from a 10 mM stock solution of $NaNO_2$ prepared in complete RPMI 1640 cell medium. SMAs in the left side of the graph were compared to complete medium while SMAs+ LPS/CpG were compared to corresponding stimulants. Results were obtained from 3 triplicate experiments and are expressed as a mean (of triplicate determinations) ± SEM and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001;****p < <0.0001.

7.2.4 Testing the effect of SMA-pretreatment on macrophages activated with *Escherichia coli* and *Salmonella* LPS in the presence of exogenous glycolysis and TCA cycle substrates, taurine, dimethyl malonate and 2-deoxy glucose on cytokine production

Pre-treatment with SMA 11a or 12b decreases IL-1β and lL-6 production in LPS-activated macrophages (Al-Riyami et al., 2013). However, their metabolomics profiles reveal that neither glycolysis nor the TCA cycle were affected to any great extent (chapter3, 4 and 5). Therefore, it was suggested to add glycolysis substrates, TCA substrates, taurine, dimethyl malonate and 2-deoxy glucose exogenously and to test if this would change the ability of the SMAs to decrease either cytokine.

Addition of the TCA cycle substrate pyruvate with the LPS stimulants (*E.coli* and *Salmonella*) for the two tested incubation times (24 and 48 hours) decreased IL-1β production significantly in comparison to LPS alone stimulation (figure 7.5.1: A-D) as well as decreasing IL-6 production (figure 7.5.2: A-D). However, adding it to 11a- and 12b-pretreated macrophages followed by further LPS stimulation did not alter the ability of SMAs to decrease either of the cytokines (figures 7.5.1 and 7.5.2: A-D).

Adding lactate did not induce any significant changes in IL-1β (7.5.1 E-H) and IL-6 production (7.5.2 E-H) in comparison to LPS stimulation alone. Adding lactate in excess to SMA-pretreated macrophages as well did not change the ability of 11a and 12b to decrease both cytokines (figures 7.5.1and 7.5.2 E-H).

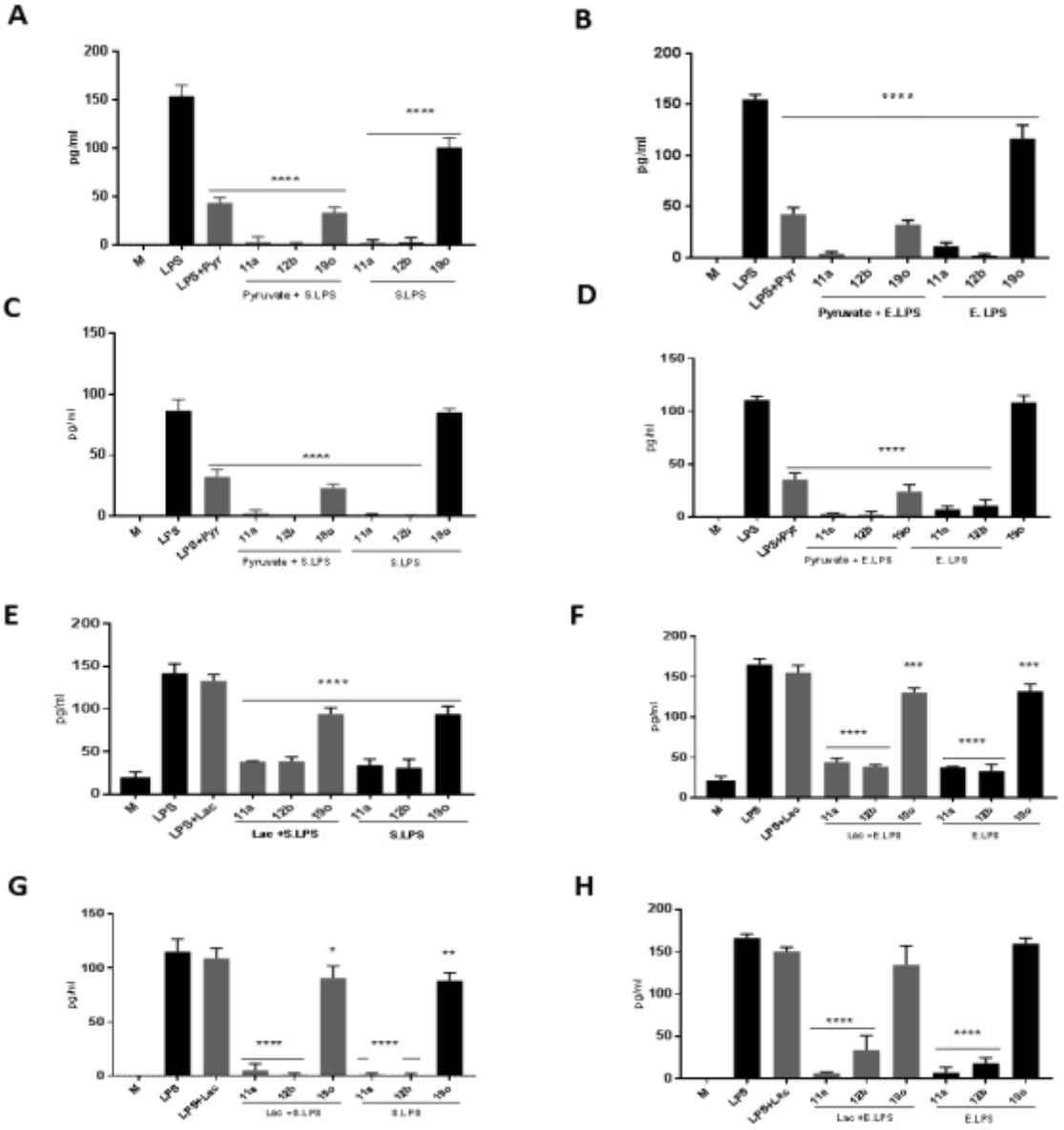

Figure 7.5.1: Pyruvate and lactate exogenous addition and their possible involvement in IL-1β production

Pyruvate (A, B, C and D) and lactate (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to *Salmonella*-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia *coli*-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS alone. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

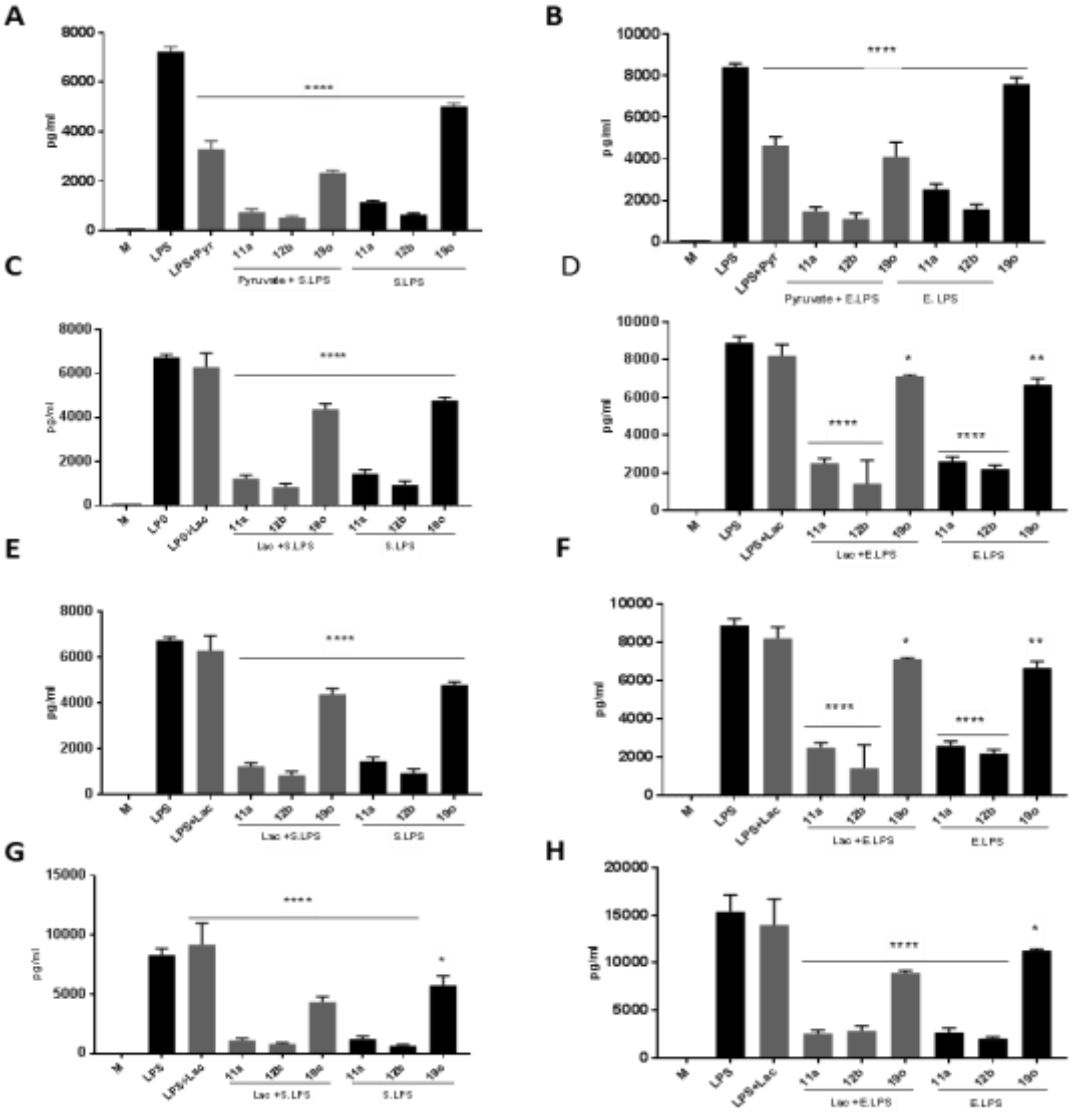

Figure 7.5.2: Pyruvate and lactate exogenous addition and their possible involvement in IL-6 production

Pyruvate (A, B, C and D) and Lactate (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS alone.SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

The addition of excess TCA cycle metabolites, citrate, α-ketoglutarate, succinate and dimethyl fumarate was tested for their effects on IL-1β and IL-6 production (figures 7.5.3- 7.5.6). Adding TCA metabolites inhibited IL-1β and IL-6 production in comparison to LPS alone except for dimethyl fumarate which increased IL-6 production significantly after 24 hours (figure 7.5.6 E-H). Likewise, addition of TCA metabolites did not interfere with the ability of SMAs to decrease either cytokine (figures 7.5.3- 7.5.6).

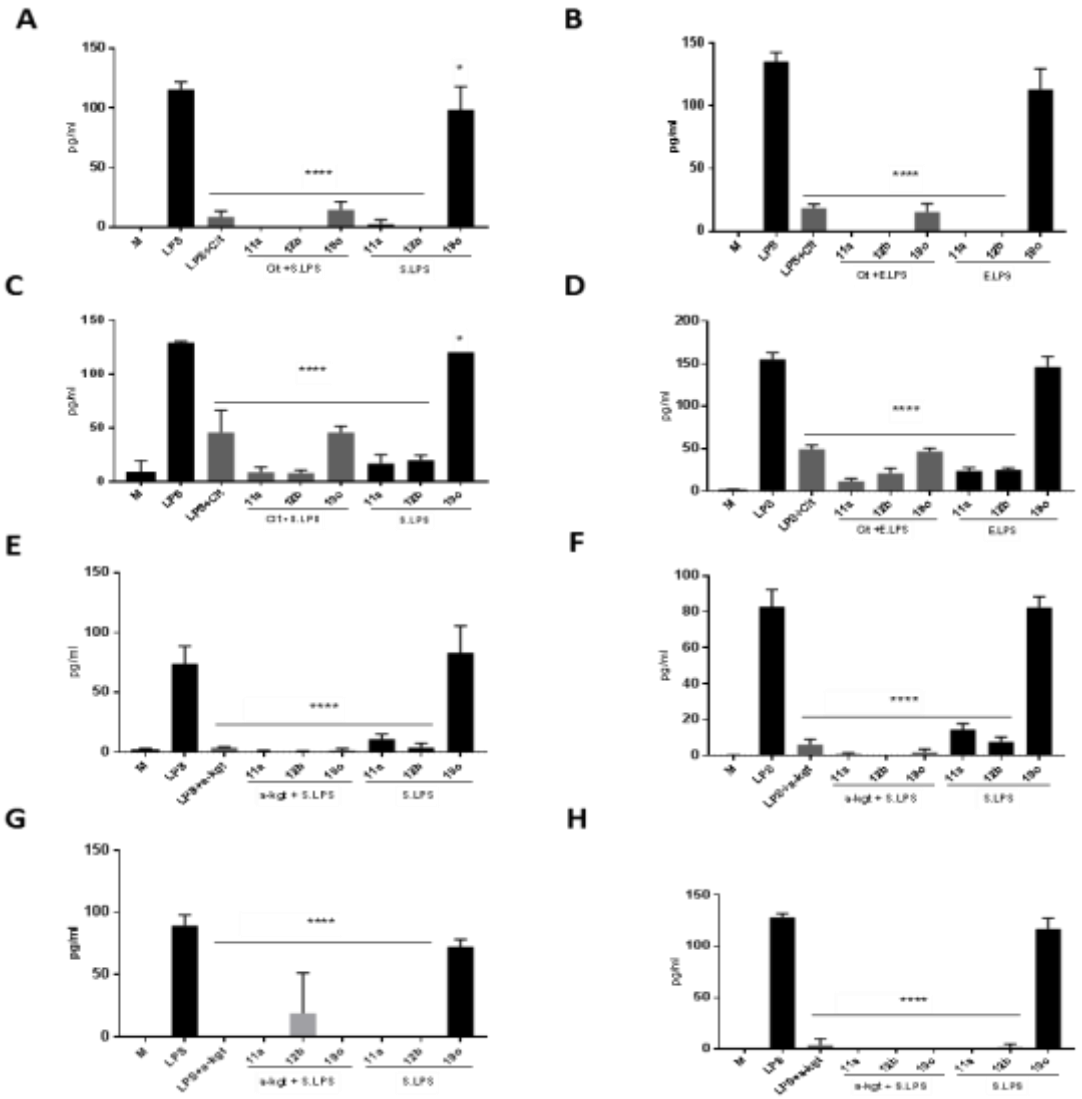

Figure 7.5.3: Citrate and α- ketoglutarate exogenous addition and their possible involvement in IL-1β production

Citrate (A, B, C and D) and α-ketoglutrate (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS alone. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

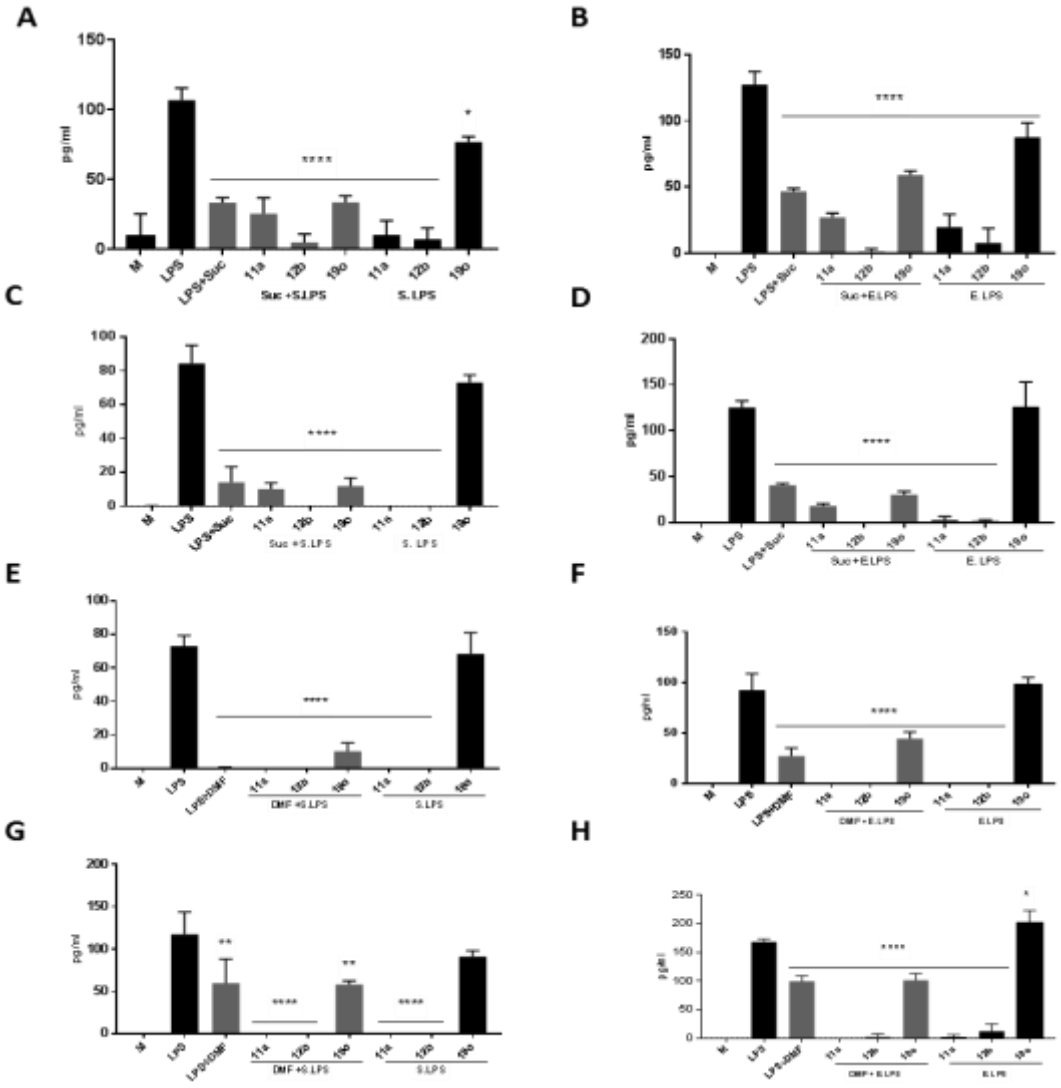

Figure 7.5.4: Succinate and DMF Citrate exogenous addition and their possible involvement in IL-1β production

Succinate (A, B, C and D) and DMF (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS alone. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

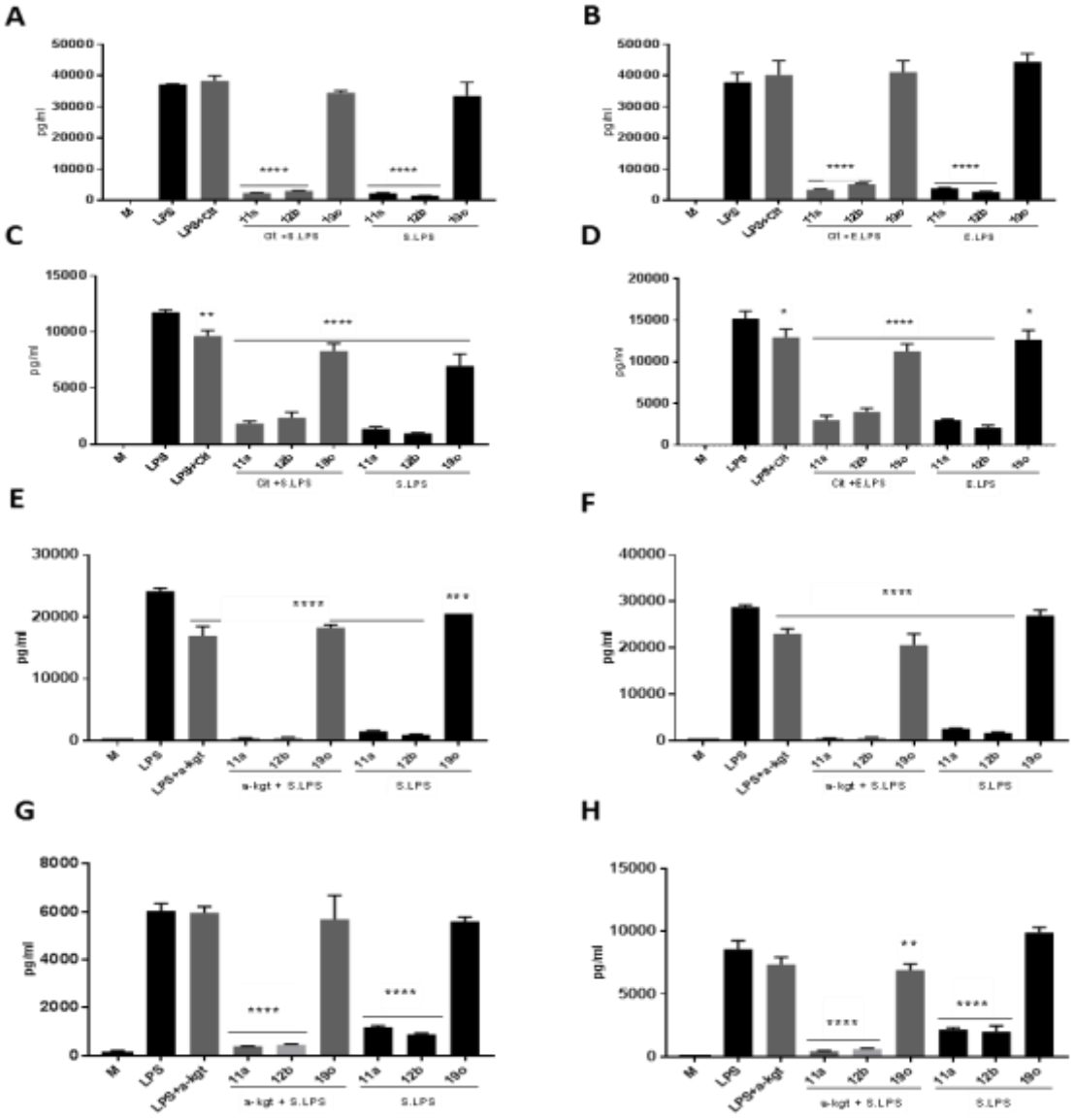

Figure 7.5.5: Citrate and α- ketoglutarate exogenous addition and their possible involvement in IL-6 production

Citrate (A, B, C and D) and a-ketoglutarate (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrates was compared to LPS alone. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

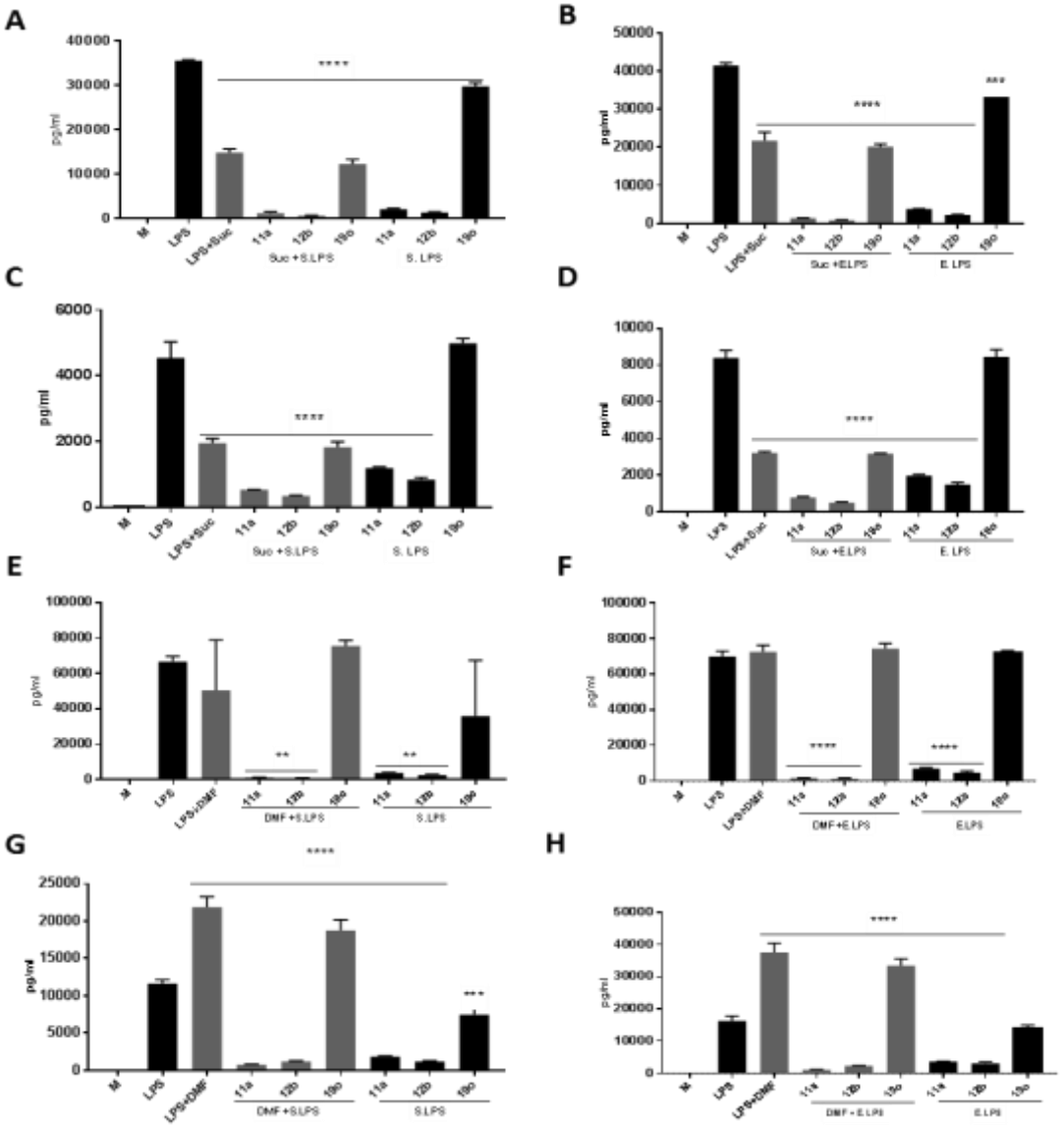

Figure 7.5.6: Succinate and DMF exogenous addition and their possible involvement in IL-6 production

Succinate (A, B, C and D) and DMF (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS alone. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

Since succinate has been reported to act as a metabolic signal in inflammation and its role in ATP production in mitochondria has been highly studied (Tannahill et al., 2013) several concentrations of succinate were added to LPS-activated macrophages. No higher induction of IL-1β and IL-6 production above that for LPS treatment alone was observed and likewise, none of the concentrations added interfered with the ability of SMAs to decrease secretion of either cytokine (figure 4.5.7).

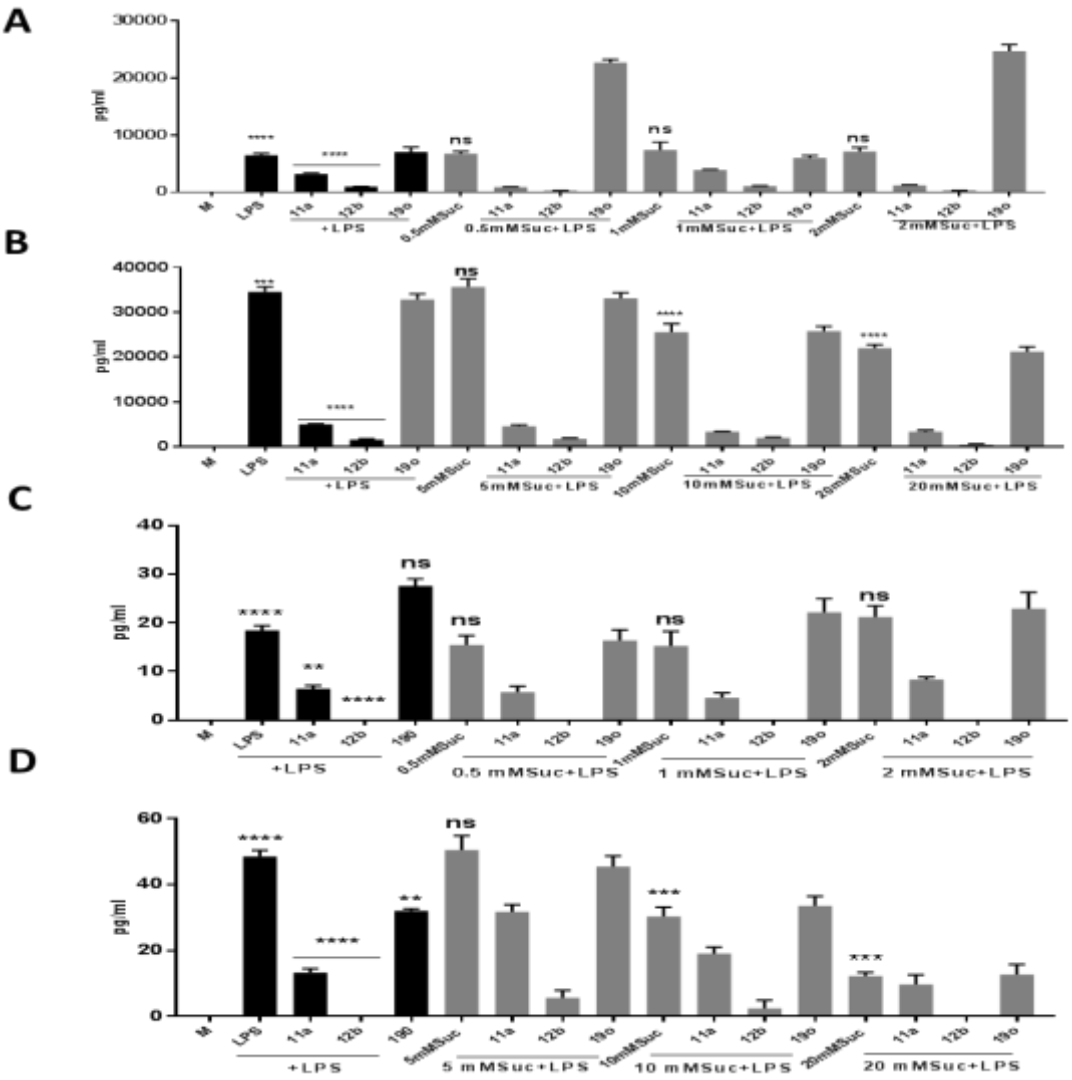

Figure 7.5.7: Succinate exogenous addition and its possible involvement in IL-6 and IL-1β production

Succinate was added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o using a range of concentrations in which A and C refers to the IL-6 and IL-1β production respectively in the abundance of 0.5,1 and 2 mM succinate concentrations whereas B and D indicates IL-6 and IL-1β production respectively in the abundance of the range of 5, 10 and 20mM. SMAs pretreated macrophages followed by LPS stimulation alone was used as a control in the left side of each panel. LPS was compared to the culture medium while LPS+any concentration of succinate was compared to LPS alone. SMAs+any provided succinate concentration+LPS were compared to LPS+corresponding succinate concentration wheras SMAs+LPS were compared to LPS. Results are expressed as a mean (of triplicates determination) ± SEM and was analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001; ****p < <0.0001.

2-DG is a glucose-like molecule, which has the 2-hydroxyl group replaced by hydrogen so that it cannot undergo further glycolysis and has an ability to reprogram LPS-activated macrophages and decrease IL-1β production (figure 7.5.8 A-D), even though it is found to increase IL-6 production significantly in E.coli as well as Sal. LPS (figure 7.5.9 A-D).

Adding dimethyl malonate, a competitive inhibitor of the enzyme succinate dehydrogenase, decreased significantly IL-1β and IL-6 production in comparison to stimulation with LPS alone (figure 7.5.8 and 7.5.9:E-H) but it did not affect the ability of the SMAs in decreasing IL-1β and IL-6 .

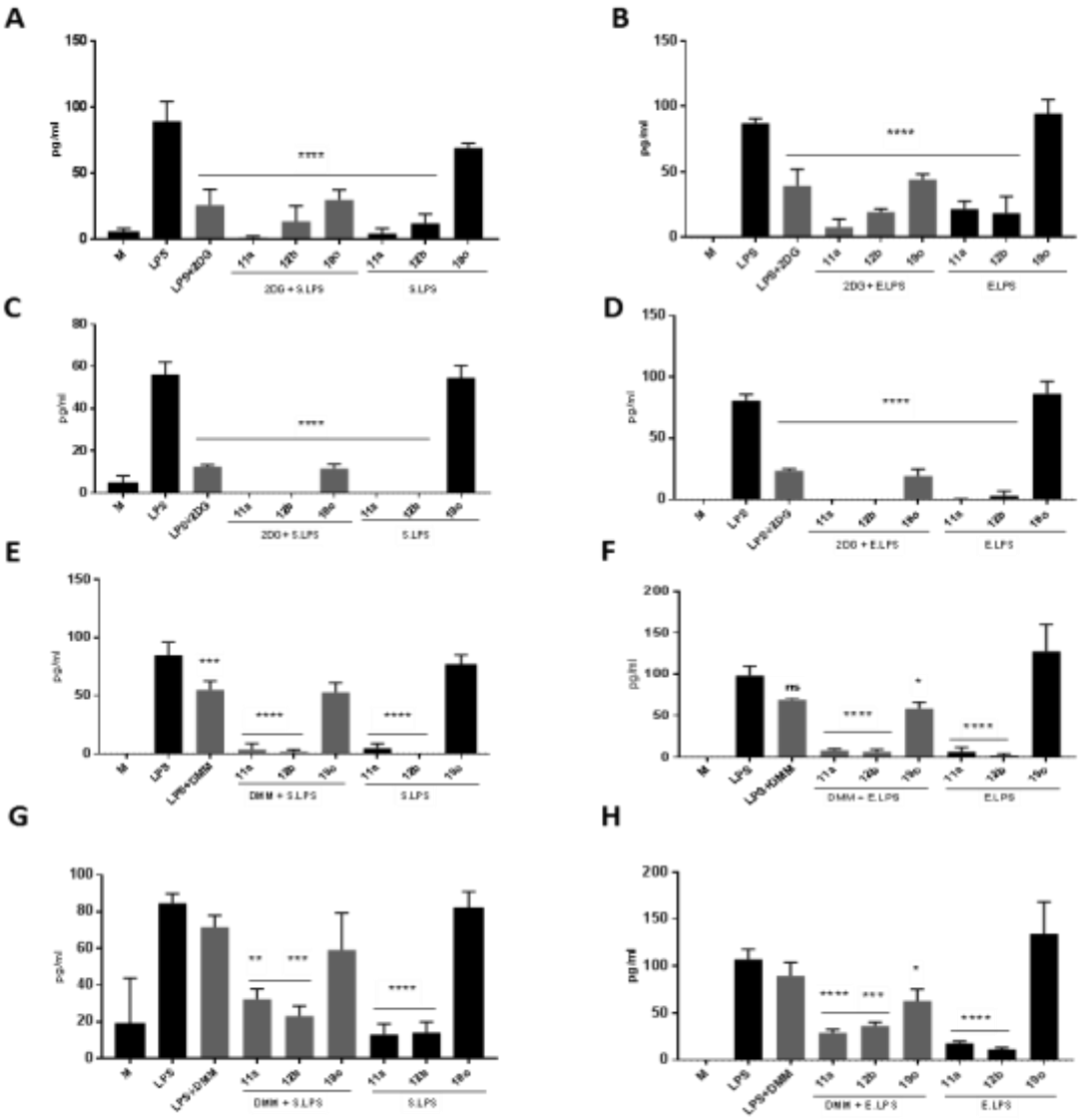

Figure 7.5.8: Exogenous addition of 2-deoxyglucose and DMM and their possible involvement in IL-1β production

2-deoxyglucose (A, B, C and D) and DMM (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs + LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

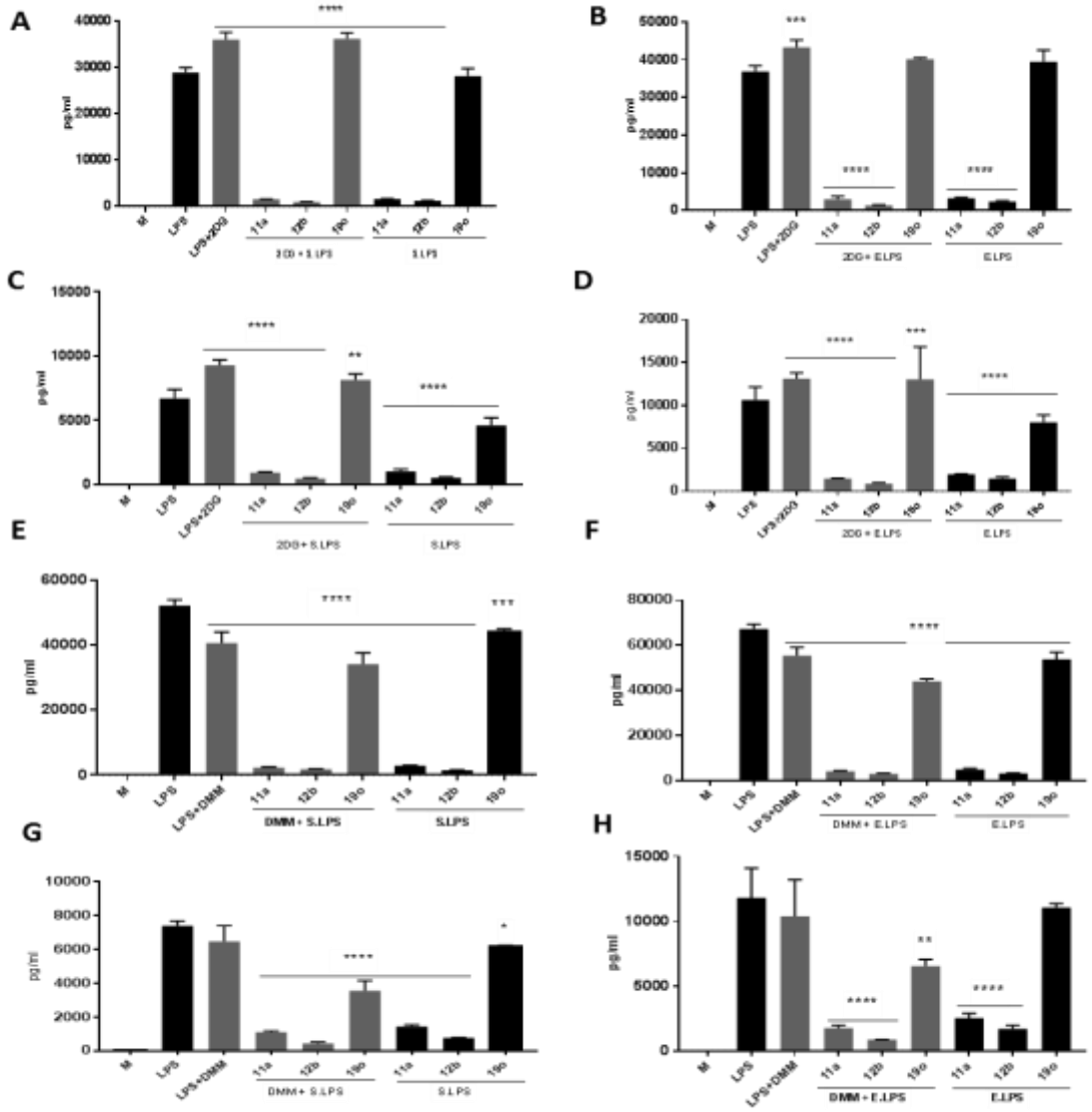

Figure 7.5.9: Exogenous addition of 2-deoxyglucose and DMM and their possible involvement in IL-6 production

2-deoxyglucose (A, B, C and D) and DMM (E, F, G and H) were added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A, C, E and G refer to Salmonella-LPS stimulation for 24 (A and E) and 48 hours (C and G) whereas B, D, F and H indicate Escherichia coli-LPS stimulation in which (B and F) shows 24 hours stimulation and (D and H) refers to 48 hours stimulation. LPS was compared to the culture medium while LPS+either substrate was compared to LPS. SMAs+substrates+LPS were compared to LPS+substrates wheras SMAs+LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

Taurine appears to be an important metabolite in the metabolomics profiles produced by the SMAs and therefore it was considered to be possibly involved in immunoregulation. Adding exogenous taurine in the presence of LPS was found to increase production of both IL-1β (24 and 48 hours) and IL-6 after 48 hours incubation above that obtained with LPS stimulation alone (figures 7.5.10 and 7.5.11). This categorises it as a proinflammatory metabolite. A study by Levy et al. reported taurine as a microbial metabolite that regulates the activation of the NLRP6 inflammasome (Levy et al., 2015). From the taurine levels found in macrophages stimulated with LPS, CpG, IFNγ and LPS+ IFNγ reported in chapters 3, 4, 5 and 6 it is clear that its elevation is part of the macrophage response. This suggests taurine's involvement in reprogramming cytokine production in LPS-activated macrophages. However, adding taurine exogenously did not interfere with the ability of 11a and 12b to decrease both cytokines (figure 7.5.10 A-D).

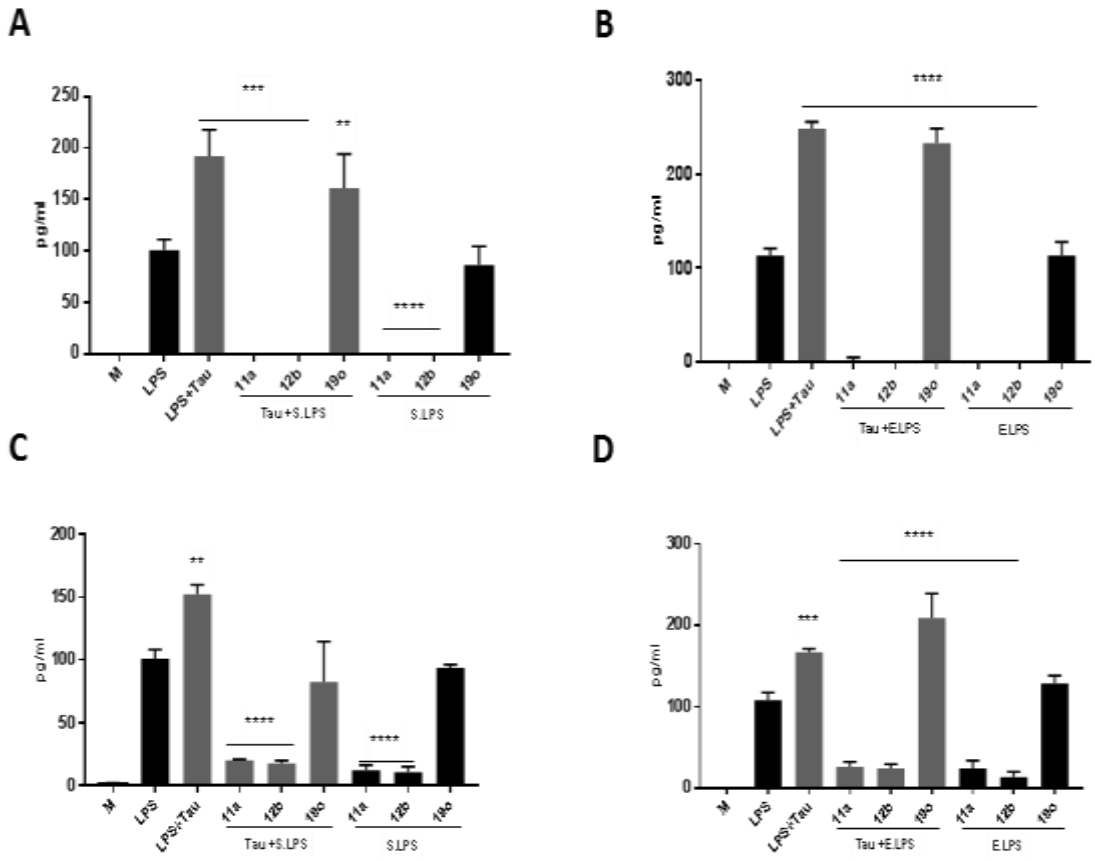

Figure 7.5.10: Exogenous addition of Taurine and its possible involvement in IL-1β production

Taurine (A, B, C and D) was added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A and C refer to Salmonella-LPS stimulation for 24 and 48 hours respectively whereas B and D indicate Escherichia coli-LPS stimulation for 24 and 48 hours respectively. LPS was compared to the culture medium while LPS+ taurine was compared to LPS. SMAs+taurine+LPS were compared to LPS+taurine wheras SMAs+LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

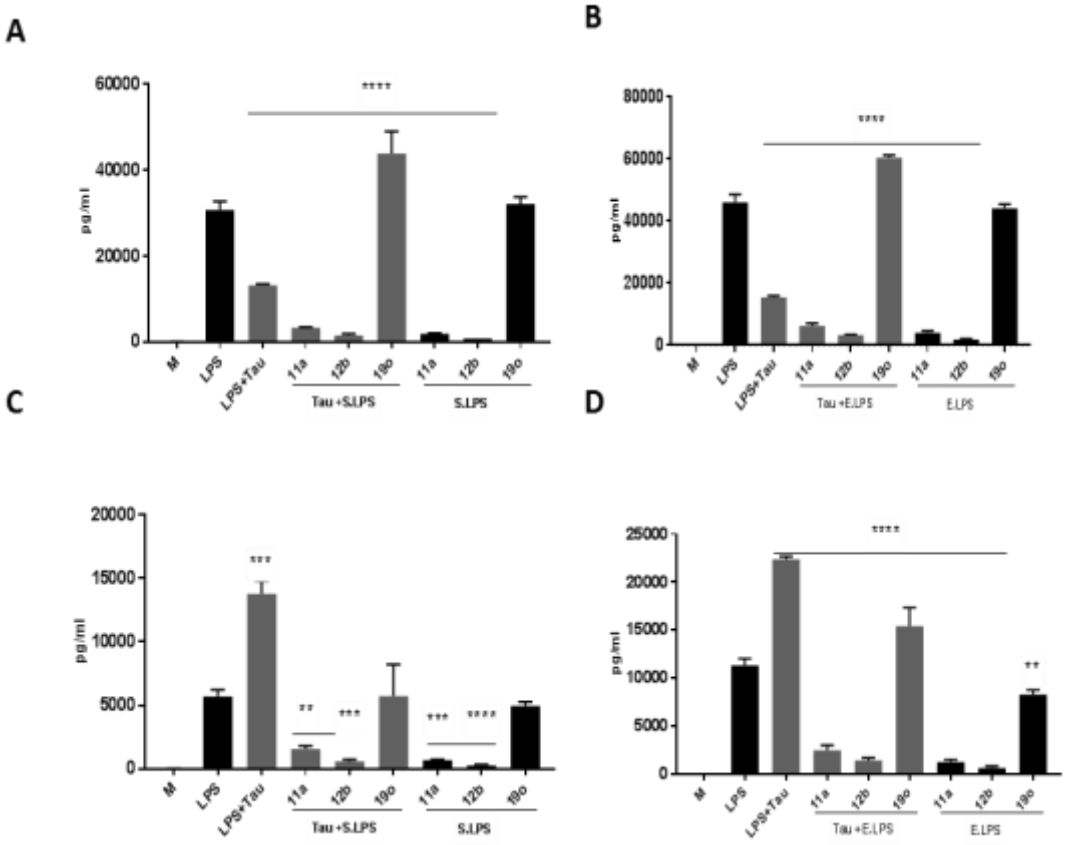

Figure 7.5.11: Exogenous addition of taurine and its possible involvement in IL-6 production

Turine (A, B, C and D) was added to LPS-activated macrophages pretreated or not with SMAs 11a, 12b or 19o. A and C refer to Salmonella-LPS stimulation for 24 and 48 hours respectively whereas B and D indicate Escherichia coli-LPS stimulation for 24 and 48 hours respectively. LPS was compared to the culture medium while LPS+ taurine was compared to LPS. SMAs+taurine+LPS were compared to LPS+taurine wheras SMAs+LPS were compared to LPS. Results are expressed as a mean (of triplicate determinations) ± SD and were analysed using one-way ANOVA with Bonferroni post-test where *p <0.05, **p <0.01, ***p<0.001, ****p < <0.0001.

7.2.5 Characterisation of SMA-effects on metabolism of the LPS / CpG activated macrophages and comparing it with M1 and M2 macrophages using Phenotype Microarrays

Using Biolog microarrays assay, the effect of SMA pre-treatment on the LPS/CpG activated macrophages was examined through assessing the consumption of carbon-energy substrates through measuring the NADH production level and then comparing with substrate consumption of M1 (LPS alone or LPS+IFNγ and M2 (IL-4) macrophages.

From the Biolog plates' examination, it was found that many of the carbon sources were used by the macrophages under study as seen in figures 7.6.1-7.6.6. However, at the same time, many of the substrates in the microarray plate do not appear to be useful as carbon sources (figure7.6.1, 7.6.3 and 7.6.5). There was a clear opposing pattern between LPS/CpG activated macrophages in comparison to SMA-pretreated, PAMP-exposed macrophages (figures 7.6.1- 7.6.2) and some similarity between the SMA pre-treatment and IL-4 metabolomic phenotype. In addition, 19o appears to be often behaving like the other SMAs. LPS-, LPS+IFNγ–, IL-4- and CpG-activated macrophages mainly favoured utilizing glucose and also mannose, glycogen and maltose as carbon sources and this utilization was slowed down by SMA-pretreatment (figures 7.6.2, 7.6.4and 7.6.6). Interestingly, SMA-pretreatment favoured galactose utilisation and this was also the case for IL-4 treatment (figures 7.6.2, 7.6.4and 7.6.6). The SMA-treated macrophages also favoured other carbon sources such as fructose, trehalose and melibiose showing their possible alternative carbon sources when there is an energy demands.

Producing more NADH from glucose-6-phosphate, glucose-1-phosphate and inosine, which also seen to be increased with IL-4- but not LPS+IFNγ-, LPS- and CpG-treated

cells (see figures 7.6.2, 7.6.4and 7.6.6,) and adenosine is suggesting possibly the conversion of glycolysis to the pentose pathway to provide more NADPH as shown from the SMAs' metabolomics profiling (chapter4 and 5). The consumption of inosine was also high in IL-4-treated macrophages (figure 7.6.6). The SMAs were additionally found to utilize adenosine (figure 7.6.2) and therefore this limits their ATP production, which was also seen in their metabolomic screen.

In the absence of glutamine, which is generally provided by complete RPMI medium but not Biolog media, neither Krebs cycle intermediates nor short chain fatty acids appear to be useful as carbon sources.

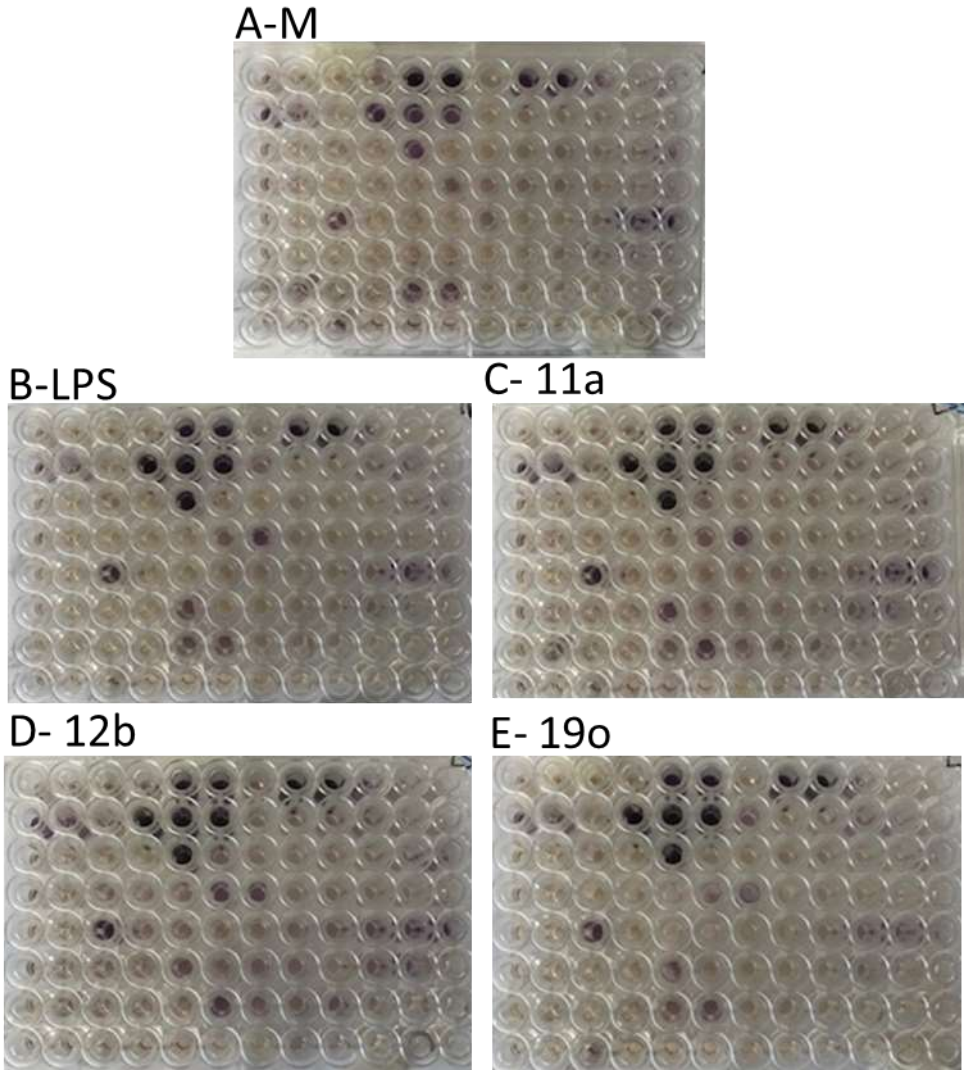

Figure 7.6.1: Carbon and energy consumption of LPS-activated macrophages and SMA-pre-treated, LPS-activated macrophages
PM-M1 carbon and energy sources BioLog plates were used to evaluate metabolic information from macrophages pre-treated with SMAs in comparison to LPS activated macrophages in which (A) refers to unstimulated macrophages (B) LPS stimulation (C), (D) and (E) shows the plates of LPS activated macrophages pre-treated with 11a, 12b or 19o respectively. Plate pictures were taken after 24 hour from dye reduction.

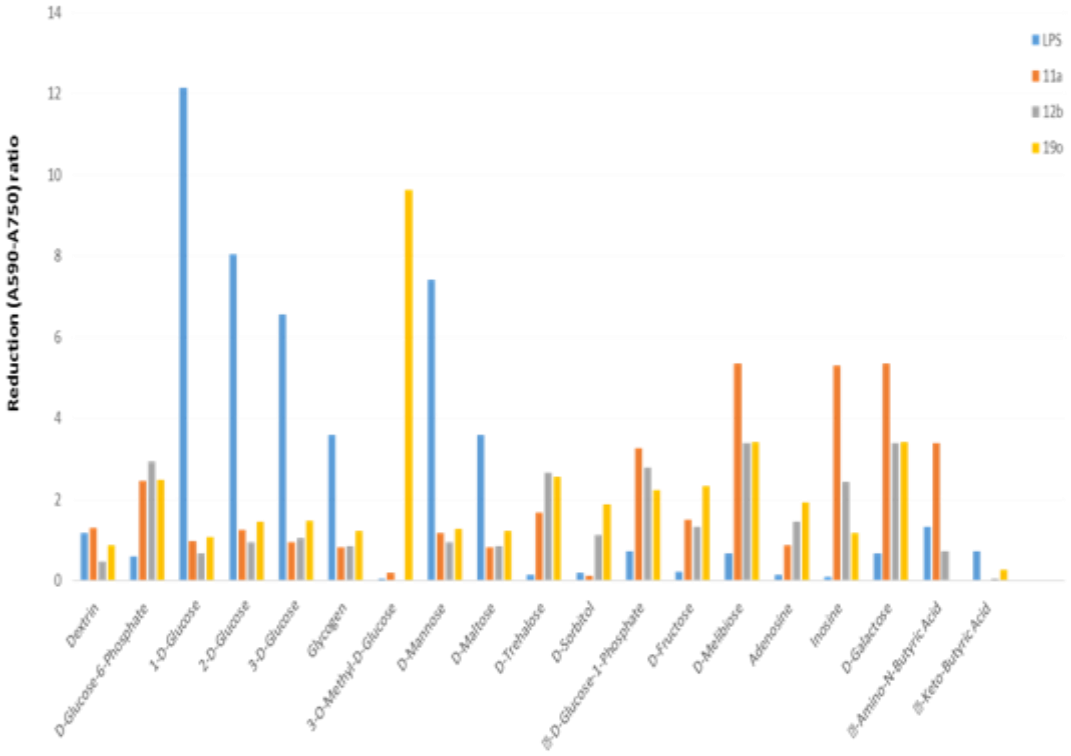

Figure 7.6.2: Carbon and energy substrate changes induced by SMA pretreatment of LPS- activated macrophages

Comparison of substrate metabolism of 24 hours LPS activation of macrophages and LPS activated macrophages pretreated with SMAs 11a, 12b or 19o for 18 hours. Dye was added after the end of the incubation time in which its reduction rate was monitored and was developed fully following 6-hour incubation of the treated cells. After subtracting the background readings, wells with no substrates, from all plates the reduction in ratio of LPS was calculated by dividing absorption of each substrate on the LPS plate with the corresponding substrate for the unstimulated macrophage sample whereas the SMAs ratios were calculated by dividing the absorption of each substrate on the LPS plate with the corresponding substrate on SMAs plates.

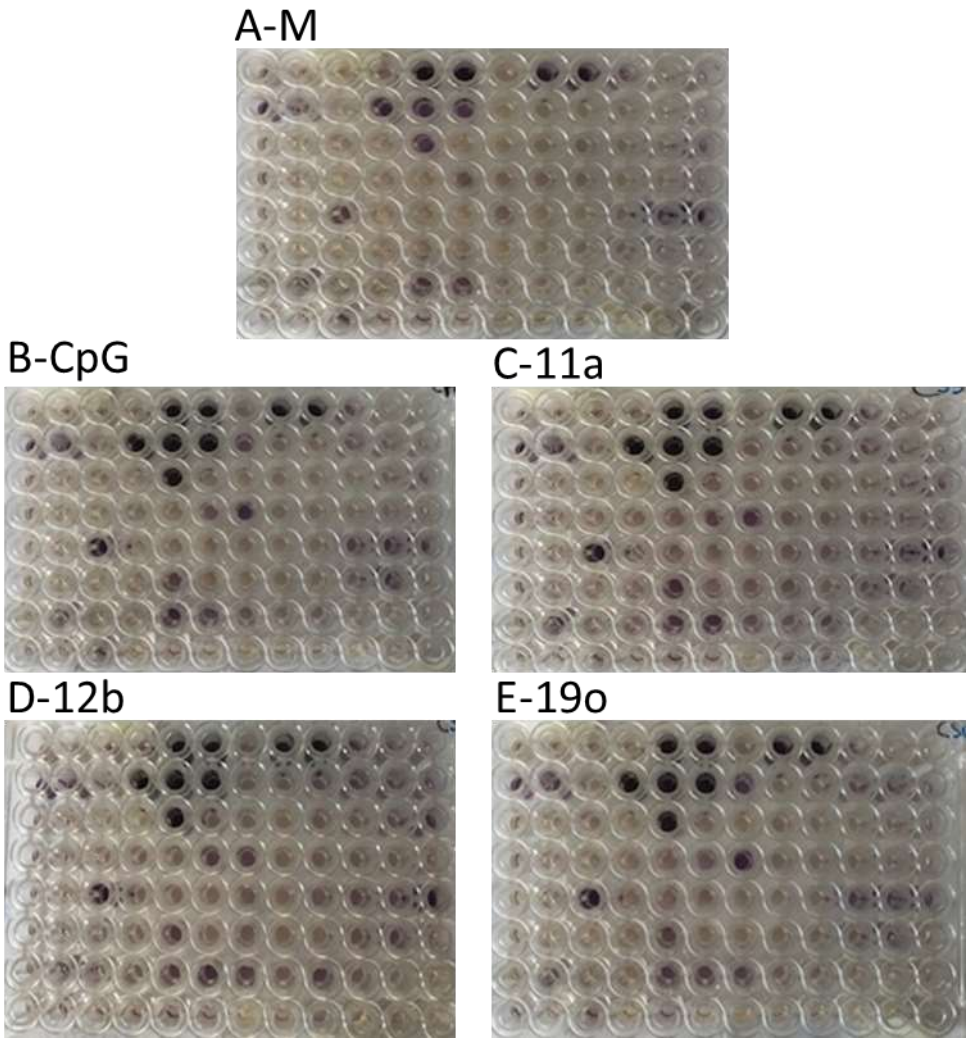

Figure 7.6.3: Carbon and energy consumption of the CpG-activated macrophages and SMA pre-treated macrophages followed by CpG treatment

PM-M1, carbon and energy sources, BioLog plates were used to evaluate metabolic information from macrophages pre-treated with SMAs in comparison to CpG activated macrophages in which (A) refers to unstimulated macrophages (B) CpG stimulation (C), (D) and (E) shows the plates of CpG activated macrophages pre-treated with 11a ,12b and 19o respectively. Plate pictures were taken after 24 hour from dye reduction.

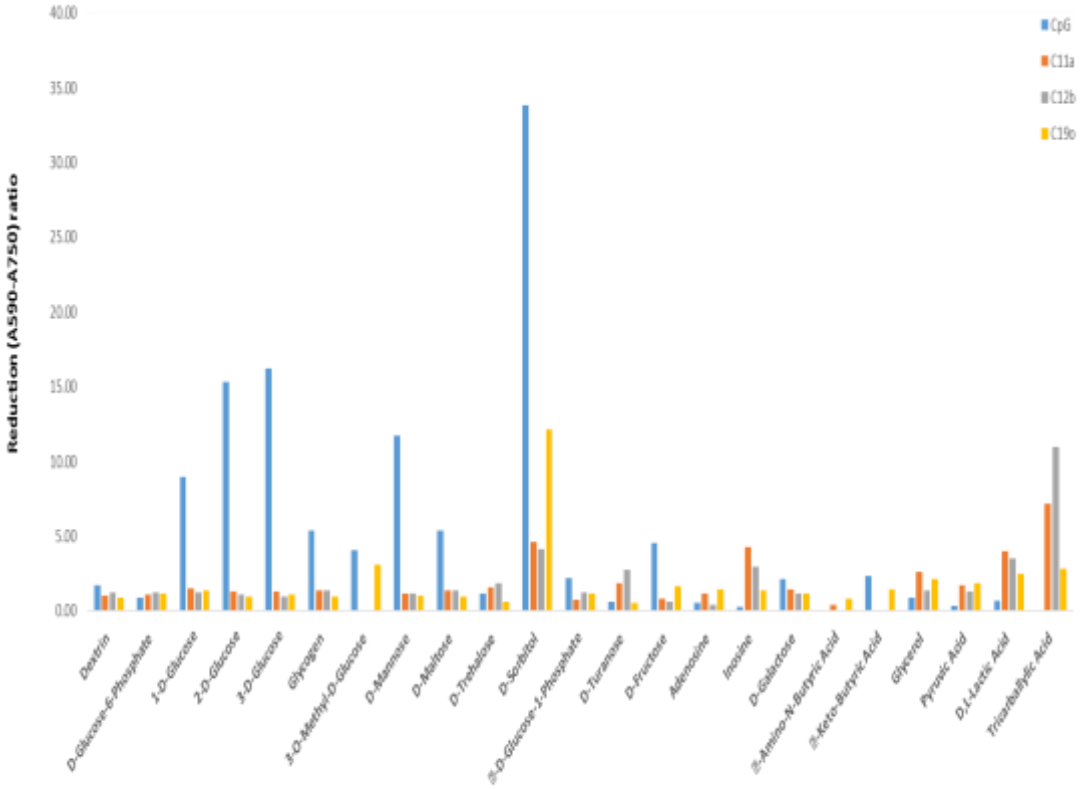

Figure 7.6.4: Carbon and energy substrates changes by SMAs pretreatment on CpG activated macrophages

Comparison of substrate metabolism of 24 hours CpG activation of macrophages and CpG activated macrophages pretreated with SMAs 11a, 12b or 19o for 18 hours. Dye was added after the end of the incubation time in which its reduction rate was monitored and was developed fully following 6-hour incubation of the treated cells. After subtracting the background readings, wells with no substrates, from all plates the reduction in ratio of CpG was calculated by dividing absorption of each substrate on the CpG plate with the corresponding substrate for the unstimulated macrophage sample whereas the SMAs ratios were calculated by dividing the absorption of each substrate on the CpG plate with the corresponding substrate on SMAs plates.

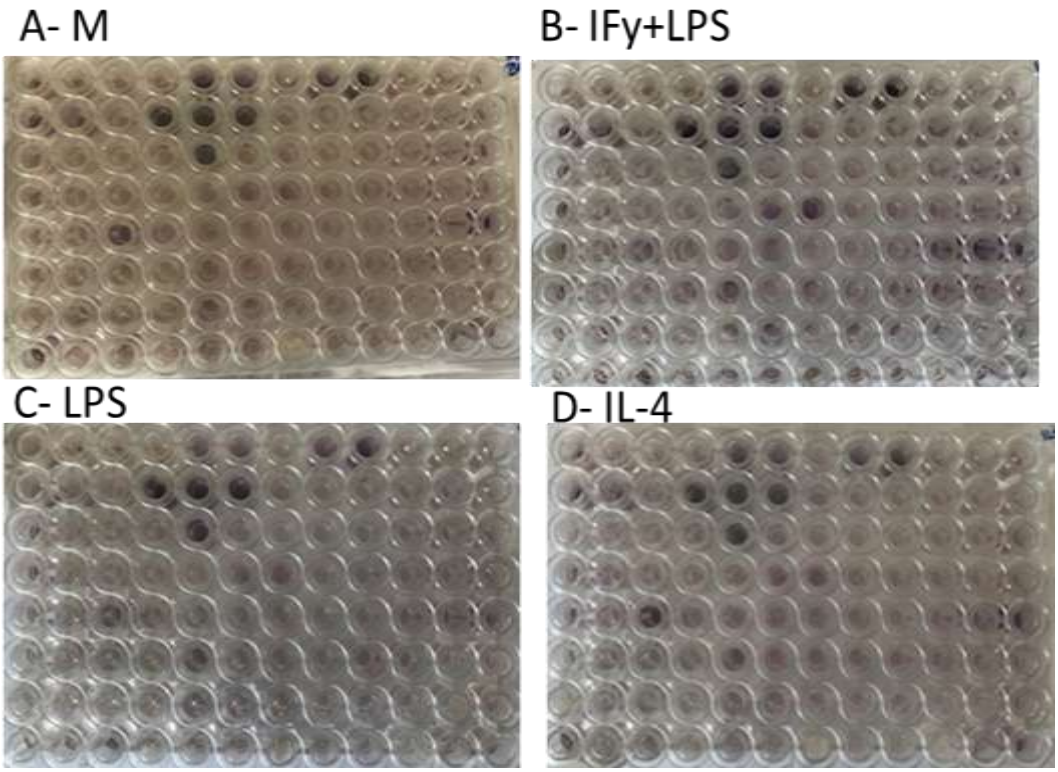

Figure 7.6.5: Carbon and energy consumption of M0, M1 and M2 activated macrophages

PM-M1, carbon and energy sources, BioLog plates were used to evaluate metabolic information from different activation status of macrophages over 24 hours. (A) refers to unstimulated macrophages (B) Co-stimulation of IFNγ+LPS (C)LPS and (D) IL-4. Plate pictures were taken after 24 hour from dye reduction.

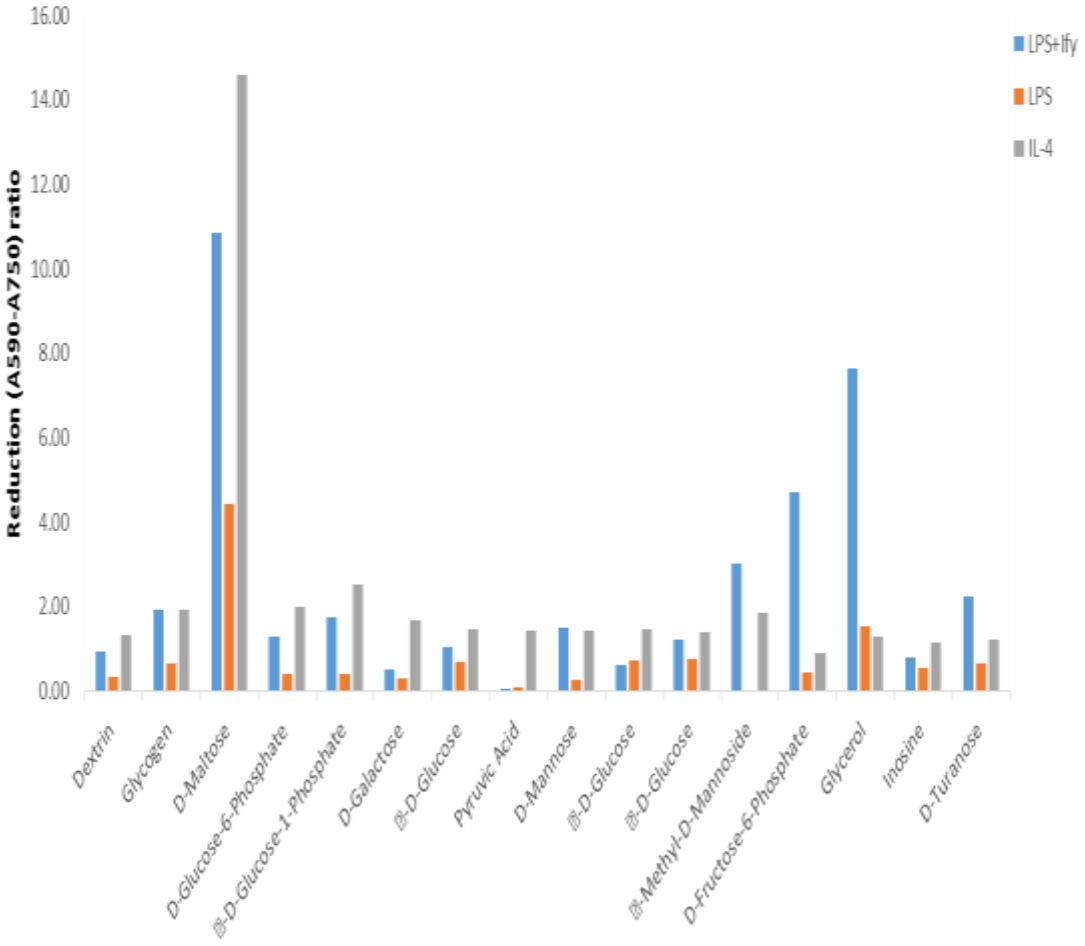

Figure 7.6.6: Carbon and energy substrate changes by the M0, M1 and M2 activated macrophages

Comparison of substrate metabolism of 24 hours LPS+IFNγ, LPS and IL-4 activation of macrophages. Dye was added after the end of incubation time in which its reduction rate was monitored and was developed fully following 6-hour incubation of the treated cells. After subtracting the background readings from the all plates the reduction ratio of LPS+IFNγ, LPS and IL-4 was calculated by dividing absorption of each substrate on each plate to the corresponding substrate on unstimulated macrophages.

7.3 Discussion

Pre-treatment of macrophages with 11a or 12b significantly alters the metabolism of the cell. Their main alteration involves the ability of the SMAs to upregulate glutathione biosynthesis, decrease creatine/phosphocreatine and taurine metabolism. SMAs as well, on their own or during activation with LPS or CpG, did not alter glycolysis and TCA cycle metabolism in comparison to unstimulated macrophages. Thus, several hypotheses were made based on changes observed with their metabolomic profile and investigated using biological assays to interpret as far as possible the SMAs' mechanism of action.

It was suggested that increased glutathione biosynthesis and GSSG formation might stem from the SMAs' effect on creatine uptake and thus indirectly on ATP transport out of the mitochondria. ROS species might be escaping from the mitochondria due to their increased permeability, which was indicated from an increase in oxidative stress metabolites. SMAs as well did not affect the activation of glycolysis and the TCA cycle by LPS/CpG so the high ATP pool level remain the same in all treatments versus control (chapter 3,4 and 5). All these changes would be expected to affect their mitochondria polarisation and thus it was suggested to investigate the SMAs effects on mitochondria membrane polarisation. This study was done using co-loading of cationic permeable fluorescent dye tetraethyl rhodamine methyl (TMRM) with mitotracker green (MTG). The stains then were assessed quantitatively by calculating the ratio of TMRM/MTG fluorescence intensities using fluorescence-activated cell sorting (FACS) in which the increases in TMRM/MTG represents hyperpolarisation and lower ratios represent the decrease in the polarisation of MMP while the qualitative assessment of them was undertaken using confocal microscopy (figures 7.2.1-7.2.9). Adding SMAs on their own did not change the MMP in

comparison to unstimulated macrophages (figure 7.1 A) whereas SMAs 11a and 12b but not 19o pre-treatment , under normal glucose stimulation, were found to reduce the MMP hyperpolarisation induced by LPS treatment significantly and still decrease it but not significantly in glucose- and glutamine-deprived conditions (figure 7.1 B-D). The mitochondria hyperpolarisation effect induced by LPS has been investigated previously and it was claimed that this hyper responsiveness is because mitochondria are no longer making ATP from oxidative phosphorylation (Tannahill et al., 2013). However, an increase in the rate of ATP synthesis can also result in an increase in mitochondrial potential (Brown, 1992). LPS had a significant effect on MMP, in comparison to unstimulated macrophages, but not in the absence of glucose or in the absence of glutamine and this suggests the importance of their presence on the MMP hyperpolarisation. The glutamine is of particular interest since it enters the TCA cycle as ketoglutarate (in terms of mass spectrometric response it is the most abundant metabolite in macrophages) and this again suggests the TCA cycle is functioning in the stimulated macrophages.

When LPS is combined with SMAs 11a, 12b, 2-DG, IL-4 or IL-10 a decrease in MMP is observed. The dissipating effect observed with IL-4 and more importantly IL-10 treatment perhaps suggests that SMA 11a and 12b pre-treatment is associated with anti-inflammatory behaviour in comparison to the pro-inflammatory phenotype of high MMP caused by LPS. 11a and 12b dissipate the MMP to a slightly higher extent in the absence of glucose in comparison to glutamine absence, suggesting the importance of glucose abundance to the the effect of SMAs in lowering MMP and showing again their similarity to 2-DG. 2-DG's ability to dissipate MMP decreased, but not significantly, in the absence of glutamine (figure 7.1 D). Moreover, the reduction in MMP does not suggest depolarisation in general as TMRM dye levels

were not lost by any treatment used or in unstimulated macrophages (figures 7.2.1-7.2.9).

The MMP-dissipating effect of the SMAs is not a result of a reduction in oxidative phosphorylation as none of SMAs affect the increased level of glycolysis and TCA metabolism stimulated by LPS /CpG. Thus, the hypothesis suggested by these data and the data in chapters 4 and 5 is that the decreased MMP is due to a lowering of creatine levels which reduces the ability of mitochondria to generate ATP (Zoratti and Szabò, 1995, Hüttemann et al., 2008). This hypothesis is supported by lower levels of ADP observed in the SMA-treated macrophages, in the case of LPS treatment, which is a major inhibitor of mitochondrial membrane permeability. Another possibility is that ROS species are escaping from mitochondria and thus leaving the mitochondria membrane more permeable. GSSG has been found to increase mitochondrial membrane permeability. Taurine might also pay a role since one of the major effectors for increasing mitochondrial membrane permeability is calcium and it has been proposed that taurine is able to regulate intracellular calcium levels (Chen et al., 2001). This can be supported by the decrease in glycerol-3-P as which is potential sources of ROS exist (Andreyev et al., 2005).

Lowering creatine levels was expected to affect motility of macrophages as creatine addition to tumor cells restores motility that has been hindered by cyclocreatine (CC) (Mulvaney et al., 1998) and therefore the effect of the SMAs on macrophage motility was tested using an *in vitro* transwell migration assay, a modified form of the classic Boyden chamber method (Boyden, 1962a), in which *calcein AM* was used to label migrated cells. LPS/CpG which produce an increase in creatine levels (chapter 4 and 5) represented positive controls for motility. Macrophages were starved for 5 hours in the top chamber (no FCS) and were tested for migration to a complete medium

supplied with all nutrients. SMA-pretreatment and LPS/CpG stimulation was carried out using the conditions applied for the cytokine study.

Adding SMAs alone (figure 7.3 A) did not affect migration of macrophages in relation to non-stimulated macrophages. However, LPS and CpG addition significantly induced cell migration to complete medium in comparison to unstimulated macrophages (figure 7.3 B-C). IL-4 addition did not alter macrophage migration in comparison to unstimulated ones (figure 7.3 B-C). SMA (11a and 12b) - pre-treatment prior to addition of LPS inhibited macrophage migration towards the complete medium in comparison with LPS activation alone and but only 11a inhibited migration with CpG stimulation. Therefore, the SMAs showed an interesting inhibitory effect on movement response in comparison to stimulation with LPS and CpG stimulation alone (figure7.3 B-C). This suggests that the SMAs by reducing creatine uptake, might inhibit macrophage motility that is induced by LPS/CpG where creatine levels within the cells are increased.

Moreover, SMA-pretreatment of LPS/CpG activated macrophages did not alter the activation level of glycolysis, TCA cycle and urea cycle, induced by both stimulants. Thus, it was expected that SMA-pretreatment would not affect nitric oxide production which is known to be induced when macrophages are activated with M1 stimulators (Murray and Wynn, 2011).

It was found that 18 hours pretreatment with SMAs alone did not induce/inhibit NO production (figure 7.4 A); however, pretreatment with SMAs 11a or 12b but not 19o, reduced nitrite production significantly after 24 hours exposure to LPS or CpG (figure 7.4 B-C). IL-4 was used in parallel to LPS and CpG, over 24 hours, and was found

not to induce any significant changes (figure 7.4 B-C).Thus, this suggests the SMAs possibly have their own mechanism of action in decreasing NO without altering glucose uptake which again may be explained by decreasing rate of ATP supply rather than the level of ATP which leads to mitochondria permeability and eventually may lead to lowering of oxidative phosphorylation. Certainly, lowering oxidative phosphorylation was previously reported to lower NO (Vats et al., 2006). Interestingly a previous study (Goodridge et al., 2001a) showed that ES-62 has no effect on nitric oxide production.

This effect could be indirect since the SMA-treated PAMP_exposed cells appear to be under greater oxidative stress than the cells treated with LPS and CpG alone (chapters 3 and 4) and thus they would require more NADPH to reduce GSSG back to GSH. NADPH is also required to convert hydroxyarginine to citrulline and NO.

Following on with inability of SMA-pretreatment of LPS/CpG activated macrophages to induce an alteration in the activation status of glycolysis and the TCA cycle, it was decided to co-stimulate SMAs pretreated macrophages for 3 hours with exogenous glycolysis and TCA cycle substrates before LPS stimulation. LPS samples from both *Escherichia coli (E. coli) and Salmonella typhimurium* (Sal.) were used in order to investigate if exogenous addition of substrates would change the ability of the SMAs to decrease IL-1β as well as IL-6. Other substrates such as dimethyl malonate, 2-deoxy glucose and taurine were tested as well (figures 7.5.1 - 7.5.11).

Adding the glycolysis substrates (figures 7.5.1-7.5.2) and TCA substrates (figures 7.5.3-7.5.6) did not induce further production of IL-1β or IL-6 by LPS. Adding 2-deoxy

glucose which inhibited IL-1β (7.5.8) but induced increased production of IL-6 (Figure 7.5.9) in comparison to LPS alone. Moreover, taurine addition induced increased production of both cytokines in comparison to LPS alone (figures 7.5.10-7.5.11). Succinate addition was further investigated using macrophages from two strains of *mice* C57BL/6 *and* BALB/c but a range of concentrations from 0.5 mM -20 mM did not induce further increases in IL-6 and IL-1β production in comparison to LPS-activated macrophages (figure 7.5.7). Pre-treatment of macrophages with SMAs and then adding the substrates described above 3 hours before LPS stimulation did not interfere with their ability to decrease either cytokine and therefore high availability of the substrate had no effect on the SMAs' immunomodulatory properties and suggested that their mode of action was not via changing activation of glycolysis or the TCA cycle by LPS (figures 7.5.1-7.5.8).Taurine which enhanced LPS production of both cytokines (figures 7.5.10-7.5.11) did not interfere with the SMAs' ability to decrease either cytokine and this points to the SMAs having some effect on either taurine uptake or biosynthesis. Indeed, the role of taurine in the inflammatory process suggested by the current work requires further investigation.

Another biological investigation was performed using Phenotype Microarrays (PMs) to examine which part of metabolism (cytosol or mitochondria) produces more energy in the form of NADH in SMAs+LPS/CpG conditions. Different macrophages activators IL-4, LPS and LPS + IFNγ, were tested as well for comparison. The Phenotype Microarrays (PMs) assay measures output of NADH production from different pathways through reducing the tetrazolium dye. The reduction level correlates positively with activation status (Berridge et al., 2005).

The SMA treatment appeared to result in less utilisation of glucose and thus less NADH production in comparison to LPS treatment alone. This is difficult to explain given that according to the metabolomics data (chapters 3 and 4) the NADH levels in the CpG- and LPS- treated macrophages were similar to those found in the macrophages treated with LPS/CpG + SMAs. However, considering that tetraethyl rhodamine methyl is not strongly retained in the mitochondria of LPS/SMA-treated macrophages it might be that the tetrazolium dye used in the Biolog assay is not strongly localised in the mitochondria of LPS/SMA treated macrophages. This would result in less efficient reduction of the dye since it largely depends on NADH (Berridge et al., 2005) and most of the NADH is localised in the mitochondria.

Thus, the Biolog assay is mainly measuring the degree of mitochondrial polarisation with high values being returned where the mitochondria are highly polarised. The utilisation of the different substrates other than glucose gives no consistent pattern and is difficult to interpret particularly since LPS and CpG appear to affect the macrophages differently with regard to their ability to utilise different substrates.

Chapter 8

General conclusions and future work

8.1 General conclusion

Treating macrophages with SMAs and then stimulating them with LPS/CpG for 24 hours decreases production of cytokines such as IL-6, IL-12 and IL-1β (Al-Riyami et al., 2013b). These important immunomodulatory effects induced by the SMAs prompted further investigation, in particular investigating their effects on the metabolome of the macrophages.

Treating the macrophages with SMAs alone induces changes in just a few metabolic pathways which include glutathione biosynthesis, taurine biosynthesis/uptake, creatine biosynthesis/uptake and glycerophosphoscholine biosynthesis/uptake (table 3.1).

From the profiles shown tables 4.1 and 5.1 in Chapters 4 and 5, LPS or CpG induce many significant alterations to the metabolism of the macrophage. These changes include increasing production of glutathione, glutathione disulphide, NADPH, taurine, glycolytic metabolites, TCA cycle metabolites, NADH and high energy phosphates such at ATP, GTP, UTP and creatine phosphate. Pre-treatment with the SMAs followed by addition of CpG or LPS consistently affected only a few pathways in comparison to CpG or LPS treatment alone. With data of this complexity it is difficult to see clear patterns but the most consistent effects of the SMAs were the same in the presence of LPS or CpG as those shown in table 3.1. They decreased intra-cellular levels of creatinine phosphate and, in the case of LPS treatment, intracellular levels of taurine. In addition, the SMAs increased the level of the cellular response to oxidative stress as indicated by increased levels of GSH and GSSG. These were largely the same effects as could be observed when the cells were treated with the SMAs alone. Thus, their key effect may be on controlling intracellular levels of creatine phosphate which would reduce the rate of ATP supply.

The question is can the above metabolomic changes be linked to the immunomodulatory effects of the SMAs? Thus, several assays were carried out to link the metabolomics effects to those produced by different activators (chapter 6), to motility (see chapter 7), and to nitric oxide production (chapter 7). Other assays included adding exogenously taurine, the glycolysis inhibitor 2-deoxy glucose and the TCA cycle substrate succinic acid to the SMA pre-treated macrophages before LPS stimulation and testing if the exogenous treatments would reprogramme/change the SMAs ability to decrease IL-6, IL-12 or IL-1β (chapter7). Moreover, with the increased level of NADH/ high activation of TCA cycle by SMA pre-treated macrophages in the presence of CpG/LPS activation it was of interest to further investigate this changed mitochondrial membrane potential (chapter 7). Carbon substrate utilisation was tested by using the BIOLOG assay to investigate whether a sole metabolite/carbon substrate would contribute more to NADH production (chapter7).

A conclusion from investigating macrophage M1/M2 phenotype, which was discussed fully in Chapter 6, over a 24h hour stimulation with LPS, IL-4, LPS+ IFNγ and LPS +IL-4 was that IFNγ produced many changes which were the same as those produced by LPS. Combination of IFNγ with LPS tended to promote these changes further. IL4 did not have the same effects as LPS and IFNγ on the metabolome. A major difference between IFNγ and IL4 was in the metabolism of arginine which was diverted into ornithine in case of M2 (IL4 treatment) and citrulline in the case of M1 (IFNγ, LPS treatment).

Other differences include a greater increase in glycolysis in the M1 phenotype without changes in the the levels of ATP in either the M1 or M2 phenotype. Upregulation of glycolysis/TCA cycle was obvious in either M1 or M2 cells judged by NADH

production and the increased levels of malate in the IFN-γ/LPS treated cells. Succinate levels were similar across all treatments. Itaconate increased in the LPS treatment and IFN-γ treatment but decreased in the combination treatment with the higher production of malate in this treatment suggesting greater flux through the TCA cycle. There was no obvious sign of a broken TCA cycle in all treatments which contradicts earlier work by O'Neill (O'Neill, 2015). In addition, pre-treating macrophages with SMAs alone (Chapter3) and then stimulating them with LPS/CpG (Chapter 4 and 5) did not affect the upregulation of glycolysis and TCA cycle induced by LPS/CpG as indicated by NADH levels which were not changed among all treatments. This possibly reveals that the central pathways, glycolysis and TCA cycle, are not the only pathways that can be linked to cytokine production as has been reported previously (O'Neill and Hardie, 2013, O'Neill, 2015, O'Neill et al., 2016) as SMA treatment decreases IL-6, IL-12 and IL-1β without affecting the central pathways and this was confirmed further using $^{13}C_6$-glucose labelling (chapters 4 and 5). This finding can be supported by the results obtained upon addition of glycolysis/TCA substrates to LPS-treated cells and to cells treated with LPS + SMAs which did not futher enhance IL-6/IL-1β production (chapter7).

The BIOLOG assay was employed to determine the effect of adding a sole carbon substrate/metabolite on NADH production in the LPS/CpG vs SMAs. Glucose used as the carbon substrate produced similar levels of NADH across the LPS and LPS+ SMA treatments (table 5.1) but in the Biolog assay the apparent utilisation of glucose was much higher in the case of the LPS treatment alone. Thus, it was proposed that the assay seemed to be largely focused on measuring the degree of mitochondrial polarisation rather than testing the effect of glycolysis/TCA substrates on central pathways. BIOLOG produced high values where the mitochondria were highly

polarized and the cationic tetrazolium dye became localised within the mitochondria as seen in Chapter 7.

Since the SMAs did not affect the increase in NADH production obtained by exposure to LPS it was of interest to determine whether the SMAs were having any effect on the polarisation of mitochondrial membrane (MMP) produced by LPS (Mills et al., 2016) and thus this was tested (Chapter 7). It was found that the SMAs dissipated the MMP in contrast to LPS which produced a high MMP. This could suggest that the mitchondria in the SMA-treated cells are operating at lower potential and thus are less effective at exporting ATP to be consumed possibly in macrophage motility, phagocytosis and perhaps signalling. Thus, motility of macrophages was tested and it was revealed that LPS-induced motility was significantly inhibited by SMA pre-treatment (Chapter 7).

As there is no change in activation of the TCA cycle by SMA treatment it was a consideration that this might be associated with higher nitric oxide production as has been shown for LPS activation. SMA pre-treatment in the presence of LPS/CpG activation decreased nitric oxide production significantly, an effect that was not shown with ES-62 treatment (Goodridge et al., 2001a).

The SMAs produce no effect on the central metabolic pathways when compared to LPS or CpG alone. Thus, it was clear that the SMA immunomodulatory effects were possibly arising from other pathways. From the metabolomic profiles, it was indicated that glutathione synthesis, creatine and taurine metabolism were the most consistently affected pathways (Tables 3.1, 4.1 and 5.1 in Chapters 3, 4 and 5). The

upregulation of the glutathione biosynthesis pathway by the SMAs may be providing more protection to the macrophages from oxidative stress and of note SMA12b has been previously linked to increased activity of the Nrf2/ARE/HO-1 anti-oxidant pathway (Suckling et al., 2018).

Overall the striking changes produced by the SMAs were in creatine and taurine metabolism, and of interest, these pathways have not been widely explored, or discussed extensively. In the case of taurine, earlier studies indicate that increased taurine production was linked with a heightening of anti-inflammatory effects (Wright et al., 1986, Learn et al., 1990, Schuller-Levis et al., 1995, Raschke et al., 1995, Warskulat et al., 1997b, Gordon et al., 1998, Seabra et al., 1998). However, taurine has recently been described as a pro- inflammatory metabolite (Guglani and Khader, 2010). In the current study, taurine was found to be pro-inflammatory and it promoted IL-1β release while the SMAs countered this effect. The decrease in the taurine biosynthesis/uptake may possibly be caused by the higher requirement for glutathione biosynthesis in the SMA-treated cells which may result in a diversion of cysteine away from the taurine pathway thus resulting in lower levels of taurine (chapter4 and 5).

A decrease in the availability of creatine may be associated with impaired transport of ATP from the mitochondria to where it is required for biological functions including cell signalling, phagocytosis, motility and possibly limiting cytokine production.

Overall, the SMAs seem to be exerting their effects by controlling the transport /availability of energy to where it's needed for possibly a higher control of immune

functions and this may help explain their immunomodulatory functions without inducing either an M1 or M2 phenotype.

Thus overall, the current working hypothesis it that the SMAs may be inhibiting creatine, possibly taurine and possibly even glycerophosphocholine uptake from the culture medium. This scenario might fit well with the original ES-62 lead compound which as a protein would be more likely to be active at the cell surface. These hypotheses are now testable and this will provide the basis for future work.

8.2 Future work

Due to limited/fixed time of lab work during the PhD study, several assays were planned/discussed but unfortunately could not be tested in this project. One of the assays was designed to understand the suggested effects of the SMAs in controlling energy transport/availability through decreasing creatine and taurine uptake/production. Guanidino propionate is a potent inhibitor of creatine uptake and it would be possible to test its effect on LPS or CpG stimulated IL-1β production. Similarly, guanidino ethane sulphonate is an inhibitor of taurine uptake and this could also be tested. Such studies could possibly reveal new anti-inflammatory drug targets.

Another interesting thing to investigate would be the effect of the SMAs on taurine and creatine levels in the growth medium and thus possibly establish if their biosynthesis what was affected or their uptake were inhibited. This study might be enhanced by using labelled versions of these substrates to measure rate of uptake.

More extensive use of $^{13}C_6$-glucose labelling could reveal more about the effects of different treatments on flux through glycolysis and TCA pathways. It would be of interest to use labelled glutamine to probe the flux through various pathways. Glutamine is the most abundant metabolite in the macrophages based on its MS response and is obviously key to their function. Three years was not enough time to fully probe the complex metabolism of these cells.

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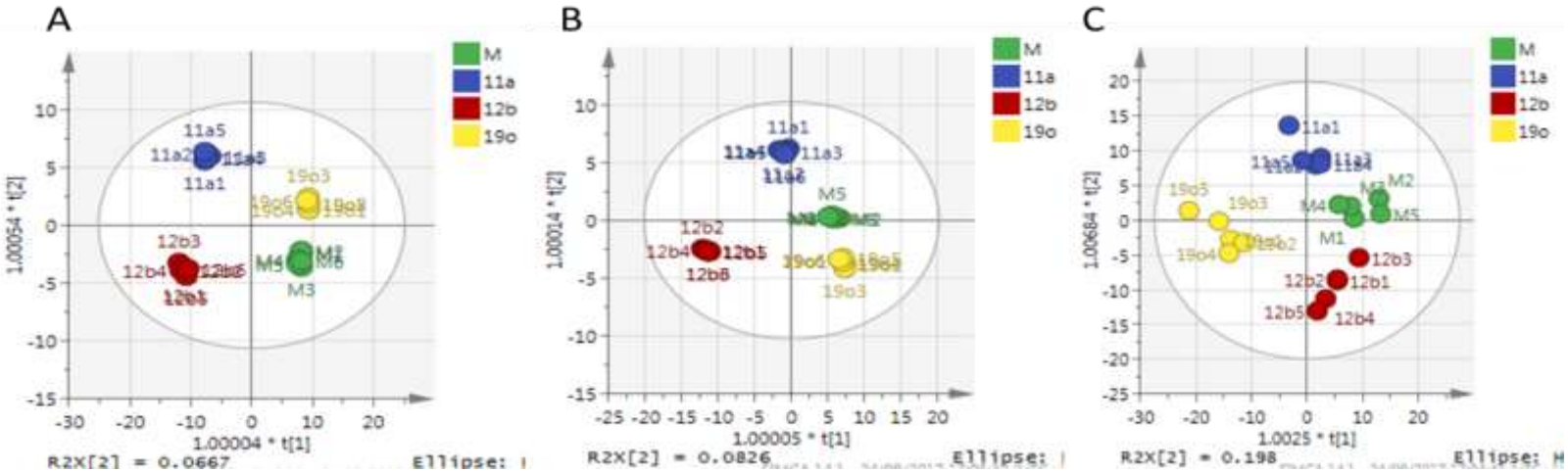
Appendix

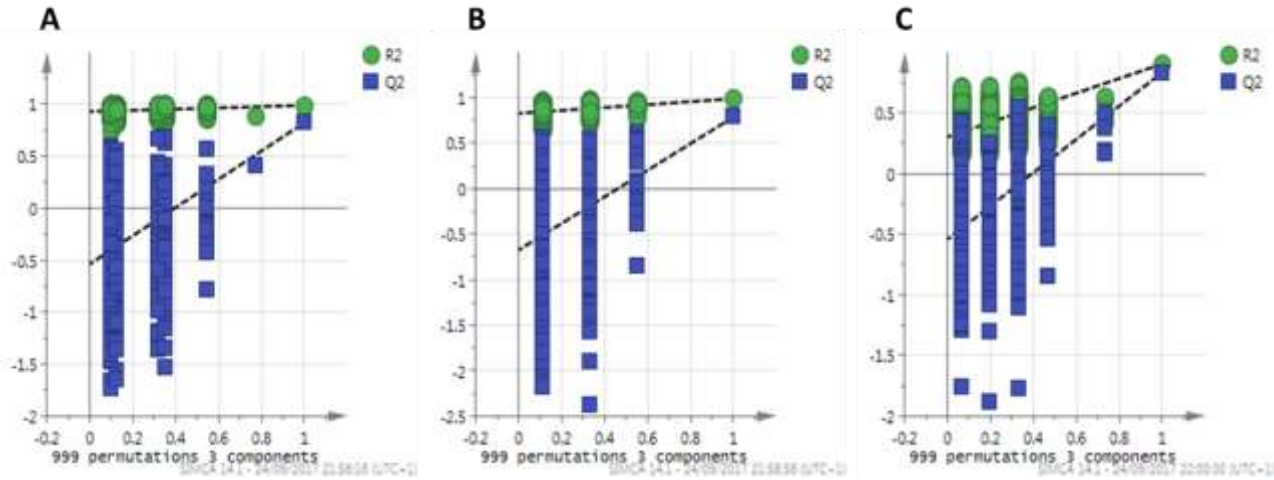
Appendix 1: Orthogonal Partial Least Square Discriminant Analysis (OPLS-DA) score plots of the three SMA runs

OPLS-DA score plots are shown for the overview of the SMA treatment models A, B and C (figure 3.2.2) obtained from three separate runs. Each model includes four groups, group 1 (green) represents unstimulated macrophages, group 2 (blue) represents 11a treatment, group 3 (red) represents 12b treatment and group 4 (yellow) represents 19o treatment. Model **A** consists of 442 variables and was explained by three predictive x-score components and 6 orthogonal ones (3+6). The predictive components explain 47.3 % of the variation in x while A orthogonal components explain 42.4% of the variation and so the total explained variation by x, R^2X (cum), is equal to 89.8%, R^2Y (cum) = 1, R^2 (cum) = 99.2 %, and the goodness of prediction Q^2 (cum) is equal to 77.5%. Model **B** includes 603 variables and was explained by three predictive x-score components and 5 orthogonal ones (3+5). Its Predictive components explain 45 % of the variation in x while its orthogonal ones explain 40 % of the variation. The R^2X explained variation is equal to 85% while R^2Y (cum) = 1, R^2 (cum) = 99.5% and the goodness of prediction Q^2 (cum) = 82.9%. 442 variables by model **C** were explained by three predictive x-score components, only (3+0) and their explanation is equal to 69.1 %. It's R^2Y (cum) = 1, R^2 (cum) = 92.5%, and C goodness of prediction Q^2 (cum) is equal to 87.6 %.



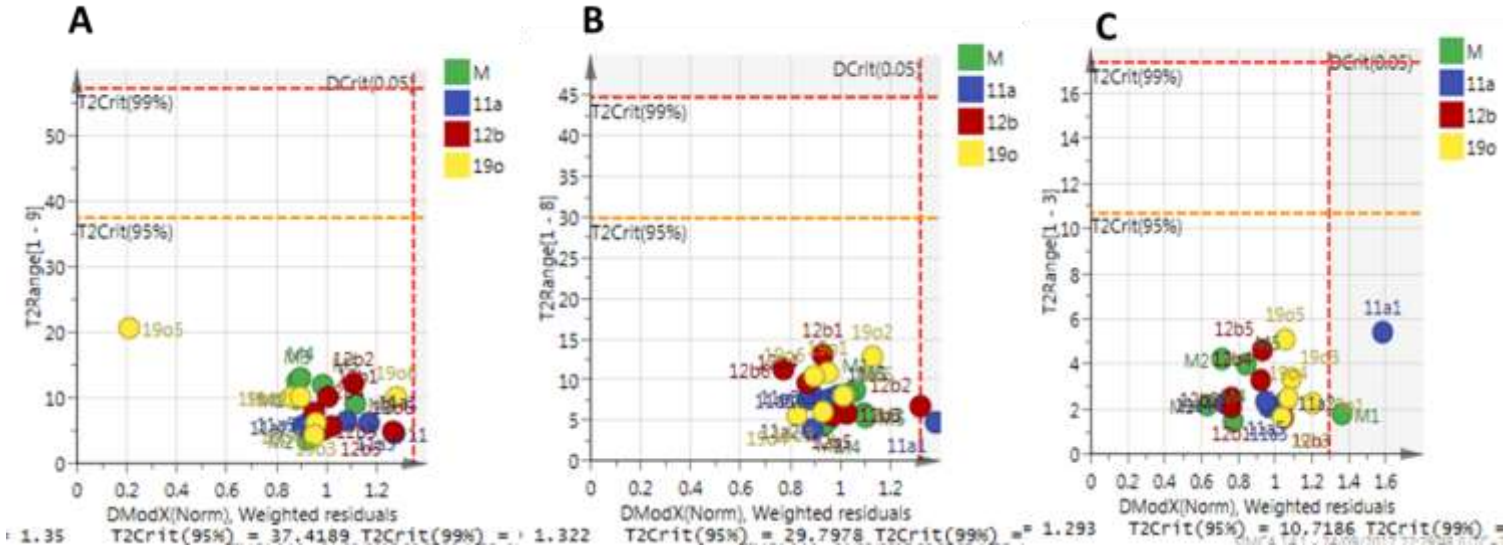
Appendix 2: Permutations test of the three SMA runs

Models' validation, using a 999 random permutations test for the supervised models of SMAs (11a, 12b or 19o)-treated macrophages versus unstimulated macrophages, has been generated using SMICA. The goodness of fit (R2) and predictive capability (Q2) values on the right-hand side of the plot are of the true model, whereas the permutated model parameters are represented on the left-hand side of the plot. The correlation coefficients between true and permutated models represent the X axis and has a correlation of 1.0 with itself. SMA-treated macrophage models (A, B and C) exhibited higher true values, R2 and Q2, than those of the permutated models. This classifies the investigated SMA models a true models. **A** model intercepts are: R 2 = (0.0, 0.927) and Q 2 = (0.0, − 0.562), **B** model intercepts are R 2 = (0.0, 0.629) and Q 2 = (0.0, − 0.591) whereas model **C** intercepts are: R 2 = (0.0, 0.307) and Q 2 = (0.0, − 0.524).



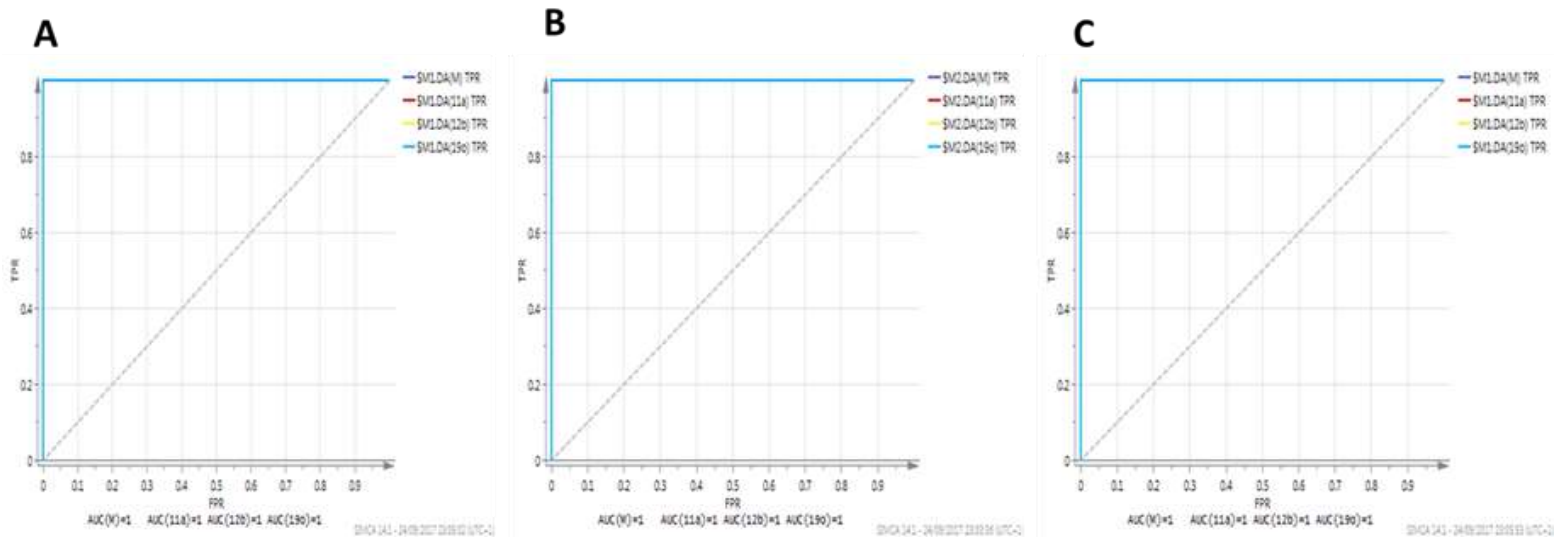
Appendix 3: Distance to model (DModX) vs Hotellings T^2 plot for the three SMA runs.

DModX on x-axis versus Hotelling's T2 on Y-axis.Hotelling's T2 on Y-axis is showing two limits on the y-axis. The first one, T2Crit (95%), is called the waring limit and represented by yellow dotted line whereas the second one, T2 Crit (99%), is called the action limit and is represented by a red dotted line. On the x-axis, the red dotted line indicates DModX and uses critical distance DCrit at level 0.05. Observations are considered as strong outliers if they are located above the action limit or above the warning limit plus DModX critical limit. The Investigated **A, B** and **C** models are showing models with no strong or even moderate outliers from the tested groups.



Appendix 4: Area under the receiver operating characteristics Curve (AUROCC) for SMA models

ROC curves show sensitivity true positive rate (TPR) on the y-axis versus false positive rate (FPR = 1 - Specificity) on the x-axis generated using cross-validated predicted-Y values of the three (**A, B and C**) investigated OPLS-DA models. The area under the ROC curves (AUC) for unstimulated macrophages (M) is 1, 11a-treated macrophages (11a) is 1, 12b-treated macrophages (12b) is 1 and AUC for 19o-treated macrophages is equal to 1. This assesses OPLS-DA models (A, B and C) as models with very strong power that have an excellent ability to distinguish features between unstimulated macrophage and SMA- treated ones.



Appendix 5: The list of detected metabolites that have changed following SMA11a, 12b and 19o treatment in comparison to untreated macrophages. DM refers to detection mood, m/z to mass to ratio, RT to raw retention time and p to P-value

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
-	191.056	13.3	Quinate	0.001	2.351	<0.001	2.081	<0.001	2.550
-	176.936	16.6	Pyrophosphate	0.001	0.351	<0.001	0.441	0.766	0.962
-	317.225	13.6	amo-1618	0.005	0.335	<0.001	0.474	0.957	1.007
+	353.157	31.8	9-[6(RS)-C-carboxamido-5,6,7-trideoxy-β-D-ribo-octofuranosyl]-9H-purin-6-amine	0.007	0.533	<0.001	0.613	0.834	1.017
-	140.978	31.8	dimethylthiophosphate	0.007	0.430	<0.001	0.579	0.959	0.995
-	215.033	14.8	2-C-Methyl-D-erythritol 4-phosphate	0.008	0.548	0.011	0.532	0.159	1.319
-	130.062	15.5	Creatine	0.009	0.509	<0.001	0.559	0.248	1.107
-	788.544	3.8	PS(18:0/18:1(9Z))	0.009	4.380	0.002	4.657	0.761	1.137
-	215.033	14.1	2-C-Methyl-D-erythritol 4-phosphate	0.010	0.313	0.001	0.314	0.752	1.084
+	106.039	31.9	Cyanopyrazine	0.012	0.533	0.002	0.679	0.065	1.213
+	234.077	14.5	2-Hydroxy-6-oxo-(2'-aminophenyl)-hexa-2,4-dienoate	0.013	1.395	0.012	1.193	0.992	1.001
+	216.063	16.3	sn-glycero-3-Phosphoethanolamine	0.013	0.535	<0.001	0.540	0.579	0.952
+	132.077	15.5	Creatine	0.014	0.482	<0.001	0.534	0.148	1.153
-	171.007	15.3	sn-Glycerol 3-phosphate	0.015	0.493	<0.001	0.453	0.381	0.928
+	146.118	14.2	4-Trimethylammoniobutanoate	0.015	0.467	<0.001	0.327	0.176	0.920
+	234.077	16.1	2-Hydroxy-6-oxo-(2'-aminophenyl)-hexa-2,4-dienoate	0.017	1.508	<0.001	1.300	0.768	0.983
+	790.561	3.8	PS(18:0/18:1(9Z))	0.020	3.732	0.002	4.283	0.965	1.019
+	162.112	14.0	L-Carnitine	0.020	0.529	<0.001	0.382	0.972	0.996
-	214.049	16.3	sn-glycero-3-Phosphoethanolamine	0.021	0.565	<0.001	0.550	0.959	0.995
-	246.057	13.5	3-Nitrofluoranthene	0.022	0.633	0.001	0.744	0.948	0.996
-	215.033	15.1	2-C-Methyl-D-erythritol 4-phosphate	0.023	0.568	0.014	0.539	0.457	1.152
+	258.11	15.2	sn-glycero-3-Phosphocholine	0.024	0.449	<0.001	0.414	0.562	1.056

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	712.068	13.6	Adenophostin B	0.025	0.181	<0.001	0.382	0.910	0.982
+	212.164	7.6	Elaeokanine C	0.026	0.681	0.029	0.762	0.002	0.692
+	752.56	4.0	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.027	3.274	0.012	3.089	0.983	1.010
+	204.123	11.5	O-Acetylcarnitine	0.027	0.588	<0.001	0.548	0.312	0.946
+	247.058	13.4	Glycerophosphoglycerol	0.029	0.486	<0.001	0.533	0.074	0.872
-	838.56	3.8	1-22:1-2-18:3-phosphatidylserine	0.032	4.127	0.006	4.846	0.991	0.993
-	308.099	13.9	N-Acetylneuraminate	0.034	0.434	<0.001	0.557	0.088	0.876
-	245.043	13.4	Glycerophosphoglycerol	0.038	0.467	<0.001	0.520	0.254	0.903
-	192.018	15.8	creatinine phosphate	0.040	0.518	<0.001	0.636	0.342	1.072
+	110.027	15.8	Hypotaurine	0.041	0.593	<0.001	0.632	0.927	0.994
+	813.685	4.2	SM(d18:1/24:1(15Z))	0.041	6.131	0.006	7.125	0.948	1.051
-	885.549	3.8	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.043	2.045	0.001	2.560	0.807	1.067
+	212.043	15.9	Phosphocreatine	0.045	0.577	<0.001	0.696	0.576	1.040
-	210.029	15.9	Phosphocreatine	0.046	0.543	<0.001	0.626	0.497	1.057
-	248.979	13.6	Oxidized Photinus luciferin	0.055	0.022	<0.001	0.190	0.688	0.915
+	734.571	4.2	[PC (16:0/16:0)] 1-hexadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.058	3.013	0.004	3.357	0.706	1.147
+	788.618	4.1	[PC (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.058	2.998	0.004	3.625	0.757	0.850
-	331.264	3.9	[FA (22:4)] 7Z,10Z,13Z,16Z-docosatetraenoic acid	0.066	0.564	<0.001	0.579	0.274	0.871
+	746.607	4.1	PC(16:0/P-18:0)//PC(18:0/P-16:0)	0.078	2.755	0.005	3.644	0.930	0.958
-	810.528	3.8	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.084	1.948	0.007	1.980	0.960	1.013
-	836.544	3.8	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.087	1.975	0.006	2.135	0.989	1.004
-	722.512	4.0	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.107	1.797	0.020	1.818	0.790	0.926
-	748.528	4.0	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.109	1.737	0.011	1.882	0.799	0.933
+	137.046	10.8	Hypoxanthine	0.112	0.519	0.002	0.606	0.325	0.852
-	188.056	14.7	N-Acetyl-L-glutamate	0.119	0.635	<0.001	0.692	0.436	1.041
+	703.575	4.3	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.129	2.106	0.003	2.499	0.799	1.075

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	724.528	4.0	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.134	1.755	0.020	1.820	0.833	0.939
+	760.586	4.2	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.139	1.934	0.003	2.551	0.977	1.009
-	834.528	3.8	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	0.144	1.749	0.008	1.910	0.923	0.976
-	346.073	13.9	Hydroxysanguinarine	0.153	0.048	<0.001	0.309	0.040	0.785
+	750.544	4.0	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.156	1.669	0.020	1.786	0.795	0.927
+	812.544	3.8	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.170	1.649	0.020	1.681	0.980	1.006
+	748.528	4.0	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.198	1.675	0.035	1.783	0.743	0.897
+	822.638	4.1	PC(22:4(7Z,10Z,13Z,16Z)/P-18:0)	0.268	1.659	0.007	2.256	0.487	0.664
+	786.603	4.1	[PC (18:1/18:1)] 1-(9Z-octadecenoyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.301	1.574	0.011	2.092	0.874	0.950
+	836.618	4.1	[PC (18:0/22:5)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.316	1.486	0.015	1.752	0.869	0.954
+	766.575	4.1	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.328	1.402	0.005	1.559	0.777	0.951
+	703.576	7.6	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.345	2.553	0.002	4.368	0.499	1.290
+	810.602	4.1	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	0.432	1.336	0.016	1.652	0.886	0.964
+	732.555	4.2	[PC (14:0/18:1)] 1-tetradecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.446	1.337	0.001	2.163	0.996	1.001
+	792.591	4.1	PC(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.510	1.260	0.002	1.593	0.850	0.967
+	758.571	4.1	[PC (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	0.572	1.225	0.001	1.853	0.931	0.983
+	820.623	4.1	PC(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	0.658	1.184	0.011	1.609	0.654	0.909
+	834.602	4.1	[PC (18:1/22:5)] 1-(11Z-octadecenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.682	1.152	0.015	1.464	0.655	0.903
+	768.591	4.1	PC(18:2(9Z,12Z)/P-18:1(11Z))	0.702	1.153	0.018	1.546	0.794	0.942
-	357.301	4.1	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.707	1.115	0.004	1.403	0.677	0.944
-	540.054	14.9	Cyclic ADP-ribose	0.801	0.928	<0.001	1.497	0.945	1.004
+	836.544	3.7	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	0.855	1.053	0.046	1.168	0.661	1.039
+	818.607	4.1	[PC (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	0.869	0.943	0.040	1.333	0.307	0.800
-	662.102	14.9	NAD+	0.877	0.957	<0.001	1.491	0.890	0.991

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	794.607	4.2	[PC (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.886	1.051	0.031	1.354	0.737	0.942
+	524.371	4.7	[PC (18:0)] 1-octadecanoyl-sn-glycero-3-phosphocholine	0.926	0.972	0.040	1.142	<0.001	1.498
+	329.267	4.1	MG(0:0/16:1(9Z)/0:0)	0.964	0.990	0.003	1.207	0.488	1.061
+	808.586	4.1	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.975	1.010	0.040	1.251	0.959	0.993
+	782.57	4.1	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.998	1.001	0.013	1.362	0.940	1.011
+	205.035	16.8	Oxaloglutarate	<0.001	1.775	<0.001	1.651	0.698	0.965

Appendix 6: The list of detected metabolites that have changed following SMA11a, 12b and 19o treatment in comparison to untreated macrophages. DM refers to detection mood, m/z to mass to ratio, RT to raw retention time and p to P-value.

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	358.164	15.6	deacetylcolchicine	<0.001	1.666	0.001	1.449	<0.001	1.877
+	372.311	4.8	Tetradecanoylcarnitine	<0.001	0.791	0.021	0.839	<0.001	1.383
+	522.355	4.7	1-Oleoylglycerophosphocholine	<0.001	1.372	<0.001	1.473	<0.001	1.525
+	408.311	3.9	Cassaidine	<0.001	0.798	0.051	0.891	0.260	0.888
+	480.345	4.7	[PC (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphocholine	<0.001	1.256	<0.001	1.323	<0.001	1.431
-	287.141	4.2	Methyl 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-p-toluate	<0.001	2.038	0.015	1.552	<0.001	2.962
-	329.249	3.8	Taxa-4(20),11(12)-dien-5alpha-yl acetate	<0.001	1.343	<0.001	1.377	<0.001	1.965
+	510.356	4.7	LysoPC(17:0)	<0.001	1.390	<0.001	1.353	<0.001	1.513
+	768.555	4.0	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.768	0.532	1.037	0.073	0.827
-	303.233	3.9	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	<0.001	1.256	0.023	1.144	<0.001	1.653
+	146.118	13.9	4-Trimethylammoniobutanoate	<0.001	0.714	<0.001	0.578	<0.001	1.482
-	500.279	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.698	0.108	1.213	0.012	1.270
+	744.591	4.1	1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphonocholine	<0.001	1.148	0.000	1.360	0.695	0.976
-	369.068	4.4	Digalacturonate	<0.001	1.627	0.205	1.129	0.001	1.564
+	496.34	4.7	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.323	<0.001	1.408	<0.001	1.484
+	502.292	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.643	0.412	1.118	0.080	1.214
-	215.033	13.9	2-C-Methyl-D-erythritol 4-phosphate	<0.001	1.512	0.607	0.944	0.001	2.323
-	130.062	15.2	Creatine	<0.001	0.713	0.026	0.779	<0.001	1.498
+	494.324	4.8	[PC (16:0)] 1-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	1.342	<0.001	1.504	<0.001	1.567
+	524.371	4.6	[PC (18:0)] 1-octadecanoyl-sn-glycero-3-phosphocholine	0.001	1.337	0.001	1.338	<0.001	1.527
+	188.071	12.3	Deethylatrazine	0.001	1.527	0.004	1.389	<0.001	2.088
+	482.361	4.8	[PC (16:2)] 1-hexadecyl-sn-glycero-3-phosphocholine	0.001	1.256	<0.001	1.511	<0.001	1.633
+	198.087	10.5	N-Acetyl-L-histidine	0.001	1.625	0.428	1.109	0.004	1.727

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	792.591	4.0	PC(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.001	1.153	0.001	1.294	<0.001	1.247
+	133.032	12.1	THTC	0.001	1.565	0.005	1.427	<0.001	2.109
+	205.097	12.3	L-Tryptophan	0.001	1.448	0.005	1.349	<0.001	1.954
+	162.076	11.5	L-2-Aminoadipate	0.001	1.244	0.009	1.166	<0.001	1.757
+	132.077	15.2	Creatine	0.001	0.769	0.048	0.843	<0.001	1.622
+	427.095	17.0	S-glutathionyl-L-cysteine	0.001	1.484	0.001	1.548	<0.001	1.738
-	140.978	32.2	dimethylthiophosphate	0.001	1.286	0.112	1.108	0.006	1.397
-	437.268	4.6	[GP (18:0)] 1-octadecanoyl-2-sn-glycero-3-phosphate	0.001	1.341	0.001	1.385	<0.001	1.689
+	228.098	10.9	Deoxycytidine	0.001	1.356	0.008	1.300	<0.001	2.137
+	150.058	12.2	L-Methionine	0.001	1.491	0.006	1.354	<0.001	1.940
-	409.236	4.8	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.001	1.338	<0.001	1.493	<0.001	1.640
-	333.048	12.9	Nicotinamide D-ribonucleotide	0.001	1.438	0.001	1.541	<0.001	2.229
-	168.067	8.4	Pyridoxine	0.001	1.270	0.544	1.037	<0.001	1.433
+	176.071	4.4	Indole-3-acetate	0.001	1.388	0.023	1.197	<0.001	1.710
+	793.557	4.0	acyl phosphatidylglycerol (n-C12:0)	0.001	0.790	0.506	1.057	0.092	0.828
-	305.249	3.9	[FA (20:3)] 8Z,11Z,14Z-eicosatrienoic acid	0.002	1.386	0.015	1.273	<0.001	1.831
+	118.061	16.4	Guanidinoacetate	0.002	0.794	0.244	1.081	<0.001	1.741
+	508.376	4.7	[PC (18:1)] 1-(11Z-octadecenyl)-sn-glycero-3-phosphocholine	0.002	1.210	<0.001	1.404	<0.001	1.549
+	792.554	4.0	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.002	0.794	0.613	1.031	0.144	0.857
+	130.05	15.7	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.002	1.372	0.014	1.251	<0.001	1.675
-	505.988	16.8	ATP	0.002	0.814	0.001	1.433	<0.001	1.406
+	335.106	4.4	Penicillin G	0.002	1.427	0.028	1.219	<0.001	1.692
+	102.055	15.0	1-Aminocyclopropane-1-carboxylate	0.002	1.235	0.004	1.328	<0.001	1.606
+	148.06	15.0	L-Glutamate	0.002	1.193	<0.001	1.388	<0.001	1.530
+	204.123	11.5	O-Acetylcarnitine	0.002	0.734	0.012	0.782	<0.001	1.393
+	157.097	12.1	N-acetyl prolinamide or isomer	0.002	1.565	0.124	1.197	0.005	1.687
+	112.051	10.9	Cytosine	0.002	1.328	0.005	1.318	<0.001	2.159

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	184.073	15.4	Choline phosphate	0.002	1.268	<0.001	1.824	<0.001	1.452
+	198.087	9.1	N-Acetyl-L-histidine	0.002	1.469	0.028	1.263	<0.001	1.866
+	245.095	9.0	Biotin	0.002	1.446	0.095	1.205	<0.001	1.834
+	137.046	10.6	Hypoxanthine	0.002	1.343	0.149	0.907	0.005	1.216
+	170.081	8.3	Pyridoxine	0.002	1.469	0.187	1.124	0.000	1.646
+	810.602	4.0	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	0.002	0.883	0.003	1.270	0.041	1.118
+	166.053	13.9	L-Methionine S-oxide	0.002	1.547	0.008	1.349	<0.001	2.113
-	435.252	4.7	LPA(0:0/18:1(9Z))	0.002	1.382	<0.001	1.564	<0.001	1.721
+	244.093	12.4	Cytidine	0.002	1.422	0.001	1.511	<0.001	2.291
+	165.055	13.7	Phenylpyruvate	0.003	1.401	0.003	1.367	<0.001	1.903
+	162.112	13.8	L-Carnitine	0.003	0.753	0.001	0.674	0.001	1.396
-	160.062	9.7	L-2-Aminoadipate	0.003	1.263	0.010	1.202	<0.001	1.466
-	191.02	18.3	Citrate	0.003	1.412	0.013	1.366	<0.001	1.965
+	132.065	15.0	L-Glutamate 5-semialdehyde	0.003	1.463	0.024	1.293	<0.001	1.827
+	106.05	16.5	L-Serine	0.003	1.238	0.002	1.194	<0.001	1.344
-	272.922	32.2	S-(4-bromophenyl)-mercaptopyruvate	0.003	1.313	0.960	1.003	0.005	1.465
+	245.186	4.8	Leucyl-leucine	0.004	1.499	0.003	1.799	<0.001	3.268
+	510.392	4.7	LysoPC(O-18:0)//[PC (10:2/8:2)] 1-decyl-2-octyl-sn-glycero-3-phosphocholine	0.004	1.268	0.000	1.422	<0.001	1.588
+	127.123	11.4	1-5-diazabicyclononane	0.004	1.546	0.273	1.189	<0.001	2.379
+	220.118	8.9	Pantothenate	0.004	1.433	0.041	1.216	<0.001	1.897
+	114.055	15.1	(S)-1-Pyrroline-5-carboxylate	0.004	1.275	0.049	1.158	<0.001	1.481
+	247.058	13.0	Glycerophosphoglycerol	0.004	0.780	0.288	0.951	<0.001	1.695
+	175.108	14.1	N-Acetylornithine	0.005	1.464	0.019	1.305	<0.001	1.931
-	834.529	3.7	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	0.005	0.842	0.232	1.081	0.014	0.791
+	613.159	17.6	Glutathione disulfide	0.005	1.614	<0.001	4.511	<0.001	1.819
+	252.109	8.5	Deoxyadenosine	0.005	0.881	<0.001	0.477	<0.001	1.272

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	780.555	4.1	[PC (16:1/20:4)] 1-(9Z-hexadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.005	0.916	0.001	1.334	<0.001	1.257
-	148.044	12.1	L-Methionine	0.005	1.487	0.030	1.269	<0.001	1.894
-	203.083	12.3	L-Tryptophan	0.005	1.487	0.015	1.354	<0.001	1.968
+	522.355	7.5	1-Oleoylglycerophosphocholine	0.005	1.195	0.009	1.299	0.059	1.165
-	333.092	4.4	Penicillin G	0.005	1.398	0.076	1.202	<0.001	1.706
+	147.076	15.5	L-Glutamine	0.005	1.310	0.046	1.186	<0.001	1.594
+	133.061	16.0	L-Asparagine	0.006	1.487	0.036	1.337	0.051	1.426
+	247.14	14.7	N2-(D-1-Carboxyethyl)-L-arginine	0.006	1.406	0.002	1.414	<0.001	1.912
+	191.085	10.7	Aldicarb	0.006	1.516	0.271	1.171	0.018	1.578
+	242.113	9.8	5-Methyl-2'-deoxycytidine	0.006	1.369	0.005	1.371	<0.001	2.238
+	718.576	4.1	PC(14:0/P-18:0)	0.006	1.146	<0.001	1.402	0.539	0.959
-	218.104	8.9	Pantothenate	0.006	1.436	0.043	1.257	<0.001	1.930
+	891.595	3.6	PI(16:0/22:2(13Z,16Z))	0.006	1.135	0.031	1.167	<0.001	1.451
+	369.128	4.2	trans-3-Hydroxycotinineglucuronide	0.006	1.544	0.388	1.135	0.000	2.103
+	148.08	15.6	5-methylthiopentanaldoxime	0.006	1.312	0.050	1.182	<0.001	1.600
+	197.103	14.3	3,5-dihydro-5-methylidene-4H-imidazol-4-one	0.006	1.572	0.228	1.215	0.002	1.992
-	175.047	8.6	Allantoate	0.006	1.604	0.032	1.400	<0.001	2.174
-	173.104	27.5	L-Arginine	0.006	1.422	0.055	1.231	<0.001	1.825
-	164.072	10.8	L-Phenylalanine	0.006	1.417	0.050	1.255	<0.001	1.924
+	263.096	8.2	Thiamine aldehyde	0.007	1.467	0.036	1.279	<0.001	1.889
+	310.113	13.7	N-Acetylneuraminate	0.007	0.918	0.025	1.106	<0.001	1.334
+	314.269	5.0	[FA (16:0)] N-hexadecanoyl-glycine	0.007	0.661	0.512	1.048	0.041	1.143
+	174.087	15.2	5-Guanidino-2-oxopentanoate	0.007	1.601	0.176	1.235	0.033	1.521
-	810.529	3.7	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.008	0.843	0.789	1.013	0.036	0.769
-	425.081	17.0	S-glutathionyl-L-cysteine	0.008	1.416	0.002	1.626	<0.001	1.750
-	327.233	3.8	Docosahexaenoicacid	0.008	1.235	0.004	1.318	<0.001	1.797
+	184.097	7.8	L-Adrenaline	0.008	0.267	0.003	0.138	0.002	0.097

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
-	241.083	7.6	Thymidine	0.008	1.389	0.004	1.438	<0.001	2.298
-	145.062	15.6	L-Glutamine	0.009	1.401	0.065	1.231	0.000	1.696
-	166.994	32.2	Desflurane	0.009	0.290	0.053	0.003	0.052	0.001
-	118.051	15.1	L-Threonine	0.009	1.453	0.029	1.355	<0.001	1.858
+	134.045	15.4	L-Aspartate	0.009	1.138	0.320	1.078	0.012	1.405
+	189.135	27.9	Homoarginine	0.009	1.389	0.156	1.184	<0.001	1.793
-	128.035	10.5	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.009	1.278	0.037	1.173	<0.001	1.553
-	241.072	3.9	Lumichrome	0.009	2.258	0.002	2.446	0.049	1.845
-	146.046	15.0	L-Glutamate	0.010	1.235	0.002	1.462	<0.001	1.658
+	664.117	14.6	NAD+	0.010	1.088	<0.001	1.543	<0.001	1.361
-	746.513	3.9	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.010	0.898	0.236	1.042	0.902	1.005
+	147.113	25.8	L-Lysine	0.011	1.311	0.052	1.185	<0.001	1.712
+	496.34	7.5	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	0.011	1.192	0.008	1.228	0.002	1.204
+	207.113	9.6	Phenylethylmalonamide	0.011	1.493	0.207	1.219	0.014	1.605
+	482.324	7.5	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	0.011	0.843	0.699	1.036	0.088	1.113
-	465.304	3.7	Cholesterolsulfate	0.011	1.154	<0.001	1.303	0.096	1.110
-	353.049	7.5	Phenolsulfonphthalein	0.011	1.317	0.458	1.073	<0.001	1.554
+	203.15	22.7	NG,NG-Dimethyl-L-arginine	0.011	1.328	0.006	1.342	<0.001	1.966
+	121.072	11.1	urea dimer	0.012	1.710	0.022	1.525	<0.001	2.568
-	498.29	4.3	[ST hydrox] N-(3alpha,7alpha-dihydroxy-5beta-cholan-24-oyl)-taurine	0.012	1.471	0.396	1.108	<0.001	1.989
+	174.124	23.9	L-Indospicine	0.012	1.566	0.317	1.171	0.006	1.825
-	507.238	7.6	[Fv Trihydroxy,hydroxy,dimethyl(9:1)] 5,3',4'-Trihydroxy-2'-geranyl-(5''-hydroxy-6'',6''-dimethyldihydropyrano[2'',3'':7,6])flavanone	0.012	1.344	0.002	1.425	<0.001	2.241
-	176.936	16.2	Pyrophosphate	0.013	1.394	0.519	0.937	0.010	1.590
-	836.544	3.7	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.013	0.857	0.104	1.115	0.018	0.745
+	703.575	4.3	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.013	0.877	0.122	0.926	0.012	0.734
+	149.081	15.6	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.013	1.288	0.109	1.147	<0.001	1.579

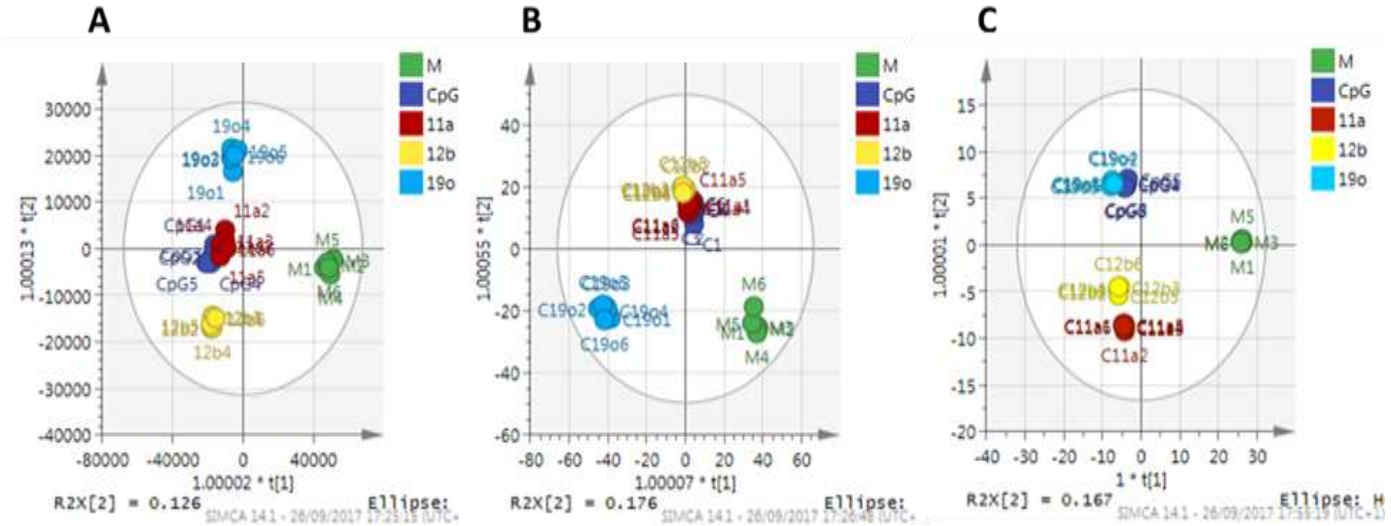
DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	188.103	14.4	5-guanidino-3-methyl-2-oxo-pentanoate	0.013	1.526	0.382	1.153	0.012	1.608
-	611.144	17.6	Glutathione disulfide	0.013	1.470	<0.001	4.704	<0.001	1.643
-	180.067	13.7	L-Tyrosine	0.013	1.428	0.010	1.413	<0.001	1.868
-	179.056	14.0	D-Glucose	0.013	1.298	0.198	1.143	<0.001	1.533
+	359.164	4.0	Cilastatin	0.014	0.788	0.062	1.253	0.416	1.144
+	241.031	16.8	L-Cystine	0.014	1.788	0.001	0.413	0.003	2.063
-	746.513	3.9	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.015	0.888	0.144	1.053	0.552	0.958
+	189.16	23.1	N6,N6,N6-Trimethyl-L-lysine	0.015	1.301	0.020	1.249	<0.001	1.786
-	181.072	14.4	D-Sorbitol	0.015	1.376	0.098	1.222	0.000	1.735
+	790.559	3.8	PS(18:0/18:1(9Z))	0.016	0.753	0.718	1.036	0.004	0.413
-	196.073	9.1	N-Acetyl-L-histidine	0.017	1.414	0.086	1.246	<0.001	1.904
-	179.056	17.6	D-Glucose	0.017	1.551	0.604	0.898	0.060	1.401
+	302.175	5.6	Dobutamine	0.018	1.060	0.001	1.073	0.001	1.086
-	149.045	15.2	D-Ribose	0.018	1.347	0.111	1.220	<0.001	1.662
-	125.001	13.2	2-Hydroxyethylphosphonate	0.018	1.278	0.551	0.943	0.016	1.354
+	129.066	15.3	5,6-Dihydrothymine	0.019	1.184	0.165	1.089	<0.001	1.500
+	144.066	7.6	Vinylacetylglycine	0.019	1.424	0.293	1.165	0.019	1.473
-	788.544	3.8	PS(18:0/18:1(9Z))	0.019	0.798	0.490	1.056	0.002	0.412
-	838.56	3.7	1-22:1-2-18:3-phosphatidylserine	0.020	0.846	0.267	1.074	0.004	0.574
-	132.03	15.5	L-Aspartate	0.020	1.214	0.058	1.196	0.001	1.851
+	117.066	14.3	Diacetylhydrazine	0.021	1.495	0.354	1.147	0.002	1.774
-	131.046	15.9	L-Asparagine	0.021	1.456	0.154	1.252	0.075	1.424
+	217.13	15.4	N-acetyl-(L)-arginine	0.022	1.359	0.237	1.149	0.054	1.338
+	782.57	4.0	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.023	0.940	<0.001	1.453	<0.001	1.295
-	127.051	15.6	5,6-Dihydrothymine	0.024	1.184	0.342	1.067	0.000	1.392
+	387.18	4.2	Burseran	0.024	1.059	0.448	0.979	0.157	1.047
+	428.037	15.5	ADP	0.024	0.863	0.004	1.304	0.001	1.358

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
-	243.062	10.2	Uridine	0.030	1.260	0.006	1.343	<0.001	1.892
+	428.373	4.5	Stearoylcarnitine	0.031	1.084	0.044	1.098	<0.001	1.548
-	245.043	13.0	Glycerophosphoglycerol	0.034	0.781	0.164	0.929	<0.001	2.014
+	123.055	7.6	Nicotinamide	0.035	1.205	0.095	1.165	<0.001	1.624
+	570.355	4.6	LysoPC(22:5(4Z,7Z,10Z,13Z,16Z))	0.035	1.274	0.013	1.441	0.001	1.700
+	159.076	16.5	4-Methylene-L-glutamine	0.036	1.168	0.017	1.212	0.002	1.335
-	482.961	18.1	UTP	0.036	0.801	0.001	1.349	<0.001	1.625
-	239.017	16.9	L-Cystine	0.037	1.644	0.001	0.338	0.004	2.047
+	327.158	13.5	[Fv Trihydrox] 2',4',6'-Trihydroxy-3'-prenyldihydrochalcone	0.038	1.383	0.001	1.782	0.013	1.641
+	118.086	13.1	L-Valine	0.042	1.316	0.007	1.378	<0.001	1.737
+	189.087	13.9	N-Acetylglutamine	0.043	1.238	0.051	1.340	0.011	1.491
+	788.544	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.047	0.864	0.056	1.169	0.015	0.727
-	786.529	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.048	0.862	0.059	1.151	0.017	0.722
+	126.055	11.5	N-Ethylmaleimide	0.048	0.918	0.049	0.916	0.008	1.148
+	232.154	9.1	O-Butanoylcarnitine	0.050	1.124	0.379	1.051	<0.001	1.416
-	179.056	15.3	D-Glucose	0.051	1.265	0.570	1.060	0.004	1.458
-	331.265	3.8	[FA (22:4)] 7Z,10Z,13Z,16Z-docosatetraenoic acid	<0.001	1.382	0.001	1.241	<0.001	1.866
-	766.54	3.9	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.716	0.435	0.956	0.074	0.818
-	210.028	15.4	Phosphocreatine	<0.001	0.563	0.005	0.793	<0.001	1.413
-	214.049	16.1	sn-glycero-3-Phosphoethanolamine	<0.001	0.430	0.001	0.672	0.019	1.164
-	171.007	15.0	sn-Glycerol 3-phosphate	<0.001	0.591	0.081	0.843	0.003	1.360
-	124.007	15.3	Taurine	<0.001	0.765	0.816	1.014	<0.001	1.422
+	143.049	15.3	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	0.690	0.199	0.928	<0.001	1.240
+	766.575	4.0	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.296	0.003	1.221	<0.001	1.205
+	740.524	4.0	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.721	0.489	1.035	0.995	1.000
+	168.964	4.5	D,L-selenocysteine	<0.001	418956.200	#DIV/0!	1.000	#DIV/0!	1.000

DM	m/z	RT	Name	11a P	11a FC	12b P	12b FC	19o P	19o FC
+	230.096	15.3	Ergothioneine	<0.001	0.521	0.000	0.558	<0.001	1.317
+	110.027	15.5	Hypotaurine	<0.001	0.549	0.003	0.803	<0.001	1.271
+	212.043	15.4	Phosphocreatine	<0.001	0.580	0.002	0.811	<0.001	1.407
+	260.114	15.0	Proacacipetalin	<0.001	0.574	0.012	0.755	<0.001	1.487
+	336.087	15.0	S-Formylglutathione	<0.001	0.525	0.007	0.734	0.026	1.198
+	258.11	15.0	sn-glycero-3-Phosphocholine	<0.001	0.595	0.033	0.774	0.000	1.490
+	216.063	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	0.457	0.001	0.700	0.002	1.198
+	126.022	15.3	Taurine	<0.001	0.746	0.938	0.996	<0.001	1.319

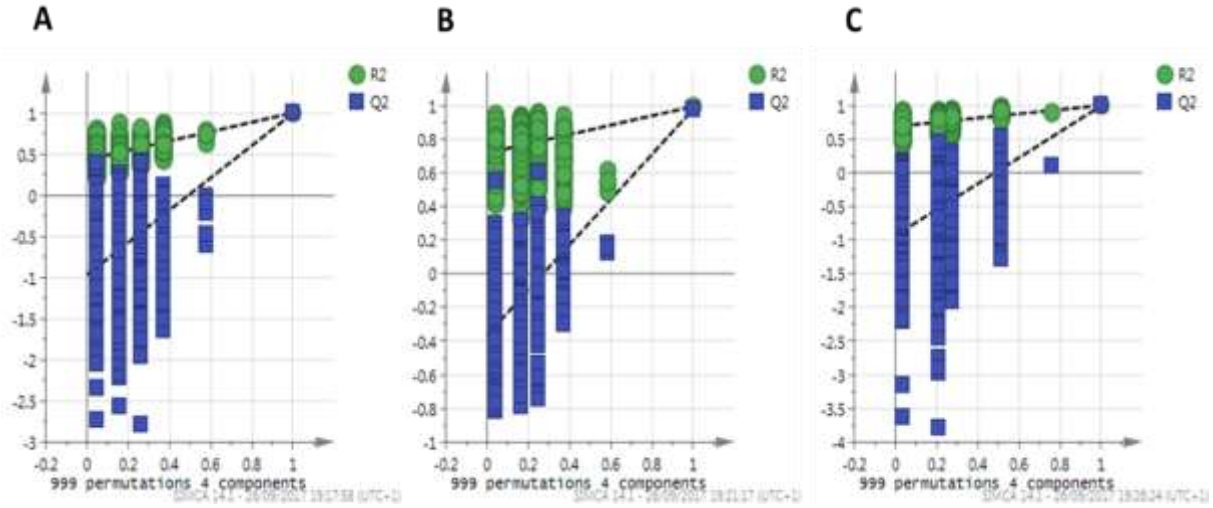
Appendix 7: Orthogonal Partial Least Square Discriminant Analysis (OPLS-DA) score plot of the three runs of SMAs +CpG conditions

OPLS-DA score plots for metabolomic effects following treatment with SMAs treatment models A, B and C following CpG treatment are shown in figure 3.2.4. Each model includes five groups, group 1 (green) represents unstimulated macrophages, group 2 (red) represents 11a treatment followed by CpG, group 3 (yellow) represents 12b treatment followed by CpG, group 4 (light blue) represents 19o treatment followed by CpG and group 5 in dark blue color indicating CpG alone treatment. Model A, consisting of 578 variables, was explained by four predictive x-score components and 5 orthogonal ones (4+5). The predictive components explain 81.8 % of the variation in x while A orthogonal components explain 16.9 % of the variation and so the total explained variation by x, R2X (cum), is equal to 98.7%, R2Y (cum) = 1, R2 (cum) = 97.9%, and the goodness of prediction Q2 (cum) is equal to 92.9%. Model B, including 612 variables, was explained by three predictive x-score components and 1 orthogonal component (3+1). Its Predictive components explain 57.2 % of the variation in x while its orthogonal ones explain 2.76 % of the variation. The R2X explained variation is equal to 59.9 % while R2Y (cum) = 1, R2 (cum) = 97.3 % and the goodness of prediction Q2 (cum) = 82.3%. 319 variables by model C were explained by four predictive x-score components and seven orthogonal ones (4+7) in which predictive components explain 83.4 % of the variation in x while its orthogonal ones explain 14.3 % which makes the total explanation of x variation is equal to 97.8%. Its R2Y (cum) = 1, R2 (cum) = 99.1 %, and C goodness of prediction Q2 (cum) is equal to 89.6 %.



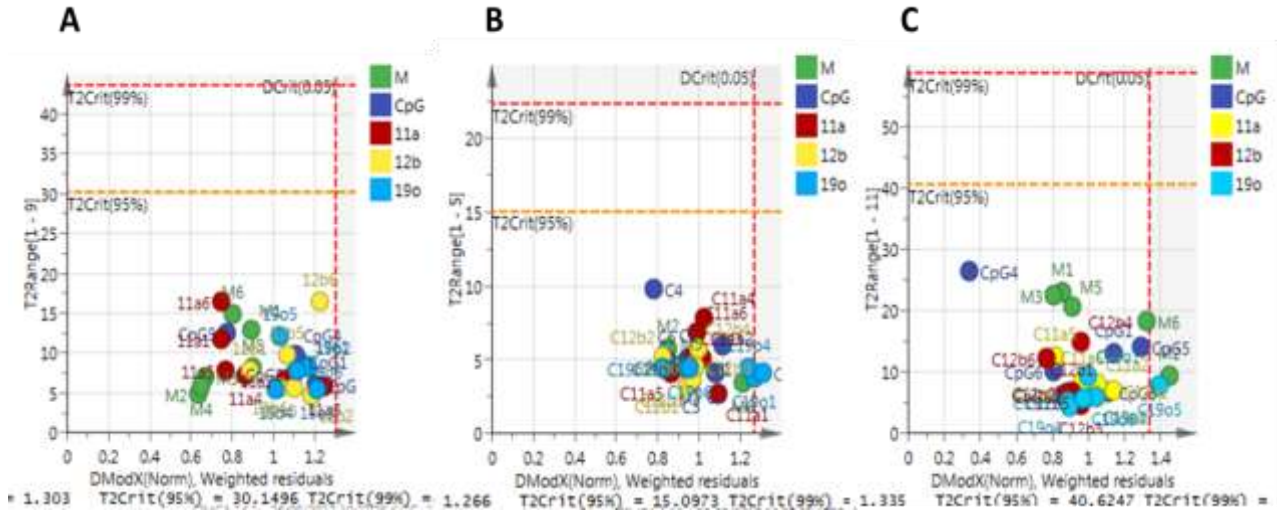
Appendix 8: Permutations tests of the three runs of SMAs +CpG conditions

Models' validation, using a 999 random permutations test for the supervised models of CpG- treated macrophages which are pre-treated with SMA (11a, 12b or 19o) versus CpG- stimulated macrophages, has been generated using SMICA. The goodness of fit (R2) and predictive capability (Q2) values on the right-hand side of the plot are of the true model, whereas the permutated model parameters are represented on the left-hand side of the plot. The correlation coefficients between true and permutated models represent the X axis and has a correlation of 1.0 with itself. SMA pre-treatment of macrophages followed by CpG stimulation in models (A, B and C) exhibited higher true values, R2 and Q2, than those of the permutated models. This classifies investigated SMA models as true models. A model intercepts are: R 2 = (0.0, 0.432) and Q 2 = (0.0, − 0.967), B model intercepts are R 2 = (0.0, 0.716) and Q 2 = (0.0, − 0.364) whereas model C intercepts are: R 2 = (0.0, 0.686) and Q 2 = (0.0, − 0.932).



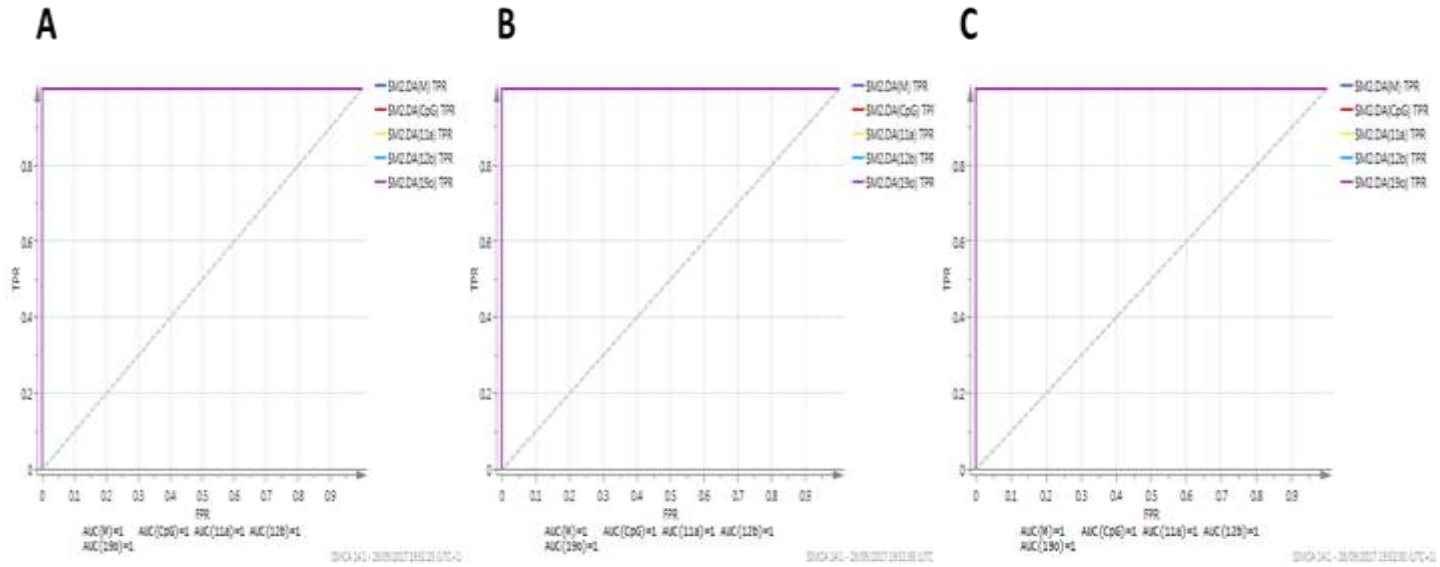
Appendix 9: Distance to model (DModX) vs Hotellings T2 plot of the three runs of SMAs +CpG conditions

DModX on x-axis versus Hotelling's T2 on Y-axis.Hotelling's T2 on Y-axis is showing two limits on the y-axis. . The first one, T2Crit (95%), is called the waring limit and is represented by a yellow dotted line whereas the second one, T2 Crit (99%), is called the action limit and is represented by a red dotted line. On the x-axis, the red dotted line indicates DModX uses critical distance DCrit at level 0.05. Observations are considered as strong outliers if they are located above the action limit or above the warning limit plus DModX critical limit. The Investigated A, B and C models are showing models with no strong or even moderate outliers from tested groups.



Appendix 10: Area under the receiver operating characteristics Curve (AUROCC) of the three runs of SMAs +CpG conditions

ROC curves show sensitivity true positive rate (TPR) on the y-axis versus false positive rate (FPR = 1 - Specificity) on the x-axis generated using cross-validated predicted-Y values of the three (A, B and C) investigated OPLS-DA models. The area under the ROC curves (AUC) for unstimulated macrophages (M) is 1, CpG-treated macrophages (CpG) is 1, 11a pre-treatment of CpG-treated macrophages (11a) is 1, 12b pre-treatment of GpG-treated macrophages (12b) is 1 and AUC for 19o pre-treatment of CpG-treated macrophages is equal to 1. This assess OPLS-DA models (A, B and C) as models with very strong power that have an excellent ability to distinguish features between unstimulated macrophage and SMAs treated ones.



Appendix 11: The list of detected metabolites that have changed following CpG treatment, CpG +11a (C11a), 12b (C12b) and 19o (C19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, RT to raw retention time and p to P-value.

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	239.0654	12.7	(3-nitrobenzoyl)alanine	<0.001	1.911	0.002	1.950	0.025	1.618	<0.001	9.768
-	89.02417	9.3	(R)-Lactate	<0.001	2.727	<0.001	2.460	<0.001	2.458	<0.001	11.196
-	133.0141	16.2	(S)-Malate	<0.001	1.714	<0.001	1.749	<0.001	2.274	<0.001	2.508
+	152.0707	8.1	(Z)-4-Hydroxyphenylacetaldehyde-oxime	<0.001	1.436	0.002	1.322	0.001	1.234	<0.001	4.331
+	143.0486	15.1	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	4.794	<0.001	5.003	<0.001	5.197	<0.001	5.152
-	359.2955	3.8	[FA (12:0)] 12-[3]-ladderane-dodecanoic acid	<0.001	2.877	0.002	2.854	<0.001	2.689	<0.001	7.401
-	365.3424	3.8	[FA (24:0)] 15Z-tetracosenoic acid	<0.001	0.462	<0.001	0.254	<0.001	0.296	0.011	0.731
-	174.0407	14.7	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	<0.001	2.410	<0.001	2.106	<0.001	1.833	<0.001	2.512
+	149.0808	15.4	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	<0.001	1.466	0.001	1.460	0.001	1.317	<0.001	5.343
-	135.0298	12.4	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	<0.001	1.400	<0.001	1.333	0.006	1.359	<0.001	4.055
+	400.3421	4.8	[FA] O-Palmitoyl-R-carnitine	<0.001	3.248	<0.001	3.554	<0.001	5.575	<0.001	4.018
+	400.3421	7.5	[FA] O-Palmitoyl-R-carnitine	<0.001	5.312	<0.001	5.797	<0.001	11.055	<0.001	7.333
+	327.1584	13.1	[Fv Trihydrox] 2',4',6'-Trihydroxy-3'-prenyldihydrochalcone	<0.001	0.161	<0.001	0.110	<0.001	0.168	<0.001	3.635
+	678.5073	4.3	[PC (14:0/14:0)] 1,2-ditetradecanoyl-sn-glycero-3-phosphocholine	<0.001	60.809	0.009	68.086	0.002	126.689	<0.001	49.064
+	704.5232	4.2	[PC (14:0/16:1)] 1-tetradecanoyl-2-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	32.078	<0.001	35.962	<0.001	60.093	<0.001	33.631
+	732.5545	4.2	[PC (14:0/18:1)] 1-tetradecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	4.506	<0.001	4.966	<0.001	6.087	<0.001	4.716
+	730.5389	4.2	[PC (14:0/18:2)] 1-tetradecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	11.420	<0.001	13.641	<0.001	17.424	<0.001	12.340
+	728.5231	4.2	[PC (14:0/18:3)] 1-tetradecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	44.368	<0.001	59.578	<0.001	70.019	<0.001	49.497
+	754.5395	4.2	[PC (14:0/20:4)] 1-tetradecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	19.238	<0.001	21.099	<0.001	26.156	<0.001	18.163

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	720.5914	4.2	[PC (14:2/18:0)] 1-tetradecyl-2-octadecanoyl-sn-glycero-3-phosphocholine	<0.001	0.129	<0.001	0.150	<0.001	0.115	<0.001	0.108
-	480.3092	4.7	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.455	<0.001	1.312	<0.001	1.388	<0.001	1.927
+	482.3242	4.7	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.515	<0.001	1.394	<0.001	1.540	<0.001	1.980
+	706.5387	4.2	[PC (15:0/15:0)] 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine	<0.001	5.811	<0.001	6.508	<0.001	8.045	<0.001	6.068
+	720.5546	4.2	[PC (15:0/16:0)] 1-pentadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	2.275	<0.001	2.400	<0.001	2.761	<0.001	2.334
+	746.5701	4.2	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	3.839	<0.001	4.032	<0.001	4.862	<0.001	4.071
+	494.324	4.9	[PC (16:0)] 1-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.121	<0.001	2.165	<0.001	3.042	<0.001	3.841
-	494.325	4.8	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.319	<0.001	1.337	<0.001	1.420	0.002	1.819
+	496.3397	4.8	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.331	0.001	1.374	<0.001	1.516	<0.001	1.859
+	496.3395	7.5	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.628	0.008	1.702	<0.001	2.081	<0.001	2.541
+	760.5859	4.2	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	3.129	<0.001	3.211	<0.001	3.562	<0.001	3.378
+	758.5703	4.2	[PC (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	5.347	<0.001	6.094	<0.001	7.286	<0.001	5.864
+	756.5551	4.2	[PC (16:0/18:3)] 1-hexadecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	9.063	<0.001	10.715	<0.001	13.652	<0.001	9.790
+	782.5701	4.2	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	2.726	<0.001	2.764	<0.001	2.762	<0.001	3.042
+	806.5702	4.2	[PC (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	3.908	<0.001	4.167	<0.001	4.431	<0.001	4.504
+	780.5545	4.2	[PC (16:1/20:4)] 1-(9Z-hexadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	4.877	<0.001	5.219	<0.001	6.004	<0.001	5.426
+	804.5544	4.2	[PC (16:1/22:6)] 1-(9Z-hexadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	16.763	<0.001	18.345	<0.001	22.267	<0.001	16.806
+	836.6176	4.2	[PC (18:0/22:5)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.078	<0.001	2.060	<0.001	2.149	<0.001	2.528
+	508.3764	4.8	[PC (18:1)] 1-(11Z-octadecenyl)-sn-glycero-3-phosphocholine	<0.001	0.727	0.004	0.783	0.002	0.790	0.272	0.851
+	786.6018	4.2	[PC (18:1/18:1)] 1-(9Z-octadecenoyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	4.120	<0.001	4.236	<0.001	5.133	<0.001	4.617
+	810.6017	4.2	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	<0.001	1.645	<0.001	1.577	<0.001	1.516	<0.001	1.876
+	808.586	4.2	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	3.657	<0.001	3.618	<0.001	3.918	<0.001	4.119

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	834.6017	4.2	[PC (18:1/22:5)] 1-(11Z-octadecenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.767	<0.001	2.751	<0.001	2.963	<0.001	3.352
+	832.586	4.2	[PC (18:1/22:6)] 1-(11Z-octadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	4.936	<0.001	5.065	<0.001	5.924	<0.001	5.625
+	818.6065	4.2	[PC (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.673	<0.001	1.544	<0.001	1.695	<0.001	1.896
+	520.3418	4.8	[PC (18:2)] 1-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	4.618	<0.001	4.363	<0.001	7.109	<0.001	11.368
+	830.5701	4.2	[PC (18:2/22:6)] 1-(9Z,12Z-octadecadienoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.786	<0.001	2.706	<0.001	3.001	<0.001	3.126
+	778.5385	4.2	[PC (18:3/18:3)] 1,2-di-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	25.333	<0.001	29.190	<0.001	37.151	<0.001	27.479
+	862.633	4.1	[PC (20:0/22:6)] 1-eicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	9.941	0.007	7.052	0.001	10.863	0.004	9.100
+	854.5702	4.1	[PC (20:5/22:5)] 1-(5Z,8Z,11Z,14Z,17Z-eicosapentaenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	9.216	<0.001	8.719	<0.001	9.370	<0.001	9.233
+	766.5753	4.2	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.472	<0.001	0.592	<0.001	0.512	<0.001	0.543
-	452.2781	4.8	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	2.926	<0.001	2.742	<0.001	3.390	<0.001	3.947
+	454.2928	4.8	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	3.018	<0.001	3.173	<0.001	3.863	<0.001	4.252
+	718.5389	4.2	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	10.746	<0.001	12.053	<0.001	15.157	<0.001	10.464
+	740.5234	4.1	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.057	<0.001	5.224	<0.001	6.102	<0.001	4.967
+	774.6017	4.2	[PE (16:0/22:1)] 1-hexadecanoyl-2-(13Z-docosenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.209	<0.001	2.235	<0.001	2.387	<0.001	2.587
-	762.5064	4.1	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	11.064	<0.001	10.607	<0.001	11.907	0.006	8.263
+	764.5237	4.1	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	12.000	<0.001	12.328	<0.001	13.511	<0.001	12.643
+	748.5283	4.1	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.395	<0.001	1.409	<0.001	1.476	<0.001	1.490
-	478.2936	4.8	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.014	<0.001	2.291	<0.001	3.106	<0.001	3.690

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	480.3085	4.7	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.279	<0.001	2.321	<0.001	3.413	<0.001	3.885
+	744.5546	4.2	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	13.352	<0.001	16.968	<0.001	22.792	<0.001	15.148
+	772.586	4.2	[PE (18:0/20:2)] 1-octadecanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	10.117	<0.001	11.658	<0.001	11.951	<0.001	10.866
+	768.5548	4.1	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.653	<0.001	1.643	<0.001	1.765	<0.001	1.844
+	792.5544	4.1	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	4.020	<0.001	3.973	<0.001	3.990	<0.001	4.620
-	750.5437	4.0	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.509	<0.001	0.555	<0.001	0.533	0.002	0.428
+	752.5603	4.1	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.494	<0.001	0.589	<0.001	0.568	<0.001	0.566
-	500.278	4.7	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.029	0.907	1.007	0.030	1.157	0.455	1.056
+	502.2925	4.7	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.122	0.589	1.041	0.023	1.195	0.723	1.029
+	766.5601	3.7	[PG (16:0/18:0)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	<0.001	2.637	<0.001	3.091	<0.001	3.203	<0.001	2.483
-	747.5157	3.7	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.842	<0.001	2.020	<0.001	2.060	<0.001	1.828
+	749.5314	4.1	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.595	<0.001	1.627	<0.001	1.684	<0.001	1.758
-	821.5333	3.7	[PG (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.537	<0.001	1.378	<0.001	1.390	<0.001	1.654
-	789.5468	3.9	[PG (8:0/8:0)] 1-(8-[3]-ladderane-octanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	0.412	<0.001	0.346	<0.001	0.474	<0.001	0.284
-	809.5159	3.9	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	8.085	<0.001	7.239	<0.001	9.229	<0.001	7.259
+	811.5322	3.8	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	7.179	<0.001	7.408	<0.001	8.319	<0.001	5.958
-	835.5314	3.8	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.679	0.001	1.462	<0.001	1.778	<0.001	1.517
+	837.548	3.8	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.449	0.002	1.212	<0.001	1.354	<0.001	1.359
+	863.5638	3.7	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.194	0.080	1.054	0.483	0.982	<0.001	1.260
+	887.5641	3.7	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.656	<0.001	1.834	<0.001	1.763	<0.001	1.827
+	762.5287	3.9	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	1.875	<0.001	1.705	<0.001	2.389	<0.001	1.432

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	524.2989	4.2	[PS (18:0)] 1-octadecanoyl-sn-glycero-3-phosphoserine	<0.001	0.719	<0.001	0.612	<0.001	0.703	0.108	0.883
-	834.5279	3.8	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	1.807	<0.001	1.539	<0.001	1.863	<0.001	1.569
+	836.5447	3.8	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	1.448	0.002	1.211	<0.001	1.340	<0.001	1.353
-	782.4964	3.9	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	9.053	<0.001	8.667	<0.001	10.375	<0.001	7.908
+	784.5131	3.8	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	8.042	<0.001	7.986	<0.001	9.334	<0.001	7.243
+	538.5198	4.1	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine	<0.001	0.175	<0.001	0.145	<0.001	0.203	<0.001	0.221
+	300.2897	7.5	[SP] 3-dehydrosphinganine	<0.001	0.389	<0.001	0.299	<0.001	0.348	<0.001	0.350
-	808.5123	3.9	1-20:2-2-18:3-phosphatidylserine	<0.001	6.949	<0.001	6.273	<0.001	8.313	<0.001	6.326
+	810.529	3.8	1-20:2-2-18:3-phosphatidylserine	<0.001	5.999	<0.001	5.748	<0.001	8.100	<0.001	5.308
+	102.055	15.4	1-Aminocyclopropane-1-carboxylate	<0.001	1.592	0.060	1.407	0.001	1.469	<0.001	5.258
+	102.055	14.8	1-Aminocyclopropane-1-carboxylate	<0.001	2.146	<0.001	2.702	<0.001	2.934	<0.001	4.932
+	134.0811	7.5	1-deoxyxylonojirimycin	<0.001	5.343	<0.001	4.840	<0.001	5.609	<0.001	4.341
+	744.5906	4.2	1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphonocholine	<0.001	2.313	<0.001	2.532	0.001	2.542	0.015	2.188
+	522.3556	4.8	1-Oleoylglycerophosphocholine	<0.001	1.564	0.003	1.467	<0.001	1.945	<0.001	2.710
-	325.1246	15.3	2,2,4-Trimethyl-3-(4-fluorophenyl)-2H-1-benzopyran-7-ol acetate	<0.001	0.278	<0.001	0.326	<0.001	0.224	<0.001	4.880
+	327.1398	13.5	2,2,4-Trimethyl-3-(4-fluorophenyl)-2H-1-benzopyran-7-ol acetate	<0.001	2.398	<0.001	1.943	<0.001	2.024	<0.001	3.050
-	170.0458	13.5	2,3,4,5-Tetrahydrodipicolinate	<0.001	2.408	<0.001	2.154	<0.001	2.450	0.001	4.190
-	290.0879	13.3	2,7-Anhydro-alpha-N-acetylneuraminic acid	<0.001	3.565	<0.001	3.833	0.002	3.190	<0.001	6.544
+	292.1027	13.5	2,7-Anhydro-alpha-N-acetylneuraminic acid	<0.001	3.325	<0.001	3.047	<0.001	2.915	<0.001	4.256
+	196.083	10.1	2-Amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine	<0.001	6.202	0.012	2.416	0.006	4.198	<0.001	31.436
-	215.0328	13.7	2-C-Methyl-D-erythritol 4-phosphate	<0.001	2.858	<0.001	3.677	<0.001	3.075	<0.001	9.622
-	111.0086	18.4	2-Furoate	<0.001	1.858	<0.001	2.031	<0.001	2.151	<0.001	5.724
+	229.0697	15.4	2-Hydroxy-3-carboxy-6-oxo-7-methylocta-2,4-dienoate	<0.001	5.342	<0.001	2.663	<0.001	2.435	<0.001	5.845
+	144.0809	10.6	2-Naphthylamine	<0.001	1.574	0.007	1.699	0.081	1.376	<0.001	8.528
-	145.0141	15.7	2-Oxoglutarate	<0.001	3.732	<0.001	3.701	<0.001	4.567	<0.001	6.099
+	146.0271	7.5	3,4-Dehydrothiomorpholine-3-carboxylate	<0.001	33.842	<0.001	41.651	<0.001	44.977	<0.001	89.300

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	146.0271	5.5	3,4-Dehydrothiomorpholine-3-carboxylate	<0.001	53.270	<0.001	66.186	<0.001	74.664	<0.001	140.014
-	246.057	13.0	3-Nitrofluoranthene	<0.001	1.493	<0.001	1.685	<0.001	1.577	0.003	1.378
-	102.0559	14.8	4-Aminobutanoate	<0.001	1.501	<0.001	1.478	<0.001	1.666	<0.001	2.109
+	104.0706	15.8	4-Aminobutanoate	<0.001	9.217	<0.001	11.440	<0.001	11.283	0.003	4.405
+	85.02841	11.3	4-Hydroxy-2-butynal	<0.001	4.703	<0.001	4.681	<0.001	5.419	<0.001	5.949
+	146.1176	13.7	4-Trimethylammoniobutanoate	<0.001	1.519	<0.001	1.458	0.001	1.341	<0.001	2.561
+	115.0502	15.0	5,6-Dihydrouracil	<0.001	3.804	0.028	1.988	0.032	1.762	<0.001	5.855
-	253.0498	15.7	5-L-Glutamyl-taurine	<0.001	11.064	<0.001	7.530	<0.001	22.828	<0.001	13.206
+	298.0969	7.5	5'-Methylthioadenosine	<0.001	5.891	<0.001	7.919	<0.001	9.465	<0.001	7.578
+	148.0798	15.4	5-methylthiopentanaldoxime	<0.001	1.415	0.001	1.416	0.004	1.264	<0.001	5.108
-	285.049	16.7	5'-Phosphoribosylglycinamide	<0.001	1455.627	<0.001	1161.995	<0.001	1279.656	<0.001	1520.741
+	287.0639	16.7	5'-Phosphoribosylglycinamide	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
+	168.0519	15.1	8-Hydroxyguanine	<0.001	6.382	<0.001	6.805	<0.001	7.349	<0.001	7.284
+	86.06006	15.8	Acetone cyanohydrin	<0.001	2.899	<0.001	3.905	<0.001	3.552	<0.001	4.600
-	162.0229	7.5	Acetylcysteine	<0.001	40.069	0.003	95.233	<0.001	53.947	0.078	12.947
+	793.5577	4.1	acyl phosphatidylglycerol (n-C12:0)	<0.001	3.805	<0.001	3.604	<0.001	3.567	<0.001	3.601
+	712.0684	13.1	Adenophostin B	<0.001	3.310	<0.001	4.632	<0.001	3.746	0.003	2.210
-	426.0219	15.5	ADP	<0.001	3.306	<0.001	3.321	<0.001	4.073	<0.001	3.223
-	426.0218	16.9	ADP	<0.001	6.001	<0.001	5.532	<0.001	6.461	<0.001	3.258
+	428.0367	15.5	ADP	<0.001	3.247	<0.001	3.408	<0.001	4.042	<0.001	2.588
-	501.2814	4.7	Ala-Lys-Trp-Val	<0.001	2.097	0.693	1.023	0.018	1.171	0.357	1.073
-	160.0436	7.5	allylcysteine	<0.001	41.607	<0.001	47.062	<0.001	39.288	<0.001	52.977
-	160.0436	5.0	allylcysteine	<0.001	30.043	<0.001	36.262	<0.001	35.102	<0.001	44.688
+	162.0584	5.0	allylcysteine	<0.001	24.053	<0.001	28.072	<0.001	26.472	<0.001	33.923
+	162.0584	7.5	allylcysteine	<0.001	27.980	<0.001	34.426	<0.001	31.554	<0.001	44.351
+	100.0216	5.5	Allylisothiocyanate	<0.001	#DIV/0!	0.001	#DIV/0!	<0.001	#DIV/0!	0.001	#DIV/0!
+	100.0216	7.5	Allylisothiocyanate	<0.001	43.146	<0.001	58.552	<0.001	72.765	0.001	123.295
+	348.0703	13.9	AMP	<0.001	3.592	<0.001	3.678	<0.001	3.694	0.688	1.073

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	505.9877	16.9	ATP	<0.001	3.972	<0.001	3.961	<0.001	4.445	<0.001	2.520
+	508.0032	16.9	ATP	<0.001	4.243	<0.001	4.351	<0.001	4.953	<0.001	2.523
+	217.1007	4.9	Benzo[b]fluorene	<0.001	30.513	<0.001	37.699	<0.001	33.033	<0.001	45.615
+	123.044	13.4	Benzoate	<0.001	2.005	0.047	1.657	0.180	1.550	<0.001	10.522
-	78.91845	12.4	Br-	<0.001	1.601	0.102	1.538	0.013	1.568	<0.001	3.933
+	274.0921	13.5	Brugine	<0.001	2.628	<0.001	2.386	<0.001	2.404	<0.001	3.103
-	347.1028	13.2	Camptothecin	<0.001	17.250	<0.001	22.714	<0.001	29.582	0.002	0.000
+	349.1176	13.2	Camptothecin	<0.001	17.858	<0.001	21.981	<0.001	28.659	<0.001	0.000
-	225.0993	16.2	Carnosine	<0.001	2.574	0.030	1.485	0.004	2.320	<0.001	11.907
+	131.0815	15.1	Casein K	<0.001	6.843	<0.001	7.421	<0.001	6.620	<0.001	39.096
+	408.3108	4.1	Cassaidine	<0.001	1.362	0.028	1.146	0.016	1.174	0.263	1.129
-	445.0527	16.6	CDP-ethanolamine	<0.001	8.548	<0.001	8.399	<0.001	9.504	<0.001	9.193
+	447.0677	16.6	CDP-ethanolamine	<0.001	5.765	<0.001	5.877	<0.001	6.740	<0.001	6.265
+	104.107	21.0	Choline	<0.001	1.632	<0.001	1.793	0.003	1.230	<0.001	5.273
+	184.0735	15.2	Choline phosphate	<0.001	2.131	<0.001	4.811	<0.001	5.498	<0.001	2.640
-	191.0197	18.4	Citrate	<0.001	1.964	<0.001	1.947	<0.001	2.102	<0.001	5.371
-	613.1389	15.5	CMP-N-acetylneuraminate	<0.001	3.653	<0.001	3.525	<0.001	3.209	<0.001	4.165
+	615.1549	15.5	CMP-N-acetylneuraminate	<0.001	3.737	<0.001	3.625	<0.001	3.291	<0.001	3.935
+	615.153	17.6	CMP-N-acetylneuraminate	<0.001	18.579	<0.001	27.211	<0.001	25.025	<0.001	8.302
-	130.062	15.0	Creatine	<0.001	3.709	0.002	1.554	0.001	1.499	<0.001	6.116
+	132.0768	15.0	Creatine	<0.001	2.971	<0.001	1.726	<0.001	1.722	<0.001	5.172
-	192.0179	15.4	creatinine phosphate	<0.001	4.720	<0.001	2.421	<0.001	2.533	<0.001	5.070
-	481.9768	18.8	CTP	<0.001	19.326	<0.001	19.093	<0.001	21.723	0.006	8.999
-	540.0533	14.4	Cyclic ADP-ribose	<0.001	4.180	<0.001	5.580	<0.001	6.033	<0.001	4.475
+	161.0921	14.9	D-Alanyl-D-alanine	<0.001	1.607	0.001	1.497	<0.001	1.380	<0.001	6.768
+	161.0921	7.5	D-Alanyl-D-alanine	<0.001	2.667	<0.001	3.228	0.004	2.034	<0.001	6.451
-	178.0719	11.5	D-Glucosamine	<0.001	2.115	0.001	2.307	0.001	1.843	<0.001	8.395
-	259.0221	17.1	D-Glucose 6-phosphate	<0.001	2.636	<0.001	2.194	<0.001	1.699	<0.001	2.657

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	85.0292	15.1	Diacetyl	<0.001	7.803	<0.001	6.603	<0.001	7.907	<0.001	10.734
+	87.04411	15.8	Diacetyl	<0.001	3.465	<0.001	5.846	<0.001	5.462	<0.001	5.088
+	91.05832	15.7	Diethyl sulfide	<0.001	14.834	<0.001	14.666	<0.001	16.438	<0.001	14.987
+	240.1092	12.9	Dihydrobiopterin	<0.001	31.768	<0.001	54.361	<0.001	72.096	<0.001	84.653
+	160.1333	13.7	DL-2-Aminooctanoicacid	<0.001	1.736	<0.001	1.691	<0.001	1.617	<0.001	3.408
+	243.027	16.7	D-myo-Inositol 1,2-cyclic phosphate	<0.001	0.226	<0.001	0.111	<0.001	0.098	<0.001	9.089
+	426.3577	4.7	Elaidiccarnitine	<0.001	3.808	<0.001	4.243	<0.001	7.108	<0.001	5.438
-	140.0117	16.2	Ethanolamine phosphate	<0.001	1.928	<0.001	1.831	<0.001	1.932	<0.001	2.248
+	142.0265	16.2	Ethanolamine phosphate	<0.001	1.947	<0.001	1.932	<0.001	2.023	<0.001	2.206
-	115.0035	16.2	Fumarate	<0.001	1.586	<0.001	1.749	<0.001	2.179	<0.001	1.924
-	572.0793	12.9	GDP-3,6-dideoxy-D-galactose	<0.001	9.964	0.002	11.471	<0.001	11.034	0.001	18.560
+	574.0948	12.9	GDP-3,6-dideoxy-D-galactose	<0.001	9.164	0.002	12.770	<0.001	12.103	<0.001	22.187
-	611.1436	17.6	Glutathione disulfide	<0.001	11.015	<0.001	16.751	<0.001	15.078	0.001	4.846
+	613.1595	17.6	Glutathione disulfide	<0.001	10.494	<0.001	15.862	<0.001	14.184	<0.001	4.586
-	245.114	12.6	Glu-Val	<0.001	3.694	<0.001	2.799	<0.001	5.318	<0.001	5.871
-	245.0429	12.8	Glycerophosphoglycerol	<0.001	1.246	0.272	0.954	0.008	1.177	<0.001	1.715
+	76.03938	16.0	Glycine	<0.001	2.161	0.006	1.377	0.091	1.422	<0.001	8.990
+	173.0922	14.8	Glycylproline	<0.001	2.458	<0.001	2.109	<0.001	1.949	<0.001	10.558
-	521.9828	19.7	GTP	<0.001	13.696	<0.001	12.226	<0.001	15.240	0.021	2.834
+	118.0611	16.2	Guanidinoacetate	<0.001	3.484	0.094	0.909	<0.001	1.832	<0.001	7.209
-	217.0483	14.1	hexitol chloride adduct	<0.001	2.368	0.010	2.706	<0.001	2.507	<0.001	10.680
-	527.2969	4.6	His-Leu-Leu-Phe	<0.001	2.853	0.007	1.486	<0.001	1.841	0.051	1.667
+	529.3117	4.6	His-Leu-Leu-Phe	<0.001	3.668	0.060	1.554	<0.001	2.388	0.006	1.951
-	556.2756	3.9	His-Lys-His-His	<0.001	2.622	<0.001	2.321	<0.001	2.549	0.001	4.704
-	166.0178	8.5	Homocysteinesulfinicacid	<0.001	4.131	<0.001	4.561	<0.001	4.785	<0.001	12.989
-	79.95698	15.1	HSO3-	<0.001	4.452	<0.001	5.209	<0.001	5.539	<0.001	5.278
-	110.9851	14.6	Hydroxymethylphosphonate	<0.001	6.533	<0.001	6.705	<0.001	5.399	<0.001	5.380
-	108.0123	15.3	Hypotaurine	<0.001	16.627	<0.001	17.735	<0.001	19.447	<0.001	17.881

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	110.0271	15.3	Hypotaurine	<0.001	11.950	<0.001	13.300	<0.001	14.652	<0.001	11.056
+	130.0499	14.8	L-1-Pyrroline-3-hydroxy-5-carboxylate	<0.001	2.812	<0.001	3.612	<0.001	4.087	<0.001	5.103
+	162.0761	11.3	L-2-Aminoadipate	<0.001	4.476	<0.001	3.808	0.001	4.144	<0.001	12.457
+	219.0977	14.9	L-Ala-L-Glu	<0.001	23.246	<0.001	15.539	<0.001	47.854	0.002	20.051
+	90.055	15.7	L-Alanine	<0.001	8.202	<0.001	8.650	<0.001	9.258	<0.001	9.343
+	175.1191	27.4	L-Arginine	<0.001	1.421	0.001	1.527	0.006	1.346	<0.001	6.232
-	132.0301	15.2	L-Aspartate	<0.001	1.502	<0.001	1.361	<0.001	1.445	<0.001	3.436
+	162.1125	13.6	L-Carnitine	<0.001	1.502	<0.001	1.427	0.186	1.057	<0.001	3.393
+	176.1031	16.3	L-Citrulline	<0.001	1.495	0.001	1.370	0.021	1.155	<0.001	7.340
-	167.9972	15.1	L-Cysteate	<0.001	6.711	<0.001	5.874	<0.001	5.985	<0.001	7.701
-	239.0164	16.7	L-Cystine	<0.001	0.227	<0.001	0.125	<0.001	0.095	<0.001	6.542
+	241.0311	16.7	L-Cystine	<0.001	0.259	<0.001	0.178	<0.001	0.131	<0.001	6.384
+	229.1548	10.4	Leu-Pro	<0.001	1.577	<0.001	1.450	0.001	1.444	<0.001	3.387
+	229.1548	13.4	Leu-Pro	<0.001	1.723	0.086	1.316	0.006	1.352	<0.001	7.096
-	146.0458	14.8	L-Glutamate	<0.001	2.619	<0.001	2.719	<0.001	3.021	<0.001	5.212
+	148.0604	14.8	L-Glutamate	<0.001	2.790	<0.001	3.082	<0.001	3.461	<0.001	4.683
-	130.0508	14.8	L-Glutamate 5-semialdehyde	<0.001	1.550	<0.001	1.388	<0.001	1.302	<0.001	4.161
+	132.0655	14.8	L-Glutamate 5-semialdehyde	<0.001	1.622	<0.001	1.725	<0.001	1.552	<0.001	5.748
+	147.0764	15.4	L-Glutamine	<0.001	1.403	<0.001	1.413	0.003	1.262	<0.001	4.921
+	424.3421	4.7	Linoelaidylcarnitine	<0.001	7.520	<0.001	8.657	<0.001	15.448	<0.001	10.327
+	150.0584	11.9	L-Methionine	<0.001	1.452	0.001	1.531	0.002	1.381	<0.001	7.069
+	133.0971	24.3	L-Ornithine	<0.001	1.435	<0.001	1.527	0.010	1.301	<0.001	5.413
-	132.0123	8.2	L-thiazolidine-4-carboxylate	<0.001	60.306	<0.001	66.657	0.001	56.280	<0.001	85.191
+	134.027	8.2	L-thiazolidine-4-carboxylate	<0.001	45.798	0.004	74.768	0.001	68.501	0.001	105.550
+	205.0973	12.1	L-Tryptophan	<0.001	1.434	0.001	1.487	0.002	1.336	<0.001	6.936
+	182.0813	13.4	L-Tyrosine	<0.001	1.381	0.008	1.351	0.003	1.320	<0.001	5.508
+	118.0863	11.5	L-Valine	<0.001	1.685	<0.001	1.839	<0.001	1.511	<0.001	4.771
+	569.344	4.7	Lys-Lys-Phe-Phe	<0.001	2.152	0.015	2.113	0.002	2.070	<0.001	5.059

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	556.3249	4.8	Lys-Lys-Trp-Pro	<0.001	1.247	0.003	1.237	<0.001	1.381	0.002	1.721
+	570.355	4.7	LysoPC(22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.382	0.018	1.983	<0.001	2.754	<0.001	4.847
-	528.3093	4.6	LysoPE(0:0/22:4(7Z,10Z,13Z,16Z))	<0.001	2.591	0.004	1.298	<0.001	1.663	0.001	1.412
+	530.3237	4.6	LysoPE(0:0/22:4(7Z,10Z,13Z,16Z))	<0.001	3.114	0.001	1.595	<0.001	2.042	0.141	1.313
-	526.2936	4.6	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.818	<0.001	1.502	<0.001	1.870	<0.001	1.768
+	528.3084	4.6	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	3.465	<0.001	1.856	<0.001	2.253	<0.001	2.021
-	524.2778	4.7	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.206	<0.001	1.602	<0.001	1.969	<0.001	2.111
+	526.2927	4.6	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.448	<0.001	1.732	<0.001	2.128	<0.001	2.032
-	525.2812	4.7	Lys-Trp-Pro-Pro	<0.001	3.095	<0.001	1.608	<0.001	1.951	<0.001	2.072
-	529.3129	4.6	Lys-Trp-Val-Val	<0.001	2.655	0.344	1.172	<0.001	1.660	0.011	1.301
-	129.0192	15.1	Itaconate	<0.001	4.943	<0.001	4.231	<0.001	4.349	<0.001	5.055
+	221.0961	4.3	Met-Ala	<0.001	0.269	<0.001	0.256	<0.001	0.294	<0.001	0.097
-	287.14	4.1	Methyl 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-p-toluate	<0.001	2.091	0.001	2.120	<0.001	2.190	<0.001	18.620
+	291.1299	17.1	N-(L-Arginino)succinate	<0.001	4.611	<0.001	4.457	<0.001	6.771	<0.001	12.655
+	339.0474	13.1	N5-carboxyaminoimidazole ribonucleotide	<0.001	2.664	<0.001	2.905	0.050	2.039	0.115	1.580
+	161.1285	24.7	N6-Methyl-L-lysine	<0.001	4.751	<0.001	4.540	<0.001	4.049	<0.001	9.021
-	222.0982	13.6	N-acetyl -D- glucosaminitol	<0.001	1.531	0.089	1.233	0.707	0.982	<0.001	3.102
+	189.0871	14.8	N-Acetylglutamine	<0.001	5.567	<0.001	4.665	<0.001	5.639	<0.001	12.718
-	308.0985	13.5	N-Acetylneuraminate	<0.001	2.375	<0.001	2.073	<0.001	2.155	<0.001	2.932
+	310.1132	13.5	N-Acetylneuraminate	<0.001	2.352	<0.001	2.054	<0.001	2.231	<0.001	2.376
-	662.1009	14.4	NAD+	<0.001	4.293	<0.001	5.518	<0.001	5.999	<0.001	4.429
+	664.1166	14.4	NAD+	<0.001	4.194	<0.001	5.425	<0.001	5.769	<0.001	4.763
+	744.0834	17.1	NADP+	<0.001	7.062	<0.001	7.559	<0.001	8.645	<0.001	6.342
+	746.0988	17.4	NADPH	<0.001	4.667	<0.001	4.725	<0.001	6.969	<0.001	4.676
-	152.0483	12.9	N-Dimethyl-2-aminoethylphosphonate	<0.001	2.306	0.002	2.341	<0.001	2.247	<0.001	5.690
+	126.055	11.3	N-Ethylmaleimide	<0.001	2.637	0.079	4.768	0.008	5.967	0.001	2.325
+	175.0714	15.2	N-Formimino-L-glutamate	<0.001	2.067	<0.001	1.923	<0.001	2.141	<0.001	6.115

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	324.0934	14.6	N-Glycoloyl-neuraminate	<0.001	3.163	<0.001	2.681	<0.001	2.990	<0.001	4.331
+	326.1081	14.6	N-Glycoloyl-neuraminate	<0.001	3.305	<0.001	2.959	<0.001	3.274	<0.001	4.159
-	293.0988	14.8	N-Glycosyl-L-asparagine	<0.001	14.274	<0.001	14.966	<0.001	20.612	0.001	63.654
+	123.0553	7.5	Nicotinamide	<0.001	1.820	<0.001	1.777	<0.001	1.800	<0.001	5.116
+	204.1232	11.3	O-Acetylcarnitine	<0.001	2.910	<0.001	2.853	<0.001	3.258	<0.001	4.218
+	232.1544	9.0	O-Butanoylcarnitine	<0.001	1.426	<0.001	1.580	0.003	1.333	<0.001	3.138
+	218.1388	10.0	O-Propanoylcarnitine	<0.001	1.458	<0.001	1.348	<0.001	1.222	<0.001	1.942
-	96.96946	16.1	Orthophosphate	<0.001	1.546	<0.001	1.660	<0.001	1.522	0.008	1.325
+	784.5858	4.2	PC(18:2(9Z,12Z)/18:1(9Z))	<0.001	6.481	<0.001	7.027	<0.001	8.188	<0.001	7.156
+	740.5595	4.2	PC(18:3(6Z,9Z,12Z)/P-16:0)	<0.001	1.762	0.013	1.581	0.002	1.719	0.012	1.744
+	738.5438	4.1	PC(18:4(6Z,9Z,12Z,15Z)/P-16:0)	<0.001	0.471	<0.001	0.664	<0.001	0.485	<0.001	0.508
+	860.6165	4.1	PC(20:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	10.256	<0.001	11.293	<0.001	11.641	0.010	9.041
+	858.6022	4.1	PC(20:2(11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.210	<0.001	2.799	<0.001	2.997	<0.001	3.675
+	856.5862	4.1	PC(20:3(5Z,8Z,11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	4.298	<0.001	3.811	<0.001	4.335	<0.001	4.767
+	792.591	4.2	PC(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	<0.001	1.151	<0.001	1.166	<0.001	1.230	<0.001	1.321
+	886.6331	4.1	PC(22:2(13Z,16Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	11.205	0.004	7.442	<0.001	6.765	0.003	10.087
+	884.6172	4.1	PC(22:4(7Z,10Z,13Z,16Z)/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	8.591	<0.001	7.304	<0.001	7.709	<0.001	9.227
+	882.6019	4.1	PC(22:4(7Z,10Z,13Z,16Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	9.527	<0.001	8.610	<0.001	9.531	<0.001	10.702
+	820.6224	4.2	PC(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	<0.001	1.435	<0.001	1.355	<0.001	1.522	<0.001	1.621
-	211.0012	12.7	P-DPD	<0.001	64.498	<0.001	61.275	<0.001	87.154	<0.001	80.176
+	722.5126	4.1	PE(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	<0.001	2.845	0.008	3.379	0.001	2.255	0.002	2.362
-	764.5239	4.1	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	8.274	<0.001	8.507	<0.001	9.900	<0.001	7.992
+	766.5396	4.1	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	12.866	<0.001	9.174	<0.001	15.644	<0.001	12.625
+	774.5436	4.0	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	<0.001	1.499	<0.001	1.584	<0.001	1.726	<0.001	1.594
+	343.1692	4.2	penicillin K	<0.001	0.208	<0.001	0.185	<0.001	0.207	0.001	0.253
-	793.5014	3.7	PG(16:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	2.460	<0.001	1.983	<0.001	2.231	<0.001	2.600
-	819.5169	3.7	PG(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.981	<0.001	1.877	<0.001	2.065	<0.001	2.150
-	815.4857	3.7	PG(18:3(6Z,9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	2.130	0.001	1.450	0.002	1.411	<0.001	2.331

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	353.0488	7.5	Phenolsulfonphthalein	<0.001	1.920	0.002	2.053	0.002	1.892	<0.001	10.815
+	165.0547	13.4	Phenylpyruvate	<0.001	1.533	0.001	1.588	0.002	1.523	<0.001	7.909
-	78.95864	15.4	Phosphite	<0.001	4.490	<0.001	2.756	<0.001	2.964	<0.001	5.018
-	78.95865	16.1	Phosphite	<0.001	1.710	<0.001	1.959	<0.001	1.821	<0.001	1.542
-	210.0284	15.4	Phosphocreatine	<0.001	4.494	<0.001	2.401	<0.001	2.449	<0.001	5.308
+	212.0432	15.4	Phosphocreatine	<0.001	4.208	<0.001	2.305	<0.001	2.410	<0.001	4.027
+	809.5163	3.8	PI(16:0/16:1(9Z))	<0.001	19.725	<0.001	19.841	0.002	18.960	0.002	14.207
+	839.564	3.8	PI(16:0/18:0)	<0.001	1.410	<0.001	1.296	<0.001	1.508	<0.001	1.308
+	861.5481	3.7	PI(16:0/20:3(5Z,8Z,11Z))	<0.001	1.570	<0.001	1.444	<0.001	1.314	<0.001	1.666
-	857.5164	3.9	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	1.962	<0.001	1.881	<0.001	2.127	0.001	1.950
+	859.533	3.7	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	3.725	<0.001	3.620	<0.001	3.818	0.002	3.725
+	889.5791	3.7	PI(16:0/22:3(10Z,13Z,16Z))	<0.001	1.348	<0.001	1.399	<0.001	1.267	<0.001	1.482
-	883.5327	3.9	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.870	<0.001	2.816	<0.001	3.284	<0.001	3.004
+	885.5484	3.7	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.700	<0.001	3.218	<0.001	3.148	<0.001	2.961
-	188.0749	4.7	Prenyl-L-cysteine	<0.001	43.539	<0.001	42.066	<0.001	42.834	<0.001	44.373
+	190.0904	14.8	Prenyl-L-cysteine	<0.001	7.123	<0.001	6.998	<0.001	8.088	<0.001	19.226
+	190.0897	4.7	Prenyl-L-cysteine	<0.001	26.591	<0.001	28.050	<0.001	29.235	<0.001	29.359
-	288.1199	13.6	Pro-Ser-Ser	<0.001	5.634	<0.001	2.086	<0.001	7.950	<0.001	7.272
+	290.1345	13.6	Pro-Ser-Ser	<0.001	5.921	0.004	2.080	<0.001	8.184	<0.001	8.807
+	760.513	3.9	PS(16:0/18:2(9Z,12Z))	<0.001	15.839	<0.001	14.680	0.001	17.115	<0.001	9.053
-	788.5435	3.9	PS(18:0/18:1(9Z))	<0.001	0.402	<0.001	0.368	<0.001	0.476	<0.001	0.377
+	790.5604	3.8	PS(18:0/18:1(9Z))	<0.001	0.371	<0.001	0.322	<0.001	0.398	<0.001	0.284
-	832.512	3.8	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	18.497	0.002	16.700	0.002	22.340	0.002	12.485
+	834.529	3.7	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.213	<0.001	3.230	<0.001	3.579	<0.001	3.532
-	806.4964	3.9	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	29.016	<0.001	29.059	<0.001	40.146	<0.001	26.113
+	808.5133	3.8	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	22.157	<0.001	24.969	<0.001	29.093	<0.001	22.955
+	858.529	3.7	PS(20:3(8Z,11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.441	<0.001	3.327	<0.001	3.424	<0.001	3.606
+	203.0849	5.0	Pyrene	<0.001	31.551	<0.001	41.466	<0.001	31.605	<0.001	47.840

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	160.0403	4.9	Quinoline-3,4-diol	<0.001	39.002	0.085	18.345	0.208	10.853	0.027	36.885
-	289.0328	16.5	Sedoheptulose 7-phosphate	<0.001	20.931	<0.001	15.962	0.001	9.518	<0.001	14.935
+	675.5441	4.5	SM(d18:1/14:0)	<0.001	1.599	<0.001	1.472	<0.001	1.584	<0.001	1.496
+	813.6856	4.4	SM(d18:1/24:1(15Z))	<0.001	0.251	<0.001	0.184	<0.001	0.103	<0.001	0.159
-	256.0954	14.8	sn-glycero-3-Phosphocholine	<0.001	1.874	0.004	0.653	0.159	0.777	0.005	1.835
+	258.1101	14.8	sn-glycero-3-Phosphocholine	<0.001	2.028	0.260	0.928	0.250	1.089	<0.001	2.702
-	214.0486	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	1.316	<0.001	0.564	<0.001	0.722	0.001	1.694
+	216.0633	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	1.341	<0.001	0.565	<0.001	0.747	<0.001	1.673
-	171.0064	14.8	sn-Glycerol 3-phosphate	<0.001	1.806	0.003	0.855	0.272	0.950	<0.001	2.093
+	428.3735	4.6	Stearoylcarnitine	<0.001	1.816	<0.001	1.901	<0.001	1.807	<0.001	2.423
-	124.0072	15.1	Taurine	<0.001	4.372	<0.001	4.661	<0.001	4.862	<0.001	5.293
+	126.022	15.1	Taurine	<0.001	4.239	<0.001	5.056	<0.001	5.414	<0.001	4.940
+	387.2892	3.7	Testosterone isocaproate	<0.001	1.484	<0.001	1.651	0.001	1.377	0.007	1.280
+	144.0519	15.1	Tet-glycine	<0.001	5.246	<0.001	5.546	<0.001	5.703	<0.001	5.619
+	372.3108	4.9	Tetradecanoylcarnitine	<0.001	3.138	<0.001	3.467	<0.001	5.309	<0.001	3.396
-	151.9844	16.7	Thiocysteine	<0.001	0.153	<0.001	0.171	<0.001	0.064	<0.001	11.560
+	148.0427	5.2	Thiomorpholine 3-carboxylate	<0.001	78.855	<0.001	102.543	<0.001	139.277	0.001	95.451
+	133.0318	11.9	THTC	<0.001	1.536	0.001	1.674	0.001	1.465	<0.001	8.559
-	367.1133	4.2	trans-3-Hydroxycotinineglucuronide	<0.001	2.739	0.036	1.799	<0.001	2.367	0.001	25.837
+	398.3265	4.8	trans-Hexadec-2-enoylcarnitine	<0.001	4.228	<0.001	4.379	<0.001	7.272	<0.001	5.484
-	402.9944	16.8	UDP	<0.001	21.334	<0.001	23.667	<0.001	27.901	<0.001	19.701
-	565.0469	16.5	UDP-glucose	<0.001	6.310	<0.001	7.445	<0.001	6.933	<0.001	7.237
-	579.0263	19.3	UDP-glucuronate	<0.001	8.576	<0.001	9.303	<0.001	9.559	<0.001	9.666
-	606.0738	15.3	UDP-N-acetyl-D-glucosamine	<0.001	4.467	<0.001	4.758	<0.001	4.522	<0.001	5.081
-	243.062	10.0	Uridine	<0.001	0.753	0.618	1.023	<0.001	0.623	<0.001	2.912
-	482.9608	18.2	UTP	<0.001	13.602	<0.001	13.722	<0.001	14.249	<0.001	8.762
-	293.1756	4.0	[6]-Gingerol	0.989	1.002	0.189	1.208	0.630	0.940	<0.001	2.571
-	122.9934	16.1	6-S-acetyl-dihydrolipoate	0.979	1.027	0.015	3.918	0.510	1.802	0.681	1.418

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	375.2901	4.3	3alpha-Hydroxy-5beta-cholanate	0.974	1.034	0.514	0.575	0.042	0.178	0.164	0.420
-	167.0713	7.5	1,3,5-trimethoxybenzene	0.974	1.015	0.882	0.922	0.742	0.868	0.573	1.667
-	155.0713	7.5	[FA oxo(8:0)] 5-oxo-7-octenoic acid	0.970	1.012	0.377	0.727	0.390	0.726	0.529	0.795
-	114.0195	15.7	Maleamate	0.953	0.989	0.748	1.061	0.982	1.004	<0.001	3.884
-	113.0355	15.7	5,6-Dihydrouracil	0.950	0.989	0.939	1.008	0.577	0.930	<0.001	2.637
-	99.04504	7.5	Tiglic acid	0.939	1.055	0.767	1.233	0.509	1.582	0.820	1.136
-	125.0355	7.5	Thymine	0.907	1.029	0.628	1.119	0.533	0.843	<0.001	3.375
-	160.0614	15.1	L-2-Aminoadipate	0.903	0.976	0.465	1.171	0.845	1.050	0.082	10.086
-	277.2174	3.9	[FA (18:3)] 9Z,12Z,15Z-octadecatrienoic acid	0.902	0.966	0.659	0.890	0.640	0.878	<0.001	2.587
-	810.5279	3.8	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.899	1.011	0.066	0.856	0.336	0.927	0.070	0.859
-	352.322	4.2	[FA (20:0)] N-(11Z-eicosaenoyl)-ethanolamine	0.897	1.082	0.095	2.053	0.079	0.538	0.894	1.093
-	397.3321	3.8	[FA (24:0/2:0)] Tetracosanedioic acid	0.887	1.021	0.356	0.858	0.724	1.053	0.172	1.177
-	616.4703	4.4	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphate	0.886	1.015	0.164	0.847	0.770	0.974	0.395	0.906
-	311.2592	3.9	[FA oxo(19:0)] 10-oxo-nonadecanoic acid	0.872	1.045	0.187	1.427	0.084	1.505	0.054	1.906
-	158.0821	5.0	5-Acetamidopentanoate	0.864	0.871	0.288	0.331	0.312	0.367	0.019	3.139
-	102.0195	13.2	2-Aminomalonate semialdehyde	0.860	0.846	0.445	0.391	0.489	0.456	0.388	0.313
-	464.3141	4.6	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	0.854	0.991	0.040	1.104	0.012	1.119	0.001	1.330
-	764.5624	4.4	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.848	1.016	0.105	0.898	0.520	0.959	0.331	0.960
-	243.1599	5.0	[FA (13:0/2:0)] Tridecanedioic acid	0.845	1.153	0.384	0.478	0.399	0.495	0.423	0.522
-	271.2278	4.0	16-hydroxypalmitate	0.843	1.011	0.508	0.963	0.765	1.014	<0.001	1.372
-	201.0768	7.5	Diethyl 2-methyl-3-oxosuccinate	0.838	1.059	0.388	0.761	0.798	0.935	0.172	0.650
-	439.3791	3.8	MG(0:0/24:1(15Z)/0:0)	0.836	0.955	0.304	1.196	0.015	1.554	0.649	0.902
-	175.0472	15.1	Allantoate	0.835	1.028	0.857	0.967	0.241	0.745	<0.001	12.484
-	391.2853	4.7	[ST hydrox] 3alpha,7alpha-Dihydroxy-5beta-cholan-24-oic Acid	0.827	1.273	0.673	0.697	0.029	0.187	0.069	0.299
-	110.0358	12.2	Cytosine	0.819	1.066	0.474	0.812	0.617	0.865	<0.001	4.030
-	109.0405	15.4	Imidazole-4-acetaldehyde	0.818	0.897	0.235	0.591	0.411	0.690	0.033	3.078

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	327.1448	7.5	[FA dioxo,hydroxy(4:0/2:0)] 9,15-dioxo-11R-hydroxy-2,3,4,5-tetranor-prostan-1,20-dioic acid	0.817	1.043	0.276	1.278	0.824	1.041	0.431	1.155
-	309.1698	4.0	Botrydial	0.814	1.062	0.740	1.119	0.098	0.614	0.052	1.558
-	143.0349	7.5	2,3-Dimethylmaleate	0.808	1.091	0.258	1.261	0.555	1.166	0.594	1.180
-	269.2121	4.0	[FA oxo(16:0)] 3-oxo-hexadecanoic acid	0.807	1.010	0.229	0.950	0.134	0.928	0.739	0.978
-	450.2988	4.7	[PC (14:1)] 1-(1E-tetradecenyl)-sn-glycero-3-phosphocholine	0.797	0.962	0.806	1.030	0.177	1.152	0.013	1.496
-	136.0402	4.5	Anthranilate	0.794	1.082	0.374	0.743	0.166	0.591	<0.001	50.434
-	185.0818	7.5	cis-2-Carboxycyclohexyl-acetic acid	0.794	1.072	0.252	0.661	0.635	0.862	0.696	0.895
-	369.0679	4.4	Digalacturonate	0.788	1.166	0.323	1.531	0.388	1.914	0.176	29.063
-	171.139	4.2	Decanoic acid	0.788	0.980	0.081	0.886	0.099	0.755	0.358	1.181
-	291.1811	5.0	octyl α-D-glucopyranoside	0.788	1.014	0.135	0.921	0.868	0.989	0.277	1.117
-	149.0471	11.9	Dipropyl disulfide	0.780	1.053	0.381	1.227	0.755	1.074	<0.001	7.438
-	127.0763	7.5	3-Isopropylbut-3-enoic acid	0.777	0.850	0.317	1.716	0.698	1.280	0.994	0.997
-	158.0821	7.5	5-Acetamidopentanoate	0.776	1.163	0.298	0.588	0.088	0.393	0.098	2.194
-	297.2433	3.9	2-Oxooctadecanoic acid	0.774	0.984	0.079	0.886	0.038	0.856	0.372	0.938
-	341.2696	3.8	[FA (20:0/2:0)] Eicosanedioic acid	0.761	0.986	0.088	0.906	0.114	0.914	0.260	0.939
-	225.186	4.0	(9Z)-Tetradecenoic acid	0.759	0.923	0.847	1.051	0.753	0.922	0.168	1.393
-	79.95693	7.5	HSO3-	0.758	1.101	0.430	0.819	0.327	0.777	0.017	1.813
-	103.0399	7.6	(R)-3-Hydroxybutanoate	0.751	1.153	0.395	4.746	0.392	5.585	0.002	7.802
-	192.0666	5.0	Phenylacetylglycine	0.743	1.099	0.777	0.919	0.929	0.974	<0.001	5.102
-	775.5471	4.0	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.740	1.075	0.915	0.973	0.349	1.258	0.719	0.925
-	155.0825	11.8	N-acetyl prolinamide or isomer	0.735	0.913	0.776	0.934	0.671	1.088	<0.001	5.369
-	129.092	4.7	[FA (7:0)] heptanoic acid	0.732	1.085	0.951	0.982	0.235	0.727	0.524	1.172
-	165.0768	11.4	L-rhamnitol	0.727	0.893	0.357	0.735	0.920	0.972	<0.001	4.717
-	343.17	4.2	[FA (24:6)] 6,9,12,15,18,21-Tetracosahexaynoic acid	0.720	1.023	0.008	0.826	0.003	0.782	0.071	0.865
-	121.0505	12.0	Erythritol	0.717	1.100	0.770	1.085	0.605	1.142	<0.001	2.948
-	187.0723	13.8	N-Acetylglutamine	0.715	1.141	0.130	2.054	0.475	1.322	0.001	21.404
-	129.0556	7.5	(S)-3-Methyl-2-oxopentanoic acid	0.706	1.147	0.791	1.107	0.463	1.253	0.818	1.091

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	80.96482	16.2	Sulfite	0.706	1.119	0.091	13.509	0.603	1.146	0.408	0.818
-	178.0509	13.1	Hippurate	0.692	0.860	0.547	0.784	0.676	0.843	0.590	0.799
-	383.3167	3.9	[FA (23:0/2:0)] Tricosanedioic acid	0.690	1.124	0.671	1.149	0.791	1.073	0.881	1.053
-	141.0557	7.5	4-Oxocyclohexanecarboxylate	0.687	1.126	0.234	1.617	0.692	0.889	0.731	1.139
-	88.04013	15.1	L-Alanine	0.687	1.120	0.288	1.322	0.033	1.465	<0.001	4.127
-	88.98779	18.0	Oxalate	0.682	1.098	0.349	1.207	0.651	0.872	0.261	0.733
-	192.0666	7.5	Phenylacetylglycine	0.663	0.799	0.637	0.782	0.467	0.658	0.011	2.668
-	199.9691	16.7	S-Sulfo-L-cysteine	0.656	1.105	0.058	0.562	0.198	0.729	<0.001	7.152
-	83.04988	7.5	3-Methylbut-2-enal	0.656	1.217	0.945	1.036	0.073	1.800	0.543	0.708
-	143.0713	7.5	trans-4-Hydroxycyclohexanecarboxylate	0.645	1.351	0.962	0.973	0.545	0.652	0.432	0.545
-	355.2853	3.9	[FA (21:0/2:0)] Heneicosanedioic acid	0.642	0.867	0.364	0.715	0.318	0.707	0.107	0.495
-	128.0352	13.1	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.638	0.867	0.377	0.763	0.985	0.995	0.202	1.425
-	125.0607	7.5	Toluene-cis-dihydrodiol	0.635	1.318	0.325	1.782	0.557	1.525	0.800	0.914
-	465.3176	4.6	[ST (3:0/3:0/3:0)] (5Z,7E)-(1S,3R)-24,24-difluoro-24a-homo-9,10-seco-5,7,10(19)-cholestatrien-1,3,25-triol	0.629	0.964	0.841	0.978	0.121	1.069	0.003	1.342
-	295.2276	4.0	[FA hydroxy(18:2)] 9S-hydroxy-10E,12Z-octadecadienoic acid	0.626	1.080	0.659	0.928	0.054	0.656	0.011	0.606
-	113.0607	7.5	6-Hexanolide	0.613	1.313	0.454	1.490	0.845	0.919	0.981	1.009
-	134.061	7.5	2-Phenylacetamide	0.605	1.317	0.973	1.017	0.537	1.357	0.002	2.977
-	104.9999	15.3	fluoropyruvate	0.605	0.582	0.906	1.114	0.175	0.055	0.413	0.404
-	134.061	5.0	2-Phenylacetamide	0.598	0.757	0.308	0.523	0.436	0.643	<0.001	5.665
-	80.96478	7.5	Sulfite	0.594	0.891	0.891	1.024	0.479	1.243	0.621	1.190
-	163.0613	4.3	L-Rhamnose	0.593	0.814	0.069	0.568	0.138	0.684	0.010	0.339
-	113.0243	7.5	2-Hydroxy-2,4-pentadienoate	0.593	1.341	0.949	1.029	0.495	0.752	0.583	0.799
-	87.0085	14.7	Pyruvate	0.584	0.857	0.266	0.736	0.712	0.914	0.157	5.102
-	157.0869	7.5	[FA oxo(8:0)] 3-oxo-octanoic acid	0.584	0.736	0.528	0.703	0.564	0.734	0.479	0.655
-	157.1233	4.3	Nonanoic acid	0.581	1.058	0.727	0.979	0.055	0.882	0.160	1.165
-	748.527	4.0	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.573	0.943	0.008	1.221	<0.001	1.302	0.570	1.071
-	155.1077	4.5	[FA hydroxy(9:1)] 4-hydroxy-2-nonenal	0.564	1.412	0.359	1.610	0.596	1.323	0.004	2.797

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	774.5439	4.0	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.562	0.919	0.086	1.274	0.543	1.114	0.655	0.931
-	245.1392	7.5	3-Hydroxydodecanedioicacid	0.553	1.086	0.444	1.085	0.558	0.939	0.315	1.175
-	217.108	5.0	3-Hydroxysebacicacid	0.543	1.299	0.675	1.206	0.636	1.225	0.445	1.389
-	303.2328	3.9	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	0.542	1.067	0.542	1.060	0.026	0.843	<0.001	1.851
-	299.2589	4.0	[FA hydroxy(18:0)] 2S-hydroxy-octadecanoic acid	0.541	0.928	0.069	0.839	0.006	0.775	0.063	0.863
-	99.0086	15.3	2-oxobut-3-enanoate	0.540	1.105	0.234	1.271	0.021	1.495	<0.001	17.034
-	360.1228	14.8	Met-Asp-Pro	0.540	0.856	0.066	0.693	0.039	0.642	<0.001	26.078
-	159.1025	4.9	Ethyl (R)-3-hydroxyhexanoate	0.535	1.145	0.979	0.996	0.058	1.265	0.009	5.983
-	111.0198	15.7	Uracil	0.531	0.670	0.925	1.051	0.995	1.003	0.103	5.324
-	173.1182	7.5	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.525	1.368	0.137	2.094	0.315	1.678	0.624	1.280
-	138.0559	4.8	Gabaculine	0.523	1.113	0.097	1.412	0.975	0.993	0.002	8.108
-	239.2017	4.0	[FA dimethyl(13:0)] 2,5-dimethyl-2E-tridecenoic acid	0.520	0.819	0.738	0.903	0.209	0.613	0.470	0.801
-	327.2329	3.9	Docosahexaenoicacid	0.512	1.034	0.069	1.144	0.505	1.037	<0.001	2.960
-	91.02189	6.3	methylmercaptoethanol	0.496	0.728	0.598	0.787	0.253	0.531	0.617	0.802
-	189.0767	5.0	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.494	1.105	0.110	3.226	0.165	1.361	0.493	1.109
-	213.186	4.0	CAI-1	0.485	1.095	0.603	1.066	0.281	0.790	0.764	1.054
-	95.01366	15.0	Protoanemonin	0.476	0.823	0.171	0.722	0.203	0.736	<0.001	15.808
-	337.3113	3.8	[FA (22:0)] 13Z-docosenoic acid	0.474	0.832	0.937	1.022	0.548	0.870	0.829	0.952
-	172.0979	5.0	N-Acetyl-L-leucine	0.464	0.869	0.774	0.957	0.916	0.982	0.009	2.925
-	164.0353	13.5	Formylanthranilate	0.462	1.149	0.245	1.535	0.354	1.465	0.004	16.299
-	145.0982	25.8	L-Lysine	0.462	1.358	0.107	1.699	0.422	1.264	<0.001	14.626
-	267.2329	3.9	omega-Cyclohexylundecanoic acid	0.461	0.861	0.517	0.869	0.303	0.795	0.782	1.056
-	251.202	3.9	[FA (16:2)] 9,12-hexadecadienoic acid	0.460	0.839	0.768	0.939	0.881	1.035	<0.001	3.301
-	147.0298	15.3	(R)-2-Hydroxyglutarate	0.449	1.161	0.594	1.111	0.600	1.110	0.126	1.363
-	353.0487	5.0	Phenolsulfonphthalein	0.449	1.087	0.030	1.242	0.097	1.222	<0.001	5.684
-	117.0556	5.2	5-Hydroxypentanoate	0.444	0.817	0.892	1.051	0.424	1.400	0.020	6.234
-	149.0453	15.1	D-Ribose	0.443	1.310	0.377	1.293	0.174	0.559	<0.001	8.808

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	116.0352	13.2	L-2-Amino-3-oxobutanoic acid	0.437	1.896	0.360	0.356	0.589	1.571	0.410	0.422
-	137.0355	7.5	Urocanate	0.437	0.699	0.365	0.693	0.138	0.488	0.393	0.667
-	133.0505	13.1	Deoxyribose	0.428	2.497	0.505	0.778	0.349	0.700	0.376	0.730
-	109.0657	7.5	[FA (7:2)] 2,4-heptadienal	0.426	0.780	0.541	1.227	0.648	0.845	0.864	1.075
-	196.0726	8.8	N-Acetyl-L-histidine	0.415	1.240	0.494	1.170	0.925	1.021	<0.001	9.477
-	115.0763	4.9	Hexanoic acid	0.415	1.555	0.834	1.058	0.174	1.765	0.042	2.695
-	183.1389	4.3	[FA (11:0)] 10-undecenoic acid	0.414	1.621	0.158	1.898	0.295	1.607	0.256	1.670
-	295.264	3.9	[FA methyl(18:0)] 11R,12S-methylene-octadecanoic acid	0.409	0.871	0.304	0.821	0.223	0.810	0.021	1.439
-	409.311	4.0	[ST hydroxy,methyl(4:0)] (22E)-(8S)-3-hydroxy-22-methyl-9,10-seco-1,3,5(10),22-cholestatetraen-9-one	0.398	0.868	0.017	0.667	0.956	1.006	0.938	0.985
-	204.1239	7.5	Pantothenol	0.398	1.265	0.261	1.452	0.196	1.336	0.307	1.354
-	142.0508	7.5	Vinylacetylglycine	0.396	1.267	0.774	1.081	0.315	1.282	0.065	3.526
-	96.96961	13.1	Orthophosphate	0.395	1.260	0.003	0.350	0.202	0.708	0.901	0.966
-	309.2798	3.9	[FA (20:0)] 11Z-eicosenoic acid	0.388	0.885	0.338	0.867	0.076	0.724	0.285	1.150
-	117.0556	14.1	5-Hydroxypentanoate	0.386	0.225	0.356	0.171	0.341	0.141	0.355	0.168
-	111.045	7.5	sorbate	0.384	1.845	0.257	2.167	0.115	3.056	0.639	1.411
-	165.0414	13.5	L-Arabinonate	0.375	2.791	0.185	3.048	0.811	0.847	0.103	12.376
-	411.3479	3.8	MG(0:0/22:1(13Z)/0:0)	0.373	1.253	0.057	1.512	0.051	1.532	0.066	1.494
-	102.0559	7.5	4-Aminobutanoate	0.371	0.731	0.133	0.528	0.121	0.506	0.353	0.725
-	178.0509	5.0	Hippurate	0.364	0.228	0.417	0.308	0.417	0.315	0.891	0.888
-	197.1546	7.5	[PR] Citronellyl acetate	0.362	0.847	0.208	0.773	0.879	1.028	0.475	1.268
-	121.0294	7.5	Benzoate	0.356	1.212	0.073	1.450	0.485	1.222	0.933	0.982
-	99.0086	5.0	2-oxobut-3-enanoate	0.356	1.265	0.250	2.833	0.183	1.387	0.093	1.429
-	178.0509	7.5	Hippurate	0.354	0.301	0.957	0.956	0.681	0.669	0.069	2.575
-	110.0358	10.7	Cytosine	0.353	0.657	0.327	0.636	0.184	0.477	0.003	2.662
-	129.0192	7.4	Itaconate	0.350	1.925	0.081	0.270	0.104	0.327	0.118	0.370
-	253.108	7.5	[FA methyl,hydroxy,oxo(5:2/4:0)] methyl 4-[2-(2-formyl-vinyl)-3-hydroxy-5-oxo-cyclopentyl]-butanoate	0.348	1.336	0.295	1.351	0.101	1.591	0.125	2.474
-	187.0975	13.1	Azelaic acid	0.346	2.581	0.394	1.303	0.919	1.029	0.636	1.148

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	185.1546	4.1	[FA (11:0)] undecanoic acid	0.337	0.692	0.187	0.554	0.471	0.745	0.992	1.004
-	127.0399	7.5	(4E)-2-Oxohexenoic acid	0.332	1.311	0.121	1.487	0.343	1.340	0.209	2.624
-	97.0657	5.0	[FA (6:1)] 2-hexenal	0.332	2.228	0.402	2.038	0.355	2.253	0.724	0.918
-	122.9934	15.2	6-S-acetyl-dihydrolipoate	0.327	6.493	0.020	1.705	0.078	1.544	0.022	19.042
-	169.0982	4.2	Levetiracetam	0.327	1.458	0.021	1.698	0.268	1.494	0.016	17.507
-	103.0036	16.0	Malonate	0.326	0.440	0.640	0.715	0.103	0.122	0.237	0.348
-	153.092	7.5	[FA (9:2)] 2,6-nonadienoic acid	0.325	0.641	0.812	0.903	0.529	1.632	0.770	1.126
-	104.9999	16.3	fluoropyruvate	0.324	0.076	0.330	0.088	0.417	0.248	0.511	0.377
-	141.092	7.5	[FA (8:0)] 2Z-octenoic acid	0.321	1.629	0.138	2.208	0.262	3.709	0.090	1.922
-	353.1963	4.1	[FA (8:1/5:2/7:0)] 5-hydroperoxy-7-[3,5-epidioxy-2-(2-octenyl)-cyclopentyl]-6-heptenoic acid	0.320	6.788	0.330	6.241	0.234	1.279	0.060	2.352
-	214.1448	5.0	N-Nonanoylglycine	0.320	0.211	0.294	0.165	0.320	0.211	0.297	0.170
-	138.0559	7.5	Gabaculine	0.319	1.134	0.735	0.951	0.195	1.154	0.085	3.502
-	160.0403	13.3	Quinoline-3,4-diol	0.315	22.867	0.634	1.203	0.723	0.872	0.884	1.056
-	111.0814	7.5	[FA (7:1)] 2-heptenal	0.314	0.829	0.708	0.940	0.118	1.261	0.611	0.896
-	179.0561	15.0	D-Glucose	0.312	1.116	0.704	1.033	0.133	0.884	<0.001	5.957
-	409.3323	3.9	MG(0:0/22:2(13Z,16Z)/0:0)	0.310	1.338	0.934	1.022	0.168	1.328	0.369	1.255
-	215.1286	5.0	[FA (11:0/2:0)] Undecanedioic acid	0.308	1.547	0.091	1.857	0.094	1.897	0.224	1.726
-	260.0232	15.2	tyrosine sulfate	0.303	1.360	0.680	1.113	0.148	1.316	<0.001	11.672
-	228.1603	4.8	N-Decanoylglycine	0.302	0.260	0.275	0.217	0.246	0.159	0.255	0.177
-	159.1026	7.5	Ethyl (R)-3-hydroxyhexanoate	0.299	1.847	0.045	2.573	0.102	1.974	0.031	2.376
-	345.2433	3.9	Taxa-4(20),11(12)-dien-5alpha-acetoxy-10beta-ol	0.290	1.467	0.026	2.120	0.029	2.075	0.007	6.489
-	186.1133	5.0	8-Amino-7-oxononanoate	0.279	0.371	0.254	0.332	0.258	0.338	0.250	0.325
-	223.0721	13.2	3-Hydroxy-L-kynurenine	0.271	37.375	0.069	4.622	0.030	3.868	0.057	2.506
-	169.1233	4.3	[PR] Limonene-1,2-diol	0.266	1.679	0.228	1.488	0.435	1.226	0.011	4.992
-	186.1134	7.5	8-Amino-7-oxononanoate	0.266	0.376	0.266	0.378	0.272	0.386	0.261	0.368
-	270.2073	4.2	Tridecanoylglycine	0.263	0.167	0.282	0.204	0.300	0.235	0.335	0.286
-	885.5482	3.8	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.260	0.891	0.306	0.903	0.653	0.959	0.700	0.967

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	307.2644	3.9	Sclareol	0.249	0.808	0.236	0.797	0.049	0.640	0.001	1.707
-	273.1707	7.5	3-Hydroxytetradecanedioicacid	0.248	1.098	0.962	1.005	0.188	1.117	0.739	1.028
-	131.0348	7.5	2-Acetolactate	0.247	1.208	0.219	1.271	0.278	1.184	0.024	2.042
-	197.1546	4.1	[PR] Citronellyl acetate	0.246	1.209	0.092	1.650	0.534	1.121	0.033	2.768
-	369.3009	3.9	2-monooleoylglycerol	0.246	0.727	0.344	0.827	0.880	1.025	0.001	0.430
-	147.0661	15.4	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.240	3.886	0.094	1.390	0.458	1.121	0.029	9.309
-	99.00862	7.5	2-oxobut-3-enanoate	0.240	0.675	0.416	0.740	0.218	0.669	0.267	0.637
-	218.1032	6.0	Pantothenate	0.237	1.619	0.307	1.534	0.223	1.375	<0.001	18.843
-	242.1761	4.6	N-Undecanoylglycine	0.227	0.263	0.248	0.302	0.246	0.294	0.246	0.296
-	149.0606	4.9	Phenylpropanoate	0.220	2.312	0.072	1.234	0.121	1.239	0.005	5.031
-	83.01353	15.1	4-Hydroxy-2-butynal	0.217	0.672	0.107	0.687	0.336	0.799	<0.001	12.880
-	133.0329	15.2	S,S-Dimethyl-beta-propiothetin	0.215	1.517	0.004	1.997	0.059	2.144	0.001	22.869
-	329.2334	4.0	[FA trihydroxy(18:0)] 9S,12S,13S-trihydroxy-10E-octadecenoic acid	0.214	1.684	0.588	0.839	0.940	1.020	<0.001	11.274
-	131.0348	14.8	2-Acetolactate	0.213	1.876	0.523	1.437	0.219	1.803	<0.001	4.903
-	273.1244	8.4	indole-3-acetyl-valine	0.212	1.306	0.022	2.085	0.297	1.264	<0.001	15.831
-	102.0195	7.8	2-Aminomalonate semialdehyde	0.208	3.003	0.486	1.354	0.495	1.384	0.312	6.508
-	213.1496	4.3	3-Oxododecanoic acid	0.207	1.916	0.358	1.413	0.156	1.951	0.024	3.041
-	223.0976	4.0	Aspidinol	0.206	1.387	0.192	1.709	0.330	5.446	0.241	1.315
-	167.0375	4.0	dihydroxypentenyl sulfate	0.205	0.364	0.098	0.154	0.571	0.634	0.910	1.109
-	440.132	16.8	Dofetilide	0.204	1.189	0.003	1.500	0.080	1.292	<0.001	7.428
-	132.0493	15.7	4-methylthiobutanaldoxime	0.204	1.233	<0.001	1.527	0.171	1.220	<0.001	6.713
-	291.1812	7.5	octyl α-D-glucopyranoside	0.202	1.154	0.052	1.127	0.059	1.272	0.050	1.198
-	150.0559	7.5	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.199	3.521	0.194	0.587	0.460	0.773	0.378	2.956
-	249.0548	14.3	gamma-L-Glutamyl-L-cysteine	0.199	19.708	0.041	460.068	0.050	215.767	0.181	0.000
-	176.0385	13.2	N-Formyl-L-methionine	0.194	94.022	0.077	4.632	0.098	7.803	0.005	3.997
-	172.1343	7.8	[FA amino(9:0)] 9-amino-nonanoic acid	0.192	0.369	0.555	0.658	0.876	1.117	0.565	1.551
-	131.0824	16.3	L-Ornithine	0.188	1.317	0.187	1.355	0.626	0.911	<0.001	8.968

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	93.00118	4.0	Sulfonylbismethane	0.184	0.233	0.167	0.199	0.460	0.522	0.978	1.027
-	88.00374	13.2	Oxamate	0.182	2.042	0.714	1.200	0.092	2.896	0.852	1.147
-	79.95695	18.1	HSO3-	0.180	1.118	0.211	1.130	0.136	1.096	<0.001	1.715
-	489.2775	3.7	Arg-Lys-Thr-Ser	0.178	1.290	0.041	1.553	0.026	1.557	0.009	1.721
-	125.0355	15.4	Thymine	0.177	1.414	0.264	1.534	0.448	1.348	0.005	5.994
-	126.9049	9.7	hydrogen iodide	0.175	0.699	0.479	0.810	<0.001	67.430	0.017	3.090
-	117.0556	7.5	5-Hydroxypentanoate	0.175	1.486	0.882	0.947	0.299	1.354	0.013	2.392
-	153.0304	12.2	Imidazol-5-yl-pyruvate	0.170	1.514	0.386	1.252	0.554	1.149	<0.001	6.319
-	150.0559	8.1	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.165	1.561	0.954	1.019	0.837	0.935	0.003	8.598
-	492.3456	4.5	[PC (17:1)] 1-(1Z-heptadecenyl)-sn-glycero-3-phosphocholine	0.164	1.342	0.056	1.396	0.104	1.309	0.004	1.737
-	187.0611	13.2	2-oxosuberate	0.161	4.971	0.742	1.118	0.213	3.500	0.344	2.651
-	297.2797	3.9	Nonadecanoicacid	0.161	1.199	0.592	1.065	0.967	1.006	0.511	0.897
-	113.0243	13.7	2-Hydroxy-2,4-pentadienoate	0.160	1.264	0.127	1.301	0.924	1.017	<0.001	9.242
-	169.0506	7.5	3,4-Dihydroxyphenylethyleneglycol	0.154	1.534	0.870	0.953	0.477	1.208	0.471	1.243
-	314.0772	4.0	Chlorprothixene	0.153	0.334	0.070	0.112	0.276	0.425	0.838	0.840
-	368.3169	4.2	[SP amino,tetramethyl(4:0/18:0/3:0)] 2S-amino-5,9,13,17-tetramethyl-8E,16-octadecadiene-1,3R,14-triol	0.149	0.259	0.322	0.511	0.131	0.218	0.136	0.225
-	174.0559	4.1	Indole-3-acetate	0.147	2.348	0.569	1.245	0.238	1.478	<0.001	12.717
-	123.045	7.5	o-Methoxyphenol	0.145	2.370	0.075	1.381	0.165	1.372	0.044	1.544
-	143.1077	4.6	[FA (8:0)] octanoic acid	0.144	2.757	0.059	3.669	0.018	2.745	<0.001	7.435
-	241.2173	3.9	[FA methyl(14:0)] 12-methyl-tetradecanoic acid	0.142	0.873	0.082	0.843	0.042	0.806	0.072	0.836
-	104.9999	19.1	fluoropyruvate	0.141	1.897	0.376	3.378	0.898	1.038	0.936	0.975
-	766.5407	4.0	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.141	1.282	0.236	1.221	0.201	1.237	0.022	1.499
-	299.2012	4.1	[PR] Tretinoin/All-Trans Retinoic Acid	0.140	6.191	0.508	1.359	0.347	1.740	0.362	8.131
-	199.1703	4.1	Dodecanoic acid	0.138	0.841	0.217	0.861	0.097	0.732	0.228	0.831
-	242.0781	12.2	Cytidine	0.137	1.112	0.386	1.067	0.076	0.893	<0.001	5.802
-	764.5624	7.5	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.137	1.678	0.352	1.235	0.112	1.750	0.055	1.599

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	350.3063	4.2	[FA (20:2)] N-(11Z,14Z-eicosadienoyl)-ethanolamine	0.135	0.373	0.495	0.738	0.087	0.278	0.170	0.399
-	279.2327	3.9	Linoleate	0.132	0.768	0.115	0.756	0.050	0.678	0.057	1.313
-	183.0661	7.5	3-Methoxy-4-hydroxyphenylethyleneglycol	0.131	1.874	0.324	1.280	0.397	1.270	0.516	1.148
-	168.0301	15.0	L-2,3-Dihydrodipicolinate	0.127	0.422	0.392	8.120	0.395	8.176	0.124	0.407
-	96.95998	18.1	Sulfate	0.126	1.146	0.384	1.070	0.492	0.951	0.001	1.486
-	165.0403	12.7	L-Arabinonate	0.125	1.763	0.153	1.638	0.161	1.657	0.002	12.551
-	187.007	7.4	4-Sulfobenzyl alcohol	0.122	0.623	0.004	0.312	0.004	0.286	0.015	0.436
-	301.1654	5.0	Tributyrin	0.121	2.761	0.143	2.584	0.126	2.757	0.061	3.511
-	151.0065	4.0	butenol sulfate	0.117	0.183	0.106	0.152	0.464	0.533	0.986	0.981
-	128.0352	15.4	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.117	1.256	0.095	1.260	0.477	1.123	0.018	3.944
-	104.0351	16.2	L-Serine	0.113	1.157	0.041	0.700	0.208	0.922	<0.001	5.542
-	85.0292	7.5	Diacetyl	0.111	1.359	0.239	1.191	0.951	0.991	0.548	1.108
-	417.2127	7.5	Leu-Thr-Trp	0.110	1.289	0.067	1.240	0.046	1.334	0.347	1.113
-	772.5275	4.0	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	0.109	1.416	<0.001	1.856	<0.001	1.755	<0.001	1.548
-	227.2016	4.0	Tetradecanoic acid	0.109	0.851	0.056	0.813	0.021	0.753	0.106	0.850
-	135.0451	5.0	Phenylacetic acid	0.109	3.744	0.164	2.396	0.005	7.008	0.101	1.368
-	143.0349	13.7	2,3-Dimethylmaleate	0.108	1.271	0.035	1.259	0.161	1.239	0.006	5.114
-	187.007	4.4	4-Sulfobenzyl alcohol	0.108	1.577	0.097	1.535	0.065	1.517	<0.001	4.827
-	174.0883	16.3	L-Citrulline	0.107	1.294	0.088	1.315	0.098	1.269	<0.001	9.574
-	118.0508	14.9	L-Threonine	0.107	1.228	0.469	1.053	0.142	0.902	<0.001	5.636
-	111.0198	10.0	Uracil	0.106	0.731	0.768	0.960	0.016	0.608	<0.001	2.625
-	165.0409	4.0	L-Arabinonate	0.104	0.302	0.071	0.203	0.219	0.451	0.591	0.685
-	131.0824	24.3	L-Ornithine	0.102	1.561	0.097	1.546	0.607	1.147	<0.001	15.891
-	167.035	4.1	[PK] Orsellinic acid	0.101	0.045	0.096	0.026	0.096	0.027	0.095	0.023
-	117.0192	13.1	Succinate	0.099	3.249	0.165	1.552	0.050	2.237	0.222	1.550
-	269.2484	3.9	[FA (17:0)] heptadecanoic acid	0.096	0.840	0.034	0.778	0.009	0.700	0.144	0.847
-	736.5281	4.1	PC(18:4(6Z,9Z,12Z,15Z)/P-16:0)	0.096	0.505	0.044	0.393	0.029	0.320	0.024	0.283
-	253.2172	3.9	(9Z)-Hexadecenoic acid	0.095	0.610	0.120	0.640	0.063	0.549	0.577	0.884

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	125.097	7.5	Sulcatone	0.095	1.577	0.004	2.083	0.011	1.958	0.079	1.732
-	325.2746	3.9	2-Oxophytanate	0.093	1.446	0.014	1.555	0.165	1.256	0.005	1.855
-	331.2642	3.9	[FA (22:4)] 7Z,10Z,13Z,16Z-docosatetraenoic acid	0.092	1.312	0.029	1.339	0.624	1.038	<0.001	2.176
-	131.0712	5.0	6-Hydroxyhexanoic acid	0.091	1.406	0.894	1.026	0.052	1.410	0.083	4.305
-	111.0199	8.7	Uracil	0.090	2.323	0.824	0.906	0.995	0.998	<0.001	9.467
-	125.0009	13.1	2-Hydroxyethylphosphonate	0.088	1.823	0.164	1.550	0.519	1.219	0.015	5.533
-	161.0455	15.0	2-Dehydro-3-deoxy-L-rhamnonate	0.088	1.290	0.238	1.188	0.950	1.014	<0.001	3.140
-	119.0348	15.1	D-Erythrose	0.086	1.290	0.440	1.118	0.724	1.052	<0.001	2.657
-	341.1963	3.8	[FA trihydroxy(2:0)] 9S,11,15S-trihydroxy-2,3-dinor-thromboxa-5Z,13E-dien-1-oic acid	0.086	0.231	0.083	0.219	0.091	0.248	0.069	0.168
-	187.0975	7.5	Azelaic acid	0.085	1.767	0.364	1.408	0.169	1.522	0.304	1.427
-	128.0352	14.8	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.085	2.177	0.004	3.175	0.006	3.243	0.012	3.393
-	91.02189	4.0	methylmercaptoethanol	0.083	0.386	0.031	0.215	0.506	0.685	0.672	0.753
-	134.061	13.2	2-Phenylacetamide	0.083	1.881	0.282	1.593	0.144	1.825	0.769	1.132
-	297.0469	4.1	Quinalphos	0.081	0.464	0.053	0.385	0.175	0.517	0.693	0.787
-	97.0657	7.5	[FA (6:1)] 2-hexenal	0.079	1.205	0.279	1.135	0.818	1.036	0.921	0.989
-	144.0454	7.5	3-Methyleneoxindole	0.077	1.809	0.466	1.245	0.970	1.007	0.137	13.221
-	205.1596	4.3	[PR] (+)-15-nor-4-thujopsen-3-one	0.076	0.682	0.032	0.620	0.054	0.666	0.228	0.707
-	147.0662	7.5	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.075	1.347	0.300	1.285	0.049	1.451	0.225	1.216
-	149.0095	4.0	(R,R)-Tartaric acid	0.075	0.311	0.044	0.195	0.247	0.494	0.754	0.801
-	129.0192	10.8	Itaconate	0.074	0.329	0.017	0.033	0.019	0.071	0.028	0.165
-	215.0328	14.6	2-C-Methyl-D-erythritol 4-phosphate	0.074	1.130	0.036	1.313	0.297	1.087	<0.001	4.284
-	181.0506	8.7	3-(4-Hydroxyphenyl)lactate	0.072	1.547	0.099	1.644	0.015	1.799	<0.001	9.349
-	357.2799	3.8	[FA (12:0)] 12-[5]-ladderane-dodecanoic acid	0.072	1.819	<0.001	2.731	0.009	2.167	<0.001	6.218
-	155.0349	7.5	2,3-Dihydro-2,3-dihydroxybenzoate	0.071	1.135	0.652	1.040	0.218	1.145	0.139	1.137
-	117.0192	15.3	Succinate	0.069	1.779	0.035	1.712	0.051	1.679	0.001	2.639
-	272.119	3.6	8-Allyl-2-phenyl-8H-1,3a,8-triaza-cyclopenta[a]indene	0.069	1.578	0.002	1.975	0.020	1.838	<0.001	9.832
-	158.061	4.4	Indole-3-acetaldehyde	0.069	1.398	<0.001	1.693	0.076	1.302	<0.001	9.096

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	327.254	3.9	MG(0:0/16:1(9Z)/0:0)	0.069	0.395	0.134	0.530	0.101	0.474	0.080	0.427
-	329.2486	3.9	Taxa-4(20),11(12)-dien-5alpha-yl acetate	0.068	1.252	0.009	1.412	0.002	1.244	<0.001	2.461
-	125.0242	14.9	Phloroglucinol	0.068	0.594	0.024	0.462	0.308	0.768	<0.001	14.157
-	333.2798	3.9	13,16,19-Docosatrienoic acid	0.067	1.881	0.005	2.629	0.005	1.954	<0.001	5.075
-	272.1244	4.0	Ala-Pro-Ser	0.065	1.865	0.009	2.236	0.074	1.790	<0.001	10.346
-	83.02472	7.5	Imidazolone	0.064	2.018	0.228	1.565	0.722	1.169	0.162	1.647
-	149.0451	13.7	D-Ribose	0.064	1.547	0.391	1.299	0.096	1.641	<0.001	10.150
-	329.2332	7.4	[FA trihydroxy(18:0)] 9S,12S,13S-trihydroxy-10E-octadecenoic acid	0.063	2.423	0.759	1.181	0.144	1.759	0.203	1.860
-	311.2955	3.9	[FA (20:0)] eicosanoic acid	0.062	0.723	0.038	0.678	0.013	0.574	0.014	0.583
-	746.512	4.1	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.062	1.254	<0.001	1.396	<0.001	1.422	<0.001	1.504
-	122.9934	9.6	6-S-acetyl-dihydrolipoate	0.055	0.615	0.009	0.413	0.032	0.540	0.026	10.591
-	221.0818	4.3	[FA (12:4/2:0)] 2E,4E,8E,10E-Dodecatetraenedioic acid	0.055	1.745	0.072	1.519	0.027	1.728	0.001	6.447
-	226.0833	10.7	Deoxycytidine	0.055	1.205	0.487	1.071	0.878	0.977	<0.001	6.988
-	201.0193	15.4	Bergaptol	0.055	0.472	0.055	0.605	0.159	0.747	<0.001	2.119
-	229.1343	8.4	Camoensine	0.054	1.662	0.008	1.908	0.093	1.574	<0.001	11.866
-	281.2484	3.9	[FA (18:0)] 9Z-octadecenoic acid	0.054	0.699	0.035	0.656	0.020	0.601	0.557	1.079
-	195.0509	14.1	D-Gluconic acid	0.052	1.455	0.004	1.325	0.050	1.221	0.002	12.328
+	161.0922	13.5	D-Alanyl-D-alanine	0.050	1.782	0.015	1.801	0.258	1.453	<0.001	9.901
+	705.5811	4.4	[ST (20:4)] cholest-5-en-3beta-yl (15S-hydroperoxy-5Z,8Z,12E,14Z-eicosatetraenoate)	0.049	1.256	0.055	1.162	0.045	1.246	0.002	1.219
+	190.0864	10.6	3-Indolepropionicacid	0.049	1.569	0.001	1.991	0.076	1.446	<0.001	10.928
+	703.5754	4.4	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.048	1.233	0.174	1.094	0.045	1.181	0.008	1.153
-	196.0726	14.6	N-Acetyl-L-histidine	0.048	1.467	0.017	1.697	0.005	1.675	<0.001	8.131
-	147.0662	5.6	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.048	1.817	0.449	1.218	0.027	1.738	0.992	0.997
+	244.0929	12.2	Cytidine	0.048	1.165	0.187	1.144	0.352	0.928	<0.001	6.303
-	241.083	7.5	Thymidine	0.048	1.224	0.266	1.125	0.446	0.933	<0.001	5.571

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	189.0768	7.5	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.048	1.464	0.001	2.050	0.032	1.650	0.073	1.703
+	217.1295	15.2	N-acetyl-(L)-arginine	0.048	0.600	0.021	0.565	0.021	0.527	0.002	2.195
-	817.5012	3.7	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.047	1.074	<0.001	0.800	<0.001	0.727	0.036	1.135
+	734.5703	4.2	[PC (16:0/16:0)] 1-hexadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.047	1.254	0.013	1.208	0.009	1.330	<0.001	1.297
-	305.2485	3.9	[FA (20:3)] 8Z,11Z,14Z-eicosatrienoic acid	0.046	1.302	0.010	1.401	0.013	1.248	<0.001	2.618
-	97.0405	15.5	Imidazole-4-methanol	0.046	1.759	0.044	1.949	0.002	2.067	<0.001	7.252
-	465.3042	3.7	Cholesterolsulfate	0.045	1.249	0.289	1.092	0.017	1.194	0.024	1.178
+	150.1278	6.1	Phentermine	0.045	1.042	0.361	1.013	0.119	0.983	0.561	1.010
-	381.3374	3.8	[FA hydroxy(24:0)] 2-hydroxy-15-tetracosenoic acid	0.045	1.142	0.124	1.106	0.296	1.072	0.270	1.072
-	179.0562	13.7	D-Glucose	0.044	1.636	0.013	1.853	0.007	1.979	<0.001	7.205
+	388.2541	5.0	Leu-Lys-Gln	0.044	0.683	0.464	0.867	0.009	0.618	0.043	0.709
+	794.6066	4.2	[PC (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.044	0.948	0.001	0.891	0.045	0.946	0.152	1.058
+	840.5761	3.8	1-22:1-2-18:3-phosphatidylserine	0.044	0.848	0.002	0.778	0.165	0.915	0.004	0.786
+	492.2804	4.2	Asn-Leu-Phe-Val	0.043	1.435	0.338	1.243	0.775	1.079	0.482	0.802
+	689.5597	4.5	[SP (18:0/14:0)] N-(octadecanoyl)-tetradecasphing-4-enine-1-phosphoethanolamine	0.043	1.239	0.437	1.058	0.116	1.091	0.067	1.107
+	144.0656	5.1	Vinylacetylglycine	0.043	1.843	0.035	1.865	0.031	2.877	<0.001	35.712
+	144.9822	10.4	2-chloroethylphosphonate	0.042	1.598	0.136	1.695	0.053	1.533	0.045	0.506
-	114.0559	13.1	L-Proline	0.042	1.220	0.140	1.154	0.032	1.188	<0.001	5.479
+	238.1438	7.5	Gigantine	0.042	4.137	0.284	2.646	0.645	0.809	0.648	1.192
+	355.0635	5.0	Phenolsulfonphthalein	0.041	1.408	0.001	1.605	0.023	1.376	<0.001	10.304
-	151.061	13.2	Xylitol	0.040	0.225	0.037	0.202	0.043	0.239	0.075	2.097
-	301.1654	7.5	Tributyrin	0.040	1.218	0.090	1.285	0.020	1.403	0.005	1.307
-	357.1494	4.0	Cilastatin	0.040	0.825	0.001	0.641	0.001	0.668	0.001	0.579
-	131.0461	15.7	L-Asparagine	0.040	1.315	0.001	1.406	0.009	1.254	<0.001	5.728
-	353.3061	3.9	[FA oxo(22:0)] 10-oxo-docosanoic acid	0.040	1.490	0.211	1.300	0.674	1.087	0.852	1.045
-	257.1757	7.5	[FA (14:0/2:0)] Tetradecanedioic acid	0.039	1.304	0.137	1.947	0.047	1.366	0.012	3.498

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	355.2115	7.5	[FA (8:1/5:2/7:0)] 5-hydroperoxy-7-[3,5-epidioxy-2-(2-octenyl)-cyclopentyl]-6-heptenoic acid	0.037	1.638	0.173	1.427	0.090	1.791	0.071	1.498
-	129.0556	4.8	(S)-3-Methyl-2-oxopentanoic acid	0.037	1.075	0.787	1.010	0.497	0.972	<0.001	2.508
-	296.0377	15.4	L-Cysteinylglycinedisulfide	0.036	0.453	0.006	0.131	0.008	0.212	<0.001	12.521
-	776.5593	4.0	PE(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	0.036	0.597	0.281	0.815	0.126	0.726	0.023	0.571
+	245.1496	11.1	N-hexenoylglutamine	0.036	1.742	0.244	1.610	0.133	1.331	<0.001	6.181
-	113.0243	15.1	2-Hydroxy-2,4-pentadienoate	0.036	1.146	0.152	1.085	0.244	1.063	<0.001	2.790
-	116.9284	21.3	chromate	0.036	1.140	0.029	1.146	0.835	0.958	0.534	1.044
+	794.5713	4.1	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.035	3.559	<0.001	7.229	<0.001	8.365	0.007	6.551
+	190.0714	4.1	N-Acetyl-L-glutamate	0.035	0.200	0.026	0.157	0.188	0.428	0.750	1.418
-	104.9999	18.5	fluoropyruvate	0.035	0.598	0.288	0.756	0.397	3.038	0.403	0.705
-	91.03985	10.5	Glycerol	0.034	2.411	0.006	2.648	0.005	2.748	0.005	2.656
+	136.0619	9.8	Adenine	0.034	4.338	0.011	2.634	0.007	2.924	0.015	2.552
+	136.1122	7.5	Amphetamine	0.034	0.774	0.043	0.789	0.470	1.654	0.422	1.270
-	101.0243	14.9	2-Oxobutanoate	0.034	1.345	0.297	1.063	0.106	1.118	<0.001	3.076
-	148.0403	11.9	5,6-Dihydroxyindole	0.034	1.326	0.177	1.146	0.105	1.169	<0.001	0.021
-	422.23	3.7	LysoPE(0:0/14:1(9Z))	0.034	1.292	0.040	1.332	0.004	1.486	<0.001	2.188
-	861.548	3.9	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.033	2.378	0.002	2.975	0.001	3.647	0.001	2.684
-	180.0335	12.2	DL-Methionine sulfone	0.033	1.510	0.035	1.450	0.424	1.224	<0.001	7.761
-	173.093	13.9	N-Acetylornithine	0.033	1.341	0.192	1.300	0.069	1.338	<0.001	8.216
+	117.0659	16.0	Diacetylhydrazine	0.033	2.392	0.796	1.082	0.744	1.151	<0.001	6.318
+	164.0918	15.0	1-deoxynojirimycin	0.032	0.655	0.862	1.030	0.366	0.829	0.004	3.639
+	134.0812	13.7	1-deoxyxylonojirimycin	0.032	2.029	0.013	1.848	0.185	1.405	<0.001	7.990
-	255.2328	3.9	Hexadecanoic acid	0.031	0.634	0.017	0.567	0.008	0.484	0.016	0.564
-	229.1343	5.0	Camoensine	0.031	2.089	<0.001	2.739	<0.001	2.513	<0.001	16.127
-	175.0473	8.4	Allantoate	0.031	1.536	0.169	1.609	0.279	1.372	<0.001	15.195
+	190.05	4.1	Kynurenate	0.031	1.212	0.486	1.075	0.650	1.043	0.885	0.986
-	313.2384	3.9	[FA hydroxy(18:0)] 9,10-dihydroxy-12Z-octadecenoic acid	0.031	1.106	0.749	1.014	0.223	0.955	0.180	0.718

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	154.1227	7.5	Pseudopelletierine	0.031	3.758	0.015	5.579	0.019	5.264	0.037	5.610
+	280.1544	7.5	Metalaxyl	0.030	1.565	0.134	1.709	0.003	1.960	0.034	1.738
+	134.0641	15.7	4-methylthiobutanaldoxime	0.029	1.276	<0.001	1.435	0.005	1.267	<0.001	6.297
-	466.1066	16.4	Asp-Cys-Cys-Gln	0.029	1.860	0.006	2.492	0.003	2.198	0.001	5.867
+	442.147	16.8	Dofetilide	0.029	1.560	0.031	1.412	0.254	1.325	<0.001	8.480
-	176.0207	5.0	Sulforaphane	0.027	1.342	0.001	1.437	0.096	1.233	<0.001	8.127
+	800.6166	4.2	[PE (20:0/20:2)] 1-eicosanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	0.027	2.525	0.048	4.501	0.003	6.708	0.012	7.335
-	117.0344	4.4	Benzofuran	0.027	1.522	0.002	1.638	0.010	1.443	<0.001	8.937
-	259.1296	11.1	Glu-Leu	0.027	3.179	0.007	2.281	<0.001	8.955	<0.001	11.068
+	177.0748	10.0	(2S)-2-Isopropylmalate	0.027	1.535	0.014	1.565	0.210	1.314	<0.001	4.397
+	772.6221	4.2	[PC (18:1/18:0)] 1-(1Z-octadecenyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.027	2.764	0.062	2.612	0.004	3.903	0.040	2.748
-	147.045	14.8	trans-Cinnamate	0.027	36.530	0.483	3.810	0.370	0.117	0.394	0.164
+	247.1403	14.5	N2-(D-1-Carboxyethyl)-L-arginine	0.026	1.303	0.001	1.591	0.039	1.487	<0.001	8.396
+	228.0979	10.7	Deoxycytidine	0.026	1.212	0.025	1.250	0.413	1.065	<0.001	6.083
+	367.2115	7.5	[FA hydroxy(20:4/2:0)] 5S,12R-dihydroxy-6Z,8E,10E,14Z-eicosatetraene-1,20-dioic acid	0.026	0.771	0.723	0.936	0.090	0.806	<0.001	0.660
+	159.0765	16.3	4-Methylene-L-glutamine	0.025	1.739	0.032	1.640	0.053	1.537	<0.001	10.249
-	122.9934	4.0	6-S-acetyl-dihydrolipoate	0.025	0.233	0.025	0.237	0.029	0.269	0.157	0.445
-	163.04	13.4	Phenylpyruvate	0.025	1.708	0.020	1.677	0.016	1.748	<0.001	7.671
+	242.1136	9.7	5-Methyl-2'-deoxycytidine	0.025	1.444	0.327	1.246	0.371	1.147	<0.001	7.971
-	124.9912	10.5	2-Hydroxyethanesulfonate	0.025	2.170	0.002	2.438	0.056	2.078	<0.001	14.095
+	354.3367	4.2	[FA (20:0)] N-(11Z-eicosaenoyl)-ethanolamine	0.025	0.380	0.162	0.658	0.077	0.528	0.028	0.377
-	312.1719	3.8	4-Oxo-13-cis-retinoate	0.024	0.417	0.015	0.322	0.010	0.265	0.010	0.264
+	354.1915	7.5	Rosmarinine	0.024	1.515	0.121	1.301	0.084	1.989	0.063	1.270
-	531.2722	3.9	Arg-Leu-Met-Asn	0.024	1.323	0.135	0.736	0.611	0.938	0.003	2.373
-	105.0191	13.1	D-Glycerate	0.023	2.593	0.006	2.593	0.003	2.824	0.042	2.444
+	254.0925	27.4	aeruginosin A	0.023	0.412	0.375	0.790	0.193	0.611	0.001	7.548
-	131.0825	27.4	L-Ornithine	0.022	1.349	0.002	1.451	0.019	1.287	<0.001	8.056

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	128.0706	13.5	2,3,4,5-Tetrahydropyridine-2-carboxylate	0.022	1.972	0.042	2.075	0.137	1.594	0.001	16.005
-	838.559	3.8	1-22:1-2-18:3-phosphatidylserine	0.022	0.746	0.003	0.674	0.042	0.810	0.001	0.628
-	283.2641	3.9	Octadecanoic acid	0.022	0.573	0.010	0.473	0.005	0.389	0.007	0.442
-	836.5434	3.8	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.022	1.287	0.156	1.129	0.005	1.347	0.227	1.107
+	190.1075	5.1	(2S)-2-{[1-(R)-Carboxyethyl]amino}pentanoate	0.021	1.846	0.261	1.401	0.022	1.579	0.099	4.845
+	174.0956	14.8	7-methylthioheptanonitrile oxide	0.021	2.522	<0.001	2.487	0.009	1.993	<0.001	18.305
+	230.0957	15.1	Ergothioneine	0.021	2.252	0.013	2.603	0.001	3.190	0.008	3.980
+	102.0663	10.9	N-acetylguanidine	0.021	1.848	0.974	0.991	0.583	0.850	0.016	6.183
+	162.0914	15.0	Indole-3-ethanol	0.021	0.642	0.399	0.844	0.035	0.740	0.358	3.294
-	127.0512	15.4	5,6-Dihydrothymine	0.021	1.365	0.022	1.347	0.032	1.313	<0.001	5.060
-	165.0409	4.6	L-Arabinonate	0.020	0.645	0.068	0.651	0.010	0.563	0.005	0.530
+	251.0697	14.4	gamma-L-Glutamyl-L-cysteine	0.020	26.774	0.010	656.741	0.010	305.435	0.061	0.000
+	144.102	10.9	Stachydrine	0.019	1.931	0.058	1.751	0.012	2.028	<0.001	26.587
+	268.104	9.3	Adenosine	0.019	1.501	0.093	1.545	0.786	1.056	0.043	0.727
+	144.0656	7.5	Vinylacetylglycine	0.018	1.551	0.014	1.806	0.008	1.696	<0.001	14.942
-	180.0665	13.4	L-Tyrosine	0.018	1.284	0.032	1.218	0.065	1.170	<0.001	6.274
+	247.0578	12.8	Glycerophosphoglycerol	0.018	1.206	0.410	0.902	0.069	1.188	0.021	1.379
+	175.1332	11.3	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.017	2.069	0.102	1.634	0.614	1.134	<0.001	29.862
-	339.2902	3.9	[FA oxo(21:0)] 2-oxo-heneicosanoic acid	0.017	1.266	0.067	1.195	0.111	1.154	0.163	1.133
-	203.0925	7.5	Diethyl (2R,3R)-2-methyl-3-hydroxysuccinate	0.017	1.912	0.006	1.422	0.051	1.416	0.090	1.270
-	182.075	14.1	Chlorphentermine	0.017	1.317	0.007	1.323	0.011	1.296	<0.001	6.708
-	466.3076	3.7	Oxethazaine	0.016	1.447	0.488	1.081	<0.001	1.427	<0.001	1.276
+	133.0608	15.7	L-Asparagine	0.016	1.272	<0.001	1.412	0.003	1.260	<0.001	5.607
-	311.2228	4.0	[FA (18:2)] 9S-hydroperoxy-10E,12Z-octadecadienoic acid	0.016	2.496	0.549	1.342	0.059	2.040	0.077	2.203
-	341.1086	15.5	Sucrose	0.016	0.743	0.035	0.799	0.008	0.759	0.670	0.974
+	177.1122	5.0	[FA hydroxy(8:0)] 6,8-dihydroxy-octanoic acid	0.015	0.496	0.095	0.631	0.014	0.468	0.003	0.364
-	160.0403	7.5	Quinoline-3,4-diol	0.015	13.252	0.020	6.329	0.065	5.634	<0.001	13.678
+	202.0864	4.9	2'-Aminobiphenyl-2,3-diol	0.015	1.616	0.003	1.646	0.002	1.588	<0.001	6.333

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	165.0402	13.7	L-Arabinonate	0.014	1.863	0.013	2.054	0.070	1.778	0.003	11.487
-	84.04513	15.4	Acetone cyanohydrin	0.014	1.684	0.074	1.601	0.052	1.586	<0.001	8.252
-	311.0991	4.1	Vicianose	0.014	0.665	0.002	0.466	0.002	0.508	0.004	0.505
+	301.0706	15.0	Peonidin	0.014	0.326	0.001	0.236	0.006	0.336	0.102	2.130
-	837.5466	3.8	PI(16:0/18:0)	0.013	1.319	0.117	1.136	0.003	1.346	0.156	1.114
+	217.0146	10.0	5-(3-Buten-1-ynyl)-2,2'-bithienyl	0.013	1.982	0.003	2.224	0.001	1.878	<0.001	10.270
+	746.6066	4.2	PC(16:0/P-18:0)	0.012	1.303	<0.001	1.333	<0.001	1.588	<0.001	1.453
-	355.2641	3.9	[FA (24:6)] 4,8,12,15,19,21-tetracosahexaenoic acid	0.012	1.740	0.021	1.928	0.063	1.564	<0.001	5.899
+	184.0735	4.4	Choline phosphate	0.012	1.915	0.119	0.503	0.034	0.293	0.097	1.697
-	85.0292	18.3	Diacetyl	0.012	1.913	0.056	1.706	0.007	2.155	<0.001	14.919
+	174.1278	11.2	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	0.011	11.820	0.013	9.699	0.014	10.387	0.001	49.216
-	498.2892	4.3	[ST hydrox] N-(3alpha,7alpha-dihydroxy-5beta-cholan-24-oyl)-taurine	0.011	1.368	0.001	1.441	0.013	1.267	<0.001	6.615
+	259.0925	10.1	(1-Ribosylimidazole)-4-acetate	0.011	3.293	0.012	4.406	0.006	3.042	<0.001	107.045
-	134.0471	7.5	Adenine	0.011	3.300	0.004	2.796	0.001	3.252	0.002	2.792
-	306.0763	14.6	Glutathione	0.011	3.381	0.086	4.576	0.045	4.718	0.001	0.011
-	182.0459	4.8	4-Pyridoxate	0.011	1.402	0.007	1.332	0.017	1.285	<0.001	6.460
-	195.0509	13.6	D-Gluconic acid	0.011	3.979	0.007	4.403	0.014	2.791	<0.001	9.102
-	790.5414	4.1	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.011	10.136	0.064	5.649	0.043	6.319	0.008	9.753
+	164.1435	5.3	Mephentermine	0.010	1.108	0.013	1.107	0.028	1.077	0.079	1.069
-	87.0085	13.5	Pyruvate	0.010	5.820	0.006	6.856	<0.001	8.139	0.003	5.047
-	147.0451	10.6	trans-Cinnamate	0.010	2.541	0.001	1.611	0.077	1.294	<0.001	8.524
-	248.9791	13.1	Oxidized Photinus luciferin	0.010	4.931	0.001	7.141	0.008	3.811	0.025	2.361
+	369.1283	4.2	trans-3-Hydroxycotinineglucuronide	0.010	2.543	0.024	2.574	0.035	1.988	<0.001	32.898
+	788.5445	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.010	1.303	0.006	1.250	<0.001	1.565	0.824	0.959
+	824.6525	4.2	PC(22:2(13Z,16Z)/P-18:1(11Z))	0.010	0.263	0.003	0.189	0.003	0.185	0.005	0.228
+	335.2215	7.5	Prostaglandin A2	0.010	2.637	0.256	2.020	0.103	2.234	0.595	1.371
-	243.0807	8.7	Biotin	0.009	2.673	0.034	2.372	0.015	2.020	<0.001	18.727

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	438.298	4.8	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	0.009	1.189	<0.001	1.348	<0.001	1.478	<0.001	1.787
+	134.0811	15.0	1-deoxyxylonojirimycin	0.009	3.879	<0.001	1.510	0.010	1.398	<0.001	2.299
-	168.0665	8.1	Pyridoxine	0.009	1.408	0.005	1.352	0.047	1.182	<0.001	6.832
+	203.1433	7.4	alpha-Amylcinnamaldehyde	0.009	1.440	0.364	1.210	0.077	1.997	0.296	4.932
-	145.0505	7.5	Adipate	0.009	1.716	0.011	1.973	0.004	2.030	0.076	5.420
-	146.0651	15.4	5-methylthiopentanaldoxime	0.009	1.388	0.002	1.365	0.067	1.161	<0.001	6.376
+	568.3395	4.7	[PC (22:6)] 1-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	0.009	1.621	0.010	1.664	<0.001	1.963	0.001	3.244
-	585.3599	4.7	Arg-Lys-Gln-Arg	0.008	0.875	0.002	0.834	0.003	0.845	0.998	1.000
-	436.283	4.8	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	0.008	1.168	<0.001	1.306	<0.001	1.448	<0.001	1.847
-	347.2437	7.5	[FA hydroxy(4:0/18:0)] 9,10,12,13-tetrahydroxy-octadecanoic acid	0.008	1.097	0.006	1.076	0.099	1.059	0.001	1.151
+	86.06005	14.8	Acetone cyanohydrin	0.008	1.635	0.040	1.866	0.028	1.477	<0.001	4.635
+	191.0849	11.9	Aldicarb	0.008	1.641	0.007	1.639	0.074	1.378	<0.001	17.888
+	151.0616	11.9	Dipropyl disulfide	0.008	1.353	0.020	1.314	0.058	1.194	<0.001	5.786
-	218.1032	8.5	Pantothenate	0.008	1.453	0.001	1.469	0.005	1.311	<0.001	8.421
+	267.0764	15.5	6-Acetophenazine-1-carboxylic acid	0.008	0.324	0.018	0.593	0.005	0.473	0.069	1.568
+	86.09645	7.3	Piperidine	0.008	1.793	0.338	4.567	0.101	1.697	0.180	1.887
-	175.0472	5.0	Allantoate	0.008	2.045	0.021	1.680	0.643	1.112	0.003	10.397
-	179.0562	17.4	D-Glucose	0.008	1.466	0.021	1.533	0.078	1.331	<0.001	7.869
+	206.0813	13.4	Indolelactate	0.008	1.752	0.046	1.819	0.186	1.486	<0.001	17.572
+	731.6074	4.4	SM(d18:0/18:1(9Z))	0.007	0.377	0.006	0.365	0.004	0.324	0.001	0.213
+	223.1078	13.4	Phe-Gly	0.007	1.510	0.007	1.477	0.057	1.257	<0.001	13.600
+	359.164	4.0	Cilastatin	0.007	0.681	0.002	0.623	<0.001	0.471	<0.001	0.469
+	253.1435	7.5	ubiquinol-1	0.007	0.203	0.168	0.538	0.500	0.785	0.069	0.461
-	173.1043	27.4	L-Arginine	0.007	1.345	0.006	1.384	0.017	1.238	<0.001	6.514
+	360.238	11.4	Loxtidine	0.007	1.761	0.019	1.837	0.132	1.363	<0.001	32.870
+	773.6254	4.2	demethylmenaquinol-9	0.007	2.579	0.064	4.205	0.028	6.722	0.020	1.914

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	779.579	4.1	[PG (18:0/18:0)] 1,2-dioctadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.007	0.393	0.192	0.637	0.649	0.870	0.037	0.526
-	909.5485	3.8	PI(18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.007	2.575	0.018	2.741	<0.001	3.434	<0.001	3.413
-	148.0437	11.9	L-Methionine	0.007	1.401	0.012	1.375	0.029	1.257	<0.001	9.646
-	145.0618	15.4	L-Glutamine	0.007	1.351	0.002	1.333	0.066	1.152	<0.001	5.627
+	163.1078	8.9	N6-Hydroxy-L-lysine	0.007	2.704	0.035	1.817	0.020	2.135	<0.001	16.673
+	468.1219	16.4	Asp-Cys-Cys-Gln	0.007	2.229	0.003	2.806	0.001	2.581	<0.001	6.429
-	129.0192	18.2	Itaconate	0.007	2.791	0.004	2.549	<0.001	3.071	<0.001	19.526
+	724.5282	4.1	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.007	0.839	0.020	0.893	0.027	0.879	0.027	0.889
+	198.0874	8.8	N-Acetyl-L-histidine	0.007	1.335	0.001	1.457	0.006	1.285	<0.001	7.652
-	98.02458	7.5	Succinimide	0.007	3.732	0.002	3.369	0.010	3.391	0.033	14.315
-	448.3065	4.7	Glycodeoxycholate	0.006	1.430	<0.001	1.435	0.005	1.239	<0.001	5.662
-	149.0094	4.6	(R,R)-Tartaric acid	0.006	0.684	0.085	0.750	0.577	0.865	0.225	0.751
-	189.0404	10.6	[FA hydroxy,oxo(7:0/2:0)] 4-hydroxy-2-oxo-Heptanedioic acid	0.006	1.939	0.003	2.229	0.008	1.967	<0.001	11.626
-	241.0123	16.7	D-myo-Inositol 1,2-cyclic phosphate	0.006	0.138	0.006	0.102	0.005	0.072	<0.001	9.064
-	146.0247	7.6	Indole-5,6-quinone	0.006	29.177	0.028	17.897	0.047	17.662	0.077	11.615
+	128.0706	15.8	2,3,4,5-Tetrahydropyridine-2-carboxylate	0.006	12.624	0.050	8.711	0.019	3.961	<0.001	6.803
-	121.0406	7.5	Nicotinamide	0.006	4.375	0.030	3.170	0.001	2.278	0.001	12.835
-	121.0406	14.5	Nicotinamide	0.006	3.169	0.032	6.181	0.037	7.822	0.010	10.528
-	116.0715	12.9	L-Valine	0.006	1.497	0.004	1.257	0.020	1.251	<0.001	4.505
-	911.5638	3.8	PI(18:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.006	1.826	0.018	1.791	0.005	1.896	0.037	1.651
-	249.1859	3.9	Triton X-100	0.006	1.418	0.001	1.621	0.001	1.599	<0.001	6.222
-	143.0349	14.9	2,3-Dimethylmaleate	0.005	1.181	0.485	1.064	0.112	1.112	<0.001	2.251
-	509.288	3.9	[PG (18:0)] 1-(9E-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.005	2.166	0.118	1.604	<0.001	2.784	<0.001	4.474
-	784.5123	3.9	[PS (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	0.005	16.727	0.002	23.942	<0.001	35.252	0.003	15.229
+	198.0874	6.2	N-Acetyl-L-histidine	0.005	3.375	0.004	3.908	0.006	3.309	<0.001	20.644
-	762.5465	4.4	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	0.005	1.501	0.185	1.255	0.191	1.274	0.440	1.224

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	87.00849	18.4	Pyruvate	0.005	1.533	0.078	3.711	0.028	3.938	<0.001	8.917
-	473.2826	3.7	Ala-Lys-Thr-Arg	0.005	1.254	0.008	1.224	0.011	1.223	0.003	1.262
-	301.2172	3.9	[FA (20:5)] 5Z,8Z,11Z,14Z,17Z-eicosapentaenoic acid	0.005	2.150	<0.001	1.976	0.002	1.780	0.001	4.210
-	437.267	4.7	[GP (18:0)] 1-octadecanoyl-2-sn-glycero-3-phosphate	0.005	0.841	0.004	0.840	0.013	0.872	0.747	1.027
-	157.0366	13.9	Allantoin	0.005	1.497	0.002	1.414	0.002	1.341	<0.001	7.495
-	421.2266	3.7	1,4-Bis(2-ethylhexyl) sulfosuccinate	0.005	1.219	0.003	1.300	0.002	1.251	<0.001	1.906
-	499.2923	4.3	Mupirocin	0.004	1.992	0.024	1.833	0.033	1.712	<0.001	8.222
-	181.0717	14.1	D-Sorbitol	0.004	1.334	0.013	1.311	0.006	1.237	<0.001	5.530
+	265.1118	21.7	Thiamin	0.004	1.393	0.003	1.462	0.006	1.342	<0.001	7.759
-	203.0925	5.0	Diethyl (2R,3R)-2-methyl-3-hydroxysuccinate	0.004	1.687	0.003	1.613	0.003	1.772	0.018	1.730
+	86.09644	11.6	Piperidine	0.004	1.652	0.008	1.625	0.089	1.465	<0.001	5.515
-	128.0352	10.1	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.004	1.329	0.005	1.356	0.012	1.264	<0.001	4.918
-	758.4963	3.9	PS(16:0/18:2(9Z,12Z))	0.004	16.462	<0.001	12.591	<0.001	27.175	<0.001	12.121
+	207.1129	10.6	Phenylethylmalonamide	0.004	1.589	0.001	1.685	0.014	1.451	<0.001	12.925
+	835.5322	3.8	PI(16:0/18:2(9Z,12Z))	0.004	3.330	0.016	2.006	0.003	2.924	<0.001	3.456
+	345.1848	4.3	[FA (24:6)] 6,9,12,15,18,21-Tetracosahexaynoic acid	0.004	0.286	0.001	0.190	0.001	0.163	0.003	0.259
+	335.1059	4.4	Penicillin G	0.004	1.384	0.002	1.423	0.005	1.350	<0.001	7.571
-	173.009	18.1	cis-Aconitate	0.004	1.668	0.009	1.649	0.021	1.553	0.008	10.337
-	786.5277	3.9	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.004	1.372	0.007	1.280	<0.001	1.650	0.039	1.162
+	822.6382	4.2	PC(22:4(7Z,10Z,13Z,16Z)/P-18:0)	0.004	1.136	0.002	1.155	<0.001	1.275	<0.001	1.304
-	164.0717	10.6	L-Phenylalanine	0.004	1.403	0.001	1.434	0.005	1.321	<0.001	7.007
-	367.358	3.8	Tetracosanoic acid	0.004	0.469	0.001	0.373	0.001	0.309	0.007	0.538
-	304.0605	17.0	Atherospermidine	0.004	1.954	0.020	2.263	0.048	1.591	<0.001	7.565
-	101.0718	15.4	N-Nitrosodiethylamine	0.004	1.685	0.030	1.701	0.016	1.510	<0.001	10.811
-	333.0914	4.4	Penicillin G	0.004	1.466	0.002	1.474	0.003	1.322	<0.001	7.406
-	339.3268	3.8	Docosanoic acid	0.003	0.609	<0.001	0.444	<0.001	0.463	0.003	0.527
+	119.0492	13.4	Benzofuran	0.003	2.410	0.011	3.126	0.009	2.100	<0.001	19.032

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	260.1857	7.6	[FA (6:0)] O-hexanoyl-R-carnitine	0.003	2.390	0.008	1.980	0.001	1.721	0.010	4.478
+	161.1074	10.6	Tryptamine	0.003	2.015	0.007	1.966	0.078	1.383	<0.001	17.931
+	414.3577	4.7	Heptadecanoylcarnitine	0.003	3.611	<0.001	4.704	<0.001	5.998	<0.001	4.674
+	176.1111	13.9	7-methylthioheptanaldoxime	0.003	1.878	0.012	2.096	0.196	1.414	<0.001	16.826
-	103.0399	9.6	(R)-3-Hydroxybutanoate	0.003	2.462	0.260	1.428	0.036	1.904	0.002	22.993
+	170.0813	8.1	Pyridoxine	0.003	1.372	0.001	1.434	0.008	1.251	<0.001	7.118
+	796.6206	4.2	PC(20:2(11Z,14Z)/P-18:1(11Z))	0.003	0.367	<0.001	0.214	0.020	0.525	0.006	0.435
+	466.3292	7.5	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	0.003	1.511	0.002	1.747	<0.001	1.992	0.001	2.308
-	773.5318	3.8	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.003	4.104	0.001	4.259	<0.001	4.979	0.001	3.940
-	167.021	12.7	Urate	0.003	1.518	0.001	1.544	0.002	1.436	<0.001	7.200
-	151.026	11.4	Xanthine	0.003	0.515	0.001	0.519	<0.001	0.441	<0.001	4.466
+	353.136	4.4	cotinine-glucuronide	0.003	1.417	0.003	1.427	0.031	1.273	<0.001	7.321
-	203.0826	12.1	L-Tryptophan	0.002	1.457	0.001	1.505	0.006	1.341	<0.001	7.493
+	147.1129	25.8	L-Lysine	0.002	1.316	0.003	1.365	0.032	1.183	<0.001	6.456
+	308.0911	14.5	Glutathione	0.002	3.495	0.046	4.701	0.019	4.834	<0.001	0.020
-	787.5313	3.9	[PG (8:0/8:0)] 1-(8-[5]-ladderane-octanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.002	1.523	0.003	1.387	<0.001	1.796	0.030	1.233
+	157.0973	13.1	N-acetyl prolinamide or isomer	0.002	1.410	0.002	1.391	0.010	1.259	<0.001	7.887
+	538.1621	4.0	Asp-Trp-Asp-Cys	0.002	0.729	0.001	0.691	0.001	0.625	<0.001	0.469
+	880.5867	4.1	PC(22:5(4Z,7Z,10Z,13Z,16Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.002	15.808	0.001	18.625	0.001	21.573	0.005	18.558
-	277.1443	4.0	2-Ethylhexyl phthalate	0.002	1.596	<0.001	1.734	0.001	1.595	<0.001	3.918
+	377.1455	8.9	Loganate	0.002	2.066	0.014	1.783	0.369	1.184	<0.001	14.237
+	134.06	8.1	Indoxyl	0.002	1.403	0.001	1.459	0.199	1.204	<0.001	7.641
-	115.0035	15.2	Fumarate	0.002	1.873	0.003	1.995	0.001	2.305	<0.001	6.745
+	864.6492	4.1	[PC (20:0/22:5)] 1-eicosanoyl-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.002	6.293	0.003	6.885	<0.001	9.980	0.007	6.789
+	134.0448	15.2	L-Aspartate	0.002	1.242	0.002	1.347	0.001	1.477	<0.001	2.840
+	544.3397	4.7	LysoPC(20:4(5Z,8Z,11Z,14Z))	0.002	1.449	0.039	1.340	<0.001	1.587	<0.001	2.848

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	87.0085	7.8	Pyruvate	0.002	2.214	0.022	1.720	0.024	1.713	<0.001	7.400
-	599.3198	4.3	Lys-Lys-Tyr-Tyr	0.002	0.676	0.001	0.628	0.003	0.572	0.068	0.772
+	537.1656	4.0	1-4-beta-D-Glucan	0.002	0.734	<0.001	0.701	0.001	0.622	<0.001	0.467
+	188.103	15.4	5-guanidino-3-methyl-2-oxo-pentanoate	0.002	1.966	0.001	1.671	0.065	1.290	<0.001	16.139
+	786.5293	3.9	[PS (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	0.002	5.518	<0.001	7.472	0.002	10.876	<0.001	6.105
+	526.3134	4.2	[PS (18:0)] 1-octadecanoyl-sn-glycero-3-phosphoserine	0.002	0.631	<0.001	0.443	0.002	0.679	0.003	0.715
-	137.0355	10.8	Urocanate	0.002	0.574	0.007	0.548	0.002	0.433	0.003	5.124
+	101.071	15.4	Gyromitrin	0.002	1.818	0.003	1.450	0.337	1.146	<0.001	4.680
-	144.0124	5.5	3,4-Dehydrothiomorpholine-3-carboxylate	0.002	72.411	0.004	86.708	0.002	107.727	0.005	277.541
-	204.0665	7.5	Indolelactate	0.002	1.903	0.022	2.830	0.001	2.076	0.001	8.916
-	87.00854	9.3	Pyruvate	0.002	3.562	0.003	3.840	0.001	4.100	0.001	30.599
+	162.0761	15.1	L-2-Aminoadipate	0.001	2.691	<0.001	2.806	<0.001	3.485	<0.001	6.258
-	229.0116	15.8	D-Ribose 5-phosphate	0.001	195.794	0.002	95.139	0.004	42.132	<0.001	54.300
-	120.0123	16.7	L-Cysteine	0.001	0.203	0.001	0.142	0.001	0.111	<0.001	11.714
-	346.0555	14.0	AMP	0.001	3.639	0.001	3.675	<0.001	3.690	0.207	1.135
+	775.5467	4.0	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.001	2.434	<0.001	2.950	<0.001	2.755	0.001	2.295
+	166.0534	13.8	L-Methionine S-oxide	0.001	1.373	0.014	1.402	0.007	1.306	<0.001	8.488
+	298.0526	15.4	L-Cysteinylglycinedisulfide	0.001	0.184	<0.001	0.039	<0.001	0.075	<0.001	10.968
+	114.055	14.8	(S)-1-Pyrroline-5-carboxylate	0.001	3.983	<0.001	4.890	0.007	3.341	<0.001	19.227
+	344.2794	4.9	1,2-dioctanoyl-1-amino-2,3-propanediol	0.001	1.954	0.023	2.508	0.014	3.169	0.008	1.952
+	204.1344	12.4	Lys-Gly	0.001	1.442	0.002	1.505	0.003	1.343	<0.001	8.010
-	453.1766	4.1	Trp-Ser-Tyr	0.001	7.927	0.004	6.428	0.001	4.157	<0.001	33.867
-	795.5168	3.7	PG(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.001	1.309	0.821	1.013	0.600	1.032	<0.001	1.387
+	838.6331	4.2	[PC (18:0/22:4)] 1-octadecanoyl-2-(7Z,10Z,13Z,16Z-docosatetraenoyl)-sn-glycero-3-phosphocholine	0.001	1.472	<0.001	1.515	<0.001	1.544	0.040	1.501
+	427.0953	17.0	S-glutathionyl-L-cysteine	0.001	1.521	0.004	1.658	0.131	1.203	<0.001	4.958
-	425.0804	17.0	S-glutathionyl-L-cysteine	0.001	1.611	0.008	1.755	0.070	1.310	<0.001	5.281
+	104.0706	14.5	4-Aminobutanoate	0.001	0.640	0.003	0.772	0.001	0.667	0.813	0.947

DM	row m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	166.0178	14.7	Homocysteinesulfinicacid	0.001	41.789	0.001	61.882	0.001	65.390	0.001	773.537
+	468.3081	4.9	[PC (14:0)] 1-tetradecanoyl-sn-glycero-3-phosphocholine	0.001	2.107	<0.001	2.534	<0.001	3.337	<0.001	4.392
-	791.5418	4.0	acyl phosphatidylglycerol (n-C12:0)	0.001	2.619	0.001	2.699	0.002	2.496	<0.001	3.449
-	409.2358	4.8	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.001	1.221	0.003	1.270	<0.001	1.426	0.002	1.788
-	130.0872	11.2	L-Leucine	0.001	1.416	0.005	1.433	0.005	1.367	<0.001	6.709
+	144.0656	13.6	Vinylacetylglycine	0.001	1.645	0.474	1.178	0.220	1.223	<0.001	4.215
-	833.5157	3.9	PI(16:0/18:2(9Z,12Z))	0.001	11.431	0.001	12.087	0.001	16.490	<0.001	9.353
-	722.5117	4.1	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.001	0.795	0.006	0.858	0.002	0.807	0.003	0.854
-	760.5121	3.9	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	0.001	1.822	<0.001	1.641	<0.001	2.268	0.001	1.548
+	166.0725	13.2	3-Methylguanine	0.001	100.387	0.002	92.190	<0.001	139.570	0.001	56.744
+	361.1461	11.9	Asn-Asn-Asn	0.001	2.127	0.001	1.917	0.002	1.828	<0.001	7.019
+	877.5636	3.9	Megalomicin A	0.001	2.051	<0.001	2.272	0.023	1.963	<0.001	2.371
-	738.5074	4.1	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.001	8.257	<0.001	9.020	<0.001	10.343	0.003	7.621
-	243.062	12.2	Uridine	0.001	1.557	0.059	1.462	0.001	1.491	<0.001	6.936
-	144.0124	7.5	3,4-Dehydrothiomorpholine-3-carboxylate	0.001	67.058	0.001	67.870	<0.001	86.919	0.002	197.064
+	572.3709	4.6	LysoPC(22:4(7Z,10Z,13Z,16Z))	0.001	2.094	0.012	1.793	<0.001	2.497	<0.001	4.651
+	174.0551	5.0	Deisopropylatrazine	0.001	2.101	0.024	1.706	0.004	1.648	<0.001	14.571
+	305.1013	14.7	[Fv hydroxy,methoxy(4:0)] 3,4,4',alpha-Tetrahydroxy-2'-methoxydihydrochalcone	0.001	16.946	<0.001	20.676	<0.001	21.578	<0.001	237.707
+	220.1181	8.5	Pantothenate	0.001	1.446	<0.001	1.627	0.002	1.438	<0.001	8.456
+	838.5605	3.8	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.001	1.412	0.001	1.297	<0.001	1.512	0.001	1.297
+	188.0707	12.1	Deethylatrazine	0.001	1.492	0.001	1.616	0.001	1.413	<0.001	8.232
+	130.0499	15.4	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.001	1.351	0.007	1.442	0.007	1.346	<0.001	5.015
+	166.0864	10.6	L-Phenylalanine	0.001	1.393	<0.001	1.493	0.002	1.330	<0.001	5.924
+	666.13251	13.5	NADH	<0.001	4.488	<0.001	4.7681	<0.001	6.849	<0.001	5.420
+	810.13398	12.6	Acetyl CoA	<0.001	9.544	<0.001	12.868	<0.001	15.586	<0.001	10.933

Appendix 12: The list of detected metabolites that have changed following CpG treatment, CpG +11a (C11a), 12b (C12b) and 19o (C19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, RT to raw retention time and p to P-value.

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	1089.691	4.7	alpha-D-Galactosyl-diphosphoundecaprenol	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	<0.001	#DIV/0!
+	294.2064	4.4	(+/-)-5-[(tert-Butylamino)-2'-hydroxypropoxy]-1,2,3,4-tetrahydro-1- naphthol	<0.001	0.371	<0.001	0.24	<0.001	0.149	<0.001	0.129
-	89.02419	9.8	(R)-Lactate	<0.001	2.775	<0.001	1.926	<0.001	2.372	<0.001	2.555
-	133.0142	16.4	(S)-Malate	<0.001	3.455	<0.001	3.639	<0.001	8.429	<0.001	2.500
-	293.1756	4.2	[6]-Gingerol	<0.001	1.693	0.010	1.837	0.005	1.309	0.004	1.741
+	143.0485	15.6	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.867	<0.001	2.801	<0.001	3.257	<0.001	2.648
-	281.2485	4.0	[FA (18:0)] 9Z-octadecenoic acid	<0.001	0.656	0.001	0.610	<0.001	0.649	0.002	0.593
-	305.2487	4.0	[FA (20:3)] 8Z,11Z,14Z-eicosatrienoic acid	<0.001	0.083	<0.001	0.112	<0.001	0.093	<0.001	0.086
-	303.233	4.0	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	<0.001	0.143	<0.001	0.196	<0.001	0.095	<0.001	0.144
-	331.2644	4.0	[FA (22:4)] 7Z,10Z,13Z,16Z-docosatetraenoic acid	<0.001	0.058	<0.001	0.048	<0.001	0.020	<0.001	0.050
-	365.3424	3.9	[FA (24:0)] 15Z-tetracosenoic acid	<0.001	0.218	<0.001	0.132	<0.001	0.135	<0.001	0.232
+	345.1848	4.4	[FA (24:6)] 6,9,12,15,18,21-Tetracosahexaynoic acid	<0.001	0.247	<0.001	0.202	<0.001	0.181	<0.001	0.227
-	295.264	4.0	[FA methyl(18:0)] 11R,12S-methylene-octadecanoic acid	<0.001	0.320	<0.001	0.241	<0.001	0.323	<0.001	0.280
-	135.0299	12.8	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	<0.001	1.515	<0.001	1.339	<0.001	1.612	<0.001	1.421
+	400.3422	4.9	[FA] O-Palmitoyl-R-carnitine	<0.001	0.637	<0.001	0.478	<0.001	0.468	0.015	0.753
+	301.1428	16	[Fv Hydroxy,dimethoxy,methy] 2'-Hydroxy-4',6'-dimethoxy-3'-methyldihydrochalcone	<0.001	6.038	<0.001	6.086	<0.001	6.737	<0.001	5.797
+	804.576	3.9	[GP (18:0/18:0)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphothreonine	<0.001	2.389	0.054	2.092	0.004	3.062	0.143	1.755
-	466.2937	4.9	[PC (14:0)] 1-tetradecanoyl-sn-glycero-3-phosphocholine	<0.001	3.012	0.005	2.186	<0.001	3.583	<0.001	2.503

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	468.3086	5	[PC (14:0)] 1-tetradecanoyl-sn-glycero-3-phosphocholine	<0.001	2.53	<0.001	2.504	<0.001	4.031	<0.001	2.08
+	678.5073	4.4	[PC (14:0/14:0)] 1,2-ditetradecanoyl-sn-glycero-3-phosphocholine	<0.001	153.687	<0.001	134.174	<0.001	245.81	<0.001	133.359
+	704.5231	4.4	[PC (14:0/16:1)] 1-tetradecanoyl-2-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	30.832	<0.001	27.013	<0.001	43.664	<0.001	27.442
+	732.5542	4.3	[PC (14:0/18:1)] 1-tetradecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	4.422	<0.001	4.236	<0.001	5.565	<0.001	3.99
+	730.5387	4.4	[PC (14:0/18:2)] 1-tetradecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	5.371	<0.001	4.956	<0.001	7.042	<0.001	4.789
-	450.299	4.8	[PC (14:1)] 1-(1E-tetradecenyl)-sn-glycero-3-phosphocholine	<0.001	1.285	0.003	1.233	<0.001	1.626	0.045	1.178
-	480.3094	4.8	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	2.041	<0.001	1.637	<0.001	2.241	<0.001	1.733
+	482.3242	4.8	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.912	<0.001	1.612	<0.001	2.143	<0.001	1.64
+	706.5386	4.3	[PC (15:0/15:0)] 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine	<0.001	10.747	<0.001	11.507	<0.001	15.653	<0.001	10.18
+	720.5546	4.3	[PC (15:0/16:0)] 1-pentadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	3.497	<0.001	3.713	<0.001	4.356	<0.001	3.539
+	746.5701	4.3	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	4.89	<0.001	4.651	<0.001	5.68	<0.001	4.657
-	464.3144	4.8	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	<0.001	1.251	0.003	1.161	<0.001	1.578	0.013	1.168
+	466.3294	4.8	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	<0.001	1.235	0.014	1.135	<0.001	1.511	0.03	1.147
+	494.3242	5	[PC (16:0)] 1-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.027	<0.001	2.053	<0.001	3.069	0.002	1.647
+	760.5855	4.3	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	3.596	<0.001	3.722	<0.001	4.175	<0.001	3.545
+	758.57	4.3	[PC (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	6.46	<0.001	5.97	<0.001	7.897	<0.001	5.888
+	756.5547	4.3	[PC (16:0/18:3)] 1-hexadecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	7.883	<0.001	6.978	<0.001	9.661	<0.001	7.211
+	806.5699	4.3	[PC (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.244	<0.001	2.114	<0.001	2.421	<0.001	2.131
+	804.5541	4.3	[PC (16:1/22:6)] 1-(9Z-hexadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	4.319	<0.001	3.779	<0.001	5.11	<0.001	3.976
+	788.617	4.3	[PC (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	1.884	<0.001	2.074	0.002	2.058	0.003	2.101

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	814.6327	4.3	[PC (18:0/20:2)] 1-octadecanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphocholine	<0.001	9.447	<0.001	8.456	<0.001	9.322	0.001	8.574
+	836.6172	4.2	[PC (18:0/22:5)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.32	<0.001	1.33	0.002	1.293	<0.001	1.338
+	772.6219	4.3	[PC (18:1/18:0)] 1-(1Z-octadecenyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	3.71	<0.001	4.108	<0.001	6.359	<0.001	3.508
+	786.6013	4.3	[PC (18:1/18:1)] 1-(9Z-octadecenoyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	6.431	<0.001	6.024	<0.001	7.546	<0.001	6.149
+	810.6014	4.3	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	<0.001	0.718	<0.001	0.674	<0.001	0.654	<0.001	0.721
+	794.6063	4.3	[PC (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.326	<0.001	0.278	<0.001	0.302	<0.001	0.332
+	808.5857	4.3	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.464	<0.001	1.377	<0.001	1.542	<0.001	1.427
+	834.6013	4.2	[PC (18:1/22:5)] 1-(11Z-octadecenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.108	<0.001	2.03	<0.001	2.228	<0.001	2.089
+	832.5856	4.3	[PC (18:1/22:6)] 1-(11Z-octadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	3.483	<0.001	3.145	<0.001	4.168	<0.001	3.321
+	830.5699	4.3	[PC (18:2/22:6)] 1-(9Z,12Z-octadecadienoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	0.671	<0.001	0.57	0.012	0.725	<0.001	0.64
+	862.6327	4.2	[PC (20:0/22:6)] 1-eicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	4.991	<0.001	4.469	<0.001	4.802	<0.001	5.023
-	764.563	4.5	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.414	<0.001	1.566	<0.001	1.724	<0.001	1.571
+	766.5749	4.3	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.144	<0.001	0.156	<0.001	0.131	<0.001	0.129
-	452.2782	4.9	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	3.635	<0.001	3.640	<0.001	5.200	<0.001	2.653
+	454.2929	4.9	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	3.414	<0.001	3.502	<0.001	4.907	<0.001	2.61
+	692.5233	4.3	[PE (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	112.933	0.003	89.909	<0.001	163.072	<0.001	97.34
+	718.5387	4.3	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	6.479	<0.001	6.411	<0.001	8.34	<0.001	6.172
-	714.5074	4.2	[PE (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	33.581	0.007	19.68	0.001	31.396	0.001	16.08

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	738.5091	4.2	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	7.234	0.001	5.987	<0.001	8.529	<0.001	6.363
+	740.5233	4.2	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	9.894	<0.001	9.694	<0.001	11.839	<0.001	9.259
+	774.6016	4.3	[PE (16:0/22:1)] 1-hexadecanoyl-2-(13Z-docosenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.476	<0.001	3.435	<0.001	3.694	<0.001	3.587
-	762.5073	4.2	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.986	0.004	4.449	<0.001	6.444	<0.001	5.941
+	764.5238	4.2	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	10.785	<0.001	8.754	0.001	10.51	0.002	8.309
-	436.2832	4.9	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.502	<0.001	1.430	<0.001	1.967	0.001	1.348
+	438.298	4.9	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.462	<0.001	1.437	<0.001	1.945	0.003	1.351
-	746.5125	4.2	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.610	<0.001	1.668	<0.001	1.732	<0.001	1.572
+	748.5281	4.2	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.706	<0.001	1.81	<0.001	1.864	<0.001	1.679
-	478.2937	4.9	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.866	<0.001	2.653	<0.001	3.582	<0.001	2.005
+	480.3086	4.9	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.878	<0.001	2.708	<0.001	3.569	<0.001	1.962
-	742.5388	4.2	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	18.791	<0.001	18.349	<0.001	20.169	<0.001	17.980
+	744.5544	4.3	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	8.604	<0.001	7.969	<0.001	10.508	<0.001	8.18
+	772.5858	4.3	[PE (18:0/20:2)] 1-octadecanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	15.765	<0.001	13.918	<0.001	18.8	<0.001	14.441
-	766.5414	4.1	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.761	<0.001	1.683	0.088	1.334	0.006	1.835
+	768.5545	4.2	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.93	<0.001	1.894	0.001	1.824	0.001	2.003
+	792.5539	4.2	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.643	<0.001	3.379	0.005	3.12	<0.001	3.718
+	742.5393	4.2	[PE (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	39.854	<0.001	36.926	<0.001	48.736	0.001	33.31
-	750.5441	4.1	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.679	0.040	0.882	0.018	0.773	0.011	0.759

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	752.5599	4.2	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	0.706	0.524	0.953	0.029	0.79	0.032	0.78
+	800.6171	4.3	[PE (20:0/20:2)] 1-eicosanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	12.069	<0.001	11.29	<0.001	13.392	<0.001	12.281
+	766.5599	3.8	[PG (16:0/18:0)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	<0.001	3.628	<0.001	4.999	<0.001	5.382	<0.001	3.263
-	747.5161	3.8	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	2.761	<0.001	3.522	<0.001	3.821	<0.001	2.498
+	749.5315	4.2	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.764	<0.001	1.941	<0.001	2.053	<0.001	1.763
-	769.5017	3.8	[PG (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	4.499	<0.001	3.156	<0.001	4.863	<0.001	3.979
-	509.2883	4.0	[PG (18:0)] 1-(9E-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	4.830	<0.001	4.119	<0.001	5.468	<0.001	3.789
-	797.5338	3.8	[PG (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	3.698	<0.001	2.883	<0.001	3.605	<0.001	3.398
-	821.5336	3.8	[PG (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	2.183	<0.001	1.726	<0.001	1.840	<0.001	2.072
-	773.532	3.8	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	9.173	<0.001	7.531	<0.001	11.445	<0.001	7.878
-	759.499	4.0	[PG (6:0/8:0)] 1-(6-[5]-ladderane-hexanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	13.658	0.003	10.287	<0.001	18.805	0.002	10.076
-	787.5313	3.9	[PG (8:0/8:0)] 1-(8-[5]-ladderane-octanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	3.064	<0.001	3.224	<0.001	3.905	0.001	2.894
-	809.5156	3.9	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	4.104	<0.001	3.540	<0.001	5.048	0.001	3.314
+	811.5319	3.9	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	3.698	<0.001	3.182	<0.001	4.32	<0.001	3.283
-	835.5317	3.9	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	2.817	<0.001	2.852	0.001	3.301	0.001	2.695
+	837.5477	3.9	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.771	<0.001	1.726	0.001	1.956	0.001	1.726
-	861.5485	4.0	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	8.083	<0.001	7.930	<0.001	10.233	<0.001	7.292
+	863.5635	3.8	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	0.41	<0.001	0.335	<0.001	0.302	<0.001	0.42
+	880.5912	4	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)(ammonium salt)	<0.001	12.875	<0.001	12.04	<0.001	15.297	<0.001	11.596

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	887.5639	3.8	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	0.601	<0.001	0.545	<0.001	0.458	<0.001	0.63
-	619.2884	4.4	[PI (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	0.124	<0.001	0.155	<0.001	0.149	<0.001	0.080
-	760.5123	4.0	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	2.558	<0.001	2.968	0.001	3.524	0.004	2.525
+	762.5285	4	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	2.466	<0.001	2.835	<0.001	3.26	0.002	2.438
+	792.5756	3.8	[PS (16:0/20:0)] 1-hexadecanoyl-2-eicosanoyl-sn-glycero-3-phosphoserine	<0.001	27.299	<0.001	21.311	<0.001	34.283	<0.001	23.404
-	524.2992	4.4	[PS (18:0)] 1-octadecanoyl-sn-glycero-3-phosphoserine	<0.001	0.374	<0.001	0.322	<0.001	0.382	<0.001	0.351
+	526.3141	4.4	[PS (18:0)] 1-octadecanoyl-sn-glycero-3-phosphoserine	<0.001	0.16	<0.001	0.138	<0.001	0.102	<0.001	0.127
-	804.5747	4.3	[PS (18:0/19:0)] 1-octadecanoyl-2-nonadecanoyl-sn-glycero-3-phosphoserine	<0.001	5.070	0.002	4.446	<0.001	7.588	0.001	4.325
+	806.591	3.8	[PS (18:0/19:0)] 1-octadecanoyl-2-nonadecanoyl-sn-glycero-3-phosphoserine	<0.001	45.888	<0.001	38.167	<0.001	67.113	<0.001	40.692
-	834.528	3.9	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	2.725	<0.001	2.763	<0.001	3.224	0.001	2.647
+	836.5443	3.9	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	1.785	<0.001	1.737	0.001	1.975	0.001	1.742
-	786.5281	4.0	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	3.037	<0.001	3.191	0.001	3.841	0.001	2.851
+	788.5442	4	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	2.865	<0.001	2.942	<0.001	3.492	0.001	2.679
-	784.5129	4.0	[PS (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	9.809	<0.001	9.480	<0.001	14.000	<0.001	9.145
+	786.5289	3.9	[PS (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	6.147	0.001	4.991	<0.001	7.539	<0.001	4.558
-	782.4969	3.9	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	6.304	<0.001	5.878	<0.001	8.252	<0.001	5.401
+	784.5126	3.9	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	4.659	<0.001	4.493	<0.001	5.914	<0.001	4.42
+	538.5196	4.1	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine	<0.001	0.408	<0.001	0.447	<0.001	0.516	<0.001	0.453
+	703.5752	4.5	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	<0.001	1.53	<0.001	1.714	<0.001	1.952	<0.001	1.668
+	689.5596	4.6	[SP (18:0/14:0)] N-(octadecanoyl)-tetradecasphing-4-enine-1-phosphoethanolamine	<0.001	1.278	<0.001	1.253	<0.001	1.417	<0.001	1.307
+	300.2898	7.9	[SP] 3-dehydrosphinganine	<0.001	0.353	<0.001	0.275	<0.001	0.401	<0.001	0.339

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	361.2736	3.8	[ST (3:0)] (5Z,7E)-(1S,3R)-24-nor-9,10-seco-5,7,10(19)-cholatriene-1,3,23-triol	<0.001	0.193	<0.001	0.137	<0.001	0.112	<0.001	0.195
-	409.3112	4.1	[ST hydroxy,methyl(4:0)] (22E)-(8S)-3-hydroxy-22-methyl-9,10-seco-1,3,5(10),22-cholestatetraen-9-one	<0.001	0.503	<0.001	0.527	0.001	0.646	<0.001	0.626
-	719.4861	3.8	1-16:0-2-trans-16:1-phosphatidylglycerol	<0.001	26.655	<0.001	35.919	<0.001	56.677	<0.001	25.317
+	865.5791	3.8	1-18:0-2-18:1-phosphatidylinositol	<0.001	0.763	<0.001	0.667	<0.001	0.628	0.002	0.765
-	749.5238	3.8	1-18:2-2-16:2-monogalactosyldiacylglycerol	<0.001	6.028	<0.001	8.606	0.083	16.618	0.002	4.882
+	818.5916	3.8	1-20:0-2-18:1-phosphatidylserine	<0.001	5.552	<0.001	4.875	<0.001	6.131	<0.001	5.22
+	816.5756	3.8	1-20:0-2-18:2-phosphatidylserine	<0.001	2.6	<0.001	2.314	<0.001	2.561	<0.001	2.442
-	808.5126	3.9	1-20:2-2-18:3-phosphatidylserine	<0.001	2.964	<0.001	2.783	<0.001	3.915	<0.001	2.904
+	810.5286	3.9	1-20:2-2-18:3-phosphatidylserine	<0.001	3.392	<0.001	2.874	<0.001	3.872	<0.001	3.016
+	844.6063	3.8	1-22:0-2-18:2-phosphatidylserine	<0.001	4.67	<0.001	4.632	0.011	3.663	<0.001	4.49
+	842.59	3.8	1-22:0-2-18:3-phosphatidylserine	<0.001	1.78	<0.001	1.547	0.001	1.54	0.001	1.74
+	840.5744	3.8	1-22:1-2-18:3-phosphatidylserine	<0.001	1.787	<0.001	1.644	<0.001	1.573	0.001	1.721
+	102.055	15.1	1-Aminocyclopropane-1-carboxylate	<0.001	1.872	<0.001	1.75	<0.001	2.255	<0.001	1.634
-	273.0381	15.7	1-Deoxy-D-altro-heptulose 7-phosphate	<0.001	0.268	0.020	0.551	0.167	0.735	<0.001	0.277
+	744.5907	4.3	1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphonocholine	<0.001	3.304	<0.001	3.368	<0.001	4.754	<0.001	3.061
+	522.3556	4.9	1-Oleoylglycerophosphocholine	<0.001	1.887	<0.001	1.856	<0.001	2.8	0.002	1.513
-	325.1252	15.7	2,2,4-Trimethyl-3-(4-fluorophenyl)-2H-1-benzopyran-7-ol acetate	<0.001	0.238	0.001	0.286	<0.001	0.195	0.001	0.259
+	327.1398	13.8	2,2,4-Trimethyl-3-(4-fluorophenyl)-2H-1-benzopyran-7-ol acetate	<0.001	1.854	0.006	0.815	0.003	1.392	0.001	1.596
+	130.9665	14.9	2,2-Dichloro-1,1-ethanediol	<0.001	54.79	<0.001	67.757	<0.001	56.551	0.006	48.545
+	144.9822	14.9	2-chloroethylphosphonate	<0.001	8.726	<0.001	12.999	<0.001	10.345	<0.001	8.592
-	277.1445	4.1	2-Ethylhexyl phthalate	<0.001	1.851	0.001	1.555	<0.001	1.868	0.001	1.746
+	229.0697	15.6	2-Hydroxy-3-carboxy-6-oxo-7-methylocta-2,4-dienoate	<0.001	5.222	<0.001	2.993	<0.001	3.606	0.002	4.403
-	145.0142	16.0	2-Oxoglutarate	<0.001	6.280	<0.001	4.978	<0.001	8.082	<0.001	5.925
+	166.0724	13.7	3-Methylguanine	<0.001	231.644	<0.001	226.754	<0.001	405.376	0.014	119.154
-	184.9856	17.4	3-Phospho-D-glycerate	<0.001	20.886	<0.001	12.693	<0.001	20.752	<0.001	20.941
-	102.0559	15.1	4-Aminobutanoate	<0.001	1.252	<0.001	1.200	<0.001	1.362	<0.001	1.205

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	102.0559	16.1	4-Aminobutanoate	<0.001	2.721	0.001	3.248	0.030	7.014	0.001	2.682
-	126.0115	15.6	4-Chloroaniline	<0.001	3.876	<0.001	3.728	<0.001	4.357	<0.001	3.499
+	146.0924	15.8	4-Guanidinobutanoate	<0.001	2.437	<0.001	1.699	<0.001	2.511	<0.001	2.27
+	146.1176	14	4-Trimethylammoniobutanoate	<0.001	1.21	0.623	1.023	0.026	1.221	0.316	1.075
+	129.0658	15.4	5,6-Dihydrothymine	<0.001	1.764	0.076	1.277	0.001	1.583	0.001	1.506
+	115.0502	15.3	5,6-Dihydrouracil	<0.001	4.41	0.001	2.311	0.015	2.419	<0.001	3.865
-	253.0499	16.0	5-L-Glutamyl-taurine	<0.001	7.175	0.009	1.841	<0.001	15.336	0.001	6.377
+	242.1136	9.9	5-Methyl-2'-deoxycytidine	<0.001	0.46	<0.001	0.341	<0.001	0.506	<0.001	0.353
-	296.0822	7.9	5'-Methylthioadenosine	<0.001	4.870	<0.001	7.009	<0.001	11.435	<0.001	3.501
+	298.0969	7.9	5'-Methylthioadenosine	<0.001	3.245	<0.001	4.724	<0.001	7.421	0.001	2.507
+	356.1186	15.3	5-methylthiopentyldesulfoglucosinolate	<0.001	0.399	<0.001	0.578	0.22	0.692	<0.001	0.613
+	230.0425	13.9	5-Phosphoribosylamine	<0.001	1923.574	<0.001	721.407	<0.001	1564.287	0.019	4856.026
-	285.0493	17.0	5'-Phosphoribosylglycinamide	<0.001	4738.678	<0.001	1767.245	<0.001	2862.567	<0.001	4650.016
+	287.0638	17	5'-Phosphoribosylglycinamide	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
+	168.0519	15.6	8-Hydroxyguanine	<0.001	3.925	<0.001	3.865	<0.001	4.629	<0.001	3.588
-	181.0288	13.9	Acenaphthenequinone	<0.001	74.441	<0.001	40.897	<0.001	56.655	<0.001	68.349
+	86.06007	16.1	Acetone cyanohydrin	<0.001	2.354	<0.001	3.195	<0.001	3.783	<0.001	2.06
+	171.0764	15.1	acetonitrile adduct of pyrroline carboxylate	<0.001	2.714	<0.001	2.606	<0.001	3.475	<0.001	2.299
-	808.1173	12.7	Acetyl-CoA	<0.001	4.173	<0.001	4.102	<0.001	6.949	0.006	2.563
+	810.1337	12.7	Acetyl-CoA	<0.001	4.141	<0.001	4.362	<0.001	6.797	<0.001	2.868
+	793.5573	4.2	acyl phosphatidylglycerol (n-C12:0)	<0.001	3.665	<0.001	3.569	<0.001	3.563	<0.001	3.906
-	426.0223	15.5	ADP	<0.001	2.075	<0.001	2.492	<0.001	2.840	<0.001	1.888
-	426.0222	16.8	ADP	<0.001	2.294	<0.001	2.911	<0.001	3.756	0.001	1.801
+	428.0367	15.5	ADP	<0.001	2.301	<0.001	2.79	<0.001	3.001	<0.001	2.056
+	401.1766	14.3	Ala-Ser-Ser-His	<0.001	17.334	<0.001	10.937	<0.001	14.546	<0.001	15.652
-	531.2728	4.0	Arg-Leu-Met-Asn	<0.001	0.088	<0.001	0.032	<0.001	0.048	<0.001	0.101
-	580.3254	4.9	Arg-Leu-Phe-Phe	<0.001	3.805	<0.001	3.517	<0.001	5.232	0.002	2.642
-	247.0571	17.9	Asp-Asp	<0.001	2.536	0.001	2.369	<0.001	3.268	0.006	2.250

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	505.9882	16.8	ATP	<0.001	1.844	<0.001	2.421	<0.001	2.979	0.003	1.503
+	508.0032	16.8	ATP	<0.001	1.952	<0.001	2.563	<0.001	3.196	0.001	1.533
-	347.1031	13.4	Camptothecin	<0.001	5.069	<0.001	12.321	<0.001	8.853	<0.001	4.164
+	349.1175	13.4	Camptothecin	<0.001	6.77	<0.001	17.595	<0.001	12.114	<0.001	5.314
+	227.1139	16.4	Carnosine	<0.001	1.694	0.271	1.184	<0.001	1.614	0.004	1.487
+	131.0815	16	Casein K	<0.001	34.967	<0.001	31.762	<0.001	38.883	0.001	29.731
-	445.0531	16.8	CDP-ethanolamine	<0.001	6.264	<0.001	4.896	<0.001	7.565	<0.001	5.287
+	447.0677	16.8	CDP-ethanolamine	<0.001	6.457	<0.001	5.095	<0.001	8.005	<0.001	5.474
-	465.3042	3.9	Cholesterolsulfate	<0.001	1.467	<0.001	1.480	0.003	1.786	0.008	1.377
+	104.107	21.8	Choline	<0.001	1.513	<0.001	1.511	0.001	1.442	0.026	1.29
+	184.0734	15.6	Choline phosphate	<0.001	2.831	<0.001	7.732	<0.001	7.323	0.001	2.144
+	229.1013	11	Chrysene	<0.001	0.323	<0.001	0.348	<0.001	0.447	<0.001	0.365
+	359.1641	4.2	Cilastatin	<0.001	0.459	0.001	0.536	<0.001	0.391	<0.001	0.363
-	429.058	15.8	CMP-2-aminoethylphosphonate	<0.001	4.110	<0.001	3.496	<0.001	6.721	<0.001	3.968
-	613.1394	15.7	CMP-N-acetylneuraminate	<0.001	2.944	<0.001	1.560	<0.001	2.057	<0.001	2.583
+	615.1548	15.7	CMP-N-acetylneuraminate	<0.001	3.332	<0.001	1.766	0.003	2.029	<0.001	2.808
-	766.1068	14.0	CoA	<0.001	5.274	0.001	6.614	<0.001	9.702	0.004	3.619
-	130.0621	15.3	Creatine	<0.001	3.678	<0.001	1.822	<0.001	2.046	<0.001	3.419
+	132.0768	15.3	Creatine	<0.001	3.587	<0.001	1.907	<0.001	2.189	<0.001	3.245
-	192.018	15.6	creatinine phosphate	<0.001	4.446	<0.001	2.530	<0.001	3.049	<0.001	4.013
-	481.9771	18.7	CTP	<0.001	7.092	<0.001	5.774	<0.001	8.147	<0.001	6.071
-	540.0537	14.6	Cyclic ADP-ribose	<0.001	3.235	<0.001	3.839	<0.001	4.998	<0.001	2.903
-	745.5021	3.8	cyclopropane phosphatidylglycerol (dihexadec-9,10-cyclo-anoyl, n-C16:0 cyclo)	<0.001	18.566	<0.001	15.696	<0.001	25.925	<0.001	15.394
-	801.5657	3.8	cyclopropane phosphatidylglycerol (dioctadec-11,12-cyclo-anoyl, n-C18:0 cyclo)	<0.001	11.026	<0.001	9.008	<0.001	13.215	<0.001	9.514
+	376.1907	4.3	Cyphenothrin	<0.001	0.235	<0.001	0.153	<0.001	0.114	<0.001	0.24
+	179.0485	14.8	Cys-Gly	<0.001	3.649	<0.001	6.068	<0.001	5.134	<0.001	3.222
-	246.0464	13.1	DCI	<0.001	3.508	<0.001	2.027	<0.001	4.049	0.001	2.761

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	771.6098	4.3	demethylmenaquinone-9	<0.001	7.019	<0.001	6.652	<0.001	9.495	<0.001	6.76
-	226.0834	11.0	Deoxycytidine	<0.001	0.494	<0.001	0.353	<0.001	0.492	<0.001	0.388
+	228.0979	11	Deoxycytidine	<0.001	0.514	<0.001	0.448	<0.001	0.536	<0.001	0.448
-	199.0014	13.2	D-Erythrose 4-phosphate	<0.001	65.798	0.001	33.251	<0.001	47.173	<0.001	57.286
-	338.9886	18.7	D-Fructose 1,6-bisphosphate	<0.001	69.248	<0.001	34.351	<0.001	53.064	<0.001	73.116
-	258.0384	15.9	D-Glucosamine 6-phosphate	<0.001	1.830	0.004	1.283	<0.001	2.147	0.001	1.706
+	260.0529	15.9	D-Glucosamine 6-phosphate	<0.001	1.994	0.105	1.336	<0.001	2.254	0.001	1.891
-	259.0223	17.3	D-Glucose 6-phosphate	<0.001	8.815	<0.001	4.707	<0.001	5.358	<0.001	5.223
-	259.0223	16.4	D-Glucose 6-phosphate	<0.001	25.332	0.004	11.733	<0.001	18.364	<0.001	18.485
-	85.02922	15.5	Diacetyl	<0.001	15.718	<0.001	12.940	<0.001	22.449	<0.001	14.789
+	87.04413	16.1	Diacetyl	<0.001	2.741	<0.001	3.737	<0.001	4.653	<0.001	2.333
+	117.0659	16.3	Diacetylhydrazine	<0.001	1.736	0.806	1.034	0.029	1.333	0.011	1.517
+	91.05834	16	Diethyl sulfide	<0.001	11.981	<0.001	10.738	<0.001	13.505	<0.001	10.962
+	240.1091	13.2	Dihydrobiopterin	<0.001	89.216	<0.001	75.125	<0.001	167.095	<0.001	92.298
-	158.1186	11.6	DL-2-Aminooctanoicacid	<0.001	2.412	<0.001	2.277	<0.001	2.563	<0.001	2.596
+	160.1333	14	DL-2-Aminooctanoicacid	<0.001	2.018	<0.001	1.949	<0.001	2.309	<0.001	1.771
-	168.9907	15.8	DL-Glyceraldehyde 3-phosphate	<0.001	15.637	<0.001	9.204	<0.001	11.146	<0.001	18.403
-	327.233	4.0	Docosahexaenoicacid	<0.001	0.162	<0.001	0.137	<0.001	0.112	<0.001	0.145
-	308.9782	17.0	D-Ribose 1,5-bisphosphate	<0.001	937.181	<0.001	269.481	<0.001	642.993	<0.001	969.222
-	229.0118	16.0	D-Ribose 5-phosphate	<0.001	114.528	<0.001	45.246	<0.001	67.971	<0.001	92.284
+	426.3577	4.8	Elaidiccarnitine	<0.001	0.512	<0.001	0.398	<0.001	0.447	0.001	0.68
-	140.0118	16.5	Ethanolamine phosphate	<0.001	1.440	<0.001	1.484	<0.001	2.025	0.013	1.287
+	142.0264	16.5	Ethanolamine phosphate	<0.001	1.463	<0.001	1.462	<0.001	1.969	0.009	1.298
-	784.1487	11.8	FAD	<0.001	2.760	<0.001	2.923	<0.001	4.015	<0.001	2.863
-	274.1046	14.9	Gamma-Glutamylglutamine	<0.001	36.050	0.434	1.296	<0.001	71.599	<0.001	29.522
-	572.0798	13.1	GDP-3,6-dideoxy-D-galactose	<0.001	78.144	0.002	29.675	<0.001	41.244	<0.001	90.736
-	588.0747	18.0	GDP-L-fucose	<0.001	1.680	<0.001	2.149	<0.001	2.489	0.047	1.400
-	203.0674	15.8	Glu-Gly	<0.001	11.555	0.580	0.871	<0.001	14.354	<0.001	10.830

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	205.0821	15.8	Glu-Gly	<0.001	10.932	0.344	0.801	<0.001	15.714	<0.001	12.147
-	259.1298	11.4	Glu-Leu	<0.001	1.974	0.236	1.115	<0.001	3.734	0.002	1.821
+	261.1445	11.4	Glu-Leu	<0.001	2.093	0.08	1.219	<0.001	4.006	0.001	1.947
-	306.0765	14.8	Glutathione	<0.001	2.936	<0.001	5.298	<0.001	4.357	<0.001	2.640
+	308.091	14.8	Glutathione	<0.001	2.859	<0.001	4.814	<0.001	4.04	<0.001	2.572
-	245.0431	13.1	Glycerophosphoglycerol	<0.001	2.827	<0.001	1.665	<0.001	3.342	0.001	2.283
+	247.0578	13.1	Glycerophosphoglycerol	<0.001	2.822	<0.001	1.653	<0.001	3.242	<0.001	2.115
+	76.03939	16.3	Glycine	<0.001	1.974	0.506	0.924	0.135	1.315	0.041	1.539
+	173.0922	15.1	Glycylproline	<0.001	1.938	0.001	1.603	<0.001	1.853	0.003	1.635
-	521.9832	19.6	GTP	<0.001	2.402	<0.001	2.535	<0.001	3.111	0.001	2.077
-	116.0464	16.5	Guanidinoacetate	<0.001	14.636	0.013	1.959	<0.001	5.586	<0.001	13.008
+	118.0611	16.5	Guanidinoacetate	<0.001	7.679	0.002	1.535	<0.001	3.728	<0.001	6.641
+	495.3275	5	His-Leu-Leu-Leu	<0.001	1.858	<0.001	1.973	<0.001	2.992	0.033	1.475
-	479.2972	4.9	His-Leu-Leu-Val	<0.001	3.009	<0.001	2.826	<0.001	3.829	<0.001	2.100
+	481.312	4.9	His-Leu-Leu-Val	<0.001	3.676	0.001	3.421	<0.001	4.833	<0.001	2.779
-	166.0179	9.0	Homocysteinesulfinicacid	<0.001	2.723	<0.001	2.430	<0.001	3.220	<0.001	2.457
-	79.95698	15.5	HSO3-	<0.001	2.572	<0.001	2.562	<0.001	2.980	<0.001	2.417
-	110.9851	14.9	Hydroxymethylphosphonate	<0.001	7.450	<0.001	5.348	<0.001	5.373	<0.001	6.981
-	108.0124	15.6	Hypotaurine	<0.001	10.858	<0.001	10.812	<0.001	13.429	<0.001	9.808
+	110.0271	15.6	Hypotaurine	<0.001	7.892	<0.001	7.866	<0.001	9.349	<0.001	7.28
+	137.0458	10.7	Hypoxanthine	<0.001	0.212	<0.001	0.103	<0.001	0.076	<0.001	0.106
-	347.0398	15.8	IMP	<0.001	6.442	<0.001	4.763	<0.001	5.052	<0.001	5.316
-	128.0353	15.1	L-1-Pyrroline-3-hydroxy-5-carboxylate	<0.001	5.196	<0.001	4.533	0.004	4.488	0.022	3.517
+	130.0499	15.1	L-1-Pyrroline-3-hydroxy-5-carboxylate	<0.001	2.658	<0.001	2.717	<0.001	3.503	<0.001	2.328
-	274.1409	17.6	L-a-glutamyl-L-Lysine	<0.001	0.113	<0.001	0.072	<0.001	0.212	<0.001	0.135
+	276.1554	17.6	L-a-glutamyl-L-Lysine	<0.001	0.147	<0.001	0.109	<0.001	0.192	<0.001	0.133
-	217.0829	10.4	L-Ala-L-Glu	<0.001	10.483	<0.001	5.234	0.001	8.603	0.002	9.130
-	88.04017	16.0	L-Alanine	<0.001	13.473	0.001	14.452	<0.001	15.703	<0.001	12.241

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	90.05501	16	L-Alanine	<0.001	9.831	<0.001	8.926	<0.001	11.162	<0.001	8.956
+	90.055	15.4	L-Alanine	<0.001	1.623	0.055	1.214	0.001	1.404	0.005	1.409
-	160.0978	11.6	L-Carnitine	<0.001	2.823	<0.001	2.683	<0.001	3.123	<0.001	2.938
+	162.1125	13.9	L-Carnitine	<0.001	1.891	<0.001	1.695	<0.001	2.123	0.001	1.584
-	174.0884	16.6	L-Citrulline	<0.001	2.067	0.237	1.194	0.727	1.066	<0.001	2.544
-	167.9972	15.6	L-Cysteate	<0.001	3.465	<0.001	3.420	<0.001	4.074	<0.001	3.223
-	243.1712	4.9	Leucyl-leucine	<0.001	0.458	<0.001	0.314	<0.001	0.312	<0.001	0.450
+	245.186	4.9	Leucyl-leucine	<0.001	0.44	<0.001	0.314	<0.001	0.268	<0.001	0.432
-	146.0458	15.1	L-Glutamate	<0.001	2.458	<0.001	2.271	<0.001	3.117	<0.001	2.162
+	148.0604	15.1	L-Glutamate	<0.001	2.542	<0.001	2.424	<0.001	3.202	<0.001	2.225
-	130.0508	15.1	L-Glutamate 5-semialdehyde	<0.001	1.568	0.010	1.253	<0.001	1.502	0.004	1.404
-	130.0508	9.1	L-Glutamate 5-semialdehyde	<0.001	5.922	0.079	3.190	<0.001	6.235	0.012	4.984
+	132.0655	15.1	L-Glutamate 5-semialdehyde	<0.001	1.636	0.001	1.426	<0.001	1.543	0.002	1.421
+	156.0768	15.2	L-Histidine	<0.001	1.693	0.018	1.197	0.001	1.389	0.004	1.589
+	118.0863	11.8	L-Valine	<0.001	1.412	<0.001	1.598	<0.001	1.515	<0.001	1.313
-	599.3204	4.4	Lys-Lys-Tyr-Tyr	<0.001	0.407	<0.001	0.552	<0.001	0.691	<0.001	0.312
+	544.3398	4.8	LysoPC(20:4(5Z,8Z,11Z,14Z))	<0.001	0.531	<0.001	0.497	<0.001	0.607	<0.001	0.396
-	526.294	4.8	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	1.569	0.002	1.528	0.741	1.032	0.004	0.750
-	524.2781	4.8	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.491	0.005	1.393	1.000	1.000	0.002	0.725
+	526.293	4.8	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.464	0.015	1.373	0.665	0.964	0.001	0.685
-	525.2815	4.8	Lys-Trp-Pro-Pro	<0.001	1.513	0.008	1.348	0.528	0.950	0.004	0.631
+	877.563	4	Megalomicin A	<0.001	2.174	0.001	2.14	0.001	2.67	0.006	1.798
+	719.5787	4.3	menaquinol-8	<0.001	2.822	<0.001	2.966	<0.001	4.165	<0.001	2.592
-	129.0193	15.5	Itaconate	<0.001	9.639	<0.001	7.710	<0.001	14.461	<0.001	9.165
+	163.0536	13.1	Methomyl	<0.001	81.255	0.002	117.441	0.002	116.274	0.004	73.423
+	125.071	15.7	Methylimidazole acetaldehyde	<0.001	0.282	0.003	0.371	<0.001	0.293	<0.001	0.269
+	141.0658	10.8	Methylimidazoleacetic acid	<0.001	8.082	<0.001	4.778	<0.001	7.68	<0.001	6.566
-	110.9756	8.3	Monomethyl sulfate	<0.001	0.530	<0.001	0.542	<0.001	0.488	<0.001	0.433

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	289.1154	17.3	N-(L-Arginino)succinate	<0.001	7.523	<0.001	6.391	<0.001	24.174	<0.001	5.343
+	291.1299	17.3	N-(L-Arginino)succinate	<0.001	5.98	<0.001	5.087	<0.001	17.087	<0.001	3.903
+	246.17	8.6	N-(octanoyl)-L-homoserine	<0.001	7.64	<0.001	4.404	<0.001	5.401	<0.001	7.118
-	222.0983	13.9	N-acetyl -D- glucosaminitol	<0.001	1.638	<0.001	1.675	0.001	1.895	0.037	1.291
+	189.087	15.1	N-Acetylglutamine	<0.001	3.303	<0.001	2.867	<0.001	4.345	<0.001	2.842
-	382.1355	14.3	N-Acetyllactosamine	<0.001	26.687	<0.001	17.435	<0.001	22.795	<0.001	26.545
-	190.0543	5.1	N-Acetylmethionine	<0.001	10.791	<0.001	7.734	<0.001	11.385	<0.001	9.684
-	308.0987	13.8	N-Acetylneuraminate	<0.001	1.935	0.017	0.817	0.003	1.446	0.001	1.762
+	310.1132	13.8	N-Acetylneuraminate	<0.001	1.88	0.01	0.84	0.004	1.374	0.001	1.56
-	662.1015	14.6	NAD+	<0.001	3.073	<0.001	3.616	<0.001	4.644	<0.001	2.722
+	664.1166	14.6	NAD+	<0.001	3	<0.001	3.276	<0.001	4.282	<0.001	2.633
-	664.1172	13.7	NADH	<0.001	2.516	<0.001	2.636	0.001	3.255	0.017	2.367
-	742.0675	17.1	NADP+	<0.001	5.234	<0.001	5.219	<0.001	7.891	<0.001	4.365
+	744.0831	17.2	NADP+	<0.001	4.972	<0.001	5.159	<0.001	7.7	<0.001	4.685
-	744.0832	17.5	NADPH	<0.001	2.511	<0.001	2.831	<0.001	3.647	0.001	2.097
+	746.0988	17.5	NADPH	<0.001	2.382	<0.001	2.601	<0.001	3.312	0.001	2.034
-	175.036	17.2	N-Carbamoyl-L-aspartate	<0.001	162.490	<0.001	126.165	<0.001	177.213	<0.001	125.587
-	202.1085	11.6	O-Acetylcarnitine	<0.001	3.159	<0.001	3.030	<0.001	3.297	<0.001	3.258
+	204.1231	11.6	O-Acetylcarnitine	<0.001	2.336	<0.001	2.208	<0.001	2.519	<0.001	2.386
+	232.1544	9.3	O-Butanoylcarnitine	<0.001	7.595	<0.001	7.311	<0.001	9.148	<0.001	5.862
+	218.1388	10.3	O-Propanoylcarnitine	<0.001	4.045	<0.001	3.854	<0.001	3.61	<0.001	3.231
-	287.052	12.7	Orotidine	<0.001	15.012	<0.001	9.112	<0.001	12.134	<0.001	13.950
-	218.0669	14.2	O-Succinyl-L-homoserine	<0.001	25.637	<0.001	17.640	<0.001	31.209	<0.001	22.779
-	466.3076	3.9	Oxethazaine	<0.001	1.522	<0.001	1.470	0.001	1.870	0.010	1.396
+	718.5753	4.3	PC(14:0/P-18:0)	<0.001	2.326	<0.001	2.552	<0.001	3.483	<0.001	2.191
+	770.5708	4.2	PC(15:0/20:3(5Z,8Z,11Z))	<0.001	193.176	0.001	179.686	<0.001	226.917	<0.001	212.196
-	792.5555	4.1	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.335	<0.001	2.284	0.003	1.820	0.001	2.634
+	794.5704	4.2	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	6.678	<0.001	6.083	<0.001	6.114	<0.001	6.906

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	746.6064	4.3	PC(16:0/P-18:0)	<0.001	2.995	<0.001	3.439	<0.001	4.311	<0.001	2.962
+	812.6169	4.3	PC(16:1(9Z)/22:2(13Z,16Z))	<0.001	126.299	<0.001	121.633	<0.001	123.529	<0.001	128.714
+	770.6068	4.3	PC(18:1(11Z)/P-18:1(11Z))	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
+	784.5859	4.3	PC(18:2(9Z,12Z)/18:1(9Z))	<0.001	3.724	<0.001	3.396	<0.001	4.137	<0.001	3.497
+	768.5907	4.3	PC(18:2(9Z,12Z)/P-18:1(11Z))	<0.001	0.286	<0.001	0.241	<0.001	0.254	<0.001	0.288
+	738.5441	4.2	PC(18:4(6Z,9Z,12Z,15Z)/P-16:0)	<0.001	0.547	0.005	0.664	<0.001	0.416	<0.001	0.594
+	764.5597	4.2	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	<0.001	0.236	<0.001	0.31	<0.001	0.245	<0.001	0.189
+	796.6219	4.3	PC(20:2(11Z,14Z)/P-18:1(11Z))	<0.001	0.449	<0.001	0.373	<0.001	0.441	<0.001	0.456
+	792.5908	4.3	PC(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	<0.001	0.505	<0.001	0.468	<0.001	0.567	<0.001	0.579
+	824.6532	4.2	PC(22:2(13Z,16Z)/P-18:1(11Z))	<0.001	0.313	0.002	0.529	0.001	0.351	0.008	0.503
+	822.6376	4.2	PC(22:4(7Z,10Z,13Z,16Z)/P-18:0)	<0.001	0.636	<0.001	0.601	<0.001	0.617	<0.001	0.648
+	820.6221	4.2	PC(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	<0.001	0.756	<0.001	0.682	0.001	0.75	<0.001	0.77
-	211.0013	13.9	P-DPD	<0.001	442.095	<0.001	161.983	<0.001	346.795	<0.001	455.674
-	211.0014	13.0	P-DPD	<0.001	343.401	<0.001	96.594	<0.001	241.124	<0.001	389.661
-	722.5124	4.2	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	<0.001	0.815	0.002	0.886	0.006	0.822	0.002	0.824
-	720.497	4.2	PE(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	<0.001	2.478	<0.001	2.486	<0.001	2.717	<0.001	2.536
-	764.5252	4.2	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	6.615	<0.001	5.532	<0.001	7.041	<0.001	6.147
+	766.5392	4.2	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	13.702	0.001	8.938	<0.001	11.151	<0.001	10.149
+	780.5907	4.2	PE(22:4(7Z,10Z,13Z,16Z)/P-18:0)	<0.001	0.252	<0.001	0.456	<0.001	0.115	<0.001	0.414
-	772.5279	4.1	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	<0.001	1.593	<0.001	1.801	<0.001	1.696	0.001	1.580
+	774.5431	4.1	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	<0.001	1.882	<0.001	1.946	<0.001	2.186	<0.001	1.814
-	771.5174	3.8	PG(16:0/20:3(5Z,8Z,11Z))	<0.001	17.300	<0.001	12.698	<0.001	19.121	<0.001	15.024
-	793.5017	3.8	PG(16:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.956	<0.001	1.552	<0.001	1.765	0.001	1.796
-	791.4857	3.8	PG(16:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	5.870	<0.001	4.455	<0.001	5.527	<0.001	5.330
-	799.5497	3.8	PG(18:0/20:3(5Z,8Z,11Z))	<0.001	11.445	<0.001	9.382	<0.001	12.336	<0.001	10.230
-	825.565	3.8	PG(18:0/22:4(7Z,10Z,13Z,16Z))	<0.001	10.778	<0.001	9.682	<0.001	11.572	<0.001	9.707
-	823.5496	3.8	PG(18:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	1.873	0.001	1.432	0.001	1.497	0.001	1.771
-	819.5173	3.8	PG(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	2.787	<0.001	2.241	<0.001	2.535	<0.001	2.602

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	821.5329	3.8	PG(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.946	<0.001	3.184	0.001	3.484	<0.001	3.793
-	817.5016	3.8	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	0.572	<0.001	0.417	<0.001	0.434	<0.001	0.541
-	815.4863	3.8	PG(18:3(6Z,9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	0.277	<0.001	0.169	<0.001	0.227	<0.001	0.314
-	78.95865	15.6	Phosphite	<0.001	4.719	<0.001	2.963	<0.001	3.454	<0.001	4.361
-	210.0286	15.6	Phosphocreatine	<0.001	3.994	<0.001	2.367	<0.001	2.793	<0.001	3.619
+	212.0431	15.6	Phosphocreatine	<0.001	3.675	<0.001	2.204	<0.001	2.572	<0.001	3.343
-	166.975	18.0	Phosphoenolpyruvate	<0.001	20.696	<0.001	10.994	<0.001	17.289	<0.001	18.769
-	196.0128	16.8	Phosphoguanidinoacetate	<0.001	8.580	0.278	0.827	<0.001	3.035	<0.001	6.171
-	807.4998	4.0	PI(16:0/16:1(9Z))	<0.001	25.613	0.008	14.965	<0.001	36.758	<0.001	21.333
-	837.547	3.9	PI(16:0/18:0)	<0.001	2.293	<0.001	2.340	0.001	2.516	0.002	2.201
+	839.5634	3.8	PI(16:0/18:0)	<0.001	2.402	<0.001	2.2	<0.001	2.402	<0.001	2.351
-	833.5162	4.0	PI(16:0/18:2(9Z,12Z))	<0.001	26.965	<0.001	23.211	<0.001	33.509	<0.001	22.225
-	859.5324	4.0	PI(16:0/20:3(5Z,8Z,11Z))	<0.001	35.581	<0.001	36.358	<0.001	50.034	<0.001	30.967
+	861.5475	3.8	PI(16:0/20:3(5Z,8Z,11Z))	<0.001	0.225	<0.001	0.165	<0.001	0.128	<0.001	0.228
-	857.5169	4.0	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	2.168	0.004	2.090	<0.001	2.842	0.001	1.95
+	859.5331	3.9	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	0.231	<0.001	0.189	<0.001	0.234	<0.001	0.172
+	891.5951	3.8	PI(16:0/22:2(13Z,16Z))	<0.001	0.396	<0.001	0.334	<0.001	0.188	<0.001	0.427
+	889.579	3.8	PI(16:0/22:3(10Z,13Z,16Z))	<0.001	0.484	<0.001	0.413	<0.001	0.313	<0.001	0.512
-	883.5331	3.9	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	3.316	<0.001	3.197	<0.001	4.090	<0.001	2.939
+	885.548	3.8	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	0.762	<0.001	0.679	<0.001	0.581	0.002	0.784
-	911.5643	3.9	PI(18:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	1.930	<0.001	2.193	0.003	2.188	0.003	1.927
-	909.5489	3.9	PI(18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.094	<0.001	3.042	<0.001	3.627	<0.001	2.950
+	190.0904	15.1	Prenyl-L-cysteine	<0.001	3.67	<0.001	3.283	<0.001	4.966	0.001	3.213
-	288.1201	13.8	Pro-Ser-Ser	<0.001	6.927	0.080	1.398	<0.001	14.063	<0.001	6.111
+	290.1346	13.8	Pro-Ser-Ser	<0.001	6.46	0.34	1.234	<0.001	13.165	<0.001	5.321
-	732.4817	4.0	PS(14:0/18:1(9Z))	<0.001	17.292	<0.001	16.642	<0.001	29.363	<0.001	14.977
+	734.4969	4	PS(14:0/18:1(9Z))	<0.001	18.145	0.001	16.934	<0.001	30.232	<0.001	15.398
-	758.4966	4.0	PS(16:0/18:2(9Z,12Z))	<0.001	9.160	<0.001	8.692	<0.001	12.698	<0.001	8.006

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	760.513	4	PS(16:0/18:2(9Z,12Z))	<0.001	7.167	<0.001	7.051	<0.001	10.373	<0.001	6.062
+	820.6074	3.8	PS(18:0/20:0)	<0.001	10.081	<0.001	8.842	<0.001	12.122	<0.001	8.955
-	836.5435	3.9	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	<0.001	2.294	<0.001	2.363	0.002	2.557	0.002	2.218
+	838.5598	3.9	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	<0.001	2.431	<0.001	2.229	<0.001	2.434	<0.001	2.368
-	832.5127	3.9	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	14.232	<0.001	12.812	<0.001	19.718	<0.001	12.066
+	808.5131	4	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	17.862	<0.001	17.123	<0.001	26.088	<0.001	16.273
+	858.5289	3.8	PS(20:3(8Z,11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	0.215	<0.001	0.122	<0.001	0.147	<0.001	0.251
-	87.00854	8.3	Pyruvate	<0.001	2.220	0.002	1.444	<0.001	1.692	0.001	1.826
-	289.033	16.7	Sedoheptulose 7-phosphate	<0.001	208.887	<0.001	89.666	<0.001	137.848	<0.001	174.628
+	336.0872	15.1	S-Formylglutathione	<0.001	0.204	<0.001	0.099	<0.001	0.081	0.001	0.282
+	675.544	4.6	SM(d18:1/14:0)	<0.001	1.757	<0.001	1.608	<0.001	2.141	<0.001	1.695
+	675.5439	7.9	SM(d18:1/14:0)	<0.001	2.568	0.001	2.402	0.006	3.619	0.018	2.136
-	333.0593	16.6	sn-glycero-3-Phospho-1-inositol	<0.001	3.773	<0.001	3.305	<0.001	6.549	0.003	2.818
-	256.0957	15.1	sn-glycero-3-Phosphocholine	<0.001	0.299	<0.001	0.094	<0.001	0.148	<0.001	0.267
+	258.1101	15.1	sn-glycero-3-Phosphocholine	<0.001	0.529	<0.001	0.263	<0.001	0.357	<0.001	0.498
-	214.0487	16.3	sn-glycero-3-Phosphoethanolamine	<0.001	0.785	<0.001	0.369	<0.001	0.572	<0.001	0.684
+	216.0633	16.3	sn-glycero-3-Phosphoethanolamine	<0.001	0.777	<0.001	0.391	<0.001	0.582	<0.001	0.666
-	171.0064	15.2	sn-Glycerol 3-phosphate	<0.001	0.487	<0.001	0.344	<0.001	0.392	<0.001	0.525
+	144.102	14	Stachydrine	<0.001	1.795	<0.001	1.594	<0.001	1.829	0.001	1.556
+	428.3735	4.8	Stearoylcarnitine	<0.001	0.342	<0.001	0.342	<0.001	0.344	<0.001	0.408
-	124.0072	15.6	Taurine	<0.001	2.751	<0.001	2.664	<0.001	3.167	<0.001	2.525
+	126.022	15.6	Taurine	<0.001	2.781	<0.001	2.727	<0.001	3.154	<0.001	2.533
-	166.0291	16.3	Taurocyamine	<0.001	7.434	0.002	6.777	<0.001	9.027	0.006	5.149
+	168.0438	16.3	Taurocyamine	<0.001	6.62	<0.001	6.714	<0.001	7.849	<0.001	6.116
-	196.0284	9.2	Tauropine	<0.001	8.560	<0.001	6.006	<0.001	8.439	<0.001	8.123
-	329.2486	4.0	Taxa-4(20),11(12)-dien-5alpha-yl acetate	<0.001	0.101	<0.001	0.049	<0.001	0.045	<0.001	0.084
+	144.0518	15.6	Tet-glycine	<0.001	3.035	<0.001	2.964	<0.001	3.44	<0.001	2.798
-	304.115	15.2	Thr-Ala-Asp	<0.001	10.42	0.097	0.383	<0.001	22.711	0.001	9.161

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	402.9946	18.1	UDP	<0.001	27.054	<0.001	18.282	<0.001	24.383	<0.001	23.689
-	402.9947	16.9	UDP	<0.001	18.940	0.001	12.714	0.001	16.945	<0.001	18.839
-	565.0474	16.8	UDP-glucose	<0.001	6.063	<0.001	5.040	<0.001	5.660	<0.001	5.456
-	579.0267	19.5	UDP-glucuronate	<0.001	9.707	<0.001	7.383	<0.001	8.517	<0.001	8.762
-	606.0742	15.5	UDP-N-acetyl-D-glucosamine	<0.001	3.714	<0.001	2.959	<0.001	3.334	<0.001	3.321
-	323.0286	15.5	UMP	<0.001	11.090	0.003	7.654	0.001	8.732	0.001	8.342
-	243.0621	10.3	Uridine	<0.001	0.441	<0.001	0.601	<0.001	0.386	<0.001	0.382
-	482.9611	18.1	UTP	<0.001	9.761	<0.001	7.392	<0.001	9.051	<0.001	8.818
+	217.1547	5.1	Val-Val	<0.001	0.275	<0.001	0.209	<0.001	0.187	<0.001	0.262
-	281.0877	14.3	Xylobiose	<0.001	19.976	<0.001	12.823	<0.001	16.213	<0.001	18.677
-	186.1133	5.1	8-Amino-7-oxononanoate	1.000	1.000	0.572	0.829	0.317	2.041	0.782	1.136
+	234.0771	11.7	2-Hydroxy-6-oxo-(2'-aminophenyl)-hexa-2,4-dienoate	0.998	0.997	0.966	0.951	0.343	0.17	0.567	1.738
+	188.1646	5.1	[FA amino(10:0)] 10-amino-decanoic acid	0.997	0.999	0.955	1.013	0.188	1.71	0.421	1.3
-	239.1401	7.2	Slaframine	0.996	0.997	0.268	0.413	0.669	0.761	0.248	0.405
+	510.3556	4.9	LysoPC(17:0)	0.995	1	0.241	1.089	0.002	1.424	0.05	0.831
-	299.259	4.1	[FA hydroxy(18:0)] 2S-hydroxy-octadecanoic acid	0.986	0.998	0.236	1.304	0.543	0.902	0.132	0.757
+	174.1489	8.1	[FA amino(9:0)] 9-amino-nonanoic acid	0.984	1.007	0.198	0.592	0.451	0.776	0.634	0.778
-	88.98783	18.3	Oxalate	0.982	1.007	0.558	1.213	0.824	1.072	0.892	0.964
+	84.08083	26.3	Piperideine	0.982	0.992	0.39	0.777	0.623	0.873	0.605	0.879
-	267.16	4.3	dihydroartemisinic acid hydroperoxide	0.979	0.978	0.163	0.101	0.178	2.268	0.154	0.074
-	175.0473	5.1	Allantoate	0.978	1.006	0.838	0.969	0.489	1.098	0.704	0.923
-	117.0556	7.9	5-Hydroxypentanoate	0.965	1.011	0.262	1.390	0.192	1.342	0.636	1.128
+	368.316	4.4	[FA dimethyl,amino,trihydrox] 1-dimethylamino-9S,11R,15S-trihydroxy-5Z,13E-prostadiene	0.963	1.027	0.466	2.177	0.291	4.024	0.178	4.262
-	410.2394	4.9	Ala-Lys-Pro-Pro	0.957	0.994	0.084	1.143	<0.001	1.532	0.032	0.803
+	139.0502	7.9	Urocanate	0.956	1.017	0.194	1.826	0.413	1.532	0.311	1.642
+	388.2541	5.1	Leu-Lys-Gln	0.955	0.999	0.459	0.984	0.806	0.994	0.398	0.894
-	255.233	4.1	Hexadecanoic acid	0.953	1.005	0.353	0.902	0.261	0.905	0.026	0.786

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	141.0669	13.5	Methylimidazoleacetic acid	0.953	1.015	0.94	1.022	0.047	1.486	0.035	1.713
-	241.2173	4.1	[FA methyl(14:0)] 12-methyl-tetradecanoic acid	0.948	0.993	0.492	0.940	0.717	1.038	0.351	0.909
-	118.0509	15.2	L-Threonine	0.945	1.006	0.309	0.904	0.965	1.004	0.724	0.963
-	341.2696	4.0	[FA (20:0/2:0)] Eicosanedioic acid	0.944	0.978	0.712	0.884	0.157	0.692	0.042	0.533
-	178.051	5.1	Hippurate	0.944	0.986	0.575	0.891	0.770	0.944	0.489	0.857
+	145.0972	14.6	L-isoglutamine	0.937	1.062	0.536	0.647	0.489	0.604	0.51	0.622
-	137.0243	7.4	4-Hydroxybenzoate	0.931	1.066	0.929	0.938	0.566	1.473	0.937	0.943
+	106.0863	20.3	Diethanolamine	0.93	1.027	0.428	2.331	0.3	1.281	0.989	0.997
-	152.9959	13.6	Propanoyl phosphate	0.930	0.921	0.355	0.261	0.508	0.472	0.618	0.604
+	146.1652	12.1	Spermidine	0.928	1.126	0.938	1.111	0.973	1.043	0.327	0.074
-	122.9935	10.5	6-S-acetyl-dihydrolipoate	0.927	0.980	0.834	0.951	0.244	2.529	0.517	1.126
-	297.2434	4.1	2-Oxooctadecanoic acid	0.923	0.991	0.409	1.079	0.665	0.957	0.493	0.919
+	102.0914	11.6	Betaine aldehyde	0.923	1.078	0.662	0.685	0.953	1.049	0.518	1.528
-	145.0983	26.3	L-Lysine	0.910	1.017	0.408	0.888	0.940	0.991	0.502	0.911
-	131.0349	7.9	2-Acetolactate	0.905	0.978	0.373	2.482	0.270	1.634	0.417	1.298
+	399.081	14.1	Ala-Cys-Cys-Cys	0.905	0.939	0.703	0.819	0.579	0.733	0.711	0.812
+	200.1646	4.8	2-Hexenoylcholine	0.904	1.051	0.245	0.646	0.537	1.427	0.212	1.711
-	159.0298	15.5	2-Oxoadipate	0.901	1.028	0.430	1.238	0.200	3.953	0.209	0.731
-	218.1034	6.0	Pantothenate	0.898	1.038	0.403	0.770	0.726	0.907	0.110	0.611
-	260.1291	7.9	Zinnimidine	0.892	1.012	0.335	0.906	0.319	0.893	0.856	1.023
-	788.5438	6.0	PS(18:0/18:1(9Z))	0.891	1.057	0.412	3.435	0.158	1.897	0.545	1.230
+	260.1969	21.8	Leu-Lys	0.889	1.049	0.93	0.967	0.313	1.477	0.553	0.795
+	254.0924	28	aeruginosin A	0.888	0.917	0.765	0.833	0.473	0.61	0.559	0.674
+	143.0816	15.2	Ectoine	0.887	0.954	0.245	1.326	0.329	1.336	0.281	1.37
-	327.2904	4.0	L-2-Hydroxyphytanate	0.883	1.042	0.526	1.166	0.032	1.722	0.845	1.047
+	552.4027	4.7	[PC (20:0)] 1-eicosanoyl-sn-glycero-3-phosphocholine	0.881	0.977	0.655	1.063	0.837	0.954	0.091	0.733
-	311.0992	4.2	Vicianose	0.879	1.042	0.391	0.807	0.379	0.787	0.199	0.711
-	411.3481	3.9	MG(0:0/22:1(13Z)/0:0)	0.878	0.926	0.333	1.442	0.218	2.919	0.526	0.718

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	165.0408	4.1	L-Arabinonate	0.874	0.951	0.303	1.368	0.456	1.308	0.277	1.700
+	136.0757	13.7	2-Phenylacetamide	0.868	0.971	0.875	0.976	0.797	0.963	0.058	0.624
+	198.0874	6.2	N-Acetyl-L-histidine	0.868	1.054	0.423	0.752	0.742	0.898	0.284	0.645
-	178.051	6.7	Hippurate	0.867	0.871	0.773	0.785	0.184	0.301	0.189	0.309
-	283.2642	4.0	Octadecanoic acid	0.866	0.980	0.555	0.907	0.231	0.855	0.050	0.740
+	182.0813	13.7	L-Tyrosine	0.86	1.019	0.523	1.06	0.52	1.055	0.122	0.815
-	233.191	4.5	[FA (16:3)] 4,6,11-hexadecatrienal	0.859	1.108	0.484	0.718	0.409	1.540	0.417	1.758
-	118.9984	17.7	2-Hydroxymalonate	0.858	0.908	0.982	0.986	0.873	0.923	0.845	0.906
+	165.0547	13.7	Phenylpyruvate	0.858	0.973	0.537	1.07	0.589	1.054	0.074	0.69
+	174.0873	15.2	5-Guanidino-2-oxopentanoate	0.855	1.088	0.713	1.194	0.791	1.135	0.17	0.514
-	219.0455	14.5	AMCC	0.852	0.957	0.060	0.572	0.118	0.663	0.672	0.912
-	104.0352	16.5	L-Serine	0.852	1.014	0.099	0.866	0.452	0.944	0.266	0.917
-	169.087	7.8	Furfural diethyl acetal	0.847	0.949	0.617	1.151	0.258	1.384	0.944	1.022
-	173.1182	4.8	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.844	1.041	0.711	1.062	0.329	1.184	0.629	1.094
+	118.0863	13.2	L-Valine	0.842	1.02	0.792	0.971	0.809	1.023	0.802	0.972
+	818.6063	4.2	[PC (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	0.83	1.01	0.007	0.857	0.716	1.021	0.877	0.991
+	202.1803	5	[FA amino(11:0)] 11-amino-undecanoic acid	0.828	0.972	0.515	1.452	0.485	1.559	0.749	0.926
-	152.0483	13.3	N-Dimethyl-2-aminoethylphosphonate	0.823	1.082	0.427	0.752	0.754	0.891	0.995	1.002
+	114.0914	7.9	epsilon-Caprolactam	0.813	1.154	0.361	0.468	0.895	1.086	0.157	0.21
-	159.1026	7.9	Ethyl (R)-3-hydroxyhexanoate	0.811	1.028	0.835	0.973	0.758	1.034	0.945	1.009
+	504.3203	3.9	Ile-Leu-Lys-Met	0.803	1.1	0.861	1.077	0.825	1.163	0.952	0.974
-	145.0506	7.9	Adipate	0.802	1.264	0.869	1.185	0.555	0.496	0.700	0.663
-	116.9285	21.9	chromate	0.796	1.034	0.845	1.028	0.641	0.907	0.877	1.025
-	179.0561	14.1	D-Glucose	0.796	1.026	0.446	1.086	0.768	1.031	0.565	0.941
-	95.98569	13.6	Phosphoramidate	0.792	1.049	0.598	1.093	0.512	1.114	0.442	1.168
+	230.2479	7.9	[SP (14:0)] 1-deoxy-tetradecasphinganine	0.791	1.018	0.656	0.971	0.557	0.951	0.71	1.032
-	219.0665	26.3	2,6-Dioxo-6-phenylhexanoate	0.788	0.871	0.366	0.646	0.518	0.728	0.629	0.787

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	161.0921	15.2	D-Alanyl-D-alanine	0.777	1.024	0.396	0.916	0.6	1.048	0.248	0.886
-	147.045	15.1	trans-Cinnamate	0.777	1.530	0.975	1.046	0.762	1.580	0.934	1.127
-	103.0036	16.3	Malonate	0.776	0.917	0.817	0.929	0.906	1.043	0.676	0.870
+	231.1704	7.9	Leu-Val	0.774	1.072	0.85	1.045	0.674	1.137	0.825	0.941
+	256.1656	7.9	L-Pyrrolysine	0.771	1.039	0.486	1.079	0.179	1.21	0.663	1.057
-	215.1288	5.1	[FA (11:0/2:0)] Undecanedioic acid	0.767	0.940	0.666	0.910	0.258	0.808	0.764	0.922
+	705.5805	4.5	[ST (20:4)] cholest-5-en-3beta-yl (15S-hydroperoxy-5Z,8Z,12E,14Z-eicosatetraenoate)	0.757	1.051	0.059	1.381	<0.001	1.807	0.253	1.214
-	217.0484	14.5	hexitol chloride adduct	0.751	0.929	0.067	0.615	0.145	0.709	0.653	0.917
-	150.9883	18.3	Oxidized dithiothreitol	0.751	0.862	0.895	0.951	0.824	0.906	0.863	0.928
-	245.0778	10.6	5-6-Dihydrouridine	0.748	1.080	0.852	1.041	0.461	1.174	0.379	0.820
+	188.128	5.1	8-Amino-7-oxononanoate	0.748	0.921	0.396	0.863	0.34	1.393	0.846	0.959
+	133.0859	7.9	6-Hydroxyhexanoic acid	0.746	0.974	0.362	0.854	0.832	0.962	0.079	0.884
-	777.5633	4.1	[PG (18:0/18:0)] 1,2-dioctadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.745	0.951	<0.001	1.590	0.038	1.348	0.030	1.267
+	229.1799	4.4	[FA oxo(13:0)] 2-oxo-tridecanoic acid	0.734	1.176	0.292	0.738	0.342	4.613	0.606	0.882
-	154.0873	7.6	Retronecine	0.728	0.947	0.631	1.056	0.935	1.007	0.852	0.969
+	147.1128	26.3	L-Lysine	0.722	1.055	0.537	0.916	0.791	1.031	0.677	0.949
-	273.0762	9.9	[Fv] Phloretin	0.721	0.917	0.337	0.859	0.695	1.050	0.326	0.878
+	134.0447	15.5	L-Aspartate	0.721	0.963	0.446	1.082	0.001	1.652	0.052	0.763
+	100.0757	7.9	N-Methyl-2-pyrrolidinone	0.718	1.172	0.177	1.616	0.423	1.353	0.529	1.288
+	104.0706	16.1	4-Aminobutanoate	0.709	0.923	0.675	1.088	0.138	1.304	0.851	0.966
-	814.5585	3.9	1-20:0-2-18:2-phosphatidylserine	0.708	1.121	0.003	2.275	0.053	1.850	0.557	1.286
-	96.96962	16.4	Orthophosphate	0.707	1.033	0.330	0.872	0.274	1.118	0.717	0.958
-	183.139	4.4	[FA (11:0)] 10-undecenoic acid	0.705	0.847	0.354	0.642	0.187	0.472	0.136	0.401
-	115.0763	7.9	Hexanoic acid	0.705	1.166	0.162	0.571	0.616	0.840	0.865	0.948
+	329.174	13.1	Crocetin	0.704	1.027	0.307	1.088	0.239	1.139	0.812	0.982
+	245.186	7.8	Leucyl-leucine	0.703	1.103	0.924	0.974	0.734	1.106	0.719	0.894
+	189.1598	5.1	N6,N6,N6-Trimethyl-L-lysine	0.703	0.937	0.013	0.701	0.006	0.625	0.446	2.445

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	339.123	10.5	6-Prenylnaringenin	0.702	1.054	0.716	0.960	0.519	1.070	0.909	0.988
-	211.1704	4.3	[FA methyl(12:0)] 2-methyl-2-dodecenoic acid	0.699	0.833	0.550	0.745	0.170	0.412	0.174	0.412
-	241.0722	4.0	Lumichrome	0.699	1.154	0.942	0.966	0.702	1.269	0.222	0.597
-	448.3068	4.8	Glycodeoxycholate	0.690	1.042	0.164	0.859	0.989	1.001	0.705	0.961
-	369.301	4.0	2-monooleoylglycerol	0.688	0.763	0.337	0.570	0.607	1.474	0.408	0.615
+	176.0707	4.6	Indole-3-acetate	0.683	1.092	0.769	1.121	0.337	1.428	0.292	0.818
-	181.0718	14.5	D-Sorbitol	0.682	1.043	0.034	0.792	0.353	0.923	0.663	0.962
-	168.0666	8.5	Pyridoxine	0.681	1.050	0.463	0.911	0.505	1.078	0.896	0.983
-	151.0611	13.5	Xylitol	0.681	0.772	0.620	0.725	0.674	0.770	0.351	0.481
-	311.2956	4.0	[FA (20:0)] eicosanoic acid	0.677	0.955	0.434	0.880	0.402	0.908	0.059	0.741
-	227.2017	4.1	Tetradecanoic acid	0.677	0.952	0.203	0.898	0.538	0.948	0.101	0.846
-	96.96967	13.6	Orthophosphate	0.676	1.055	0.536	0.909	0.866	1.024	0.261	1.166
+	311.1641	4.5	[Fv] Dihydrocordoin	0.672	1.453	0.392	1.644	0.365	1.796	0.657	1.518
-	116.9284	14.8	chromate	0.672	0.916	0.105	0.676	0.003	0.445	0.453	1.810
-	99.08139	4.5	[FA (6:0)] 3Z-hexenol	0.671	0.828	0.426	0.744	0.736	1.183	0.401	0.715
-	274.1045	15.7	Gamma-Glutamylglutamine	0.670	0.949	0.479	0.906	0.842	1.031	0.188	0.764
-	295.2276	4.1	[FA hydroxy(18:2)] 9S-hydroxy-10E,12Z-octadecadienoic acid	0.669	1.197	0.763	1.172	0.808	0.889	0.450	1.444
+	566.4543	4.7	[PC (10:2/12:2)] 1-decyl-2-dodecyl-sn-glycero-3-phosphocholine	0.666	0.956	0.031	0.72	0.096	0.765	0.074	0.706
-	145.0869	4.9	[FA hydroxy(7:0)] 2-hydroxy-heptanoic acid	0.661	1.097	0.436	1.123	0.197	1.977	0.809	1.052
-	179.0561	17.8	D-Glucose	0.656	1.087	0.748	0.961	0.720	1.048	0.389	1.099
-	116.9284	7.3	chromate	0.652	0.719	0.084	0.078	0.457	0.578	0.147	0.244
+	157.0972	12.1	N-acetyl prolinamide or isomer	0.651	1.153	0.571	1.174	0.543	1.209	0.275	0.748
+	79.02125	8	Mercaptoethanol	0.65	0.543	<0.001	14.531	<0.001	24.286	<0.001	19.097
-	182.075	14.5	Chlorphentermine	0.644	1.047	0.028	0.785	0.522	0.948	0.669	0.961
+	203.1504	23.2	NG,NG-Dimethyl-L-arginine	0.644	1.094	0.913	1.019	0.322	1.169	0.699	1.056
-	297.2435	7.1	2-Oxooctadecanoic acid	0.642	0.873	0.404	0.850	0.173	5.905	0.381	6.490
-	164.012	13.6	L-2-amino-4-oxo-5-chloropentanoate	0.641	1.175	0.321	0.642	0.379	1.267	0.090	1.803

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	151.04	7.9	[PK] 6-Methylsalicylic acid	0.639	0.841	0.674	1.183	0.394	2.373	0.376	0.727
+	335.1059	4.5	Penicillin G	0.639	1.058	0.312	0.879	0.894	1.015	0.556	0.931
-	117.0193	13.6	Succinate	0.636	0.617	0.336	0.244	0.399	0.342	0.465	0.438
-	163.0764	4.6	Eugenol	0.631	0.852	0.917	1.032	0.936	0.968	0.321	1.302
+	130.0863	5.1	L-Pipecolate	0.631	0.863	0.325	0.722	0.908	1.033	0.479	0.801
-	157.0869	5.0	[FA oxo(8:0)] 3-oxo-octanoic acid	0.629	0.845	0.059	0.470	0.970	0.987	0.116	0.585
-	874.6725	7.2	PC(o-22:3(10Z,13Z,16Z)/22:3(10Z,13Z,16Z))	0.629	1.194	0.296	7.393	0.146	10.764	0.985	1.007
-	143.0349	14.1	2,3-Dimethylmaleate	0.628	1.083	0.310	1.163	0.761	1.050	0.539	1.088
-	157.0505	7.9	2-Isopropylmaleate	0.626	0.891	0.722	1.094	0.659	1.110	0.568	1.174
+	371.2276	7.9	Ala-Leu-Ala-Pro	0.619	0.833	0.291	2.858	0.051	8.783	0.381	3.545
-	201.1132	4.5	[FA (10:0/2:0)] Decanedioic acid	0.617	0.736	0.177	0.386	0.070	1.888	0.183	0.402
+	216.1959	5	[FA amino(12:0)] 12-amino-dodecanoic acid	0.617	1.254	0.919	1.038	0.276	2.096	0.775	1.121
+	104.0706	5.2	4-Aminobutanoate	0.616	1.165	0.891	0.949	0.46	0.758	0.522	1.184
-	115.0763	5.0	Hexanoic acid	0.612	1.043	0.648	1.045	0.219	0.867	0.527	0.894
+	152.107	7.9	N-Methyltyramine	0.601	0.932	0.755	1.052	0.898	1.021	0.303	0.861
-	309.1704	4.2	Botrydial	0.597	1.127	0.609	1.106	0.209	1.286	0.188	1.296
+	242.1751	4.8	Valeroidine	0.597	1.322	0.896	1.074	0.361	2.407	0.581	1.282
-	241.1446	5.0	2-isocapryloyl-3R-hydroxymethyl-γ-butyrolactone	0.595	0.859	0.695	0.924	0.158	1.448	0.911	1.021
-	239.2018	4.1	[FA dimethyl(13:0)] 2,5-dimethyl-2E-tridecenoic acid	0.593	0.788	0.535	0.764	0.899	0.961	0.391	0.671
+	206.1388	7.9	Pantothenol	0.593	0.955	0.593	1.064	0.798	1.03	0.356	0.897
+	252.0292	18.2	Uracil mustard	0.591	0.766	0.759	0.891	0.868	1.144	0.362	0.651
+	106.0499	16.5	L-Serine	0.59	1.073	0.802	0.964	0.911	0.985	0.446	0.89
-	165.0193	14.4	Phthalate	0.588	1.542	0.336	2.465	0.202	2.448	0.517	1.762
-	341.1957	3.9	[FA trihydroxy(2:0)] 9S,11,15S-trihydroxy-2,3-dinor-thromboxa-5Z,13E-dien-1-oic acid	0.581	1.331	0.603	0.780	0.906	1.045	0.327	0.648
+	494.3606	4.7	[PC (17:1)] 1-(1Z-heptadecenyl)-sn-glycero-3-phosphocholine	0.579	1.175	0.725	1.117	0.388	1.305	0.292	1.449
-	309.108	5.1	Glu-Tyr	0.573	0.860	0.604	0.891	0.250	0.747	0.211	0.730
+	546.3555	4.8	LysoPC(20:3(5Z,8Z,11Z))	0.571	0.934	0.258	0.876	0.169	1.226	0.006	0.743

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	146.1652	16	Spermidine	0.569	0.569	0.709	0.707	0.436	0.47	0.699	0.72
-	171.0121	5.0	Toluene-4-sulfonate	0.567	0.732	0.265	0.509	0.281	0.526	0.242	0.480
-	116.9828	20.1	Oxomalonate	0.565	1.507	0.510	1.607	0.987	1.013	0.609	1.444
-	180.0666	13.7	L-Tyrosine	0.558	0.916	0.928	0.987	0.606	0.930	0.073	0.715
-	155.1077	4.5	[FA hydroxy(9:1)] 4-hydroxy-2-nonenal	0.556	1.066	0.741	0.944	0.800	0.964	0.955	0.993
-	133.0327	15.4	S,S-Dimethyl-beta-propiothetin	0.556	0.779	0.608	0.798	0.716	0.836	0.109	0.446
-	271.0815	28.0	Arbutin	0.555	1.318	0.795	1.134	0.290	1.505	0.197	1.567
+	152.0706	8.5	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.554	1.088	0.537	0.917	0.554	1.075	0.779	0.959
-	241.1445	7.9	2-isocapryloyl-3R-hydroxymethyl-γ-butyrolactone	0.554	1.278	0.465	1.255	0.357	1.375	0.867	0.944
-	161.0091	19.2	4-Hydroxy-2-oxoglutarate	0.553	0.679	0.792	0.859	0.559	0.702	0.868	0.913
-	213.1497	4.5	3-Oxododecanoic acid	0.552	1.632	0.752	0.921	0.350	0.748	0.402	0.786
-	79.95698	18.4	HSO3-	0.550	0.926	0.448	0.926	0.377	1.060	0.100	0.724
-	243.1713	7.8	Leucyl-leucine	0.548	1.301	0.812	1.110	0.663	1.230	0.816	1.107
-	312.1722	3.9	4-Oxo-13-cis-retinoate	0.547	1.211	0.387	0.774	0.819	1.056	0.234	0.681
+	188.128	7.9	8-Amino-7-oxononanoate	0.544	1.161	0.841	1.05	0.287	1.399	0.991	1.002
-	498.2895	4.5	[ST hydrox] N-(3alpha,7alpha-dihydroxy-5beta-cholan-24-oyl)-taurine	0.536	0.949	0.061	0.808	0.265	0.861	0.141	0.853
-	76.96954	6.9	monothiocarbonate	0.535	0.589	0.261	0.333	0.280	0.360	0.647	0.690
+	354.1283	4.5	Asp-Gly-Tyr	0.532	1.079	0.273	0.862	0.943	1.008	0.657	0.945
-	149.0454	15.4	D-Ribose	0.527	0.877	0.240	0.765	0.251	0.726	0.104	0.633
-	215.1288	4.4	[FA (11:0/2:0)] Undecanedioic acid	0.526	0.815	0.142	1.401	0.344	1.568	0.562	0.838
+	291.1954	4.4	[FA hydroxy(18:1/2:0)] 8-hydroxy-13Z-octadecene-9,11-diynoic acid	0.519	2.151	0.281	2.404	0.305	2.403	0.447	2.494
-	178.051	7.9	Hippurate	0.515	1.104	0.935	1.013	0.249	1.186	0.875	1.026
+	312.1675	4.5	Val-Gly-His	0.515	2.183	0.433	2.219	0.573	1.459	0.388	4.66
-	269.2486	4.0	[FA (17:0)] heptadecanoic acid	0.514	0.898	0.616	0.938	0.356	0.894	0.105	0.780
+	161.0921	7.9	D-Alanyl-D-alanine	0.513	1.062	0.201	0.893	0.268	0.841	0.94	1.009
+	272.222	4.5	Tridecanoylglycine	0.509	1.598	0.115	0.508	0.255	3.135	0.117	0.525
+	235.0925	16.2	Glu-Ser	0.507	1.114	0.29	0.905	0.922	1.012	0.307	1.121

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	145.0506	13.6	Adipate	0.505	0.732	0.720	0.870	0.335	1.443	0.358	2.998
-	112.9991	13.6	parabanate	0.504	1.165	0.074	0.502	0.687	0.890	0.420	1.192
+	482.3606	5	[PC (16:2)] 1-hexadecyl-sn-glycero-3-phosphocholine	0.501	1.039	0.603	1.034	0.001	1.484	0.116	0.877
-	165.0407	4.8	L-Arabinonate	0.501	0.883	0.266	0.788	0.756	1.068	0.474	0.816
+	189.1598	23.6	N6,N6,N6-Trimethyl-L-lysine	0.501	0.817	0.283	0.754	0.609	0.897	0.363	0.808
-	175.0248	18.7	Ascorbate	0.500	0.399	0.724	1.413	0.923	1.117	0.885	1.170
-	178.051	13.6	Hippurate	0.497	0.518	0.455	3.623	0.474	0.501	0.460	0.475
+	298.3468	8	Tetrapentylammonium	0.497	2.228	0.351	7.465	0.362	3.79	0.522	1.554
+	372.3109	5	Tetradecanoylcarnitine	0.492	1.048	0.004	0.612	0.004	0.781	0.207	1.159
+	354.3366	4.3	[FA (20:0)] N-(11Z-eicosaenoyl)-ethanolamine	0.491	1.377	0.371	1.757	0.391	1.989	0.188	2.243
-	422.2301	3.9	LysoPE(0:0/14:1(9Z))	0.490	0.829	0.304	1.467	0.467	1.514	0.609	1.429
+	122.0812	14.9	Tromethamine	0.488	1.27	0.919	0.96	0.863	0.935	0.463	1.281
-	144.0302	10.8	2-Oxoglutaramate	0.485	1.087	0.914	1.013	0.109	1.197	0.489	0.917
-	199.9702	13.5	S-Sulfo-L-cysteine	0.484	1.379	0.814	1.153	0.634	1.247	0.260	1.572
+	116.107	13.1	Trimethylaminoacetone	0.484	0.828	0.189	5.033	0.416	0.873	0.338	1.259
-	129.092	4.8	[FA (7:0)] heptanoic acid	0.483	0.889	0.484	0.910	0.677	0.948	0.914	1.015
-	204.1241	7.9	Pantothenol	0.479	1.380	0.591	0.899	0.977	1.006	0.225	1.523
+	146.0812	8.1	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.475	0.473	0.321	0.266	0.361	0.33	0.347	0.308
+	370.3316	4.4	[SP amino,tetramethyl(4:0/18:0/3:0)] 2S-amino-5,9,13,17-tetramethyl-8E,16-octadecadiene-1,3R,14-triol	0.475	1.406	0.457	2.239	0.316	3.305	0.142	4.063
-	131.0712	7.9	6-Hydroxyhexanoic acid	0.467	1.569	0.101	0.642	0.258	0.773	0.600	1.181
+	208.0605	4.2	4-(2-Aminophenyl)-2,4-dioxobutanoate	0.466	0.817	0.452	0.841	0.986	0.996	0.117	0.645
+	225.1962	4.9	Anapheline	0.466	2.182	0.037	0.628	0.537	0.885	0.011	0.643
+	731.6065	7.7	SM(d18:0/18:1(9Z))	0.465	1.246	0.045	3.097	0.05	3.571	0.336	1.877
-	397.3323	3.9	[FA (24:0/2:0)] Tetracosanedioic acid	0.464	0.715	0.486	0.756	0.520	1.595	0.294	0.609
-	146.0652	15.7	5-methylthiopentanaldoxime	0.463	1.072	0.361	0.914	0.307	1.086	0.603	0.949
+	129.0658	7.9	5,6-Dihydrothymine	0.46	0.879	0.751	1.064	0.8	1.04	0.848	0.969
+	342.17	11.9	5,8,13,13a-Tetrahydrocolumbamine	0.456	0.658	0.282	0.511	0.327	0.56	0.912	1.096

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	188.0564	14.5	N-Acetyl-L-glutamate	0.456	1.259	0.615	1.364	0.253	1.659	0.950	0.983
+	146.1652	28	Spermidine	0.456	2.886	0.928	0.904	0.672	0.618	0.944	1.086
+	190.1074	10.5	(2S)-2-{[1-(R)-Carboxyethyl]amino}pentanoate	0.455	0.747	0.785	1.074	0.802	1.07	0.327	0.667
-	243.1601	7.9	[FA (13:0/2:0)] Tridecanedioic acid	0.454	0.898	0.910	1.028	0.899	0.979	0.837	0.962
-	159.0662	7.9	[FA (7:0/2:0)] Heptanedioic acid	0.453	1.444	0.703	1.129	0.012	4.318	0.081	2.739
-	160.0251	16.1	N-Formyl-L-aspartate	0.453	2.720	0.456	2.163	0.818	1.190	0.993	1.008
+	133.0971	24.7	L-Ornithine	0.45	1.143	0.777	1.045	0.443	1.11	0.474	1.094
+	716.5593	4.3	PC(14:0/P-18:1(11Z))	0.45	1.383	0.009	2.614	0.01	3.067	0.231	1.585
+	177.1122	5.1	[FA hydroxy(8:0)] 6,8-dihydroxy-octanoic acid	0.449	0.907	0.003	0.628	0.217	0.865	0.009	0.708
+	353.136	4.5	cotinine-glucuronide	0.449	1.088	0.41	0.9	0.734	1.039	0.778	0.966
+	101.071	8.5	Gyromitrin	0.447	0.862	0.788	1.044	0.481	0.867	0.339	1.973
-	272.1867	4.6	Heptanoylcarnitine	0.447	1.847	0.817	1.133	0.168	5.839	0.342	1.942
+	133.0971	13.4	L-Ornithine	0.446	0.767	0.913	0.968	0.797	1.077	0.779	0.924
+	538.423	4.8	[PC (10:2/10:2)] 1-decyl-2-decyl-sn-glycero-3-phosphocholine	0.444	1.086	0.476	0.895	0.428	1.1	0.179	0.88
-	353.0489	5.0	Phenolsulfonphthalein	0.443	1.099	0.757	0.964	0.419	1.093	0.826	1.026
+	244.1908	4.8	N-Undecanoylglycine	0.44	1.537	0.34	0.794	0.233	2.529	0.799	0.927
+	245.1748	4.5	[FA (13:0/2:0)] Tridecanedioic acid	0.439	1.636	0.007	0.413	0.302	5.117	0.072	0.596
+	181.1336	7.9	Rilmenidine	0.437	0.883	0.814	0.957	0.541	1.159	0.311	0.86
-	167.021	12.9	Urate	0.436	0.911	0.210	0.863	0.436	0.924	0.191	0.863
+	712.0685	13.5	Adenophostin B	0.434	1.524	0.328	1.532	0.118	1.872	0.193	2.004
+	139.0502	5.2	Urocanate	0.434	1.546	0.815	0.862	0.565	1.412	0.461	1.481
-	131.0826	28.0	L-Ornithine	0.433	1.101	0.955	0.994	0.199	1.129	0.927	0.990
-	246.9943	27.9	4-(2,4-Dichlorophenoxy)butyric acid	0.432	0.441	0.407	0.408	0.420	0.424	0.517	0.543
+	408.3109	4.2	Cassaidine	0.432	0.956	0.395	0.938	0.563	1.048	0.308	0.918
-	116.0716	13.2	L-Valine	0.432	1.069	0.567	0.950	0.478	1.064	0.580	0.942
-	322.0415	13.4	Pirinixic acid	0.431	0.559	0.287	0.397	0.225	0.301	0.327	0.434
-	309.108	8.6	Glu-Tyr	0.427	1.181	0.895	1.025	0.230	1.244	0.258	1.191

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	422.2301	7.3	LysoPE(0:0/14:1(9Z))	0.427	0.760	0.049	0.383	0.998	0.999	0.486	0.784
+	432.2804	5.1	Ala-Leu-Lys-Thr	0.424	0.983	0.515	0.987	0.29	0.853	0.354	0.869
-	113.0356	16.0	5,6-Dihydrouracil	0.423	1.066	0.656	0.960	0.906	1.009	0.655	1.043
+	882.6032	4.1	PC(22:4(7Z,10Z,13Z,16Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.422	1.35	0.023	1.98	0.628	1.204	0.148	2.152
-	267.233	7.2	omega-Cyclohexylundecanoic acid	0.421	0.334	0.723	1.549	0.614	1.594	0.882	1.183
-	164.0717	10.8	L-Phenylalanine	0.420	1.100	0.741	0.961	0.257	1.127	0.756	0.962
+	216.1595	5	N-Nonanoylglycine	0.417	1.618	0.763	0.907	0.188	3.097	0.721	1.15
-	248.9793	13.5	Oxidized Photinus luciferin	0.417	1.360	0.887	0.937	0.650	1.178	0.131	1.933
+	510.3923	4.9	LysoPC(O-18:0)	0.416	1.05	0.673	1.027	0.003	1.407	0.134	0.893
-	179.0561	15.0	D-Glucose	0.414	0.931	0.161	0.868	0.267	0.868	0.182	0.869
+	175.119	28	L-Arginine	0.413	1.11	0.961	1.006	0.138	1.156	0.848	1.019
+	146.1652	26.2	Spermidine	0.412	0.253	0.44	0.296	0.41	0.25	0.391	0.225
+	161.1074	10.8	Tryptamine	0.41	1.205	0.616	0.879	0.071	1.403	0.296	1.258
-	331.0462	15.2	2'-Deoxyinosine 5'-phosphate	0.408	1.690	0.290	1.694	0.706	1.281	0.585	1.363
+	180.0655	7.9	Hippurate	0.407	2.9	0.689	0.823	0.745	0.86	0.498	0.708
-	102.0196	13.6	2-Aminomalonate semialdehyde	0.406	1.295	0.610	0.848	0.357	3.266	0.553	1.216
-	175.0441	15.0	2-oxo-6-methylthiohexanoate	0.406	0.957	0.001	0.745	0.002	0.744	0.125	0.883
-	201.0194	15.8	Bergaptol	0.404	0.587	0.260	0.437	0.237	0.426	0.249	0.446
-	117.0193	15.4	Succinate	0.404	1.572	0.751	1.201	0.153	2.023	0.977	1.018
-	182.9975	13.6	hydroxybutyric acid sulfate	0.403	1.446	0.302	1.387	0.324	1.422	0.041	2.202
+	86.09645	11.9	Piperidine	0.402	1.149	0.319	1.103	0.013	1.248	0.285	1.111
-	173.1045	28.0	L-Arginine	0.400	1.104	0.989	0.999	0.153	1.143	0.899	1.013
+	162.055	8	Quinoline-3,4-diol	0.399	9.141	0.4	8.799	0.764	0.745	0.974	0.97
+	162.055	5.1	Quinoline-3,4-diol	0.396	11.402	0.395	13.76	0.355	0.153	0.427	0.271
+	102.055	15.7	1-Aminocyclopropane-1-carboxylate	0.395	1.182	0.584	1.1	0.133	1.296	0.397	1.17
+	854.5705	4.2	[PC (20:5/22:5)] 1-(5Z,8Z,11Z,14Z,17Z-eicosapentaenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.394	0.818	0.381	0.822	0.199	1.238	0.694	1.075
-	214.1449	5.0	N-Nonanoylglycine	0.394	1.729	0.821	0.924	0.180	3.396	0.668	1.192

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	242.1762	4.8	N-Undecanoylglycine	0.394	1.728	0.554	0.836	0.199	3.220	0.939	1.028
+	133.0714	15.1	Methylenediurea	0.393	0.098	0.318	3.647	0.648	2.033	0.38	0.071
-	425.3639	3.9	[FA (26:0/2:0)] Hexacosanedioic acid	0.391	0.673	0.185	0.533	0.337	2.284	0.469	0.695
+	720.5917	4.3	[PC (14:2/18:0)] 1-tetradecyl-2-octadecanoyl-sn-glycero-3-phosphocholine	0.391	1.097	0.029	1.342	0.042	1.527	0.212	1.245
+	229.1215	15.1	[PR] Cacalol	0.387	10.982	0.011	0.409	0.18	0.691	0.069	0.609
+	134.0641	16	4-methylthiobutanaldoxime	0.387	1.084	0.282	0.905	0.646	1.033	0.867	0.986
-	173.0818	13.6	Suberic acid	0.384	0.236	0.370	0.211	0.356	0.186	0.351	0.177
+	188.103	14.5	5-guanidino-3-methyl-2-oxo-pentanoate	0.381	1.23	0.169	1.396	0.092	1.447	0.742	0.94
+	261.1486	4.2	Lacinilene C 7-methyl ether	0.381	0.766	0.572	0.88	0.547	0.872	0.789	0.941
-	171.0663	14.9	[FA dioxo(8:0)] 4,7-dioxo-octanoic acid	0.379	0.172	0.370	0.154	0.376	0.167	0.382	0.177
-	571.3445	4.9	Arg-Lys-Asn-Arg	0.379	0.923	0.468	0.924	0.179	1.210	0.014	0.663
+	122.0812	12.8	Tromethamine	0.379	1.166	0.382	1.164	0.406	1.156	0.393	1.16
+	121.0761	11.3	Benzamidine	0.378	5.221	0.394	0.838	0.902	0.972	0.653	1.093
-	127.04	7.9	(4E)-2-Oxohexenoic acid	0.377	0.555	0.470	0.638	0.348	0.514	0.172	0.293
+	537.1656	4.1	1-4-beta-D-Glucan	0.377	0.815	0.1	0.638	0.151	0.689	0.154	0.698
-	203.0827	12.3	L-Tryptophan	0.375	1.123	0.792	0.968	0.319	1.109	0.974	0.996
-	138.9704	16.0	Sulfoacetate	0.375	3.066	0.628	1.111	0.401	1.232	0.407	1.181
-	151.0261	10.8	Xanthine	0.375	32.277	0.412	0.398	0.922	0.923	0.609	0.637
+	284.3312	8.2	CTAB	0.374	1.396	0.752	1.115	0.557	1.216	0.277	1.876
-	178.0721	16.6	D-Glucosamine	0.374	0.131	0.403	0.186	0.381	0.146	0.375	0.133
+	813.6849	4.4	SM(d18:1/24:1(15Z))	0.374	0.857	0.02	1.479	0.193	1.241	0.396	1.192
+	452.3137	4.8	[PC (14:1)] 1-(1E-tetradecenyl)-sn-glycero-3-phosphocholine	0.372	1.118	0.051	0.72	0.249	1.202	0.693	0.941
-	174.056	4.9	Indole-3-acetate	0.372	22.062	0.374	25.287	0.375	27.545	0.597	0.615
-	131.0712	5.1	6-Hydroxyhexanoic acid	0.370	1.244	0.873	0.955	0.074	1.486	0.339	1.279
+	288.2533	4.6	[SP hydroxy,hydroxy,methyl(10:2/2:0)] 6R-(8-hydroxydecyl)-2R-(hydroxymethyl)-piperidin-3R-ol	0.368	2.226	0.264	1.747	0.504	1.407	0.612	1.501
-	78.91848	13.2	Br-	0.364	1.120	0.998	1.000	0.104	1.205	0.230	1.166
-	231.1138	3.6	Melatonin	0.364	0.008	0.366	0.012	0.362	0.003	0.363	0.007

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	89.10732	15.1	Putrescine	0.364	0.003	0.363	0	0.363	0	0.363	0
+	89.10734	11.9	Putrescine	0.364	0.003	0.363	0.001	0.363	0	0.363	0
+	89.10733	5.5	Putrescine	0.364	0.002	0.364	0.003	0.363	0.001	0.363	0.001
-	114.0559	13.4	L-Proline	0.361	1.124	0.583	0.940	0.067	1.179	0.404	1.127
-	455.3529	4.3	Ursolic acid	0.361	#DIV/0!	0.363	#DIV/0!	#DIV/0!	#DIV/0!	0.363	#DIV/0!
+	146.1651	15.1	Spermidine	0.36	0.099	0.372	0.123	0.364	0.107	0.384	0.147
-	445.1933	28.0	Asp-Val-Val-Asp	0.359	1.566	0.528	1.394	0.551	1.305	0.459	1.220
-	256.1922	4.6	N-Lauroylglycine	0.359	1.860	0.623	1.272	0.215	3.928	0.251	1.886
-	421.2266	7.3	1,4-Bis(2-ethylhexyl) sulfosuccinate	0.358	0.673	0.436	1.169	0.941	0.979	0.593	0.835
+	361.1461	12.2	Asn-Asn-Asn	0.354	1.184	0.637	1.077	0.185	1.201	0.688	1.057
+	350.3052	4.4	[FA (20:3)] N-(8Z,11Z,14Z-eicosatrienoyl)-ethanolamine	0.352	1.856	0.425	1.942	0.363	4.986	0.173	2.337
-	129.0193	11.6	Itaconate	0.351	0.494	0.120	0.119	0.109	0.084	0.128	0.142
-	135.0451	7.9	Phenylacetic acid	0.348	1.392	0.818	1.126	0.396	0.713	0.287	1.438
+	476.3067	5	Netilmicin	0.347	0.909	0.162	0.777	0.07	0.69	0.067	0.697
-	143.0349	7.9	2,3-Dimethylmaleate	0.346	0.818	0.239	0.774	0.716	0.917	0.862	0.958
-	295.1339	4.2	4-Prenylresveratrol	0.345	0.858	0.131	0.794	0.149	0.742	0.037	0.666
-	226.0123	10.5	L-Glutamyl 5-phosphate	0.340	1.397	0.023	1.745	0.168	1.674	0.104	1.647
+	190.1074	11.6	(2S)-2-{[1-(R)-Carboxyethyl]amino}pentanoate	0.336	0.239	0.949	1.067	0.424	0.378	0.449	0.41
-	105.0191	13.6	D-Glycerate	0.336	1.396	0.778	1.106	0.159	1.504	0.185	1.471
+	230.1751	4.9	N-Decanoylglycine	0.334	1.574	0.696	1.133	0.169	2.605	0.404	1.386
-	270.2074	4.5	Tridecanoylglycine	0.334	2.289	0.515	0.755	0.174	5.111	0.624	0.802
-	269.2122	7.1	[FA oxo(16:0)] 3-oxo-hexadecanoic acid	0.333	0.110	0.341	0.127	0.319	0.081	0.330	0.104
+	104.0706	12.8	4-Aminobutanoate	0.332	1.177	0.922	1.023	0.234	1.228	0.241	1.226
-	112.0515	10.3	Creatinine	0.332	0.850	0.069	0.761	0.098	0.810	0.926	1.010
+	241.1547	10.6	Slaframine	0.332	0.782	0.158	0.694	0.241	0.772	0.065	0.603
-	327.2542	4.0	MG(0:0/16:1(9Z)/0:0)	0.330	1.603	0.812	0.940	0.178	2.848	0.340	0.778
+	260.1857	4.9	[FA (6:0)] O-hexanoyl-R-carnitine	0.326	0.768	0.119	0.655	0.401	1.674	0.639	0.898
-	85.02922	7.9	Diacetyl	0.326	0.794	0.205	0.742	0.388	0.823	0.072	0.616

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	128.0353	13.6	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.325	0.734	0.190	0.641	0.294	0.727	0.538	1.244
-	228.1604	4.9	N-Decanoylglycine	0.324	1.620	0.640	1.173	0.168	2.911	0.353	1.498
+	335.2945	4.4	13,16,19-Docosatrienoic acid	0.322	2.294	0.365	4.365	0.34	11.736	0.124	6.4
+	130.159	15.6	Octylamine	0.322	4.625	0.094	0.667	0.377	4.493	0.52	1.154
-	269.2122	4.1	[FA oxo(16:0)] 3-oxo-hexadecanoic acid	0.321	0.705	0.250	1.253	0.911	1.028	0.170	0.617
-	215.0329	14.1	2-C-Methyl-D-erythritol 4-phosphate	0.321	1.329	0.932	0.976	0.363	1.267	0.114	1.587
-	115.0036	7.2	Fumarate	0.320	5.634	0.920	0.964	0.397	1.450	0.759	0.879
+	220.118	6	Pantothenate	0.317	1.233	0.635	0.871	0.592	1.132	0.964	0.989
-	99.00862	7.9	2-oxobut-3-enanoate	0.316	2.607	0.377	2.377	0.302	1.939	0.943	0.988
-	116.9284	8.1	chromate	0.315	0.459	0.120	0.182	0.896	1.090	0.827	0.850
-	154.0275	15.5	N-Methylethanolamine phosphate	0.314	1.255	<0.001	6.188	<0.001	8.450	0.517	1.142
+	116.107	11.5	Trimethylaminoacetone	0.313	0.449	0.977	0.983	0.91	0.938	0.707	1.196
-	115.0399	5.1	3-Methyl-2-oxobutanoic acid	0.311	2.135	0.320	1.682	0.787	1.095	0.689	1.117
-	243.1601	5.1	[FA (13:0/2:0)] Tridecanedioic acid	0.308	1.259	0.546	1.127	0.765	1.102	0.727	1.152
+	124.0758	7.9	2-amino-4-methylphenol	0.305	0.66	0.342	0.718	0.443	0.758	0.725	0.884
+	212.1645	4.9	Elaeokanine C	0.303	1.615	0.605	1.172	0.186	2.642	0.374	1.485
-	343.1245	16.2	Melibiitol	0.3	0.502	0.202	0.44	0.618	0.7	0.083	0.253
-	473.2825	3.9	Ala-Lys-Thr-Arg	0.297	1.447	0.157	1.249	0.201	1.376	0.095	1.670
+	170.0812	8.5	Pyridoxine	0.297	1.137	0.852	0.978	0.137	1.167	0.824	1.028
-	279.2329	7.3	Linoleate	0.294	2.384	0.973	0.963	0.653	1.548	0.372	0.236
-	148.0438	12.2	L-Methionine	0.294	1.144	0.999	1.000	0.144	1.178	0.789	1.033
-	160.0404	4.9	Quinoline-3,4-diol	0.291	6.678	0.246	6.810	0.600	2.322	0.687	1.793
+	117.1023	11.5	5-Aminopentanamide	0.289	1.229	0.367	1.228	0.161	3.371	0.886	0.97
-	145.0618	15.7	L-Glutamine	0.289	1.102	0.477	0.935	0.188	1.110	0.801	0.976
+	341.0442	13.5	(6R)-6-fluoro-EPSP	0.285	1.411	0.77	0.891	0.275	1.345	0.104	1.725
+	202.1438	5.1	Capryloylglycine	0.285	1.666	0.489	1.248	0.167	2.369	0.282	1.412
+	177.0547	4.5	4-Methylumbelliferone	0.282	0.56	0.556	0.784	0.038	0.214	0.217	0.549
+	288.2897	4.9	[SP (17:0)] heptadecasphinganine	0.281	1.672	0.282	2.422	0.976	1.015	0.28	1.732

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	149.0091	17.6	(R,R)-Tartaric acid	0.280	1.310	0.098	1.683	0.116	2.248	0.383	1.419
+	198.1125	7.9	L-Metanephrine	0.276	0.595	0.225	0.547	0.789	0.899	0.38	0.67
+	122.0812	8.2	Tromethamine	0.276	0.456	0.39	0.581	0.273	0.452	0.452	0.638
-	160.0404	7.9	Quinoline-3,4-diol	0.274	13.854	0.298	11.924	0.262	4.884	0.475	3.441
-	176.0208	5.0	Sulforaphane	0.271	1.306	0.387	1.159	0.359	1.191	0.317	1.174
-	116.0352	13.6	L-2-Amino-3-oxobutanoic acid	0.270	4.121	0.895	1.042	0.335	1.358	0.027	16.370
+	265.1118	22.6	Thiamin	0.27	1.148	0.592	0.902	0.227	1.146	0.654	0.914
-	114.0195	16.0	Maleamate	0.269	2.630	0.153	4.043	0.142	4.235	0.827	1.051
-	171.1027	7.9	9-Oxononanoic acid	0.266	0.748	0.488	0.838	0.549	1.395	0.136	0.659
-	171.0663	11.4	[FA dioxo(8:0)] 4,7-dioxo-octanoic acid	0.264	1.442	0.594	1.126	0.202	1.420	0.370	1.153
+	130.0863	7.9	L-Pipecolate	0.264	1.174	0.725	1.049	0.235	1.104	0.876	1.016
-	119.0349	15.4	D-Erythrose	0.261	0.961	0.266	0.811	0.130	0.950	0.230	0.829
-	138.9705	18.4	Sulfoacetate	0.261	3.910	0.146	1.628	0.092	1.728	0.122	1.506
-	157.0869	7.9	[FA oxo(8:0)] 3-oxo-octanoic acid	0.259	1.331	0.141	1.422	0.512	1.320	0.755	1.125
-	313.2385	4.0	[FA hydroxy(18:0)] 9,10-dihydroxy-12Z-octadecenoic acid	0.258	2.371	0.288	2.600	0.118	1.970	0.160	1.553
+	133.0859	5.1	6-Hydroxyhexanoic acid	0.258	0.8	0.024	0.683	0.254	0.854	0.028	0.695
+	223.1078	13.7	Phe-Gly	0.256	1.109	0.461	1.07	0.06	1.159	0.808	0.973
+	205.0973	12.3	L-Tryptophan	0.254	1.176	0.867	1.022	0.147	1.174	0.749	1.04
-	258.1708	4.8	[FA (6:0)] O-hexanoyl-R-carnitine	0.253	2.248	0.339	1.730	0.171	6.987	0.222	2.162
+	355.0634	5	Phenolsulfonphthalein	0.25	0.728	0.159	0.708	0.644	0.84	0.599	0.884
+	256.1656	5.1	L-Pyrrolysine	0.248	0.835	0.112	0.721	0.086	0.688	0.047	0.593
+	244.1908	7.9	N-Undecanoylglycine	0.245	1.529	0.759	0.966	0.175	2.54	0.778	1.06
-	267.233	4.1	omega-Cyclohexylundecanoic acid	0.245	0.827	0.376	0.787	0.419	0.905	0.297	0.759
+	180.0768	11.1	N-Acetylisoniazid	0.244	0.522	0.178	0.432	0.305	0.584	0.188	0.447
-	341.1089	16.0	Sucrose	0.244	0.442	0.734	0.792	0.168	0.317	0.439	1.683
+	188.0707	12.3	Deethylatrazine	0.242	1.2	0.751	1.047	0.118	1.201	0.687	1.054
+	174.1126	5.1	N-Acetyl-L-leucine	0.242	0.853	0.312	0.872	0.203	2.142	0.061	0.77

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	366.3011	4.4	[FA dimethyl,amino,trihydrox] 1-dimethylamino-9S,11R,15S-trihydroxy-5Z,13E-prostadiene	0.241	1.890	0.277	3.550	0.264	5.935	0.113	6.557
-	299.2014	4.2	[PR] Tretinoin/All-Trans Retinoic Acid	0.241	1.731	0.153	5.915	0.807	0.920	0.110	5.243
-	227.1289	7.9	Traumatic acid	0.237	2.296	0.375	1.471	0.209	2.163	0.700	1.162
-	116.9285	10.5	chromate	0.236	2.046	0.218	1.570	0.202	4.943	0.147	1.826
-	242.1762	7.9	N-Undecanoylglycine	0.236	1.633	0.698	0.948	0.157	2.891	0.727	1.090
-	143.0713	7.9	trans-4-Hydroxycyclohexanecarboxylate	0.236	0.664	0.297	0.692	0.273	0.699	0.298	0.701
+	324.2898	4.4	[FA (18:2)] N-(9Z,12Z-octadecadienoyl)-ethanolamine	0.233	3.317	0.235	6.108	0.373	5.059	0.116	10.456
-	199.1704	4.2	Dodecanoic acid	0.232	0.891	0.144	0.893	0.243	0.905	0.381	0.897
+	276.1806	4.8	[FA hydroxy(10:0)] N-(3S-hydroxydecanoyl)-L-serine	0.229	0.535	0.59	0.724	0.983	1.01	0.907	0.939
-	279.2329	4.0	Linoleate	0.228	0.844	0.100	0.773	0.038	0.774	0.145	0.758
+	139.0502	11.1	Urocanate	0.228	0.654	0.004	0.306	0.126	0.599	0.052	0.455
-	522.2835	4.4	[PS (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	0.227	1.243	0.189	1.217	0.006	1.770	0.939	0.983
+	134.0448	14.9	L-Aspartate	0.227	1.247	0.47	0.808	0.545	0.836	0.808	1.047
-	199.9693	17.3	S-Sulfo-L-cysteine	0.226	0.797	0.002	0.322	0.056	0.657	0.109	0.722
-	96.96019	18.4	Sulfate	0.222	1.090	0.950	0.997	0.111	1.109	0.614	0.971
-	147.0662	7.9	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.221	0.829	0.557	1.073	0.731	0.939	0.039	0.715
+	115.0866	11.5	L-proline amide	0.221	1.391	0.148	1.262	0.241	1.502	0.169	1.256
+	813.6849	7.2	SM(d18:1/24:1(15Z))	0.22	1.624	0.02	2.696	0.049	2.663	0.49	1.556
-	409.236	4.9	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.218	1.085	0.031	1.194	<0.001	1.574	0.181	0.885
-	158.0822	5.1	5-Acetamidopentanoate	0.216	1.419	0.472	1.209	0.466	1.199	0.610	0.901
-	121.0406	8.0	Nicotinamide	0.210	1.399	0.608	0.893	0.034	1.693	0.240	1.254
-	221.082	4.5	[FA (12:4/2:0)] 2E,4E,8E,10E-Dodecatetraenedioic acid	0.209	1.367	0.328	1.280	0.001	2.035	0.167	1.469
-	147.0662	5.7	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.209	0.676	0.582	1.129	0.838	0.944	0.08	0.52
-	99.04501	7.9	Tiglic acid	0.207	1.894	0.251	1.975	0.212	2.370	0.706	1.137
-	163.0248	16.2	2-Dehydro-D-xylonate	0.206	3.323	0.551	0.854	0.008	3.008	0.627	0.873
-	229.1444	7.9	Dodecanedioic acid	0.206	1.464	0.140	1.763	0.123	1.883	0.307	1.278

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	369.0681	4.5	Digalacturonate	0.205	0.766	0.049	0.630	0.127	0.681	0.101	0.716
+	369.3516	5.1	[ST] (5Z,7E)-9,10-seco-5,7,10(19)-cholestatriene	0.204	1.299	0.169	1.485	0.078	1.84	0.295	1.384
+	88.0393	15.5	2-Aminoacrylate	0.204	1.106	0.188	1.249	<0.001	2.896	0.023	0.648
+	252.0292	21.8	Uracil mustard	0.203	0.454	0.556	0.744	0.874	1.079	0.373	17.851
-	127.0512	15.7	5,6-Dihydrothymine	0.201	1.133	0.499	0.936	0.296	1.094	0.887	0.987
-	165.0193	13.0	Phthalate	0.201	18.815	0.326	7.407	0.084	9.322	0.296	1.451
-	165.0405	13.1	L-Arabinonate	0.199	1.255	0.364	1.165	0.163	1.275	0.929	1.018
-	196.0727	9.0	N-Acetyl-L-histidine	0.196	1.168	0.667	1.054	0.110	1.217	0.601	1.071
+	148.0968	12.8	Fagomine	0.194	2.031	0.224	1.891	0.01	2.852	0.084	2.273
+	104.0706	14.8	4-Aminobutanoate	0.192	1.36	0.554	0.93	0.099	1.141	0.116	1.147
-	83.02476	7.9	Imidazolone	0.191	1.209	0.017	1.385	0.046	1.230	0.016	1.463
+	339.0473	13.5	N5-carboxyaminoimidazole ribonucleotide	0.191	1.382	0.911	0.968	0.277	1.294	0.068	1.676
+	399.0811	14.9	Ala-Cys-Cys-Cys	0.188	0.361	0.133	0.256	0.128	0.247	0.167	0.324
-	127.0149	13.6	Barbiturate	0.188	9.843	0.436	2.947	0.208	6.551	0.115	6.726
-	121.0294	7.9	Benzoate	0.188	1.327	0.192	1.388	0.373	1.226	0.628	1.118
+	146.0812	13.8	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.187	1.843	0.481	0.915	0.196	1.397	0.743	0.937
-	171.1027	4.8	9-Oxononanoic acid	0.187	2.657	0.704	1.090	0.731	1.089	0.538	1.474
+	779.5789	4.1	[PG (18:0/18:0)] 1,2-dioctadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.186	0.879	0.005	1.515	0.859	1.032	0.395	1.169
-	160.0615	15.4	L-2-Aminoadipate	0.186	1.402	0.030	3.544	0.001	2.058	0.009	1.696
-	101.0243	15.2	2-Oxobutanoate	0.185	0.791	0.042	0.612	0.044	0.534	0.517	0.945
-	275.0918	13.7	Lactucin	0.185	0.744	0.963	1.010	0.636	0.916	0.097	0.603
-	398.3274	4.3	[FA] O-Palmitoyl-R-carnitine	0.183	0.336	0.250	0.414	0.269	0.460	0.761	0.795
-	141.0192	16.6	cis,cis-Muconate	0.177	7.903	0.355	1.217	0.080	14.708	0.352	4.912
+	133.0608	16	L-Asparagine	0.176	1.126	0.417	0.934	0.327	1.068	0.865	1.013
-	129.0557	5.0	(S)-3-Methyl-2-oxopentanoic acid	0.175	0.869	0.048	0.806	0.487	0.941	0.053	0.807
-	355.2853	4.0	[FA (21:0/2:0)] Heneicosanedioic acid	0.175	2.220	0.168	1.429	0.098	2.044	0.065	1.583
-	88.00378	13.7	Oxamate	0.173	2.253	0.783	0.775	0.368	1.829	0.174	2.287

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	159.0662	13.6	[FA (7:0/2:0)] Heptanedioic acid	0.169	11.093	0.094	1.384	0.026	20.628	0.068	12.138
-	137.0356	11.1	Urocanate	0.168	0.540	0.033	0.355	0.135	0.539	0.052	0.377
-	433.1404	3.9	Asp-Thr-Cys-Pro	0.167	0.675	0.544	0.862	0.361	1.239	0.409	0.824
+	150.0584	12.2	L-Methionine	0.162	1.199	0.534	1.076	0.036	1.247	0.563	1.07
-	152.9863	16.9	3-sulfopropanoate	0.161	1.514	0.043	1.899	0.001	4.950	0.358	1.319
-	301.0467	16.1	Olsalazine	0.160	0.442	0.219	0.508	0.187	0.473	0.325	0.575
-	101.0243	16.0	2-Oxobutanoate	0.159	4.190	<0.001	1.947	0.040	9.332	<0.001	2.079
+	550.3869	4.8	LysoPC(20:1(11Z))	0.159	1.237	0.078	1.314	0.002	1.884	0.856	0.965
-	791.5466	4.2	acyl phosphatidylglycerol (n-C12:0)	0.158	5.671	<0.001	2.433	<0.001	2.289	<0.001	2.648
+	130.1591	10.2	Octylamine	0.157	1.033	0.947	1.002	0.693	0.99	0.972	1.001
+	143.0816	7.9	Ectoine	0.156	2.062	0.886	0.974	0.221	2.077	0.494	0.884
+	219.1744	4.8	Solavetivone	0.156	0.632	0.156	0.607	0.505	1.579	0.846	1.052
+	191.0849	12.2	Aldicarb	0.155	1.169	0.58	1.071	0.067	1.252	0.51	1.09
+	166.0863	10.8	L-Phenylalanine	0.153	1.177	0.931	1.01	0.131	1.155	0.853	1.02
+	112.0506	12.5	Cytosine	0.152	0.794	0.031	0.71	0.453	0.86	0.315	0.841
+	267.0764	15.8	6-Acetophenazine-1-carboxylic acid	0.15	0.302	0.289	0.481	0.108	0.201	0.171	0.336
+	125.071	7.9	Methylimidazole acetaldehyde	0.15	1.23	0.84	1.033	0.102	1.325	0.461	1.154
-	91.03989	10.9	Glycerol	0.149	1.525	0.419	1.320	0.583	1.236	0.215	1.503
-	173.1182	7.9	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.148	0.725	0.331	0.789	0.337	0.818	0.173	0.741
+	352.321	4.3	[FA (20:2)] N-(11Z,14Z-eicosadienoyl)-ethanolamine	0.147	2.286	0.252	2.354	0.291	3.544	0.08	3.772
-	353.049	7.9	Phenolsulfonphthalein	0.147	1.233	0.464	1.107	0.054	1.309	0.166	1.202
-	556.3252	4.9	Lys-Lys-Trp-Pro	0.146	1.090	0.026	1.188	<0.001	1.577	0.237	0.908
-	78.95869	16.4	Phosphite	0.146	1.259	0.996	1.001	0.256	1.180	0.054	1.392
+	172.1332	5.1	Gabapentin	0.145	0.847	0.035	0.762	0.039	0.753	0.534	1.442
+	133.0318	12.2	THTC	0.145	1.224	0.477	1.089	0.022	1.28	0.426	1.098
+	268.104	9.5	Adenosine	0.144	0.693	0.113	0.684	0.702	0.93	0.004	0.336
-	130.0872	11.5	L-Leucine	0.144	1.156	0.687	1.037	0.049	1.187	0.490	1.067
-	129.0556	7.9	(S)-3-Methyl-2-oxopentanoic acid	0.143	2.648	0.237	2.345	0.355	2.167	0.365	2.440

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	151.0617	12.2	Dipropyl disulfide	0.143	1.212	0.51	1.083	0.034	1.244	0.585	1.066
+	145.0972	11.9	L-isoglutamine	0.143	1.474	0.133	1.489	0.116	1.519	0.131	1.492
-	144.0302	13.6	2-Oxoglutaramate	0.141	1.445	0.217	1.408	0.344	1.287	0.307	4.672
-	187.007	4.7	4-Sulfobenzyl alcohol	0.141	1.249	0.219	0.770	0.105	1.258	0.225	1.226
+	112.0506	11	Cytosine	0.141	0.551	0.135	0.562	0.091	0.52	0.058	0.452
+	204.1344	12.6	Lys-Gly	0.141	1.204	0.897	1.016	0.075	1.206	0.552	1.076
-	175.0473	8.6	Allantoate	0.140	1.204	0.479	1.099	0.071	1.261	0.428	1.118
-	227.1288	5.1	Traumatic acid	0.140	1.691	0.717	0.902	0.342	1.542	0.315	1.476
-	128.0353	10.5	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.139	1.170	0.455	1.077	0.014	1.252	0.430	1.079
-	311.1866	4.3	Granisetron	0.137	1.466	0.276	1.299	0.161	1.900	0.112	1.553
-	125.0243	15.3	Phloroglucinol	0.137	0.881	0.070	0.729	0.015	0.804	0.035	0.685
-	159.1026	5.0	Ethyl (R)-3-hydroxyhexanoate	0.136	0.559	0.132	0.522	0.425	0.741	0.708	0.864
-	368.317	4.4	[SP amino,tetramethyl(4:0/18:0/3:0)] 2S-amino-5,9,13,17-tetramethyl-8E,16-octadecadiene-1,3R,14-triol	0.135	3.942	0.148	4.674	0.247	6.034	0.077	7.373
+	127.0503	12.1	Thymine	0.134	5.148	0.042	1.609	0.007	3.097	0.061	1.868
-	174.0408	15.0	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	0.133	0.934	<0.001	0.749	<0.001	0.748	0.018	0.840
+	120.0656	15.2	L-Threonine	0.13	0.853	0.041	0.802	0.066	0.838	0.016	0.76
+	168.0656	8.4	Pyridoxal	0.13	1.244	0.944	1.011	0.268	1.18	0.406	1.152
-	143.1077	4.6	[FA (8:0)] octanoic acid	0.128	0.882	0.140	0.886	0.062	0.844	0.098	0.868
-	177.0921	4.5	Eugenol methyl ether	0.126	0.619	0.022	0.430	0.575	0.884	0.396	0.816
-	192.0667	5.1	Phenylacetylglycine	0.126	1.175	0.589	0.944	0.108	1.136	0.555	1.081
-	143.0713	5.1	trans-4-Hydroxycyclohexanecarboxylate	0.126	0.635	0.357	0.812	0.042	0.530	0.076	0.576
-	253.2173	4.1	(9Z)-Hexadecenoic acid	0.124	0.700	0.199	0.711	0.178	0.772	0.066	0.624
-	88.04016	15.4	L-Alanine	0.122	1.377	0.924	1.022	0.360	1.207	0.309	1.245
+	150.1125	9.9	Triethanolamine	0.122	1.654	0.455	1.24	0.329	1.317	0.437	1.223
+	230.0444	13.7	Resazurin	0.121	#DIV/0!	#DIV/0!	#DIV/0!	0.175	#DIV/0!	0.28	#DIV/0!
-	243.0622	12.5	Uridine	0.120	1.207	0.849	1.021	0.044	1.248	0.395	1.095

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	379.1552	4.1	[Fv] Praecanson A	0.119	0.772	0.449	0.890	0.025	0.633	0.077	0.717
-	243.0808	9.0	Biotin	0.119	1.193	0.628	1.057	0.095	1.198	0.527	1.077
+	146.0812	9.3	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.116	1.206	0.091	1.182	0.012	1.328	0.175	1.171
+	148.0797	15.7	5-methylthiopentanaldoxime	0.116	1.133	0.787	0.981	0.032	1.143	0.763	1.021
-	874.6724	4.4	PC(o-22:3(10Z,13Z,16Z)/22:3(10Z,13Z,16Z))	0.116	0.529	0.215	1.550	0.700	0.857	0.963	1.017
-	272.1244	4.1	Ala-Pro-Ser	0.114	1.414	0.792	1.065	0.973	0.993	0.321	1.210
-	350.3064	4.3	[FA (20:2)] N-(11Z,14Z-eicosadienoyl)-ethanolamine	0.113	3.332	0.177	3.435	0.253	5.585	0.071	5.724
-	776.5604	4.1	PE(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	0.113	1.417	<0.001	1.957	0.062	1.814	0.078	1.558
+	785.6526	4.4	SM(d18:1/22:1(13Z))	0.113	0.502	0.339	0.689	0.192	0.59	0.706	0.869
+	132.1019	11.6	L-Leucine	0.112	1.259	0.615	0.907	0.073	1.276	0.715	0.933
+	230.2479	5	[SP (14:0)] 1-deoxy-tetradecasphinganine	0.111	2.514	0.427	1.326	0.346	1.551	0.219	2.364
-	775.547	4.0	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.109	2.023	0.069	2.115	0.088	2.080	0.012	2.865
-	315.0685	15.2	2-(4-Chlorophenyl)-3-phenyl-3-(2-pyridinyl)acrylonitrile	0.108	1.576	0.004	2.883	0.027	2.601	0.069	1.965
-	229.1444	5.1	Dodecanedioic acid	0.108	1.826	0.774	1.083	0.178	1.573	0.371	1.814
-	103.0399	9.4	(R)-3-Hydroxybutanoate	0.106	0.416	0.096	0.391	0.128	0.455	0.100	0.401
-	816.5742	4.0	1-20:0-2-18:1-phosphatidylserine	0.106	0.547	0.986	1.004	0.273	0.690	0.898	0.933
+	729.5912	4.5	SM(d18:1/18:1(9Z))	0.106	0.555	0.291	0.7	0.186	0.605	0.494	0.815
-	229.1343	8.6	Camoensine	0.103	1.423	0.252	1.275	0.067	1.473	0.175	1.329
-	137.0355	7.9	Urocanate	0.103	1.985	0.184	1.730	0.521	1.295	0.012	2.284
-	195.051	14.4	D-Gluconic acid	0.102	0.696	0.006	0.507	0.020	0.646	0.034	0.624
+	91.05833	15.4	Diethyl sulfide	0.102	1.414	0.023	1.258	<0.001	1.482	0.178	1.275
-	113.0243	15.2	2-Hydroxy-2,4-pentadienoate	0.101	0.838	0.045	0.789	0.124	0.859	0.037	0.787
-	111.0199	10.3	Uracil	0.1	0.296	0.136	0.378	0.091	0.27	0.084	0.248
-	404.1504	4.2	(+/-)-6-Acetonyldihydrochelerythrine	0.098	0.421	0.035	0.296	0.029	0.263	0.036	0.302
-	288.9966	18.6	3-phosphoglucarate	0.098	1.589	0.283	1.371	0.017	1.830	0.053	1.653
-	779.5612	4.4	[PR] Siphonaxanthin ester/ Siphonaxanthin dodecenoate/ (Siphonein)	0.096	1.668	0.027	2.424	0.007	1.926	0.068	1.548
-	333.0915	4.5	Penicillin G	0.095	1.207	0.861	1.020	0.041	1.241	0.442	1.099

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	149.0807	15.7	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.094	1.136	0.789	0.98	0.04	1.127	0.613	1.036
+	170.0925	13.5	N(pi)-Methyl-L-histidine	0.094	1.397	0.115	1.371	0.125	1.37	0.562	1.131
+	190.0864	10.8	3-Indolepropionicacid	0.093	1.295	0.971	1.007	0.045	1.327	0.972	0.992
-	352.3222	4.4	[FA (20:0)] N-(11Z-eicosaenoyl)-ethanolamine	0.090	2.578	0.200	2.911	0.291	2.941	0.096	3.843
-	134.0472	7.9	Adenine	0.090	2.835	0.015	3.294	0.005	4.061	0.222	2.119
+	371.2276	5.1	Ala-Leu-Ala-Pro	0.089	0.781	0.007	0.91	0.091	0.836	0.171	0.861
-	390.1622	4.2	Linopirdine	0.089	0.658	0.936	0.984	0.025	0.606	0.018	0.602
+	118.1226	18.5	2-Methylcholine	0.088	0.062	0.191	0.293	0.513	0.634	0.204	0.341
+	147.0764	15.7	L-Glutamine	0.088	1.138	0.849	0.987	0.023	1.154	0.741	1.023
-	144.0665	8.0	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.087	1.368	0.633	1.098	0.254	3.151	0.131	1.310
-	179.0713	4.9	Coniferyl alcohol	0.087	4.203	0.666	1.274	0.349	1.618	0.383	3.020
+	130.0499	15.7	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.087	1.173	0.391	0.937	0.116	1.099	0.662	1.031
-	324.2908	4.4	[FA (18:0)] N-(9Z-octadecenoyl)-ethanolamine	0.086	6.166	0.092	8.309	0.026	8.073	0.035	13.702
+	868.6074	3.8	1-24:1-2-18:3-phosphatidylserine	0.086	1.29	0.609	1.107	0.222	0.768	0.281	1.21
+	166.0533	14	L-Methionine S-oxide	0.085	1.447	0.288	1.217	0.008	1.55	0.339	1.167
+	130.9665	9.6	2,2-Dichloro-1,1-ethanediol	0.084	1.71	0.221	7.522	0.068	1.712	0.089	2.26
+	198.0874	9	N-Acetyl-L-histidine	0.083	1.214	0.397	1.094	0.063	1.259	0.348	1.107
-	122.9934	4.1	6-S-acetyl-dihydrolipoate	0.082	0.626	0.292	0.746	0.420	3.115	0.066	0.616
+	244.0928	12.5	Cytidine	0.082	0.757	0.017	0.654	0.017	0.66	0.023	0.683
-	726.5449	4.2	PE(18:1(11Z)/P-18:1(11Z))	0.082	1.637	0.002	2.958	0.025	2.208	0.024	1.725
-	80.97452	13.5	Phosphonate	0.082	1.228	0.650	0.929	0.220	1.149	0.092	1.403
-	116.9285	9.9	chromate	0.081	2.277	0.866	1.045	0.207	1.506	0.332	3.590
-	243.1602	4.2	[FA (13:0/2:0)] Tridecanedioic acid	0.080	0.583	0.050	0.549	0.862	1.035	0.156	0.674
+	245.0961	12.5	Biotin	0.079	0.743	0.002	0.492	0.011	0.64	0.013	0.653
+	175.1078	14.1	N-Acetylornithine	0.077	1.468	0.194	1.282	0.007	1.565	0.129	1.297
-	367.3581	3.9	Tetracosanoic acid	0.076	0.701	0.059	0.76	0.966	0.992	0.078	0.672
+	245.0955	9	Biotin	0.072	1.233	0.46	1.077	0.015	1.266	0.355	1.093

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	362.0508	17.1	GMP	0.072	1.581	0.002	2.022	0.007	2.076	0.782	1.064
+	229.1547	13.7	Leu-Pro	0.072	1.125	0.058	0.853	0.396	1.059	0.679	1.038
-	143.0349	15.2	2,3-Dimethylmaleate	0.071	0.811	0.036	0.766	0.091	0.829	0.031	0.758
+	162.0761	15.4	L-2-Aminoadipate	0.071	1.554	0.006	2.134	0.016	1.875	0.065	1.617
+	102.0662	11.3	N-acetylguanidine	0.07	1.238	0.375	1.115	0.005	1.376	0.235	1.157
-	556.3252	7.9	Lys-Lys-Trp-Pro	0.069	1.102	0.005	1.283	<0.001	1.768	0.503	0.956
+	867.5952	3.8	[PI (18:0/18:0)] 1,2-dioctadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	0.068	1.087	0.862	1.009	0.214	0.829	0.117	1.1
+	230.0958	15.5	Ergothioneine	0.067	1.485	0.004	1.711	<0.001	4.126	0.22	1.483
-	744.5553	4.2	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.064	2.171	0.006	3.110	0.026	2.044	0.014	3.124
+	570.3559	4.8	LysoPC(22:5(4Z,7Z,10Z,13Z,16Z))	0.064	0.795	0.002	0.584	0.116	0.771	0.006	0.559
-	149.0454	14.1	D-Ribose	0.063	1.304	0.751	0.937	0.141	1.223	0.537	1.091
+	524.289	3.9	Lys-Met-Phe-Val	0.062	0.773	<0.001	0.782	0.001	0.756	0.001	0.76
-	190.0357	17.6	Nitrilotriacetic acid	0.060	1.246	0.230	0.819	0.004	1.587	0.542	1.189
-	297.2801	4.0	Nonadecanoicacid	0.060	0.647	0.258	0.817	0.230	0.869	0.006	0.545
+	613.3449	3.9	Arg-Lys-Phe-Tyr	0.059	0.629	0.098	0.725	0.027	0.584	0.04	0.617
-	165.0768	11.8	L-rhamnitol	0.058	1.274	0.352	1.111	0.011	1.339	0.202	1.163
-	157.1233	4.4	Nonanoic acid	0.058	0.842	0.022	0.812	0.004	0.720	0.223	0.902
-	111.0199	12.7	Uracil	0.058	5.065	0.007	2.665	0.133	5.687	<0.001	2.982
+	136.0618	10.1	Adenine	0.057	5.119	0.001	3.746	<0.001	5.104	0.009	3.378
+	171.1128	5.2	Levetiracetam	0.057	2.652	0.396	1.406	0.086	2.036	0.546	1.226
-	161.0455	15.2	2-Dehydro-3-deoxy-L-rhamnonate	0.056	0.876	0.037	0.864	0.174	0.842	0.041	0.811
+	207.1129	10.8	Phenylethylmalonamide	0.055	1.206	0.536	1.074	0.056	1.228	0.406	1.104
-	239.115	13.8	Homocarnosine	0.054	0.434	0.480	0.798	0.057	0.440	0.020	0.280
-	165.0404	14.0	L-Arabinonate	0.054	1.265	0.510	1.059	0.032	1.235	0.038	1.205
+	145.0972	16.1	L-isoglutamine	0.054	5.946	<0.001	11.436	<0.001	11.866	0.059	5.859
-	788.5438	3.9	PS(18:0/18:1(9Z))	0.054	1.230	0.003	1.653	0.048	1.489	0.168	1.377
-	241.0831	8.0	Thymidine	0.054	0.316	0.053	0.311	0.071	0.378	0.044	0.272

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	135.0451	5.0	Phenylacetic acid	0.053	1.403	0.152	0.654	0.738	1.077	0.065	1.362
+	748.588	4.3	[PE (16:0/20:0)] 1-hexadecanoyl-2-eicosanoyl-sn-glycero-3-phosphoethanolamine	0.052	1.818	0.001	2.292	0.432	0.749	0.092	2.087
+	128.0706	16.1	2,3,4,5-Tetrahydropyridine-2-carboxylate	0.052	1.717	0.004	2.121	<0.001	2.296	0.106	1.368
-	296.038	15.7	L-Cysteinylglycinedisulfide	0.052	0.371	0.028	0.248	0.058	0.394	0.086	0.455
+	496.3398	4.9	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	0.051	1.13	0.005	1.276	<0.001	1.675	0.503	0.945
+	171.0764	15.7	acetonitrile adduct of pyrroline carboxylate	0.051	1.154	0.607	0.961	0.076	1.129	0.387	1.074
-	489.2776	3.8	Arg-Lys-Thr-Ser	0.051	1.685	0.022	1.898	0.043	2.072	0.629	1.155
+	117.0659	14.4	Diacetylhydrazine	0.051	1.954	0.994	0.997	0.151	1.716	0.117	1.778
+	528.3089	4.7	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.051	1.279	0.007	1.606	0.748	0.967	0.001	0.544
-	144.0665	9.3	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.05	1.6	0.173	1.449	0.002	1.915	0.078	1.55
+	325.154	10.3	Dolasetron	0.05	1.474	0.501	1.177	0.378	1.196	0.38	1.189
-	528.3096	4.7	LysoPE(0:0/22:4(7Z,10Z,13Z,16Z))	0.049	1.277	0.049	1.317	0.096	0.695	0.005	0.525
-	673.481	3.9	[GP (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphate	0.047	3.983	0.036	4.134	0.007	8.445	0.020	5.020
-	140.9174	16.3	Arsenate	0.047	0.666	0.303	0.840	0.061	0.689	0.171	0.777
-	103.0148	11.3	Urea-1-carboxylate	0.047	1.694	0.198	1.452	0.041	1.723	0.056	1.654
+	782.5699	4.3	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.046	0.926	0.023	0.905	0.248	0.939	0.023	0.884
+	127.123	11.5	1-5-diazabicyclononane	0.046	1.332	0.297	1.182	0.121	1.334	0.563	1.126
+	190.1075	5.1	(2S)-2-{[1-(R)-Carboxyethyl]amino}pentanoate	0.045	0.286	0.454	0.717	0.595	0.803	0.628	1.151
-	225.186	4.1	(9Z)-Tetradecenoic acid	0.045	0.480	0.158	0.602	0.019	0.587	0.171	0.636
-	180.0336	12.5	DL-Methionine sulfone	0.045	1.350	0.281	1.479	0.003	1.449	0.156	1.219
+	259.0925	10.5	(1-Ribosylimidazole)-4-acetate	0.043	1.628	0.077	1.459	0.001	1.955	0.22	1.331
-	301.2173	4.2	[FA (20:5)] 5Z,8Z,11Z,14Z,17Z-eicosapentaenoic acid	0.043	0.328	0.117	0.485	0.033	0.275	0.031	0.265
+	812.5442	3.9	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.043	1.133	0.642	1.028	0.678	1.033	0.277	1.101
+	613.1594	15.3	Glutathione disulfide	0.042	#DIV/0!	0.069	#DIV/0!	0.009	#DIV/0!	0.066	#DIV/0!
-	616.4705	7.8	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphate	0.041	3.337	0.037	3.840	0.016	5.637	0.102	3.115
+	798.6035	4.3	PE(18:1(11Z)/22:2(13Z,16Z))	0.041	44.9	0.012	41.361	0.004	60.036	0.021	32.257

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	131.0349	14.9	2-Acetolactate	0.04	1.775	0.048	1.733	0.005	2.251	0.079	1.634
+	378.2061	4.4	Cryptopleurine	0.04	0.204	0.05	0.262	0.045	0.238	0.04	0.21
+	125.071	15.2	Methylimidazole acetaldehyde	0.04	8.104	0.144	5.823	0.002	12.239	0.127	5.576
+	326.3053	4.4	[FA (18:0)] N-(9Z-octadecenoyl)-ethanolamine	0.037	2.935	0.254	4.068	0.105	2.308	0.082	3.754
-	913.5786	3.9	PI(18:0/22:4(10Z,13Z,16Z,19Z))	0.035	1.715	0.002	2.230	0.005	2.041	0.013	1.982
+	121.0721	11.3	urea dimer	0.035	1.598	0.11	1.349	0.001	1.704	0.184	1.295
-	173.0931	14.1	N-Acetylornithine	0.034	1.303	0.143	1.193	0.007	1.373	0.282	1.136
+	223.0966	4.5	[FA (12:4/2:0)] 2E,4E,8E,10E-Dodecatetraenedioic acid	0.033	0.362	0.019	0.369	0.008	0.251	0.467	0.723
+	705.5808	7.8	[ST (20:4)] cholest-5-en-3beta-yl (15S-hydroperoxy-5Z,8Z,12E,14Z-eicosatetraenoate)	0.032	1.82	0.004	2.222	0.031	2.818	0.141	1.684
+	279.1591	4.3	2-Ethylhexyl phthalate	0.031	0.817	0.002	0.744	0.001	0.718	0.001	0.709
-	185.1546	4.3	[FA (11:0)] undecanoic acid	0.030	0.743	0.329	0.898	0.105	0.801	0.710	0.960
+	362.2113	4.4	Leu-Met-Val	0.03	0.309	0.038	0.352	0.019	0.215	0.021	0.238
-	218.1034	8.8	Pantothenate	0.030	1.267	0.203	1.149	0.025	1.322	0.095	1.203
+	508.3764	4.9	[PC (18:1)] 1-(11Z-octadecenyl)-sn-glycero-3-phosphocholine	0.029	1.12	0.34	1.066	<0.001	1.593	0.634	0.966
+	101.071	15.7	Gyromitrin	0.029	0.408	0.004	0.203	0.317	0.72	0.019	0.391
+	102.1278	11.9	Hexylamine	0.029	0.131	0.13	0.386	0.128	0.352	0.097	0.328
+	840.6477	4.2	PC(18:1(11Z)/22:2(13Z,16Z))	0.029	6.873	0.041	8.618	0.043	4.429	0.005	12.178
-	215.0329	14.9	2-C-Methyl-D-erythritol 4-phosphate	0.028	0.652	0.004	0.507	0.007	0.554	0.017	0.635
+	732.5874	4.3	PC(15:0/P-18:0)	0.028	4.596	0.11	7.172	0.124	4.975	0.269	4.818
-	125.001	9.8	2-Hydroxyethylphosphonate	0.027	7.589	0.011	3.812	0.008	5.446	0.006	6.365
-	179.035	8.0	3-(4-Hydroxyphenyl)pyruvate	0.027	1.841	0.995	0.998	0.249	1.307	0.233	1.448
+	742.5754	4.3	[PC (16:1/18:2)] 1-(1Z-hexadecenyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	0.026	5.349	0.043	5.399	0.002	13.3	0.018	5.993
-	339.3268	4.0	Docosanoic acid	0.026	0.643	0.008	0.579	0.380	0.893	0.010	0.625
-	810.5281	3.9	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.025	1.175	0.217	1.084	0.379	1.102	0.229	1.148
-	181.0507	9.1	3-(4-Hydroxyphenyl)lactate	0.025	1.313	0.371	1.098	0.016	1.279	0.176	1.175
+	174.1278	11.5	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	0.024	1.193	0.347	0.733	0.069	1.256	0.474	1.062

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	213.1861	4.2	CAI-1	0.024	0.802	0.332	0.911	0.185	0.897	0.051	0.822
+	670.5465	4.2	[GL hydroxy(20:4/20:4)] 1,3-di-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-2-hydroxy-glycerol (d5)	0.023	0.636	0.002	0.595	0.001	0.4	<0.001	0.435
-	157.0366	14.4	Allantoin	0.023	1.287	0.448	1.081	0.008	1.305	0.134	1.166
-	750.5469	7.8	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.022	2.177	0.028	2.682	0.019	3.669	0.204	1.900
+	790.5598	3.9	PS(18:0/18:1(9Z))	0.022	1.284	0.002	1.614	0.021	1.471	0.094	1.4
+	344.2789	5.1	1,2-dioctanoyl-1-amino-2,3-propanediol	0.021	2.546	0.037	1.529	0.06	2.162	0.027	3.04
-	162.023	8.0	Acetylcysteine	0.021	9.438	0.004	16.806	0.028	14.366	0.004	8.663
+	229.1547	10.7	Leu-Pro	0.02	1.164	0.024	0.839	0.496	1.046	0.904	1.01
+	802.5597	3.9	[PG (17:0/20:4)] 1-heptadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	0.019	3.434	0.018	3.437	0.003	4.615	0.036	2.039
-	346.0725	13.7	Hydroxysanguinarine	0.019	3.071	0.750	0.866	0.057	2.166	0.010	3.426
+	820.5867	4.3	PE(20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.019	27.72	0.009	27.442	0.003	34.101	0.013	30.893
+	692.5598	4.3	[PC (14:2/16:0)] 1-tetradecyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.017	4.61	0.004	5.889	0.005	9.896	0.029	3.81
-	597.3044	4.4	[PI (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.017	1.424	0.564	1.125	<0.001	2.252	0.643	1.085
+	220.118	8.8	Pantothenate	0.017	1.335	0.104	1.2	0.009	1.402	0.067	1.228
+	856.5857	4.2	PC(20:3(5Z,8Z,11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.017	0.883	0.001	0.578	0.012	0.674	0.04	0.859
-	333.28	4.0	13,16,19-Docosatrienoic acid	0.016	0.108	0.016	0.125	0.016	0.105	0.018	0.135
+	136.0618	7.9	Adenine	0.016	4.734	0.003	6.621	0.027	12.157	0.001	1.813
-	121.0505	12.3	Erythritol	0.016	1.364	0.157	1.177	0.004	1.423	0.143	1.208
-	762.547	4.5	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	0.016	1.983	0.005	1.984	0.009	2.265	0.015	1.974
-	775.5515	4.0	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.015	2.218	0.075	3.611	0.010	3.292	0.026	2.209
-	606.3416	4.8	Lys-Lys-Phe-Trp	0.015	1.473	0.077	1.270	0.004	1.815	0.143	1.278
+	222.1125	15.9	Metaxalone	0.015	43.755	0.168	20.969	0.004	50.234	<0.001	62.175
+	805.4728	3.9	Okadaic acid	0.015	0.902	0.051	0.728	0.029	0.712	0.016	0.63
-	132.0301	15.5	L-Aspartate	0.014	1.216	0.005	1.265	<0.001	1.856	0.835	0.986
+	778.5754	4.1	PE(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	0.014	1.201	<0.001	1.662	0.013	1.447	0.032	1.337

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	125.0355	8.0	Thymine	0.014	0.592	<0.001	0.468	0.272	0.736	<0.001	0.428
-	144.0124	5.7	3,4-Dehydrothiomorpholine-3-carboxylate	0.013	14.647	0.012	29.667	0.019	21.930	0.004	10.267
+	174.0955	15.1	7-methylthioheptanonitrile oxide	0.013	1.967	0.113	1.605	0.061	1.915	0.178	1.591
+	171.0765	10.5	acetonitrile adduct of pyrroline carboxylate	0.013	1.43	0.315	1.201	0.001	1.565	0.101	1.242
+	348.0702	14.1	AMP	0.013	1.871	0.003	2.507	0.006	2.828	0.014	1.609
+	114.0663	10.3	Creatinine	0.013	1.356	0.115	1.19	0.003	1.381	0.188	1.18
-	239.0166	16.9	L-Cystine	0.013	0.659	0.002	0.487	0.003	0.541	0.010	0.626
-	222.0983	12.5	N-acetyl -D- glucosaminitol	0.013	1.617	0.142	1.286	0.015	1.538	0.009	1.654
-	202.1085	5.0	O-Acetylcarnitine	0.013	1.634	0.033	1.310	<0.001	1.878	0.008	1.456
+	790.5765	4.3	PC(20:5(5Z,8Z,11Z,14Z,17Z)/P-18:1(11Z))	0.013	0.229	0.021	0.323	0.016	0.285	0.013	0.239
+	802.6308	4.3	[PE (18:0/22:1)] 1-octadecanoyl-2-(13Z-docosenoyl)-sn-glycero-3-phosphoethanolamine	0.012	3.313	0.004	4.732	0.024	4.028	0.229	10.567
-	774.5442	4.1	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.012	1.215	0.015	1.657	<0.001	1.461	0.017	1.441
-	242.0783	12.5	Cytidine	0.012	0.691	0.002	0.575	0.003	0.589	0.004	0.632
-	121.0406	14.8	Nicotinamide	0.012	13.741	0.001	20.838	0.001	21.973	0.032	15.802
-	425.0807	17.4	S-glutathionyl-L-cysteine	0.012	1.402	0.041	1.309	0.002	1.443	0.113	1.215
+	427.0953	17.4	S-glutathionyl-L-cysteine	0.012	1.39	0.036	1.318	0.003	1.407	0.135	1.188
+	76.07577	11.5	(R)-1-Aminopropan-2-ol	0.011	1.461	0.051	1.328	0.002	1.639	0.103	1.286
-	189.0405	11.1	[FA hydroxy,oxo(7:0/2:0)] 4-hydroxy-2-oxo-Heptanedioic acid	0.011	1.525	0.190	1.181	0.001	1.564	0.014	1.395
-	124.9913	11.0	2-Hydroxyethanesulfonate	0.011	1.397	0.021	1.339	<0.001	1.618	0.010	1.327
-	103.0399	8.2	(R)-3-Hydroxybutanoate	0.010	1.549	0.074	1.388	0.035	1.497	0.105	1.274
+	703.5751	7.8	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.01	2.09	0.006	2.417	0.014	3.069	0.051	2.055
-	613.1377	17.9	CMP-N-acetylneuraminate	0.010	4.183	0.001	9.914	<0.001	8.272	0.008	3.504
+	690.5079	4.3	PC(14:1(9Z)/15:0)	0.01	204.061	0.002	199.732	0.144	386.27	<0.001	247.632
+	740.5591	4.3	PC(18:3(6Z,9Z,12Z)/P-16:0)	0.01	0.303	0.006	0.222	0.005	0.165	0.009	0.285
+	399.2507	4.3	Tris(butoxyethyl)phosphate	0.01	0.771	0.027	0.627	0.01	0.743	0.012	0.638

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
+	777.5627	4.1	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.009	1.452	0.005	1.685	0.001	1.835	0.182	1.379
-	132.0494	16.0	4-methylthiobutanaldoxime	0.009	1.304	0.647	1.048	0.423	1.122	0.093	1.186
-	346.0558	14.1	AMP	0.009	1.924	0.002	2.900	0.004	3.111	0.011	1.748
-	131.0461	16.0	L-Asparagine	0.009	1.312	0.269	1.106	0.012	1.262	0.086	1.179
+	175.0714	15.4	N-Formimino-L-glutamate	0.009	1.312	0.002	1.373	<0.001	2.197	0.797	0.979
+	731.6069	4.5	SM(d18:0/18:1(9Z))	0.009	0.474	0.492	1.171	0.272	0.787	0.01	0.509
-	290.0882	13.6	2,7-Anhydro-alpha-N-acetylneuraminic acid	0.008	1.950	0.272	1.262	0.168	1.435	0.194	1.474
-	245.1142	12.9	Glu-Val	0.008	3.323	0.101	2.124	<0.001	5.292	0.005	2.535
+	545.3432	4.8	Ile-Lys-Trp-Val	0.008	0.493	0.004	0.42	0.013	0.533	0.002	0.335
+	866.6639	4.2	PC(18:3(6Z,9Z,12Z)/24:1(15Z))	0.008	2.563	0.003	3.343	0.006	2.253	0.046	3.553
-	187.0378	13.5	xylitol chloride adduct	0.008	1.394	0.045	1.333	0.001	1.516	0.423	1.122
-	337.3113	4.0	[FA (22:0)] 13Z-docosenoic acid	0.007	0.403	0.330	0.705	0.052	0.558	0.695	0.868
-	645.4501	3.9	[GP (14:0/18:1)] 1-tetradecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphate	0.007	11.886	0.037	9.779	0.015	21.160	0.005	9.291
-	740.5239	4.2	[PE (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	0.007	30.880	0.002	34.358	<0.001	49.787	0.008	20.618
+	751.5473	4.2	[PG (17:0/17:0)] 1,2-diheptadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.007	1.128	<0.001	1.351	0.002	1.329	0.016	1.141
+	208.075	15.6	2H-Dibenz[b,f]azepin-2-one	0.007	11.425	0.011	12.499	0.008	20.51	0.003	15.067
+	761.4466	3.9	Avermectin A2a monosaccharide	0.007	0.644	0.004	0.624	0.015	0.737	0.002	0.631
+	155.0927	10.3	creatinine acetonitrile adduct	0.007	1.286	0.182	1.154	0.008	1.349	0.206	1.167
-	171.1391	4.3	Decanoic acid	0.007	0.828	0.038	0.876	0.104	0.864	0.188	0.912
-	437.2672	4.8	[GP (18:0)] 1-octadecanoyl-2-sn-glycero-3-phosphate	0.006	0.720	0.049	0.830	0.995	1.001	0.001	0.614
+	776.5596	4.1	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.006	1.442	0.007	1.541	0.003	1.635	0.065	1.372
-	225.0994	16.4	Carnosine	0.006	1.873	0.208	1.384	0.124	1.474	0.300	1.361
-	126.905	10.3	hydrogen iodide	0.006	0.579	<0.001	0.244	<0.001	44.093	<0.001	0.186
+	162.0761	11.6	L-2-Aminoadipate	0.006	4.056	0.002	4.392	<0.001	4.518	0.036	3.701
+	241.0311	16.9	L-Cystine	0.006	0.639	0.001	0.479	0.001	0.512	0.005	0.61

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	291.1248	4.0	SB 206553	0.006	68.607	0.005	52.267	<0.001	199.445	0.004	53.170
-	111.0199	9.0	Uracil	0.006	1.776	0.333	1.247	0.005	1.892	0.004	1.993
-	343.1703	4.4	[FA (24:6)] 6,9,12,15,18,21-Tetracosahexaynoic acid	0.005	0.824	0.099	0.903	0.342	0.918	0.006	0.779
-	671.4655	4.0	[GP (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphate	0.005	10.773	0.005	7.973	0.004	17.648	0.003	8.188
+	864.6486	4.2	[PC (20:0/22:5)] 1-eicosanoyl-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.005	3.844	0.004	3.821	<0.001	3.957	<0.001	4.667
+	689.5595	7.8	[SP (18:0/14:0)] N-(octadecanoyl)-tetradecasphing-4-enine-1-phosphoethanolamine	0.005	1.989	0.007	1.97	0.031	2.6	0.144	1.688
+	134.0811	7.9	1-deoxyxylonojirimycin	0.005	3.949	<0.001	4.97	<0.001	7.304	0.012	2.165
-	113.0243	14.1	2-Hydroxy-2,4-pentadienoate	0.005	1.846	0.005	1.847	0.026	1.719	0.031	1.767
+	146.027	5.6	3,4-Dehydrothiomorpholine-3-carboxylate	0.005	11.809	0.002	18.999	0.001	15.585	<0.001	8.834
+	146.027	7.9	3,4-Dehydrothiomorpholine-3-carboxylate	0.005	9.844	0.001	15.838	0.005	13.791	<0.001	8.073
+	205.0858	15.6	3-Butylidene-7-hydroxyphthalide	0.005	27.707	0.219	1.459	0.028	31.033	0.077	18.771
+	311.0902	14.8	6-Deoxyjacareubin	0.005	2.55	0.025	3.644	0.002	3.342	0.012	2.125
+	100.0216	7.9	Allylisothiocyanate	0.005	11.878	0.001	19.133	0.004	16.676	<0.001	9.632
-	178.0721	11.8	D-Glucosamine	0.005	1.453	<0.001	1.699	0.001	1.589	0.008	1.407
+	392.1856	4.1	Glu-Ile-Met	0.005	0.642	<0.001	0.7	<0.001	0.617	<0.001	0.596
+	90.0914	18.6	N-dimethylethanolamine	0.005	1.473	0.668	1.063	0.758	0.945	0.431	1.899
-	762.5471	7.8	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	0.005	2.822	0.038	2.404	0.016	4.094	0.032	2.364
+	822.6027	4.3	PE(18:4(6Z,9Z,12Z,15Z)/24:1(15Z))	0.005	22.029	0.02	16.958	0.034	15.907	0.003	26.617
+	754.5756	4.3	PE(20:2(11Z,14Z)/P-18:1(11Z))	0.005	0.09	0.006	0.112	0.006	0.122	0.008	0.178
-	748.5278	4.1	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.005	1.307	<0.001	1.624	0.005	1.563	0.270	1.132
-	423.0299	15.1	Thiamin diphosphate	0.005	7.443	0.002	6.131	0.006	9.133	0.009	8.171
-	147.0298	15.6	(R)-2-Hydroxyglutarate	0.004	1.231	0.275	1.080	<0.001	1.510	0.069	1.096
-	409.236	4.3	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.004	0.389	0.018	0.551	0.008	0.474	0.003	0.360
-	735.5006	4.0	[GP (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phosphosulfocholine	0.004	18.560	0.002	20.080	0.005	27.137	0.006	29.771
-	885.5487	3.9	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.004	1.284	0.001	1.502	0.016	1.525	0.064	1.305

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	465.3178	4.8	[ST (3:0/3:0/3:0)] (5Z,7E)-(1S,3R)-24,24-difluoro-24a-homo-9,10-seco-5,7,10(19)-cholestatrien-1,3,25-triol	0.004	1.232	0.007	1.125	<0.001	1.540	0.022	1.147
-	812.544	3.9	1-20:0-2-18:3-phosphatidylserine	0.004	1.450	0.001	1.648	0.019	1.658	0.068	1.471
-	325.2747	4.0	2-Oxophytanate	0.004	2.506	0.036	1.964	0.001	3.417	0.012	2.451
+	205.0861	4.3	3-Butylidene-7-hydroxyphthalide	0.004	0.33	0.007	0.368	0.003	0.29	0.003	0.277
-	437.1623	15.0	3'-O-demethyl-4'-N-demethyl-staurosporine	0.004	0.123	0.003	0.039	0.003	0.030	0.004	0.118
-	357.1498	4.2	Cilastatin	0.004	0.619	0.005	0.687	0.003	0.565	<0.001	0.600
+	147.0304	7.9	Diallyl disulfide	0.004	11.331	0.001	18.099	0.004	15.204	<0.001	9.188
-	527.2971	4.8	His-Leu-Leu-Phe	0.004	1.548	0.021	1.571	0.607	0.902	0.048	0.680
+	176.103	16.6	L-Citrulline	0.004	1.885	0.02	1.544	0.067	1.349	0.009	1.979
+	750.544	4.2	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.004	1.125	<0.001	1.34	0.003	1.313	0.023	1.122
+	835.5315	3.9	PI(16:0/18:2(9Z,12Z))	0.004	3.337	<0.001	3.253	0.001	4.506	<0.001	3.249
+	736.5128	4	PS(16:0/16:0)	0.004	11.369	<0.001	20.536	<0.001	22.787	0.002	16.296
+	325.0547	18.5	ribavirin-5'-monophosphate	0.004	1.531	0.01	1.467	<0.001	1.852	0.04	1.418
+	622.4434	4.3	[PC (10:0/14:0)] 1-decanoyl-2-tetradecanoyl-sn-glycero-3-phosphocholine	0.003	0.337	0.01	0.489	0.005	0.404	0.008	0.469
+	728.523	4.4	[PC (14:0/18:3)] 1-tetradecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	0.003	7.808	<0.001	8.03	0.002	11.233	0.005	7.521
-	500.2782	4.8	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.003	0.752	0.003	0.718	<0.001	0.438	<0.001	0.328
+	775.5469	4.2	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.003	2.559	0.007	2.491	0.017	2.569	0.156	1.602
-	743.4868	3.8	1-18:2-2-trans-16:1-phosphatidylglycerol	0.003	70.369	<0.001	72.063	<0.001	118.591	<0.001	71.210
-	144.0124	7.9	3,4-Dehydrothiomorpholine-3-carboxylate	0.003	14.479	0.002	22.747	0.001	21.620	<0.001	11.868
+	146.1176	5.1	4-Trimethylammoniobutanoate	0.003	0.447	0.004	0.481	0.005	0.502	0.005	0.486
+	174.0874	16	5-Guanidino-2-oxopentanoate	0.003	1.303	0.257	1.115	0.005	1.413	0.129	1.193
+	188.103	15.7	5-guanidino-3-methyl-2-oxo-pentanoate	0.003	1.439	0.244	1.189	0.007	1.605	0.197	1.262
-	501.2817	4.8	Ala-Lys-Trp-Val	0.003	0.747	0.005	0.736	<0.001	0.436	<0.001	0.325
-	585.3602	4.8	Arg-Lys-Gln-Arg	0.003	0.719	0.032	0.825	0.886	1.011	0.001	0.628
-	241.0124	16.9	D-myo-Inositol 1,2-cyclic phosphate	0.003	0.492	<0.001	0.211	<0.001	0.271	0.003	0.474
-	442.017	18.3	GDP	0.003	3.290	0.002	3.674	0.008	3.862	0.006	3.334

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	611.1442	16.0	Glutathione disulfide	0.003	30.919	0.012	1143.958	0.100	434.500	0.025	19.159
-	160.0615	9.7	L-2-Aminoadipate	0.003	1.546	0.009	1.446	<0.001	1.907	0.019	1.406
-	201.1245	5.1	Leu-Ala	0.003	0.321	0.002	0.253	0.003	0.259	0.003	0.288
+	203.1392	5.1	Leu-Ala	0.003	0.478	0.001	0.334	0.001	0.335	0.001	0.361
+	116.0707	13.4	L-Proline	0.003	1.358	0.107	1.173	0.008	1.288	0.142	1.184
-	736.5291	4.2	PC(18:4(6Z,9Z,12Z,15Z)/P-16:0)	0.003	0.501	0.021	0.688	<0.001	0.333	0.034	0.673
+	722.513	4.2	PE(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	0.003	2.737	0.028	2.269	0.024	1.902	0.089	1.559
+	343.1692	4.4	penicillin K	0.003	0.211	0.004	0.246	0.002	0.116	0.003	0.203
-	278.1145	8.0	Phe-Asn	0.003	0.063	0.003	0.035	0.003	0.032	0.003	0.029
-	320.1001	15.1	S-Glutaryldihydrolipoamide	0.003	0.367	0.001	0.087	0.001	0.105	0.002	0.361
-	103.0399	10.0	(R)-3-Hydroxybutanoate	0.002	2.739	0.006	2.453	0.003	2.672	0.006	2.580
+	496.3398	7.9	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	0.002	1.243	0.003	1.41	<0.001	1.981	0.644	1.034
+	480.3449	4.9	[PC (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphocholine	0.002	0.775	0.028	0.858	0.497	0.952	<0.001	0.676
-	492.3459	4.6	[PC (17:1)] 1-(1Z-heptadecenyl)-sn-glycero-3-phosphocholine	0.002	1.632	0.496	1.149	0.005	1.559	0.002	1.660
+	524.3713	4.8	[PC (18:0)] 1-octadecanoyl-sn-glycero-3-phosphocholine	0.002	0.756	0.108	0.888	0.399	1.065	<0.001	0.642
-	716.5233	4.2	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	0.002	8.342	0.005	10.558	0.001	11.993	<0.001	10.600
+	502.2929	4.8	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.002	0.746	0.003	0.718	<0.001	0.421	<0.001	0.33
-	271.2281	4.0	16-hydroxypalmitate	0.002	0.394	0.148	0.800	0.003	0.438	0.021	0.470
+	134.0811	15.3	1-deoxyxylonojirimycin	0.002	2.298	0.074	1.791	0.038	1.731	0.008	1.946
-	791.5428	4.1	acyl phosphatidylglycerol (n-C12:0)	0.002	2.820	<0.001	2.549	<0.001	2.708	<0.001	3.149
-	160.0437	5.1	allylcysteine	0.002	11.675	<0.001	17.000	0.001	14.100	<0.001	9.444
+	249.0718	17.9	Asp-Asp	0.002	2.335	<0.001	1.936	0.001	2.894	0.002	1.955
-	304.0609	19.2	Atherospermidine	0.002	0.115	0.003	0.257	0.003	0.245	0.001	0.098
-	402.0108	17.4	CDP	0.002	7.328	0.001	5.899	<0.001	9.043	0.001	6.630
-	173.0091	18.3	cis-Aconitate	0.002	1.362	0.018	1.293	<0.001	1.679	0.009	1.357
-	191.0198	18.6	Citrate	0.002	1.561	0.006	1.41	<0.001	1.857	0.001	1.498

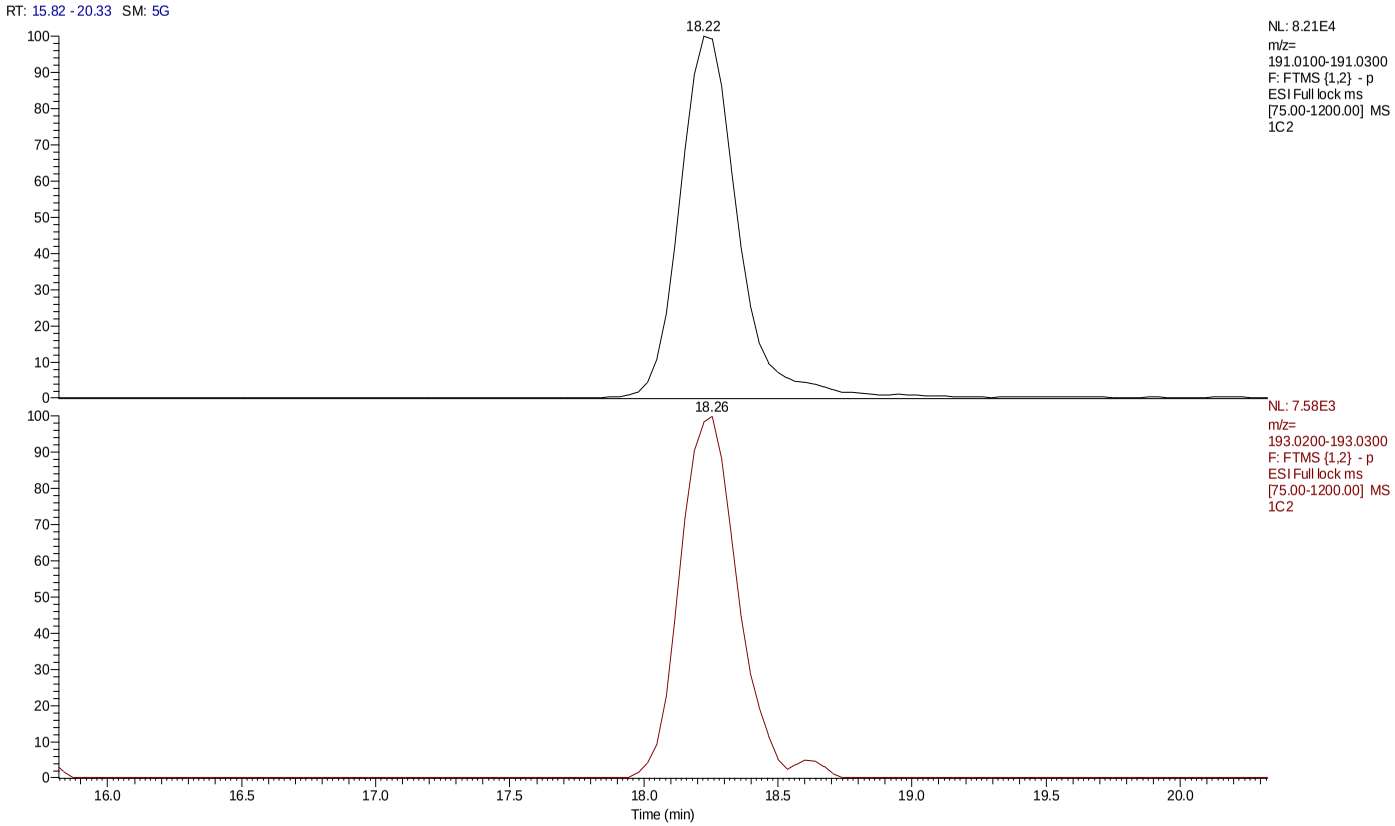
DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	611.1442	17.9	Glutathione disulfide	0.002	3.408	0.001	7.271	<0.001	6.201	0.002	2.756
+	613.1595	17.9	Glutathione disulfide	0.002	3.21	0.001	6.693	<0.001	5.378	0.002	2.519
+	190.0499	4.2	Kynurenate	0.002	0.827	<0.001	0.721	0.001	0.77	0.001	0.735
-	435.2516	4.2	LPA(0:0/18:1(9Z))	0.002	0.195	0.002	0.197	0.004	0.317	0.003	0.314
+	134.027	8.5	L-thiazolidine-4-carboxylate	0.002	9.412	<0.001	13.408	<0.001	11.245	<0.001	7.612
-	438.2706	4.8	Lys-Val-Pro-Pro	0.002	0.580	0.025	0.770	0.742	0.971	<0.001	0.513
+	332.2009	4.5	Mahanimbine	0.002	0.453	0.001	0.297	<0.001	0.267	0.001	0.374
-	558.0641	15.2	N10-(bromoacetyl)-5,8-dideazafolate	0.002	53.826	<0.001	76.385	0.006	81.026	0.003	53.247
+	161.1285	25.2	N6-Methyl-L-lysine	0.002	1.949	0.004	1.534	0.003	1.877	0.002	1.805
-	176.0386	7.9	N-Formyl-L-methionine	0.002	3.416	0.011	3.808	0.006	5.596	<0.001	2.466
+	156.0419	15.5	N-Methylethanolamine phosphate	0.002	2.312	0.007	5.582	<0.001	8.256	0.623	0.894
-	688.492	4.3	PC(14:1(9Z)/15:0)	0.002	21.684	0.006	27.690	0.001	47.303	0.014	21.940
-	307.2645	4.0	Sclareol	0.002	0.389	<0.001	0.289	0.001	0.356	0.001	0.328
-	251.2022	4.1	[FA (16:2)] 9,12-hexadecadienoic acid	0.001	0.247	<0.001	0.227	0.001	0.326	0.003	0.285
-	309.2799	4.0	[FA (20:0)] 11Z-eicosenoic acid	0.001	0.536	0.001	0.381	<0.001	0.387	<0.001	0.415
-	494.3252	4.9	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	0.001	1.816	0.225	1.318	0.002	1.820	0.009	1.570
+	734.5703	4.3	[PC (16:0/16:0)] 1-hexadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.001	1.584	<0.001	1.841	0.006	1.877	0.013	1.78
+	780.5543	4.3	[PC (16:1/20:4)] 1-(9Z-hexadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.001	1.163	0.617	1.021	0.004	1.259	0.075	1.095
+	508.3397	4.9	[PC (17:0)] 1-(10Z-heptadecenoyl)-sn-glycero-3-phosphocholine	0.001	1.889	<0.001	2.05	<0.001	3.24	0.021	1.509
+	838.6326	4.2	[PC (18:0/22:4)] 1-octadecanoyl-2-(7Z,10Z,13Z,16Z-docosatetraenoyl)-sn-glycero-3-phosphocholine	0.001	1.219	0.002	1.253	0.065	1.147	0.005	1.247
+	568.34	4.8	[PC (22:6)] 1-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	0.001	1.486	0.002	1.499	0.002	1.894	0.86	1.03
+	538.3868	4.8	[PC acetyl(17:2)] 1-heptadecyl-2-acetyl-sn-glycero-3-phosphocholine	0.001	0.619	0.066	0.821	0.694	0.945	<0.001	0.639
-	721.501	4.0	[PG (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.001	2.682	0.006	5.783	0.004	8.042	0.010	2.341
-	880.6058	4.3	[PG (21:0/22:6)] 1-heneicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	0.001	0.226	<0.001	0.192	0.001	0.250	0.001	0.207

DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	616.4705	4.5	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphate	0.001	1.725	<0.001	1.884	0.016	1.881	<0.001	1.872
+	467.3327	4.8	[ST (3:0/3:0/3:0)] (5Z,7E)-(1S,3R)-24,24-difluoro-24a-homo-9,10-seco-5,7,10(19)-cholestatrien-1,3,25-triol	0.001	1.236	0.912	1.012	0.007	1.423	0.493	1.069
+	814.56	3.9	1-20:0-2-18:3-phosphatidylserine	0.001	1.284	0.014	1.231	0.035	1.259	0.043	1.265
-	838.559	3.9	1-22:1-2-18:3-phosphatidylserine	0.001	1.594	0.001	1.865	0.015	1.721	0.038	1.617
-	111.0086	18.6	2-Furoate	0.001	1.679	0.094	1.323	<0.001	1.764	0.007	1.471
-	125.001	13.5	2-Hydroxyethylphosphonate	0.001	2.147	0.374	1.229	0.006	1.795	0.020	2.427
+	356.1186	14.4	5-methylthiopentyldesulfoglucosinolate	0.001	0.765	<0.001	0.655	<0.001	0.667	0.001	0.748
+	86.06006	15.1	Acetone cyanohydrin	0.001	1.433	0.002	1.294	0.001	1.369	0.004	1.277
-	260.0888	16.3	Ala-Asp-Gly	0.001	5.816	0.051	1.595	<0.001	12.990	<0.001	5.198
+	503.2962	4.8	Ala-Lys-Trp-Val	0.001	0.712	0.008	0.747	<0.001	0.416	<0.001	0.292
+	162.0583	5.1	allylcysteine	0.001	8.039	<0.001	12.132	<0.001	9.904	<0.001	7.088
-	403.1486	15.1	Asp-Pro-Ser-Ser	0.001	0.776	<0.001	0.384	<0.001	0.487	<0.001	0.751
-	182.0588	15.6	Choline phosphate	0.001	3.957	0.008	24.902	<0.001	13.422	0.033	2.124
-	310.1257	15.3	Citalopram alcohol	0.001	1.614	0.133	0.893	0.019	0.822	<0.001	1.610
+	175.0537	8.5	D-5-(2'-methylthioethyl)-hydantoin	0.001	9.291	<0.001	13.603	<0.001	11.455	<0.001	7.881
+	773.6253	4.3	demethylmenaquinol-9	0.001	9.607	<0.001	10.987	<0.001	17.119	<0.001	8.984
-	227.0674	8.7	Deoxyuridine	0.001	1.468	0.105	1.201	<0.001	1.570	0.027	1.321
-	115.0035	16.4	Fumarate	0.001	3.442	0.001	3.015	<0.001	6.246	0.002	2.792
-	249.055	14.6	gamma-L-Glutamyl-L-cysteine	0.001	2.403	<0.001	157.199	<0.001	38.607	<0.001	2.784
+	251.0696	14.6	gamma-L-Glutamyl-L-cysteine	0.001	2.987	<0.001	141.928	<0.001	38.682	0.004	2.78
-	604.0697	18.6	GDP-mannose	0.001	3.112	<0.001	18.436	<0.001	10.726	0.001	2.700
+	247.1289	12.9	Glu-Val	0.001	3.079	0.059	1.694	<0.001	5.669	0.002	2.751
-	146.0247	7.9	Indole-5,6-quinone	0.001	17.633	0.001	21.200	<0.001	16.204	0.007	11.030
-	616.2219	15.0	Labriformin	0.001	0.103	0.001	0.025	0.001	0.028	0.001	0.154
+	203.1392	7.9	Leu-Ala	0.001	0.457	0.009	0.435	<0.001	0.364	0.004	0.488
-	132.0124	8.5	L-thiazolidine-4-carboxylate	0.001	8.997	<0.001	13.474	<0.001	11.206	<0.001	7.386
-	502.2945	4.8	LysoPE(0:0/20:3(11Z,14Z,17Z))	0.001	1.785	0.001	1.772	0.105	1.286	0.154	0.743

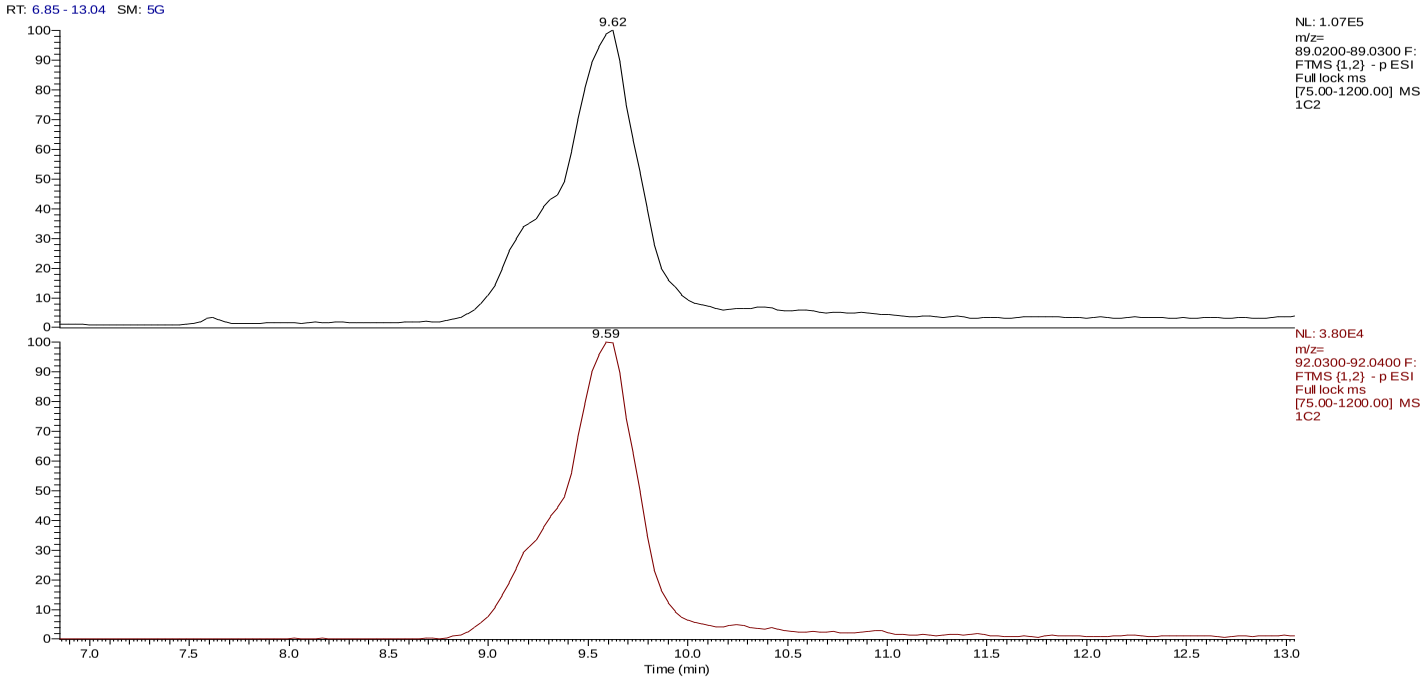
DM	m/z	RT	Name	CpG P	CpG FC	C11a P	C11a FC	C12b P	C12 FC	C19o P	C19o FC
-	360.123	15.0	Met-Asp-Pro	0.001	0.456	<0.001	0.407	<0.001	0.321	<0.001	0.442
+	141.0658	9.8	Methylimidazoleacetic acid	0.001	1.868	0.131	1.311	0.004	1.673	0.017	1.534
+	170.0924	15.4	N(pi)-Methyl-L-histidine	0.001	7.033	0.002	4.093	<0.001	5.348	<0.001	6.961
-	334.1257	16.6	N4-(Acetyl-beta-D-glucosaminyl)asparagine	0.001	4.196	0.023	3.337	0.001	5.807	0.006	3.495
+	157.0972	13.4	N-acetyl prolinamide or isomer	0.001	1.457	0.129	1.204	0.004	1.481	0.041	1.326
-	380.0154	17.4	N-Acetyl-D-glucosamine 1,6-bisphosphate	0.001	19.036	<0.001	13.216	0.003	31.997	0.011	21.857
+	123.0553	8	Nicotinamide	0.001	1.695	0.008	1.379	<0.001	1.617	0.002	1.559
+	860.6169	4.2	PC(20:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.001	2.458	<0.001	2.416	0.007	2.607	<0.001	2.669
+	858.602	4.2	PC(20:2(11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.001	0.708	0.002	0.456	0.004	0.459	0.001	0.737
+	796.5869	4.2	PE(18:0/22:4(7Z,10Z,13Z,16Z))	0.001	14.901	<0.001	15.606	<0.001	15.402	<0.001	17.383
+	824.6179	4.3	PE(18:3(6Z,9Z,12Z)/24:1(15Z))	0.001	13.541	0.014	4.573	0.027	7.507	0.009	10.388
+	724.528	4.2	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.001	0.839	0.15	0.934	0.037	0.863	0.011	0.855
-	795.5173	3.8	PG(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.001	1.175	0.001	0.829	0.163	0.934	0.217	1.087
+	809.5161	3.9	PI(16:0/16:1(9Z))	0.001	18.323	<0.001	17.702	<0.001	29.82	<0.001	17.879
-	188.075	4.8	Prenyl-L-cysteine	0.001	10.460	<0.001	15.509	<0.001	13.415	<0.001	8.168
+	190.0897	4.8	Prenyl-L-cysteine	0.001	7.66	<0.001	11.389	<0.001	9.106	<0.001	5.883
-	734.4977	4.0	PS(16:0/16:0)	0.001	9.776	0.001	11.814	<0.001	16.127	0.004	14.346
+	834.5283	3.9	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.001	2.339	<0.001	2.187	<0.001	3.075	0.008	2.098
-	806.4969	3.9	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	0.001	12.857	<0.001	12.793	<0.001	22.564	<0.001	14.742
+	203.085	5.1	Pyrene	0.001	10.691	0.001	16.334	<0.001	13.386	<0.001	8.725
-	307.1147	16.4	S-8-methylthiooctylhydroximoyl-L-cysteine	0.001	4.403	0.001	3.778	<0.001	5.420	0.002	3.912
+	144.1019	11.3	Stachydrine	0.001	1.619	0.009	1.669	0.004	2.01	0.124	1.38
+	387.2892	3.8	Testosterone isocaproate	0.001	0.664	<0.001	0.509	<0.001	0.393	<0.001	0.71
-	151.0261	11.7	Xanthine	0.001	0.223	0.001	0.203	0.001	0.259	0.001	0.181
+	666.1324	13.8	NADH	<0.001	1.881	<0.001	2.631	<0.001	2.705	<0.001	2.071
+	810.1336	12.7	AcetylCoA	<0.001	3.907	<0.001	4.081	<0.001	6.584	<0.001	2.655

Appendix 13: Unlabelled (C12) and labelled (C13) (A) Citrate, (B) Lactate,(C) malate,(D) Acetyl carnitine and (E) Itaconate raw peaks.

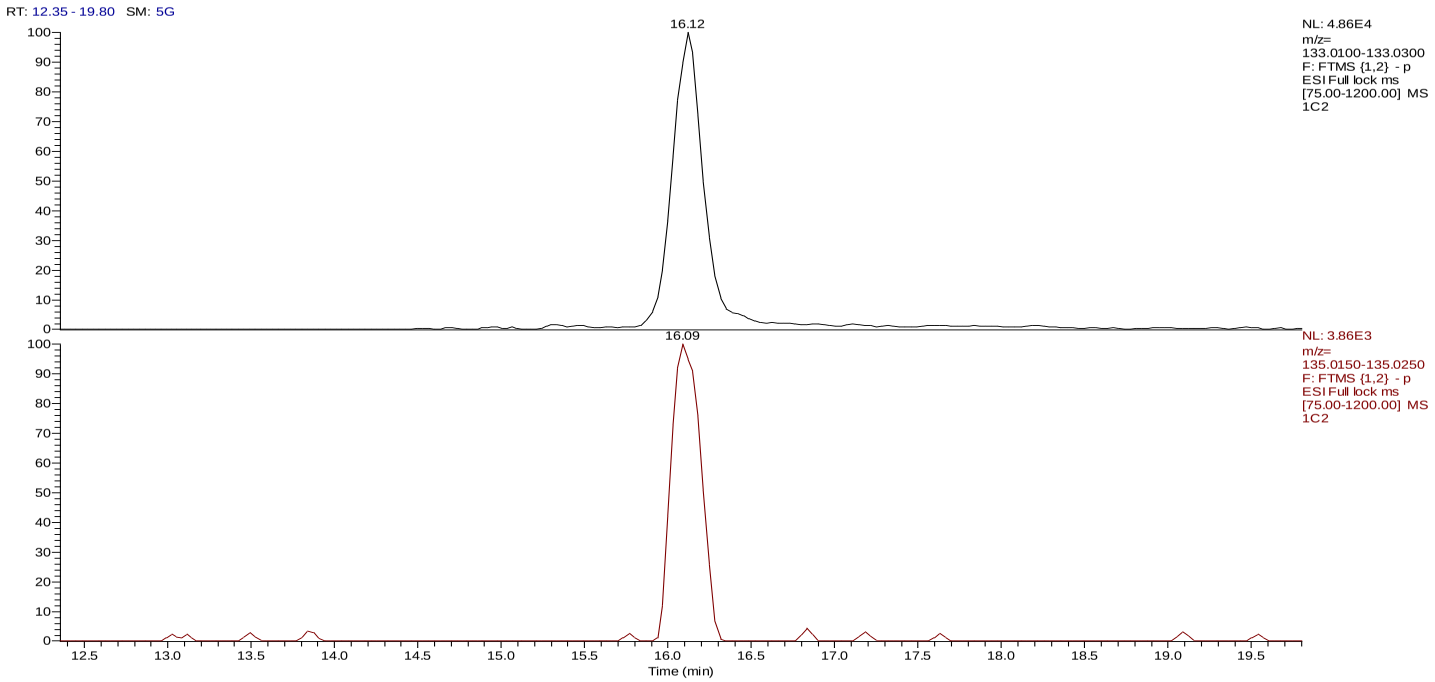
(A) Citrate and 13C2citrate



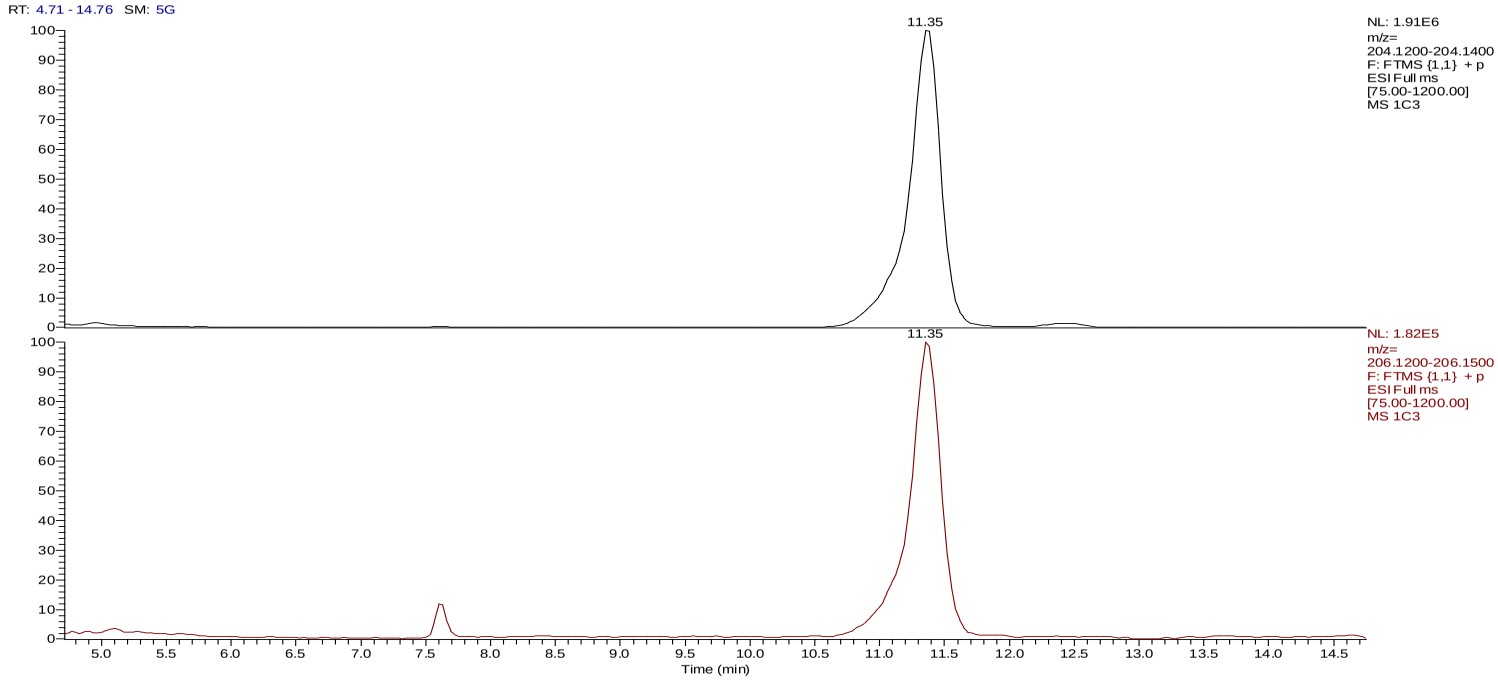
(B) Lactate and 13C3lactate



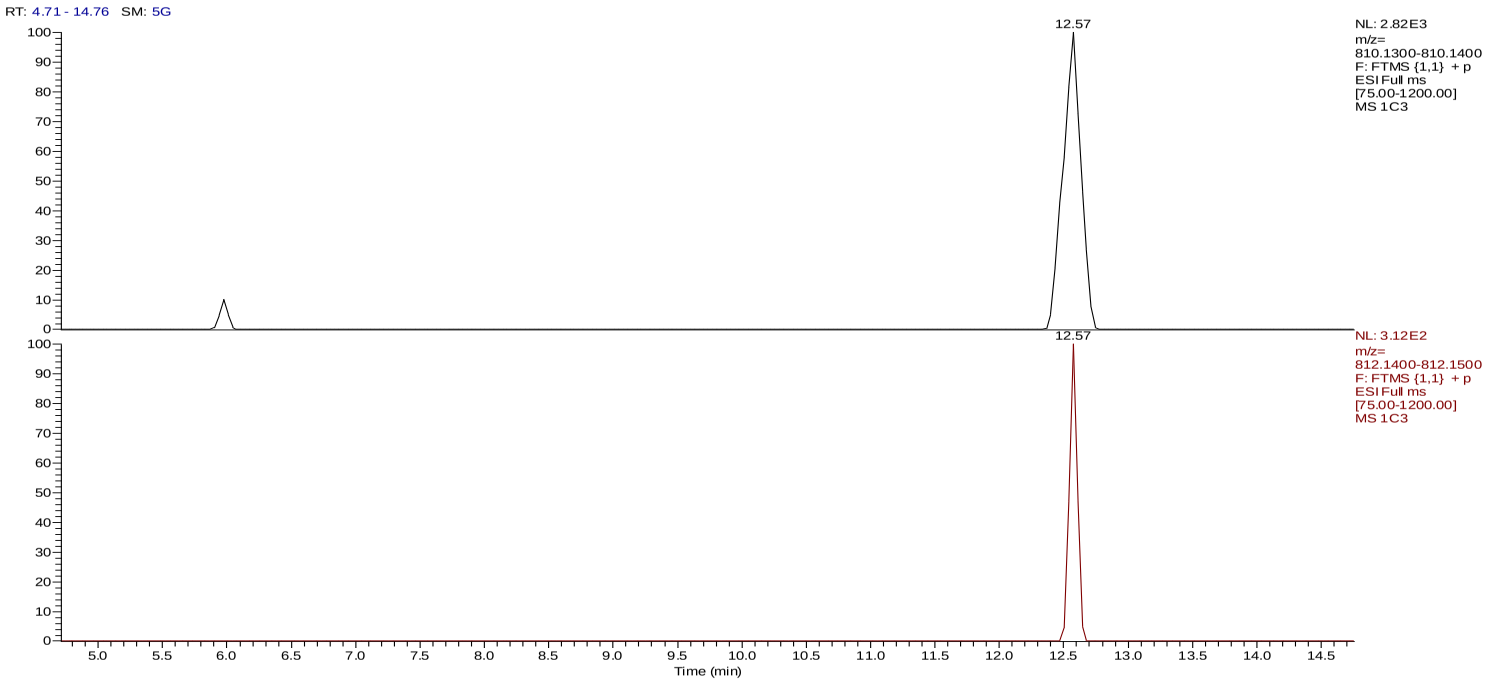
(C) Malate and 13C2 malate



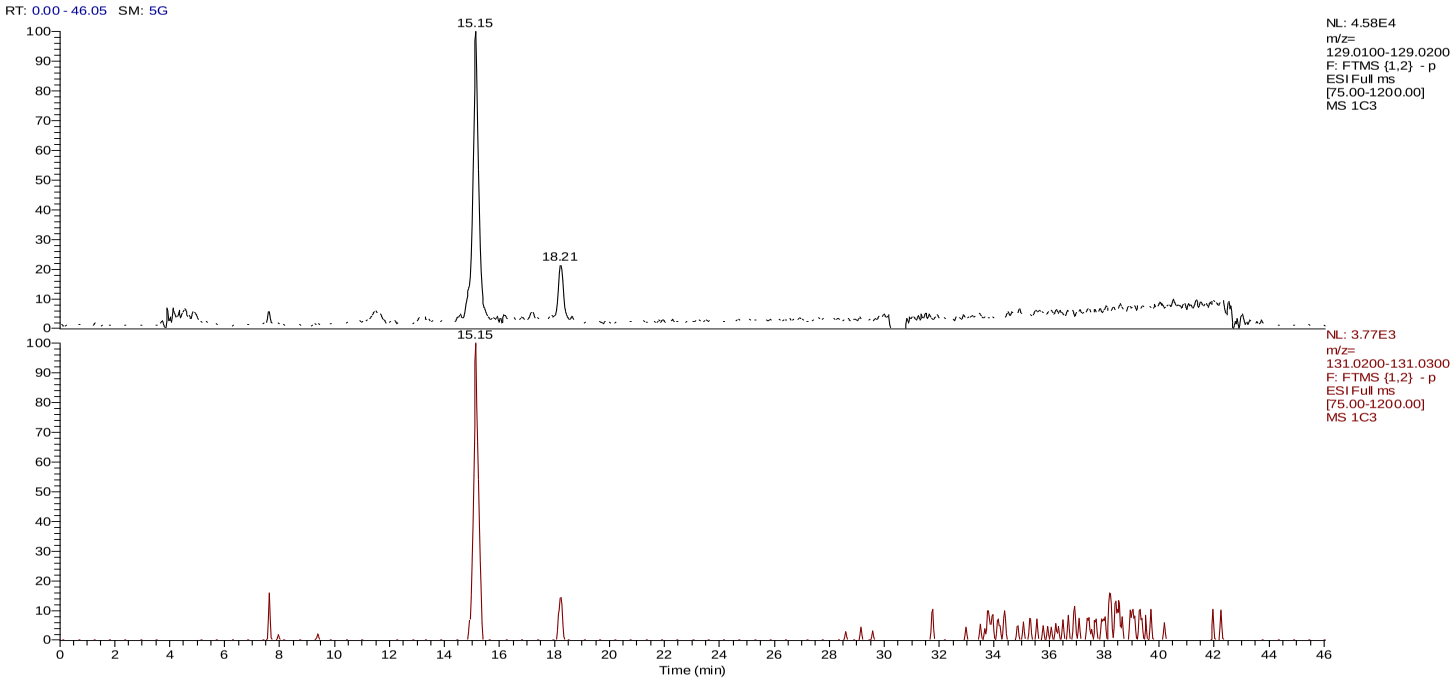
(D) Acetyl carnitine 13C2 acetylcarnitine



(E) Acetyl CoA and 13C2 acetyl CoA (cannot be seen in most samples)

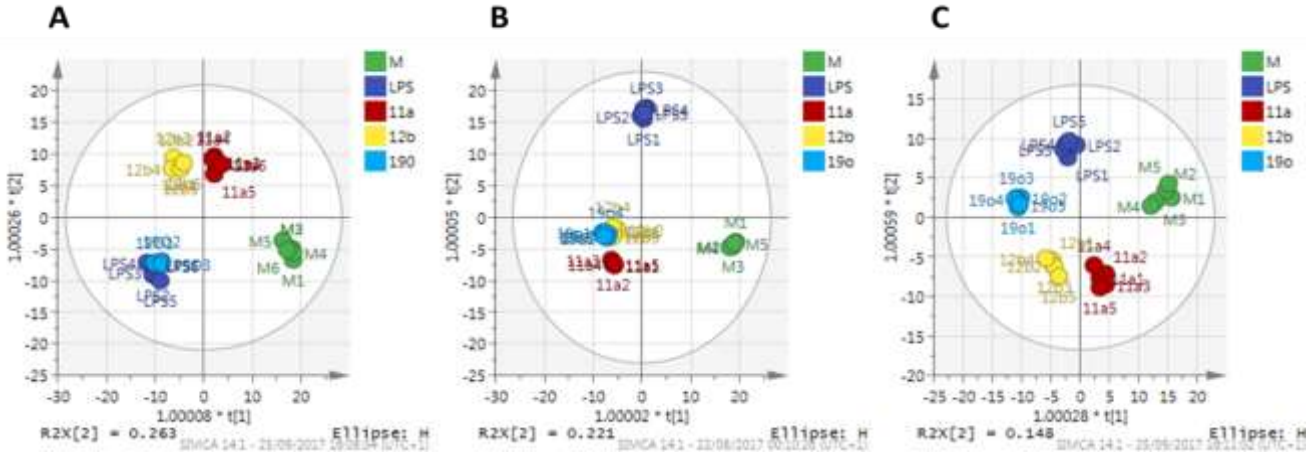


(F) Itaconate 13C2 itaconate



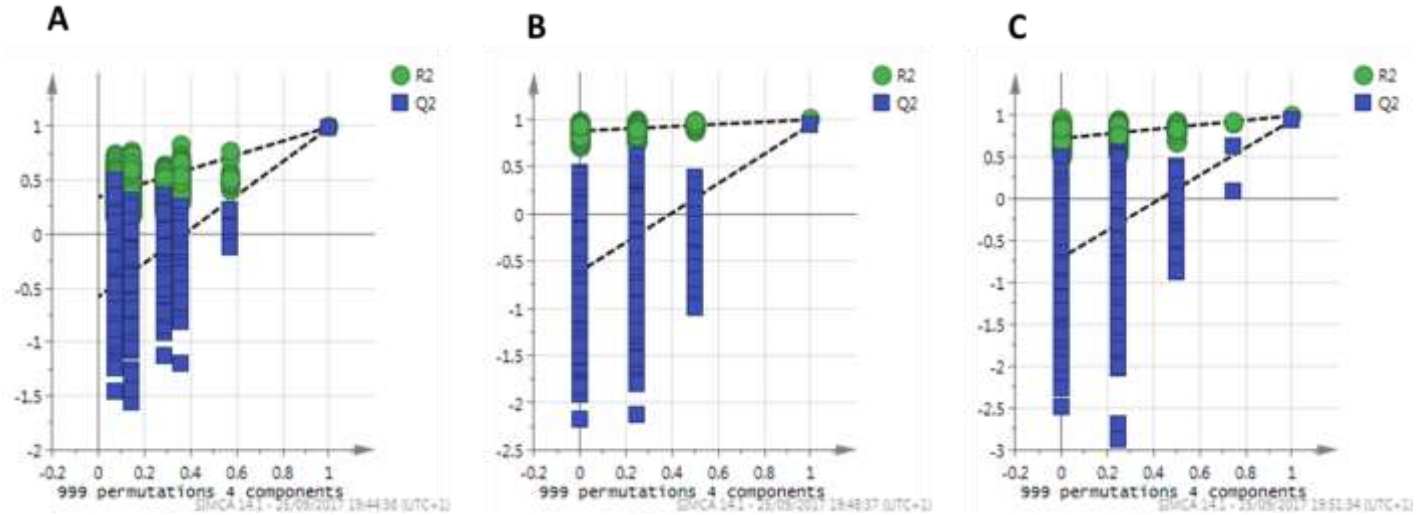
Appendix 14: **Orthogonal Partial Least Square Discriminant Analysis (OPLS-DA) score plots of the three runs of SMAs +LPS conditions**

OPLS-DA score plots for the overview of the SMAs treatment models A, B and C following LPS treatment are shown in figure 3.2.3. Each model includes five groups, group 1 (green) represents unstimulated macrophages, group 2 (red) represents 11a treatment followed by LPS, group 3 (yellow) represents 12b treatment followed by LPS, group 4 (light blue) represents 19o treatment followed by LPS, and group 5 in dark blue colour indicates LPS alone treatment. Model A consists of 347 variables and was explained by four predictive x-score components and 1orthogonal ones (4+1). The predictive components explain 83.8 % of the variation in x while orthogonal components explain 4.31% of the variation and so the total explained variation by x, R2X (cum), is equal to 88.1%, R2Y (cum) = 1, R2 (cum) = 94.6%, and the goodness of prediction Q2 (cum) is equal to 87.1%. Model B includes 589 variables and was explained by four predictive x-score components and 6 orthogonal ones (4+6). Its Predictive components explain 60.3 % of the variation in x while its orthogonal ones explain 27.1 % of the variation. The R2X explained variation is equal to 87.4 % while R2Y (cum) = 1, R2 (cum) = 99.3% and the goodness of prediction Q2 (cum) = 88.4%. 433 variables by model C were explained by four predictive x-score components and four orthogonal ones (4+4) in which predictive components explain 54.1 % of the variation in x while its orthogonal ones explain 30.4 % of the variation. It's R2Y (cum) = 1, R2 (cum) = 92.5%, and C goodness of prediction Q2 (cum) is equal to 81.5 %.



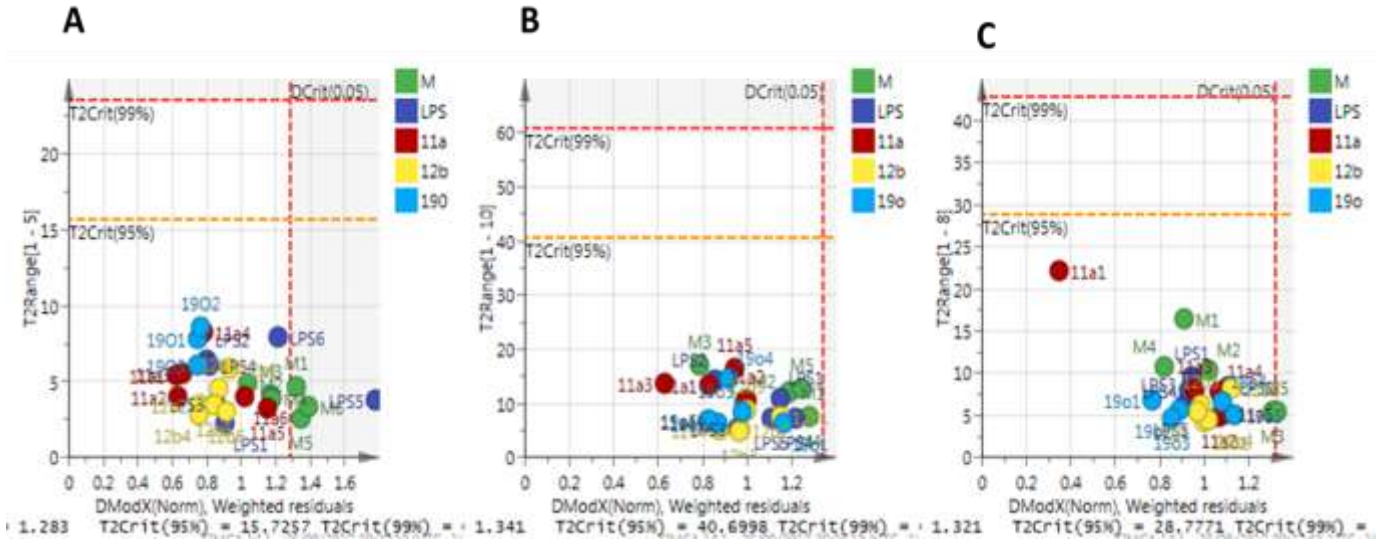
Appendix 15: Permutations test of models of SMAs in the presence of the three runs of SMAs +LPS conditions

Models' validation, using a 999 random permutations test for the supervised models of SMA (11a, 12b or 19o) pre-treated macrophages followed by LPS versus LPS alone stimulation has was generated by using SMICA. The goodness of fit (R2) and predictive capability (Q2) values on the right-hand side of the plot are of the true model, whereas the permutated model parameters are represented on the left-hand side of the plot. The correlation coefficients between true and permutated models represent the X axis and has a correlation of 1.0 with itself. SMA pre-treatment of macrophages followed by LPS stimulation in models (A, B and C) exhibited higher true values, R2 and Q2, than those of the permutated models. This classifies investigated the SMA models a true models. A model intercepts are: R 2 = (0.0, 0.0337) and Q 2 = (0.0, − 0.582), B model intercepts are R 2 = (0.0, 0.876) and Q 2 = (0.0, − 0.649) whereas model C intercepts are: R 2 = (0.0, 0.703) and Q 2 = (0.0, − 0.759).



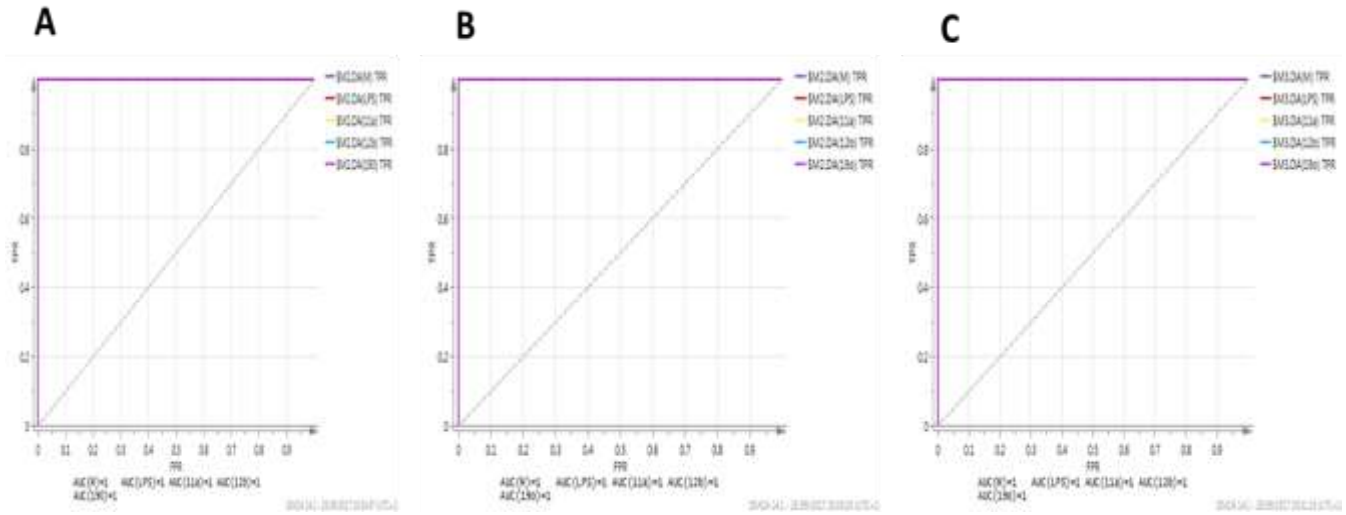
Appendix 16: Distance to model (DModX) vs Hotellings T^2 plot of the three runs of SMAs +LPS conditions

DModX on x-axis versus Hotelling's T2 on Y-axis.Hotelling's T2 on Y-axis is showing two limits on the y-axis. The first one, T2Crit (95%), is called the waring limit and is represented by a yellow dotted line whereas the second one, T2 Crit (99%), is called action limit and represented by a red dotted line. On the x-axis, the red dotted line indicates DModX uses critical distance DCrit at level 0.05. Observations are considered as strong outliers if they are located above the action limit or above the warning limit plus DModX critical limit. The Investigated **A, B** and **C** models are showing models with no strong or even moderate outliers from tested groups.



Appendix 17: Area under the receiver operating characteristics Curve (AUROCC) the three runs of SMAs +LPS conditions

ROC curves show sensitivity true positive rate (TPR) on the y-axis versus false positive rate (FPR = 1 - Specificity) on the x-axis generated using cross-validated predicted-Y values of the three (**A, B and C**) investigated OPLS-DA models. The area under the ROC curves (AUC) for unstimulated macrophages (M) is 1, LPS-treated macrophages (LPS) is 1, 11a pre-treatment of LPS-treated macrophages (11a) is 1, 12b pre-treatment of LPS-treated macrophages (12b) is 1 and AUC for 19o pre-treatment of LPS-treated macrophages is equal to 1. This assesses OPLS-DA models (A, B and C) as models with very strong power that have an excellent ability to distinguish features between unstimulated macrophages and SMA-treated ones.



Appendix 18: The list of detected metabolites that have changed following LPS treatment, LPS +11a (L11a), 12b (L12b) and 19o (L19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, RT to raw retention time and p to P-value.

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	357.1342	15.2	(+)-pinoresinol	<0.001	0.567	<0.001	0.756	0.02	0.889	<0.001	0.431
-	269.1763	4.3	(10S)-Juvenile hormone III acid diol	<0.001	9.316	<0.001	9.433	<0.001	8.9	<0.001	8.18
-	263.0384	17.7	(1R,2R)-3-[(1,2-Dihydro-2-hydroxy-1-naphthalenyl)thio]-2- oxopropanoic acid	<0.001	0.558	0.005	0.709	0.001	0.675	<0.001	0.409
-	263.0385	14.1	(1R,2R)-3-[(1,2-Dihydro-2-hydroxy-1-naphthalenyl)thio]-2- oxopropanoic acid	<0.001	0.586	0.007	0.772	0.014	0.785	<0.001	0.465
-	225.1862	4.3	(9Z)-Tetradecenoic acid	<0.001	3.725	<0.001	4.693	0.001	4.814	<0.001	6.112
-	225.1862	4.0	(9Z)-Tetradecenoic acid	<0.001	2.336	<0.001	2.397	<0.001	2.421	<0.001	3.028
+	114.055	15.1	(S)-1-Pyrroline-5-carboxylate	<0.001	0.637	0.460	0.906	0.167	0.880	<0.001	0.576
-	293.1755	4.1	[6]-Gingerol	<0.001	2.806	<0.001	3.367	<0.001	3.752	0.011	3.366
+	143.0485	15.4	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.217	<0.001	1.280	<0.001	1.683	<0.001	1.942
-	183.1391	4.2	[FA (11:0)] 10-undecenoic acid	<0.001	11.819	<0.001	11.639	<0.001	9.87	<0.001	13.149
-	191.1079	4.3	[FA (12:4)] 2E,4E,8Z,10E-dodecatetraenoic acid	<0.001	3.692	0.005	2.607	0.024	2.744	0.002	3.532
+	209.19	4.3	[FA (14:2)] 5,8-tetradecadienal	<0.001	43.104	<0.001	42.586	<0.001	38.051	<0.001	44.626
-	251.2022	4.0	[FA (16:2)] 9,12-hexadecadienoic acid	<0.001	0.429	0.742	1.043	0.107	1.179	0.069	0.761
-	305.2487	3.9	[FA (20:3)] 8Z,11Z,14Z-eicosatrienoic acid	<0.001	0.612	0.932	1.01	0.706	0.972	0.002	0.602
-	303.2332	3.9	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	<0.001	0.51	0.134	0.865	0.002	0.719	0.001	0.518
+	675.5439	4.4	[FA (32:0/2:0)] 1-(O-alpha-D-glucopyranosyl)-29-keto-(3R,31R)-dotriacontanediol	<0.001	1.413	<0.001	1.327	<0.001	1.272	<0.001	1.444
-	99.08148	4.3	[FA (6:0)] 3Z-hexenol	<0.001	51.937	<0.001	51.052	<0.001	48.391	<0.001	45.254
-	141.0922	4.6	[FA (8:0)] 2Z-octenoic acid	<0.001	3.229	<0.001	2.785	<0.001	2.689	<0.001	3.251
-	141.0921	4.9	[FA (8:0)] 2Z-octenoic acid	<0.001	2.222	0.069	1.524	0.001	1.815	<0.001	2.101
-	174.0409	15.1	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	<0.001	1.208	<0.001	0.577	<0.001	0.66	0.023	1.08

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	155.1078	4.4	[FA hydroxy(9:1)] 4-hydroxy-2-nonenal	<0.001	3.946	0.021	3.093	<0.001	3.857	0.001	4.337
-	295.2643	3.9	[FA methyl(18:0)] 11R,12S-methylene-octadecanoic acid	<0.001	0.593	0.677	0.949	0.955	0.992	0.885	0.978
+	149.0807	15.6	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	<0.001	0.715	0.112	0.859	0.007	0.828	0.002	0.671
+	159.0279	10.6	[FA methyl,oxo(5:0/2:0)] 2-methylene-4-oxo-pentanedioic acid	<0.001	0.119	0.510	1.110	0.019	0.511	0.083	0.583
+	137.0458	10.7	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	<0.001	0.277	0.656	1.049	<0.001	0.589	<0.001	0.570
+	400.3421	4.7	[FA] O-Palmitoyl-R-carnitine	<0.001	2.653	<0.001	1.730	<0.001	2.008	<0.001	2.760
+	400.342	7.7	[FA] O-Palmitoyl-R-carnitine	<0.001	2.649	<0.001	1.806	<0.001	2.015	<0.001	2.873
-	398.3279	4.7	[FA] O-Palmitoyl-R-carnitine	<0.001	3.065	<0.001	2.136	<0.001	2.632	<0.001	3.032
+	301.1427	16.0	[Fv Hydroxy,dimethoxy,methy] 2'-Hydroxy-4',6'-dimethoxy-3'-methyldihydrochalcone	<0.001	5.179	0.005	1.427	<0.001	3.190	<0.001	3.921
-	437.1625	15.0	[Fv hydroxy,hydroxy,methyl,dimethyl(4:2/9:1)] 5,4-Dihydroxy-8-(1-hydroxy-2,3-epoxy-3-methylbutyl)-6'',6''-dimethylpyrano[2'',3'':7,6]flavanone	<0.001	1.34	<0.001	0.714	<0.001	0.672	0.994	1.001
+	393.1687	13.8	[Fv] Anguvetin	<0.001	0.536	<0.001	0.295	0.002	0.652	<0.001	0.339
-	563.1793	15.0	[Fv] Isoliquiritigenin 2'-glucosyl-(1->4)-rhamnoside	<0.001	27.463	<0.001	17.11	<0.001	10.478	<0.001	19.84
-	273.0763	9.8	[Fv] Phloretin	<0.001	0.633	0.016	0.699	0.109	0.87	<0.001	0.541
+	359.3156	4.1	[GL (18:0)] 1-octadecanoyl-rac-glycerol	<0.001	0.707	0.016	0.815	<0.001	0.684	0.023	0.707
-	224.9798	13.1	[GP (2:0)] 1,2-diacyl-sn-glycero-3-phosphate	<0.001	0.544	0.103	0.783	0.002	0.699	0.001	0.514
+	509.0073	16.9	[GP (2:0)] 1',3'-Bis-(1,2-diacyl-sn-glycero-3-phospho)-sn-glycerol	<0.001	2.346	0.037	1.199	0.003	1.296	<0.001	1.884
-	506.9924	16.9	[GP (2:0)] 1',3'-Bis-(1,2-diacyl-sn-glycero-3-phospho)-sn-glycerol	<0.001	2.841	<0.001	1.59	<0.001	1.724	<0.001	2.2
+	704.5227	4.2	[PC (14:0/16:1)] 1-tetradecanoyl-2-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	<0.001	30.738	0.075	5.152	0.002	13.383	<0.001	34.341
+	732.5542	4.1	[PC (14:0/18:1)] 1-tetradecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.348	<0.001	1.666	<0.001	2.339	<0.001	2.310
+	730.5387	4.1	[PC (14:0/18:2)] 1-tetradecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	4.388	<0.001	2.016	<0.001	3.080	<0.001	4.119
+	728.5232	4.2	[PC (14:0/18:3)] 1-tetradecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	39.403	0.027	4.551	<0.001	12.765	<0.001	35.902
+	754.5393	4.1	[PC (14:0/20:4)] 1-tetradecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	11.151	0.001	3.546	<0.001	7.282	<0.001	10.209
+	720.5918	4.1	[PC (14:2/18:0)] 1-tetradecyl-2-octadecanoyl-sn-glycero-3-phosphocholine	<0.001	0.340	0.004	0.367	<0.001	0.535	0.001	0.462

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	482.3243	4.6	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.499	<0.001	1.217	0.001	1.150	<0.001	1.371
-	480.3098	4.6	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.548	<0.001	1.184	0.002	1.145	<0.001	1.428
+	706.5386	4.2	[PC (15:0/15:0)] 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine	<0.001	2.731	<0.001	1.595	<0.001	2.517	<0.001	2.998
+	720.5545	4.1	[PC (15:0/16:0)] 1-pentadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	<0.001	1.546	0.289	1.149	<0.001	1.644	<0.001	1.792
+	746.5701	4.1	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.210	<0.001	1.604	<0.001	2.224	<0.001	2.240
+	746.5702	4.6	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	3.311	0.003	2.012	<0.001	2.619	<0.001	2.881
-	464.3147	4.6	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	<0.001	1.268	<0.001	1.207	0.008	1.116	0.015	1.158
+	760.5853	4.1	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.064	<0.001	1.594	<0.001	2.139	<0.001	2.173
+	758.5698	4.1	[PC (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	3.081	<0.001	2.154	<0.001	3.007	<0.001	3.019
+	756.5548	4.1	[PC (16:0/18:3)] 1-hexadecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	4.619	<0.001	2.104	<0.001	3.410	<0.001	4.230
+	782.5698	4.1	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.723	<0.001	1.391	<0.001	1.460	<0.001	1.731
+	782.5694	5.7	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	4.487	0.069	2.046	0.016	2.059	0.156	2.470
+	806.57	4.1	[PC (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.107	<0.001	1.387	<0.001	1.730	<0.001	2.046
+	780.5543	4.1	[PC (16:1/20:4)] 1-(9Z-hexadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	2.371	<0.001	1.340	<0.001	1.974	<0.001	2.260
+	836.6171	4.0	[PC (18:0/22:5)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.518	<0.001	1.279	<0.001	1.265	<0.001	1.529
+	786.6015	4.1	[PC (18:1/18:1)] 1-(9Z-octadecenoyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.727	<0.001	1.901	<0.001	2.659	<0.001	2.700
+	810.6015	4.0	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	<0.001	1.247	0.067	1.089	0.881	0.995	<0.001	1.288
+	808.5857	4.1	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	2.182	<0.001	1.516	<0.001	1.782	<0.001	2.115
+	808.5854	5.7	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	8.148	0.013	2.883	0.001	3.541	0.147	2.793
+	834.6015	4.0	[PC (18:1/22:5)] 1-(11Z-octadecenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.800	<0.001	1.354	<0.001	1.461	<0.001	1.781

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	832.5857	4.0	[PC (18:1/22:6)] 1-(11Z-octadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	2.308	<0.001	1.382	<0.001	1.810	<0.001	2.156
+	818.6064	4.0	[PC (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.413	0.848	1.006	0.001	1.143	<0.001	1.424
+	830.5698	4.1	[PC (18:2/22:6)] 1-(9Z,12Z-octadecadienoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.329	<0.001	0.695	0.747	0.989	<0.001	1.276
+	778.5378	4.1	[PC (18:3/18:3)] 1,2-di-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	19.976	0.143	1.764	<0.001	9.231	<0.001	17.532
+	864.6483	4.0	[PC (20:0/22:5)] 1-eicosanoyl-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	3.578	0.041	2.139	<0.001	3.048	<0.001	3.058
+	862.6326	4.0	[PC (20:0/22:6)] 1-eicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	4.096	0.053	1.852	<0.001	2.350	<0.001	3.442
+	854.5702	4.0	[PC (20:5/22:5)] 1-(5Z,8Z,11Z,14Z,17Z-eicosapentaenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.911	0.073	0.746	0.094	1.245	0.004	1.814
+	878.5699	3.9	[PC (22:6/22:6)] 1,2-di-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	4.368	0.015	2.333	0.018	2.908	0.004	4.346
+	766.5752	4.1	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.486	<0.001	0.802	<0.001	0.538	<0.001	0.519
+	766.5754	4.6	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.448	0.037	0.803	<0.001	0.435	<0.001	0.455
-	452.2786	4.8	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	1.917	<0.001	1.513	<0.001	1.677	<0.001	1.771
+	718.5381	4.1	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	4.495	<0.001	2.717	<0.001	4.403	<0.001	4.690
+	740.5234	4.0	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.347	<0.001	1.649	<0.001	2.840	<0.001	3.272
-	738.5079	4.0	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.957	0.001	1.883	<0.001	4.879	<0.001	5.456
-	738.508	4.2	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	7.557	0.125	1.507	0.003	4.929	0.007	3.695
+	774.6014	4.1	[PE (16:0/22:1)] 1-hexadecanoyl-2-(13Z-docosenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.717	0.021	1.298	<0.001	1.584	<0.001	1.870
+	764.5231	4.0	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.468	<0.001	2.356	<0.001	3.934	<0.001	5.075

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	764.5234	4.4	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	9.962	0.126	1.846	<0.001	6.741	<0.001	9.597
-	762.5069	4.0	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	8.52	<0.001	2.757	<0.001	5.753	<0.001	7.799
+	438.298	4.7	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.220	<0.001	1.333	<0.001	1.187	0.034	1.124
+	748.5278	4.0	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.566	0.004	1.181	<0.001	1.269	<0.001	1.545
-	746.5129	4.0	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.608	<0.001	1.212	<0.001	1.354	<0.001	1.565
+	480.3085	4.7	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.584	<0.001	1.885	<0.001	2.206	<0.001	2.595
-	478.2941	4.7	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.109	0.001	1.695	<0.001	1.837	<0.001	2.431
+	744.5544	4.1	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.457	<0.001	2.833	<0.001	4.773	<0.001	5.292
+	772.5852	4.1	[PE (18:0/20:2)] 1-octadecanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.354	<0.001	2.165	<0.001	3.142	<0.001	3.188
+	768.5543	4.0	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.753	0.220	1.089	<0.001	1.376	<0.001	1.831
-	766.5403	3.9	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	1.718	0.599	1.039	<0.001	1.372	<0.001	1.798
+	792.554	4.0	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.565	0.001	1.280	<0.001	1.732	<0.001	2.565
-	790.5399	4.0	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	4.275	0.125	1.433	<0.001	2.676	<0.001	4.247
+	502.2929	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	5.112	<0.001	3.481	<0.001	2.091	<0.001	4.418
-	500.2785	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	4.447	<0.001	2.896	<0.001	2.167	<0.001	4.155
+	766.5598	3.7	[PG (16:0/18:0)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	<0.001	1.875	<0.001	1.947	<0.001	1.942	<0.001	1.852
+	749.5312	4.0	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.608	0.001	1.220	<0.001	1.304	<0.001	1.565
-	747.5166	3.7	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.73	<0.001	1.581	<0.001	1.684	<0.001	1.773

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	747.5157	4.2	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	3.165	0.339	1.324	0.036	2.16	<0.001	3.251
-	509.2884	4.0	[PG (18:0)] 1-(9E-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	2.494	<0.001	1.806	0.001	1.614	0.001	2.012
-	775.5484	3.9	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.547	0.057	1.308	<0.001	1.713	0.001	1.781
+	775.5464	4.0	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.837	0.008	1.417	0.003	1.436	0.004	1.615
-	773.5329	3.9	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	2.024	<0.001	1.504	<0.001	2.014	<0.001	2.049
-	787.5315	3.8	[PG (8:0/8:0)] 1-(8-[5]-ladderane-octanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	<0.001	1.842	0.104	1.265	<0.001	1.69	<0.001	1.864
+	811.5316	3.8	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	3.566	<0.001	1.514	<0.001	3.015	<0.001	2.904
-	809.5161	3.8	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	2.953	<0.001	1.486	<0.001	2.667	<0.001	2.924
+	837.5474	3.7	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.414	0.206	0.940	0.252	1.060	<0.001	1.321
-	835.5315	3.8	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.904	0.015	1.292	<0.001	1.446	<0.001	1.876
-	861.5487	3.8	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	2.933	<0.001	2.501	<0.001	3.49	<0.001	3.178
-	885.5491	3.8	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	1.421	0.004	1.347	<0.001	1.407	<0.001	1.441
-	169.1235	4.3	[PR] Limonene-1,2-diol	<0.001	8.087	<0.001	7.776	<0.001	6.276	<0.001	8.429
+	762.528	3.8	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	1.899	0.034	1.329	<0.001	1.973	<0.001	1.883
-	760.5122	3.8	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	2.049	0.017	1.465	<0.001	2.154	<0.001	2.08
+	792.5757	3.7	[PS (16:0/20:0)] 1-hexadecanoyl-2-eicosanoyl-sn-glycero-3-phosphoserine	<0.001	3.306	<0.001	2.546	<0.001	3.837	<0.001	3.220
-	524.2995	4.3	[PS (18:0)] 1-octadecanoyl-sn-glycero-3-phosphoserine	<0.001	1.386	0.409	0.974	0.221	0.945	0.001	1.173
-	804.5755	4.1	[PS (18:0/19:0)] 1-octadecanoyl-2-nonadecanoyl-sn-glycero-3-phosphoserine	<0.001	6.288	0.067	3.04	0.033	3.514	0.415	1.599
+	836.5441	3.7	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	1.448	0.555	0.967	0.142	1.078	<0.001	1.371
-	834.528	3.8	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	<0.001	2.015	0.012	1.279	<0.001	1.469	<0.001	1.94

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	788.544	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	1.691	0.094	1.197	<0.001	1.436	<0.001	1.617
-	786.5284	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	<0.001	1.847	0.046	1.282	<0.001	1.739	<0.001	1.851
+	786.5288	3.8	[PS (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	5.329	0.012	2.196	<0.001	4.841	<0.001	5.181
+	784.5124	3.8	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	2.997	<0.001	1.722	<0.001	2.885	<0.001	3.025
-	782.4972	3.8	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	3.361	<0.001	1.953	<0.001	3.545	<0.001	3.457
+	316.2844	4.4	[SP hydrox] 6-hydroxysphing-4E-enine	<0.001	0.209	0.315	0.716	0.453	0.819	0.035	0.374
+	300.2896	7.7	[SP] 3-dehydrosphinganine	<0.001	0.452	<0.001	0.216	<0.001	0.299	<0.001	0.592
-	393.2782	4.1	[ST (4:0/2:0)] (5Z,7E)-(3S)-9,10-seco-5,7,10(19),16-cholestatetraen-23-yne-3,25-diol	<0.001	0.416	0.009	0.749	<0.001	0.59	0.017	0.594
-	337.0545	14.9	1-(5'-Phosphoribosyl)-5-amino-4-imidazolecarboxamide	<0.001	0.477	0.124	0.844	0.038	0.816	<0.001	0.41
-	808.5126	3.8	1-20:2-2-18:3-phosphatidylserine	<0.001	3.157	<0.001	1.636	<0.001	2.925	<0.001	3.182
-	310.1146	15.0	1-7-Dimethylguanosine	<0.001	0.489	0.415	0.878	0.004	0.677	0.002	0.464
+	302.074	15.0	1-Guanidino-1-deoxy-scyllo-inositol 4-phosphate	<0.001	3.412	0.292	0.678	0.008	0.242	<0.001	4.776
+	744.5906	4.1	1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphonocholine	<0.001	1.430	0.005	1.252	<0.001	1.574	<0.001	1.513
+	237.0808	26.5	2-(4'-methylthio)butylmalate	<0.001	13.210	<0.001	34.226	<0.001	36.631	<0.001	13.920
+	265.1117	21.1	2-(6'-methylthio)hexylmalate	<0.001	0.633	0.177	0.838	0.027	0.802	0.005	0.627
-	325.1254	15.6	2,2,4-Trimethyl-3-(4-fluorophenyl)-2H-1-benzopyran-7-ol acetate	<0.001	0.274	<0.001	0.619	<0.001	0.512	<0.001	0.272
+	134.0697	15.1	2-Aminobenzimidazole	<0.001	0.602	0.314	0.882	0.238	0.893	<0.001	0.535
-	213.0171	15.2	2-Deoxy-D-ribose 5-phosphate	<0.001	12.532	0.021	2.583	<0.001	11.521	<0.001	9.028
-	211.0257	15.7	2-Hydroxy-6-ketononatrienedioate	<0.001	2.865	0.028	0.564	0.15	1.239	<0.001	2.914
-	205.0354	17.2	2-Hydroxybutane-1,2,4-tricarboxylate	<0.001	0.397	0.231	0.721	0.271	0.771	0.002	0.506
+	167.0485	15.4	2-methylphosphinoyl-2-hydroxyacetate	<0.001	2.232	<0.001	1.265	<0.001	1.720	<0.001	2.005
+	349.054	16.0	2-O-(6-phospho-α-mannosyl)-D-glycerate	<0.001	2.960	<0.001	4.480	0.029	1.967	<0.001	3.650
-	347.0399	16.0	2-O-(6-phospho-α-mannosyl)-D-glycerate	<0.001	1.929	<0.001	3.09	<0.001	1.773	<0.001	2.414
-	175.0442	15.1	2-oxo-6-methylthiohexanoate	<0.001	1.275	<0.001	0.489	<0.001	0.605	0.013	1.157
+	147.0304	7.9	2-Oxoglutarate	<0.001	29.664	<0.001	38.785	<0.001	22.715	0.001	16.464

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	145.0143	15.9	2-Oxoglutarate	<0.001	1.911	0.093	1.186	<0.001	1.611	<0.001	1.7
+	136.0757	13.7	2-Phenylacetamide	<0.001	0.678	0.003	0.705	0.017	0.795	0.004	0.635
+	245.0801	25.0	3,3',4'5-Tetrahydroxystilbene	<0.001	0.560	0.028	0.756	0.002	0.745	<0.001	0.381
+	146.027	5.8	3,4-Dehydrothiomorpholine-3-carboxylate	<0.001	15.865	<0.001	17.261	<0.001	12.293	0.002	7.161
+	146.027	7.9	3,4-Dehydrothiomorpholine-3-carboxylate	<0.001	12.176	<0.001	15.683	<0.001	9.291	0.002	6.078
+	215.0696	15.9	3,4-Dihydroxy-3,4-dihydro-9-fluorenone	<0.001	27.441	0.008	4.380	<0.001	12.504	<0.001	17.683
+	215.0695	15.4	3,4-Dihydroxy-3,4-dihydro-9-fluorenone	<0.001	0.552	0.003	0.769	<0.001	0.701	<0.001	0.478
+	205.1547	7.8	3-Hydroxy-N6,N6,N6-trimethyl-L-lysine	<0.001	0.227	<0.001	0.394	0.239	0.730	0.014	0.334
+	205.1547	5.0	3-Hydroxy-N6,N6,N6-trimethyl-L-lysine	<0.001	0.254	<0.001	0.344	0.185	0.687	0.035	0.376
+	166.0724	13.4	3-Methylguanine	<0.001	523.637	<0.001	177.182	<0.001	399.186	<0.001	472.665
+	207.0143	15.9	3-Oxalomalate	<0.001	0.483	0.197	0.906	0.022	0.847	<0.001	0.404
-	554.9292	16.8	3'-Phosphoadenylylselenate	<0.001	0.199	<0.001	0.375	<0.001	0.283	0.001	0.191
-	184.9856	17.3	3-Phospho-D-glycerate	<0.001	3.209	<0.001	1.855	<0.001	3.028	0.002	1.717
-	182.0589	15.6	4-Amino-2-hydroxylamino-6-nitrotoluene	<0.001	2.545	<0.001	3.358	<0.001	2.588	<0.001	2.565
-	126.0114	15.4	4-Chloroaniline	<0.001	1.66	0.012	1.168	<0.001	1.445	<0.001	1.642
+	178.0725	10.7	4-Hydroxy-4-methylglutamate	<0.001	0.261	0.988	1.002	0.002	0.701	0.004	0.595
-	212.0328	15.7	4-Hydroxylamino-2,6-dinitrotoluene	<0.001	3.199	0.001	0.504	0.012	1.339	<0.001	3.342
-	134.0472	7.8	4-Hydroxy-L-threonine	<0.001	3.275	0.193	1.257	<0.001	3.528	<0.001	4.671
+	157.0608	15.8	4-Imidazolone-5-propanoate	<0.001	0.540	0.316	0.862	0.030	0.829	0.003	0.539
+	134.0641	15.9	4-methylthiobutanaldoxime	<0.001	0.598	0.025	0.796	0.010	0.806	<0.001	0.546
-	132.0495	15.8	4-methylthiobutanaldoxime	<0.001	0.553	0.035	0.79	0.012	0.792	0.001	0.577
+	144.0471	15.4	5-(2-Hydroxyethyl)-4-methylthiazole	<0.001	2.529	0.020	1.181	<0.001	1.755	<0.001	1.998
+	148.9934	9.8	5,6-Dichloro-1,3-cyclohexadiene	<0.001	0.693	0.401	0.943	0.106	0.916	0.002	0.715
-	127.0513	15.6	5,6-Dihydrothymine	<0.001	0.643	0.011	0.77	0.001	0.743	<0.001	0.53
+	115.0503	15.3	5,6-Dihydrouracil	<0.001	2.422	0.279	0.754	0.837	0.964	<0.001	2.649
-	158.0823	5.0	5-Acetamidopentanoate	<0.001	0.444	0.207	0.774	0.312	0.784	0.028	0.569
-	225.0617	15.1	5-Acetylamino-6-formylamino-3-methyluracil	<0.001	0.524	0.003	0.663	<0.001	0.539	<0.001	0.377
-	225.0617	17.7	5-Acetylamino-6-formylamino-3-methyluracil	<0.001	0.565	0.001	0.576	<0.001	0.509	<0.001	0.393

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	225.0617	14.1	5-Acetylamino-6-formylamino-3-methyluracil	<0.001	0.475	<0.001	0.583	<0.001	0.562	0.001	0.452
+	188.103	15.6	5-guanidino-3-methyl-2-oxo-pentanoate	<0.001	0.497	0.010	0.674	<0.001	0.653	<0.001	0.407
+	185.0323	15.8	5-Hydroxyisourate	<0.001	0.453	<0.001	0.843	<0.001	0.749	<0.001	0.425
-	183.0178	15.8	5-Hydroxyisourate	<0.001	0.629	<0.001	0.815	<0.001	0.857	<0.001	0.601
+	178.0863	5.0	5-Hydroxytryptophol	<0.001	2.088	0.064	1.536	0.300	1.355	0.011	2.013
+	255.0644	16.0	5-L-Glutamyl-taurine	<0.001	2.462	0.088	0.745	<0.001	2.310	0.003	2.101
-	253.0501	16.0	5-L-Glutamyl-taurine	<0.001	1.89	0.001	0.741	<0.001	2.082	<0.001	1.767
+	298.0967	7.8	5'-Methylthioadenosine	<0.001	4.152	<0.001	2.247	<0.001	4.326	<0.001	6.109
+	148.0797	15.6	5-methylthiopentanaldoxime	<0.001	0.726	0.086	0.846	0.010	0.828	0.002	0.676
-	146.0653	15.6	5-methylthiopentanaldoxime	<0.001	0.559	0.024	0.772	0.001	0.724	<0.001	0.516
+	267.0715	25.0	5'-Oxoinosine	<0.001	0.506	0.070	0.781	0.017	0.809	<0.001	0.272
+	287.0638	17.0	5'-Phosphoribosylglycinamide	<0.001	#DIV/0!	#DIV/0!	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
-	285.0494	17.0	5'-Phosphoribosylglycinamide	<0.001	#DIV/0!	#DIV/0!	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
-	244.0591	15.6	6-aza-uridine	<0.001	2.215	<0.001	3.36	<0.001	2.351	<0.001	2.261
+	182.1024	9.4	6-methyltetrahydropterin	<0.001	0.431	<0.001	0.592	<0.001	0.697	0.002	0.649
+	162.0954	15.0	6-methylthiohexanaldoxime	<0.001	0.457	0.062	0.741	0.003	0.682	<0.001	0.409
+	174.0954	15.1	7-methylthioheptanonitrile oxide	<0.001	0.547	0.062	0.734	0.002	0.716	<0.001	0.453
-	272.1194	3.6	8-Allyl-2-phenyl-8H-1,3a,8-triaza-cyclopenta[a]indene	<0.001	0.624	0.263	0.876	0.078	0.781	0.001	0.657
-	186.1136	5.1	8-Amino-7-oxononanoate	<0.001	0.263	<0.001	0.342	0.316	0.763	0.059	0.469
+	168.0518	15.4	8-Hydroxyguanine	<0.001	2.447	<0.001	1.306	<0.001	1.843	<0.001	2.214
+	228.0655	16.0	9-Hydroxy-2-nitrofluorene	<0.001	6.417	0.007	0.133	0.013	0.228	<0.001	16.028
+	635.1419	17.9	Actinorhodine	<0.001	8.846	<0.001	18.929	<0.001	15.902	<0.001	11.951
-	633.127	17.9	Actinorhodine	<0.001	9.911	<0.001	14.667	<0.001	13.227	<0.001	7.762
+	793.5573	4.0	acyl phosphatidylglycerol (n-C12:0)	<0.001	2.520	0.016	1.288	<0.001	1.702	<0.001	2.488
+	793.5573	4.3	acyl phosphatidylglycerol (n-C12:0)	<0.001	5.191	0.288	1.450	<0.001	2.803	<0.001	4.884
-	791.5424	3.9	acyl phosphatidylglycerol (n-C12:0)	<0.001	3.483	0.678	1.042	<0.001	2.168	<0.001	3.365
+	428.0368	15.6	ADP	<0.001	2.384	<0.001	1.587	<0.001	1.665	<0.001	2.032
-	426.0225	16.9	ADP	<0.001	3.51	<0.001	1.768	<0.001	1.755	<0.001	2.708

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	426.0225	15.6	ADP	<0.001	2.213	<0.001	1.577	<0.001	1.698	<0.001	1.944
-	318.0961	15.1	Ala-Asp-Asp	<0.001	1.691	<0.001	0.714	<0.001	0.66	<0.001	1.623
-	353.1566	14.1	Ala-Gln-His	<0.001	0.524	0.016	0.658	0.137	0.845	<0.001	0.425
-	501.2818	4.6	Ala-Lys-Trp-Val	<0.001	5.72	0.001	3.247	<0.001	2.69	<0.001	5.395
+	177.0611	23.3	Allantoate	<0.001	0.569	0.144	0.834	0.013	0.787	<0.001	0.315
+	162.0583	5.0	allylcysteine	<0.001	14.345	<0.001	16.333	<0.001	13.933	<0.001	9.444
+	162.0583	7.8	allylcysteine	<0.001	11.537	<0.001	15.969	<0.001	11.234	<0.001	7.900
-	160.0438	7.8	allylcysteine	<0.001	11.352	0.001	16.371	0.002	11.602	<0.001	7.771
+	100.0216	7.9	Allylisothiocyanate	<0.001	43.836	<0.001	57.257	0.002	31.962	0.001	22.552
-	307.0737	15.6	Alprazolam	<0.001	2.538	<0.001	4.089	<0.001	3.032	0.001	2.166
-	346.056	14.4	AMP	<0.001	2.564	<0.001	1.99	<0.001	1.843	<0.001	2.197
-	312.1132	15.8	Angustine	<0.001	0.35	0.372	0.878	0.045	0.744	0.002	0.394
-	557.2889	3.9	Arg-Asn-Asn-Arg	<0.001	1.711	0.486	1.069	0.004	0.728	<0.001	1.524
-	531.273	3.9	Arg-Leu-Met-Asn	<0.001	1.428	0.614	0.974	<0.001	0.682	<0.001	1.613
+	508.0034	16.9	ATP	<0.001	2.528	<0.001	1.490	<0.001	1.665	<0.001	2.229
-	505.9883	16.9	ATP	<0.001	2.567	<0.001	1.499	<0.001	1.614	<0.001	2.006
+	245.0961	12.5	Biotin	<0.001	0.393	0.037	0.706	0.003	0.670	0.001	0.400
-	369.0681	4.4	BPH-674	<0.001	0.352	0.068	0.837	0.001	0.685	<0.001	0.465
+	349.1175	13.6	Camptothecin	<0.001	7.311	<0.001	9.916	<0.001	7.944	<0.001	6.872
-	347.1032	13.6	Camptothecin	<0.001	8.158	<0.001	10.576	<0.001	8.564	<0.001	7.289
+	447.0676	16.9	CDP-ethanolamine	<0.001	2.286	<0.001	1.341	0.001	1.476	<0.001	1.848
-	445.0546	16.9	CDP-ethanolamine	<0.001	3.273	<0.001	1.495	<0.001	2.28	<0.001	2.784
+	461.0817	14.1	CDP-N-methylethanolamine	<0.001	0.448	<0.001	0.072	<0.001	0.014	0.041	0.735
-	243.0388	15.7	CGP 52608	<0.001	0.344	0.024	0.727	0.015	0.709	<0.001	0.247
+	316.0927	26.5	Chlorprothixene	<0.001	0.326	<0.001	0.174	<0.001	0.033	0.681	0.918
+	104.107	20.5	Choline	<0.001	0.656	0.043	0.793	0.010	0.773	0.005	0.645
+	229.1012	11.0	Chrysene	<0.001	0.415	0.070	0.730	0.002	0.651	0.002	0.508
+	370.2954	4.9	cis-5-Tetradecenoylcarnitine	<0.001	4.535	0.100	1.239	<0.001	1.848	<0.001	3.570

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	431.0727	15.9	CMP-2-aminoethylphosphonate	<0.001	7.075	<0.001	3.698	<0.001	5.407	<0.001	6.781
-	429.0584	15.9	CMP-2-aminoethylphosphonate	<0.001	4.121	0.022	1.452	<0.001	2.481	<0.001	3.404
+	615.153	17.9	CMP-N-acetylneuraminate	<0.001	22.147	<0.001	52.065	<0.001	47.707	<0.001	35.720
+	615.1546	15.8	CMP-N-acetylneuraminate	<0.001	1.492	0.412	1.043	0.236	0.941	<0.001	1.519
-	613.1399	15.8	CMP-N-acetylneuraminate	<0.001	1.649	0.429	1.026	0.099	0.943	<0.001	1.564
+	132.0768	15.3	Creatine	<0.001	1.721	<0.001	0.682	0.003	0.812	<0.001	1.826
-	130.0622	15.3	Creatine	<0.001	1.71	<0.001	0.606	<0.001	0.712	<0.001	1.702
+	114.0662	15.3	Creatinine	<0.001	1.446	0.150	0.876	0.936	1.017	0.007	1.602
-	192.0181	15.7	creatinine phosphate	<0.001	2.974	<0.001	0.577	0.361	1.042	<0.001	2.768
+	483.9919	18.7	CTP	<0.001	7.431	<0.001	2.675	<0.001	4.056	<0.001	5.653
-	481.9774	18.7	CTP	<0.001	3.964	0.022	1.224	<0.001	1.891	<0.001	2.293
-	540.0539	14.8	Cyclic ADP-ribose	<0.001	2.604	<0.001	2.416	<0.001	2.322	<0.001	2.551
+	244.0928	12.4	Cytidine	<0.001	0.443	0.080	0.787	0.004	0.710	0.001	0.501
+	112.0506	12.4	Cytosine	<0.001	0.467	0.099	0.791	0.007	0.731	0.003	0.538
+	161.092	15.0	D-Alanyl-D-alanine	<0.001	0.545	0.075	0.791	0.003	0.747	<0.001	0.475
-	246.0463	13.3	DCI	<0.001	1.313	<0.001	0.338	<0.001	0.588	0.431	1.062
+	358.164	15.7	deacetylcolchicine	<0.001	0.697	<0.001	0.700	0.014	0.861	<0.001	0.612
-	356.15	15.7	deacetylcolchicine	<0.001	0.328	<0.001	0.585	<0.001	0.633	<0.001	0.27
+	168.0438	16.2	demethyl-phosphinothricin	<0.001	2.316	0.080	1.276	0.033	1.321	<0.001	2.201
+	399.1443	17.0	Deoxypodophyllotoxin	<0.001	5.906	0.006	2.579	<0.001	4.534	<0.001	4.158
-	338.9889	18.5	D-Fructose 1,6-bisphosphate	<0.001	13.216	0.001	4.388	<0.001	12.499	<0.001	15.492
-	338.9895	16.8	D-Fructose 1,6-bisphosphate	<0.001	0.364	0.001	0.547	<0.001	0.504	0.001	0.355
+	180.0867	15.0	D-Glucosamine	<0.001	0.291	0.090	0.675	0.348	0.818	0.005	0.245
-	179.0562	15.0	D-Glucose	<0.001	0.586	0.008	0.757	0.018	0.77	0.003	0.583
+	87.04413	16.1	Diacetyl	<0.001	1.933	<0.001	1.653	<0.001	2.171	<0.001	1.954
+	91.05835	16.0	Diethyl sulfide	<0.001	5.509	<0.001	1.743	<0.001	3.148	<0.001	4.894
+	240.1089	13.2	Dihydrobiopterin	<0.001	18.809	<0.001	12.050	<0.001	17.328	<0.001	17.819
+	721.5942	4.1	dihydromenaquinone-8	<0.001	0.255	<0.001	0.182	0.002	0.324	0.015	0.310

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	160.1332	5.1	DL-2-Aminooctanoicacid	<0.001	0.314	<0.001	0.295	<0.001	0.364	0.015	0.376
-	168.9908	15.8	DL-Glyceraldehyde 3-phosphate	<0.001	2.648	0.156	1.263	<0.001	2.79	0.002	2.295
+	182.0482	12.3	DL-Methionine sulfone	<0.001	0.648	0.082	0.780	0.007	0.780	0.003	0.581
+	243.0269	16.8	D-myo-Inositol 1,2-cyclic phosphate	<0.001	0.311	<0.001	0.383	<0.001	0.351	<0.001	0.263
-	241.0125	16.8	D-myo-Inositol 1,2-cyclic phosphate	<0.001	0.315	<0.001	0.374	<0.001	0.328	<0.001	0.268
-	327.2332	3.9	Docosahexaenoicacid	<0.001	0.587	0.234	0.876	0.013	0.79	0.004	0.624
-	229.1447	4.2	Dodecanedioic acid	<0.001	0.152	0.034	0.565	0.007	0.497	0.003	0.292
+	285.0209	16.8	DTP	<0.001	0.317	<0.001	0.329	<0.001	0.328	<0.001	0.244
+	426.3577	4.6	Elaidiccarnitine	<0.001	3.049	<0.001	1.785	<0.001	2.532	<0.001	3.200
-	140.0119	16.6	Ethanolamine phosphate	<0.001	2.308	0.001	1.131	<0.001	1.401	<0.001	2.104
-	163.0765	4.6	Eugenol	<0.001	4.882	<0.001	4.777	0.005	3.832	0.005	5.155
-	169.0871	5.0	Furfural diethyl acetal	<0.001	1.833	0.001	1.651	0.005	1.784	<0.001	2.148
-	274.1046	15.8	Gamma-Glutamylglutamine	<0.001	0.522	0.328	0.865	0.202	0.856	0.001	0.444
+	251.0696	14.7	gamma-L-Glutamyl-L-cysteine	<0.001	9.706	<0.001	116.523	<0.001	118.553	<0.001	10.838
-	249.0552	14.7	gamma-L-Glutamyl-L-cysteine	<0.001	25.018	<0.001	268.791	<0.001	278.948	<0.001	24.759
-	881.5182	3.8	geranylgeranyl-bacteriopheophytin	<0.001	3.802	0.04	1.957	0.001	3.06	<0.001	3.506
+	331.1532	15.0	Gibberellin A51-catabolite	<0.001	0.550	<0.001	0.650	0.001	0.791	<0.001	0.409
-	445.1843	26.5	Gln-Tyr-His	<0.001	0.542	0.123	0.786	0.02	0.711	<0.001	0.252
+	308.0909	14.9	Glutathione	<0.001	3.520	<0.001	4.216	<0.001	3.018	<0.001	2.014
-	306.0767	14.9	Glutathione	<0.001	4.21	<0.001	4.795	<0.001	3.358	<0.001	2.595
+	613.1594	17.9	Glutathione disulfide	<0.001	7.509	<0.001	15.726	<0.001	12.002	<0.001	8.189
-	611.1446	17.9	Glutathione disulfide	<0.001	7.954	<0.001	16.225	<0.001	11.787	<0.001	8.345
+	247.0577	13.2	Glycerophosphoglycerol	<0.001	1.745	<0.001	0.492	<0.001	0.566	<0.001	1.569
-	245.0432	13.2	Glycerophosphoglycerol	<0.001	1.571	<0.001	0.481	<0.001	0.612	0.002	1.243
-	298.1145	15.0	Gly-Ser-His	<0.001	0.524	0.057	0.771	0.004	0.728	0.001	0.556
+	523.9982	19.6	GTP	<0.001	3.268	0.325	1.287	0.134	1.309	0.003	1.977
-	521.9834	19.6	GTP	<0.001	3.552	<0.001	1.443	0.023	1.273	<0.001	2.183
+	118.0611	16.5	Guanidinoacetate	<0.001	1.856	<0.001	0.618	<0.001	0.758	<0.001	1.539

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	414.3574	4.6	Heptadecanoylcarnitine	<0.001	2.981	0.002	1.533	<0.001	2.043	<0.001	2.874
-	556.2764	3.9	His-Lys-His-His	<0.001	1.943	0.566	1.039	0.012	0.831	<0.001	1.705
-	79.95706	15.4	HSO3-	<0.001	1.579	0.001	1.15	<0.001	1.468	<0.001	1.617
+	248.1492	11.9	Hydroxybutyrylcarnitine	<0.001	2.808	0.294	1.246	0.083	1.387	0.003	2.360
-	110.9852	15.0	Hydroxymethylphosphonate	<0.001	4.025	0.001	2.1	<0.001	2.45	<0.001	3.89
+	110.0271	15.6	Hypotaurine	<0.001	5.209	<0.001	1.720	<0.001	3.214	<0.001	4.699
-	108.0124	15.6	Hypotaurine	<0.001	5.266	<0.001	1.743	<0.001	3.562	<0.001	5.197
+	261.1484	11.9	Lacinilene C 7-methyl ether	<0.001	0.214	0.832	0.981	0.088	0.723	0.179	0.670
+	148.0734	15.6	L-Albizziine	<0.001	0.706	0.060	0.834	0.010	0.811	0.001	0.652
-	146.0589	15.7	L-Albizziine	<0.001	0.494	0.023	0.751	0.003	0.685	0.001	0.478
-	165.0409	4.6	L-Arabinonate	<0.001	0.274	<0.001	0.252	0.023	0.526	0.022	0.43
+	175.119	26.5	L-Arginine	<0.001	0.696	0.189	0.874	0.052	0.872	0.001	0.613
+	133.0608	15.9	L-Asparagine	<0.001	0.611	0.022	0.808	0.007	0.812	<0.001	0.583
+	133.0624	15.1	L-Asparagine	<0.001	0.555	0.406	0.873	0.042	0.799	0.004	0.538
-	131.0462	15.8	L-Asparagine	<0.001	0.606	0.04	0.819	0.024	0.841	0.001	0.615
+	134.0447	15.5	L-Aspartate	<0.001	0.736	0.012	0.829	0.004	0.831	<0.001	0.581
-	167.9973	15.4	L-Cysteate	<0.001	2.824	0.001	1.27	<0.001	2.025	<0.001	2.32
-	120.0124	16.8	L-Cysteine	<0.001	0.377	<0.001	0.372	<0.001	0.381	<0.001	0.342
+	298.0524	15.8	L-Cysteinylglycinedisulfide	<0.001	0.346	0.036	0.664	0.001	0.479	<0.001	0.316
+	298.0524	17.5	L-Cysteinylglycinedisulfide	<0.001	2.183	<0.001	4.138	<0.001	3.835	0.005	3.021
-	296.0381	15.8	L-Cysteinylglycinedisulfide	<0.001	0.512	0.012	0.622	0.006	0.673	0.001	0.382
+	241.031	16.8	L-Cystine	<0.001	0.337	<0.001	0.412	<0.001	0.384	<0.001	0.284
-	239.0167	16.8	L-Cystine	<0.001	0.379	<0.001	0.43	<0.001	0.396	<0.001	0.321
+	132.0655	15.1	L-Glutamate 5-semialdehyde	<0.001	0.651	0.357	0.894	0.116	0.876	0.001	0.588
+	147.0764	15.6	L-Glutamine	<0.001	0.728	0.077	0.845	0.008	0.828	0.001	0.678
+	147.0764	10.6	L-Glutamine	<0.001	0.596	0.445	0.891	0.004	0.734	0.001	0.618
-	145.0619	15.6	L-Glutamine	<0.001	0.593	0.023	0.784	0.002	0.754	<0.001	0.556
+	174.1256	11.3	L-Indospicine	<0.001	0.429	0.182	0.829	0.019	0.667	<0.001	0.351

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	424.342	4.6	Linoelaidylcarnitine	<0.001	5.777	<0.001	2.329	<0.001	3.891	<0.001	6.097
+	147.1128	25.0	L-Lysine	<0.001	0.608	0.130	0.815	0.018	0.788	<0.001	0.472
+	106.0499	16.3	L-Serine	<0.001	0.679	0.034	0.827	0.051	0.864	0.002	0.661
+	134.027	8.6	L-thiazolidine-4-carboxylate	<0.001	14.069	<0.001	19.435	<0.001	13.097	0.002	9.317
+	120.0655	15.0	L-Threonine	<0.001	0.593	0.151	0.839	0.041	0.829	<0.001	0.548
-	118.051	15.0	L-Threonine	<0.001	0.576	0.09	0.808	0.007	0.758	0.003	0.615
-	526.2942	4.6	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	9.56	<0.001	5.753	0.003	4.63	<0.001	9.608
-	524.2784	4.6	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	7.566	<0.001	3.667	<0.001	4.275	<0.001	5.778
+	877.5631	3.8	Megalomicin A	<0.001	1.875	<0.001	1.612	<0.001	1.729	<0.001	1.830
+	191.1026	25.0	meso-2,6-Diaminoheptanedioate	<0.001	0.555	0.129	0.791	0.014	0.742	0.002	0.501
-	390.1442	14.1	Met-Asn-Gln	<0.001	0.598	<0.001	0.556	0.009	0.801	<0.001	0.543
-	360.1232	14.9	Met-Asp-Pro	<0.001	0.473	0.079	0.817	0.001	0.696	<0.001	0.455
-	360.1232	15.2	Met-Asp-Pro	<0.001	0.248	0.035	0.711	<0.001	0.464	0.001	0.217
-	360.1233	14.1	Met-Asp-Pro	<0.001	0.457	0.001	0.499	0.019	0.726	0.006	0.488
+	267.0621	25.0	Methoxybrassinin	<0.001	0.573	0.014	0.779	0.004	0.817	<0.001	0.323
-	265.0479	25.0	Methoxybrassinin	<0.001	0.5	0.096	0.769	0.007	0.653	<0.001	0.179
+	133.0737	15.3	Methylenediurea	<0.001	1.708	0.001	0.678	0.002	0.800	<0.001	1.827
+	522.3428	15.1	Mycinamicin VII	<0.001	0.681	0.132	0.888	0.236	0.943	<0.001	0.590
+	246.17	4.5	N-(octanoyl)-L-homoserine	<0.001	0.306	0.656	0.897	0.731	1.074	0.203	0.653
+	301.0906	15.9	N1-Amidinostreptamine 6-phosphate	<0.001	49.072	0.720	0.776	<0.001	8.889	<0.001	41.236
+	194.1025	16.1	N1-hydroxypropyladenine	<0.001	0.470	0.469	0.900	0.051	0.793	0.169	0.757
+	189.1598	22.5	N6,N6,N6-Trimethyl-L-lysine	<0.001	0.624	0.096	0.809	0.012	0.805	<0.001	0.527
+	157.0972	23.3	N-acetyl prolinamide or isomer	<0.001	0.569	0.009	0.712	0.126	0.882	<0.001	0.477
+	180.0768	11.2	N-Acetylisoniazid	<0.001	0.416	0.143	0.793	0.004	0.643	0.005	0.483
+	174.1125	5.7	N-Acetyl-L-leucine	<0.001	0.276	<0.001	0.300	0.002	0.471	0.004	0.359
-	173.0932	14.1	N-Acetylornithine	<0.001	0.603	0.042	0.753	0.035	0.805	0.002	0.492
+	246.1236	12.2	N-acetyl-tryptophanamide	<0.001	0.339	0.038	0.678	0.004	0.606	0.002	0.367
+	664.1167	14.8	NAD+	<0.001	1.745	<0.001	1.877	<0.001	1.832	<0.001	1.451

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	662.1018	14.8	NAD+	<0.001	2.313	<0.001	2.118	<0.001	2.109	<0.001	2.043
-	664.1174	13.9	NADH	<0.001	1.951	0.004	1.619	0.005	1.707	0.007	1.875
+	744.0831	17.2	NADP+	<0.001	3.714	<0.001	2.273	<0.001	2.607	0.002	2.419
+	746.0989	17.4	NADPH	<0.001	2.731	<0.001	2.298	<0.001	2.391	<0.001	2.405
-	744.0833	17.4	NADPH	<0.001	2.09	<0.001	1.742	<0.001	1.822	<0.001	1.785
+	358.2005	25.0	Nalbuphine	<0.001	0.401	0.039	0.660	0.016	0.701	<0.001	0.210
+	510.3429	15.0	Narbomycin	<0.001	0.613	0.065	0.858	0.009	0.870	<0.001	0.533
+	175.1441	21.7	Ne,Ne dimethyllysine	<0.001	0.601	0.029	0.734	0.016	0.774	<0.001	0.452
+	175.0713	15.5	N-Formimino-L-glutamate	<0.001	0.571	0.071	0.838	0.003	0.784	<0.001	0.458
+	144.0307	16.6	N-formylmaleamate	<0.001	2.069	0.002	1.419	<0.001	1.765	0.004	1.871
+	203.1503	21.9	NG,NG-Dimethyl-L-arginine	<0.001	0.641	0.129	0.816	0.023	0.812	0.002	0.579
-	316.0554	15.6	Nilutamide	<0.001	0.28	0.505	0.914	0.234	0.835	0.002	0.283
+	216.1595	5.0	N-Nonanoylglycine	<0.001	0.154	0.006	0.382	0.233	0.718	0.131	0.511
+	213.0748	26.5	n-Propyl gallate	<0.001	0.655	0.056	0.836	0.007	0.823	<0.001	0.445
+	303.0611	15.9	Olsalazine	<0.001	0.428	<0.001	0.241	<0.001	0.068	0.735	1.032
+	794.5707	4.0	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	3.269	0.004	1.754	<0.001	2.546	<0.001	3.299
-	792.5566	3.9	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.681	0.462	1.113	0.001	1.819	<0.001	3.312
+	784.5855	4.1	PC(18:2(9Z,12Z)/18:1(9Z))	<0.001	2.899	<0.001	1.848	<0.001	2.654	<0.001	2.804
+	764.5591	4.1	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	<0.001	0.440	0.839	0.971	0.019	0.637	0.307	0.874
-	762.5474	4.4	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	<0.001	1.913	<0.001	1.737	<0.001	1.603	<0.001	1.864
+	860.6164	4.0	PC(20:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.647	0.008	1.859	0.002	2.722	<0.001	3.177
+	858.6016	4.0	PC(20:2(11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.854	0.051	0.863	<0.001	1.287	<0.001	1.752
+	856.5855	4.0	PC(20:3(5Z,8Z,11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.938	0.003	0.891	<0.001	1.322	<0.001	1.869
+	884.6171	4.0	PC(22:4(7Z,10Z,13Z,16Z)/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	3.764	0.089	1.427	0.003	2.119	<0.001	3.720
+	882.6016	4.0	PC(22:4(7Z,10Z,13Z,16Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.986	0.290	1.205	<0.001	2.071	<0.001	3.187
+	820.6222	4.0	PC(22:4(7Z,10Z,13Z,16Z)/P-18:1(11Z))	<0.001	1.403	0.012	1.130	<0.001	1.272	<0.001	1.390
-	211.0015	13.1	P-DPD	<0.001	35.199	0.34	1.502	<0.001	30.62	<0.001	32.501
+	796.5881	4.0	PE(18:0/22:4(7Z,10Z,13Z,16Z))	<0.001	15.803	<0.001	4.273	0.001	8.259	<0.001	14.993

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	796.5879	4.7	PE(18:0/22:4(7Z,10Z,13Z,16Z))	<0.001	12.137	0.006	4.917	<0.001	7.566	<0.001	10.930
+	796.5885	4.3	PE(18:0/22:4(7Z,10Z,13Z,16Z))	<0.001	58.022	0.009	14.251	0.002	29.920	0.034	24.509
+	790.538	4.0	PE(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	359.803	0.063	34.215	0.003	121.085	<0.001	292.996
+	766.5393	4.0	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	3.797	<0.001	1.637	<0.001	2.954	<0.001	3.522
+	766.5392	4.4	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	7.725	0.238	1.612	<0.001	4.576	<0.001	5.983
-	764.5239	4.0	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	6.469	0.011	1.653	<0.001	4.067	<0.001	5.937
+	774.5434	4.0	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	<0.001	1.598	<0.001	1.271	<0.001	1.367	<0.001	1.552
-	243.0462	14.5	penem CGP31608	<0.001	0.664	0.269	0.903	0.147	0.91	<0.001	0.48
+	153.1274	4.3	Perillyl alcohol	<0.001	6.749	<0.001	6.701	0.003	6.078	<0.001	6.301
-	771.5179	3.7	PG(16:0/20:3(5Z,8Z,11Z))	<0.001	2.408	<0.001	2.707	<0.001	3.287	0.001	2.539
-	795.5175	3.7	PG(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	1.211	0.983	1	<0.001	1.343	<0.001	1.224
-	793.5018	3.7	PG(16:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.714	<0.001	1.22	<0.001	1.894	<0.001	1.678
-	819.5176	3.6	PG(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.367	0.008	0.935	<0.001	1.275	<0.001	1.206
-	817.5017	3.7	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	0.835	<0.001	0.603	<0.001	0.786	<0.001	0.848
+	343.1532	15.1	Phaseollidin hydrate	<0.001	0.699	0.014	0.801	0.555	0.969	<0.001	0.551
-	319.0993	15.1	Phenolphthalin	<0.001	1.833	0.003	0.678	0.001	0.612	0.001	1.66
-	125.0243	15.0	Phloroglucinol	<0.001	0.632	0.127	0.847	0.004	0.758	0.001	0.601
+	799.4515	4.0	Phosphatidylglycerophosphate (dihexadec-9-enoyl, n-C16:1)	<0.001	0.446	0.093	0.764	0.013	0.606	0.094	0.764
-	78.95875	15.7	Phosphite	<0.001	3.219	<0.001	0.684	0.001	1.202	<0.001	3.13
+	212.0431	15.7	Phosphocreatine	<0.001	2.692	<0.001	0.632	0.056	1.054	<0.001	2.443
-	210.0287	15.7	Phosphocreatine	<0.001	2.412	<0.001	0.598	0.519	1.02	<0.001	2.213
+	809.516	3.8	PI(16:0/16:1(9Z))	<0.001	12.272	<0.001	4.684	<0.001	12.117	<0.001	11.686
-	807.5001	3.8	PI(16:0/16:1(9Z))	<0.001	17.112	0.001	6.388	<0.001	17.214	<0.001	15.785
+	839.5634	3.7	PI(16:0/18:0)	<0.001	1.514	0.091	1.121	0.004	1.210	<0.001	1.418
-	837.5477	3.8	PI(16:0/18:0)	<0.001	1.634	0.071	1.215	<0.001	1.346	<0.001	1.653
+	835.5318	3.7	PI(16:0/18:2(9Z,12Z))	<0.001	1.621	0.002	0.748	0.003	1.212	0.001	1.448
-	833.5156	3.8	PI(16:0/18:2(9Z,12Z))	<0.001	9.857	<0.001	5.067	<0.001	8.112	<0.001	9.849

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	859.5324	3.7	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	1.462	0.003	0.765	0.010	1.158	0.006	1.232
-	857.5173	3.8	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	1.874	<0.001	1.623	<0.001	1.898	<0.001	1.856
+	891.5954	3.6	PI(16:0/22:2(13Z,16Z))	<0.001	0.663	<0.001	0.484	<0.001	0.467	<0.001	0.572
+	889.5786	3.6	PI(16:0/22:3(10Z,13Z,16Z))	<0.001	0.813	<0.001	0.546	<0.001	0.600	<0.001	0.692
-	883.5334	3.8	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.302	<0.001	1.537	<0.001	2.086	<0.001	2.176
+	84.08083	25.0	Piperideine	<0.001	0.576	0.104	0.779	0.008	0.752	<0.001	0.445
+	267.1719	4.1	Practolol	<0.001	11.948	<0.001	10.012	<0.001	9.087	<0.001	11.323
+	190.0896	4.8	Prenyl-L-cysteine	<0.001	13.774	<0.001	17.459	<0.001	12.646	0.001	8.719
-	188.0751	4.8	Prenyl-L-cysteine	<0.001	18.589	<0.001	24.068	<0.001	17.404	<0.001	12.635
+	290.1345	14.0	Pro-Ser-Ser	<0.001	2.005	<0.001	0.519	<0.001	2.150	<0.001	1.525
-	288.1202	14.0	Pro-Ser-Ser	<0.001	2.614	<0.001	0.81	<0.001	2.58	<0.001	2.17
-	95.01377	15.0	Protoanemonin	<0.001	0.452	0.043	0.744	0.012	0.682	0.002	0.521
-	758.4968	3.8	PS(16:0/18:2(9Z,12Z))	<0.001	9.069	0.001	4.248	<0.001	8.995	<0.001	9.733
+	838.5599	3.7	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	<0.001	1.504	0.252	1.064	0.011	1.202	<0.001	1.419
-	836.5441	3.8	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	<0.001	1.635	0.066	1.202	<0.001	1.337	<0.001	1.662
+	834.5284	3.7	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.411	<0.001	0.743	0.007	1.132	<0.001	1.344
-	832.5123	3.8	PS(18:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	4.421	0.04	1.593	<0.001	2.42	<0.001	3.977
+	808.5129	3.8	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	6.341	<0.001	2.867	<0.001	6.293	<0.001	6.216
-	806.4965	3.8	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	8.056	0.002	2.778	0.002	6.816	<0.001	7.875
-	460.3283	4.7	Psychosine	<0.001	2.596	<0.001	1.866	<0.001	2.189	<0.001	2.511
+	170.0812	5.0	Pyridoxine	<0.001	3.131	0.044	2.667	0.003	3.039	0.596	1.264
+	309.1292	14.5	S-8-methylthiooctylhydroximoyl-L-cysteine	<0.001	0.351	0.050	0.637	0.001	0.495	0.002	0.298
-	307.1147	14.5	S-8-methylthiooctylhydroximoyl-L-cysteine	<0.001	0.426	0.074	0.703	0.011	0.634	0.001	0.279
+	398.1146	4.4	S-Adenosyl-4-methylthio-2-oxobutanoate	<0.001	0.400	0.007	0.749	<0.001	0.592	<0.001	0.470
+	336.0873	15.1	S-Formylglutathione	<0.001	2.268	0.226	0.898	0.630	1.043	<0.001	2.419
+	427.0952	17.5	S-glutathionyl-L-cysteine	<0.001	1.656	<0.001	2.963	<0.001	2.809	<0.001	1.919
+	344.1485	15.9	sinapoyltyramine	<0.001	0.423	<0.001	0.612	0.026	0.816	<0.001	0.382
+	799.6688	4.2	SM(d17:1/24:1(15Z))	<0.001	0.441	0.071	0.589	0.051	0.635	0.069	0.763

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	785.6535	4.2	SM(d18:1/22:1(13Z))	<0.001	0.183	<0.001	0.352	<0.001	0.315	0.002	0.394
+	216.0632	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	1.465	<0.001	0.502	<0.001	0.587	0.003	1.241
-	214.0488	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	1.626	<0.001	0.514	<0.001	0.616	<0.001	1.452
-	171.0065	15.1	sn-Glycerol 3-phosphate	<0.001	1.712	<0.001	0.754	<0.001	0.689	<0.001	1.671
-	199.9694	17.2	S-Sulfo-L-cysteine	<0.001	0.55	<0.001	0.531	<0.001	0.611	<0.001	0.47
+	428.3734	4.6	Stearoylcarnitine	<0.001	2.189	<0.001	1.357	<0.001	1.419	<0.001	2.360
-	125.0972	4.3	Sulcatone	<0.001	8.019	<0.001	7.684	<0.001	7.344	<0.001	7.615
-	96.9602	16.2	Sulfate	<0.001	0.708	0.001	0.76	0.01	0.823	0.001	0.611
-	286.0657	15.8	Sulmazole	<0.001	0.438	0.716	0.948	0.051	0.784	0.001	0.259
+	126.022	15.4	Taurine	<0.001	2.382	<0.001	1.322	<0.001	1.804	<0.001	2.255
-	124.0073	15.4	Taurine	<0.001	1.575	<0.001	1.152	<0.001	1.436	<0.001	1.54
+	144.0518	15.4	Tet-glycine	<0.001	2.553	<0.001	1.357	<0.001	1.905	<0.001	2.204
+	372.3108	4.8	Tetradecanoylcarnitine	<0.001	3.298	<0.001	1.377	<0.001	1.840	<0.001	2.908
+	148.0427	5.4	Thiomorpholine 3-carboxylate	<0.001	98.158	<0.001	108.278	0.005	47.686	0.001	34.103
-	241.0831	7.8	Thymidine	<0.001	0.614	0.102	0.812	0.006	0.756	0.003	0.639
+	398.3265	4.7	trans-Hexadec-2-enoylcarnitine	<0.001	2.755	<0.001	1.517	<0.001	2.454	<0.001	2.871
-	249.1858	4.0	Triton X-100	<0.001	0.436	0.863	1.026	0.525	1.054	0.002	0.613
-	393.2631	3.8	Tylactone	<0.001	3.519	0.179	1.648	0.024	2.294	0.005	2.859
-	402.995	16.9	UDP	<0.001	7.794	<0.001	3.072	<0.001	4.932	<0.001	4.476
-	565.0477	16.8	UDP-glucose	<0.001	3.244	<0.001	1.571	<0.001	2.76	<0.001	2.892
-	579.027	19.3	UDP-glucuronate	<0.001	4.443	<0.001	3.266	<0.001	3.546	<0.001	3.674
-	606.0744	15.6	UDP-N-acetyl-D-glucosamine	<0.001	2.747	<0.001	1.533	<0.001	1.989	<0.001	2.578
-	111.02	10.2	Uracil	<0.001	0.463	0.213	0.917	<0.001	0.736	0.001	0.636
+	134.0577	15.9	Ureidoglycine	<0.001	0.541	0.064	0.761	0.029	0.830	<0.001	0.547
-	243.0622	10.2	Uridine	<0.001	0.29	0.204	0.873	<0.001	0.591	<0.001	0.366
-	482.9614	18.1	UTP	<0.001	5.626	<0.001	1.557	<0.001	2.778	<0.001	3.792
-	151.0262	11.8	Xanthine	<0.001	0.358	0.299	0.86	0.024	0.744	0.001	0.464
+	153.0771	11.0	Xylitol	<0.001	0.468	0.041	0.711	<0.001	0.640	<0.001	0.468

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	88.04021	6.4	L-Alanine	0.969	0.971	0.592	0.648	0.766	0.77	0.574	0.448
-	88.04019	6.7	L-Alanine	0.96	1.011	0.478	0.802	0.27	0.685	0.254	0.612
-	147.0299	10.6	(R)-2-Hydroxyglutarate	0.942	0.965	0.026	0.305	0.03	0.275	0.181	0.433
-	179.056	23.3	D-Glucose	0.932	0.973	0.008	1.705	0.075	1.818	0.564	0.888
-	147.03	4.3	(R)-2-Hydroxyglutarate	0.921	1.069	0.32	0.462	0.66	1.292	0.397	0.337
-	88.04023	5.2	L-Alanine	0.9	0.96	0.728	1.096	0.54	0.828	0.334	1.291
-	88.04023	11.3	L-Alanine	0.888	0.961	0.556	1.196	0.128	1.431	0.454	1.256
-	113.0356	4.4	5,6-Dihydrouracil	0.872	0.921	0.528	2.156	0.725	1.196	0.578	1.358
-	179.0561	9.8	D-Glucose	0.867	1.046	0.361	0.787	0.851	1.052	0.48	1.232
-	88.04025	4.5	L-Alanine	0.831	0.872	0.466	0.595	0.188	0.407	0.512	1.504
-	149.0455	11.6	D-Ribose	0.826	0.929	0.871	1.055	0.97	0.988	0.318	0.611
-	129.0193	3.5	Itaconate	0.8	1.04	0.001	1.656	0.066	1.404	0.02	1.536
-	129.0193	5.1	Itaconate	0.789	0.93	0.017	1.43	0.635	1.118	0.005	1.802
-	88.04021	9.8	L-Alanine	0.732	0.863	0.088	0.397	0.069	0.338	0.358	0.521
-	149.047	27.5	D-Ribose	0.73	1.168	0.222	1.869	0.071	1.632	0.716	1.152
-	149.047	29.3	D-Ribose	0.728	1.119	0.306	0.643	0.538	1.242	0.321	0.511
-	115.0036	16.4	Fumarate	0.665	1.049	0.192	0.879	0.607	1.047	0.956	1.006
-	102.056	4.1	4-Aminobutanoate	0.635	0.791	0.584	0.756	0.93	0.959	0.546	0.687
-	102.056	5.2	4-Aminobutanoate	0.605	0.911	0.834	0.95	0.564	0.885	0.208	0.644
-	88.04023	11.1	L-Alanine	0.591	1.179	0.192	1.545	0.699	1.157	0.441	1.371
-	308.0989	13.9	N-Acetylneuraminate	0.551	0.956	0.001	0.679	<0.001	0.624	0.001	0.737
-	88.04025	4.2	L-Alanine	0.548	1.594	0.312	0.267	0.248	0.157	0.455	0.206
-	179.0561	11.8	D-Glucose	0.47	0.713	0.977	1.012	0.906	0.952	0.089	0.17
-	88.04024	3.9	L-Alanine	0.447	1.439	0.676	1.157	0.828	0.924	0.328	1.442
-	115.0036	7.3	Fumarate	0.43	1.628	0.918	1.036	0.53	0.791	0.682	1.214
-	149.0455	13.2	D-Ribose	0.426	0.908	0.154	0.786	0.184	0.829	0.03	0.687
-	115.0036	15.0	Fumarate	0.424	0.722	0.405	0.705	0.711	0.871	0.565	0.712
-	147.0299	4.5	(R)-2-Hydroxyglutarate	0.422	0.477	0.44	0.502	0.874	1.126	0.703	0.64

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	115.0036	15.2	Fumarate	0.417	0.708	0.961	0.978	0.256	0.584	0.235	1.651
-	179.0561	12.6	D-Glucose	0.407	0.807	0.846	0.968	0.043	0.574	0.841	1.055
-	147.0299	7.0	(R)-2-Hydroxyglutarate	0.401	0.743	0.146	0.572	0.795	1.075	0.334	0.587
-	129.0193	4.1	Itaconate	0.394	0.574	0.617	1.304	0.597	0.74	0.689	1.392
-	147.0299	7.3	(R)-2-Hydroxyglutarate	0.384	0.772	0.05	0.501	0.186	0.617	0.115	0.443
-	179.056	26.6	D-Glucose	0.349	0.741	0.718	0.874	0.181	1.602	0.836	1.074
-	88.04023	12.5	L-Alanine	0.347	1.305	0.883	0.965	0.556	1.207	0.006	0.526
-	149.047	29.8	D-Ribose	0.34	1.142	0.299	0.876	0.191	1.616	0.449	1.17
-	147.0299	6.5	(R)-2-Hydroxyglutarate	0.321	0.731	0.039	0.497	0.532	0.906	0.316	0.791
-	179.0561	20.3	D-Glucose	0.302	0.552	0.843	0.915	0.453	0.681	0.696	0.763
-	137.0357	17.4	Urocanate	0.287	4.996	0.343	3.343	0.415	0.784	0.103	9.923
-	179.0559	27.3	D-Glucose	0.286	0.619	0.74	1.148	0.541	1.297	0.498	0.667
-	179.056	26.8	D-Glucose	0.278	0.557	0.848	1.093	0.402	1.482	0.488	0.604
-	88.04018	7.2	L-Alanine	0.275	1.879	0.448	1.926	0.243	1.503	0.829	1.13
-	102.056	6.5	4-Aminobutanoate	0.266	2.223	0.969	1.031	0.331	1.936	0.065	3.731
-	115.0036	19.7	Fumarate	0.231	1.552	0.397	1.469	0.098	2.09	0.106	1.927
-	149.047	28.5	D-Ribose	0.23	0.316	0.471	0.576	0.967	1.026	0.6	0.558
-	102.056	5.5	4-Aminobutanoate	0.224	0.892	0.007	0.858	0.679	1.079	0.058	0.871
-	149.0458	12.1	D-Ribose	0.22	0.753	0.577	1.137	0.24	0.84	0.042	0.534
-	102.056	3.4	4-Aminobutanoate	0.214	1.253	0.54	1.117	0.16	1.274	0.487	1.218
-	102.056	4.3	4-Aminobutanoate	0.209	0.399	0.626	0.755	0.492	0.584	0.142	0.119
-	88.04019	7.0	L-Alanine	0.203	0.606	0.046	0.315	0.093	0.458	0.417	0.662
-	102.056	3.9	4-Aminobutanoate	0.192	1.173	0.886	1.033	0.254	0.839	0.381	1.311
-	147.0299	5.1	(R)-2-Hydroxyglutarate	0.169	0.853	0.019	0.715	0.182	0.887	0.111	0.817
-	179.0561	13.4	D-Glucose	0.168	1.447	0.785	1.103	0.102	1.676	0.117	1.721
-	179.0561	18.8	D-Glucose	0.16	0.528	0.585	1.207	0.243	1.498	0.667	1.231
-	102.056	7.3	4-Aminobutanoate	0.132	1.423	0.573	0.889	0.929	1.028	0.029	1.798
+	193.035	23.3	Citrate	0.125	0.691	0.122	0.717	0.758	0.956	0.008	0.317

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	104.107	4.9	Choline	0.123	0.596	0.014	0.514	0.157	0.668	0.438	0.860
+	148.0604	20.9	L-Glutamate	0.122	1.399	0.734	1.117	0.736	0.866	0.518	0.734
+	104.107	25.8	Choline	0.119	0.678	0.125	0.712	0.060	0.612	0.108	0.630
+	148.0604	11.5	L-Glutamate	0.117	2.284	0.009	3.085	0.695	1.065	0.935	0.982
+	204.1231	17.0	O-Acetylcarnitine	0.117	1.496	0.577	1.189	0.536	0.819	0.863	1.058
+	166.0865	26.5	L-Phenylalanine	0.116	4.537	0.168	1.997	0.181	1.605	0.018	2.810
+	104.107	24.8	Choline	0.116	0.558	0.015	0.301	0.010	0.277	0.229	0.533
+	104.1069	9.0	Choline	0.115	1.619	0.645	1.195	0.706	1.132	0.264	1.765
+	106.0487	12.0	L-Serine	0.114	0.671	0.827	0.964	0.293	0.852	0.112	0.658
-	179.0561	19.6	D-Glucose	0.109	0.349	0.775	0.878	0.578	0.776	0.565	0.651
-	88.04023	13.1	L-Alanine	0.102	0.306	0.621	1.266	0.129	0.349	0.286	0.35
+	180.0867	24.5	D-Glucosamine	0.091	0.467	0.432	0.762	0.584	1.270	0.270	0.533
-	102.056	7.0	4-Aminobutanoate	0.084	1.371	0.004	0.468	0.158	0.741	0.484	1.149
+	132.0768	25.4	Creatine	0.082	1.408	0.304	1.275	0.469	1.304	0.509	1.470
-	179.0559	27.9	D-Glucose	0.081	0.477	0.372	0.737	0.385	0.737	0.081	0.399
+	148.0604	14.0	L-Glutamate	0.077	0.550	0.645	0.875	0.136	3.563	0.598	0.798
+	132.0768	20.6	Creatine	0.075	1.691	0.508	1.202	0.170	1.340	0.559	1.227
+	147.0764	25.3	L-Glutamine	0.073	0.418	0.302	0.634	0.116	0.540	0.041	0.122
-	88.04023	12.8	L-Alanine	0.072	2.121	0.714	1.103	0.485	1.296	0.418	0.787
-	129.0193	7.9	Itaconate	0.072	0.467	0.595	1.222	0.495	0.753	0.393	0.806
+	132.0768	21.7	Creatine	0.069	1.563	0.469	1.232	0.720	0.895	0.202	2.014
+	148.0604	23.3	L-Glutamate	0.066	2.040	0.040	2.096	0.192	1.564	0.437	0.590
+	132.0768	26.0	Creatine	0.064	1.445	0.614	1.072	0.968	0.988	0.040	1.627
-	174.0885	16.5	L-Citrulline	0.063	0.68	0.228	0.831	0.062	0.756	0.076	0.701
+	162.0761	29.3	L-2-Aminoadipate	0.059	0.637	0.520	1.422	0.633	1.202	0.808	1.082
+	147.0764	21.2	L-Glutamine	0.056	0.655	0.873	0.962	0.190	0.687	0.529	0.719
+	180.0867	4.5	D-Glucosamine	0.056	0.458	0.333	0.778	0.223	0.712	0.059	0.401
-	88.04022	9.0	L-Alanine	0.055	0.493	0.042	0.455	0.032	0.415	0.1	0.358

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	88.04023	12.1	L-Alanine	0.054	1.827	0.01	2.263	0.025	1.757	0.048	2.21
+	180.0867	14.1	D-Glucosamine	0.054	0.479	0.075	0.540	0.127	0.603	0.121	0.401
-	89.02426	7.7	(R)-Lactate	0.053	11.999	0.05	12.923	0.001	21.037	<0.001	22.801
-	171.0664	6.5	[FA dioxo(8:0)] 4,7-dioxo-octanoic acid	0.053	1.68	0.142	1.602	0.342	1.223	0.05	1.749
-	148.0405	29.4	5,6-Dihydroxyindole	0.052	0.411	0.042	0.372	0.464	0.701	0.532	0.714
-	199.9703	13.6	S-Sulfo-L-cysteine	0.052	1.537	0.065	1.562	0.442	1.251	0.701	1.134
-	137.0357	4.3	Urocanate	0.052	2.098	0.215	1.681	0.284	2.274	0.342	1.753
-	136.9914	7.8	3-sulfopropanal	0.051	0.824	0.155	0.872	0.752	1.018	0.727	0.967
-	148.0405	29.8	5,6-Dihydroxyindole	0.051	3.857	0.573	1.573	0.911	1.105	0.752	1.358
-	116.9285	22.4	chromate	0.051	2.793	0.158	2.881	0.08	4.554	0.012	1.786
-	116.9285	16.0	chromate	0.051	2.43	0.116	2.495	0.639	1.083	0.679	0.933
-	86.02451	7.4	2-Aminoacrylate	0.05	1.926	0.495	0.807	0.593	1.198	0.617	0.816
-	165.0194	14.4	Phthalate	0.05	2.528	0.033	2.515	0.066	2.375	0.025	2.925
-	205.0508	23.3	Scoparone	0.05	0.715	<0.001	0.327	<0.001	0.105	0.261	1.193
+	812.6551	3.9	PE(24:1(15Z)/P-18:1(11Z))	0.050	0.724	0.066	0.715	0.851	0.975	0.083	0.754
+	169.0859	4.7	1,3,5-trimethoxybenzene	0.049	1.218	0.794	1.029	0.686	1.046	0.391	1.139
+	330.2639	4.1	4-8dimethylnonanoylcarnitine	0.049	0.721	0.690	0.951	0.280	1.196	0.176	0.738
-	312.1723	3.8	4-Oxo-13-cis-retinoate	0.049	0.856	0.944	1.006	0.747	0.978	0.942	0.994
-	216.9813	18.3	5-Sulfosalicylate	0.049	0.781	0.373	0.886	0.429	0.909	0.403	0.902
+	166.0863	11.7	L-Phenylalanine	0.049	1.883	0.261	1.710	0.047	2.479	0.479	1.430
-	147.0429	15.2	O-Carbamoyl-L-serine	0.048	0.815	0.01	0.754	0.016	0.848	0.01	0.768
-	125.0607	7.1	Toluene-cis-dihydrodiol	0.048	0.466	0.069	0.472	0.605	0.843	0.184	0.491
+	222.0971	12.3	N-Acetyl-D-glucosamine	0.048	0.572	0.488	0.856	0.017	0.535	0.119	0.595
-	175.0628	26.8	(2S)-2-Isopropylmalate	0.047	0.45	0.484	1.242	0.49	1.275	0.283	0.569
-	189.0769	4.3	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.047	1.931	0.027	2.447	0.091	3.116	0.193	3.814
-	189.0769	15.8	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.047	1.431	0.745	1.059	0.459	1.167	0.879	1.041
-	329.27	10.5	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.047	0.352	0.649	0.846	0.812	0.917	0.855	0.909
+	102.0663	23.0	N-acetylguanidine	0.047	0.342	0.807	0.895	0.136	0.516	0.171	0.372

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	244.1907	4.8	N-Undecanoylglycine	0.047	0.281	0.085	0.393	0.506	0.761	0.277	0.435
+	230.0956	15.4	Ergothioneine	0.046	1.579	0.048	1.408	0.003	1.884	0.242	1.354
-	311.2958	4.1	[FA (20:0)] eicosanoic acid	0.046	0.741	0.971	1.006	0.012	0.818	0.036	0.76
-	125.0244	14.1	Phloroglucinol	0.046	0.807	0.373	0.922	0.099	0.83	0.048	0.741
-	270.2074	4.4	Tridecanoylglycine	0.046	0.173	0.071	0.263	0.962	0.979	0.466	0.528
+	101.0598	10.2	Tiglic acid	0.046	1.968	0.799	0.936	0.817	1.064	0.935	1.027
+	166.0863	5.0	L-Phenylalanine	0.046	0.703	0.240	0.815	0.103	0.789	0.034	0.610
+	167.0485	14.0	2-methylphosphinoyl-2-hydroxyacetate	0.046	3.410	0.047	1.763	0.005	2.683	0.004	2.653
-	95.98569	14.5	Phosphoramidate	0.045	1.211	0.169	1.175	0.354	1.136	0.232	1.15
+	260.0528	15.9	D-Glucosamine 6-phosphate	0.045	1.260	0.564	0.941	0.044	1.367	0.016	1.422
+	203.0401	14.8	5-Hydroxy-2-oxo-4-ureido-2,5-dihydro-1H-imidazole-5-carboxylate	0.044	10.929	<0.001	24.740	<0.001	25.704	<0.001	18.930
+	129.0658	16.2	5,6-Dihydrothymine	0.044	0.631	0.755	0.959	0.137	0.764	0.919	1.033
-	187.1339	7.8	10-Hydroxydecanoic acid	0.044	0.771	0.21	0.839	0.11	0.798	0.201	0.774
-	172.958	14.6	2,5-dichloro-benzaldehyde	0.044	2.563	0.005	1.975	<0.001	2.945	<0.001	4.209
-	304.071	15.4	Phenylamil	0.044	0.861	0.351	0.965	0.327	1.044	0.074	0.884
+	150.1125	12.7	Triethanolamine	0.044	0.542	0.533	0.835	0.379	1.366	0.416	0.704
-	175.0612	14.1	(2S)-2-Isopropylmalate	0.043	0.448	0.972	0.989	0.536	0.797	0.796	1.094
-	367.3582	3.8	Tetracosanoic acid	0.043	0.589	0.084	0.656	0.136	0.699	0.32	0.719
+	126.055	3.2	N-Ethylmaleimide	0.042	1.600	0.433	0.763	0.122	0.554	0.099	0.336
+	189.1122	4.3	Azelaic acid	0.042	0.502	0.216	0.707	0.964	1.012	0.276	0.655
-	695.5635	4.2	[GL (20:0/22:6)] 1-eicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycerol	0.042	0.724	0.134	0.859	0.82	0.982	0.756	1.051
-	834.5281	4.1	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	0.042	2.915	0.544	0.83	0.055	1.874	0.949	0.981
-	169.0254	13.1	3,4,-dihydroxybutylphosphonate	0.042	0.77	0.412	0.908	0.797	0.973	0.053	0.701
+	300.1804	7.8	Indicine	0.042	0.728	0.858	0.982	0.183	0.864	0.199	0.836
+	125.071	3.2	Methylimidazole acetaldehyde	0.042	0.702	0.005	0.559	0.001	0.398	0.007	0.358
+	144.102	11.2	Stachydrine	0.042	0.701	0.169	0.767	0.209	0.829	0.073	0.633

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	341.3049	4.2	[FA oxo(21:0)] 2-oxo-heneicosanoic acid	0.041	0.281	0.531	0.768	0.029	0.234	0.150	0.288
+	140.0819	8.0	L-Histidinal	0.041	0.686	0.073	0.696	0.040	0.715	0.067	0.606
-	153.0921	4.6	[FA (9:2)] 2,6-nonadienoic acid	0.041	1.776	0.536	1.276	0.452	1.334	0.789	1.137
-	175.0249	15.6	Ascorbate	0.041	0.747	0.005	0.568	0.003	0.592	0.042	0.613
-	103.0038	14.6	Malonate	0.041	0.325	0.661	1.247	0.149	33.577	0.164	34.691
-	121.0407	7.8	Nicotinamide	0.04	0.809	0.778	0.955	0.107	0.85	0.16	0.759
+	194.1026	14.1	N1-hydroxypropyladenine	0.040	0.610	0.357	0.864	0.942	0.988	0.584	0.888
+	165.0679	26.4	S-(2-aminoethyl)-L-cysteine	0.039	18.460	0.022	35.798	0.005	51.909	0.016	17.813
+	111.0553	15.8	Imidazole-4-acetaldehyde	0.039	3.184	0.071	3.892	0.277	1.606	0.039	3.264
+	165.068	17.7	S-(2-aminoethyl)-L-cysteine	0.039	25.975	0.193	138.496	<0.001	53.343	<0.001	46.129
+	131.0471	15.6	3-ureidoacrylate	0.039	0.607	0.046	0.643	0.086	0.715	0.003	0.339
-	155.1078	4.6	[FA hydroxy(9:1)] 4-hydroxy-2-nonenal	0.039	2.006	0.003	2.298	0.014	2.31	0.034	2.201
-	187.0612	12.3	2-oxosuberate	0.039	1.24	0.164	0.716	0.011	1.694	0.085	0.823
-	187.0612	11.6	2-oxosuberate	0.039	2.236	0.555	1.372	0.077	2.841	0.221	2.001
-	105.0192	6.6	D-Glycerate	0.039	1.899	0.112	2.036	0.033	2.297	0.144	1.853
-	99.04512	4.4	Tiglic acid	0.039	2.373	0.865	0.886	0.484	1.516	0.062	2.638
+	544.3397	4.7	LysoPC(20:4(5Z,8Z,11Z,14Z))	0.039	1.426	0.015	1.429	0.205	1.181	0.025	1.502
+	447.3469	4.1	3-Dehydroteasterone	0.038	0.314	0.064	0.403	0.195	0.527	0.351	2.396
+	796.6207	4.3	PC(20:2(11Z,14Z)/P-18:1(11Z))	0.038	0.451	0.118	0.557	0.494	0.792	0.175	0.531
-	764.5633	4.4	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.038	1.085	0.033	0.858	0.524	1.025	0.035	1.086
-	277.1446	7.3	2-Ethylhexyl phthalate	0.038	1.539	0.097	1.479	0.577	1.15	0.021	0.302
-	179.0561	20.8	D-Glucose	0.038	0.522	0.038	0.5	0.183	0.62	0.026	0.304
+	324.208	4.2	Lysergic acid diethylamide	0.038	0.787	0.639	1.043	0.158	0.771	0.239	0.833
+	314.2689	4.3	[FA (16:0)] N-hexadecanoyl-glycine	0.038	0.240	0.232	0.558	0.080	0.370	0.324	0.507
+	348.0691	13.9	AMP	0.038	0.703	0.001	0.514	<0.001	0.490	0.020	0.517
+	241.1546	14.7	Slaframine	0.037	0.635	0.009	0.530	0.339	0.872	0.496	1.143
-	150.0561	4.0	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.037	0.559	0.044	0.58	0.061	0.59	0.083	0.421

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	159.0661	25.5	[FA (7:0/2:0)] Heptanedioic acid	0.037	1.851	0.056	1.638	0.328	1.298	0.067	1.633
-	277.1446	13.7	2-Ethylhexyl phthalate	0.037	2.432	0.136	2.194	0.034	2.509	0.012	3.257
+	180.0867	22.5	D-Glucosamine	0.036	0.433	0.205	0.659	0.852	0.933	0.091	0.335
+	213.1485	4.3	[FA oxo(12:0)] 12-oxo-10E-dodecenoic acid	0.036	0.907	0.006	0.785	0.318	0.945	0.549	0.961
-	485.2829	3.7	Ala-Leu-Gln-Arg	0.036	1.123	0.894	1.01	0.26	1.059	0.031	1.227
-	339.327	3.9	Docosanoic acid	0.036	0.65	0.332	0.82	0.084	0.671	0.313	0.781
+	505.2816	4.1	Phorbol 12,13-dibutanoate	0.036	0.475	0.221	0.702	0.624	0.875	0.860	0.933
+	174.0873	15.2	5-Guanidino-2-oxopentanoate	0.035	0.721	0.619	0.935	0.474	0.948	0.093	0.778
-	81.04554	28.9	acetonitrile dimer with Na	0.035	0.383	0.127	0.523	0.639	0.856	0.88	0.941
-	112.0516	10.1	Creatinine	0.035	0.658	0.636	0.948	0.039	0.851	0.014	0.729
-	169.0871	7.8	Furfural diethyl acetal	0.035	1.758	0.009	1.973	0.05	1.545	<0.001	1.783
-	327.1805	3.8	Gly-Pro-Arg	0.035	0.856	0.992	1.001	0.698	0.975	0.899	1.01
-	192.0668	7.8	Phenylacetylglycine	0.035	0.713	0.568	0.92	0.259	0.891	0.009	0.533
-	173.0818	27.4	Suberic acid	0.035	2.601	0.095	2.446	0.964	0.971	0.077	2.821
+	187.1441	7.8	N-(3-acetamidopropyl)-4-aminobutanal	0.034	0.736	0.162	0.870	0.266	0.886	0.173	0.869
-	121.0764	7.8	2,4-Diaminotoluene	0.034	0.626	0.029	0.619	0.906	0.975	0.27	0.753
-	179.0561	16.3	D-Glucose	0.034	0.383	0.381	0.706	0.269	0.621	0.12	0.36
-	149.0455	12.4	D-Ribose	0.034	0.764	0.065	0.76	0.129	0.852	0.014	0.569
-	248.9794	13.5	Oxidized Photinus luciferin	0.034	1.245	0.047	1.446	0.006	1.333	0.504	1.077
+	165.0678	12.7	Ricinine	0.034	15.859	<0.001	39.887	<0.001	28.644	<0.001	27.490
+	258.1084	11.2	5-Methylcytidine	0.033	0.570	0.479	0.890	0.810	0.964	0.073	0.691
-	299.2225	4.0	[FA methyl(16:0/2:0)] 2-methyl-hexadecanedioic acid	0.033	0.422	0.059	0.521	0.074	0.556	0.049	0.292
-	117.0557	6.7	5-Hydroxypentanoate	0.033	2.112	0.014	3.093	0.059	2.63	0.02	3.125
+	163.1229	29.4	Nicotine	0.033	1.625	0.116	1.428	0.958	1.019	0.612	1.164
+	104.107	25.3	Choline	0.033	0.464	0.102	0.603	0.036	0.516	0.147	0.488
+	165.0679	18.7	S-(2-aminoethyl)-L-cysteine	0.033	20.522	0.024	349.629	0.184	153.023	<0.001	25.451
+	126.022	15.9	Taurine	0.032	5.528	0.203	1.656	0.046	1.648	0.013	2.665
+	314.269	4.1	[FA (16:0)] N-hexadecanoyl-glycine	0.032	0.475	0.654	0.893	0.329	0.744	0.250	0.628

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	198.1125	27.5	L-Metanephrine	0.032	0.485	0.199	0.699	0.511	0.817	0.761	0.899
-	130.0509	26.6	L-Glutamate 5-semialdehyde	0.032	2.36	0.179	1.895	0.195	1.88	0.486	1.528
-	114.056	29.0	L-Proline	0.032	0.619	0.27	1.527	0.399	0.85	0.56	0.914
+	819.5178	12.5	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.032	0.843	0.246	0.948	0.698	0.960	0.038	0.852
+	213.0984	5.2	Volemitol	0.032	0.747	<0.001	0.757	0.095	0.763	0.052	0.881
+	244.1543	19.6	Tiglylcarnitine	0.032	1.846	0.271	1.380	0.307	1.430	0.223	1.524
+	120.0656	9.3	L-Threonine	0.031	1.631	0.041	1.435	0.252	1.385	0.821	0.917
+	148.0604	22.4	L-Glutamate	0.031	1.924	0.442	0.749	0.108	2.222	0.148	0.413
+	154.1226	7.8	Pseudopelletierine	0.031	1.563	0.394	0.706	0.418	0.716	0.648	1.187
-	389.1771	16.3	[Fv] Lespeol	0.031	0.707	0.405	1.123	0.432	1.141	0.129	0.737
-	114.056	15.2	L-Proline	0.031	0.411	0.134	0.626	0.374	0.751	0.902	0.951
-	242.1763	4.8	N-Undecanoylglycine	0.031	0.207	0.056	0.315	0.379	0.681	0.227	0.367
-	75.04477	13.4	Propane-1,2-diol	0.031	1.696	0.578	0.827	0.17	1.817	0.257	1.516
+	286.2376	7.8	Myristoylglycine	0.030	1.351	0.192	1.393	0.029	1.455	0.684	1.181
+	183.053	16.6	1-Methyluric acid	0.030	1.783	0.252	0.789	0.412	1.154	0.074	1.543
-	150.056	15.1	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.03	0.342	0.55	0.789	0.178	0.542	0.389	0.628
-	181.087	4.3	[PR] Iridotrial	0.03	2.884	0.123	2.215	0.502	1.557	0.007	4.178
-	473.2829	3.7	Ala-Lys-Thr-Arg	0.03	1.142	0.503	0.948	0.618	1.037	0.062	1.146
-	185.082	7.2	cis-2-Carboxycyclohexyl-acetic acid	0.03	0.7	0.336	0.841	0.007	0.514	0.89	0.978
-	97.04066	7.0	Imidazole-4-methanol	0.03	0.468	0.029	0.503	0.076	0.569	0.243	0.683
-	116.0717	13.1	L-Valine	0.03	0.581	0.266	0.855	0.767	0.951	0.021	0.541
-	135.0452	27.2	Phenylacetic acid	0.03	0.558	0.486	0.808	0.679	0.913	0.024	0.387
+	167.1067	17.2	Perillic acid	0.030	2.148	0.313	1.434	0.609	1.198	0.594	1.251
+	148.0757	10.6	3-Methyloxindole	0.029	0.489	0.179	0.756	0.141	0.757	0.131	0.625
-	271.2281	4.0	16-hydroxypalmitate	0.029	0.864	0.301	0.894	0.614	1.029	<0.001	2.348
-	86.02453	7.0	2-Aminoacrylate	0.029	2.172	0.259	1.678	0.186	1.763	0.013	2.57
-	487.2894	3.7	Asp-Lys-Lys-Val	0.029	1.259	0.112	1.196	0.016	1.171	0.008	1.538
-	177.0405	15.4	D-Glucono-1,5-lactone	0.029	0.775	0.047	0.829	0.268	0.813	0.025	0.703

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	274.141	17.5	L-a-glutamyl-L-Lysine	0.029	0.892	<0.001	0.578	<0.001	0.699	0.004	0.736
+	170.0924	19.0	N(pi)-Methyl-L-histidine	0.029	0.548	0.128	0.686	0.207	0.793	0.026	0.403
+	372.3108	4.1	Tetradecanoylcarnitine	0.029	0.762	0.050	0.708	0.251	0.857	0.013	0.481
+	272.2583	4.7	[FA amino(16:0)] 2R-aminohexadecanoic acid	0.028	2.841	0.003	3.912	0.001	4.727	0.019	3.331
+	156.1019	5.0	Retronecine	0.028	0.805	0.031	0.842	0.182	0.889	0.554	0.947
+	258.1086	14.2	5-Methylcytidine	0.028	0.459	0.245	0.732	0.513	0.840	0.962	0.984
+	165.0679	14.5	S-(2-aminoethyl)-L-cysteine	0.028	14.088	<0.001	56.686	<0.001	47.923	<0.001	35.089
-	86.02455	11.7	2-Aminoacrylate	0.028	1.82	0.367	1.389	0.639	1.222	0.362	1.455
-	246.9616	15.4	4-bromoisophthalate	0.028	0.416	0.048	0.45	0.021	0.351	0.319	0.616
-	161.082	5.0	beta-Cymaropyranose	0.028	2.015	0.003	2.108	0.008	2.267	0.039	2.373
-	179.056	22.7	D-Glucose	0.028	0.463	0.32	1.291	0.385	1.319	0.455	0.812
-	100.004	26.4	oxazoladindione	0.028	1.727	0.028	2.07	0.071	1.881	0.063	1.952
-	243.0622	12.5	Uridine	0.028	0.626	0.64	0.942	0.294	0.91	0.028	0.694
+	131.0704	15.4	(S)-3-Methyl-2-oxopentanoic acid	0.028	10.633	0.528	2.101	0.598	1.834	0.160	98.046
+	718.5753	4.1	PC(14:0/P-18:0)	0.027	1.154	0.996	1.000	0.006	1.205	0.003	1.248
+	126.0551	15.5	N-Ethylmaleimide	0.027	0.474	0.196	0.616	0.121	0.510	0.043	0.315
-	246.9616	13.0	4-bromoisophthalate	0.027	0.183	0.042	0.246	0.102	0.351	0.114	0.164
-	340.1267	10.5	6-(alpha-D-Glucosaminyl)-1D-myo-inositol	0.027	0.645	0.005	0.709	0.084	0.893	0.008	0.519
-	135.0452	25.1	Phenylacetic acid	0.027	2.005	0.251	1.771	0.334	1.793	0.03	2.251
+	167.1067	12.1	Perillic acid	0.027	0.326	0.786	1.102	0.665	1.208	0.991	1.005
+	576.1335	11.6	dTDP-D-mycaminose	0.026	0.596	0.095	1.441	0.484	1.087	0.011	0.607
+	256.0589	5.9	Imidacloprid	0.026	0.746	0.038	0.646	0.245	1.166	0.784	0.968
-	205.1598	15.5	[PR] (+)-15-nor-4-thujopsen-3-one	0.026	2.509	0.277	1.569	0.272	1.626	0.012	2.983
-	217.1082	12.2	3-Hydroxysebacicacid	0.026	1.376	0.804	0.934	0.017	1.359	0.03	1.447
-	146.0459	13.9	L-Glutamate	0.026	2.697	0.127	2.006	0.033	3.448	0.008	2.685
+	300.2896	5.4	[SP] 3-dehydrosphinganine	0.026	0.418	0.003	0.265	0.003	0.328	0.039	0.364
+	174.1126	16.0	N-Acetyl-L-leucine	0.025	0.180	0.248	0.568	0.847	1.114	0.437	0.577
+	260.1645	4.8	2-Heptyl-4-hydroxyquinoline-N-oxide	0.025	0.939	0.017	0.947	<0.001	0.924	0.012	0.923

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	194.0814	7.8	Phenylacetylglycine	0.025	0.714	0.802	0.982	0.103	0.861	0.051	0.769
+	288.2896	4.6	[SP (17:0)] heptadecasphinganine	0.025	27.286	0.018	28.005	0.050	50.149	0.002	31.267
+	129.0658	9.2	5,6-Dihydrothymine	0.025	1.638	0.272	1.340	0.041	1.983	0.565	0.786
+	316.2845	4.0	[SP hydrox] 6-hydroxysphing-4E-enine	0.025	0.741	0.654	1.064	0.365	0.884	0.073	0.631
-	175.025	15.4	Ascorbate	0.025	0.406	0.166	0.627	0.038	0.409	0.439	0.661
-	146.0459	15.2	L-Glutamate	0.025	0.877	0.216	0.914	0.772	1.015	0.024	0.841
-	91.02196	22.3	methylmercaptoethanol	0.025	0.301	0.552	0.838	0.56	0.821	0.768	1.089
-	248.991	4.2	Thienodolin	0.025	0.436	0.843	0.953	0.023	0.432	0.058	0.342
+	132.0768	21.4	Creatine	0.025	1.776	0.462	1.325	0.711	0.910	0.713	1.228
+	133.0989	11.3	L-Ornithine	0.025	0.489	0.292	0.740	0.089	0.644	0.025	0.401
+	170.0579	11.3	Phosphodimethylethanolamine	0.025	0.525	0.330	0.839	0.002	0.659	0.003	0.413
+	298.274	4.2	[SP (2:0)] sphinga-4E,14Z-dienine	0.024	0.218	0.182	0.546	0.205	0.567	0.124	0.248
+	510.3557	4.7	LysoPC(17:0)	0.024	1.170	<0.001	1.661	<0.001	1.452	0.004	1.219
-	140.9193	12.9	Arsenate	0.024	0.88	0.092	0.894	0.618	1.023	0.06	0.856
-	185.082	4.0	cis-2-Carboxycyclohexyl-acetic acid	0.024	2.95	0.02	2.953	0.007	3.453	0.141	2.626
+	160.1332	13.9	DL-2-Aminooctanoicacid	0.024	1.284	0.024	0.812	0.040	0.871	0.535	1.052
+	256.1656	5.0	L-Pyrrolysine	0.024	0.764	0.011	0.751	0.090	0.853	0.028	0.686
+	142.0863	5.1	L-Hypoglycin	0.023	1.322	0.047	0.765	0.069	0.789	0.462	0.894
-	750.5448	4.0	[PE (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.023	0.9	0.566	1.049	0.307	1.033	0.701	0.989
-	205.1598	29.2	[PR] (+)-15-nor-4-thujopsen-3-one	0.023	0.821	0.007	0.627	0.747	1.019	0.029	0.841
-	299.2015	4.1	[PR] Tretinoin/All-Trans Retinoic Acid	0.023	6.855	0.038	17.119	0.034	14.62	0.085	3.372
-	215.033	14.0	2-C-Methyl-D-erythritol 4-phosphate	0.023	0.673	0.496	1.109	0.516	0.948	0.019	0.723
-	373.275	3.8	3-Oxo-5beta-cholanate	0.023	1.928	0.779	1.126	0.084	2.772	0.124	4.031
+	220.118	6.4	Pantothenate	0.023	0.674	0.005	0.513	0.727	0.943	0.026	0.549
+	234.1335	10.7	Hydroxypropionylcarnitine	0.022	1.909	0.220	2.255	0.212	1.657	0.127	1.671
-	885.5491	4.1	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.022	1.722	0.473	1.274	0.969	1.011	0.062	1.805

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	124.0516	29.8	5-Methylcytosine	0.022	2.571	0.163	2.378	0.176	2.398	0.033	3.375
-	265.0571	25.0	5'-Oxoinosine	0.022	0.721	0.679	0.951	0.883	0.986	0.003	0.441
-	309.1697	4.1	Botrydial	0.022	0.35	0.176	0.502	0.2	0.628	0.119	0.375
-	201.077	12.3	Diethyl 2-methyl-3-oxosuccinate	0.022	0.773	0.013	0.683	0.104	0.811	0.028	0.579
-	83.02484	4.0	Imidazolone	0.022	0.207	0.063	0.41	0.015	0.162	0.06	0.096
+	333.0984	13.9	Sulochrin	0.022	0.862	<0.001	0.688	<0.001	0.735	0.003	0.645
+	760.5854	7.1	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.022	5.415	<0.001	5.686	<0.001	5.710	0.019	4.234
+	204.1231	18.2	O-Acetylcarnitine	0.021	1.693	0.967	0.986	0.112	1.492	0.543	1.223
+	194.1025	18.4	N1-hydroxypropyladenine	0.021	0.705	0.905	0.986	0.010	0.647	0.026	0.689
+	506.3483	13.8	Mycinamicin VIII	0.021	0.526	0.002	0.485	<0.001	0.567	0.001	0.270
-	352.1057	8.8	5-hydroxytryptophol glucuronide	0.021	0.607	0.428	0.926	0.021	0.828	<0.001	0.568
-	227.9918	10.6	Dimethoate	0.021	0.896	0.761	0.984	0.126	0.94	0.018	0.825
-	169.0872	4.5	Furfural diethyl acetal	0.021	2.017	0.161	1.712	0.062	1.771	0.006	2.385
-	83.02484	13.3	Imidazolone	0.021	0.603	0.025	0.607	0.973	1.018	0.156	0.69
-	122.0359	23.3	Pyrazinamide	0.021	0.542	0.845	1.093	0.824	1.077	0.641	1.106
-	239.1402	7.4	Slaframine	0.021	0.552	0.011	0.601	0.002	0.443	0.042	0.516
-	99.04511	4.7	Tiglic acid	0.021	1.16	0.416	1.056	0.214	1.101	0.887	1.019
+	308.0909	15.4	Glutathione	0.021	6.852	0.001	6.126	0.029	3.769	0.021	2.656
+	508.3765	4.7	[PC (18:1)] 1-(11Z-octadecenyl)-sn-glycero-3-phosphocholine	0.021	0.846	0.013	1.141	0.864	0.992	0.073	0.854
+	256.0589	11.1	Imidacloprid	0.020	1.245	0.259	0.881	0.355	1.086	0.397	0.923
+	157.0971	15.1	N-acetyl prolinamide or isomer	0.020	0.508	0.825	1.043	0.934	0.986	0.052	0.681
-	199.1342	4.4	[FA hydroxy(11:0)] 2-hydroxy-10-undecenoic acid	0.02	1.564	0.101	1.721	0.006	1.786	0.014	1.815
-	189.0405	11.0	[FA hydroxy,oxo(7:0/2:0)] 4-hydroxy-2-oxo-Heptanedioic acid	0.02	0.612	0.503	0.909	0.13	0.858	0.011	0.652
-	329.27	4.2	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.02	0.804	0.238	0.91	0.137	0.907	0.21	0.871
-	265.0572	12.2	5'-Oxoinosine	0.02	0.724	0.869	1.021	0.479	0.938	0.014	0.634
-	138.0197	28.1	6-Hydroxynicotinate	0.02	0.514	0.054	0.572	0.29	0.685	0.913	0.983
+	308.091	15.8	Glutathione	0.020	9.947	0.005	12.751	<0.001	9.599	<0.001	7.785

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	538.5197	4.0	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine	0.020	0.792	0.080	0.799	0.008	0.765	0.018	0.758
-	127.0513	29.9	5,6-Dihydrothymine	0.019	5.368	0.174	3.241	0.336	2.289	0.175	0.89
-	466.3081	3.7	Oxethazaine	0.019	1.61	0.043	1.57	0.014	1.685	0.01	2.115
-	125.0356	6.5	Thymine	0.019	0.362	0.077	0.496	0.97	0.99	0.219	0.506
+	120.0656	14.3	L-Threonine	0.019	0.782	0.163	0.765	0.882	0.990	0.010	0.487
+	222.1125	5.0	Metaxalone	0.019	0.586	0.015	0.791	0.020	0.849	0.831	0.980
+	189.0739	12.2	2-oxosuberate	0.018	0.700	0.231	0.797	0.279	0.870	0.047	0.549
+	209.0687	10.6	N-acetyl-demethylphophinothricin	0.018	0.570	<0.001	0.379	0.002	0.471	<0.001	0.261
+	402.2852	4.1	[SP] Myriocin	0.018	0.409	0.026	0.468	0.004	0.384	0.061	0.459
+	135.0275	12.0	(S)-Malate	0.018	0.491	0.218	0.771	0.119	0.720	0.120	0.688
+	310.2012	7.8	Metipranolol	0.018	0.532	0.613	0.925	0.161	0.663	0.826	0.968
-	201.1134	10.7	[FA (10:0/2:0)] Decanedioic acid	0.018	2.742	0.103	2.854	0.026	2.665	0.024	3.013
-	132.0567	19.5	2-Aminobenzimidazole	0.018	0.5	0.022	0.488	0.006	0.401	0.03	0.406
-	163.0249	13.2	2-Dehydro-D-xylonate	0.018	0.753	0.196	0.794	0.058	0.77	0.017	0.563
-	339.1233	10.6	6-Prenylnaringenin	0.018	0.642	0.023	0.79	0.164	0.909	0.002	0.644
-	191.0199	18.5	Citrate	0.018	0.851	0.284	0.915	0.655	1.025	0.013	0.779
-	121.0506	12.2	Erythritol	0.018	0.594	0.652	0.942	0.692	0.961	0.037	0.712
-	183.9265	9.8	iodoacetamide	0.018	0.797	0.142	0.74	0.017	0.811	0.002	0.526
-	146.0459	11.0	L-Glutamate	0.018	1.194	0.384	1.082	0.01	1.211	0.237	1.105
-	75.04477	24.8	Propane-1,2-diol	0.018	0.49	0.175	0.672	0.925	0.975	0.396	0.787
+	162.0761	11.7	L-2-Aminoadipate	0.018	2.829	0.059	1.970	0.653	1.181	0.541	1.274
+	822.6026	4.3	PE(18:4(6Z,9Z,12Z,15Z)/24:1(15Z))	0.018	2.089	0.228	1.432	0.472	1.279	0.014	3.611
+	146.1176	14.0	4-Trimethylammoniobutanoate	0.017	1.236	<0.001	0.727	<0.001	0.799	0.457	1.052
+	315.1873	25.0	Pergolide	0.017	5.438	<0.001	15.545	<0.001	16.331	0.028	4.219
-	409.2361	4.3	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.017	0.634	0.249	0.911	0.001	0.61	0.001	0.514
-	144.0302	10.8	2-Oxoglutaramate	0.017	0.653	0.468	0.873	0.32	0.872	0.071	0.637
-	117.0557	15.2	5-Hydroxypentanoate	0.017	2.266	0.044	1.849	0.133	2.51	0.15	1.854
-	373.1876	4.2	Leu-Trp-Gly	0.017	1.746	0.88	1.053	0.138	2.273	0.601	0.857

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	141.0659	9.8	Methylimidazoleacetic acid	0.017	0.774	0.206	0.845	0.064	0.832	0.024	0.739
+	260.1492	20.8	N-(3-oxooctanoyl)-L-homoserine	0.017	2.505	0.052	3.196	0.966	1.013	0.066	5.440
+	316.2482	4.2	[FA (10:0)] O-decanoyl-R-carnitine	0.017	0.488	0.951	0.984	0.655	0.908	0.189	0.681
+	142.0863	9.6	L-Hypoglycin	0.017	0.440	0.006	0.363	0.073	0.585	0.068	0.456
+	556.944	16.8	3'-Phosphoadenylylselenate	0.016	0.300	0.043	0.436	0.044	0.442	0.051	0.200
+	172.0734	15.6	6-diazo-5-oxonorleucine	0.016	0.679	0.938	0.985	0.361	0.870	0.029	0.663
+	170.0811	7.8	Pyridoxine	0.016	2.669	0.025	2.659	0.296	1.596	0.056	2.703
-	185.1547	13.9	[FA (11:0)] undecanoic acid	0.016	0.181	0.452	0.717	0.415	2.024	0.375	0.579
-	450.2992	4.7	[PC (14:1)] 1-(1E-tetradecenyl)-sn-glycero-3-phosphocholine	0.016	1.296	0.073	1.196	0.214	1.156	0.557	0.913
-	207.0122	4.8	1-Naphthalenesulfonic acid	0.016	0.333	0.143	0.608	0.681	0.887	0.413	0.717
-	410.2397	4.8	Ala-Lys-Pro-Pro	0.016	1.214	<0.001	1.694	<0.001	1.588	0.038	1.231
-	309.1082	5.3	Glu-Tyr	0.016	0.622	0.287	0.838	0.004	0.713	0.007	0.516
-	99.01993	5.9	Hydantoin	0.016	1.613	0.061	1.523	0.151	1.396	0.198	2.179
-	136.0516	29.1	Isoniazid	0.016	0.335	0.043	0.426	0.423	0.802	0.116	0.346
-	353.0491	6.4	Phenolsulfonphthalein	0.016	0.582	0.815	1.049	0.002	0.469	0.013	0.391
-	176.0208	5.0	Sulforaphane	0.016	0.522	0.038	0.584	0.167	0.698	0.045	0.452
+	258.1699	4.3	2-Hexenoylcarnitine	0.016	0.783	0.013	0.793	0.523	0.949	0.315	0.893
+	168.0473	15.4	Phenylthioacetohydroximate	0.016	2.170	0.007	1.657	0.002	2.560	0.028	2.351
+	192.0883	12.0	2-amino-3,7-dideoxy-D-threo-hept-6-ulosonate	0.016	0.518	0.052	0.656	0.051	0.685	0.019	0.403
+	295.1902	4.3	[6]-Gingerol	0.015	0.448	0.042	0.558	0.119	0.651	0.051	0.475
-	149.0091	16.2	(R,R)-Tartaric acid	0.015	0.775	0.766	0.975	0.678	0.953	0.409	0.923
-	100.0404	12.2	1-Aminocyclopropane-1-carboxylate	0.015	0.532	0.008	0.533	0.048	0.641	0.009	0.434
-	290.0883	13.7	2,7-Anhydro-alpha-N-acetylneuraminic acid	0.015	0.811	<0.001	0.456	<0.001	0.478	0.001	0.547
-	118.9985	17.6	2-Hydroxymalonate	0.015	0.854	0.001	0.73	0.034	0.846	<0.001	0.579
-	194.0458	8.9	Dopaquinone	0.015	0.61	0.065	0.776	0.011	0.764	0.006	0.6
-	165.0769	11.7	L-rhamnitol	0.015	0.574	0.343	0.864	0.158	0.833	0.007	0.6
-	125.0243	15.3	Phloroglucinol	0.015	0.61	0.104	0.759	0.013	0.623	0.029	0.492

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	122.0359	28.9	Pyrazinamide	0.015	0.388	0.099	0.543	0.421	0.812	0.035	0.289
-	248.08	3.9	S-Acetyldihydrolipoamide	0.015	0.371	0.849	0.944	0.851	0.954	0.308	0.679
+	258.2063	4.6	N-Lauroylglycine	0.015	0.325	0.023	0.372	0.254	0.697	0.210	0.472
+	132.0655	9.4	L-Glutamate 5-semialdehyde	0.015	0.477	0.005	0.410	0.586	1.095	0.009	0.197
+	198.0874	6.8	N-Acetyl-L-histidine	0.015	0.303	0.048	0.450	0.803	0.920	0.162	0.521
+	538.387	4.6	[PC acetyl(17:2)] 1-heptadecyl-2-acetyl-sn-glycero-3-phosphocholine	0.014	1.594	0.010	1.653	0.004	1.582	0.141	1.479
-	258.1707	4.8	[FA (6:0)] O-hexanoyl-R-carnitine	0.014	0.127	0.019	0.189	0.026	0.235	0.075	0.111
-	744.5553	4.0	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.014	2.877	0.239	1.651	0.001	2.57	<0.001	2.784
-	132.0567	29.9	2-Aminobenzimidazole	0.014	6.621	0.089	3.881	0.137	4.738	0.2	2.61
-	81.04554	27.9	acetonitrile dimer with Na	0.014	1.721	0.325	1.925	0.302	2.358	0.228	2.195
-	197.082	4.6	cis-2,3-Dihydroxy-2,3-dihydro-p-cumate	0.014	3.965	<0.001	4.201	0.002	3.512	<0.001	5.356
-	194.0459	13.8	Dopaquinone	0.014	0.751	0.057	0.793	0.215	0.9	0.033	0.723
-	76.96971	16.0	monothiocarbonate	0.014	1.518	0.001	1.579	0.001	1.808	<0.001	3.105
+	524.3715	4.7	[PC (18:0)] 1-octadecanoyl-sn-glycero-3-phosphocholine	0.014	1.173	<0.001	1.555	<0.001	1.356	0.019	1.188
+	204.1231	7.8	O-Acetylcarnitine	0.014	0.740	0.006	0.833	0.004	0.812	0.022	0.804
+	824.653	4.0	PC(22:2(13Z,16Z)/P-18:1(11Z))	0.014	0.437	0.009	0.526	0.038	0.577	0.248	0.790
+	812.5434	3.8	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.014	1.230	0.071	0.869	0.043	0.888	<0.001	1.228
+	232.1543	4.8	O-Butanoylcarnitine	0.014	0.812	0.048	0.811	0.778	0.976	0.007	0.771
+	247.1401	14.8	N2-(D-1-Carboxyethyl)-L-arginine	0.014	0.732	0.191	0.815	0.069	0.831	0.025	0.723
+	142.1227	7.8	Hygrine	0.014	1.956	0.313	1.545	0.355	0.747	0.083	2.518
+	133.0989	11.8	L-Ornithine	0.013	0.465	0.101	0.627	0.033	0.565	0.013	0.346
+	359.148	15.2	2-Phenylaminoadenosine	0.013	0.743	<0.001	0.765	0.467	0.971	<0.001	0.577
+	189.087	14.1	N-Acetylglutamine	0.013	1.917	<0.001	1.836	0.029	1.641	<0.001	2.022
+	865.5792	3.6	1-18:0-2-18:1-phosphatidylinositol	0.013	0.859	<0.001	0.637	<0.001	0.683	<0.001	0.784
+	220.118	9.0	Pantothenate	0.013	0.592	0.435	0.900	0.026	0.788	0.009	0.615
+	326.2324	4.4	12-Nitro-9Z,12Z-octadecadienoic acid	0.013	2.896	0.006	2.576	<0.001	5.585	0.134	2.374

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	171.0529	23.3	5-Ureido-4-imidazole carboxylate	0.013	0.595	0.031	0.731	0.241	0.873	<0.001	0.248
-	309.2802	3.9	[FA (20:0)] 11Z-eicosenoic acid	0.013	0.748	0.355	1.095	0.172	1.159	0.999	1
-	165.0337	14.0	2-methylphosphinoyl-2-hydroxyacetate	0.013	6.552	0.015	3.195	<0.001	4.911	0.007	4.151
-	164.0718	10.6	L-Phenylalanine	0.013	0.587	0.288	0.875	0.087	0.849	0.008	0.664
-	168.0779	13.5	N(pi)-Methyl-L-histidine	0.013	0.592	0.006	0.538	0.042	0.598	0.04	0.509
-	307.2645	3.9	Sclareol	0.013	0.596	0.963	0.992	0.855	1.027	0.904	1.029
+	260.1492	13.0	N-(3-oxooctanoyl)-L-homoserine	0.013	0.430	0.083	0.618	0.021	0.479	0.068	0.457
+	253.1435	4.6	ubiquinol-1	0.013	2.157	0.375	1.367	0.205	1.775	0.702	1.232
+	837.5463	4.4	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.012	2.485	0.370	1.398	0.800	0.917	0.081	2.163
+	282.279	4.3	[FA (18:1)] 9Z-octadecenamide	0.012	12.381	<0.001	24.439	0.014	41.439	0.002	11.892
+	170.0924	15.4	N(pi)-Methyl-L-histidine	0.012	0.580	0.768	1.043	0.868	0.985	0.055	0.689
+	114.0663	10.1	Creatinine	0.012	0.586	0.147	0.843	0.059	0.844	0.006	0.673
+	312.1288	15.1	1-7-Dimethylguanosine	0.012	0.535	0.933	0.988	0.186	0.782	0.007	0.351
+	127.123	11.8	1-5-diazabicyclononane	0.012	0.573	0.092	0.775	0.003	0.661	0.002	0.414
-	150.056	6.8	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.012	6.901	0.139	4.217	0.748	1.15	0.023	7.826
-	378.0799	15.7	2'-Carboxy-4-[bis(2-chloroethyl)amino]-2-methylazobenzene	0.012	1.197	<0.001	0.575	0.106	0.917	0.248	1.126
-	225.0994	16.2	Carnosine	0.012	0.711	0.55	0.921	0.208	0.875	0.036	0.718
-	180.0337	12.3	DL-Methionine sulfone	0.012	0.556	0.115	0.766	0.121	0.821	0.011	0.552
-	259.1299	11.6	Glu-Leu	0.012	1.271	0.001	0.567	<0.001	1.391	0.621	1.039
-	242.1762	7.7	N-Undecanoylglycine	0.012	0.443	0.041	0.568	0.414	0.82	0.177	0.582
+	88.03932	15.5	2-Aminoacrylate	0.012	0.642	0.752	0.932	0.144	0.845	<0.001	0.410
+	165.0679	16.0	S-(2-aminoethyl)-L-cysteine	0.012	14.644	<0.001	34.102	<0.001	37.577	<0.001	30.735
+	89.07096	12.0	N,N'-Dimethylurea	0.012	4.107	0.357	1.932	0.886	1.059	0.295	2.711
+	284.2947	4.2	Octadecanamide	0.011	1.389	0.010	1.761	0.011	1.958	0.169	1.206
+	506.3481	13.3	Mycinamicin VIII	0.011	0.429	0.474	0.862	0.018	0.540	0.066	0.493
-	357.3013	4.1	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.011	0.791	0.251	0.923	0.039	0.86	0.208	0.857
-	129.0323	10.5	3-ureidoacrylate	0.011	0.571	0.495	0.9	0.11	0.849	0.015	0.607

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	179.0542	8.5	D-Glucose	0.011	0.771	0.434	0.902	0.005	0.742	0.004	0.617
-	203.0892	25.0	Dimethylenetriurea	0.011	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!	<0.001	#DIV/0!
-	164.0388	13.9	L-Methionine S-oxide	0.011	0.696	0.13	0.773	0.103	0.792	0.024	0.619
-	173.0092	18.1	Phenylmethanesulfonyl fluoride	0.011	0.78	0.372	0.908	0.664	0.966	0.046	0.773
-	125.0356	15.6	Thymine	0.011	0.713	0.026	0.761	0.023	0.773	0.007	0.555
+	182.0812	14.8	L-Tyrosine	0.011	0.518	0.144	0.702	0.111	0.755	0.063	0.587
+	537.3537	15.6	[GP (12:0/12:0)] 1,2-didodecanoyl-sn-glycero-3-phosphate	0.011	0.838	0.030	0.884	0.003	0.900	<0.001	0.802
+	166.0723	10.3	3-Methylguanine	0.011	0.587	0.081	0.805	0.144	0.874	0.040	0.752
+	702.5442	4.0	PE(16:0/P-18:1(11Z))	0.011	0.266	0.924	1.038	0.257	0.674	0.072	0.288
+	188.0919	7.8	[FA hydroxy(4:0)] N-(3S-hydroxy-butanoyl)-homoserine lactone	0.011	3.169	0.040	2.451	0.023	4.681	0.017	2.324
+	162.076	15.5	L-2-Aminoadipate	0.010	0.816	0.226	1.145	0.109	1.403	0.163	0.904
+	325.1539	10.2	Dolasetron	0.010	0.548	0.016	0.730	0.018	0.801	<0.001	0.528
-	145.0505	28.4	Adipate	0.01	1.923	0.056	1.857	0.036	1.935	0.013	2.237
-	145.0505	26.8	Adipate	0.01	1.93	0.157	1.636	0.301	1.531	0.024	2.172
-	440.1325	17.1	Dofetilide	0.01	0.681	0.297	0.888	0.02	0.769	0.01	0.627
-	136.0516	21.7	Isoniazid	0.01	3.03	0.637	1.24	0.101	1.436	0.061	2.371
-	154.0622	20.3	L-Histidine	0.01	0.562	0.325	0.869	0.096	0.734	0.005	0.357
-	114.056	6.6	L-Proline	0.01	1.479	0.258	1.414	0.045	1.405	0.793	1.057
-	76.9697	27.2	monothiocarbonate	0.01	2.857	0.285	2.058	0.125	2.039	0.038	2.704
-	88.00385	3.4	Oxamate	0.01	0.618	0.182	1.378	0.391	1.208	0.015	1.437
-	111.0199	28.1	Uracil	0.01	0.445	0.01	0.413	0.319	1.217	0.005	0.353
+	135.0649	15.8	Deoxyribose	0.010	0.692	0.218	0.766	0.218	0.835	0.006	0.482
+	136.0618	10.1	4-Hydroxy-L-threonine	0.010	3.116	0.002	1.904	<0.001	3.491	<0.001	4.551
+	194.1024	15.4	N1-hydroxypropyladenine	0.010	0.424	0.956	1.014	0.048	0.609	0.006	0.158
+	216.1594	4.4	N-Nonanoylglycine	0.010	0.613	0.250	0.758	0.213	1.444	0.701	0.941
+	510.3924	4.7	LysoPC(O-18:0)	0.010	1.242	<0.001	1.325	<0.001	1.213	0.123	1.141
+	242.1749	4.6	Valeroidine	0.010	0.167	0.013	0.202	0.135	0.435	0.139	0.353

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	858.5285	3.7	PS(20:3(8Z,11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.010	1.239	<0.001	0.582	0.061	0.917	0.713	1.017
+	107.0532	16.2	methionol	0.009	0.641	0.099	0.800	0.121	0.835	0.302	0.859
+	202.1802	4.9	[FA amino(11:0)] 11-amino-undecanoic acid	0.009	0.326	0.012	0.353	0.008	0.313	0.057	0.318
+	274.0709	23.3	Adefovir	0.009	0.536	<0.001	0.251	<0.001	0.059	0.208	1.255
-	162.94	9.8	[FA (4:0)] 2-bromo-2-butenoic acid	0.009	0.662	0.26	0.8	0.046	0.76	0.032	0.625
-	144.0666	9.4	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.009	0.679	0.581	0.922	0.172	0.872	0.048	0.703
-	179.0561	12.4	D-Glucose	0.009	0.673	0.281	0.891	0.581	1.068	0.05	0.756
-	295.0428	14.0	Disulfiram	0.009	0.661	0.044	0.776	0.005	0.798	0.001	0.552
-	159.1027	4.8	Ethyl (R)-3-hydroxyhexanoate	0.009	1.591	0.026	1.539	0.027	1.568	<0.001	1.872
-	306.0766	16.1	Glutathione	0.009	6.985	0.009	5.151	0.006	4.006	0.002	3.714
-	148.0438	12.0	L-Methionine	0.009	0.554	0.264	0.859	0.097	0.84	0.008	0.618
-	114.056	29.8	L-Proline	0.009	0.915	0.725	0.988	0.495	1.027	0.076	0.722
-	254.9134	16.8	Metrifonate	0.009	1.05	<0.001	1.193	<0.001	1.549	<0.001	1.15
-	122.0247	29.7	Nicotinate	0.009	0.929	0.002	0.808	<0.001	0.854	0.216	2.991
-	192.0668	5.0	Phenylacetylglycine	0.009	0.62	0.179	0.768	0.077	0.74	0.015	0.528
+	200.1645	4.6	2-Hexenoylcholine	0.009	0.437	0.067	0.630	0.185	0.693	0.081	0.482
+	151.0617	12.0	D-Ribose	0.009	0.557	0.174	0.836	0.027	0.803	0.004	0.590
+	150.0584	12.0	L-Methionine	0.009	0.565	0.171	0.843	0.021	0.807	0.003	0.610
+	165.0679	29.2	S-(2-aminoethyl)-L-cysteine	0.008	17.278	<0.001	22.632	<0.001	24.672	<0.001	16.408
+	174.1255	11.8	L-Indospicine	0.008	0.593	0.096	0.684	0.025	0.648	0.007	0.461
+	178.1074	12.9	validamine	0.008	4.107	<0.001	5.234	<0.001	4.837	0.005	3.935
+	133.0318	12.0	THTC	0.008	0.557	0.174	0.832	0.021	0.792	0.003	0.599
-	100.0404	4.0	1-Aminocyclopropane-1-carboxylate	0.008	0.489	0.104	0.605	0.079	0.681	<0.001	0.183
-	341.1961	3.8	Ala-Pro-Arg	0.008	0.525	0.54	0.888	0.24	0.834	0.259	0.798
-	114.056	13.4	L-Proline	0.008	0.572	0.942	0.989	0.833	0.968	0.165	0.727
-	308.0576	17.1	N-(6-Oxo-6H-dibenzo[b,d]pyran-3-yl)maleamic acid	0.008	0.751	<0.001	0.488	0.054	0.879	<0.001	0.633
-	122.0247	29.5	Nicotinate	0.008	0.932	0.001	0.83	<0.001	0.857	0.229	2.457
-	99.04508	6.9	Tiglic acid	0.008	1.9	0.841	0.93	0.089	2.199	0.495	1.335

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	742.5406	4.2	[PE (18:1/18:2)] 1-(9Z-octadecenoyl)-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	0.008	5.540	0.617	1.217	0.030	2.286	0.020	3.111
+	785.6532	4.5	SM(d18:1/22:1(13Z))	0.008	0.438	0.002	0.356	0.007	0.411	0.085	0.532
+	146.0924	15.8	4-Guanidinobutanoate	0.008	1.109	0.074	0.910	0.059	0.936	0.072	1.142
+	414.3365	4.0	[ST] (22R,25R)-spirosol-5-en-3beta-ol	0.007	0.862	0.151	0.936	0.009	0.838	0.136	0.880
+	329.1423	11.8	Pencycuron	0.007	0.618	0.129	0.778	0.024	0.623	0.024	0.459
+	194.1024	17.6	N1-hydroxypropyladenine	0.007	0.716	0.365	0.881	0.264	0.887	0.071	0.772
+	166.0863	10.6	L-Phenylalanine	0.007	0.556	0.276	0.863	0.017	0.785	0.004	0.602
+	148.0604	21.8	L-Glutamate	0.007	0.352	0.535	0.891	0.266	0.781	0.079	0.513
+	230.1751	4.9	N-Decanoylglycine	0.007	0.257	0.014	0.334	0.157	0.622	0.123	0.415
+	120.1019	13.5	betaine aldehyde hydrate	0.007	1.539	0.001	1.790	<0.001	2.249	0.047	1.582
+	216.1958	4.8	[FA amino(12:0)] 12-amino-dodecanoic acid	0.007	0.245	0.016	0.341	0.116	0.564	0.049	0.216
+	228.2321	4.4	myristic amide	0.007	17.241	<0.001	12.463	<0.001	14.692	0.001	11.695
+	274.2011	4.3	Heptanoylcarnitine	0.007	0.745	0.018	0.811	0.076	0.819	0.042	0.773
-	243.1604	4.2	[FA (13:0/2:0)] Tridecanedioic acid	0.007	0.418	0.003	0.298	0.009	0.446	0.04	0.362
-	155.0714	4.9	[FA oxo(8:0)] 5-oxo-7-octenoic acid	0.007	1.218	0.128	1.139	0.448	1.068	0.013	1.278
-	145.0505	27.7	Adipate	0.007	1.66	0.04	1.628	0.314	1.365	0.009	1.89
-	378.1092	13.1	Asn-Cys-Gly-Ser	0.007	0.513	0.163	0.804	0.049	0.723	0.005	0.463
-	229.1342	8.8	Camoensine	0.007	0.435	0.54	0.89	0.081	0.651	0.036	0.502
-	179.0561	22.0	D-Glucose	0.007	0.396	0.947	0.983	0.388	1.439	0.02	0.342
-	295.0427	26.6	Disulfiram	0.007	0.77	0.002	0.873	0.366	0.97	<0.001	0.494
-	149.0455	15.0	D-Ribose	0.007	0.661	0.628	0.933	0.104	0.824	0.032	0.641
-	448.307	4.8	Glycodeoxycholate	0.007	0.667	0.313	0.872	0.071	0.799	0.024	0.636
-	177.0228	7.8	hexadieneol sulfate	0.007	0.678	0.123	0.826	0.003	0.753	0.001	0.575
-	178.0511	7.8	Hippurate	0.007	0.696	0.665	0.947	0.042	0.831	0.019	0.686
-	166.018	9.0	Homocysteinesulfinicacid	0.007	1.323	0.98	1.003	0.023	1.248	0.03	1.263
-	457.248	14.9	Ile-Met-Val-Pro	0.007	0.524	0.904	1.02	0.673	0.937	0.16	0.676
-	203.0828	12.2	L-Tryptophan	0.007	0.539	0.154	0.823	0.027	0.787	0.005	0.577

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	301.2386	4.2	MG(0:0/14:0/0:0)	0.007	0.795	0.174	0.907	0.033	0.873	0.055	0.82
+	295.0681	26.5	Pyrimidine 5'-nucleotide	0.007	0.669	0.011	0.843	0.005	0.883	<0.001	0.431
+	165.0547	13.8	Phenylpyruvate	0.007	0.725	<0.001	0.605	0.017	0.772	0.004	0.606
+	142.1227	5.0	Hygrine	0.007	0.753	0.028	0.828	0.020	0.832	0.185	0.866
+	260.1492	4.5	N-(3-oxooctanoyl)-L-homoserine	0.007	0.843	0.015	0.876	<0.001	0.813	0.050	0.856
+	482.3608	4.8	[PC (16:2)] 1-hexadecyl-sn-glycero-3-phosphocholine	0.007	1.244	<0.001	1.455	<0.001	1.310	0.002	1.257
+	157.0972	26.5	N-acetyl prolinamide or isomer	0.007	0.642	0.005	0.737	0.010	0.775	<0.001	0.515
+	127.1118	3.5	Sulcatone	0.007	0.711	0.008	0.512	0.268	1.062	0.032	0.738
+	180.0867	29.5	D-Glucosamine	0.006	0.461	0.096	1.201	0.340	2.164	0.251	0.748
+	209.0921	11.4	L-Kynurenine	0.006	0.535	0.188	0.798	0.021	0.740	0.004	0.466
+	167.0928	7.9	L-rhamnitol	0.006	0.710	0.383	0.895	0.032	0.819	0.024	0.705
+	738.544	4.0	PC(18:4(6Z,9Z,12Z,15Z)/P-16:0)	0.006	0.822	0.165	0.897	<0.001	0.827	0.005	0.875
+	773.6253	4.1	demethylmenaquinol-9	0.006	3.490	0.031	2.151	0.004	4.671	0.147	1.895
-	313.2386	7.3	[FA hydroxy(18:0)] 9,10-dihydroxy-12Z-octadecenoic acid	0.006	2.265	0.146	2.011	0.042	1.868	0.807	0.907
-	173.1183	5.0	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.006	0.483	0.001	0.401	0.019	0.596	0.022	0.42
-	219.1097	26.5	1D-1-Guanidino-3-amino-1,3-dideoxy-scyllo-inositol	0.006	0.627	0.006	0.687	<0.001	0.429	<0.001	0.256
-	215.033	13.3	2-C-Methyl-D-erythritol 4-phosphate	0.006	0.805	0.172	0.897	0.325	1.063	0.007	0.708
-	116.9285	20.4	chromate	0.006	3.432	0.06	2.807	0.276	2.45	0.082	3.927
-	201.077	13.7	Diethyl 2-methyl-3-oxosuccinate	0.006	1.792	0.076	2.094	0.023	2.763	0.001	3.185
-	306.0767	17.4	Glutathione	0.006	4.07	<0.001	5.495	<0.001	4.391	<0.001	4.153
-	165.0405	13.1	L-Arabinonate	0.006	0.7	0.013	0.692	0.004	0.736	0.001	0.494
-	131.0825	23.3	L-Ornithine	0.006	0.698	0.75	0.958	0.463	0.935	0.007	0.64
-	165.0751	10.6	L-rhamnitol	0.006	0.551	0.265	0.855	0.082	0.83	0.005	0.606
-	172.098	8.5	N-Acetyl-L-leucine	0.006	0.343	0.007	0.333	0.036	0.493	0.058	0.372
-	228.1605	4.9	N-Decanoylglycine	0.006	0.17	0.012	0.257	0.095	0.496	0.097	0.295
+	121.0626	15.0	serine hydroxamate	0.006	0.401	0.252	0.778	0.320	0.869	0.003	0.229
+	144.0808	10.6	2-Naphthylamine	0.006	0.524	0.282	0.817	0.072	0.742	0.010	0.554

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	205.0972	12.2	L-Tryptophan	0.006	0.538	0.140	0.827	0.016	0.780	0.003	0.570
+	820.5875	4.2	PE(20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.006	7.972	0.054	2.072	0.011	2.600	0.010	2.998
+	467.3329	4.6	[ST (3:0/3:0/3:0)] (5Z,7E)-(1S,3R)-24,24-difluoro-24a-homo-9,10-seco-5,7,10(19)-cholestatrien-1,3,25-triol	0.006	1.319	0.006	1.233	0.795	0.974	0.160	1.111
+	167.0896	10.6	L-rhamnitol	0.006	0.544	0.247	0.855	0.015	0.773	0.003	0.581
+	174.055	5.1	Deisopropylatrazine	0.006	0.555	0.006	0.580	<0.001	0.694	0.002	0.530
+	718.5385	4.4	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	0.006	6.809	0.001	3.151	<0.001	5.037	0.075	3.837
+	297.0571	26.5	Disulfiram	0.006	0.639	0.019	0.818	0.004	0.849	<0.001	0.362
+	102.055	15.2	1-Aminocyclopropane-1-carboxylate	0.005	0.807	0.298	0.910	0.578	0.966	0.004	0.745
+	87.04411	4.9	Diacetyl	0.005	0.366	0.448	0.839	0.070	0.617	0.044	0.609
-	127.0205	7.0	[FA (9:1/3:0)] 2-nonene-4,6,8-triynal	0.005	0.088	0.818	0.928	0.067	0.31	0.043	0.096
-	173.1183	4.2	[FA hydroxy(9:0)] 2-hydroxy-nonanoic acid	0.005	0.219	0.403	0.668	0.097	0.472	0.078	0.32
-	616.4708	4.3	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphate	0.005	1.191	0.14	0.869	0.202	1.087	0.005	1.369
-	83.01363	15.1	4-Hydroxy-2-butynal	0.005	0.617	0.012	0.656	0.001	0.618	0.007	0.529
-	182.046	4.9	4-Pyridoxate	0.005	0.697	0.021	0.7	0.031	0.735	0.013	0.578
-	175.0474	15.5	Allantoate	0.005	0.444	0.035	0.588	0.078	0.733	0.021	0.393
-	585.3605	4.7	Arg-Lys-Gln-Arg	0.005	1.19	<0.001	1.548	<0.001	1.356	0.073	1.128
-	465.3045	3.7	Cholesterolsulfate	0.005	1.358	0.017	1.297	0.004	1.381	0.001	1.722
-	179.0561	17.7	D-Glucose	0.005	0.749	0.185	0.911	0.237	0.887	0.159	0.857
-	259.0224	17.4	D-Glucose 6-phosphate	0.005	1.434	0.258	1.11	0.001	1.304	0.296	1.08
-	178.0511	5.0	Hippurate	0.005	0.686	0.322	0.882	0.072	0.835	0.024	0.694
-	130.0509	15.1	L-Glutamate 5-semialdehyde	0.005	0.586	0.034	0.736	0.692	0.945	0.12	0.777
-	748.5283	4.0	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.005	1.123	0.002	1.141	0.005	1.144	0.059	1.059
-	548.2866	3.7	Phe-Trp-Val-Val	0.005	1.293	0.373	0.922	0.542	1.054	0.003	1.414
+	746.6065	4.1	PC(16:0/P-18:0)	0.005	1.310	0.677	1.039	<0.001	1.418	<0.001	1.419
+	161.1285	23.9	N6-Methyl-L-lysine	0.005	1.300	0.032	0.899	0.089	1.041	0.394	0.966
+	76.03941	16.2	Glycine	0.005	0.728	0.220	0.874	0.052	0.846	0.017	0.746

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	496.34	4.8	[PC (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphocholine	0.005	1.197	<0.001	1.645	<0.001	1.490	0.002	1.272
+	206.1005	12.2	N-Acetyl-D-fucosamine	0.005	0.523	0.139	0.819	0.012	0.762	0.003	0.538
+	819.5179	20.6	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.005	2.475	0.186	1.448	0.006	3.231	0.071	1.775
+	370.2337	11.8	Prostaglandin G1	0.005	0.543	0.035	0.720	0.043	0.734	0.005	0.426
+	822.6378	4.0	PC(22:4(7Z,10Z,13Z,16Z)/P-18:0)	0.005	1.212	0.058	1.121	<0.001	1.254	<0.001	1.280
+	182.0812	13.7	L-Tyrosine	0.004	0.540	0.001	0.694	0.006	0.771	0.002	0.597
+	166.0533	13.9	L-Methionine S-oxide	0.004	0.634	0.135	0.788	0.051	0.787	0.004	0.504
+	244.1907	12.7	N-Undecanoylglycine	0.004	1.772	0.409	1.228	0.836	1.064	0.189	1.398
+	183.0846	13.7	D-Sorbitol	0.004	0.536	0.001	0.678	0.005	0.768	0.001	0.578
+	245.0954	9.2	Biotin	0.004	0.519	0.201	0.823	0.003	0.716	0.002	0.519
+	157.0972	13.4	N-acetyl prolinamide or isomer	0.004	0.508	0.106	0.809	0.004	0.732	0.002	0.546
+	188.0706	12.2	Deethylatrazine	0.004	0.519	0.144	0.818	0.016	0.774	0.003	0.563
+	506.3501	10.2	Mycinamicin VIII	0.004	0.556	0.106	0.810	0.117	0.860	0.002	0.590
-	257.0781	10.5	(1-Ribosylimidazole)-4-acetate	0.004	0.445	0.477	0.863	0.107	0.766	0.01	0.469
-	436.2835	4.7	[PE (16:1)] 1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	0.004	1.197	<0.001	1.294	0.001	1.183	0.094	1.13
-	888.5599	3.8	[PI (17:0/20:4)] 1-heptadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)(ammonium salt)	0.004	1.567	0.02	1.413	0.032	1.496	0.018	1.522
-	324.2179	4.4	12-Nitro-9Z,12Z-octadecadienoic acid	0.004	5.723	0.037	4.158	0.002	10.523	0.092	4.974
-	265.0208	15.7	2,2-Bis(4'-chlorophenyl)ethanol	0.004	0.772	<0.001	0.68	0.044	0.671	0.001	0.674
-	238.0253	13.8	2,4-dinitrophenyl propionate	0.004	0.551	0.001	0.48	0.019	0.676	0.008	0.463
-	102.0196	6.7	2-Aminomalonate semialdehyde	0.004	0.478	0.312	0.782	0.044	0.708	0.49	0.741
-	215.033	14.9	2-C-Methyl-D-erythritol 4-phosphate	0.004	0.662	0.869	0.985	0.231	0.934	0.013	0.792
-	195.9762	13.6	2-propenyl-thiohydroximate-O-sulfate	0.004	1.295	0.036	1.445	0.003	1.365	0.198	1.146
-	181.0507	9.1	3-(4-Hydroxyphenyl)lactate	0.004	0.678	0.245	0.857	0.024	0.787	0.007	0.604
-	155.027	4.1	4-Chloro-3,5-dimethylphenol	0.004	2.911	0.509	0.69	0.8	0.9	0.341	1.611
-	225.0647	12.2	5-Acetylamino-6-formylamino-3-methyluracil	0.004	0.527	0.239	0.871	0.03	0.816	0.001	0.553
-	161.082	7.8	beta-Cymaropyranose	0.004	2.475	0.009	2.343	0.034	2.009	0.022	2.622

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	227.0675	8.6	Deoxyuridine	0.004	0.722	0.217	0.843	0.019	0.801	0.021	0.728
-	247.0936	15.3	Glu-Thr	0.004	1.393	0.018	0.688	<0.001	2.443	0.056	1.305
-	204.0667	7.9	Indolelactate	0.004	0.666	0.351	0.865	0.058	0.799	0.008	0.618
-	154.0622	26.6	L-Histidine	0.004	0.34	0.69	0.9	0.378	0.783	0.031	0.344
-	556.3256	4.8	Lys-Lys-Trp-Pro	0.004	1.207	<0.001	1.66	<0.001	1.5	0.008	1.232
-	287.0521	12.7	Orotidine	0.004	3.995	<0.001	1.263	<0.001	2.085	<0.001	4.077
-	764.5248	4.2	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	0.004	14.466	0.081	2.344	0.005	8.059	0.009	9.39
-	219.036	17.7	thidiazuron	0.004	4.178	<0.001	6.993	<0.001	6.523	<0.001	5.083
-	167.0211	13.1	Urate	0.004	0.685	0.179	0.827	0.578	0.95	0.019	0.656
-	455.3533	6.6	Ursolic acid	0.004	0.474	<0.001	0.373	0.002	0.331	0.003	0.265
+	455.1807	12.5	Methotrexate	0.004	0.508	0.156	0.763	0.322	0.867	0.003	0.269
+	273.0858	26.5	1,2-Bis(4-nitrophenyl)ethane	0.004	0.543	0.045	0.784	0.006	0.763	<0.001	0.239
+	325.0547	18.5	ribavirin-5'-monophosphate	0.004	0.691	0.033	0.820	<0.001	0.675	<0.001	0.332
+	838.6325	4.0	[PC (18:0/22:4)] 1-octadecanoyl-2-(7Z,10Z,13Z,16Z-docosatetraenoyl)-sn-glycero-3-phosphocholine	0.004	1.271	0.030	1.212	0.011	1.171	<0.001	1.361
+	170.0924	19.3	N(pi)-Methyl-L-histidine	0.004	0.539	0.101	0.671	0.018	0.661	0.004	0.318
+	234.1335	9.6	Hydroxypropionylcarnitine	0.004	3.362	0.152	1.711	0.330	1.396	0.760	1.115
+	230.1751	7.8	N-Decanoylglycine	0.004	0.325	0.014	0.462	0.052	0.567	0.070	0.432
+	246.17	8.5	N-(octanoyl)-L-homoserine	0.004	5.070	0.141	1.164	0.147	2.218	0.008	4.770
+	174.1126	8.5	N-Acetyl-L-leucine	0.004	0.231	0.006	0.283	0.016	0.386	0.041	0.248
+	218.1387	5.0	O-Propanoylcarnitine	0.004	0.782	0.001	0.750	0.001	0.750	0.025	0.777
+	256.2634	4.3	Palmiticamide	0.004	22.642	<0.001	23.927	<0.001	35.914	<0.001	14.133
+	666.1323	13.9	NADH	0.004	1.927	0.032	1.369	0.034	1.497	0.004	1.924
+	297.0567	18.5	Disulfiram	0.004	3.155	<0.001	6.782	<0.001	7.230	<0.001	4.743
+	121.072	11.1	urea dimer	0.004	0.602	0.352	0.842	0.046	0.752	0.013	0.574
+	885.5479	3.6	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	0.004	1.198	<0.001	0.604	0.001	0.855	0.042	0.920
+	168.0768	14.5	2,4-Diamino-6-nitrotoluene	0.004	0.594	0.396	0.868	0.143	0.835	0.013	0.530
+	258.1084	9.7	5-Methylcytidine	0.003	0.509	0.093	0.783	0.029	0.783	0.004	0.536

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	91.05832	15.4	Diethyl sulfide	0.003	0.770	0.074	0.831	0.005	0.809	0.025	0.782
+	210.0609	18.5	uric acid acetonitrile adduct	0.003	0.690	0.079	0.815	<0.001	0.732	<0.001	0.340
+	126.055	25.3	N-Ethylmaleimide	0.003	0.435	0.006	0.444	0.002	0.355	0.004	0.259
+	112.0506	10.9	Cytosine	0.003	0.525	0.077	0.787	0.002	0.711	0.004	0.622
+	105.104	20.5	N-hydroxyputrescine	0.003	0.620	0.092	0.728	0.028	0.699	0.009	0.561
+	796.6203	4.1	PC(20:2(11Z,14Z)/P-18:1(11Z))	0.003	0.666	0.012	0.757	0.036	0.779	0.084	0.889
+	260.1138	15.1	Proacacipetalin	0.003	1.437	<0.001	0.663	<0.001	0.608	0.011	1.287
+	127.123	11.3	1-5-diazabicyclononane	0.003	0.410	0.145	0.801	0.023	0.697	0.003	0.426
+	273.0886	4.3	1,2-Bis(4-nitrophenyl)ethane	0.003	0.185	0.002	0.124	0.001	0.098	0.033	0.185
+	772.6215	4.1	[PC (18:1/18:0)] 1-(1Z-octadecenyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.003	2.178	0.010	1.747	<0.001	2.512	0.004	2.246
+	174.0874	15.8	5-Guanidino-2-oxopentanoate	0.003	0.436	0.016	0.594	0.278	0.771	0.017	0.403
-	409.2363	4.8	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.003	1.216	<0.001	1.686	<0.001	1.542	0.004	1.285
-	196.9318	18.3	2,4,5-Trichloro-2,5-cyclohexadiene-1-ol	0.003	0.805	0.077	0.895	0.239	1.029	<0.001	0.654
-	157.0367	14.3	Allantoin	0.003	0.683	0.277	0.877	0.072	0.838	0.004	0.628
-	271.0814	26.5	Arbutin	0.003	0.679	0.144	0.865	0.078	0.894	<0.001	0.44
-	385.1719	26.5	Asp-Val-Gly-Pro	0.003	0.494	0.08	0.781	0.011	0.739	<0.001	0.018
-	183.0759	14.5	barbital	0.003	0.657	0.316	0.896	0.008	0.77	0.007	0.58
-	226.0835	11.0	Deoxycytidine	0.003	0.437	0.021	0.628	0.044	0.675	0.019	0.504
-	133.0505	15.8	Deoxyribose	0.003	1.418	0.124	1.263	0.146	1.283	0.008	1.396
-	195.0511	14.5	D-Gluconic acid	0.003	0.66	0.099	0.817	0.141	0.883	0.008	0.478
-	181.07	13.6	D-Sorbitol	0.003	0.6	0.016	0.681	0.008	0.69	0.006	0.523
-	193.0523	4.4	Ferulate	0.003	0.676	0.141	0.825	0.031	0.796	0.008	0.628
-	115.0036	12.0	Fumarate	0.003	0.352	0.008	0.436	0.003	0.374	0.041	0.397
-	277.0235	17.8	hexanediol 1,6-bisphosphate	0.003	0.656	0.717	0.958	0.803	0.976	0.018	0.653
-	131.0826	26.5	L-Ornithine	0.003	0.7	0.367	0.897	0.073	0.851	0.003	0.615
-	104.0353	16.2	L-Serine	0.003	0.705	0.202	0.854	0.165	0.889	0.032	0.74
-	204.086	12.2	N-Acetyl-D-fucosamine	0.003	0.489	0.192	0.795	0.018	0.718	0.007	0.484

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	353.0492	5.0	Phenolsulfonphthalein	0.003	0.645	0.358	0.877	0.022	0.77	0.005	0.575
-	293.054	26.5	Pyrimidine 5'-nucleotide	0.003	0.709	0.025	0.858	0.178	0.948	<0.001	0.444
-	260.0234	15.6	tyrosine sulfate	0.003	0.633	0.113	0.773	0.016	0.671	0.033	0.634
-	290.1052	4.4	uniconazole-P	0.003	0.667	0.143	0.819	0.024	0.782	0.008	0.618
-	187.0379	13.4	xylitol chloride adduct	0.003	0.653	0.036	0.736	0.023	0.753	0.013	0.622
+	258.11	15.1	5-Methylcytidine	0.003	1.425	<0.001	0.669	<0.001	0.628	0.015	1.263
+	288.2168	4.3	L-Octanoylcarnitine	0.003	0.832	0.005	0.888	0.160	0.931	0.047	0.893
+	175.1078	14.1	N-Acetylornithine	0.003	0.595	0.229	0.816	0.040	0.770	0.002	0.470
+	332.0687	14.9	Piroxicam	0.003	5.245	0.001	5.259	0.012	3.447	0.233	1.896
+	819.5178	16.1	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.003	0.706	0.317	0.930	0.078	0.883	0.181	0.879
+	370.2337	11.3	Prostaglandin G1	0.003	0.611	0.006	0.660	0.055	0.772	0.001	0.459
+	311.0902	14.9	6-Deoxyjacareubin	0.003	5.303	<0.001	6.759	<0.001	4.591	0.001	3.251
+	126.0662	9.9	5-Methylcytosine	0.003	0.653	0.090	0.784	0.029	0.806	0.006	0.645
+	777.5626	4.0	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.003	1.373	0.006	1.274	<0.001	1.397	<0.001	1.442
+	196.083	10.3	2-Amino-2-deoxy-D-gluconate	0.003	3.763	0.009	2.322	<0.001	4.328	<0.001	5.837
+	331.2842	4.2	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.003	0.751	0.021	0.840	0.001	0.737	0.117	0.803
+	291.1298	17.4	N-(L-Arginino)succinate	0.003	1.920	0.851	1.033	0.042	1.408	0.021	1.570
+	229.1184	15.1	(S)-ATPA	0.002	0.413	0.153	0.739	0.014	0.575	0.005	0.389
+	198.1043	26.5	3-Amino-1-methyl-5H-pyrido[4,3-b]indole	0.002	0.661	0.156	0.866	0.019	0.825	<0.001	0.416
+	297.0573	14.0	Disulfiram	0.002	0.563	0.362	0.857	0.085	0.766	0.017	0.426
+	295.1188	26.5	Tutin	0.002	0.644	<0.001	0.236	<0.001	0.117	0.025	1.298
+	203.0849	5.0	Pyrene	0.002	12.369	<0.001	14.618	<0.001	12.941	0.002	7.162
+	191.0849	12.0	Aldicarb	0.002	0.423	0.061	0.744	0.005	0.710	<0.001	0.423
+	308.091	17.0	Glutathione	0.002	9.441	<0.001	12.942	0.003	7.655	<0.001	4.112
+	94.92964	28.8	MgCl2	0.002	0.506	0.207	0.805	0.045	0.686	0.006	0.344
+	176.0706	4.4	Indole-3-acetate	0.002	0.633	0.101	0.792	0.006	0.712	0.007	0.570
+	800.6172	4.1	[PE (20:0/20:2)] 1-eicosanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	0.002	10.394	0.023	2.007	<0.001	11.540	<0.001	19.036

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	327.1584	13.3	[Fv Trihydrox] 2',4',6'-Trihydroxy-3'-prenyldihydrochalcone	0.002	0.497	0.244	0.822	0.001	0.611	<0.001	0.446
+	188.1645	5.0	[FA amino(10:0)] 10-amino-decanoic acid	0.002	0.301	0.001	0.244	0.005	0.395	0.028	0.340
+	85.0284	11.5	4-Hydroxy-2-butynal	0.002	1.506	0.005	0.652	<0.001	0.476	0.058	1.356
-	390.2686	3.8	[FA (18:0)] N-octadecanoyl-taurine	0.002	2.334	0.015	1.484	<0.001	1.912	<0.001	2.336
-	145.087	4.8	[FA hydroxy(7:0)] 2-hydroxy-heptanoic acid	0.002	2.747	0.002	3.048	0.035	3.351	0.001	3.551
-	437.2675	4.7	[GP (18:0)] 1-octadecanoyl-2-sn-glycero-3-phosphate	0.002	1.209	<0.001	1.589	<0.001	1.41	0.006	1.181
-	774.5448	3.9	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.002	1.75	<0.001	1.61	<0.001	1.921	<0.001	1.82
-	821.5336	3.6	[PG (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.002	1.143	0.002	0.888	0.044	1.067	0.129	1.058
-	197.082	4.8	cis-2,3-Dihydroxy-2,3-dihydro-p-cumate	0.002	1.662	0.005	1.484	0.004	1.294	<0.001	1.769
-	110.0359	29.9	Cytosine	0.002	3.753	0.132	2.844	0.048	3.812	0.174	2.569
-	194.0447	4.4	Dopaquinone	0.002	0.658	0.132	0.813	0.026	0.778	0.008	0.608
-	352.0652	5.0	Glu-Cys-Cys	0.002	0.664	0.392	0.875	0.01	0.781	0.002	0.569
-	130.0509	25.2	L-Glutamate 5-semialdehyde	0.002	3.803	0.515	1.191	0.068	2.392	0.09	2.511
-	163.0627	29.9	L-Rhamnose	0.002	2.984	0.602	1.282	0.054	3.456	0.198	1.683
-	556.3255	7.8	Lys-Lys-Trp-Pro	0.002	1.249	<0.001	1.781	<0.001	1.606	<0.001	1.385
-	499.2933	4.4	Mupirocin	0.002	0.466	0.091	0.625	0.012	0.636	0.011	0.479
-	196.0728	9.2	N-Acetyl-L-histidine	0.002	0.487	0.2	0.814	0.006	0.735	0.002	0.487
-	214.145	5.0	N-Nonanoylglycine	0.002	0.196	0.009	0.319	0.215	0.654	0.137	0.434
-	211.0604	26.5	n-Propyl gallate	0.002	0.741	0.177	0.906	0.117	0.922	<0.001	0.549
-	333.0917	4.4	Penicillin G	0.002	0.67	0.112	0.818	0.016	0.779	0.006	0.618
-	125.0356	7.8	Thymine	0.002	0.666	0.159	0.828	0.006	0.766	0.007	0.622
-	289.129	4.4	Trimethoprim	0.002	1.312	0.591	1.071	0.009	1.117	<0.001	1.614
-	311.0995	4.1	Vicianose	0.002	0.231	0.004	0.289	0.07	0.556	0.062	0.4
+	330.2273	4.2	6-Keto-decanoylcarnitine	0.002	0.684	0.015	0.805	0.051	0.793	0.010	0.583
+	249.061	12.2	pentane-1,3,4,5-tetracarboxylate	0.002	0.527	0.315	0.882	0.012	0.781	<0.001	0.469

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	104.107	15.1	Choline	0.002	1.404	0.022	0.738	0.018	0.680	0.059	1.248
+	207.1129	10.6	Phenylethylmalonamide	0.002	0.429	0.146	0.800	0.003	0.696	0.001	0.465
+	228.0978	10.9	Deoxycytidine	0.002	0.492	0.081	0.782	0.002	0.707	0.002	0.579
+	205.0349	16.7	Oxaloglutarate	0.002	1.733	0.897	1.020	0.021	1.363	0.003	1.716
+	313.2735	4.2	[FA oxo(19:0)] 10-oxo-nonadecanoic acid	0.002	0.434	0.004	0.732	<0.001	0.516	0.095	0.714
+	189.1346	27.0	Homoarginine	0.002	0.567	0.200	0.799	0.055	0.790	0.004	0.456
+	278.1234	12.9	S-(2-Methylpropanoyl)-dihydrolipoamide	0.002	0.628	0.093	0.787	0.003	0.720	0.001	0.520
+	190.0863	10.6	3-Indolepropionicacid	0.002	0.477	0.256	0.824	0.022	0.766	0.004	0.569
+	466.3294	4.6	[PC (15:1)] 1-(1Z-pentadecenyl)-sn-glycero-3-phosphocholine	0.002	1.253	<0.001	1.201	0.075	1.069	0.032	1.166
+	426.3576	7.7	Elaidiccarnitine	0.002	3.017	<0.001	1.907	<0.001	2.275	<0.001	3.087
+	94.92964	29.2	MgCl2	0.002	0.477	0.107	0.734	0.335	0.821	0.002	0.315
+	161.046	4.5	2-Oxoadipate	0.002	0.588	0.128	0.796	0.008	0.696	0.007	0.571
+	208.1162	10.6	N-Ethylglycocyamine	0.002	0.395	0.117	0.770	0.004	0.670	0.002	0.422
+	184.0605	4.9	4-Pyridoxate	0.002	0.699	0.014	0.714	0.020	0.753	0.001	0.488
+	286.3104	8.8	[SP] 1-deoxy-sphinganine	0.002	0.314	<0.001	0.065	<0.001	0.175	0.012	0.220
+	194.0815	5.0	Phenylacetylglycine	0.002	0.719	0.036	0.795	0.009	0.787	0.022	0.693
+	170.0924	13.5	N(pi)-Methyl-L-histidine	0.001	0.598	0.006	0.650	0.016	0.716	0.002	0.460
+	229.0696	15.7	2-Hydroxy-3-carboxy-6-oxo-7-methylocta-2,4-dienoate	0.001	3.305	0.010	0.292	0.046	0.502	0.003	2.877
+	348.07	14.4	AMP	0.001	2.779	0.002	2.213	<0.001	1.524	<0.001	1.651
+	156.0768	16.3	L-Histidine	0.001	0.633	0.340	23.359	0.159	0.869	0.013	0.641
+	130.0499	10.5	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.001	0.678	0.563	0.922	0.039	0.805	0.018	0.681
+	165.0757	9.4	L-Rhamnose	0.001	0.546	0.008	0.747	0.001	0.619	0.220	0.830
+	115.0866	5.2	L-proline amide	0.001	0.533	0.012	0.598	0.006	0.450	0.003	0.301
+	776.5595	4.0	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	1.359	0.005	1.282	<0.001	1.328	<0.001	1.384
+	133.0971	23.3	L-Ornithine	0.001	0.714	0.321	0.908	0.144	0.922	<0.001	0.574
+	223.1077	13.6	Phe-Gly	0.001	0.427	0.003	0.652	0.001	0.680	<0.001	0.427

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	153.0771	12.5	Xylitol	0.001	0.569	0.303	0.854	0.098	0.830	0.005	0.461
+	173.0921	15.1	Glycylproline	0.001	0.608	0.097	0.800	0.008	0.776	<0.001	0.504
+	216.1594	7.8	N-Nonanoylglycine	0.001	0.288	0.006	0.438	0.174	0.701	0.071	0.461
+	778.5383	4.4	[PC (18:3/18:3)] 1,2-di-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	0.001	15.352	0.014	2.483	0.001	7.818	0.152	5.123
+	130.0499	15.6	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.001	0.761	0.125	0.866	0.025	0.858	0.002	0.724
+	176.1111	14.1	7-methylthioheptanaldoxime	0.001	0.563	0.240	0.808	0.065	0.730	0.003	0.476
+	176.103	16.6	L-Citrulline	0.001	0.724	0.001	0.720	<0.001	0.721	0.006	0.722
+	316.2117	4.3	Butoctamide hydrogen succinate	0.001	0.752	0.009	0.839	0.004	0.823	0.082	0.865
+	168.0656	8.3	Pyridoxal	0.001	0.627	0.654	0.944	0.030	0.782	0.009	0.625
+	863.5634	3.6	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.001	0.835	<0.001	0.583	<0.001	0.661	<0.001	0.734
+	195.138	4.3	4-Hexyloxyphenol	0.001	0.339	0.183	0.781	<0.001	0.353	0.002	0.335
+	164.9673	9.7	Methoxyflurane	0.001	0.658	0.339	0.916	0.048	0.877	<0.001	0.609
+	161.1074	10.6	Tryptamine	0.001	0.389	0.274	0.818	0.015	0.689	0.004	0.454
+	242.1135	9.9	5-Methyl-2'-deoxycytidine	0.001	0.461	0.074	0.741	0.027	0.748	0.004	0.539
+	190.1186	15.8	L-Homocitrulline	0.001	0.579	0.181	0.823	0.049	0.757	0.002	0.531
+	162.0385	4.4	N-Formyl-L-aspartate	0.001	0.608	0.091	0.776	0.006	0.686	0.007	0.554
+	329.1423	11.3	Pencycuron	0.001	0.659	0.938	0.990	0.042	0.791	0.011	0.616
+	170.0812	8.4	Pyridoxine	0.001	0.624	0.128	0.824	0.014	0.775	0.003	0.587
+	335.1059	4.4	Penicillin G	0.001	0.645	0.121	0.813	0.005	0.732	0.004	0.575
+	792.5539	4.5	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	3.846	0.055	1.477	0.005	1.902	<0.001	3.449
+	207.0507	25.0	2-Hydroxybutane-1,2,4-tricarboxylate	0.001	0.576	0.038	0.779	0.007	0.776	<0.001	0.322
+	263.096	8.3	Thiamine aldehyde	0.001	0.562	0.244	0.827	0.012	0.701	0.006	0.530
-	263.0385	14.9	(1R,2R)-3-[(1,2-Dihydro-2-hydroxy-1-naphthalenyl)thio]-2- oxopropanoic acid	0.001	0.585	0.171	0.914	0.016	0.816	<0.001	0.424
-	277.2177	3.9	[FA (18:3)] 9Z,12Z,15Z-octadecatrienoic acid	0.001	0.519	0.526	1.097	0.098	1.16	0.031	1.655
-	301.2175	4.1	[FA (20:5)] 5Z,8Z,11Z,14Z,17Z-eicosapentaenoic acid	0.001	1.678	0.018	2.425	0.007	2.28	0.033	1.415
-	331.2645	3.9	[FA (22:4)] 7Z,10Z,13Z,16Z-docosatetraenoic acid	0.001	0.684	0.242	0.895	0.003	0.767	0.004	0.666

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	365.3428	3.8	[FA (24:0)] 15Z-tetracosenoic acid	0.001	0.718	<0.001	0.532	<0.001	0.688	0.006	0.782
-	147.0662	15.7	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.001	0.707	0.337	0.914	0.146	0.93	0.324	0.864
-	742.5388	4.0	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	0.001	7.956	0.013	3.395	<0.001	9.979	<0.001	10.915
-	810.5283	3.8	[PS (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoserine	0.001	1.292	0.191	0.896	0.32	0.961	<0.001	1.37
-	465.3182	4.6	[ST (3:0/3:0/3:0)] (5Z,7E)-(1S,3R)-24,24-difluoro-24a-homo-9,10-seco-5,7,10(19)-cholestatrien-1,3,25-triol	0.001	1.401	0.001	1.321	0.003	1.229	0.034	1.245
-	498.2897	4.4	[ST hydrox] N-(3alpha,7alpha-dihydroxy-5beta-cholan-24-oyl)-taurine	0.001	0.584	0.14	0.806	0.018	0.723	0.005	0.504
-	271.0718	26.5	1,2-Bis(4-nitrophenyl)ethane	0.001	0.662	0.02	0.81	0.003	0.817	<0.001	0.412
-	144.0125	7.9	3,4-Dehydrothiomorpholine-3-carboxylate	0.001	14.754	<0.001	18.273	0.001	11.921	0.006	6.863
-	405.2629	3.8	3alpha,12alpha-Dihydroxy-7-oxo-5beta-cholanate	0.001	1.442	0.075	0.864	0.272	1.086	<0.001	1.427
-	187.0071	4.5	4-Sulfobenzyl alcohol	0.001	0.593	0.107	0.788	0.02	0.75	0.018	0.621
-	117.0557	7.8	5-Hydroxypentanoate	0.001	0.624	0.003	0.61	0.76	0.983	<0.001	0.545
-	186.1135	7.8	8-Amino-7-oxononanoate	0.001	0.303	0.001	0.354	0.361	0.8	0.059	0.465
-	417.2111	3.8	Ala-Lys-Asn-Ser	0.001	0.227	0.749	0.928	0.401	0.808	0.314	0.725
-	160.0438	5.0	allylcysteine	0.001	11.891	0.003	17.209	0.004	11.402	0.002	7.003
-	108.0203	29.6	Benzosemiquinone	0.001	0.598	0.029	0.68	0.064	0.801	0.718	0.888
-	182.0753	14.5	Chlorphentermine	0.001	0.652	0.184	0.849	0.056	0.84	0.002	0.573
-	310.1258	15.3	Citalopram alcohol	0.001	0.585	<0.001	0.497	<0.001	0.367	0.005	0.575
-	427.0765	17.5	Cys-Thr-Cys-Cys	0.001	1.955	<0.001	3.534	<0.001	3.281	0.001	2.217
-	242.0784	12.4	Cytidine	0.001	0.45	0.106	0.807	0.006	0.737	0.001	0.493
-	242.0799	15.1	Cytidine	0.001	1.353	<0.001	0.666	<0.001	0.588	0.221	1.157
-	258.0385	15.9	D-Glucosamine 6-phosphate	0.001	1.37	0.268	0.947	<0.001	1.347	0.78	1.022
-	179.0544	7.8	D-Glucose	0.001	0.655	0.432	0.906	0.011	0.737	0.004	0.652
-	149.0455	14.1	D-Ribose	0.001	0.699	0.051	0.803	0.032	0.846	0.007	0.665
-	181.0719	14.5	D-Sorbitol	0.001	0.689	0.209	0.874	0.066	0.864	0.001	0.624
-	309.0167	15.2	Edifenphos	0.001	0.786	0.637	0.974	0.682	1.021	0.001	0.627
-	91.03993	7.6	Glycerol	0.001	2.401	0.325	23.003	0.026	73.9	0.017	88.705

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	136.0516	29.9	Isoniazid	0.001	6.137	0.074	3.794	0.011	6.609	<0.001	6.622
-	165.0405	14.1	L-Arabinonate	0.001	0.707	0.02	0.765	0.218	0.902	0.006	0.652
-	173.1044	26.5	L-Arginine	0.001	0.7	0.235	0.88	0.026	0.835	0.001	0.598
-	132.0302	15.6	L-Aspartate	0.001	0.713	0.251	0.9	0.048	0.875	0.001	0.612
-	169.0983	16.0	Levetiracetam	0.001	1.46	0.899	0.992	0.001	1.612	0.044	1.689
-	154.0622	18.8	L-Histidine	0.001	0.072	0.064	0.4	0.094	0.466	0.03	0.192
-	145.0983	25.0	L-Lysine	0.001	0.618	0.32	0.866	0.05	0.809	0.003	0.531
-	132.0124	8.6	L-thiazolidine-4-carboxylate	0.001	4.166	0.002	6.009	0.002	3.959	<0.001	2.848
-	180.0667	13.6	L-Tyrosine	0.001	0.647	0.014	0.747	0.006	0.764	0.004	0.604
-	308.0725	14.9	Met-Cys-Gly	0.001	5.304	<0.001	6.337	<0.001	4.23	<0.001	2.895
-	218.1034	8.3	Pantothenate	0.001	0.584	0.96	1.008	0.004	0.599	<0.001	0.518
-	353.0491	7.8	Phenolsulfonphthalein	0.001	0.66	0.546	0.924	0.018	0.797	0.002	0.623
-	168.0667	8.4	Pyridoxine	0.001	0.642	0.183	0.84	0.028	0.801	0.007	0.628
-	133.0335	15.6	S,S-Dimethyl-beta-propiothetin	0.001	0.676	0.282	0.896	0.053	0.861	0.001	0.567
-	425.081	17.5	S-glutathionyl-L-cysteine	0.001	1.813	<0.001	3.095	<0.001	2.911	0.001	2.003
-	342.1343	15.9	sinapoyltyramine	0.001	0.685	0.314	0.917	0.004	0.807	<0.001	0.519
-	329.2489	3.9	Taxa-4(20),11(12)-dien-5alpha-yl acetate	0.001	0.666	0.364	0.906	0.012	0.783	0.008	0.644
-	279.0269	15.5	Tos-Ph-CH2Cl	0.001	0.64	0.227	1.09	0.04	1.166	0.004	0.593
-	111.0199	29.8	Uracil	0.001	9.953	0.158	4.668	0.146	5.678	<0.001	10.145

Appendix 19: The list of detected metabolites that have changed following LPS treatment, LPS +11a (L11a), 12b (L12b) and 19o (L19o) treatment in comparison to untreated macrophages. DM refers to detection mode, m/z to mass to ratio, RT to raw retention time and p to P-value.

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	764.5233	4	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	7.776	0.032	2.454	<0.001	5.943	<0.001	7.925
+	126.0219	15.3	Taurine	<0.001	2.306	0.027	1.189	<0.001	1.837	<0.001	2.548
+	740.5233	4	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.662	0.141	1.59	<0.001	3.586	<0.001	3.836
+	110.0271	15.5	Hypotaurine	<0.001	3.335	0.277	1.099	<0.001	2.377	<0.001	4.677
+	766.5396	3.9	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	5.835	0.004	1.924	<0.001	5.267	<0.001	6.117
+	298.0968	7.6	5'-Methylthioadenosine	<0.001	3.502	<0.001	1.72	<0.001	3.997	<0.001	4.715
+	167.0485	15.3	2-methylphosphinoyl-2-hydroxyacetate	<0.001	2.34	0.154	1.13	<0.001	1.83	<0.001	2.915
+	758.5701	4.1	[PC (16:0/18:2)] 1-hexadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	2.505	<0.001	1.721	<0.001	2.73	<0.001	2.812
+	786.6015	4	[PC (18:1/18:1)] 1-(9Z-octadecenoyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.594	<0.001	1.702	<0.001	2.657	<0.001	2.798
+	784.5854	4	PC(18:2(9Z,12Z)/18:1(9Z))	<0.001	2.239	<0.001	1.434	<0.001	2.282	<0.001	2.478
+	372.3108	4.8	Tetradecanoylcarnitine	<0.001	2.137	0.855	0.986	0.073	1.209	<0.001	2.406
+	730.5387	4.1	[PC (14:0/18:2)] 1-tetradecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	2.699	<0.001	1.5	<0.001	2.716	<0.001	3.58
+	142.0264	16.4	Ethanolamine phosphate	<0.001	1.609	0.09	0.902	0.005	1.262	<0.001	2.249
+	772.5859	4	[PE (18:0/20:2)] 1-octadecanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.636	0.002	1.598	<0.001	2.812	<0.001	2.828
+	732.5543	4.1	[PC (14:0/18:1)] 1-tetradecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.019	<0.001	1.449	<0.001	2.209	<0.001	2.171
+	143.0485	15.3	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.148	0.032	1.199	<0.001	1.853	<0.001	2.756
+	144.0518	15.3	Tet-glycine	<0.001	2.198	0.907	0.993	<0.001	1.865	<0.001	2.99
+	794.5705	3.9	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	26.405	0.007	9.188	<0.001	21.718	<0.001	25.819
+	756.555	4.1	[PC (16:0/18:3)] 1-hexadecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	<0.001	2.749	0.075	1.356	<0.001	2.981	<0.001	3.462

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	212.0431	15.4	Phosphocreatine	<0.001	2.352	<0.001	0.506	0.343	0.905	<0.001	2.624
+	426.3576	4.6	Elaidiccarnitine	<0.001	2.139	0.068	1.174	<0.001	1.709	<0.001	2.301
+	808.5856	4	[PC (18:1/20:4)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.781	0.001	1.227	<0.001	1.703	<0.001	2.064
+	774.5435	3.9	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z))	<0.001	1.39	0.56	0.923	<0.001	1.334	<0.001	1.653
+	832.5858	4	[PC (18:1/22:6)] 1-(11Z-octadecenoyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.692	0.03	1.123	<0.001	1.661	<0.001	2.033
+	508.003	16.7	ATP	<0.001	2.007	0.247	1.12	<0.001	1.888	<0.001	3.205
+	744.5545	4.1	[PE (18:0/18:2)] 1-octadecanoyl-2-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	7.698	0.031	2.929	<0.001	7.267	<0.001	7.492
+	780.5544	4.1	[PC (16:1/20:4)] 1-(9Z-hexadecenoyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.589	0.424	1.037	<0.001	1.693	<0.001	1.98
+	782.5699	4	[PC (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	1.522	0.001	1.2	<0.001	1.514	<0.001	1.775
+	706.5386	4.1	[PC (15:0/15:0)] 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine	<0.001	3.308	<0.001	1.984	<0.001	2.928	<0.001	3.156
+	760.5855	4.1	[PC (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.605	<0.001	1.682	<0.001	2.446	<0.001	2.357
+	746.57	4.1	[PC (15:0/18:1)] 1-pentadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phosphocholine	<0.001	2.336	<0.001	1.561	<0.001	2.341	<0.001	2.214
+	400.342	4.6	[FA] O-Palmitoyl-R-carnitine	<0.001	1.956	0.193	1.114	0.001	1.556	<0.001	2.104
+	806.5699	4	[PC (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	1.507	0.415	1.041	<0.001	1.428	<0.001	1.742
+	664.1165	14.6	NAD+	<0.001	1.41	<0.001	1.462	0.002	1.429	<0.001	1.732
+	91.05833	15.9	Diethyl sulfide	<0.001	1.933	0.502	1.062	0.075	1.492	<0.001	2.881
+	168.0518	15.3	8-Hydroxyguanine	<0.001	2.469	0.914	1.016	0.002	1.959	<0.001	3.446
+	133.0737	15.3	Methylenediurea	<0.001	1.992	0.013	0.704	0.014	0.737	<0.001	2.1
+	766.5754	4	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	0.431	<0.001	0.616	<0.001	0.483	<0.001	0.46
+	810.5285	3.8	1-20:2-2-18:3-phosphatidylserine	<0.001	3.303	0.388	1.254	<0.001	2.78	<0.001	3.079
+	132.0767	15.3	Creatine	<0.001	1.895	0.012	0.723	0.017	0.754	<0.001	1.988
+	398.3264	4.7	trans-Hexadec-2-enoylcarnitine	<0.001	2.263	0.721	0.954	0.009	1.494	<0.001	2.321

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	754.5397	4.1	[PC (14:0/20:4)] 1-tetradecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	<0.001	5.726	0.179	1.807	<0.001	4.995	<0.001	7.34
+	613.1593	17.7	Glutathione disulfide	<0.001	3.119	<0.001	4.891	0.001	4.27	<0.001	4.038
+	216.0632	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	1.56	<0.001	0.504	0.002	0.63	<0.001	1.875
+	184.0734	15.5	4-Amino-2-hydroxylamino-6-nitrotoluene	<0.001	1.582	<0.001	1.972	<0.001	1.997	<0.001	1.714
+	296.0659	15	Aminoimidazole ribotide	<0.001	1.728	0.003	0.719	0.007	0.733	<0.001	1.926
+	260.1139	15.1	Proacacipetalin	<0.001	1.896	0.014	0.643	0.02	0.637	<0.001	2.228
+	258.1101	15.1	5-Methylcytidine	<0.001	1.759	0.018	0.717	0.018	0.706	<0.001	2.026
+	298.0968	6.9	5'-Methylthioadenosine	<0.001	2.289	0.008	1.548	0.001	2.603	<0.001	3.016
+	718.5385	4.1	[PE (16:0/18:1)] 1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	4.486	<0.001	2.525	<0.001	4.152	<0.001	3.953
+	784.5121	3.8	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	2.842	0.247	1.211	<0.001	2.692	<0.001	2.877
+	800.6172	4	[PE (20:0/20:2)] 1-eicosanoyl-2-(11Z,14Z-eicosadienoyl)-sn-glycero-3-phosphoethanolamine	<0.001	9.797	0.067	3.166	0.025	4.614	<0.001	7.967
+	503.2958	4.6	Arg-Leu-Gln-Ser	<0.001	3.57	0.965	1.012	<0.001	2.542	<0.001	3.719
+	134.0811	6.9	1-deoxyxylonojirimycin	<0.001	2.078	0.781	1.044	<0.001	1.905	<0.001	2.295
+	891.5954	3.6	PI(16:0/22:2(13Z,16Z))	<0.001	0.353	<0.001	0.299	<0.001	0.358	<0.001	0.444
+	858.6019	4	PC(20:2(11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	1.446	0.025	0.621	0.011	1.223	<0.001	1.771
+	462.0925	15	3-Phosphoglycerol-glutathione	<0.001	1.895	0.074	0.814	0.664	0.967	<0.001	2.391
+	863.5635	3.6	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	0.538	<0.001	0.357	<0.001	0.523	<0.001	0.594
+	428.0366	15.4	ADP	<0.001	1.966	0.747	1.041	0.016	1.365	<0.001	1.962
+	300.2897	7.5	[SP] 3-dehydrosphinganine	<0.001	0.46	<0.001	0.333	<0.001	0.454	<0.001	0.562
+	889.5788	3.6	PI(16:0/22:3(10Z,13Z,16Z))	<0.001	0.485	<0.001	0.347	<0.001	0.451	<0.001	0.579
+	862.6327	3.9	[PC (20:0/22:6)] 1-eicosanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphocholine	<0.001	3.711	0.495	1.447	0.005	2.63	<0.001	4.46
+	865.5794	3.6	1-18:0-2-18:1-phosphatidylinositol	<0.001	0.553	<0.001	0.389	<0.001	0.516	<0.001	0.586
+	861.5478	3.6	PI(16:0/20:3(5Z,8Z,11Z))	<0.001	0.524	<0.001	0.372	<0.001	0.508	<0.001	0.646
+	229.0698	15.5	2-Hydroxy-3-carboxy-6-oxo-7-methylocta-2,4-dienoate	<0.001	3.123	0.016	0.163	0.787	1.105	<0.001	4.192
+	520.3406	4.7	[PC (18:2)] 1-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphocholine	<0.001	2.895	0.341	1.24	<0.001	2.664	<0.001	3.733

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	808.5117	3.8	PS(20:3(8Z,11Z,14Z)/18:3(9Z,12Z,15Z))	<0.001	11.629	0.038	3.68	<0.001	10.556	<0.001	8.54
+	427.0951	17.1	S-glutathionyl-L-cysteine	<0.001	2.206	<0.001	2.367	<0.001	1.912	<0.001	1.891
+	860.6169	4	PC(20:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.627	0.774	1.114	0.002	2.608	<0.001	4.04
+	454.2928	4.7	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	2.408	0.649	0.961	<0.001	1.86	<0.001	2.502
+	196.083	10.3	2-Amino-2-deoxy-D-gluconate	<0.001	11.75	<0.001	3.175	<0.001	5.146	<0.001	7.383
+	502.2924	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.063	0.623	1.085	0.001	1.856	0.001	3.278
+	528.308	4.5	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	5.548	0.514	1.305	0.025	2.709	0.001	6.239
+	480.3084	4.6	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.516	0.185	1.215	0.004	1.633	0.001	2.48
+	167.0485	14	2-methylphosphinoyl-2-hydroxyacetate	<0.001	2.322	0.529	0.841	0.224	1.291	0.001	2.504
+	887.5639	3.7	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	0.604	<0.001	0.443	<0.001	0.578	0.001	0.685
+	276.1553	17.6	L-a-glutamyl-L-Lysine	<0.001	0.729	<0.001	0.366	<0.001	0.441	0.001	0.777
+	148.0604	15.1	L-Glutamate	<0.001	1.517	0.844	1.02	0.069	1.216	0.002	1.434
+	526.2927	4.5	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.387	0.287	0.75	0.017	1.751	0.002	3.908
+	880.5907	3.8	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)(ammonium salt)	<0.001	3.289	0.406	1.406	<0.001	3.628	0.002	2.977
+	811.5312	3.8	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	<0.001	2.836	0.826	1.045	<0.001	2.476	0.002	2.37
+	400.342	7.5	[FA] O-Palmitoyl-R-carnitine	<0.001	2.306	0.298	0.836	0.008	1.517	0.002	2.233
+	885.5479	3.6	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	0.567	<0.001	0.388	<0.001	0.569	0.006	0.752
+	468.1217	16.6	Asp-Cys-Cys-Gln	<0.001	1.884	0.023	1.533	0.002	1.382	0.01	1.647
+	166.0863	7.6	L-Phenylalanine	<0.001	2.051	0.035	1.518	0.013	1.9	0.012	2.041
-	817.5022	3.6	PG(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	0.588	<0.001	0.387	<0.001	0.608	<0.001	0.709
-	883.5337	3.7	PI(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	2.155	<0.001	1.395	<0.001	2.215	<0.001	2.555
-	611.1446	17.7	Glutathione disulfide	<0.001	6.831	<0.001	11.362	<0.001	11.119	<0.001	10.904
-	244.059	15.5	6-aza-uridine	<0.001	1.991	<0.001	3.079	<0.001	3.196	<0.001	2.586
-	792.5573	3.9	PC(15:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	4.943	<0.001	1.784	<0.001	2.714	<0.001	3.588
-	857.5173	3.8	PI(16:0/20:4(5Z,8Z,11Z,14Z))	<0.001	1.948	<0.001	1.663	<0.001	2.107	<0.001	2.102

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	782.4971	3.7	[PS (18:2/18:2)] 1,2-di-(9Z,12Z-octadecadienoyl)-sn-glycero-3-phosphoserine	<0.001	4.072	0.001	2.459	<0.001	4.429	<0.001	4.463
-	134.0473	7.6	4-Hydroxy-L-threonine	<0.001	3.395	0.003	1.947	<0.001	4.092	<0.001	4.87
-	565.0475	16.5	UDP-glucose	<0.001	3.625	0.025	1.612	<0.001	3.87	<0.001	5.165
-	124.0074	15.3	Taurine	<0.001	2.157	0.044	1.185	<0.001	1.852	<0.001	2.724
-	764.5236	3.9	PE(20:2(11Z,14Z)/18:3(6Z,9Z,12Z))	<0.001	7.426	0.045	2.342	<0.001	8.544	<0.001	12.514
-	505.9883	16.7	ATP	<0.001	1.887	0.054	1.148	<0.001	1.768	<0.001	2.789
-	478.2941	4.6	[PE (18:0)] 1-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	3.289	0.215	1.256	<0.001	2.154	<0.001	3.209
-	808.513	3.8	1-20:2-2-18:3-phosphatidylserine	<0.001	2.761	0.681	0.902	<0.001	2.841	<0.001	3.026
-	425.0809	17.1	S-glutathionyl-L-cysteine	<0.001	2.242	<0.001	2.553	0.001	2.048	<0.001	2.013
-	214.0487	16.2	sn-glycero-3-Phosphoethanolamine	<0.001	1.612	<0.001	0.438	0.001	0.576	<0.001	2.002
-	452.2785	4.7	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	<0.001	2.39	0.549	1.069	0.001	1.933	<0.001	2.613
-	500.2786	4.6	[PE (20:4)] 1-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	2.636	0.952	0.992	0.002	1.704	<0.001	2.899
-	145.0142	15.7	2-Oxoglutarate	<0.001	1.879	0.725	1.044	0.006	1.504	<0.001	2.174
-	140.0118	16.4	Ethanolamine phosphate	<0.001	1.696	0.254	0.914	0.009	1.273	<0.001	2.45
-	91.03994	25.2	Glycerol	<0.001	3.005	0.01	2.962	0.01	2.934	<0.001	3.302
-	130.0622	15.3	Creatine	<0.001	1.888	0.008	0.635	0.014	0.69	<0.001	2.066
-	738.5081	3.9	[PE (16:0/20:4)] 1-hexadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	<0.001	6.798	0.002	2.95	0.043	5.356	<0.001	7.162
-	318.0961	15	Ala-Asp-Asp	<0.001	1.854	0.015	0.78	0.113	0.851	<0.001	2.47
-	210.0286	15.4	Phosphocreatine	<0.001	2.312	<0.001	0.506	0.311	0.906	<0.001	2.742
-	171.0069	15	sn-Glycerol 3-phosphate	<0.001	1.842	0.204	0.86	0.517	0.936	<0.001	2.574
-	192.0182	15.4	creatinine phosphate	<0.001	3.761	0.009	0.115	0.852	1.067	<0.001	4.725
-	78.95873	15.4	Phosphite	<0.001	2.965	0.004	0.305	0.889	1.043	<0.001	3.756
-	524.2785	4.5	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	<0.001	3.695	0.481	1.13	0.013	2.175	0.001	4.901
-	357.3012	20.5	[GL (18:0)] 1-octadecanoyl-rac-glycerol	<0.001	#DIV/0!	0.012	#DIV/0!	0.001	#DIV/0!	0.003	#DIV/0!
-	113.0356	18.6	5,6-Dihydrouracil	<0.001	4.081	0.011	4.315	0.034	2.723	0.006	4.392
-	526.2944	4.5	LysoPE(0:0/22:5(4Z,7Z,10Z,13Z,16Z))	<0.001	5.154	0.741	0.88	<0.001	3.412	0.007	4.795

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	409.3114	3.9	[ST hydroxy,methyl(4:0)] (22E)-(8S)-3-hydroxy-22-methyl-9,10-seco-1,3,5(10),22-cholestatetraen-9-one	<0.001	0.107	<0.001	0.036	<0.001	0.104	0.011	0.484
-	133.0521	29.5	Deoxyribose	<0.001	6.421	0.177	3.882	0.067	6.379	0.014	10.932
-	501.282	4.6	Ala-Lys-Trp-Val	<0.001	3.309	0.667	0.797	0.205	1.581	0.02	2.799
-	154.0262	29	N-Methylethanolamine phosphate	<0.001	2.664	0.345	3.492	0.331	23.378	0.026	11.038
-	425.0808	17.4	S-glutathionyl-L-cysteine	<0.001	3.123	0.126	2.806	<0.001	3.781	0.045	3.392
-	97.04069	16.8	Imidazole-4-methanol	<0.001	5.271	<0.001	4.37	0.016	5.498	0.057	5.705
-	88.98789	28.8	Oxalate	<0.001	4.491	0.003	2.198	0.064	1.924	0.115	2.405
-	190.0737	26.6	2-amino-3,7-dideoxy-D-threo-hept-6-ulosonate	<0.001	#DIV/0!	<0.001	#DIV/0!	0.099	#DIV/0!	0.241	#DIV/0!
-	182.0568	26.5	4-Amino-2-hydroxylamino-6-nitrotoluene	<0.001	#DIV/0!	0.012	#DIV/0!	0.107	#DIV/0!	0.314	#DIV/0!
-	179.0562	26	D-Glucose	0.994	1.006	0.91	0.908	0.565	0.534	0.663	1.412
-	115.0036	29.1	Fumarate	0.991	1.004	0.653	0.861	0.294	0.726	0.972	1.01
-	179.0562	20.9	D-Glucose	0.986	1.01	0.111	2.25	0.518	1.457	0.007	3.414
-	102.056	23	4-Aminobutanoate	0.984	0.991	0.657	0.819	0.221	0.448	0.671	0.82
-	102.056	24	4-Aminobutanoate	0.974	1.012	0.763	0.861	0.522	1.409	0.21	1.768
+	174.0874	15.9	5-Guanidino-2-oxopentanoate	0.97	0.991	0.864	1.038	0.692	0.92	0.427	0.829
-	102.056	28.7	4-Aminobutanoate	0.967	1.016	0.109	2.408	0.401	1.359	0.27	1.955
-	102.056	17	4-Aminobutanoate	0.96	1.026	0.213	0.506	0.363	0.646	0.378	1.702
-	115.0036	16.1	Fumarate	0.959	1.018	0.372	1.531	0.612	1.333	0.5	1.361
-	102.056	5	4-Aminobutanoate	0.945	0.98	0.733	0.905	0.695	1.171	0.342	1.3
-	102.056	25.5	4-Aminobutanoate	0.94	1.035	0.791	0.913	0.102	2.43	0.892	0.95
+	104.107	20.9	Choline	0.937	1.009	0.171	0.842	0.025	0.684	0.178	0.778
+	248.1493	4.3	Hydroxybutyrylcarnitine	0.925	1.048	0.91	0.944	0.732	0.872	0.207	1.537
-	102.056	18.8	4-Aminobutanoate	0.92	0.934	0.412	1.594	0.885	1.088	0.349	1.716
-	102.056	11.6	4-Aminobutanoate	0.919	1.033	0.1	2.16	0.987	1.005	0.512	0.81
-	179.0561	23.6	D-Glucose	0.917	1.093	0.203	2.648	0.956	1.043	0.403	1.803
-	102.056	20.4	4-Aminobutanoate	0.917	0.934	0.801	1.139	0.444	1.491	0.67	0.788
-	115.0036	25.7	Fumarate	0.913	0.948	0.5	0.684	0.894	0.938	0.787	0.893

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	102.056	22.1	4-Aminobutanoate	0.911	1.033	0.118	2.194	0.778	1.175	0.058	2.394
-	129.0192	28.6	Mesaconate	0.911	1.05	0.05	0.467	0.111	0.589	0.388	1.898
-	115.0036	18.9	Fumarate	0.91	1.046	0.252	0.671	0.333	0.688	0.238	0.613
-	179.0562	19	D-Glucose	0.906	0.937	0.449	0.687	0.824	1.128	0.397	1.38
-	147.0314	29.6	(R)-2-Hydroxyglutarate	0.901	0.959	0.398	1.87	0.373	2.369	0.222	7.167
-	115.0036	11.3	Fumarate	0.899	0.944	0.532	0.814	0.118	0.503	0.504	0.796
-	102.056	25.2	4-Aminobutanoate	0.895	1.105	0.923	1.056	0.901	0.939	0.909	1.047
+	189.1598	23	N6,N6,N6-Trimethyl-L-lysine	0.89	1.021	0.361	0.857	0.08	0.709	0.166	0.775
-	115.0036	28.4	Fumarate	0.887	1.055	0.189	0.666	0.79	1.132	0.138	1.504
-	179.0561	22.3	D-Glucose	0.882	1.1	0.142	1.957	0.767	1.144	0.033	2.789
-	179.0562	27.6	D-Glucose	0.875	1.099	0.603	1.452	0.902	1.095	0.17	1.937
+	146.0923	15.7	4-Guanidinobutanoate	0.872	1.017	0.199	0.863	0.069	0.798	0.925	0.975
-	179.0561	26.8	D-Glucose	0.862	0.856	0.795	0.795	0.656	0.662	0.236	2.531
-	102.056	20.9	4-Aminobutanoate	0.859	0.938	0.133	1.655	0.601	0.868	0.218	2.439
-	129.0192	27.4	itaconate	0.851	1.092	0.946	1.032	0.096	0.502	0.46	1.567
+	247.1402	14.7	N2-(D-1-Carboxyethyl)-L-arginine	0.85	0.977	0.899	1.015	0.564	0.923	0.357	1.127
-	147.0301	17.5	(R)-2-Hydroxyglutarate	0.844	1.078	0.224	0.572	0.974	1.01	0.844	0.924
-	115.0036	24.2	Fumarate	0.836	1.089	0.668	1.264	0.487	0.791	0.201	0.593
+	129.0658	15.4	5,6-Dihydrothymine	0.835	1.035	0.306	0.823	0.169	0.761	0.604	0.912
-	115.0036	21.6	Fumarate	0.83	0.925	0.136	0.45	0.291	0.566	0.914	1.089
-	102.056	12.5	4-Aminobutanoate	0.816	1.083	0.104	2.453	0.011	2.456	0.017	3.598
-	102.056	19.2	4-Aminobutanoate	0.815	1.079	0.169	1.676	0.455	0.762	0.185	1.428
-	179.0561	25.2	D-Glucose	0.814	0.793	0.429	2.526	0.381	0.349	0.393	1.736
-	102.056	24.5	4-Aminobutanoate	0.811	1.074	0.882	1.053	0.098	1.674	0.124	2.028
-	115.0036	21.1	Fumarate	0.811	1.107	0.833	1.103	0.556	1.499	0.557	0.745
-	179.0561	23.9	D-Glucose	0.802	1.23	0.283	1.663	0.794	0.842	0.101	4.447
-	115.0036	15.4	Fumarate	0.792	0.932	0.578	1.168	0.115	0.682	0.47	1.208
-	115.0036	12.4	Fumarate	0.787	0.882	0.921	0.961	0.068	2.175	0.046	3.162

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	102.056	20.1	4-Aminobutanoate	0.784	0.858	0.651	1.236	0.781	0.857	0.403	1.43
-	102.056	16.6	4-Aminobutanoate	0.783	0.907	0.305	2.043	0.246	1.55	0.157	1.529
+	204.1231	11.5	O-Acetylcarnitine	0.776	1.027	0.001	0.6	0.002	0.604	0.024	1.253
-	115.0036	18.1	Fumarate	0.776	1.146	0.937	0.957	0.457	0.68	0.855	0.894
-	102.056	26.2	4-Aminobutanoate	0.769	1.107	0.217	1.648	0.932	0.965	0.592	1.247
-	147.0302	15	(R)-2-Hydroxyglutarate	0.762	1.23	0.965	1.016	0.193	0.527	0.285	0.606
-	129.0193	24.4	Mesaconate	0.753	1.339	0.098	0.413	0.027	0.203	0.041	0.268
-	179.0563	27	D-Glucose	0.741	0.745	0.893	1.109	0.494	2.032	0.312	3.149
-	115.0036	29.4	Fumarate	0.736	0.875	0.316	0.596	0.134	0.499	0.967	0.986
-	147.0308	28.2	(R)-2-Hydroxyglutarate	0.728	0.856	0.633	1.195	0.421	4.135	0.569	1.357
-	102.056	13.7	4-Aminobutanoate	0.719	1.082	0.47	1.491	0.644	1.218	0.612	1.114
-	115.0036	16.4	Fumarate	0.714	0.864	0.072	0.399	0.058	0.398	0.08	0.469
-	102.056	23.2	4-Aminobutanoate	0.713	0.765	0.766	0.796	0.408	1.523	0.273	2.481
-	102.056	17.5	4-Aminobutanoate	0.711	1.143	0.076	1.722	0.741	1.18	0.027	1.969
-	102.056	25.7	4-Aminobutanoate	0.694	0.844	0.704	1.226	0.953	0.975	0.74	1.107
-	115.0036	20	Fumarate	0.687	0.871	0.902	0.954	0.059	0.488	0.83	1.087
-	102.056	15.8	4-Aminobutanoate	0.681	0.853	0.736	0.889	0.544	1.257	0.644	1.27
+	76.03939	16.5	Glycine	0.664	1.125	0.3	1.364	0.478	1.245	0.036	1.815
-	147.0301	17.2	(R)-2-Hydroxyglutarate	0.656	1.211	0.421	0.708	0.286	0.641	0.121	0.516
-	115.0036	26.5	Fumarate	0.651	0.782	0.691	0.795	0.296	0.501	0.18	0.347
-	115.0036	18.7	Fumarate	0.648	0.764	0.243	0.495	0.304	0.55	0.283	0.542
-	115.0036	22.1	Fumarate	0.648	0.86	0.333	0.76	0.258	1.684	0.744	1.141
-	179.0561	12.3	D-Glucose	0.64	0.707	0.126	5.716	0.087	1.834	0.12	16.93
-	102.056	22.5	4-Aminobutanoate	0.63	1.253	0.637	1.197	0.575	0.781	0.656	1.152
-	147.0301	11.8	(R)-2-Hydroxyglutarate	0.628	1.322	0.549	1.259	0.422	1.369	0.806	0.89
-	115.0036	23.9	Fumarate	0.624	0.883	0.486	1.31	0.708	0.897	0.192	0.618
-	102.056	14.6	4-Aminobutanoate	0.622	0.831	0.116	0.545	0.848	0.947	0.884	1.065
-	102.056	17.2	4-Aminobutanoate	0.609	1.698	0.204	1.494	0.14	1.684	0.186	1.659

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	102.056	6	4-Aminobutanoate	0.607	1.209	0.695	0.857	0.354	1.29	0.454	1.31
-	104.0353	16.7	L-Serine	0.604	0.842	0.276	1.361	0.323	0.679	0.656	0.856
-	102.056	5.5	4-Aminobutanoate	0.603	1.199	0.949	1.02	0.208	1.45	0.277	1.512
-	102.056	17.9	4-Aminobutanoate	0.594	1.13	0.267	1.482	0.272	1.648	0.204	1.384
-	179.0561	22.5	D-Glucose	0.593	0.647	0.288	3.09	0.839	1.131	0.026	3.92
-	115.0036	25.3	Fumarate	0.593	1.386	0.496	1.642	0.794	1.149	0.766	1.17
-	115.0036	16.8	Fumarate	0.591	0.864	0.116	0.647	0.364	0.794	0.005	0.47
-	179.0562	18.4	D-Glucose	0.591	0.693	0.479	0.693	0.212	0.45	0.62	1.24
-	147.0302	14.4	(R)-2-Hydroxyglutarate	0.585	0.809	0.105	0.609	0.357	0.726	0.035	0.46
-	147.0301	18.5	(R)-2-Hydroxyglutarate	0.583	0.784	0.839	0.923	0.413	1.279	0.329	0.667
-	129.0193	11.2	Mesaconate	0.577	0.716	0.748	0.808	0.025	0.246	0.028	0.264
+	180.0867	15.1	D-Glucosamine	0.569	0.903	0.356	0.822	0.029	0.679	0.494	0.883
-	115.0036	12.6	Fumarate	0.56	0.704	0.214	0.404	0.447	1.473	0.048	2.959
-	179.0563	28.2	D-Glucose	0.556	1.381	0.226	1.925	0.312	4.852	0.107	3.001
+	168.0656	8.5	Pyridoxal	0.542	0.905	0.225	0.796	0.124	0.744	0.405	1.134
+	203.1504	22.6	NG,NG-Dimethyl-L-arginine	0.517	1.087	0.406	0.892	0.07	0.754	0.378	0.879
-	102.056	27.9	4-Aminobutanoate	0.504	1.452	0.465	1.315	0.292	1.61	0.61	1.224
-	129.0192	29.1	Mesaconate	0.503	0.653	0.62	0.734	0.21	2.746	0.357	0.53
+	141.0658	9.9	Methylimidazoleacetic acid	0.495	1.126	0.508	0.877	0.219	0.771	0.848	0.963
-	179.0562	20.1	D-Glucose	0.486	0.681	0.793	1.105	0.73	0.843	0.64	1.3
+	133.0988	12	L-Ornithine	0.473	0.639	0.256	0.409	0.186	0.306	0.257	0.409
+	162.1125	13.9	L-Carnitine	0.465	0.921	0.04	0.75	0.003	0.621	0.76	0.969
-	115.0036	18.3	Fumarate	0.444	0.741	0.329	0.647	0.229	0.547	0.121	0.47
-	115.0036	17.3	Fumarate	0.444	0.62	0.224	0.424	0.256	0.45	0.411	0.578
-	102.056	21.5	4-Aminobutanoate	0.438	0.761	0.619	1.241	0.042	2.132	0.454	1.674
-	115.0036	25.1	Fumarate	0.434	0.721	0.355	0.6	0.89	1.059	0.581	0.826
-	147.0301	16.5	(R)-2-Hydroxyglutarate	0.431	0.701	0.136	0.445	0.328	0.644	0.247	0.56
-	102.056	29.7	4-Aminobutanoate	0.43	1.488	0.027	2.773	0.215	2.979	0.009	2.955

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	147.0301	16	(R)-2-Hydroxyglutarate	0.43	0.669	0.692	1.213	0.366	0.613	0.563	0.767
-	102.056	15.1	4-Aminobutanoate	0.427	0.75	0.181	1.645	0.227	1.461	0.579	1.194
-	102.056	12.9	4-Aminobutanoate	0.426	1.386	0.207	1.653	0.08	2.217	0.009	6.734
-	147.0301	13.7	(R)-2-Hydroxyglutarate	0.424	0.748	0.216	0.654	0.315	0.722	0.308	0.741
-	147.0302	14	(R)-2-Hydroxyglutarate	0.423	0.733	0.036	0.371	0.045	0.415	0.02	0.278
-	102.056	18.2	4-Aminobutanoate	0.422	0.753	0.726	1.09	0.425	1.367	0.504	1.256
-	102.056	21.3	4-Aminobutanoate	0.42	0.82	0.915	1.026	0.991	0.996	0.509	1.261
-	179.0566	26.5	D-Glucose	0.409	0.258	0.447	0.32	0.5	0.387	0.827	0.802
-	147.0301	15.8	(R)-2-Hydroxyglutarate	0.404	0.65	0.823	0.894	0.523	0.739	0.708	0.837
-	102.056	20.6	4-Aminobutanoate	0.399	0.695	0.293	1.482	0.337	1.715	0.108	0.516
-	102.056	27.2	4-Aminobutanoate	0.397	1.396	0.156	2.225	0.313	1.825	0.339	1.49
-	102.056	7.6	4-Aminobutanoate	0.391	0.869	0.399	0.897	0.221	0.904	0.208	0.86
-	179.0562	19.6	D-Glucose	0.385	0.476	0.742	0.807	0.686	0.761	0.424	2.471
-	115.0036	15.7	Fumarate	0.374	2.163	0.558	1.41	0.652	1.538	0.629	1.437
-	129.0193	11.9	itaconate	0.369	1.881	0.013	3.102	0.435	0.784	0.21	0.626
-	102.056	16.1	4-Aminobutanoate	0.36	1.506	0.323	2.181	0.214	2.075	0.299	1.531
+	241.0311	16.9	L-Cystine	0.359	0.86	0.007	0.573	0.001	0.455	0.003	0.49
-	129.0193	25.6	Mesaconate	0.359	0.767	0.758	0.912	0.744	0.919	0.75	0.923
-	102.056	11.1	4-Aminobutanoate	0.359	0.632	0.925	0.964	0.662	0.815	0.782	0.879
-	129.0192	28	Mesaconate	0.357	0.627	0.187	0.475	0.888	1.069	0.315	0.597
-	179.0562	24.7	D-Glucose	0.349	1.856	0.158	2.89	0.856	1.112	0.004	5.433
-	129.0192	26.3	Mesaconate	0.348	0.594	0.176	0.411	0.863	0.877	0.291	0.544
-	102.056	27.4	4-Aminobutanoate	0.348	1.534	0.826	1.107	0.495	1.331	0.813	1.115
-	179.0561	23.1	D-Glucose	0.347	2.246	0.211	1.779	0.597	1.217	0.015	2.434
-	104.0353	16.4	L-Serine	0.335	1.143	0.4	1.138	0.591	0.923	0.897	0.98
-	115.0036	11.9	Fumarate	0.329	0.408	0.232	0.266	0.227	0.253	0.183	0.171
-	179.0562	25.8	D-Glucose	0.328	3.023	0.047	2.767	0.602	1.372	0.018	2.786
-	147.0301	15.3	(R)-2-Hydroxyglutarate	0.328	0.904	0.067	0.746	0.036	0.775	0.117	0.847

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	115.0036	27.8	Fumarate	0.328	0.546	0.313	0.512	0.551	0.695	0.44	0.648
-	115.0036	24.8	Fumarate	0.32	0.622	0.985	0.993	0.256	0.56	0.956	0.974
-	102.056	23.5	4-Aminobutanoate	0.313	1.433	0.955	1.026	0.553	0.746	0.46	1.374
+	133.0987	11.8	L-Ornithine	0.305	0.433	0.244	0.347	0.203	0.291	0.283	0.407
-	129.0193	21.6	Mesaconate	0.3	0.29	0.305	0.299	0.956	0.949	0.351	0.365
-	102.056	14.1	4-Aminobutanoate	0.299	2.859	0.35	1.562	0.181	1.604	0.081	1.876
-	115.0036	22.6	Fumarate	0.297	0.483	0.915	0.947	0.858	0.931	0.656	0.824
-	179.0562	20.4	D-Glucose	0.289	3.348	0.054	5.32	0.062	2.257	0.059	3.849
+	76.03939	16	Glycine	0.286	2.368	0.33	2.042	0.968	1.04	0.141	3.497
-	179.0561	21.9	D-Glucose	0.273	0.274	0.232	2.532	0.975	0.979	0.225	2.189
-	129.0193	12.7	Mesaconate	0.271	0.139	0.307	0.2	0.441	0.369	0.265	0.128
-	115.0036	27.3	Fumarate	0.264	1.823	0.407	1.34	0.986	0.992	0.944	1.028
-	102.056	15.5	4-Aminobutanoate	0.253	1.618	0.488	1.262	0.991	1.006	0.207	1.466
-	147.0301	20.4	(R)-2-Hydroxyglutarate	0.249	0.457	0.688	0.818	0.37	0.577	0.509	0.657
+	90.05498	5.9	L-Alanine	0.243	0.589	0.26	0.638	0.232	0.635	0.153	0.532
-	115.0036	14	Fumarate	0.242	0.495	0.318	0.571	0.845	1.091	0.854	0.916
-	115.0036	27.1	Fumarate	0.239	0.658	0.69	0.786	0.22	0.615	0.115	0.596
-	191.02	22	Citrate	0.238	0.713	0.023	0.314	0.052	0.432	0.071	0.47
-	179.0561	22.8	D-Glucose	0.238	0.31	0.335	1.709	0.7	0.775	0.199	2.464
+	151.0617	12.2	D-Ribose	0.236	1.161	0.725	0.956	0.112	0.799	0.358	0.872
-	179.0562	19.3	D-Glucose	0.236	1.953	0.161	2.056	0.135	2.204	0.089	2.102
-	102.056	25	4-Aminobutanoate	0.235	0.773	0.953	0.976	0.517	1.279	0.405	1.298
-	129.0194	7	Mesaconate	0.232	0.171	0.257	0.217	0.246	0.197	0.213	0.134
-	147.0301	13.2	(R)-2-Hydroxyglutarate	0.226	0.443	0.293	0.508	0.115	0.25	0.13	0.287
-	147.03	19.4	(R)-2-Hydroxyglutarate	0.221	0.569	0.312	0.631	0.558	0.776	0.332	0.56
-	179.0562	28.4	D-Glucose	0.217	2.276	0.356	1.607	0.232	1.915	0.195	3.663
-	115.0036	19.1	Fumarate	0.217	1.709	0.991	0.996	0.926	1.043	0.425	1.736

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	747.5159	4.2	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.215	2.254	0.338	1.635	0.134	2.452	0.155	3.19
-	115.0037	10.8	Fumarate	0.213	0.615	0.355	0.683	0.047	0.382	0.142	0.529
-	129.0193	25.9	Mesaconate	0.211	0.416	0.109	0.282	0.142	0.339	0.712	0.814
-	147.0301	16.8	(R)-2-Hydroxyglutarate	0.207	0.491	0.143	0.375	0.08	0.266	0.068	0.226
-	147.0309	27.1	(R)-2-Hydroxyglutarate	0.202	0.66	0.183	0.676	0.711	0.9	0.807	0.933
-	115.0036	28.1	Fumarate	0.198	0.576	0.762	0.889	0.385	0.702	0.834	0.895
-	129.0194	3.9	Mesaconate	0.196	0.415	0.129	0.296	0.091	0.219	0.152	0.362
-	239.0168	16.9	L-Cystine	0.193	0.815	0.008	0.572	0.001	0.455	0.003	0.492
-	115.0037	10.3	Fumarate	0.186	0.539	0.086	0.384	0.085	0.366	0.063	0.311
-	147.0313	28.9	(R)-2-Hydroxyglutarate	0.186	1.763	0.125	1.844	0.344	12.748	0.134	7.176
-	179.0562	11.5	D-Glucose	0.183	0.61	0.064	4.311	0.092	2.753	0.084	5.605
-	147.0301	13.5	(R)-2-Hydroxyglutarate	0.183	0.171	0.289	0.334	0.23	0.256	0.209	0.219
-	129.0193	12.4	Mesaconate	0.177	0.192	0.189	0.19	0.165	0.164	0.192	0.221
+	141.0658	10.8	Methylimidazoleacetic acid	0.176	1.135	0.192	0.871	0.965	0.993	0.039	1.207
-	115.0036	26.8	Fumarate	0.176	0.479	0.836	0.873	0.075	0.39	0.211	0.555
+	76.03939	15.4	Glycine	0.174	0.157	0.325	2.021	0.209	0.227	0.207	0.224
-	115.0036	23.2	Fumarate	0.174	0.479	0.194	0.543	0.59	0.808	0.056	0.289
-	115.0036	17.5	Fumarate	0.173	0.135	0.374	0.438	0.188	0.166	0.221	0.23
-	102.056	18.6	4-Aminobutanoate	0.167	1.95	0.272	1.803	0.463	1.362	0.789	1.12
-	129.0194	3.4	Mesaconate	0.156	0.303	0.11	0.202	0.153	0.303	0.139	0.27
-	129.0194	6.2	Mesaconate	0.156	0.147	0.124	0.065	0.139	0.104	0.165	0.165
-	115.0036	21.3	Fumarate	0.156	0.507	0.093	0.409	0.103	0.391	0.459	0.676
-	179.0576	29.6	D-Glucose	0.154	1.771	0.521	1.746	0.222	4.578	0.052	9.77
+	188.1031	14.5	5-guanidino-3-methyl-2-oxo-pentanoate	0.152	1.25	0.386	0.823	0.113	0.739	0.62	0.898
-	129.0194	7.9	Mesaconate	0.151	0.197	0.131	0.163	0.114	0.123	0.098	0.074
-	115.0036	23.5	Fumarate	0.147	0.402	0.26	0.502	0.585	1.382	0.193	0.443
-	151.0263	11.7	Xanthine	0.138	1.685	0.209	1.644	0.055	1.649	0.599	0.744

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	414.3577	4.6	Heptadecanoylcarnitine	0.135	1.166	0.211	0.85	0.017	1.337	0.065	1.305
-	129.0194	9.8	Mesaconate	0.134	0.235	0.114	0.19	0.186	0.318	0.109	0.177
-	102.056	29.3	4-Aminobutanoate	0.132	1.709	0.009	3.954	0.227	2.012	0.359	1.79
-	147.0313	29.3	(R)-2-Hydroxyglutarate	0.13	1.446	0.947	0.984	0.338	4.672	0.049	7.012
-	179.0571	29.1	D-Glucose	0.128	1.948	0.029	2.579	0.29	15.929	0.032	9.397
-	102.056	12.2	4-Aminobutanoate	0.127	1.889	0.744	1.199	0.016	3.571	0.067	2.214
-	102.056	26.8	4-Aminobutanoate	0.124	2.176	0.302	1.696	0.329	1.897	0.063	2.465
-	115.0036	13.2	Fumarate	0.124	0.127	0.111	0.09	0.115	0.103	0.112	0.092
-	102.056	27.7	4-Aminobutanoate	0.123	2.299	0.055	2.572	0.191	1.969	0.373	2.033
-	102.056	19.5	4-Aminobutanoate	0.116	0.467	0.286	1.684	0.812	0.897	0.57	1.285
-	129.0192	13.1	Mesaconate	0.115	0.09	0.196	0.271	0.144	0.163	0.184	0.229
-	115.0036	11.7	Fumarate	0.114	0.604	0.037	0.495	0.131	0.576	0.007	0.313
-	115.0037	6.7	Fumarate	0.11	0.332	0.116	0.362	0.04	0.119	0.038	0.112
-	102.056	26.6	4-Aminobutanoate	0.108	0.673	0.534	1.333	0.144	2.492	0.316	1.369
-	102.056	19.8	4-Aminobutanoate	0.102	1.939	0.041	2.9	0.039	2.606	0.022	2.496
-	129.0193	5.6	Mesaconate	0.102	0.249	0.08	0.188	0.104	0.255	0.131	0.309
-	129.0194	7.7	Mesaconate	0.097	0.108	0.108	0.135	0.091	0.085	0.082	0.055
-	147.0308	27.9	(R)-2-Hydroxyglutarate	0.097	0.47	0.357	0.721	0.575	1.786	0.754	0.894
-	129.0192	29.4	Mesaconate	0.095	0.504	0.328	0.652	0.585	0.818	0.077	0.472
+	106.0499	16.4	L-Serine	0.09	1.194	0.696	1.033	0.85	0.982	0.605	1.063
-	115.0036	19.7	Fumarate	0.087	0.559	0.145	0.503	0.178	0.61	0.2	0.65
-	129.0194	10.2	Mesaconate	0.083	0.173	0.109	0.245	0.115	0.262	0.087	0.191
-	115.0036	13.6	Fumarate	0.082	0.086	0.079	0.074	0.073	0.056	0.087	0.101
-	115.0036	14.3	Fumarate	0.082	0.543	0.595	0.804	0.313	0.665	0.31	0.814
+	90.05499	15.4	L-Alanine	0.079	1.236	0.231	0.853	0.533	0.932	0.012	1.363
-	115.0037	3.6	Fumarate	0.077	0.204	0.131	0.325	0.067	0.168	0.071	0.18
-	179.0562	15.3	D-Glucose	0.076	1.226	0.28	1.107	0.723	0.969	0.907	1.014
-	147.0311	27.6	(R)-2-Hydroxyglutarate	0.072	0.534	0.92	0.96	0.893	1.053	0.701	1.176

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	129.0192	26.9	Mesaconate	0.069	0.388	0.04	0.31	0.026	0.218	0.258	0.524
-	129.0193	5.3	Mesaconate	0.059	0.221	0.066	0.243	0.063	0.227	0.055	0.201
+	170.0812	8.4	Pyridoxine	0.058	1.311	0.309	1.15	0.944	1.009	0.773	1.042
-	115.0035	29.8	Fumarate	0.055	0.62	0.017	0.457	0.052	0.608	0.399	1.204
+	175.119	27.4	L-Arginine	0.054	1.246	0.384	1.106	0.903	1.013	0.386	1.103
-	115.0036	26.3	Fumarate	0.052	0.265	0.258	0.558	0.219	0.511	0.389	0.64
-	303.2331	3.9	[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid	0.051	0.862	0.022	0.786	0.007	0.785	0.026	0.843
-	115.0036	19.4	Fumarate	0.05	0.265	0.212	0.526	0.044	0.239	0.312	0.563
-	115.0036	20.4	Fumarate	0.05	0.25	0.054	0.284	0.062	0.306	0.946	1.049
-	191.02	25.2	Citrate	0.049	0.442	0.017	0.317	0.006	0.161	0.005	0.137
-	357.301	14.1	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.049	3.006	0.06	2.431	<0.001	6.325	0.011	11.704
-	220.9767	25	3-Sulfomuconate	0.049	2.213	0.045	2.011	0.007	4.737	0.011	4.204
-	333.2072	15.1	Prostaglandin A2	0.049	3.827	0.006	7.03	0.002	17.383	0.023	23.289
-	199.0976	21.5	[FA (10:1/2:0)] 2E-Decenedioic acid	0.049	2.142	0.271	1.642	0.192	2.729	0.028	2.629
-	149.0468	27.8	D-Ribose	0.049	2.541	0.446	1.391	0.17	5.477	0.075	4.434
-	107.0502	22.9	Benzyl alcohol	0.049	2	0.161	2.752	0.044	5.144	0.096	4.69
-	135.0452	6.2	Phenylacetic acid	0.049	1.96	0.039	2.044	0.249	1.613	0.138	2.153
-	127.0151	13.1	Barbiturate	0.049	2.155	0.085	1.837	0.666	1.246	0.205	0.532
-	108.0204	24.6	Benzosemiquinone	0.049	1.681	0.161	3.456	0.133	3.821	0.267	3.185
-	88.04023	18.1	L-Alanine	0.049	2.446	0.162	1.604	<0.001	2.57	0.894	1.045
-	88.98792	24.6	Oxalate	0.049	0.345	0.527	1.342	0.087	1.784	0.997	0.999
-	116.9286	19.6	chromate	0.048	0.361	0.042	0.45	0.056	0.567	0.003	0.205
-	171.0125	10.8	Toluene-4-sulfonate	0.048	0.67	0.001	0.267	<0.001	0.209	0.005	0.438
-	122.0248	26	Nicotinate	0.048	0.417	0.017	0.326	0.022	0.327	0.017	0.295
-	113.0357	21.7	5,6-Dihydrouracil	0.048	2.465	0.055	2.395	0.017	4.482	0.021	4.764
-	329.2699	18.1	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.048	2.554	0.089	10.739	0.014	12.125	0.023	23.603
-	122.0359	27.6	Pyrazinamide	0.048	2.113	0.277	8.691	0.163	4.777	0.045	4.199
-	111.02	14.7	Uracil	0.048	0.242	0.128	0.427	0.052	0.268	0.057	0.268

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	885.5493	3.7	[PI (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.048	1.478	0.033	1.284	0.009	1.428	0.092	1.255
-	556.3256	4.7	Lys-Lys-Trp-Pro	0.048	1.135	0.865	1.011	0.028	1.171	0.121	1.117
-	269.2487	11.8	[FA (17:0)] heptadecanoic acid	0.048	2.539	0.341	1.632	0.001	3.365	0.146	2.185
-	201.1134	3.3	[FA (10:0/2:0)] Decanedioic acid	0.048	1.715	0.166	1.368	0.16	1.402	0.167	1.402
-	821.5338	3.6	[PG (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.048	0.869	<0.001	0.682	0.833	1.017	0.255	1.073
-	127.0401	21.7	(4E)-2-Oxohexenoic acid	0.048	1.646	0.658	1.092	0.637	1.232	0.428	1.313
-	116.0353	19.1	L-2-Amino-3-oxobutanoic acid	0.048	0.503	0.97	1.008	0.747	1.094	0.535	0.854
+	740.5597	4.1	PC(18:3(6Z,9Z,12Z)/P-16:0)	0.047	0.826	0.001	0.529	0.008	0.753	0.449	0.947
+	204.1232	29.8	O-Acetylcarnitine	0.047	0.917	0.011	0.884	0.439	1.63	0.56	1.318
-	162.0231	8.1	Acetylcysteine	0.047	26.875	0.131	24.277	0.026	23.258	0.001	109.235
-	113.0357	8.9	5,6-Dihydrouracil	0.047	2.689	0.144	2.559	0.133	1.982	0.002	3.843
-	186.0787	29.3	[FA hydroxy(4:0)] N-(3S-hydroxy-butanoyl)-homoserine lactone	0.047	3.429	0.332	3.996	0.307	7.507	0.002	15.462
-	237.0881	11.4	Gly-Tyr	0.047	0.081	0.038	0.032	0.035	0.013	0.035	0.014
-	112.0404	27.5	(S)-1-Pyrroline-5-carboxylate	0.047	3.009	0.082	2.756	0.003	3.558	0.048	6.272
-	108.0204	22	Benzosemiquinone	0.047	2.382	0.279	5.427	0.039	3.408	0.084	4.253
-	146.0248	11.6	Indole-5,6-quinone	0.047	0.68	0.788	1.152	0.282	1.531	0.097	0.557
-	116.9285	27.2	chromate	0.047	0.325	0.096	0.418	0.23	0.606	0.176	0.56
-	136.0403	22.8	Anthranilate	0.047	0.363	0.827	1.094	0.527	1.206	0.479	1.285
+	188.103	15.6	5-guanidino-3-methyl-2-oxo-pentanoate	0.046	1.771	0.578	1.179	0.851	1.058	0.079	1.685
-	329.2701	10.3	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.046	2.091	0.126	2.908	0.001	4.587	0.002	4.365
-	357.301	23.8	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.046	2.891	0.003	3.652	0.125	11.112	0.004	11.15
-	183.1029	28.5	1,6,6-Trimethyl-2,7-dioxabicyclo[3.2.2]nonan-3-one	0.046	2.178	0.204	1.508	0.5	1.508	0.01	3.536
-	86.02456	22.8	2-Aminoacrylate	0.046	1.451	0.018	2.566	0.121	3.795	0.091	14.02
-	112.0404	27.3	(S)-1-Pyrroline-5-carboxylate	0.046	2.582	0.103	2.153	0.034	2.31	0.164	2.136
-	141.0307	26.4	5-Hydroxymethyluracil	0.046	2.315	0.091	2.443	0.221	3.323	0.254	3.191

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	189.0784	23.6	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.046	#DIV/0!	0.052	#DIV/0!	0.165	#DIV/0!	0.305	#DIV/0!
-	116.0717	24.2	L-Valine	0.046	0.278	0.225	0.553	0.055	0.312	0.419	0.652
-	125.0357	18.2	Thymine	0.046	0.528	0.169	0.546	0.486	0.836	0.475	1.482
-	281.2487	17.7	[FA (18:0)] 9Z-octadecenoic acid	0.046	0.566	0.564	0.853	0.477	1.197	0.506	1.177
-	91.02196	14.1	methylmercaptoethanol	0.046	1.774	0.471	1.194	0.191	4.25	0.545	0.844
+	176.0918	12	Calystegin B2	0.045	0.319	0.025	0.217	0.013	0.126	0.01	0.076
+	252.123	28	Ac-Tyr-OEt	0.045	0.621	0.009	0.552	0.682	1.179	0.513	0.881
-	147.0664	13.7	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.045	0.441	0.006	0.175	0.005	0.125	0.003	0.074
-	191.0199	29.7	Citrate	0.045	0.529	0.027	0.414	0.005	0.246	0.003	0.188
-	111.0199	15.1	Uracil	0.045	0.419	0.012	0.35	0.03	0.445	0.003	0.203
-	269.2487	12	[FA (17:0)] heptadecanoic acid	0.045	6.395	0.037	8.075	0.023	6.153	0.028	4.869
-	151.0626	29.4	Xylitol	0.045	3.122	0.265	2.246	0.24	7.209	0.028	18.995
-	127.015	5.3	Barbiturate	0.045	0.272	0.027	0.184	0.032	0.204	0.032	0.212
-	127.015	24.6	Barbiturate	0.045	0.484	0.136	0.58	0.173	0.678	0.041	0.363
-	124.0515	27.6	5-Methylcytosine	0.045	2.902	0.019	3.486	0.024	5.057	0.073	4.394
-	134.0359	26.9	3-N4-ethenocytosine	0.045	3.13	0.071	4.128	0.124	15.722	0.077	4.725
-	191.0577	26.6	Quinate	0.045	2.283	0.2	2.992	0.29	17.421	0.249	6.667
-	127.04	14.6	(4E)-2-Oxohexenoic acid	0.045	0.415	0.044	0.382	0.395	0.628	0.281	0.591
-	168.0668	8.4	Pyridoxine	0.045	1.373	0.196	1.239	0.492	1.1	0.319	1.179
-	115.0036	20.9	Fumarate	0.045	0.338	0.072	0.468	0.818	0.907	0.371	0.676
-	157.0868	17.3	[FA oxo(8:0)] 3-oxo-octanoic acid	0.045	0.567	0.128	1.359	0.607	1.167	0.617	0.844
-	122.9935	14.9	6-S-acetyl-dihydrolipoate	0.045	0.418	0.192	1.423	0.201	2.256	0.755	1.122
+	121.072	11.1	urea dimer	0.044	1.461	0.602	1.096	0.833	0.968	0.338	1.18
-	91.02196	24.6	methylmercaptoethanol	0.044	4.251	0.023	4.224	0.069	4.779	0.001	12.447
-	187.0625	29.3	2-oxosuberate	0.044	9.673	0.312	6.066	0.316	27.144	0.006	10.635
-	150.0562	20	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.044	0.339	0.019	0.282	0.007	0.11	0.007	0.12
-	148.0627	29.3	4-amino-4-deoxy-L-arabinose	0.044	#DIV/0!	0.347	#DIV/0!	0.15	#DIV/0!	0.019	#DIV/0!

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	357.301	28.6	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.044	4.316	0.005	5.965	0.091	20.897	0.026	10.612
-	108.0566	29.4	Brunfelsamidine	0.044	1.605	0.475	1.265	0.475	1.68	0.032	7.382
-	100.004	27.6	oxazoladindione	0.044	1.747	0.08	2.774	0.255	7.539	0.091	2.373
+	796.5883	4.3	PE(18:0/22:4(7Z,10Z,13Z,16Z))	0.043	#DIV/0!	0.04	#DIV/0!	0.003	#DIV/0!	0.001	#DIV/0!
+	176.0918	3.7	Calystegin B2	0.043	0.14	0.074	0.274	0.043	0.148	0.029	0.068
+	120.0655	27.1	L-Threonine	0.043	0.482	0.453	0.777	0.01	0.333	0.088	0.579
-	333.2072	14.6	Prostaglandin A2	0.043	2.656	0.01	12.221	<0.001	23.377	0.003	49.877
-	178.0509	23.7	Hippurate	0.043	0.296	0.031	0.231	0.012	0.069	0.012	0.067
-	94.02973	28.9	2-Hydroxypyridine	0.043	2.834	0.005	3.394	0.118	8.37	0.02	6.217
-	139.015	26.6	2-hydroxy-4-carboxypyrimidine	0.043	1.946	0.057	2.809	0.229	6.79	0.058	5.188
-	804.5758	4.1	[PS (18:0/19:0)] 1-octadecanoyl-2-nonadecanoyl-sn-glycero-3-phosphoserine	0.043	2.586	0.599	1.205	0.105	2.892	0.117	2.344
-	161.0456	7	2-Dehydro-3-deoxy-L-rhamnonate	0.043	0.552	0.725	0.908	0.79	0.941	0.228	0.701
-	177.0927	14.9	Eugenol methyl ether	0.043	0.645	0.352	1.496	0.966	0.984	0.228	0.69
-	112.0516	24.2	Creatinine	0.043	0.312	0.024	0.231	0.071	0.337	0.547	0.804
-	125.0243	15	Phloroglucinol	0.043	1.898	0.471	1.303	0.811	1.099	0.757	0.873
+	258.1101	15.5	5-Methylcytidine	0.042	2.332	0.373	0.783	0.022	1.517	<0.001	5.109
+	223.0966	27.9	[FA (12:4/2:0)] 2E,4E,8E,10E-Dodecatetraenedioic acid	0.042	0.329	0.958	0.983	0.112	0.425	0.036	0.307
+	132.0767	23.9	Creatine	0.042	1.71	0.713	0.894	0.712	1.156	0.335	1.474
+	171.1128	5	Levetiracetam	0.042	21.426	0.715	1.327	0.06	0.485	0.397	5.908
+	130.0499	10.6	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.042	1.299	0.776	1.037	0.352	0.899	0.832	0.976
-	162.0053	21.3	S-allylmercapto-L-cysteine	0.042	1.595	0.03	1.781	<0.001	0.07	<0.001	0.063
-	113.0356	23.7	5,6-Dihydrouracil	0.042	2.847	0.033	2.838	0.076	3.434	0.009	2.724
-	150.0562	8.7	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.042	0.41	0.006	0.137	0.006	0.113	0.01	0.194
-	97.04067	19.8	Imidazole-4-methanol	0.042	2.112	0.243	1.659	0.175	2.03	0.014	2.768
-	96.00908	21.3	Maleimide	0.042	2.6	0.291	1.624	0.012	2.779	0.017	5.315
-	232.0842	28.8	Dihydroxycoprostanoicacid	0.042	2.839	0.321	3.051	0.345	13.97	0.034	14.533
-	164.0361	13.5	Formylanthranilate	0.042	0.525	0.779	1.085	0.678	1.149	0.038	1.745

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	89.02429	20.7	(R)-Lactate	0.042	1.035	0.551	0.883	0.117	0.643	0.043	0.484
-	178.0625	29.6	N-Acetylisoniazid	0.042	4.682	0.234	7.403	0.17	5.525	0.05	11.545
-	98.03587	29.5	fragment of guanidino acetate	0.042	2.635	0.101	1.672	0.378	1.49	0.073	8.155
-	75.0448	4.1	Propane-1,2-diol	0.042	0.393	0.16	0.603	0.555	0.74	0.147	0.522
-	189.0783	25.6	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.042	1.946	0.291	4.039	0.159	8.307	0.211	8.031
-	137.0458	26.1	8-Hydroxypurine	0.042	0.529	0.477	0.831	<0.001	0.245	0.301	0.686
-	202.0735	26.7	N2-Acetyl-L-aminoadipate	0.042	2.215	0.195	2.128	0.056	3.743	0.332	24.056
+	750.544	3.9	PE(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.041	1.146	0.033	1.12	0.001	1.193	0.001	1.203
+	124.0757	29.7	2-amino-4-methylphenol	0.041	0.9	0.395	2.445	0.379	2.568	0.003	0.816
+	203.085	5	Pyrene	0.041	4.083	0.105	3.719	0.171	2.322	0.007	4.507
+	252.1231	4.4	Ac-Tyr-OEt	0.041	0.145	0.34	0.472	0.061	0.196	0.501	0.59
+	276.1805	5	[FA hydroxy(10:0)] N-(3S-hydroxydecanoyl)-L-serine	0.041	0.433	0.735	0.899	0.444	0.773	0.884	0.952
-	162.0053	21.8	S-allylmercapto-L-cysteine	0.041	1.602	0.031	1.789	<0.001	0.063	<0.001	0.037
-	178.0508	19.2	Hippurate	0.041	0.428	0.008	0.223	0.002	0.055	0.005	0.165
-	333.2072	13.5	Prostaglandin A2	0.041	2.801	0.064	5.432	<0.001	11.227	0.007	11.057
-	150.0562	17.3	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.041	0.25	0.053	0.27	0.015	0.052	0.022	0.119
-	393.2781	4.1	[ST (4:0/2:0)] (5Z,7E)-(3S)-9,10-seco-5,7,10(19),16-cholestatetraen-23-yne-3,25-diol	0.041	0.755	0.054	0.799	0.902	1.015	0.045	0.767
-	160.0626	29.6	L-2-Aminoadipate	0.041	2.581	0.284	3.579	0.363	6.101	0.053	10.994
-	175.063	27.8	(2S)-2-Isopropylmalate	0.041	3.035	0.239	5.038	0.124	12.067	0.08	3.456
-	123.02	28.1	pyrazinoate	0.041	2.823	0.053	4.598	0.056	7.766	0.105	2.263
-	160.0625	29	L-2-Aminoadipate	0.041	3.121	0.026	1.601	0.334	24.393	0.128	15.3
-	111.0087	18.2	2-Furoate	0.041	1.757	0.547	1.249	0.712	1.146	0.141	1.557
-	105.0193	12.5	D-Glycerate	0.041	0.416	0.396	1.521	0.537	1.316	0.154	2.152
-	110.0359	22.1	Cytosine	0.041	0.487	0.614	1.318	0.673	0.869	0.512	1.683
-	131.0715	20.2	1,1-Diethyl-2-hydroxy-2-nitrosohydrazine	0.041	1.915	0.684	1.151	0.146	1.897	0.638	1.178
+	248.1493	5	Hydroxybutyrylcarnitine	0.04	1.243	0.848	1.032	0.008	1.381	0.049	1.504
-	809.5162	3.7	[PI (16:0/16:0)] 1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	0.04	3.064	0.144	1.587	<0.001	3.465	<0.001	3.935

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	220.9767	22.2	3-Sulfomuconate	0.04	2.707	0.029	2.847	0.006	5.078	0.007	3.836
-	171.0128	23.4	Toluene-4-sulfonate	0.04	0.277	0.055	0.312	0.038	0.255	0.03	0.217
-	151.0517	28.9	N1-Methyl-2-pyridone-5-carboxamide	0.04	3.156	0.343	3.507	0.34	10.64	0.093	6.437
-	132.0567	26.1	2-Aminobenzimidazole	0.04	2.181	0.349	9.93	0.157	2.727	0.165	5.364
-	143.035	6.4	2,3-Dimethylmaleate	0.04	0.485	0.421	0.775	0.202	0.602	0.186	0.581
-	173.0474	26.4	Shikimate	0.04	#DIV/0!	0.005	#DIV/0!	0.303	#DIV/0!	0.251	#DIV/0!
-	80.9746	24.5	Phosphonate	0.04	0.465	0.036	0.424	0.01	0.271	0.695	0.829
-	201.1134	9.2	[FA (10:0/2:0)] Decanedioic acid	0.04	0.568	0.623	0.836	0.524	1.161	0.721	1.117
+	858.5287	3.6	PS(20:3(8Z,11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.039	0.659	0.001	0.321	0.041	0.671	0.233	0.806
-	215.02	29.8	5-Carboxy-2-oxohept-3-enedioate	0.039	3.216	0.193	6.446	0.211	3.937	0.007	9.741
-	116.9285	15.4	chromate	0.039	0.289	0.26	0.488	0.014	0.142	0.008	0.057
-	150.0561	11.7	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.039	0.474	0.014	0.342	0.005	0.21	0.012	0.274
-	171.0128	12.1	Toluene-4-sulfonate	0.039	0.358	0.106	0.425	0.026	0.287	0.013	0.169
-	155.0465	29.8	4-Imidazolone-5-propanoate	0.039	3.414	0.172	1.604	0.164	2.085	0.035	3.486
-	115.0036	17.9	Fumarate	0.039	0.398	0.497	0.786	0.001	0.392	0.038	0.574
-	329.2699	28	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.039	8.162	0.114	27.627	0.019	11.276	0.038	62.169
-	281.2487	27.9	[FA (18:0)] 9Z-octadecenoic acid	0.039	2.638	0.415	1.62	0.067	2.36	0.059	2.341
-	329.2699	25.8	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.039	3.02	0.089	8.636	0.001	13.045	0.069	15.579
-	353.0492	6	Phenolsulfonphthalein	0.039	1.359	0.246	1.181	0.019	1.329	0.07	2.077
-	137.0357	11.2	Urocanate	0.039	0.717	0.618	0.899	0.321	0.877	0.181	0.799
-	125.0356	18.9	Thymine	0.039	0.355	0.15	0.536	0.117	0.526	0.739	1.131
+	344.2791	5	1,2-dioctanoyl-1-amino-2,3-propanediol	0.038	1.654	0.076	0.759	0.754	1.048	<0.001	2.185
+	146.0812	5	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.038	0.396	0.023	0.319	0.023	0.318	0.025	0.329
+	838.56	3.7	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.038	1.414	0.64	0.958	0.067	1.185	0.026	1.282
+	180.0867	14.2	D-Glucosamine	0.038	1.343	0.032	1.254	0.164	1.656	0.054	1.902
+	242.1386	5	N-(3-Oxooctanoyl)homoserine lactone	0.038	1.272	0.411	0.831	0.203	1.228	0.637	0.862
-	162.0053	22.4	S-allylmercapto-L-cysteine	0.038	1.621	0.031	1.802	0.021	0.25	<0.001	0.042
-	162.0053	22.8	S-allylmercapto-L-cysteine	0.038	1.622	0.031	1.805	0.021	0.251	<0.001	0.034

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	269.2488	22.6	[FA (17:0)] heptadecanoic acid	0.038	2.212	0.035	2.338	0.037	3.747	0.038	4.13
-	129.0193	4.3	Mesaconate	0.038	0.233	0.03	0.17	0.054	0.291	0.048	0.265
-	138.0672	27.3	L-Histidinal	0.038	4.475	0.051	4.377	0.103	6.848	0.059	6.923
-	204.0304	22	Xanthurenic acid	0.038	0.311	0.054	0.375	0.033	0.294	0.09	0.437
-	112.0516	3.8	Creatinine	0.038	0.168	0.115	0.388	0.068	0.278	0.139	0.427
-	190.0736	29.6	2-amino-3,7-dideoxy-D-threo-hept-6-ulosonate	0.038	3.355	0.244	2.29	0.192	2.896	0.162	15.667
-	131.035	7.7	2-Acetolactate	0.038	0.234	0.412	0.652	0.289	0.556	0.319	0.593
-	145.0508	22.4	Adipate	0.038	0.561	0.067	0.536	0.023	0.507	0.491	1.462
-	111.02	21.9	Uracil	0.038	0.336	0.119	0.529	0.895	0.959	0.968	0.981
-	133.0143	26.2	(S)-Malate	0.037	0.584	<0.001	0.245	0.002	0.303	<0.001	0.252
-	162.0053	23	S-allylmercapto-L-cysteine	0.037	1.63	0.031	1.81	0.022	0.253	0.001	0.072
-	162.0053	23.4	S-allylmercapto-L-cysteine	0.037	1.636	0.031	1.819	0.026	0.294	0.001	0.078
-	147.0664	13.9	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.037	0.558	0.008	0.373	0.002	0.209	0.002	0.168
-	86.02455	15.8	2-Aminoacrylate	0.037	4.278	0.098	1.852	0.004	3.445	0.005	6.158
-	130.0145	28.9	Iminoaspartate	0.037	1.813	0.885	0.949	0.327	3.169	0.015	3.726
-	111.02	3.3	Uracil	0.037	0.532	0.033	0.461	0.024	0.406	0.02	0.442
-	150.0562	16.6	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.037	0.229	0.044	0.239	0.024	0.145	0.029	0.17
-	100.004	22	oxazoladindione	0.037	2.556	0.006	4.113	0.028	6.882	0.056	5.741
-	135.0564	28.1	1-Methylnicotinamide	0.037	3.471	0.085	2.51	0.04	4.067	0.059	3.012
-	89.02428	23.9	(R)-Lactate	0.037	1.03	0.037	1.064	0.689	0.985	0.069	0.947
-	213.1862	24.3	CAI-1	0.037	2.209	0.208	2.115	0.048	2.437	0.296	2.296
-	173.0826	28.2	Suberic acid	0.037	0.495	0.71	0.893	0.434	2.403	0.413	1.6
+	839.5636	3.7	PI(16:0/18:0)	0.036	1.463	0.837	0.98	0.06	1.206	0.014	1.346
+	370.3315	4.2	[SP amino,tetramethyl(4:0/18:0/3:0)] 2S-amino-5,9,13,17-tetramethyl-8E,16-octadecadiene-1,3R,14-triol	0.036	0.291	0.677	1.509	0.772	0.842	0.036	0.287
+	111.0553	7.5	Imidazole-4-acetaldehyde	0.036	0.395	0.942	0.981	0.446	0.765	0.212	0.573
+	301.2156	5.4	[PR] Tretinoin/All-Trans Retinoic Acid	0.036	6.433	0.173	1.365	0.029	9.139	0.246	4.851

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	156.0768	29.6	L-Histidine	0.036	1.194	0.266	1.382	0.441	0.94	0.776	1.022
-	162.0053	23.7	S-allylmercapto-L-cysteine	0.036	1.644	0.031	1.826	0.023	0.245	0.001	0.067
-	99.00874	23.4	2-oxobut-3-enanoate	0.036	0.502	0.327	0.746	0.303	0.777	0.024	0.4
-	178.051	9.1	Hippurate	0.036	0.198	0.027	0.165	0.027	0.163	0.029	0.179
-	149.0468	27.6	D-Ribose	0.036	4.962	0.101	2.193	0.239	7.083	0.091	5.07
-	117.0557	17.5	5-Hydroxypentanoate	0.036	0.396	0.033	0.37	0.828	0.885	0.111	0.516
-	149.061	22.3	Phenylpropanoate	0.036	0.26	0.03	0.238	0.026	0.212	0.123	0.409
-	89.02429	22	(R)-Lactate	0.036	1.034	0.041	1.06	0.954	1.002	0.125	0.645
-	151.0516	26.8	N1-Methyl-2-pyridone-5-carboxamide	0.036	4.315	0.131	1.437	0.121	7.311	0.153	4.097
-	139.9757	15.3	Carbamoyl phosphate	0.036	2.091	0.993	1.004	0.281	1.668	0.287	1.565
-	88.04022	26.5	L-Alanine	0.036	0.555	0.195	0.681	0.288	1.868	0.566	1.117
-	135.0452	5	Phenylacetic acid	0.036	0.771	0.056	0.827	0.078	0.821	0.818	0.979
+	250.1438	7.6	Ruspolinone	0.035	0.46	0.466	1.063	0.759	0.972	0.469	0.82
-	139.9758	12.7	Carbamoyl phosphate	0.035	1.531	0.371	1.529	0.148	2.085	<0.001	2.344
-	162.0053	24.6	S-allylmercapto-L-cysteine	0.035	1.658	0.03	1.837	0.026	0.259	0.001	0.101
-	97.0407	15.1	Imidazole-4-methanol	0.035	2.602	0.159	2.194	0.027	5.45	0.001	9.195
-	113.0356	23.1	5,6-Dihydrouracil	0.035	1.481	0.247	1.5	0.138	2.157	0.001	2.945
-	113.0356	14.9	5,6-Dihydrouracil	0.035	5.163	0.023	3.132	0.017	2.698	0.011	4.865
-	133.0142	29.8	(S)-Malate	0.035	0.149	0.055	0.238	0.059	0.264	0.029	0.121
-	89.02428	20.9	(R)-Lactate	0.035	1.035	0.538	0.874	0.266	0.78	0.128	0.65
-	127.0513	27.7	5,6-Dihydrothymine	0.035	2.139	0.164	2.553	0.141	5.994	0.148	4.056
-	143.0349	17.8	2,3-Dimethylmaleate	0.035	1.768	0.131	1.86	0.026	2.006	0.195	1.881
+	242.2113	4.4	[SP (14:0/2:0)] tetradecasphinga-4E,6E-dienine	0.034	0.354	0.434	2.673	0.892	1.125	0.129	0.493
+	354.1283	4.4	Asp-Gly-Tyr	0.034	1.382	0.492	1.098	0.921	1.011	0.522	1.089
-	162.0053	26	S-allylmercapto-L-cysteine	0.034	1.696	0.029	1.886	0.033	0.264	0.001	0.056
-	146.0249	7.6	Indole-5,6-quinone	0.034	0.256	0.014	0.093	0.025	0.193	0.015	0.109
-	139.9757	19.7	Carbamoyl phosphate	0.034	2.286	0.068	2.463	0.068	2.594	0.022	2.685
-	159.0683	28.9	[FA (7:0/2:0)] Heptanedioic acid	0.034	2.826	0.397	1.827	0.344	23.887	0.043	20.996

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	139.0514	25.5	Methylimidazoleacetic acid	0.034	2.43	0.176	5.38	0.325	5.846	0.233	4.222
-	105.0193	14.3	D-Glycerate	0.034	0.437	0.189	0.637	0.159	0.653	0.372	1.448
-	162.0053	25.2	S-allylmercapto-L-cysteine	0.033	1.674	0.029	1.855	0.027	0.257	0.001	0.1
-	162.0053	25.6	S-allylmercapto-L-cysteine	0.033	1.685	0.029	1.872	0.028	0.242	0.001	0.066
-	162.0053	26.8	S-allylmercapto-L-cysteine	0.033	1.735	0.028	1.937	0.04	0.266	0.002	0.088
-	162.0053	27	S-allylmercapto-L-cysteine	0.033	1.785	0.029	1.985	0.052	0.272	0.004	0.088
-	333.2072	16.4	Prostaglandin A2	0.033	2.019	0.04	5.887	0.005	8.472	0.007	27.32
-	162.0053	27.5	S-allylmercapto-L-cysteine	0.033	1.83	0.03	2.036	0.071	0.304	0.007	0.096
-	151.0625	29.2	Xylitol	0.033	3.768	0.163	3.77	0.331	24.161	0.007	16.648
-	99.0451	28.5	Tiglic acid	0.033	1.961	0.045	1.869	0.033	1.636	0.015	2.587
-	243.0623	10.2	Uridine	0.033	0.7	0.247	0.827	0.014	0.641	0.018	0.61
-	80.9746	20	Phosphonate	0.033	0.346	0.392	0.701	0.062	0.481	0.028	0.369
-	127.015	20.3	Barbiturate	0.033	0.281	0.097	0.442	0.022	0.243	0.031	0.297
-	159.0658	13.5	[FA (7:0/2:0)] Heptanedioic acid	0.033	0.427	0.029	0.425	0.048	0.473	0.036	0.422
-	114.0196	26.7	Maleamate	0.033	1.898	0.173	2.258	0.053	2.842	0.066	3.626
-	122.9934	14	6-S-acetyl-dihydrolipoate	0.033	0.357	0.781	0.906	0.277	0.697	0.134	0.577
-	189.0783	26.2	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.033	4.007	0.091	4.422	0.264	14.642	0.233	8.305
-	111.0199	22.6	Uracil	0.033	0.401	0.077	0.465	0.965	1.018	0.379	0.719
-	167.9972	15.3	L-Cysteate	0.032	2.966	0.571	1.364	0.018	3.5	<0.001	6.852
-	162.0053	26.4	S-allylmercapto-L-cysteine	0.032	1.724	0.029	1.914	0.036	0.252	0.005	0.167
-	162.0777	29.7	1-deoxynojirimycin	0.032	1.543	0.131	2.291	0.245	4.053	0.014	2.72
-	215.0199	27.6	5-Carboxy-2-oxohept-3-enedioate	0.032	1.803	0.106	10.676	0.197	8.939	0.017	9.081
-	220.9768	21.9	3-Sulfomuconate	0.032	2.69	0.003	4.225	0.002	6.935	0.025	4.863
-	147.0664	26.7	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.032	0.134	0.029	0.112	0.025	0.076	0.025	0.078
-	178.0625	28.9	N-Acetylisoniazid	0.032	7.031	0.258	4.441	0.333	9.559	0.025	13.761
-	86.02456	14.7	2-Aminoacrylate	0.032	3.29	0.091	3.969	0.02	2.426	0.026	4.723
-	101.0356	14.4	N-Formiminoglycine	0.032	2.4	0.97	1.014	0.098	2.585	0.031	1.99

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	101.0356	29.2	N-Formiminoglycine	0.032	3.385	0.044	7.209	0.137	4.929	0.043	10.019
-	132.0301	27	L-Aspartate	0.032	2.82	0.074	2.642	0.004	6.658	0.08	3.893
-	180.0416	28.5	Phosphinothricin	0.032	11.546	0.176	14.59	0.291	59.1	0.141	62.224
-	245.0429	13.1	Glycerophosphoglycerol	0.032	1.329	<0.001	0.135	<0.001	0.151	0.144	1.192
-	409.2363	4.7	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.032	1.159	0.978	0.998	0.036	1.171	0.174	1.103
-	124.0516	22.1	5-Methylcytosine	0.032	2.185	0.084	1.995	0.074	5.46	0.216	7.415
-	102.0196	10.3	2-Aminomalonate semialdehyde	0.032	0.618	0.125	0.701	0.837	0.966	0.231	0.728
-	116.0353	13.5	L-2-Amino-3-oxobutanoic acid	0.032	0.315	0.079	0.467	0.052	0.415	0.503	0.74
-	129.0193	12.2	Mesaconate	0.032	0.357	0.876	1.111	0.513	1.455	0.657	0.872
-	329.2698	13.3	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.031	2.748	0.015	4.3	0.014	12.428	0.004	11.06
-	162.0053	29.8	S-allylmercapto-L-cysteine	0.031	1.58	0.026	1.801	0.017	0.361	0.007	0.354
-	333.2075	4.4	Prostaglandin A2	0.031	1.683	0.018	2.94	0.073	12.381	0.007	41.127
-	116.9286	17.9	chromate	0.031	0.267	0.014	0.156	0.021	0.186	0.009	0.083
-	248.08	7.3	S-Acetyldihydrolipoamide	0.031	1.842	0.757	1.2	0.221	1.697	0.011	2.29
-	121.052	29.6	Erythritol	0.031	3.364	0.336	9.346	0.333	10.265	0.014	42.809
-	191.0577	29.1	Quinate	0.031	2.416	0.268	1.291	0.352	3.919	0.022	6.558
-	199.0976	19.4	[FA (10:1/2:0)] 2E-Decenedioic acid	0.031	3.679	0.052	1.946	0.105	2.339	0.061	2.359
-	130.0873	29.7	L-Leucine	0.031	1.761	0.26	1.648	0.105	3.451	0.096	2.166
-	163.0629	20.1	L-Rhamnose	0.031	1.569	0.364	1.714	0.524	1.394	0.177	2.85
-	113.0356	13.9	5,6-Dihydrouracil	0.031	3.536	0.118	2.144	0.054	2.755	0.183	2.588
-	220.0841	29.9	N-Acetyl-D-glucosamine	0.031	3.135	0.362	3.099	0.305	11.693	0.212	5.819
-	139.015	25.8	2-hydroxy-4-carboxypyrimidine	0.031	1.641	0.153	1.335	0.15	2.477	0.341	9.946
-	187.0974	28.3	Azelaic acid	0.031	0.38	0.917	1.065	0.123	0.569	0.588	0.844
+	162.0761	28.6	L-2-Aminoadipate	0.03	0.326	0.012	0.18	0.006	0.055	0.006	0.071
+	119.0834	11.8	L-2,4-Diaminobutanoate	0.03	1.374	0.112	1.13	0.554	0.959	0.248	1.162
+	166.0533	14	L-Methionine S-oxide	0.03	1.395	0.264	1.202	0.986	0.998	0.758	1.047
-	178.0509	24.3	Hippurate	0.03	0.505	<0.001	0.176	<0.001	0.103	<0.001	0.097
-	135.03	13.9	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	0.03	2.528	0.192	1.531	0.006	4.059	0.004	3.907

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	133.0521	27.3	Deoxyribose	0.03	1.739	0.191	5.291	0.101	7.028	0.018	3.215
-	177.042	29.3	D-Glucono-1,5-lactone	0.03	2.272	0.419	2.226	0.336	19.917	0.024	6.859
-	113.0356	20	5,6-Dihydrouracil	0.03	2.933	0.001	2.546	0.024	2.872	0.074	3.537
-	126.0306	29.8	5-Amino-4-imidazole carboxylate	0.03	3.554	0.246	3.413	0.17	3.05	0.12	10.117
+	162.0761	29.2	L-2-Aminoadipate	0.029	0.325	0.025	0.237	0.008	0.106	0.009	0.123
+	777.5628	3.9	[PG (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.029	1.546	0.772	1.082	0.008	1.394	0.028	1.338
+	123.0553	7.6	Nicotinamide	0.029	1.298	0.85	1.024	0.899	1.014	0.13	1.175
-	147.0664	6.5	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.029	0.476	0.009	0.305	0.003	0.235	0.001	0.11
-	117.0194	8.6	Succinate	0.029	0.146	0.034	0.175	0.025	0.118	0.026	0.123
-	107.0157	29.8	p-Benzoquinone	0.029	0.631	0.005	0.441	0.01	0.681	0.029	0.678
-	112.9992	13.5	parabanate	0.029	0.294	0.25	0.615	0.06	0.414	0.045	0.369
-	127.0206	21.5	[FA (9:1/3:0)] 2-nonene-4,6,8-triynal	0.029	1.999	0.147	1.652	0.234	1.587	0.046	1.93
-	116.9285	26.4	chromate	0.029	0.368	0.081	0.426	0.126	0.428	0.052	0.442
-	149.0468	29.9	D-Ribose	0.029	1.764	0.077	7.627	0.308	1.884	0.08	2.855
-	120.0666	22.6	Tromethamine	0.029	3.649	0.025	4.18	0.012	3.503	0.098	4.041
-	135.03	21	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	0.029	3.181	0.055	4.333	0.003	2.761	0.124	1.917
-	269.2488	19.3	[FA (17:0)] heptadecanoic acid	0.029	2.007	0.163	1.697	0.036	2.907	0.38	1.58
-	114.056	6.8	L-Proline	0.029	0.595	0.235	0.779	0.107	1.342	0.426	1.232
-	115.0036	20.6	Fumarate	0.029	0.399	0.009	0.249	0.226	0.63	0.968	0.973
+	788.6172	4	[PC (18:0/18:1)] 1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.028	1.786	0.055	1.313	0.021	1.4	0.092	1.304
+	522.3554	4.6	1-Oleoylglycerophosphocholine	0.028	1.255	0.689	0.959	0.079	1.186	0.269	1.141
+	148.0734	15.6	L-Albizziine	0.028	1.291	0.511	1.075	0.839	0.977	0.371	1.11
-	162.0052	29.2	S-allylmercapto-L-cysteine	0.028	1.579	0.031	1.773	0.014	0.334	<0.001	0.107
-	187.0072	7.4	4-Sulfobenzyl alcohol	0.028	0.284	0.011	0.121	0.009	0.096	0.007	0.045
-	147.0664	26.4	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.028	0.158	0.025	0.135	0.017	0.06	0.02	0.092
-	151.0398	17.7	[PK] 6-Methylsalicylic acid	0.028	0.491	0.396	0.8	0.989	1.003	0.029	0.532

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	127.015	26.3	Barbiturate	0.028	2.59	0.227	1.368	0.056	0.473	0.048	0.49
-	102.0196	5.4	2-Aminomalonate semialdehyde	0.028	0.443	0.049	0.533	0.119	0.674	0.073	0.599
-	98.03588	29.2	fragment of guanidino acetate	0.028	2.369	0.682	1.217	0.302	12.155	0.077	10.125
-	135.0677	29.8	D-Apiitol	0.028	2.935	0.137	2.663	0.158	3.663	0.152	8.585
-	138.0673	25.8	L-Histidinal	0.028	3.636	0.124	4.855	0.164	10.282	0.154	13.97
-	82.04078	29.4	5-Aminoimidazole	0.028	3.418	0.048	2.536	0.221	1.624	0.184	13.014
-	89.02429	22.4	(R)-Lactate	0.028	1.034	0.025	1.066	0.804	0.992	0.225	0.785
-	281.2487	19.4	[FA (18:0)] 9Z-octadecenoic acid	0.028	1.807	0.989	1.004	0.18	1.453	0.228	1.418
-	157.0509	3.7	2-Isopropylmaleate	0.028	0.392	0.003	0.316	0.952	1.012	0.314	0.771
-	112.0516	28.3	Creatinine	0.028	0.512	0.01	0.338	0.747	1.097	0.441	1.635
+	828.2568	17.7	Deshydroxy-C-1027 chromophore	0.027	2.773	0.214	1.816	0.001	4.84	<0.001	6.375
+	776.5597	3.9	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.027	1.438	0.475	1.123	0.005	1.369	0.015	1.336
+	194.1177	3.9	3,4-Methylenedioxymethamphetamine	0.027	0.511	0.19	0.819	0.021	0.497	0.021	0.551
-	171.0129	27.3	Toluene-4-sulfonate	0.027	0.359	0.006	0.146	0.01	0.204	0.008	0.173
-	173.0817	13.5	Suberic acid	0.027	0.331	0.014	0.246	0.085	0.513	0.024	0.353
-	175.063	27.5	(2S)-2-Isopropylmalate	0.027	9.4	0.016	7.605	0.075	11.131	0.026	8.581
-	123.0564	21.5	Methylimidazole acetaldehyde	0.027	1.929	0.196	2.448	0.005	3.391	0.031	5.102
-	115.0512	27.2	Diacetylhydrazine	0.027	2.079	0.117	2.485	0.028	5.066	0.032	3.598
-	109.0042	26.1	ethylphosphonate	0.027	2.976	0.201	3.771	0.25	2.369	0.046	2.639
-	124.0152	28.8	(2-Aminoethyl)phosphonate	0.027	1.998	0.346	1.707	0.36	6.391	0.16	7.316
-	99.04509	29.4	Tiglic acid	0.027	2.534	0.135	1.658	0.061	2.851	0.318	2.127
-	308.0989	13.8	N-Acetylneuraminate	0.027	0.854	<0.001	0.512	<0.001	0.527	0.352	1.056
-	102.056	28.4	4-Aminobutanoate	0.027	2.959	0.716	1.211	0.224	1.358	0.629	1.149
+	252.123	29.4	Ac-Tyr-OEt	0.026	0.845	0.001	0.784	0.504	1.672	<0.001	0.706
+	96.04439	28.8	2-Hydroxypyridine	0.026	0.544	0.511	0.809	0.174	0.828	0.048	0.647
+	335.1059	4.4	Penicillin G	0.026	1.296	0.729	1.035	0.509	0.941	0.487	0.936
+	286.2741	4.3	[SP (17:0)] heptadecasphing-4-enine	0.026	0.324	0.032	0.361	0.004	0.168	0.942	1.044

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	162.0052	27.9	S-allylmercapto-L-cysteine	0.026	1.579	0.031	1.757	0.011	0.238	<0.001	0.113
-	162.0053	28.3	S-allylmercapto-L-cysteine	0.026	1.572	0.031	1.755	0.012	0.269	<0.001	0.139
-	147.0664	4.8	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.026	0.224	0.007	0.024	0.007	0.02	0.008	0.028
-	91.03994	26.5	Glycerol	0.026	1.468	0.034	1.554	0.274	1.644	0.018	1.565
-	171.0129	19.1	Toluene-4-sulfonate	0.026	0.152	0.033	0.197	0.04	0.229	0.024	0.139
-	116.9285	26.7	chromate	0.026	0.295	0.217	0.493	0.023	0.281	0.034	0.332
-	151.0401	3.4	[PK] 6-Methylsalicylic acid	0.026	0.538	0.009	0.577	0.007	0.609	0.072	0.722
-	122.0248	25	Nicotinate	0.026	0.283	0.211	0.637	0.033	0.316	0.073	0.449
-	138.0196	27.6	6-Hydroxynicotinate	0.026	1.927	0.592	1.194	0.72	1.143	0.085	1.939
-	127.015	19.2	Barbiturate	0.026	0.385	0.008	0.209	0.009	0.28	0.088	0.493
-	133.0143	23.4	(S)-Malate	0.026	0.306	0.857	0.89	0.409	0.737	0.13	0.507
-	143.035	4.3	2,3-Dimethylmaleate	0.026	0.127	0.497	0.643	0.51	0.644	0.415	0.564
-	145.0506	24.9	Adipate	0.026	0.575	0.005	0.407	0.054	0.547	0.573	0.805
-	155.083	12.1	N-acetyl prolinamide or isomer	0.026	1.317	0.877	0.966	0.742	0.956	0.621	1.096
+	118.0611	16.4	Guanidinoacetate	0.025	1.238	0.001	0.599	0.004	0.659	<0.001	1.607
+	156.0768	15.2	L-Histidine	0.025	1.291	0.954	0.994	0.379	0.903	0.135	1.172
+	267.1591	4.2	[PR] (+)-Blennin D	0.025	0.326	0.04	0.401	0.082	0.483	0.779	1.237
-	91.03995	24.2	Glycerol	0.025	2.958	0.257	2.052	0.001	3.606	<0.001	3.749
-	162.0053	28.6	S-allylmercapto-L-cysteine	0.025	1.589	0.032	1.764	0.015	0.3	<0.001	0.128
-	187.0072	4.6	4-Sulfobenzyl alcohol	0.025	0.53	0.001	0.365	<0.001	0.38	0.001	0.475
-	162.0052	29.5	S-allylmercapto-L-cysteine	0.025	1.595	0.029	1.788	0.014	0.336	0.001	0.224
-	357.3011	19.2	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.025	4.844	0.005	8.863	0.004	13.363	0.002	10.013
-	162.0052	29	S-allylmercapto-L-cysteine	0.025	1.591	0.032	1.772	0.014	0.304	0.002	0.221
-	178.051	3.7	Hippurate	0.025	0.361	0.013	0.288	0.006	0.178	0.006	0.176
-	127.015	15.5	Barbiturate	0.025	0.459	0.112	0.554	0.022	0.427	0.01	0.316
-	93.03452	22.5	Phenol	0.025	0.551	0.635	1.367	0.996	1.003	0.011	0.377
-	171.0128	28.1	Toluene-4-sulfonate	0.025	0.25	0.043	0.334	0.013	0.163	0.017	0.202

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	178.0509	12.4	Hippurate	0.025	0.099	0.02	0.048	0.018	0.025	0.019	0.037
-	171.0128	12.8	Toluene-4-sulfonate	0.025	0.129	0.036	0.187	0.028	0.149	0.019	0.077
-	122.0247	28.4	Nicotinate	0.025	0.203	0.139	0.49	0.057	0.374	0.023	0.194
-	110.0247	25.3	Pyrrole-2-carboxylate	0.025	1.923	0.068	1.969	0.222	2.483	0.047	2.295
-	154.0262	29.7	N-Methylethanolamine phosphate	0.025	3.003	0.245	4.563	0.043	2.421	0.127	13.107
-	177.042	29.7	D-Glucono-1,5-lactone	0.025	2.818	0.415	3.284	0.451	2.286	0.169	5.323
-	147.0668	29	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.025	0.237	0.012	0.123	0.097	0.347	0.176	0.453
-	218.0681	28	O-Succinyl-L-homoserine	0.025	3.395	0.04	4.028	0.198	9.036	0.193	10.045
+	734.57	4.1	[PC (16:0/16:0)] 1-hexadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.024	2.198	0.115	1.355	0.006	1.698	0.043	1.567
+	102.055	15.1	1-Aminocyclopropane-1-carboxylate	0.024	1.295	0.729	0.958	0.728	0.96	0.609	1.061
-	333.2075	4.6	Prostaglandin A2	0.024	2.134	0.045	3.888	0.006	18.13	0.006	21.913
-	178.0508	29.4	Hippurate	0.024	0.244	0.031	0.268	0.014	0.13	0.008	0.046
-	115.0037	4.1	Fumarate	0.024	0.272	0.027	0.303	0.023	0.286	0.012	0.175
-	91.03995	23.5	Glycerol	0.024	2.738	0.668	1.308	0.067	2.615	0.017	3.041
-	112.0516	18.6	Creatinine	0.024	0.301	0.293	0.647	0.051	0.421	0.296	0.685
-	77.03934	5.1	Benzene	0.024	1.3	0.579	1.151	0.235	1.477	0.48	1.126
-	115.0036	22.9	Fumarate	0.024	0.369	0.814	0.883	0.516	1.389	0.565	0.843
+	201.1023	7.3	4-Aminophenyl ether	0.023	0.342	0.006	0.155	0.005	0.134	0.004	0.085
+	867.595	3.7	[PI (18:0/18:0)] 1,2-dioctadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol)	0.023	0.666	0.007	0.578	0.018	0.654	0.035	0.681
-	579.0266	18.9	UDP-glucuronate	0.023	10.278	0.013	6.27	0.024	10.207	0.002	19.225
-	97.04073	14.2	Imidazole-4-methanol	0.023	2.062	0.055	3.65	0.003	4.304	0.008	3.487
-	146.0553	29.3	L-Albizziine	0.023	2.279	0.6	0.764	0.292	2.768	0.008	8.829
-	163.0629	26.9	L-Rhamnose	0.023	3.586	0.118	3.332	0.251	14.523	0.009	4.231
-	157.0509	5	2-Isopropylmaleate	0.023	0.57	0.042	0.63	0.006	0.448	0.025	0.439
-	122.0248	16.8	Nicotinate	0.023	0.121	0.023	0.124	0.018	0.078	0.026	0.14
-	329.2699	19.2	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.023	4.287	0.024	11.22	0.088	17.586	0.035	23.648
-	112.9993	14.3	parabanate	0.023	0.41	0.052	0.515	0.053	0.529	0.087	0.576

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	269.2121	6.1	[FA oxo(16:0)] 3-oxo-hexadecanoic acid	0.023	1.833	0.025	2.603	0.025	2.508	0.093	2.09
-	145.0521	28.9	Adipate	0.023	3.329	0.072	2.205	0.302	5.91	0.176	18.115
-	82.04081	25.2	5-Aminoimidazole	0.023	3.733	0.185	3.288	0.032	5.758	0.292	13.681
-	112.0516	22.5	Creatinine	0.023	0.409	0.214	0.682	0.158	0.622	0.603	0.845
+	746.6063	4.1	PC(16:0/P-18:0)	0.022	1.63	0.215	1.148	0.003	1.534	0.03	1.341
+	796.5885	3.9	PE(18:0/22:4(7Z,10Z,13Z,16Z))	0.022	23.692	0.042	10.293	0.019	18.389	0.113	14.537
-	171.0127	13.3	Toluene-4-sulfonate	0.022	0.446	0.004	0.26	0.003	0.219	0.003	0.218
-	114.0196	12.7	Maleamate	0.022	2.425	0.051	1.813	0.014	1.71	0.003	2.69
-	75.04481	10.3	Propane-1,2-diol	0.022	0.591	0.041	0.711	0.018	0.539	0.003	0.43
-	357.301	17.8	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.022	4.732	0.011	5.111	0.052	11.42	0.007	15.991
-	220.9767	21.2	3-Sulfomuconate	0.022	1.771	0.101	1.707	0.227	2.516	0.015	6.052
-	122.0248	12.1	Nicotinate	0.022	0.155	0.031	0.211	0.042	0.256	0.032	0.214
-	111.0199	15.9	Uracil	0.022	0.26	0.044	0.344	0.03	0.278	0.034	0.323
-	113.0356	11.9	5,6-Dihydrouracil	0.022	3.214	0.037	2.059	0.156	3.66	0.072	2.431
-	91.03993	28.3	Glycerol	0.022	1.277	0.321	1.256	0.18	2.253	0.143	2.083
-	96.96011	18	Sulfate	0.022	1.199	0.147	1.195	0.163	1.108	0.264	1.197
-	103.0037	28.3	Malonate	0.022	0.54	0.71	1.115	0.821	1.098	0.96	0.979
+	810.6013	4	[PC (18:1/20:3)] 1-(9Z-octadecenoyl)-2-(5Z,8Z,11Z-eicosatrienoyl)-sn-glycero-3-phosphocholine	0.021	1.242	0.863	1.01	0.374	1.063	0.001	1.298
+	838.6326	4	[PC (18:0/22:4)] 1-octadecanoyl-2-(7Z,10Z,13Z,16Z-docosatetraenoyl)-sn-glycero-3-phosphocholine	0.021	1.439	0.051	1.205	0.033	1.295	0.004	1.342
+	147.0764	15.6	L-Glutamine	0.021	1.275	0.55	1.062	0.7	0.963	0.577	1.061
+	148.0797	15.6	5-methylthiopentanaldoxime	0.021	1.28	0.501	1.072	0.694	0.961	0.588	1.06
+	203.1391	13.4	Leu-Ala	0.021	1.307	0.591	1.059	0.725	0.965	0.801	1.026
-	357.3008	18.5	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.021	4.524	0.004	7.789	0.012	10.933	0.001	23.456
-	133.0143	28.1	(S)-Malate	0.021	0.415	0.003	0.183	0.006	0.255	0.003	0.205
-	94.02974	29.2	2-Hydroxypyridine	0.021	3.625	0.274	2.119	0.141	5.201	0.01	7.254
-	97.04068	17.5	Imidazole-4-methanol	0.021	2.431	0.011	2.406	0.023	2.233	0.011	2.745
-	116.9285	25.4	chromate	0.021	0.248	0.014	0.251	0.012	0.268	0.012	0.237

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	178.051	20.4	Hippurate	0.021	0.163	0.021	0.157	0.012	0.052	0.014	0.086
-	112.0404	23.1	(S)-1-Pyrroline-5-carboxylate	0.021	2.245	0.007	2.933	0.053	3.496	0.029	4.087
-	99.00873	27.5	2-oxobut-3-enanoate	0.021	2.502	0.358	1.738	0.092	2.761	0.047	2.608
-	154.0263	29.3	N-Methylethanolamine phosphate	0.021	2.177	0.309	4.885	0.37	3.391	0.048	13.622
-	448.307	4.8	Glycodeoxycholate	0.021	1.242	0.203	1.179	0.407	1.097	0.11	1.186
-	91.03996	22.7	Glycerol	0.021	2.833	0.52	0.727	0.054	2.733	0.116	2.527
-	102.056	10.8	4-Aminobutanoate	0.021	0.481	0.081	0.622	0.037	0.552	0.226	0.683
-	112.9992	15.1	parabanate	0.021	0.43	0.346	0.637	0.858	0.92	0.254	0.673
-	122.0359	19.7	Pyrazinamide	0.021	2.137	0.125	1.648	0.004	1.823	0.274	4.179
-	93.03448	29.3	Phenol	0.021	2.984	0.052	2.277	0.152	2.667	0.546	1.365
+	215.0696	15.3	3,4-Dihydroxy-3,4-dihydro-9-fluorenone	0.02	1.445	0.492	1.085	0.504	1.082	0.285	1.172
-	172.9914	6.9	Phenol sulfate	0.02	0.356	0.009	0.271	0.005	0.239	0.005	0.188
-	177.0786	29.4	beta-D-Digitalopyranose	0.02	3.605	0.509	1.285	0.326	16.668	0.007	8.986
-	837.5475	3.7	PI(16:0/18:0)	0.02	1.695	0.368	1.119	0.036	1.321	0.022	1.458
-	122.0359	21.2	Pyrazinamide	0.02	2.863	0.093	1.866	0.232	2.693	0.043	3.286
-	112.0039	28.5	Nitrofuran	0.02	1.956	0.554	0.797	0.202	2.305	0.061	4.966
-	132.0301	28.8	L-Aspartate	0.02	2.091	0.372	1.74	0.276	3.336	0.065	8.916
-	113.0245	7.8	2-Hydroxy-2,4-pentadienoate	0.02	6.448	0.132	1.89	0.188	3.131	0.073	5.183
-	159.0683	29.1	[FA (7:0/2:0)] Heptanedioic acid	0.02	8.833	0.063	3.761	0.084	8.707	0.076	12.337
-	113.0356	15.9	5,6-Dihydrouracil	0.02	2.738	<0.001	3.733	0.053	4.488	0.112	2.006
-	131.0714	29.2	1,1-Diethyl-2-hydroxy-2-nitrosohydrazine	0.02	0.33	0.859	0.948	0.305	0.657	0.272	0.651
-	186.0788	26.1	[FA hydroxy(4:0)] N-(3S-hydroxy-butanoyl)-homoserine lactone	0.02	3.499	0.169	5.199	0.309	13.726	0.323	45.073
-	139.9757	20.1	Carbamoyl phosphate	0.02	2.148	0.546	1.482	0.874	1.06	0.362	2.108
-	133.0143	17.8	(S)-Malate	0.02	0.368	0.037	0.469	0.183	0.65	0.995	0.998
+	206.1388	5.1	Pantothenol	0.019	1.108	0.084	1.084	0.117	1.21	0.004	1.11
+	146.0811	27.1	[FA oxo,amino(6:0)] 3-oxo-5S-amino-hexanoic acid	0.019	0.262	0.017	0.239	0.056	0.375	0.027	0.277
+	411.2495	4.1	[GP (16:0)] 1-hexadecanoyl-2-sn-glycero-3-phosphate	0.019	0.273	0.015	0.235	0.022	0.286	0.036	0.363

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	104.107	26	Choline	0.019	0.437	0.123	0.613	0.154	0.608	0.145	0.621
+	149.0807	15.6	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.019	1.293	0.421	1.088	0.797	0.974	0.548	1.068
+	175.0714	14.2	N-Formimino-L-glutamate	0.019	1.44	0.16	0.701	0.104	0.738	0.89	0.965
-	746.5131	3.9	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.019	1.452	0.236	1.191	<0.001	1.602	<0.001	2.106
-	178.072	11.8	D-Glucosamine	0.019	1.563	0.004	1.673	0.022	1.412	0.003	1.725
-	329.27	24	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.019	6.008	0.002	11.456	0.001	16.667	0.007	23.717
-	172.9914	4.2	Phenol sulfate	0.019	0.122	0.02	0.124	0.016	0.09	0.014	0.065
-	122.0248	29.6	Nicotinate	0.019	0.33	0.066	0.445	0.063	0.453	0.019	0.368
-	836.5442	3.7	PS(18:0/22:5(7Z,10Z,13Z,16Z,19Z))	0.019	1.669	0.36	1.114	0.037	1.316	0.022	1.431
-	153.0308	28.7	Imidazol-5-yl-pyruvate	0.019	4.461	0.157	3.264	0.095	4.727	0.027	8.147
-	139.9757	17.4	Carbamoyl phosphate	0.019	2.293	0.077	3.165	0.001	4.883	0.045	4.1
-	123.0564	29	Methylimidazole acetaldehyde	0.019	2.872	0.823	1.085	0.374	3.058	0.051	5.02
-	115.0036	15	Fumarate	0.019	0.331	0.565	1.253	0.959	1.019	0.057	0.434
-	163.0629	25.7	L-Rhamnose	0.019	2.923	0.31	23.21	0.145	7.269	0.238	7.147
-	129.0305	24.5	3-ureidoacrylate	0.019	2.773	0.045	2.561	0.038	3.398	0.345	4.465
+	286.2013	4.5	2-Octenoylcarnitine	0.018	0.38	0.303	0.76	0.989	1.004	0.212	0.63
-	100.0404	20.3	1-Aminocyclopropane-1-carboxylate	0.018	2.53	0.191	3.511	0.061	2.617	0.004	6.233
-	178.0509	25.4	Hippurate	0.018	0.221	0.015	0.18	0.008	0.076	0.007	0.061
-	329.27	17.6	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.018	2.393	0.018	4.227	<0.001	9.838	0.008	7.458
-	116.9285	25.6	chromate	0.018	0.089	0.025	0.161	0.065	0.265	0.031	0.198
-	101.0356	18.1	N-Formiminoglycine	0.018	2.219	0.012	4.246	0.141	3.293	0.041	3.894
-	116.9285	27.7	chromate	0.018	0.203	0.088	0.377	0.563	0.778	0.043	0.336
-	116.9285	28.4	chromate	0.018	0.203	0.14	0.456	0.851	0.933	0.084	0.413
-	253.2175	13.3	(9Z)-Hexadecenoic acid	0.018	3.081	0.192	2.703	0.207	1.627	0.089	1.899
-	209.0676	28.2	Sedoheptulose	0.018	3.096	0.042	2.514	0.191	8.859	0.148	6.783
-	185.0822	22.1	cis-2-Carboxycyclohexyl-acetic acid	0.018	3.373	0.238	1.432	0.048	2.756	0.153	1.69

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	99.00875	14.7	2-oxobut-3-enanoate	0.018	0.426	0.05	0.5	0.621	0.862	0.308	0.628
-	95.98569	13.9	Phosphoramidate	0.018	1.672	0.042	1.712	0.176	1.932	0.339	4.448
-	159.066	10.3	[FA (7:0/2:0)] Heptanedioic acid	0.018	0.418	0.02	0.475	0.154	0.681	0.383	0.747
-	103.0037	22.8	Malonate	0.018	0.306	0.069	0.446	0.022	0.308	0.618	0.83
-	147.0664	17.1	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.017	0.218	0.015	0.204	0.008	0.104	0.016	0.208
-	149.0358	29.8	alpha-Fluoro-beta-ureidopropionic acid	0.017	2.597	0.193	2.293	0.101	3.998	0.04	13.802
-	138.031	26.4	2-amino-4-carboxypyrimidine	0.017	4.507	0.005	4.378	0.157	5.838	0.065	8.458
-	105.0193	10.2	D-Glycerate	0.017	0.326	0.852	0.903	0.015	0.286	0.091	0.49
-	173.0473	29.8	Shikimate	0.017	3.457	0.254	7.505	0.31	4.339	0.159	15.529
-	135.03	21.2	[FA trihydroxy(4:0)] 2,3,4-trihydroxy-butanoic acid	0.017	2.374	0.059	2.939	0.07	1.945	0.554	1.291
+	130.9665	3.2	2,2-Dichloro-1,1-ethanediol	0.016	1.248	0.009	1.34	0.004	1.27	0.001	1.329
-	132.0125	8.7	L-thiazolidine-4-carboxylate	0.016	3.767	0.013	4.296	0.003	4.966	<0.001	9.583
-	82.04082	22.3	5-Aminoimidazole	0.016	2.168	0.08	1.97	0.011	5.167	0.01	7.771
-	329.27	19.6	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.016	4.623	0.004	7.229	0.012	13.206	0.015	36.561
-	347.2441	4.2	[FA hydroxy(4:0/18:0)] 9,10,12,13-tetrahydroxy-octadecanoic acid	0.016	0.428	0.003	0.272	0.01	0.391	0.016	0.421
-	122.0247	29	Nicotinate	0.016	0.223	0.022	0.265	0.019	0.221	0.017	0.226
-	152.0462	26.3	N-Dimethyl-2-aminoethylphosphonate	0.016	2.644	0.128	2.372	0.153	3.951	0.128	6.179
-	122.0359	26	Pyrazinamide	0.016	2.758	0.3	2.51	0.132	2.508	0.155	4.21
-	131.0714	22.6	1,1-Diethyl-2-hydroxy-2-nitrosohydrazine	0.016	0.528	0.339	0.846	0.612	1.218	0.741	0.888
+	134.0811	28.5	1-deoxyxylonojirimycin	0.015	0.388	0.006	0.367	0.002	0.251	0.001	0.177
+	132.0655	5.4	L-Glutamate 5-semialdehyde	0.015	0.109	0.018	0.14	0.012	0.065	0.02	0.157
+	570.3553	4.5	LysoPC(22:5(4Z,7Z,10Z,13Z,16Z))	0.015	1.532	0.402	0.816	0.389	1.158	0.021	1.614
+	174.0874	15.2	5-Guanidino-2-oxopentanoate	0.015	1.589	0.782	1.063	0.981	1.004	0.714	1.096
-	133.0143	27.2	(S)-Malate	0.015	0.49	0.042	0.431	0.008	0.386	<0.001	0.213
-	187.0072	4.4	4-Sulfobenzyl alcohol	0.015	0.515	0.003	0.363	0.001	0.252	0.001	0.275
-	97.04068	9.8	Imidazole-4-methanol	0.015	2.584	0.056	3.346	0.057	3.989	0.001	3.085
-	188.0751	4.7	Prenyl-L-cysteine	0.015	6.106	0.01	7.997	0.012	6.405	0.003	15.296

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	329.27	12.5	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.015	3.418	0.005	6.943	<0.001	13.193	0.005	20.304
-	150.0562	22.1	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.015	0.285	0.028	0.357	0.004	0.11	0.005	0.124
-	116.9285	19.9	chromate	0.015	0.19	0.006	0.083	0.007	0.111	0.005	0.061
-	116.9285	17.2	chromate	0.015	0.234	0.009	0.169	0.007	0.145	0.005	0.086
-	152.0463	27.7	N-Dimethyl-2-aminoethylphosphonate	0.015	5.045	0.023	3.18	0.084	11.196	0.012	7.053
-	199.0976	23.9	[FA (10:1/2:0)] 2E-Decenedioic acid	0.015	3.161	0.03	2.296	0.008	2.06	0.013	2.961
-	469.1303	21.7	[Fv] Didymocalyxin B	0.015	1.882	0.302	1.464	<0.001	2.969	0.016	3.73
-	480.3098	7.5	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	0.015	1.431	0.02	0.786	0.924	1.007	0.016	1.391
-	122.0248	19.1	Nicotinate	0.015	0.22	0.016	0.226	0.017	0.221	0.022	0.254
-	96.00904	27.4	Maleimide	0.015	3.961	0.007	6.098	0.089	6.091	0.059	6.88
-	134.0359	22.3	3-N4-ethenocytosine	0.015	1.67	0.294	3.849	0.042	11.444	0.085	5.117
-	131.0462	15.9	L-Asparagine	0.015	1.556	0.008	1.554	0.083	1.34	0.108	1.354
-	124.0152	26.9	(2-Aminoethyl)phosphonate	0.015	2.352	0.394	1.82	0.095	5.444	0.118	8.596
+	176.0918	29.8	Calystegin B2	0.014	0.513	0.003	4.04	0.682	0.774	0.001	0.219
+	424.342	4.6	Linoelaidylcarnitine	0.014	2.657	0.511	1.228	0.06	1.777	0.029	2.388
+	374.2384	5	Leu-Lys-Asn	0.014	0.654	0.177	0.823	0.74	0.942	0.174	1.141
+	171.0764	15.6	acetonitrile adduct of pyrroline carboxylate	0.014	1.317	0.654	1.05	0.889	0.986	0.356	1.108
-	331.0461	19	2'-Deoxyinosine 5'-phosphate	0.014	0.639	0.794	0.917	0.012	0.54	0.001	0.404
-	146.0249	3.6	Indole-5,6-quinone	0.014	0.72	0.015	0.623	0.017	0.526	0.001	0.359
-	143.0348	28.1	2,3-Dimethylmaleate	0.014	0.458	0.021	0.437	0.025	0.573	0.002	0.364
-	213.1862	24.6	CAI-1	0.014	2.768	0.286	2.766	0.402	1.751	0.005	3.468
-	191.02	23.1	Citrate	0.014	0.332	0.009	0.311	0.004	0.194	0.008	0.279
-	333.2072	15.7	Prostaglandin A2	0.014	4.152	0.037	9.001	0.001	9.366	0.009	40.807
-	123.0564	27.7	Methylimidazole acetaldehyde	0.014	3.632	0.009	2.539	0.239	17.439	0.016	5.795
-	124.0404	28.1	N-Ethylmaleimide	0.014	3.608	0.155	3.157	0.222	2.23	0.017	1.865
-	357.3011	20.2	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.014	8.833	0.024	15.394	0.02	20.016	0.025	35.388
-	82.0408	28.8	5-Aminoimidazole	0.014	2.835	0.101	2.803	0.03	5.962	0.051	10.191

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	151.0399	27.6	[PK] 6-Methylsalicylic acid	0.014	0.463	0.198	0.702	0.28	1.883	0.057	0.6
-	177.0926	16.6	Eugenol methyl ether	0.014	0.32	0.37	0.75	0.445	0.743	0.072	0.575
-	95.98567	25.1	Phosphoramidate	0.014	3.135	0.497	1.432	0.191	8.161	0.13	1.784
-	100.004	23	oxazoladindione	0.014	2.017	0.01	3.448	0.088	3.67	0.191	8.822
-	138.0672	29.3	L-Histidinal	0.014	4.329	0.126	3.963	0.305	8.101	0.228	10.597
+	100.1121	3.9	Cyclohexylamine	0.013	0.409	0.005	0.325	0.012	0.429	<0.001	0.118
+	705.5812	4.3	[ST (20:4)] cholest-5-en-3beta-yl (15S-hydroperoxy-5Z,8Z,12E,14Z-eicosatetraenoate)	0.013	1.646	0.078	1.218	0.009	1.412	0.003	1.493
+	153.0771	10.9	Xylitol	0.013	0.778	0.003	0.666	<0.001	0.603	0.004	0.719
+	545.3431	4.6	Glu-Leu-Lys-Arg	0.013	1.53	0.707	0.931	0.94	1.014	0.013	1.701
+	232.1544	9.2	O-Butanoylcarnitine	0.013	1.396	0.619	1.063	0.91	0.986	0.052	1.267
+	522.3553	7.5	1-Oleoylglycerophosphocholine	0.013	1.271	0.064	0.825	0.107	1.125	0.462	1.071
-	116.9286	10.6	chromate	0.013	0.409	0.264	0.725	0.001	0.119	0.001	0.156
-	97.0407	5.6	Imidazole-4-methanol	0.013	2.305	0.016	2.511	0.033	1.769	0.007	4.208
-	127.0149	11.1	Barbiturate	0.013	0.42	0.007	0.333	0.266	0.784	0.008	0.37
-	365.3427	3.8	[FA (24:0)] 15Z-tetracosenoic acid	0.013	0.653	0.001	0.434	0.003	0.555	0.021	0.645
-	202.0735	27.6	N2-Acetyl-L-aminoadipate	0.013	2.666	0.19	5.448	0.22	10.247	0.082	7.851
-	149.036	28.8	alpha-Fluoro-beta-ureidopropionic acid	0.013	2.127	0.229	1.702	0.329	9.125	0.133	7.466
-	123.02	21.8	pyrazinoate	0.013	2.171	0.092	2.158	0.003	3.86	0.138	6.756
-	357.3011	22.8	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.013	4.668	0.012	6.747	0.074	25.156	0.158	22.905
-	99.01996	5.2	Hydantoin	0.013	2.024	0.014	2.11	0.029	2.61	0.191	2.016
-	201.1132	19	[FA (10:0/2:0)] Decanedioic acid	0.013	1.944	0.494	0.788	0.348	1.428	0.196	1.503
-	98.03589	26.2	fragment of guanidino acetate	0.013	2.471	0.06	4.435	0.259	8.501	0.287	33.788
-	149.061	22.9	Phenylpropanoate	0.013	0.318	0.019	0.311	0.023	0.325	0.577	0.788
+	110.0601	29.8	4-Hydroxyaniline	0.012	0.806	0.423	2.106	0.491	1.679	0.001	0.709
+	532.3546	3.7	Arg-Lys-Lys-Thr	0.012	0.637	0.001	0.466	0.001	0.299	0.003	0.598
-	86.02455	17.1	2-Aminoacrylate	0.012	3.607	0.092	7.849	0.001	4.94	<0.001	6.375
-	160.0442	5	allylcysteine	0.012	4.239	0.028	3.932	0.081	2.399	0.005	8.73

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	151.0397	13.5	[PK] 6-Methylsalicylic acid	0.012	0.316	0.027	0.467	0.002	0.192	0.006	0.303
-	178.051	11	Hippurate	0.012	0.146	0.011	0.137	0.013	0.154	0.009	0.104
-	127.0149	16.9	Barbiturate	0.012	0.317	0.006	0.22	0.004	0.19	0.011	0.271
-	100.0041	13.1	oxazoladindione	0.012	2.564	0.069	3.375	0.04	2.667	0.019	5.114
-	116.9285	26.1	chromate	0.012	0.174	0.566	0.661	0.064	0.418	0.027	0.264
-	91.03995	22.4	Glycerol	0.012	3.933	0.819	1.146	0.031	3.781	0.029	3.801
-	136.0515	25.1	Isoniazid	0.012	2.043	<0.001	3.979	0.004	6.945	0.151	5.524
-	101.0356	18.3	N-Formiminoglycine	0.012	2.293	0.275	2.078	0.223	2.955	0.209	2.264
-	202.0735	28.9	N2-Acetyl-L-aminoadipate	0.012	3.279	0.41	2.19	0.12	4.526	0.22	13.86
-	82.0408	25.5	5-Aminoimidazole	0.012	2.875	0.089	2.688	0.156	2.197	0.27	8.694
-	127.015	23.7	Barbiturate	0.012	0.435	<0.001	0.276	<0.001	0.243	0.439	0.607
+	751.5474	3.9	[PG (17:0/17:0)] 1,2-diheptadecanoyl-sn-glycero-3-phospho-(1'-sn-glycerol)	0.011	1.183	0.036	1.151	<0.001	1.226	0.001	1.217
+	703.5751	4.3	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphocholine	0.011	1.761	0.044	1.267	0.003	1.491	0.004	1.56
+	544.3396	4.6	LysoPC(20:4(5Z,8Z,11Z,14Z))	0.011	1.377	0.228	0.824	0.914	1.014	0.022	1.491
+	130.0499	15.6	L-1-Pyrroline-3-hydroxy-5-carboxylate	0.011	1.315	0.73	1.035	0.62	0.953	0.843	1.021
-	112.0404	11.3	(S)-1-Pyrroline-5-carboxylate	0.011	2.257	0.026	1.696	0.009	2.137	0.003	3.968
-	133.0521	29.8	Deoxyribose	0.011	3.658	0.295	2.112	0.426	2.078	0.006	4.729
-	91.03994	25.8	Glycerol	0.011	2.219	0.066	2.353	0.075	2.108	0.007	2.393
-	109.0407	5.2	Imidazole-4-acetaldehyde	0.011	1.971	0.046	1.723	0.203	2.441	0.007	2.473
-	147.0454	24.6	trans-Cinnamate	0.011	0.296	0.217	0.663	0.021	0.367	0.016	0.316
-	180.0416	29.2	Phosphinothricin	0.011	2.858	0.269	2.051	0.328	42.159	0.033	29.246
-	100.0404	26.3	1-Aminocyclopropane-1-carboxylate	0.011	2.17	0.189	2.091	0.016	3.468	0.079	3.036
-	132.0567	25.8	2-Aminobenzimidazole	0.011	3.805	0.106	3.654	0.205	4.953	0.083	7.598
-	88.04025	9.1	L-Alanine	0.011	0.544	0.145	0.665	0.856	0.953	0.109	0.755
-	127.0149	29.8	Barbiturate	0.011	0.748	0.071	4.375	0.395	0.904	0.176	3.156
-	138.0673	25.4	L-Histidinal	0.011	2.27	0.154	7.342	0.068	10.145	0.249	17.087
-	102.056	14.4	4-Aminobutanoate	0.011	0.196	0.086	0.44	0.03	0.319	0.362	0.732

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	187.0974	16.6	Azelaic acid	0.011	0.311	0.741	0.875	0.902	1.034	0.479	1.301
+	689.5596	4.3	[SP (18:0/14:0)] N-(octadecanoyl)-tetradecasphing-4-enine-1-phosphoethanolamine	0.01	1.369	0.442	1.045	0.077	1.137	0.001	1.221
+	716.5584	4.1	PC(14:0/P-18:1(11Z))	0.01	0.46	0.011	0.534	0.47	0.913	0.167	0.734
+	159.0764	16.5	4-Methylene-L-glutamine	0.01	1.339	0.004	1.278	0.011	1.172	0.2	1.204
-	108.0125	15.6	Hypotaurine	0.01	15.805	0.43	1.632	0.032	7.069	<0.001	26.778
-	160.044	7.6	allylcysteine	0.01	4.181	0.017	3.938	0.007	4.081	0.001	9.222
-	127.0513	29.4	5,6-Dihydrothymine	0.01	3.801	0.06	3.804	0.043	2.675	0.015	7.405
-	220.9767	19.1	3-Sulfomuconate	0.01	2.156	0.135	2.923	0.106	3.053	0.017	7.714
-	91.02196	15	methylmercaptoethanol	0.01	2.648	0.025	4.029	0.006	2.742	0.079	3.771
-	209.0678	28.4	Sedoheptulose	0.01	4.036	0.11	4.741	0.077	6.487	0.168	13.619
-	189.0784	29	(R)-3-((R)-3-Hydroxybutanoyloxy)butanoate	0.01	2.836	0.527	1.593	0.349	2.703	0.237	12.809
-	85.02931	7.6	Diacetyl	0.01	0.516	0.238	0.779	0.029	0.571	0.259	0.841
-	127.0401	26.2	(4E)-2-Oxohexenoic acid	0.01	0.416	0.127	0.593	0.04	0.454	0.274	0.752
-	75.04475	29.4	Propane-1,2-diol	0.01	1.983	0.232	1.445	0.499	1.251	0.275	1.414
+	176.0918	17.5	Calystegin B2	0.009	0.026	0.009	0.012	0.009	0.009	0.008	0.005
+	314.165	15.1	ethidium	0.009	0.263	0.018	0.365	0.028	0.377	0.011	0.265
+	260.1969	21.2	Leu-Lys	0.009	0.762	<0.001	0.529	0.001	0.578	0.049	0.822
+	297.0567	18.2	Disulfiram	0.009	1.575	0.867	0.977	0.132	1.247	0.063	1.364
+	748.5879	4.1	[PE (16:0/20:0)] 1-hexadecanoyl-2-eicosanoyl-sn-glycero-3-phosphoethanolamine	0.009	5.782	0.255	2.082	0.087	3.008	0.099	2.931
+	764.5583	4	PC(18:4(6Z,9Z,12Z,15Z)/P-18:1(11Z))	0.009	0.549	0.075	0.7	0.077	0.613	0.141	0.801
+	353.1359	4.4	Cotinineglucuronide	0.009	1.392	0.236	1.141	0.64	1.045	0.343	1.096
+	398.217	4.2	Echimidine	0.009	1.371	0.799	0.922	0.245	1.227	0.348	5.2
+	198.1126	7.6	L-Metanephrine	0.009	0.726	0.432	1.457	0.005	0.613	0.583	1.443
-	172.9914	7.4	Phenol sulfate	0.009	0.398	0.002	0.196	0.001	0.174	0.001	0.141
-	127.015	9.8	Barbiturate	0.009	0.513	0.002	0.405	0.002	0.371	0.002	0.461
-	774.5454	3.9	[PE (18:1/22:6)] 1-(1Z-octadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.009	1.596	0.013	1.66	0.11	1.598	0.006	1.642

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	97.04071	5.9	Imidazole-4-methanol	0.009	2.478	0.039	2.312	0.009	3.744	0.013	3.48
-	213.1862	19.5	CAI-1	0.009	3.443	0.215	1.994	0.053	2.944	0.015	4.234
-	269.2488	12.2	[FA (17:0)] heptadecanoic acid	0.009	3.64	0.074	4.846	0.031	3.94	0.016	6.302
-	790.5399	4.2	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.009	7.887	0.621	1.14	0.112	2.084	0.02	4.217
-	616.4709	4.3	[SP (16:0)] N-(hexadecanoyl)-sphing-4-enine-1-phosphate	0.009	3.902	0.027	2.416	0.345	1.504	0.057	2.842
-	161.0449	27.1	2-Dehydro-3-deoxy-L-rhamnonate	0.009	0.346	0.369	0.776	0.544	2.066	0.107	0.571
-	139.015	26.2	2-hydroxy-4-carboxypyrimidine	0.009	1.976	0.016	3.659	0.099	1.777	0.169	5.747
-	127.0206	26.6	[FA (9:1/3:0)] 2-nonene-4,6,8-triynal	0.009	2.067	0.142	1.561	0.285	2.363	0.471	1.25
-	97.02941	27.1	[FA (5:2)] 2,4-pentadienoic acid	0.009	0.35	0.457	0.784	0.076	0.568	0.563	1.227
-	116.9286	22.5	chromate	0.009	0.3	0.949	1.057	0.086	0.571	0.67	1.428
-	204.0304	13.9	Xanthurenic acid	0.009	0.439	0.305	0.767	0.575	0.845	0.739	0.894
-	102.056	21.8	4-Aminobutanoate	0.009	0.395	0.04	0.648	0.783	0.912	0.818	1.078
+	762.5279	3.8	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	0.008	2.333	0.036	1.438	0.001	1.962	0.007	1.712
+	788.5438	3.8	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.008	1.881	0.353	1.133	0.003	1.566	0.008	1.581
+	251.1641	7.5	Xanthoxin	0.008	1.258	0.02	1.215	0.006	1.272	0.008	1.256
+	186.1126	26.5	Ecgonine	0.008	0.172	0.653	0.856	0.939	0.974	0.575	1.249
-	121.0407	7.6	Nicotinamide	0.008	1.815	0.061	1.695	0.001	1.874	0.001	2.456
-	147.0664	14.3	[FA methyl,hydroxy(5:0)] 3R-methyl-3,5-dihydroxy-pentanoic acid	0.008	0.294	0.007	0.256	0.002	0.165	0.001	0.102
-	861.5491	3.8	[PI (18:0/18:0)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.008	2.698	0.006	2.505	0.005	3.206	0.002	2.865
-	127.0513	29.1	5,6-Dihydrothymine	0.008	4.776	0.107	3.299	0.326	11.511	0.006	8.281
-	123.0564	28.5	Methylimidazole acetaldehyde	0.008	2.166	0.301	2.097	0.235	7.256	0.024	5.119
-	101.0356	22.3	N-Formiminoglycine	0.008	2.863	0.025	3.032	0.002	4.947	0.029	5.345
-	116.9285	23.7	chromate	0.008	0.244	0.641	0.853	0.296	0.743	0.037	0.413
-	329.27	23.7	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.008	4.3	0.011	14.845	0.147	50.422	0.043	27.863
-	96.00904	25.7	Maleimide	0.008	2.897	0.263	3.523	0.049	4.882	0.124	2.444

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	329.27	19.9	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.008	3.186	0.006	11.98	0.001	11.999	0.13	50.17
-	107.0502	26.9	Benzyl alcohol	0.008	2.201	0.06	3.074	0.114	3.211	0.267	7.981
-	115.0036	14.8	Fumarate	0.008	0.223	0.832	1.084	0.555	0.814	0.359	0.636
-	143.0348	28.4	2,3-Dimethylmaleate	0.008	0.43	0.662	0.89	0.193	0.636	0.537	0.843
+	482.3241	4.6	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	0.007	1.456	0.327	0.902	0.777	1.03	0.011	1.38
+	213.0749	27.4	n-Propyl gallate	0.007	1.469	0.161	1.284	0.249	1.217	0.064	1.362
+	134.064	15.9	4-methylthiobutanaldoxime	0.007	1.731	0.008	1.595	0.153	1.327	0.219	1.321
-	97.0407	3.5	Imidazole-4-methanol	0.007	1.625	0.009	2.037	0.014	1.905	<0.001	2.397
-	144.0125	8	3,4-Dehydrothiomorpholine-3-carboxylate	0.007	7.152	0.051	4.935	0.048	4.349	<0.001	16.994
-	786.5286	3.7	[PS (18:1/18:1)] 1,2-di-(9E-octadecenoyl)-sn-glycero-3-phosphoserine	0.007	2.095	0.055	1.331	<0.001	1.754	0.002	1.854
-	178.0508	11.8	Hippurate	0.007	0.131	0.006	0.094	0.005	0.084	0.006	0.091
-	150.0562	4	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.007	0.123	0.013	0.216	0.004	0.038	0.009	0.173
-	127.015	10.7	Barbiturate	0.007	0.297	0.012	0.41	0.046	0.478	0.038	0.513
-	129.0192	29.8	Mesaconate	0.007	0.401	0.024	0.659	0.085	0.742	0.052	0.623
-	155.0466	27.3	4-Imidazolone-5-propanoate	0.007	3.911	0.109	3.875	0.377	3.511	0.094	3.423
-	153.0308	29.1	Imidazol-5-yl-pyruvate	0.007	4.811	0.016	7.36	0.358	5.003	0.173	23.817
-	108.0203	26.2	Benzosemiquinone	0.007	4.371	0.072	3.659	0.001	3.685	0.186	10.065
-	161.0471	25.5	2-Dehydro-3-deoxy-L-rhamnonate	0.007	0.474	0.05	0.709	0.895	0.966	0.655	1.259
+	147.0304	8	2-Oxoglutarate	0.006	5.772	0.159	3.381	0.056	4.024	<0.001	14.316
+	146.027	8	3,4-Dehydrothiomorpholine-3-carboxylate	0.006	4.21	0.077	2.774	0.041	2.708	<0.001	7.756
+	162.0583	7.6	allylcysteine	0.006	3.556	0.021	3.169	0.007	3.192	0.001	6.724
+	162.0761	4.4	L-2-Aminoadipate	0.006	0.078	0.005	0.056	0.006	0.072	0.005	0.053
+	189.0871	14	N-Acetylglutamine	0.006	1.514	0.245	0.768	0.898	1.02	0.122	1.378
+	133.0607	15.9	L-Asparagine	0.006	1.616	0.01	1.5	0.069	1.347	0.169	1.296
+	251.1641	3.8	Xanthoxin	0.006	2.091	0.03	1.985	0.027	2.277	0.363	1.515
-	662.1019	14.6	NAD+	0.006	1.707	0.006	1.919	<0.001	2.53	<0.001	3.129

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	764.5637	4.4	[PC (P-16:0/20:4)] 1-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.006	1.856	0.01	1.54	0.002	1.71	<0.001	1.987
-	220.9768	23.5	3-Sulfomuconate	0.006	1.893	0.03	2.712	0.042	5.537	<0.001	4.435
-	112.9992	25	parabanate	0.006	0.406	0.078	0.618	0.002	0.335	0.001	0.288
-	146.0459	15.1	L-Glutamate	0.006	1.358	0.854	0.98	0.089	1.208	0.001	1.487
-	835.5321	3.7	[PI (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-myo-inositol)	0.006	1.922	0.146	1.188	0.014	1.419	0.002	1.648
-	120.0665	16.2	Tromethamine	0.006	2.519	0.067	3.041	0.065	2.495	0.005	4.089
-	237.0882	29.5	Gly-Tyr	0.006	0.135	0.002	0	0.009	0.171	0.013	0.234
-	145.0505	25.8	Adipate	0.006	0.327	0.017	0.493	0.699	0.797	0.014	0.353
-	202.0735	29.2	N2-Acetyl-L-aminoadipate	0.006	4.582	0.138	2.242	0.283	27.381	0.022	12.95
-	111.0199	20.9	Uracil	0.006	0.225	0.012	0.322	0.063	0.463	0.033	0.325
-	469.1303	22.7	[Fv] Didymocalyxin B	0.006	3.416	0.033	3.17	0.032	3.351	0.037	3.142
-	269.2488	25.7	[FA (17:0)] heptadecanoic acid	0.006	2.1	0.112	2.798	0.046	3.456	0.114	2.028
-	120.0666	4.2	Tromethamine	0.006	2.074	0.025	2.173	0.102	4.042	0.165	8.622
-	118.0145	29.3	Aminomalonate	0.006	2.516	0.055	1.708	0.002	3.125	0.171	3.768
-	131.0825	27.4	L-Ornithine	0.006	1.894	0.282	1.318	0.989	0.995	0.175	1.465
-	187.0625	26	2-oxosuberate	0.006	2.147	0.352	5.949	0.19	7.661	0.301	14.137
-	469.1304	23.9	[Fv] Didymocalyxin B	0.006	0.514	0.428	1.307	0.232	1.488	0.441	1.346
-	157.0518	26.4	2-Isopropylmaleate	0.006	0.497	0.948	0.981	0.018	0.583	0.449	3.678
+	161.1285	24.5	N6-Methyl-L-lysine	0.005	1.308	0.032	0.793	0.201	0.881	<0.001	1.625
+	162.0583	5	allylcysteine	0.005	6.662	0.025	5.026	0.016	4.794	<0.001	11.075
+	148.0426	7.6	Thiomorpholine 3-carboxylate	0.005	3.288	0.041	2.828	0.014	2.824	0.001	5.882
+	190.0897	4.7	Prenyl-L-cysteine	0.005	3.347	0.027	3.106	0.008	2.738	0.002	6.009
+	110.0601	29.3	4-Hydroxyaniline	0.005	0.665	0.012	0.81	0.612	1.298	0.003	0.594
+	675.544	4.3	SM(d18:1/14:0)	0.005	1.214	0.734	0.985	0.196	1.074	0.003	1.181
+	744.5905	4	1-Hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphonocholine	0.005	1.42	0.413	1.075	0.001	1.394	0.005	1.265
+	241.1547	10.6	Slaframine	0.005	0.701	<0.001	0.396	<0.001	0.402	0.006	0.726

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	508.3762	4.7	[PC (18:1)] 1-(11Z-octadecenyl)-sn-glycero-3-phosphocholine	0.005	0.702	0.002	0.63	0.005	0.693	0.01	0.502
+	268.104	9.5	Neuraminic acid	0.005	0.617	0.678	0.881	0.055	0.759	0.014	0.721
+	454.2932	7.6	[PE (16:0)] 1-hexadecanoyl-sn-glycero-3-phosphoethanolamine	0.005	1.799	0.619	0.925	0.003	1.615	0.016	1.753
+	133.0971	24	L-Ornithine	0.005	1.17	0.013	1.145	0.025	1.103	0.019	1.185
+	145.0972	5.2	L-isoglutamine	0.005	0.676	0.06	0.759	0.793	1.025	0.261	0.841
-	773.533	3.7	[PG (18:1/18:1)] 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.005	2.413	0.04	2.146	<0.001	4.089	<0.001	4.008
-	722.5128	4.5	PE(18:3(6Z,9Z,12Z)/P-18:1(11Z))	0.005	1.562	0.867	0.965	0.224	1.287	<0.001	1.831
-	178.051	25.8	Hippurate	0.005	0.211	0.006	0.229	0.001	0.057	0.001	0.054
-	116.9286	10.4	chromate	0.005	0.23	0.016	0.376	0.003	0.179	0.001	0.064
-	95.98567	26.9	Phosphoramidate	0.005	8.215	0.014	6.92	0.005	7.52	0.001	9.465
-	480.3097	4.6	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	0.005	1.402	0.061	0.837	0.842	0.984	0.001	1.438
-	357.301	25.3	[GL (18:0)] 1-octadecanoyl-rac-glycerol	0.005	5.426	0.01	12.437	0.004	27.939	0.002	32.901
-	151.0401	7.1	[PK] 6-Methylsalicylic acid	0.005	0.337	0.4	0.821	0.006	0.467	0.002	0.395
-	146.0249	8.2	Indole-5,6-quinone	0.005	0.318	0.159	0.635	0.012	0.316	0.003	0.242
-	146.0248	16	Indole-5,6-quinone	0.005	0.4	0.087	0.641	0.512	2.022	0.003	0.334
-	220.9767	28.8	3-Sulfomuconate	0.005	2.77	0.052	2.95	0.116	3.961	0.004	6.051
-	760.5125	3.8	[PS (16:0/18:1)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoserine	0.005	2.388	0.075	1.392	0.001	2.068	0.009	1.821
-	130.0508	16.6	L-Glutamate 5-semialdehyde	0.005	0.313	0.021	0.522	0.032	0.452	0.013	0.507
-	86.02458	3.4	2-Aminoacrylate	0.005	1.81	0.008	2.286	0.007	1.893	0.014	2.086
-	173.083	29.2	Suberic acid	0.005	3.015	0.057	2.613	0.315	20.535	0.015	25.384
-	116.9285	24.5	chromate	0.005	0.171	0.041	0.389	0.039	0.473	0.02	0.393
-	127.0401	27	(4E)-2-Oxohexenoic acid	0.005	2.749	0.295	1.662	0.138	2.104	0.022	2.907
-	209.0679	28.8	Sedoheptulose	0.005	12.853	0.186	8.352	0.154	12.084	0.045	22.694
-	145.0506	17.2	Adipate	0.005	0.461	0.562	0.85	0.751	1.221	0.051	0.716
-	107.0502	28.9	Benzyl alcohol	0.005	0.378	0.236	1.603	0.311	4.77	0.064	5.287
-	213.1861	26.2	CAI-1	0.005	2.382	0.07	5.691	0.073	4.412	0.119	4.043

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	86.02455	24.4	2-Aminoacrylate	0.005	2.29	0.028	2.482	0.183	5.925	0.185	8.083
-	187.0625	25.6	2-oxosuberate	0.005	3.905	0.295	9.813	0.241	12.882	0.265	16.699
-	112.004	27.7	Nitrofuran	0.005	3.001	0.27	2.879	0.145	6.795	0.331	4.288
-	433.1405	3.7	Asp-Thr-Cys-Pro	0.005	0.295	<0.001	0.106	<0.001	0.082	0.78	1.146
+	154.1226	15.6	Pseudopelletierine	0.004	0.5	0.385	5.214	0.004	0.488	<0.001	0.353
+	766.5596	3.7	[PG (16:0/18:0)] 1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol) (ammonium salt)	0.004	2.156	<0.001	1.927	<0.001	2.119	<0.001	1.865
+	720.5544	4.1	[PC (15:0/16:0)] 1-pentadecanoyl-2-hexadecanoyl-sn-glycero-3-phosphocholine	0.004	2.518	0.002	1.648	<0.001	2.209	0.002	1.92
+	260.1856	7.6	[FA (6:0)] O-hexanoyl-R-carnitine	0.004	0.538	0.513	0.842	0.012	0.512	0.013	0.631
+	792.5908	4	PC(20:4(5Z,8Z,11Z,14Z)/P-18:1(11Z))	0.004	0.799	<0.001	0.641	0.001	0.744	0.019	0.856
+	494.324	4.8	[PC (16:0)] 1-(9Z-hexadecenoyl)-sn-glycero-3-phosphocholine	0.004	1.508	0.914	0.984	0.019	1.374	0.051	1.43
-	127.015	24.1	Barbiturate	0.004	0.382	0.001	0.464	<0.001	0.351	<0.001	0.371
-	111.0199	17.8	Uracil	0.004	0.439	0.003	0.383	0.003	0.307	0.001	0.238
-	187.0072	3.3	4-Sulfobenzyl alcohol	0.004	0.308	0.006	0.364	0.006	0.311	0.001	0.131
-	834.5287	3.7	[PS (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoserine	0.004	1.92	0.165	1.17	0.008	1.458	0.001	1.755
-	787.5317	3.7	[PG (8:0/8:0)] 1-(8-[5]-ladderane-octanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.004	2.286	0.85	0.953	0.003	1.862	0.018	1.722
-	78.95872	19	Phosphite	0.004	6.522	0.793	1.313	0.009	4.621	0.019	6.283
-	329.2699	26.9	[GL (16:0)] 1-hexadecanoyl-rac-glycerol	0.004	7.187	0.058	6.53	0.004	6.495	0.032	16.662
-	112.0404	27.8	(S)-1-Pyrroline-5-carboxylate	0.004	4.301	0.037	4.519	0.047	7.186	0.043	8.919
-	175.0475	8.7	Allantoate	0.004	1.567	0.031	1.54	0.38	1.268	0.046	1.61
-	201.1134	5.3	[FA (10:0/2:0)] Decanedioic acid	0.004	2.087	0.076	1.759	0.272	1.702	0.081	2.283
-	123.0563	27.9	Methylimidazole acetaldehyde	0.004	4.646	0.004	4.439	0.221	24.437	0.117	11.573
-	101.0608	7.6	Pentanoate	0.004	2.08	0.237	1.568	0.969	1.014	0.165	0.572
-	293.1753	4	[6]-Gingerol	0.004	0.506	0.002	0.434	0.001	0.372	0.214	0.801
-	91.02192	29.8	methylmercaptoethanol	0.004	1.163	<0.001	1.362	0.317	6.916	0.311	7.477

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	130.0508	24.9	L-Glutamate 5-semialdehyde	0.004	0.601	0.75	1.085	0.972	0.996	0.644	0.887
+	177.0775	4.9	(2S)-2-Isopropylmalate	0.003	7.437	0.01	5.517	0.008	5.107	<0.001	9.942
+	774.6014	4	[PE (16:0/22:1)] 1-hexadecanoyl-2-(13Z-docosenoyl)-sn-glycero-3-phosphoethanolamine	0.003	2.211	0.004	1.438	<0.001	1.844	<0.001	1.888
+	146.027	6.4	3,4-Dehydrothiomorpholine-3-carboxylate	0.003	10.84	0.052	6.413	0.07	4.491	<0.001	13.323
+	129.0658	7.5	5,6-Dihydrothymine	0.003	0.364	0.024	0.644	0.05	0.66	0.011	0.457
+	176.1031	16.5	L-Citrulline	0.003	1.482	0.135	1.188	0.338	1.121	0.036	1.371
-	747.5175	3.7	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.003	1.981	<0.001	1.703	<0.001	1.966	<0.001	2.032
-	150.0562	20.4	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.003	0.368	<0.001	0.196	<0.001	0.082	<0.001	0.078
-	506.9923	16.7	[GP (2:0)] 1',3'-Bis-(1,2-diacyl-sn-glycero-3-phospho)-sn-glycerol	0.003	3.315	0.517	0.724	0.004	3.075	<0.001	5.475
-	99.01992	28.9	Hydantoin	0.003	3.758	0.13	8.447	0.247	6.172	0.007	10.934
-	115.0512	29.8	Diacetylhydrazine	0.003	3.456	0.05	4.221	0.001	5.599	0.026	6.027
-	136.0513	12.1	Isoniazid	0.003	3.015	0.041	3.263	0.006	3.093	0.034	4.497
-	435.2518	4.6	LPA(0:0/18:1(9Z))	0.003	1.23	0.877	0.984	0.045	1.147	0.164	1.144
-	116.9285	23.4	chromate	0.003	0.15	0.038	0.422	0.288	0.729	0.182	0.572
-	143.0714	13.2	trans-4-Hydroxycyclohexanecarboxylate	0.003	0.482	0.653	0.846	0.356	3.705	0.191	0.628
-	124.0152	29.8	(2-Aminoethyl)phosphonate	0.003	2.632	0.047	3.039	0.26	5.677	0.21	10.254
-	110.036	22.3	Cytosine	0.003	0.324	0.716	0.859	0.945	0.985	0.698	1.356
+	200.201	4.3	Dodecanamide	0.002	2.656	0.001	3.894	<0.001	5.228	<0.001	6.106
+	856.586	4	PC(20:3(5Z,8Z,11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	0.002	1.319	0.005	0.622	0.012	1.155	<0.001	1.714
+	836.6173	4	[PC (18:0/22:5)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.002	1.474	0.059	1.163	0.01	1.291	<0.001	1.481
+	768.5546	4	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.002	2.193	0.025	1.284	<0.001	1.711	<0.001	1.932
+	176.0918	18.9	Calystegin B2	0.002	0.118	<0.001	0.006	<0.001	0.013	<0.001	0.006
+	301.2155	3.3	[PR] Tretinoin/All-Trans Retinoic Acid	0.002	1.18	0.008	1.318	0.005	1.341	0.001	1.566
+	877.5631	3.8	Megalomicin A	0.002	1.847	0.4	1.209	0.528	1.225	0.001	1.634
+	754.5757	4.1	PE(20:2(11Z,14Z)/P-18:1(11Z))	0.002	0.757	<0.001	0.362	0.005	0.69	0.003	0.82
+	794.6063	4	[PC (18:1/20:4)] 1-(1Z-octadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphocholine	0.002	0.799	<0.001	0.602	<0.001	0.708	0.005	0.844

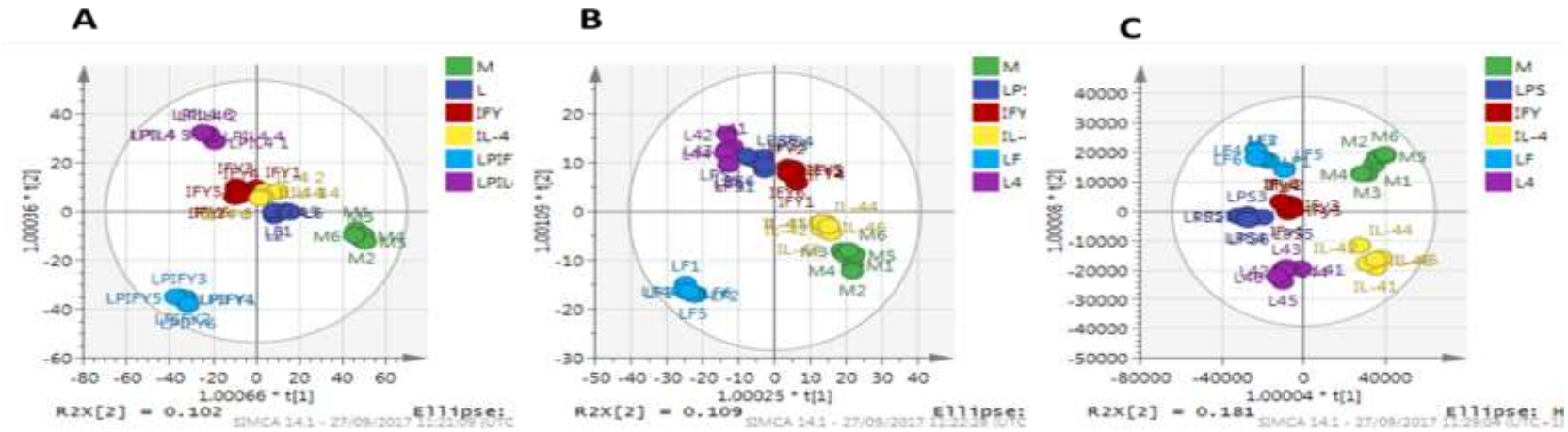
DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	728.5231	4.1	[PC (14:0/18:3)] 1-tetradecanoyl-2-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	0.002	3.023	0.561	0.759	0.152	2.428	0.006	9.174
+	768.5908	4	PC(18:2(9Z,12Z)/P-18:1(11Z))	0.002	0.789	<0.001	0.583	<0.001	0.702	0.007	0.843
+	252.123	27.7	Ac-Tyr-OEt	0.002	0.395	0.007	0.586	0.34	0.662	0.008	0.476
+	208.1161	9.6	N-Ethylglycocyamine	0.002	1.461	0.507	0.891	0.206	0.846	0.964	1.009
-	178.051	10.7	Hippurate	0.002	0.377	0.001	0.286	<0.001	0.204	<0.001	0.215
-	178.0508	27.3	Hippurate	0.002	0.243	0.003	0.229	0.001	0.099	<0.001	0.073
-	426.0225	15.4	ADP	0.002	1.734	0.771	0.937	0.014	1.55	<0.001	2.091
-	122.0248	20.9	Nicotinate	0.002	0.197	0.005	0.286	0.004	0.245	0.002	0.205
-	116.9286	22.8	chromate	0.002	0.425	0.004	0.258	0.229	0.746	0.002	0.41
-	151.0626	29.8	Xylitol	0.002	3.4	0.334	7.604	0.321	3.363	0.002	6.483
-	79.95699	15.3	HSO3-	0.002	6.532	0.309	2.021	0.045	4.651	0.006	5.225
-	153.0308	29.4	Imidazol-5-yl-pyruvate	0.002	5.858	0.138	5.23	0.308	10.149	0.018	14.147
-	115.0512	25.6	Diacetylhydrazine	0.002	3.337	0.022	2.786	0.053	3.128	0.024	6.181
-	557.2888	3.9	Arg-Asn-Asn-Arg	0.002	0.72	<0.001	0.404	<0.001	0.467	0.04	0.845
-	218.0682	27.6	O-Succinyl-L-homoserine	0.002	6.74	0.025	9.797	0.222	11.91	0.18	15.999
-	116.9285	29.7	chromate	0.002	0.256	0.006	0.23	0.158	0.572	0.198	0.677
-	95.98565	25.5	Phosphoramidate	0.002	2.362	0.373	3.152	0.327	1.407	0.979	1.009
+	100.1121	3.4	Cyclohexylamine	0.001	0.757	<0.001	0.624	<0.001	0.577	<0.001	0.517
+	793.5572	3.9	acyl phosphatidylglycerol (n-C12:0)	0.001	3.008	0.238	1.261	<0.001	2.021	<0.001	2.863
+	792.5538	3.9	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	2.842	0.003	1.375	<0.001	1.951	<0.001	2.69
+	749.5316	3.9	[PG (16:0/18:1)] 1-hexadecanoyl-2-(11Z-octadecenoyl)-sn-glycero-3-phospho-(1'-sn-glycerol)	0.001	1.613	0.06	1.139	<0.001	1.417	<0.001	1.75
+	748.5282	3.9	[PE (16:1/22:6)] 1-O-(1Z-hexadecenyl)-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	1.537	0.077	1.12	0.001	1.326	<0.001	1.682
+	834.6013	4	[PC (18:1/22:5)] 1-(11Z-octadecenoyl)-2-(7Z,10Z,13Z,16Z,19Z-docosapentaenoyl)-sn-glycero-3-phosphocholine	0.001	1.561	0.095	1.143	0.002	1.358	<0.001	1.608

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
+	778.5378	4	[PC (18:3/18:3)] 1,2-di-(9Z,12Z,15Z-octadecatrienoyl)-sn-glycero-3-phosphocholine	0.001	3.861	0.004	0.396	0.084	2.138	<0.001	5.98
+	189.087	15.1	N-Acetylglutamine	0.001	2.011	0.494	0.861	0.359	1.191	<0.001	2.629
+	428.3734	4.5	Stearoylcarnitine	0.001	1.458	0.162	0.862	0.834	0.979	<0.001	1.587
+	183.053	16.4	1-Methyluric acid	0.001	1.575	0.259	0.875	0.022	1.257	<0.001	2.392
+	136.0618	10.1	4-Hydroxy-L-threonine	0.001	1.966	0.955	1.011	0.004	1.835	<0.001	2.21
+	200.1282	5	Ecgonine methyl ester	0.001	1.177	0.122	1.121	0.005	1.271	<0.001	1.488
+	134.0811	7.6	1-deoxyxylonojirimycin	0.001	2.682	0.414	0.727	0.003	2.433	<0.001	2.934
+	184.0752	14	Choline phosphate	0.001	2.526	0.862	0.948	0.212	1.428	0.002	3.119
+	143.0815	15.2	Ectoine	0.001	0.489	0.01	0.629	0.002	0.384	0.002	0.301
+	183.0531	15.6	1-Methyluric acid	0.001	1.811	0.114	0.628	0.879	1.024	0.005	2.24
+	482.324	7.5	[PC (15:0)] 1-pentadecanoyl-sn-glycero-3-phosphocholine	0.001	1.423	0.013	0.748	0.574	0.964	0.01	1.33
+	772.6213	4	[PC (18:1/18:0)] 1-(1Z-octadecenyl)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	0.001	2.106	0.316	1.36	<0.001	2.637	0.014	2.006
+	572.3712	4.5	LysoPC(22:4(7Z,10Z,13Z,16Z))	0.001	2.139	0.376	0.712	0.463	1.213	0.149	1.601
-	150.0562	24.4	(Z)-4-Hydroxyphenylacetaldehyde-oxime	0.001	0.378	0.007	0.484	<0.001	0.129	<0.001	0.195
-	762.5061	3.9	[PE (16:0/22:6)] 1-hexadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	11.867	0.033	4.29	<0.001	13.359	<0.001	13.996
-	766.5401	3.9	[PE (18:0/20:4)] 1-octadecanoyl-2-(5Z,8Z,11Z,14Z-eicosatetraenoyl)-sn-glycero-3-phosphoethanolamine	0.001	2.791	0.217	1.315	<0.001	2.303	<0.001	2.806
-	790.5385	3.9	[PE (18:0/22:6)] 1-octadecanoyl-2-(4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoyl)-sn-glycero-3-phosphoethanolamine	0.001	8.138	0.004	3.538	0.003	4.296	<0.001	10.757
-	482.9614	18	UTP	0.001	3.896	0.274	0.608	0.005	3.776	<0.001	7.406
-	606.0745	15.3	UDP-N-acetyl-D-glucosamine	0.001	2.588	0.451	1.175	0.014	1.955	<0.001	3.601
-	113.0356	19.6	5,6-Dihydrouracil	0.001	4.659	0.09	5.997	0.017	7.544	<0.001	4.813
-	116.9285	28.6	chromate	0.001	0.215	<0.001	0.153	0.041	0.481	0.001	0.406
-	127.015	20.6	Barbiturate	0.001	0.226	0.006	0.357	0.002	0.221	0.002	0.302
-	115.0512	29.4	Diacetylhydrazine	0.001	6.519	0.112	2.878	0.009	6.252	0.005	7.217
-	113.0357	22.6	5,6-Dihydrouracil	0.001	1.871	0.161	2.007	0.136	2.506	0.009	2.3
-	101.0356	19.4	N-Formiminoglycine	0.001	2.025	0.127	2.014	0.144	2.29	0.01	4.575

DM	m/z	RT	Name	LPS P	LPS FC	L11a P	L 11a FC	L12b P	L12b FC	L190 P	L19o FC
-	221.0681	29.8	6-Acetyl-D-glucose	0.001	9.489	0.117	9.75	0.239	13.77	0.01	26.127
-	86.02455	13.9	2-Aminoacrylate	0.001	4.024	0.046	2.8	0.04	4.657	0.017	5.073
-	333.2073	15.4	Prostaglandin A2	0.001	12.908	<0.001	26.317	<0.001	65.461	0.019	84.106
-	194.0572	29.2	D,L-α-methylphosphinothricin	0.001	4.735	0.031	1.507	0.322	11.728	0.022	28.753
-	97.04068	19.3	Imidazole-4-methanol	0.001	3.487	0.006	2.786	0.014	2.466	0.053	4.745
-	134.0359	26	3-N4-ethenocytosine	0.001	4.339	0.003	4.673	0.141	6.156	0.123	6.64
-	105.0192	11.9	D-Glycerate	0.001	0.436	0.009	0.615	0.021	0.537	0.276	0.756
-	94.02975	27.5	2-Hydroxypyridine	0.001	2.207	0.17	3.098	0.177	6.151	0.505	2.102
-	205.1598	4.2	[PR] (+)-15-nor-4-thujopsen-3-one	0.001	0.744	0.575	1.355	0.005	0.762	0.567	0.955
-	174.0412	14.8	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	0.001	0.701	<0.001	0.313	<0.001	0.499	0.802	0.985
+	666.1323	13.6	NADH	<0.001	4.552	<0.001	1.628	<0.001	2.718	<0.001	4.006

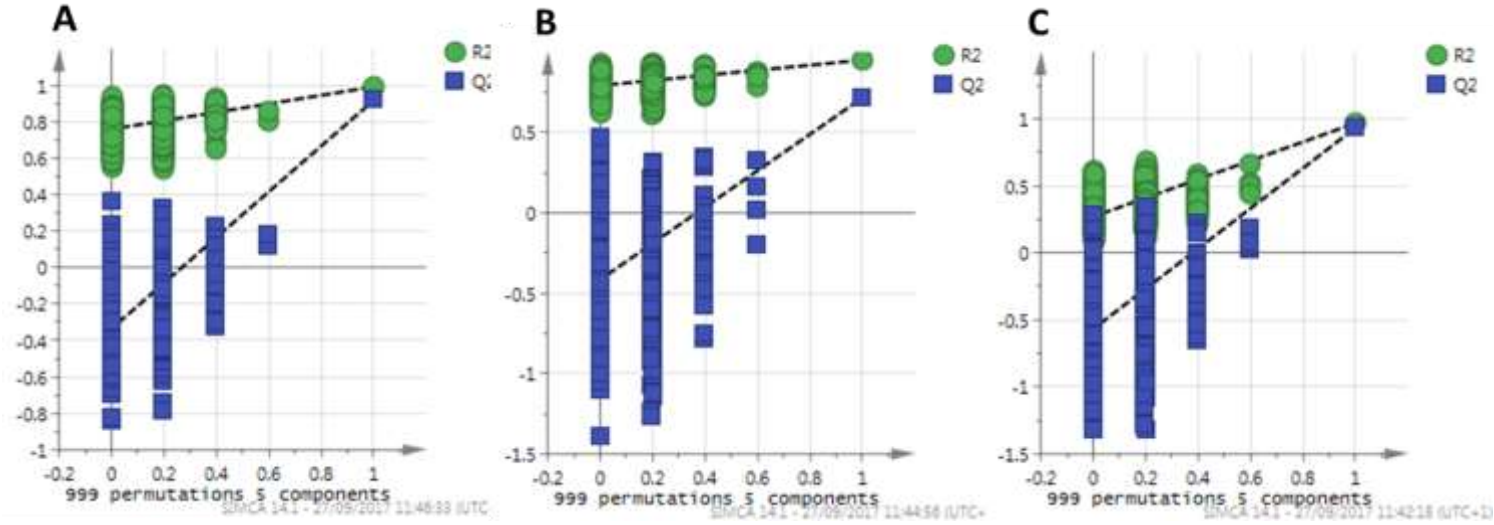
Appendix 20: Orthogonal Partial Least Square Discriminant Analysis (OPLS-DA) score plot of the three runs of macrophages with M1 and M2 activators (LPS, IFN-γ, IL-4, LPS co-stimulation with IFN-γ and LPS co-stimulation with IL4)

OPLS-DA score plots for the overview of the macrophages models A, B and C following different combinations of stimulants on macrophages are shown in figure 3.2.5of macrophages. Each model includes six groups, group 1 (green) represents unstimulated macrophages, group 2 (red) represents IFy treatment, group 3 (yellow) represents IL-4 treatment, group 4 (light blue) represents LPS and IFy co-stimulation treatment, group 5 in dark blue colour indicates the LPS treatment and group six (purple) represents LPS and IL-4 co-stimulation treatment . Model A, consisting of 976 variables, was explained by five predictive x-score components and 1 orthogonal one (5+1). The predictive components explain 42.1% % of the variation in x while the orthogonal component explain 4.12 % and so the total explained variation by x, R2X (cum), is equal to 46.2%, R2Y (cum) = 1, R2 (cum) = 98.1%, and the goodness of prediction Q2 (cum) is equal to 81.5%. Model B, including 305 variables, was explained by five predictive x-score components and 3 orthogonal components (5+3). Its Predictive components explain 45.6 % of the variation in x while its orthogonal ones explain 15.7 % of the variation. The R2X explained variation is equal to 61.3 % while R2Y (cum) = 1, R2 (cum) = 96.2% and the goodness of prediction Q2 (cum) = 70.2%. 414 variables by model C were explained by five predictive x-score components and three orthogonal ones (5+3) in which predictive components explain 81.6 % of the variation in x while its orthogonal ones explain 16.7 %, which makes the total explanation of x variation is equal to 98.2%. It's R2Y (cum) = 1, R2 (cum) = 97.1 %, and C goodness of prediction Q2 (cum) is equal to 93.2 %.


A
B
C
M
L
IFY
IL-4
LPIF
LPIL
LPS
LF
L4
1.00066 * t[1]
1.00025 * t[1]
1.00004 * t[1]
R2X[2] = 0.102
R2X[2] = 0.109
R2X[2] = 0.181
Ellipse:

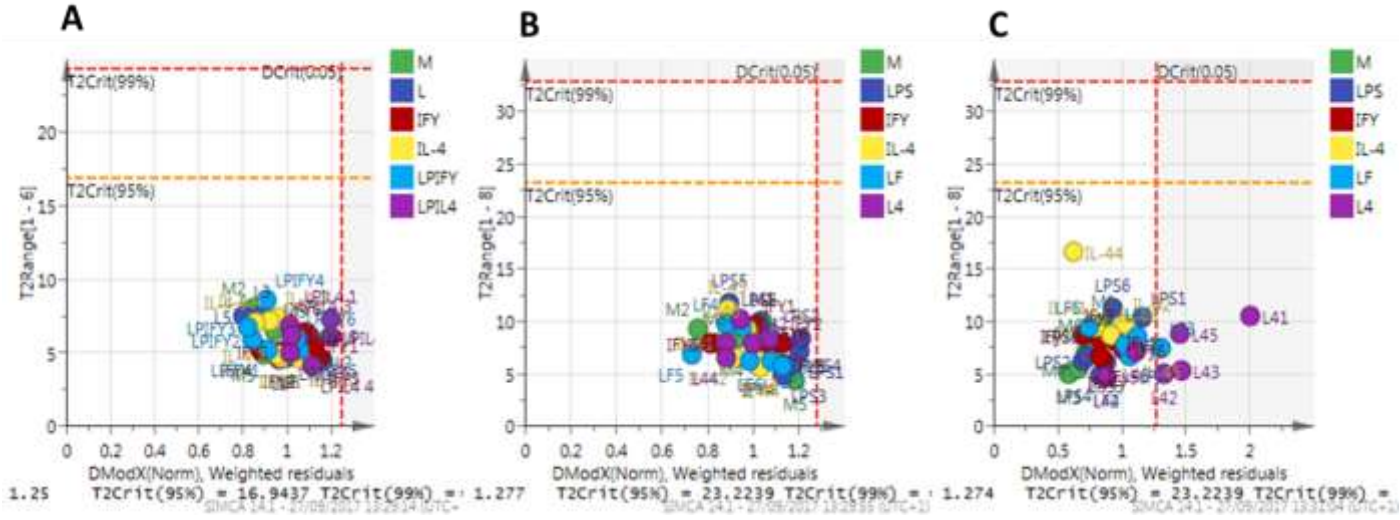
Appendix 21: Permutations test of the three runs of macrophages with M1 and M2 activators

Models' validation, using a 999 random permutations test for the supervised models of different macrophages stimulants versus unstimulated macrophages, has been generated using SMICA. The goodness of fit (R2) and predictive capability (Q2) values on the right-hand side of the plot are of the true model, whereas the permutated model parameters are represented on the left-hand side of the plot. The correlation coefficients between true and permutated models represent the X axis and has a correlation of 1.0 with itself. Macrophages with different stimulants - LPS, IFN-γ, IL-4, LPS IFN-γ and LPSIL4 in models (A, B and C) exhibited higher true values, R2 and Q2, than those of the permutated models. This classifies the investigated SMA models as true models. **A** model intercepts are: R 2 = (0.0, 0.759) and Q 2 = (0.0, − 0.335), **B** model intercepts are R 2 = (0.0, 0.791) and Q 2 = (0.0, − 0.416) whereas model **C** intercepts are: R 2 = (0.0, 0.271) and Q 2 = (0.0, − 0.567).



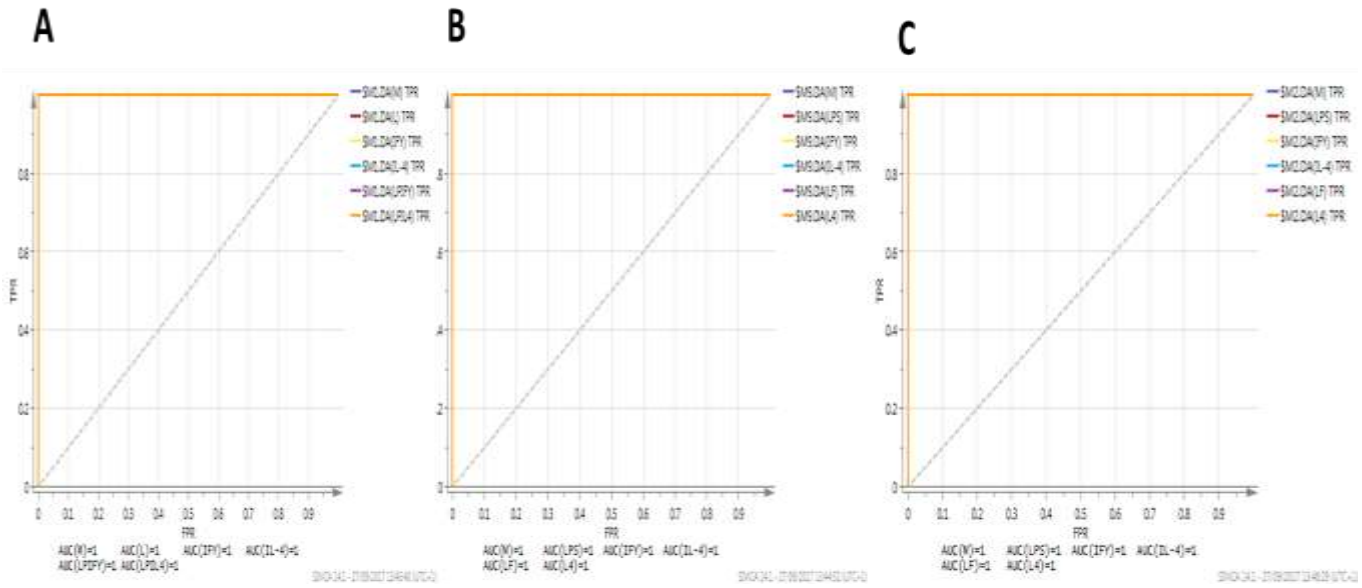
Appendix 22: Distance to model (DModX) vs Hotellings T2 plot of the three runs of macrophages with M1 and M2 activators

DModX on x-axis versus Hotelling's T2 on Y-axis.Hotelling's T2 on Y-axis is showing two limits on the y-axis. The first one, T2Crit (95%), is called the waring limit and is represented by a yellow dotted line whereas the second one, T2 Crit (99%), is called the action limit and is represented by a red dotted line. On the x-axis, the red dotted line indicates DModX uses critical distance DCrit at level 0.05. Observations are considered as strong outliers if they are located above the action limit or above the warning limit plus DModX critical limit. The Investigated A, B and C models are showing models with no strong or even moderate outliers from tested groups.



Appendix 23: Area under the receiver operating characteristics Curve (AUROCC) of the three runs of macrophages with M1 and M2 activators

ROC curves show sensitivity true positive rate (TPR) on the y-axis versus false positive rate (FPR = 1 - Specificity) on the x-axis generated using cross-validated predicted-Y values of the three (A, B and C) investigated OPLS-DA models. The area under the ROC curves (AUC) for unstimulated macrophages (M) is 1, LPS-treated macrophages (LPS) is 1, I IFN-γ -treated macrophages (IFN-γ) is 1, IL-4 treated macrophages (IL-4) is 1 , LPS and IFN-γ co-stimulation of macrophages (LPSIFY) is 1, and AUC for LPS and IL-4 treated macrophages (LPSIL4) is equal to 1. This assesses OPLS-DA models (A, B and C) as models with very strong power that have an excellent ability to distinguish features between unstimulated macrophages and SMAs treated ones.



Appendix 24: The list of detected metabolites that have changed following stimulating untreated macrophages with different activators: LPS, IFY, IL-4, LPS+IFY and LPS+IL-4. DM refers to detection mood, m/z to mass to ratio, RT to raw retention time and P to p-value.

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	89.024	9.5	(R)-Lactate	<0.001	5.134	0.004	1.628	0.330	1.159	<0.001	1.968	0.228	0.881
-	133.014	16.1	(S)-Malate	<0.001	1.584	0.003	1.487	0.912	1.011	<0.001	2.246	0.184	0.942
+	143.049	15.1	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.261	<0.001	2.126	<0.001	1.583	0.008	1.160	0.241	1.036
-	174.041	14.7	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	<0.001	0.421	<0.001	0.556	0.181	0.920	0.564	1.047	0.189	1.079
+	235.042	15.2	2-(2-Hydroxyphenyl)benzenesulfinate	<0.001	58313.810	<0.001	51649.500	0.076	488.958	0.003	1.422	0.343	1.067
-	213.017	14.8	2-Deoxy-D-ribose 5-phosphate	<0.001	3.495	<0.001	3.480	<0.001	0.679	<0.001	1.826	0.367	1.054
-	211.026	15.3	2-Hydroxy-6-ketononatrienedioate	<0.001	4.363	<0.001	2.845	<0.001	2.232	0.062	0.873	<0.001	1.476
-	125.001	13.0	2-Hydroxyethylphosphonate	<0.001	2.833	0.050	1.577	0.719	1.092	0.005	2.447	0.290	1.250
-	145.014	15.6	2-Oxoglutarate	<0.001	2.279	<0.001	1.852	0.528	1.074	<0.001	1.565	0.030	0.874
+	166.072	13.1	3-Methylguanine	<0.001	662028.300	<0.001	250563.500	#DIV/0!	1.000	0.234	0.931	0.018	0.859
+	251.037	15.1	4,4'-Sulfonyldiphenol	<0.001	3.567	<0.001	3.267	<0.001	2.097	0.002	1.361	0.296	1.086
+	159.077	16.2	4-Methylene-L-glutamine	<0.001	48294.900	0.145	62.040	#DIV/0!	1.000	0.050	123.586	0.387	7.055
-	285.049	16.7	5'-Phosphoribosylglycinamide	<0.001	89599.310	<0.001	19054.140	<0.001	8296.862	<0.001	0.445	<0.001	2.917
-	426.022	16.8	ADP	<0.001	2.120	<0.001	2.090	0.079	1.224	0.007	1.229	0.099	0.917
-	426.022	15.4	ADP	<0.001	2.356	<0.001	1.987	0.082	1.279	0.846	0.989	0.118	0.917
+	428.037	15.4	ADP	<0.001	2.194	<0.001	1.897	0.198	1.228	0.539	0.952	0.127	0.885
-	346.056	13.9	AMP	<0.001	4.875	<0.001	2.913	0.085	1.261	<0.001	0.384	0.001	0.596
-	505.988	16.8	ATP	<0.001	2.019	<0.001	1.991	0.014	1.246	0.020	1.181	0.048	0.918
+	508.003	16.7	ATP	<0.001	2.000	<0.001	2.019	0.033	1.285	0.004	1.227	0.156	0.940
-	487.100	15.6	CDP-choline	<0.001	0.053	<0.001	0.085	0.022	0.794	<0.001	10.289	0.014	1.414
+	489.115	15.5	CDP-choline	<0.001	0.000	<0.001	0.000	0.517	0.108	0.145	53.443	#DIV/0!	1.000

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	445.053	16.5	CDP-ethanolamine	<0.001	2.448	<0.001	2.063	0.001	1.457	<0.001	2.445	<0.001	1.457
-	182.059	15.2	Choline phosphate	<0.001	6.437	<0.001	6.172	<0.001	2.739	0.004	0.643	0.399	1.079
+	184.073	15.2	Choline phosphate	<0.001	4.051	<0.001	4.037	<0.001	2.111	<0.001	0.628	0.607	1.037
+	184.073	14.8	Choline phosphate	<0.001	0.000	<0.001	0.000	<0.001	0.000	<0.001	57991.350	#DIV/0!	1.000
-	173.009	18.0	cis-Aconitate	<0.001	1.767	0.026	1.348	0.030	1.304	0.344	0.918	0.132	0.854
-	310.126	15.0	Citalopram alcohol	<0.001	2.450	0.003	2.179	0.005	2.069	0.043	1.474	<0.001	2.091
-	191.020	18.3	Citrate	<0.001	1.859	0.030	1.405	0.016	1.428	<0.001	1.560	0.978	0.998
-	429.058	15.5	CMP-2-aminoethylphosphonate	<0.001	6.066	<0.001	3.646	<0.001	1.642	<0.001	0.718	0.019	0.876
+	431.073	15.5	CMP-2-aminoethylphosphonate	<0.001	31021.910	0.145	52.952	#DIV/0!	1.000	0.240	0.014	0.249	0.015
+	132.077	15.0	Creatine	<0.001	3.507	<0.001	2.175	<0.001	1.604	0.058	1.180	<0.001	1.473
-	130.062	15.0	Creatine	<0.001	4.412	<0.001	2.483	<0.001	1.668	0.255	1.114	<0.001	1.500
-	192.018	15.3	creatinine phosphate	<0.001	4.341	<0.001	2.705	<0.001	2.063	0.039	0.852	<0.001	1.461
-	481.977	18.6	CTP	<0.001	1.806	0.002	1.581	0.043	1.364	<0.001	2.561	<0.001	1.664
-	540.054	14.4	Cyclic ADP-ribose	<0.001	1.982	<0.001	2.645	0.006	1.388	<0.001	1.593	0.013	1.149
-	216.916	31.8	delta-3,4,5,6-Tetrachlorocyclohexene	<0.001	3.944	<0.001	2.986	0.022	1.626	0.071	1.319	0.654	1.064
+	228.098	10.7	Deoxycytidine	<0.001	0.000	0.020	0.001	0.028	0.774	0.015	4432.434	0.985	1.057
-	178.072	11.5	D-Glucosamine	<0.001	2.031	<0.001	1.670	0.008	1.463	0.055	0.856	<0.001	2.526
-	259.022	16.1	D-Glucose 6-phosphate	<0.001	2.448	0.003	1.919	0.043	0.635	<0.001	4.946	<0.001	1.383
-	259.022	17.0	D-Glucose 6-phosphate	<0.001	1.812	0.003	2.057	0.153	0.773	<0.001	2.261	<0.001	1.848
-	85.029	15.0	Diacetyl	<0.001	3.507	<0.001	2.323	0.568	0.958	<0.001	0.340	0.314	0.950
-	168.991	16.2	DL-Glyceraldehyde 3-phosphate	<0.001	379.413	0.014	35.718	0.289	0.103	<0.001	1.570	0.002	0.763
-	168.991	15.5	DL-Glyceraldehyde 3-phosphate	<0.001	22.138	<0.001	6.104	0.002	2.360	<0.001	3.138	<0.001	0.721
-	229.012	15.8	D-Ribose 5-phosphate	<0.001	75.856	<0.001	14.888	0.099	1.548	<0.001	2.373	<0.001	0.630
+	142.026	16.2	Ethanolamine phosphate	<0.001	1.627	<0.001	1.469	0.759	0.975	0.117	0.930	0.002	0.862
-	140.012	16.2	Ethanolamine phosphate	<0.001	1.643	<0.001	1.512	0.285	0.927	0.201	0.933	<0.001	0.837
-	306.077	14.5	Glutathione	<0.001	2.220	0.332	1.079	0.019	1.311	<0.001	1.404	0.002	1.194
+	308.091	14.5	Glutathione	<0.001	2.102	0.362	1.080	0.016	1.318	<0.001	1.400	0.004	1.198

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	611.144	17.6	Glutathione disulfide	<0.001	3.302	0.789	0.948	0.047	1.675	0.003	2.451	0.246	1.339
-	245.043	12.8	Glycerophosphoglycerol	<0.001	1.303	<0.001	2.284	0.002	1.419	0.704	1.024	<0.001	1.737
-	362.051	16.8	GMP	<0.001	2.531	<0.001	2.255	0.065	1.274	0.647	1.046	0.173	0.901
-	521.983	19.5	GTP	<0.001	1.918	<0.001	1.586	0.216	1.135	0.003	1.326	0.210	1.062
-	116.046	16.1	Guanidinoacetate	<0.001	2.273	<0.001	2.606	<0.001	2.901	<0.001	0.460	0.003	1.450
+	118.061	16.1	Guanidinoacetate	<0.001	2.485	<0.001	2.445	<0.001	3.024	<0.001	0.499	<0.001	1.381
-	166.018	8.7	Homocysteinesulfinicacid	<0.001	3.189	<0.001	2.250	0.001	1.632	<0.001	2.641	0.516	1.042
-	79.957	15.1	HSO3-	<0.001	2.213	<0.001	2.112	<0.001	1.629	<0.001	1.238	0.161	1.080
-	110.985	14.6	Hydroxymethylphosphonate	<0.001	5.336	<0.001	2.382	0.039	1.377	<0.001	0.633	0.023	1.165
-	108.012	15.3	Hypotaurine	<0.001	5.525	<0.001	4.947	<0.001	2.474	0.004	1.311	0.006	1.132
+	110.027	15.3	Hypotaurine	<0.001	4.514	<0.001	3.899	<0.001	2.333	0.001	1.209	0.115	1.079
-	267.074	11.1	Inosine	<0.001	0.164	0.036	0.505	0.240	1.336	<0.001	178.210	0.001	3.791
+	90.055	15.6	L-Alanine	<0.001	6.079	<0.001	4.393	<0.001	2.164	<0.001	1.350	0.210	1.087
-	174.088	16.2	L-Citrulline	<0.001	2.140	0.429	1.080	0.198	1.040	<0.001	23.803	0.707	0.976
+	176.103	16.2	L-Citrulline	<0.001	2.099	0.666	1.050	0.434	1.098	<0.001	15.568	0.895	0.987
-	167.997	15.1	L-Cysteate	<0.001	2.709	<0.001	2.550	<0.001	1.675	0.664	1.044	0.850	0.987
-	146.046	14.8	L-Glutamate	<0.001	1.463	<0.001	1.732	<0.001	1.399	0.974	0.998	0.004	1.198
-	131.083	16.2	L-Ornithine	<0.001	2.772	<0.001	1.249	0.099	1.172	<0.001	24.197	0.277	0.901
-	129.019	14.8	Mesaconate	<0.001	4.462	<0.001	2.759	0.218	0.815	<0.001	0.289	0.118	0.899
+	141.066	10.5	Methylimidazoleacetic acid	<0.001	518451.700	0.341	7.777	#DIV/0!	1.000	0.106	1.139	0.329	0.106
+	94.930	31.8	MgCl2	<0.001	3.009	<0.001	2.451	0.015	1.493	0.037	1.232	0.558	1.056
-	289.116	17.0	N-(L-Arginino)succinate	<0.001	6.430	0.025	1.538	<0.001	2.301	<0.001	11.120	0.002	1.416
-	662.102	14.4	NAD+	<0.001	2.042	<0.001	2.668	0.003	1.383	<0.001	1.547	0.032	1.097
+	664.117	14.4	NAD+	<0.001	1.988	<0.001	2.586	0.006	1.341	<0.001	1.510	0.068	1.075
-	664.118	13.5	NADH	<0.001	3.732	0.002	1.595	0.014	1.450	<0.001	1.813	0.004	0.745
+	666.132	13.5	NADH	<0.001	176762.200	0.341	6.592	#DIV/0!	1.000	<0.001	1.801	0.042	0.002
+	744.083	16.9	NADP+	<0.001	209274.000	0.145	49.865	#DIV/0!	1.000	0.131	1.160	0.010	0.798
-	744.083	17.3	NADPH	<0.001	1.823	<0.001	2.681	0.008	1.292	0.587	0.964	0.609	1.032

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	154.028	15.1	N-Methylethanolamine phosphate	<0.001	3.210	<0.001	2.987	0.008	1.244	0.041	0.877	0.082	0.938
-	202.109	11.3	O-Acetylcarnitine	<0.001	2.460	<0.001	1.999	0.001	1.700	<0.001	0.536	0.189	1.100
-	211.001	12.6	P-DPD	<0.001	29.462	<0.001	9.072	<0.001	3.553	0.032	1.159	<0.001	3.084
-	78.959	15.3	Phosphite	<0.001	3.318	<0.001	2.233	<0.001	1.735	0.245	0.932	<0.001	1.351
+	212.043	15.3	Phosphocreatine	<0.001	3.645	<0.001	2.419	<0.001	1.934	0.013	0.853	<0.001	1.405
-	210.029	15.3	Phosphocreatine	<0.001	3.837	<0.001	2.543	<0.001	1.992	0.090	0.884	<0.001	1.434
+	170.058	14.3	Phosphodimethylethanolamine	<0.001	197336.700	0.010	2602.351	#DIV/0!	1.000	0.219	0.079	0.116	0.014
-	196.013	16.5	Phosphoguanidinoacetate	<0.001	1.647	<0.001	2.203	<0.001	3.483	<0.001	0.387	0.003	1.195
-	307.115	16.1	S-8-methylthiooctylhydroximoyl-L-cysteine	<0.001	1.755	<0.001	1.344	0.082	1.149	0.983	1.001	0.579	1.025
-	289.033	16.4	Sedoheptulose 7-phosphate	<0.001	40.796	<0.001	8.791	0.531	0.754	<0.001	2.962	0.002	0.822
-	320.100	14.8	S-Glutaryldihydrolipoamide	<0.001	1.384	<0.001	1.626	0.002	0.641	<0.001	2.114	0.018	0.816
-	333.059	16.2	sn-glycero-3-Phospho-1-inositol	<0.001	4.189	<0.001	2.210	<0.001	1.631	<0.001	1.344	0.107	1.093
+	216.063	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	2.488	<0.001	2.125	0.003	0.743	0.006	0.880	0.003	0.871
-	214.049	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	2.548	<0.001	2.187	0.002	0.732	0.007	0.861	<0.001	0.870
+	126.022	15.1	Taurine	<0.001	2.055	<0.001	1.943	0.004	1.568	0.003	1.229	0.246	1.084
-	124.007	15.1	Taurine	<0.001	2.265	<0.001	2.146	<0.001	1.578	0.018	1.145	0.254	1.036
-	166.029	15.8	Taurocyamine	<0.001	4.043	<0.001	3.490	<0.001	3.010	0.088	0.911	0.360	1.053
-	402.995	16.7	UDP	<0.001	2.831	0.042	1.637	0.121	1.439	0.297	0.853	0.011	1.584
-	565.048	16.4	UDP-glucose	<0.001	1.829	<0.001	1.342	<0.001	1.537	0.181	1.086	<0.001	1.378
-	579.027	19.1	UDP-glucuronate	<0.001	2.473	<0.001	1.788	0.006	1.323	0.004	1.219	<0.001	1.561
-	606.075	15.2	UDP-N-acetyl-D-glucosamine	<0.001	1.582	0.002	1.283	0.038	1.226	<0.001	1.273	<0.001	1.243
-	323.029	15.2	UMP	<0.001	3.060	0.010	1.686	0.018	1.564	<0.001	0.578	<0.001	1.338
-	243.062	10.0	Uridine	<0.001	0.398	<0.001	0.199	0.011	0.748	<0.001	0.535	<0.001	0.579
-	482.961	18.1	UTP	<0.001	2.116	<0.001	1.554	<0.001	1.608	0.149	0.906	<0.001	1.655
-	129.0194	15.1	itaconate	<0.001	4.005	<0.001	2.501	0.272	0.849	0.063	1.325	<0.001	3.633
-	133.0143	16.1	(S)-Malate	<0.001	1.429	<0.001	1.343	0.350	1.058	<0.001	2.876	<0.001	1.329
-	145.0142	15.0	2-Oxoglutarate	0.673	1.356	0.329	1.791	0.320	1.735	0.849	1.140	0.820	1.174

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	425.081	17.1	S-glutathionyl-L-cysteine	0.258	1.533	0.599	1.250	0.110	1.851	0.038	1.713	0.468	1.213
-	347.103	13.2	Camptothecin	0.050	3.892	0.577	1.457	0.173	2.419	0.285	1.564	0.630	1.253
+	85.028	11.3	4-Hydroxy-2-butynal	0.028	803.461	0.033	621.675	0.037	519.837	0.033	0.001	0.113	1.195
-	157.037	13.9	Allantoin	0.026	1.405	0.019	1.481	0.028	1.454	0.004	1.452	0.055	1.223
-	256.096	14.8	sn-glycero-3-Phosphocholine	0.013	1.291	<0.001	1.579	0.001	0.601	<0.001	2.222	0.010	0.831
+	260.114	14.8	Proacacipetalin	0.011	1.325	<0.001	1.692	0.006	0.670	<0.001	2.105	0.018	0.797
+	87.044	15.8	Diacetyl	0.010	3345.254	0.341	7.106	#DIV/0!	1.000	0.091	0.002	0.113	86.854
+	115.050	15.0	5,6-Dihydrouracil	0.010	3379.436	0.145	50.985	#DIV/0!	1.000	0.624	0.147	0.953	1.251
+	213.040	15.3	2-Hydroxy-6-ketononatrienedioate	0.010	2648.207	0.341	6.753	#DIV/0!	1.000	0.010	0.000	0.949	1.264
+	287.064	16.7	5'-Phosphoribosylglycinamide	0.010	2221.189	#DIV/0!	1.000	#DIV/0!	1.000	0.010	0.000	0.066	151.489
+	258.110	14.8	sn-glycero-3-Phosphocholine	0.010	1.308	<0.001	1.662	0.003	0.679	<0.001	2.082	0.022	0.828
+	168.066	8.1	Pyridoxal	0.010	5640.797	0.009	6139.902	0.091	638.688	0.884	1.024	0.932	0.986
-	338.989	18.3	D-Fructose 1,6-bisphosphate	0.010	3.041	0.103	1.900	0.847	0.932	<0.001	9.219	0.005	1.477
-	162.954	31.8	Methoxyflurane	0.009	2.206	0.019	2.019	0.137	1.489	0.146	1.176	0.695	1.042
-	249.055	14.4	gamma-L-Glutamyl-L-cysteine	0.009	2.161	0.012	0.406	0.369	1.274	<0.001	23.296	<0.001	1.430
-	139.976	31.8	Carbamoyl phosphate	0.008	1.778	0.017	1.632	0.147	1.292	0.258	1.154	0.475	1.096
+	613.159	17.6	Glutathione disulfide	0.007	9018.364	0.323	46.237	0.293	66.138	0.003	2.405	0.426	0.149
+	746.099	17.3	NADPH	0.006	5678.982	0.005	8654.491	0.082	512.278	0.845	0.981	0.640	1.040
+	174.149	7.8	[FA amino(9:0)] 9-amino-nonanoic acid	0.004	0.485	<0.001	0.305	0.210	0.051	0.195	0.731	0.323	1.541
-	117.0193	15.2	Succinate	0.004	1.337	0.176	1.177	0.876	1.016	0.845	1.018	0.137	1.160
-	111.009	18.3	2-Furoate	0.003	1.336	0.649	1.034	0.998	1.000	<0.001	1.370	0.464	0.955
-	132.030	15.1	L-Aspartate	0.002	0.705	<0.001	1.358	0.005	1.253	0.006	1.364	0.218	1.143
+	134.045	15.1	L-Aspartate	0.002	0.527	0.154	1.160	0.104	1.210	0.052	1.355	0.654	1.073
-	173.0092	18.2	cis-Aconitate	0.002	2.211	0.093	1.468	0.001	1.917	<0.001	4.806	0.001	2.235
-	171.007	14.8	sn-Glycerol 3-phosphate	0.002	1.336	<0.001	1.527	<0.001	0.612	<0.001	2.019	<0.001	0.795

Appendix 25: The list of detected metabolites that have changed following stimulating untreated macrophages with different activators: LPS, IFY, IL-4, LPS+IFY and LPS+IL-4. DM refers to detection mood, m/z to mass to ratio, RT to raw retention time and P to p-value.

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	89.024	9.5	(R)-Lactate	<0.001	5.134	0.004	1.628	0.330	1.159	<0.001	1.968	0.228	0.881
-	133.014	16.1	(S)-Malate	<0.001	1.584	0.003	1.487	0.912	1.011	<0.001	2.246	0.184	0.942
+	143.049	15.1	[FA (10:1/3:0)] 2-decene-4,6,8-triyn-1-al	<0.001	2.261	<0.001	2.126	<0.001	1.583	0.008	1.160	0.241	1.036
-	174.041	14.7	[FA amino,oxo(6:0/2:0)] 2-amino-3-oxo-hexanedioic acid	<0.001	0.421	<0.001	0.556	0.181	0.920	0.564	1.047	0.189	1.079
+	235.042	15.2	2-(2-Hydroxyphenyl)benzenesulfinate	<0.001	58313.810	<0.001	51649.500	0.076	488.958	0.003	1.422	0.343	1.067
-	213.017	14.8	2-Deoxy-D-ribose 5-phosphate	<0.001	3.495	<0.001	3.480	<0.001	0.679	<0.001	1.826	0.367	1.054
-	211.026	15.3	2-Hydroxy-6-ketononatrienedioate	<0.001	4.363	<0.001	2.845	<0.001	2.232	0.062	0.873	<0.001	1.476
-	125.001	13.0	2-Hydroxyethylphosphonate	<0.001	2.833	0.050	1.577	0.719	1.092	0.005	2.447	0.290	1.250
-	145.014	15.6	2-Oxoglutarate	<0.001	2.279	<0.001	1.852	0.528	1.074	<0.001	1.565	0.030	0.874
+	166.072	13.1	3-Methylguanine	<0.001	662028.300	<0.001	250563.500	#DIV/0!	1.000	0.234	0.931	0.018	0.859
+	251.037	15.1	4,4'-Sulfonyldiphenol	<0.001	3.567	<0.001	3.267	<0.001	2.097	0.002	1.361	0.296	1.086
+	159.077	16.2	4-Methylene-L-glutamine	<0.001	48294.900	0.145	62.040	#DIV/0!	1.000	0.050	123.586	0.387	7.055
-	285.049	16.7	5'-Phosphoribosylglycinamide	<0.001	89599.310	<0.001	19054.140	<0.001	8296.862	<0.001	0.445	<0.001	2.917
-	426.022	16.8	ADP	<0.001	2.120	<0.001	2.090	0.079	1.224	0.007	1.229	0.099	0.917
-	426.022	15.4	ADP	<0.001	2.356	<0.001	1.987	0.082	1.279	0.846	0.989	0.118	0.917
+	428.037	15.4	ADP	<0.001	2.194	<0.001	1.897	0.198	1.228	0.539	0.952	0.127	0.885
-	346.056	13.9	AMP	<0.001	4.875	<0.001	2.913	0.085	1.261	<0.001	0.384	0.001	0.596
-	505.988	16.8	ATP	<0.001	2.019	<0.001	1.991	0.014	1.246	0.020	1.181	0.048	0.918
+	508.003	16.7	ATP	<0.001	2.000	<0.001	2.019	0.033	1.285	0.004	1.227	0.156	0.940
-	487.100	15.6	CDP-choline	<0.001	0.053	<0.001	0.085	0.022	0.794	<0.001	10.289	0.014	1.414
+	489.115	15.5	CDP-choline	<0.001	0.000	<0.001	0.000	0.517	0.108	0.145	53.443	#DIV/0!	1.000

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	445.053	16.5	CDP-ethanolamine	<0.001	2.448	<0.001	2.063	0.001	1.457	<0.001	2.445	<0.001	1.457
-	182.059	15.2	Choline phosphate	<0.001	6.437	<0.001	6.172	<0.001	2.739	0.004	0.643	0.399	1.079
+	184.073	15.2	Choline phosphate	<0.001	4.051	<0.001	4.037	<0.001	2.111	<0.001	0.628	0.607	1.037
+	184.073	14.8	Choline phosphate	<0.001	0.000	<0.001	0.000	<0.001	0.000	<0.001	57991.350	#DIV/0!	1.000
-	173.009	18.0	cis-Aconitate	<0.001	1.767	0.026	1.348	0.030	1.304	0.344	0.918	0.132	0.854
-	310.126	15.0	Citalopram alcohol	<0.001	2.450	0.003	2.179	0.005	2.069	0.043	1.474	<0.001	2.091
-	191.020	18.3	Citrate	<0.001	1.859	0.030	1.405	0.016	1.428	<0.001	1.560	0.978	0.998
-	429.058	15.5	CMP-2-aminoethylphosphonate	<0.001	6.066	<0.001	3.646	<0.001	1.642	<0.001	0.718	0.019	0.876
+	431.073	15.5	CMP-2-aminoethylphosphonate	<0.001	31021.910	0.145	52.952	#DIV/0!	1.000	0.240	0.014	0.249	0.015
+	132.077	15.0	Creatine	<0.001	3.507	<0.001	2.175	<0.001	1.604	0.058	1.180	<0.001	1.473
-	130.062	15.0	Creatine	<0.001	4.412	<0.001	2.483	<0.001	1.668	0.255	1.114	<0.001	1.500
-	192.018	15.3	creatinine phosphate	<0.001	4.341	<0.001	2.705	<0.001	2.063	0.039	0.852	<0.001	1.461
-	481.977	18.6	CTP	<0.001	1.806	0.002	1.581	0.043	1.364	<0.001	2.561	<0.001	1.664
-	540.054	14.4	Cyclic ADP-ribose	<0.001	1.982	<0.001	2.645	0.006	1.388	<0.001	1.593	0.013	1.149
-	216.916	31.8	delta-3,4,5,6-Tetrachlorocyclohexene	<0.001	3.944	<0.001	2.986	0.022	1.626	0.071	1.319	0.654	1.064
+	228.098	10.7	Deoxycytidine	<0.001	0.000	0.020	0.001	0.028	0.774	0.015	4432.434	0.985	1.057
-	178.072	11.5	D-Glucosamine	<0.001	2.031	<0.001	1.670	0.008	1.463	0.055	0.856	<0.001	2.526
-	259.022	16.1	D-Glucose 6-phosphate	<0.001	2.448	0.003	1.919	0.043	0.635	<0.001	4.946	<0.001	1.383
-	259.022	17.0	D-Glucose 6-phosphate	<0.001	1.812	0.003	2.057	0.153	0.773	<0.001	2.261	<0.001	1.848
-	85.029	15.0	Diacetyl	<0.001	3.507	<0.001	2.323	0.568	0.958	<0.001	0.340	0.314	0.950
-	168.991	16.2	DL-Glyceraldehyde 3-phosphate	<0.001	379.413	0.014	35.718	0.289	0.103	<0.001	1.570	0.002	0.763
-	168.991	15.5	DL-Glyceraldehyde 3-phosphate	<0.001	22.138	<0.001	6.104	0.002	2.360	<0.001	3.138	<0.001	0.721
-	229.012	15.8	D-Ribose 5-phosphate	<0.001	75.856	<0.001	14.888	0.099	1.548	<0.001	2.373	<0.001	0.630
+	142.026	16.2	Ethanolamine phosphate	<0.001	1.627	<0.001	1.469	0.759	0.975	0.117	0.930	0.002	0.862
-	140.012	16.2	Ethanolamine phosphate	<0.001	1.643	<0.001	1.512	0.285	0.927	0.201	0.933	<0.001	0.837
-	306.077	14.5	Glutathione	<0.001	2.220	0.332	1.079	0.019	1.311	<0.001	1.404	0.002	1.194
+	308.091	14.5	Glutathione	<0.001	2.102	0.362	1.080	0.016	1.318	<0.001	1.400	0.004	1.198

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	611.144	17.6	Glutathione disulfide	<0.001	3.302	0.789	0.948	0.047	1.675	0.003	2.451	0.246	1.339
-	245.043	12.8	Glycerophosphoglycerol	<0.001	1.303	<0.001	2.284	0.002	1.419	0.704	1.024	<0.001	1.737
-	362.051	16.8	GMP	<0.001	2.531	<0.001	2.255	0.065	1.274	0.647	1.046	0.173	0.901
-	521.983	19.5	GTP	<0.001	1.918	<0.001	1.586	0.216	1.135	0.003	1.326	0.210	1.062
-	116.046	16.1	Guanidinoacetate	<0.001	2.273	<0.001	2.606	<0.001	2.901	<0.001	0.460	0.003	1.450
+	118.061	16.1	Guanidinoacetate	<0.001	2.485	<0.001	2.445	<0.001	3.024	<0.001	0.499	<0.001	1.381
-	166.018	8.7	Homocysteinesulfinicacid	<0.001	3.189	<0.001	2.250	0.001	1.632	<0.001	2.641	0.516	1.042
-	79.957	15.1	HSO3-	<0.001	2.213	<0.001	2.112	<0.001	1.629	<0.001	1.238	0.161	1.080
-	110.985	14.6	Hydroxymethylphosphonate	<0.001	5.336	<0.001	2.382	0.039	1.377	<0.001	0.633	0.023	1.165
-	108.012	15.3	Hypotaurine	<0.001	5.525	<0.001	4.947	<0.001	2.474	0.004	1.311	0.006	1.132
+	110.027	15.3	Hypotaurine	<0.001	4.514	<0.001	3.899	<0.001	2.333	0.001	1.209	0.115	1.079
-	267.074	11.1	Inosine	<0.001	0.164	0.036	0.505	0.240	1.336	<0.001	178.210	0.001	3.791
+	90.055	15.6	L-Alanine	<0.001	6.079	<0.001	4.393	<0.001	2.164	<0.001	1.350	0.210	1.087
-	174.088	16.2	L-Citrulline	<0.001	2.140	0.429	1.080	0.198	1.040	<0.001	23.803	0.707	0.976
+	176.103	16.2	L-Citrulline	<0.001	2.099	0.666	1.050	0.434	1.098	<0.001	15.568	0.895	0.987
-	167.997	15.1	L-Cysteate	<0.001	2.709	<0.001	2.550	<0.001	1.675	0.664	1.044	0.850	0.987
-	146.046	14.8	L-Glutamate	<0.001	1.463	<0.001	1.732	<0.001	1.399	0.974	0.998	0.004	1.198
-	131.083	16.2	L-Ornithine	<0.001	2.772	<0.001	1.249	0.099	1.172	<0.001	24.197	0.277	0.901
-	129.019	14.8	Mesaconate	<0.001	4.462	<0.001	2.759	0.218	0.815	<0.001	0.289	0.118	0.899
+	141.066	10.5	Methylimidazoleacetic acid	<0.001	518451.700	0.341	7.777	#DIV/0!	1.000	0.106	1.139	0.329	0.106
+	94.930	31.8	MgCl2	<0.001	3.009	<0.001	2.451	0.015	1.493	0.037	1.232	0.558	1.056
-	289.116	17.0	N-(L-Arginino)succinate	<0.001	6.430	0.025	1.538	<0.001	2.301	<0.001	11.120	0.002	1.416
-	662.102	14.4	NAD+	<0.001	2.042	<0.001	2.668	0.003	1.383	<0.001	1.547	0.032	1.097
+	664.117	14.4	NAD+	<0.001	1.988	<0.001	2.586	0.006	1.341	<0.001	1.510	0.068	1.075
-	664.118	13.5	NADH	<0.001	3.732	0.002	1.595	0.014	1.450	<0.001	1.813	0.004	0.745
+	666.132	13.5	NADH	<0.001	176762.200	0.341	6.592	#DIV/0!	1.000	<0.001	1.801	0.042	0.002
+	744.083	16.9	NADP+	<0.001	209274.000	0.145	49.865	#DIV/0!	1.000	0.131	1.160	0.010	0.798
-	744.083	17.3	NADPH	<0.001	1.823	<0.001	2.681	0.008	1.292	0.587	0.964	0.609	1.032

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	154.028	15.1	N-Methylethanolamine phosphate	<0.001	3.210	<0.001	2.987	0.008	1.244	0.041	0.877	0.082	0.938
-	202.109	11.3	O-Acetylcarnitine	<0.001	2.460	<0.001	1.999	0.001	1.700	<0.001	0.536	0.189	1.100
-	211.001	12.6	P-DPD	<0.001	29.462	<0.001	9.072	<0.001	3.553	0.032	1.159	<0.001	3.084
-	78.959	15.3	Phosphite	<0.001	3.318	<0.001	2.233	<0.001	1.735	0.245	0.932	<0.001	1.351
+	212.043	15.3	Phosphocreatine	<0.001	3.645	<0.001	2.419	<0.001	1.934	0.013	0.853	<0.001	1.405
-	210.029	15.3	Phosphocreatine	<0.001	3.837	<0.001	2.543	<0.001	1.992	0.090	0.884	<0.001	1.434
+	170.058	14.3	Phosphodimethylethanolamine	<0.001	197336.700	0.010	2602.351	#DIV/0!	1.000	0.219	0.079	0.116	0.014
-	196.013	16.5	Phosphoguanidinoacetate	<0.001	1.647	<0.001	2.203	<0.001	3.483	<0.001	0.387	0.003	1.195
-	307.115	16.1	S-8-methylthiooctylhydroximoyl-L-cysteine	<0.001	1.755	<0.001	1.344	0.082	1.149	0.983	1.001	0.579	1.025
-	289.033	16.4	Sedoheptulose 7-phosphate	<0.001	40.796	<0.001	8.791	0.531	0.754	<0.001	2.962	0.002	0.822
-	320.100	14.8	S-Glutaryldihydrolipoamide	<0.001	1.384	<0.001	1.626	0.002	0.641	<0.001	2.114	0.018	0.816
-	333.059	16.2	sn-glycero-3-Phospho-1-inositol	<0.001	4.189	<0.001	2.210	<0.001	1.631	<0.001	1.344	0.107	1.093
+	216.063	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	2.488	<0.001	2.125	0.003	0.743	0.006	0.880	0.003	0.871
-	214.049	16.0	sn-glycero-3-Phosphoethanolamine	<0.001	2.548	<0.001	2.187	0.002	0.732	0.007	0.861	<0.001	0.870
+	126.022	15.1	Taurine	<0.001	2.055	<0.001	1.943	0.004	1.568	0.003	1.229	0.246	1.084
-	124.007	15.1	Taurine	<0.001	2.265	<0.001	2.146	<0.001	1.578	0.018	1.145	0.254	1.036
-	166.029	15.8	Taurocyamine	<0.001	4.043	<0.001	3.490	<0.001	3.010	0.088	0.911	0.360	1.053
-	402.995	16.7	UDP	<0.001	2.831	0.042	1.637	0.121	1.439	0.297	0.853	0.011	1.584
-	565.048	16.4	UDP-glucose	<0.001	1.829	<0.001	1.342	<0.001	1.537	0.181	1.086	<0.001	1.378
-	579.027	19.1	UDP-glucuronate	<0.001	2.473	<0.001	1.788	0.006	1.323	0.004	1.219	<0.001	1.561
-	606.075	15.2	UDP-N-acetyl-D-glucosamine	<0.001	1.582	0.002	1.283	0.038	1.226	<0.001	1.273	<0.001	1.243
-	323.029	15.2	UMP	<0.001	3.060	0.010	1.686	0.018	1.564	<0.001	0.578	<0.001	1.338
-	243.062	10.0	Uridine	<0.001	0.398	<0.001	0.199	0.011	0.748	<0.001	0.535	<0.001	0.579
-	482.961	18.1	UTP	<0.001	2.116	<0.001	1.554	<0.001	1.608	0.149	0.906	<0.001	1.655
-	129.02	15.1	itaconate	<0.001	4.005	<0.001	2.501	0.272	0.849	0.063	1.325	<0.001	3.633
-	133.01	16.1	(S)-Malate	<0.001	1.429	<0.001	1.343	0.350	1.058	<0.001	2.876	<0.001	1.329
-	145.01	15.0	2-Oxoglutarate	0.673	1.356	0.329	1.791	0.320	1.735	0.849	1.140	0.820	1.174

DM	m/z	RT	Name	LPS P	LPS F	IFN-γ P	IFN-γ F	IL-4 P	IL-4 F	LPS+IFN-γ P	LPS+IFN-γ F	LPS+IL-4 P	LPS+IL-4 F
-	425.081	17.1	S-glutathionyl-L-cysteine	0.258	1.533	0.599	1.250	0.110	1.851	0.038	1.713	0.468	1.213
-	347.103	13.2	Camptothecin	0.050	3.892	0.577	1.457	0.173	2.419	0.285	1.564	0.630	1.253
+	85.028	11.3	4-Hydroxy-2-butynal	0.028	803.461	0.033	621.675	0.037	519.837	0.033	0.001	0.113	1.195
-	157.037	13.9	Allantoin	0.026	1.405	0.019	1.481	0.028	1.454	0.004	1.452	0.055	1.223
-	256.096	14.8	sn-glycero-3-Phosphocholine	0.013	1.291	<0.001	1.579	0.001	0.601	<0.001	2.222	0.010	0.831
+	260.114	14.8	Proacacipetalin	0.011	1.325	<0.001	1.692	0.006	0.670	<0.001	2.105	0.018	0.797
+	87.044	15.8	Diacetyl	0.010	3345.254	0.341	7.106	#DIV/0!	1.000	0.091	0.002	0.113	86.854
+	115.050	15.0	5,6-Dihydrouracil	0.010	3379.436	0.145	50.985	#DIV/0!	1.000	0.624	0.147	0.953	1.251
+	213.040	15.3	2-Hydroxy-6-ketononatrienedioate	0.010	2648.207	0.341	6.753	#DIV/0!	1.000	0.010	0.000	0.949	1.264
+	287.064	16.7	5'-Phosphoribosylglycinamide	0.010	2221.189	#DIV/0!	1.000	#DIV/0!	1.000	0.010	0.000	0.066	151.489
+	258.110	14.8	sn-glycero-3-Phosphocholine	0.010	1.308	<0.001	1.662	0.003	0.679	<0.001	2.082	0.022	0.828
+	168.066	8.1	Pyridoxal	0.010	5640.797	0.009	6139.902	0.091	638.688	0.884	1.024	0.932	0.986
-	338.989	18.3	D-Fructose 1,6-bisphosphate	0.010	3.041	0.103	1.900	0.847	0.932	<0.001	9.219	0.005	1.477
-	162.954	31.8	Methoxyflurane	0.009	2.206	0.019	2.019	0.137	1.489	0.146	1.176	0.695	1.042
-	249.055	14.4	gamma-L-Glutamyl-L-cysteine	0.009	2.161	0.012	0.406	0.369	1.274	<0.001	23.296	<0.001	1.430
-	139.976	31.8	Carbamoyl phosphate	0.008	1.778	0.017	1.632	0.147	1.292	0.258	1.154	0.475	1.096
+	613.159	17.6	Glutathione disulfide	0.007	9018.364	0.323	46.237	0.293	66.138	0.003	2.405	0.426	0.149
+	746.099	17.3	NADPH	0.006	5678.982	0.005	8654.491	0.082	512.278	0.845	0.981	0.640	1.040
+	174.149	7.8	[FA amino(9:0)] 9-amino-nonanoic acid	0.004	0.485	<0.001	0.305	0.210	0.051	0.195	0.731	0.323	1.541
-	117.02	15.2	Succinate	0.004	1.337	0.176	1.177	0.876	1.016	0.845	1.018	0.137	1.160
-	111.009	18.3	2-Furoate	0.003	1.336	0.649	1.034	0.998	1.000	<0.001	1.370	0.464	0.955
-	132.030	15.1	L-Aspartate	0.002	0.705	<0.001	1.358	0.005	1.253	0.006	1.364	0.218	1.143
+	134.045	15.1	L-Aspartate	0.002	0.527	0.154	1.160	0.104	1.210	0.052	1.355	0.654	1.073
-	173.01	18.2	cis-Aconitate	0.002	2.211	0.093	1.468	0.001	1.917	<0.001	4.806	0.001	2.235
-	171.007	14.8	sn-Glycerol 3-phosphate	0.002	1.336	<0.001	1.527	<0.001	0.612	<0.001	2.019	<0.001	0.795