High Performance Chemical Isotope Labeling LC-MS Metabolomics Analysis Report

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1 Overview

This document reports the results for "Metabolomics of …" (4-Channel Analysis). Data was collected using Dansyl-labeling Kit or DmPA-labeling Kit. Analysis was performed using IsoMS Pro 1.4.0 (NovaMT Inc.) and NovaMT Metabolite Database v3.0.

2 Materials and Methods

2.1 General Information

Sample Type:	xxx
Sample Group:	A total of 34 samples with 12 in the "Group A" group, 11 in the "Group B" group, and 11 in the "Group C" group.
Replicates:	Single replicate
Analysis Method:	4-channel analysis
Number of Kits Used:	2 labelling kit(s) per channel

2.2 Sample Preparation

2.2.1 Sample Randomization

Samples were randomized before any procedures to eliminate potential technical variations from sample preparation and instrument drift. The randomized samples were used for the following preparations and analyses.

2.2.1 Metabolite Extraction

To extract metabolites from cells, 50 µL of LC-MS grade methanol/water (1:1 v/v), were added to samples. Samples were sonicated for 10 minutes, then centrifuged for 10 minutes. Solvents were aliquoted and dried, then resuspended in LC-MS grade water.

2.2.2 Sample Normalization

The total concentrations of samples were determined by NovaMT Sample Normalization kit. According to the quantification results, different volumes of water were added to adjust samples to the same concentration of 1000 cells/ µL.

2.2.3 Aliquoting and Generation of the Pooled Sample

Each individual sample was vortexed then centrifuged at 15,000 g for 1 min. Supernatant was taken and split into four aliquots for different labeling methods, backup and preparation of pooled sample. For the one aliquot for preparing of pooled sample, 15 µL was taken from each individual sample, and then combined and mixed thoroughly to prepare the pooled sample, which was used as the reference.

2.2.4 Chemical Isotope Labeling

2.2.5 Mixing

The $^{12}C_2$-labeled individual sample was mixed with $^{13}C_2$-labeled reference sample in equal volume. The mixture was ready to be analyzed by LC-MS. Prior to LC-MS analysis of the entire sample set, quality control (QC) sample was prepared by equal volume mix of a ^{12}C-labeled and a ^{13}C-labeled pooled sample.

2.3 LC-MS Analysis Condition

The LC-MS analysis was strictly followed the SOP. QC samples were injected every 20 sample runs to monitor instrument performance.

Instrument:	Themo Scientific Vanquish Neo LC linked to Thermo Scientific Orbitrap Exploris 240 Mass Spectrometer
Column:	Thermo Scientific Hypersil Gold reversed phase C18 column (100 x 1 mm, 1.9 µm particle size)
MPA:	0.1% (v/v) formic acid in water
MPB:	0.1% (v/v) formic acid in 95% acetonitrile with 5% water
Gradient:	t = 0 min, 1% B; t = 1 min, 20% B; t = 12 min, 99% B; t = 16 min, 1% B; t=18 min, 1% B
Flow Rate:	100 µL/min
Column Oven Temperature:	40 °C
Mass Range:	m/z 220-1000
Acquisition Rate:	1 Hz

2.4 Data Processing

A total of 148 LC-MS data from 4-channel analysis (37 LC-MS data, including 3 QC, in each channel) were first exported to .csv file with ProteoWizard MS convert 3.0 software. The exported data were uploaded to IsoMS Pro 1.4.0. After Data Quality Check, Data Processing was performed. Parameters used for data processing are below.

Minimum m/z:	220
Maximum m/z:	1000
Saturation Intensity:	1000000000
Retention Time Tolerance	9 seconds
Mass Tolerance:	10 ppm

2.5 Data Cleansing

Four groups were assigned to 37 LC-MS data in each channel: 12 data files labeled as 'Group A' group, 11 data files labeled as 'Group B' group, 11 data files labeled as 'Group C' group and 3 data files labeled as 'QC' group. Peak pairs without data present in at least 80.0% of samples in any group were filtered out (see section 3.2). Data were normalized by Ratio of Total Useful Signal.

2.6 Metabolite Identification

The parameters used for metabolite identification are below.

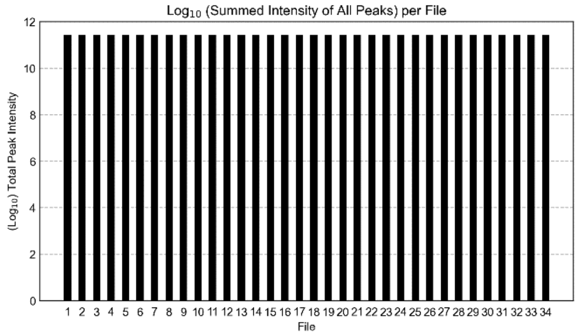
Retention Time Tolerance for CIL Library ID	10 seconds
Retention Time Tolerance for LI Library ID	75 seconds
Mass Tolerance for CIL Library ID	10 ppm
Mass Tolerance for LI Library ID	10 ppm
Mass Tolerance for Mass-Based Database ID	10 ppm

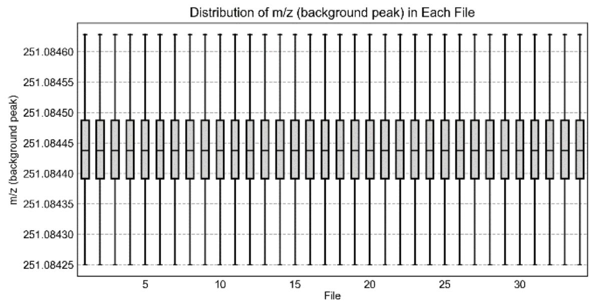
3 Results

3.1 Data Quality Check

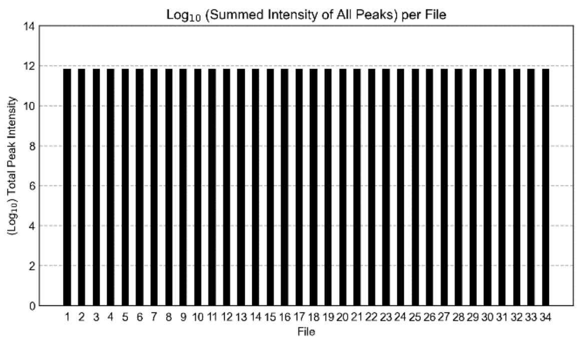
3.1.1 Mass Accuracy Check

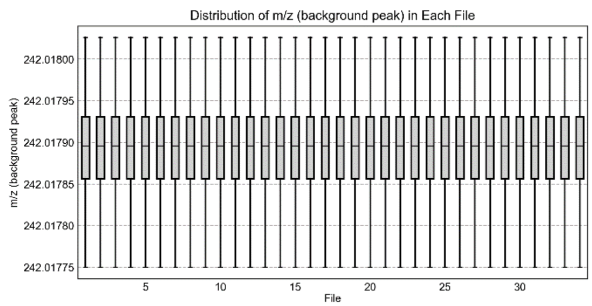
m/z 251.0849 was selected as background peak to check the mass accuracy for 34 samples in amine/phenol channel analysis. The summed intensity of all peaks was consistent during all runs. The mass of the background peak was consistent during all runs and all are within the expected range, showing good stability and mass accuracy for data acquisition.



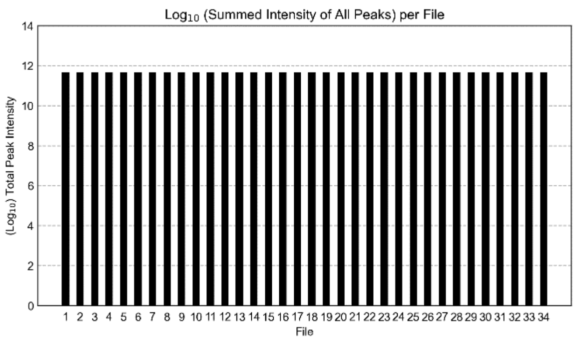


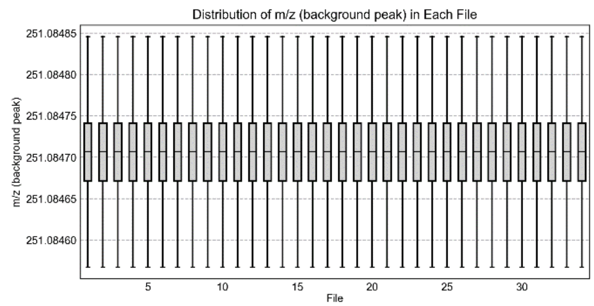
m/z 242.0175 was selected as background peak to check the mass accuracy for 34 samples in carboxyl channel analysis. The summed intensity of all peaks was consistent during all runs. The mass of the background peak was consistent during all runs and all are within the expected range, showing good stability and mass accuracy for data acquisition.



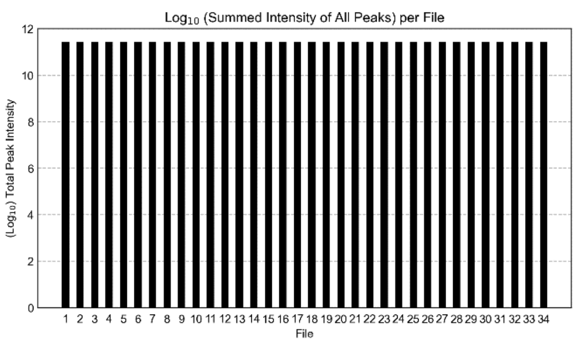


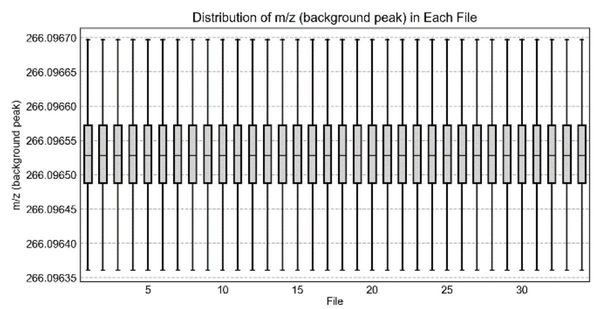
m/z 251.0849 was selected as background peak to check the mass accuracy for 34 samples in hydroxyl channel analysis. The summed intensity of all peaks was consistent during all runs. The mass of the background peak was consistent during all runs and all are within the expected range, showing good stability and mass accuracy for data acquisition.





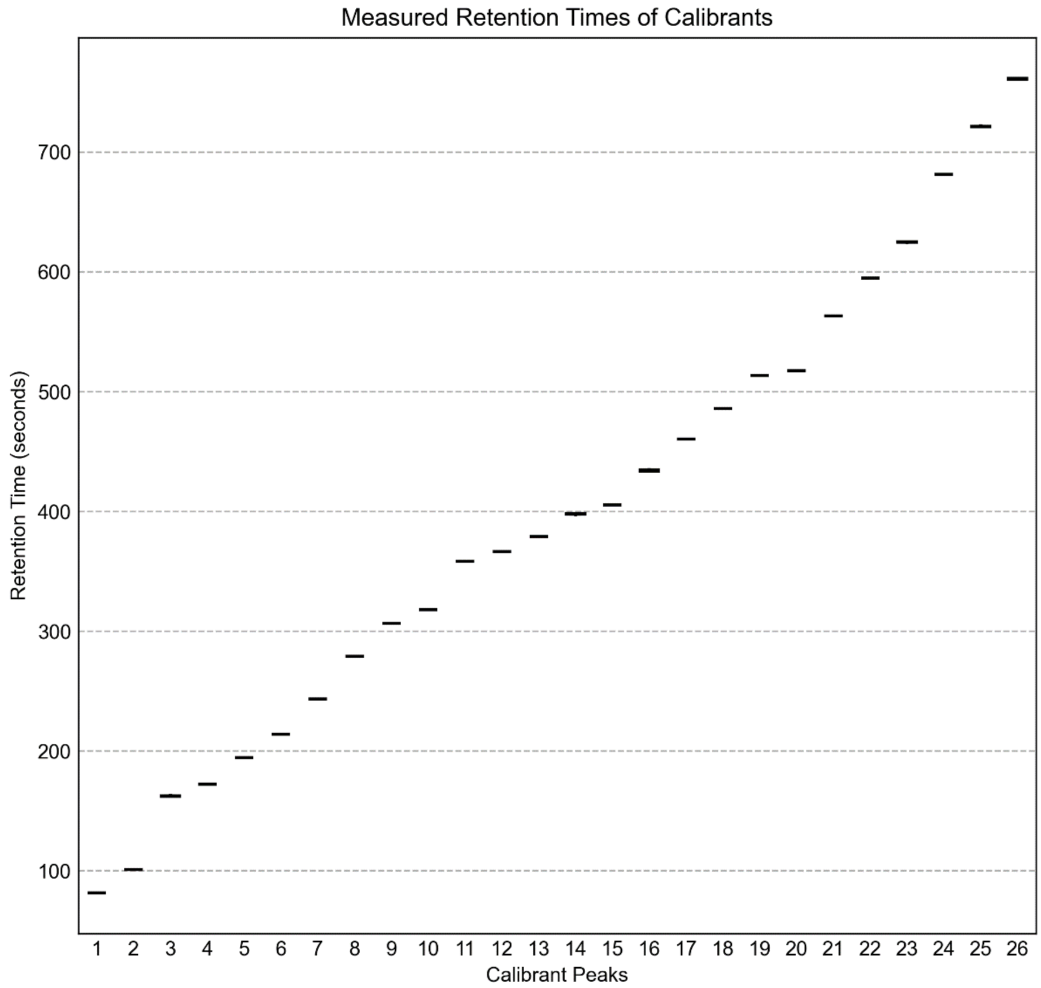
m/z 266.0958 was selected as background peak to check the mass accuracy for 34 samples in carbonyl channel analysis. The summed intensity of all peaks was consistent during all runs. The mass of the background peak was consistent during all runs and all are within the expected range, showing good stability and mass accuracy for data acquisition.





3.1.2 Retention Time Check

Four calibration data were used to check the retention time in each channel. All calibrant peaks were well aligned. The retention times of calibrants were consistent for all calibration data, showing good RT stability for data acquisition.



3.2 Data Processing and Cleansing

A total of 37 LC-MS data were processed for each channel. 4-channel LC-MS data of one sample were combined after data processing. Less commonly detected peak pairs were filtered out to ensure data quality. After filtering, 5707 ± 30 peak pairs per sample were retained (from Supplemental Table 1). The table below (Table 1) shows the peak pair numbers detected in each sample. One supplemental table showing the list of peak pairs was generated with this report (Supplemental Table 1), which is the final metabolite-intensity table from the CIL LC-MS measurement of the samples.

In the Supplemental Table 1, peak pairs without data present in at least 80.0% of samples in any group were filtered out. Applying this 80%-rule ensures that only the commonly detectable peak pairs are retained for further analysis, without the use of excessive missing-value imputation. This 80% rule states that, if all the analyzed samples belong to one group, the retained peak pairs are those detectable in >= 80% of the samples. If the analyzed samples belong to two or more groups, the retained peak pairs are those detectable in >= 80% of the samples in any one of the groups. For example, in a study comparing group A (100 samples) and group B (100 samples), a peak pair will be retained if it is detectable in >=80% of the samples in group A, even though this peak pair may be detectable in none or a few of the group B samples. However, if a peak pair is detectable in <80% of the group A samples and <80% of the group B samples, this peak pair will be filtered out, as this peak pair is considered to be less commonly detected.

After filtering, all data were normalized by the ratio of total useful signals. The missing values of peak pairs in some samples due to low signal intensity (i.e., below the detection limit) was replaced with a rationally determined ratio by a unique zero-imputation program. This table can be used for statistical analysis without the need of applying any missing value imputation method given in a statistical tool.

Table 1. Number of Metabolites Detected in Each Sample

Sample Name	Group	Number of Peak Pairs
sample 1	A	5693
sample 2	A	5709
sample 3	A	5700
sample 4	A	5697
sample 5	A	5713
sample 6	A	5719
sample 7	A	5686
sample 8	A	5658
sample 9	A	5723
sample 10	A	5693
sample 11	A	5709
sample 12	A	5686
sample 13	B	5757
sample 14	B	5692
sample 15	B	5708
sample 16	B	5701
sample 17	B	5698
sample 18	B	5712
sample 19	B	5720
sample 20	B	5687
sample 21	B	5659
sample 22	B	5724
sample 23	B	5690
sample 24	C	5718
sample 25	C	5680
sample 26	C	5763

Sample Name	Group	Number of Peak Pairs
sample 27	C	5690
sample 28	C	5712
sample 29	C	5705
sample 30	C	5692
sample 31	C	5710
sample 32	C	5722
sample 33	C	5682
sample 34	C	5662
QC 1	QC	5721
QC 2	QC	5695
QC 3	QC	5708

3.3 Metabolite Identification

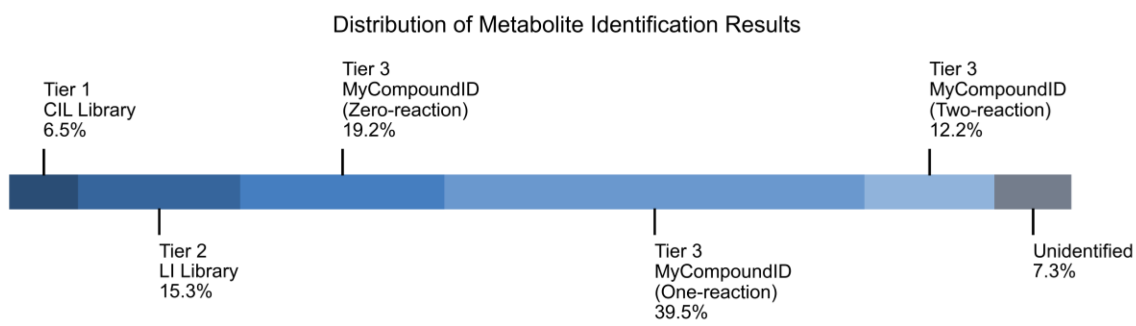
Three-tier ID approach was used to perform metabolite identification.

In tier 1, peak pairs were searched against a labeled metabolite library (CIL Library) based on accurate mass and retention time. The CIL Library contains more than 1,500 experimental entries. 378 peak pairs were positively identified in tier 1.

In tier 2, linked identity library (LI Library) was used for identification of the remaining peak pairs. LI Library includes over 9,000 pathway-related metabolites, providing high-confidence putative identification results based on accurate mass and predicted retention time matches. 893 peak pairs were putatively identified in tier 2.

In tier 3, the remaining peak pairs were searched, based on accurate mass match, against the MyCompoundID (MCID) library composed of 8,021 known human endogenous metabolites (zero-reaction library), their predicted metabolic products from one metabolic reaction (375,809 compounds) (one-reaction library) and two metabolic reactions (10,583,901 compounds) (two-reaction library). 1124, 2311 and 715 peak pairs were matched in the zero-, one- and two-reaction libraries, respectively.

Thus, out of 5845 unique peak pairs detected, 5421 (92.7%) pairs could be positively identified or putatively matched. Among them, 490 peak pairs were identified as high-confidence results (tier 1 and tier 2), which can be used for other analysis (e.g., pathway analysis).



The identification results for each peak pair are shown in Supplemental Table 1. Metabolites that were identified in tier 1 and tier 2 are listed below.

Table 2. 378 Metabolites that were positively identified in tier 1 (CIL Library)

NovaMT Library No.	External Identifier	Compound
AN02027002	C08362	(9Z)-Hexadecenoic Acid
BM00647000	C01983, C01984	(S)-Mandelic acid
BM00132006		2,3-Butanediol
BM00670003	C00196	2,3-Dihydroxybenzoic acid
BM00761001	C02625	2,4-Dichlorophenol
AN00670004	C00628	2,5-Dihydroxybenzoic acid
AN00189000	C02356	2-Aminobutyric acid/2-Aminoisobutyric acid
AN00726001		2-Aminooctanoic acid
AN00219002	C01987	2-Aminophenol
AN00197004	C05984	2-Hydroxybutyric acid
AN00594002	C02630	2-Hydroxyglutaric Acid
AN00647005	C05852	2-Hydroxyphenylacetic acid
AN00177004	C00109	2-Ketobutyric acid
AN00396002	C00902	2-Ketohexanoic acid
AN01210001		2-Methylhippuric acid
AN00638001		2-Phenylglycine
BM00626003		2-Phenylpropionic acid
AN01076000	C05580	3,4-Dihydroxymandelic acid
AN00856002	C01161	3,4-Dihydroxyphenylacetic acid
AN00670001		3,5-Dihydroxybenzoic acid
BM00823019	C11457	3-(3-Hydroxyphenyl)propanoic acid
AN01052008	C03672	3-(4-Hydroxyphenyl)lactic acid
AN00189001	C05145	3-Aminoisobutyric acid
BM00216000	C01467	3-Cresol
AN00167001		3-Hexanone
BM00311000	C03067	3-Hydroxybenzaldehyde
AN00477007	C00587	3-Hydroxybenzoic Acid
BM00326002	C03351	3-Hydroxybenzyl alcohol
AN00197001		3-Hydroxybutanoic acid
AN00197000	C06001	3-Hydroxyisobutyric Acid
AN00283004	C20827	3-Hydroxyisovaleric Acid
AN00769001	C03761	3-Hydroxymethylglutaric acid
AN00647003	C05593	3-Hydroxyphenylacetic Acid
AN00130007	C01013	3-Hydroxypropanoic acid
AN01266002	C05584	3-Methoxy-4-hydroxymandelic acid
AN00396000	C03465	3-Methyl-2-oxovaleric acid
AN00109007	C07329	3-Methylbutanal
BM00647013	C14088	3-Methylsalicylic acid
AN00419002	C02642	3-Ureidopropionic Acid
AN03968005		3-keto-7alpha,12alpha-Dihydroxy-5alpha-cholanic acid
AN03980014		3beta-Cholic acid
AN00793000	C00811	4-Coumaric acid
BM00216003	C01468	4-Cresol/3-Cresol
AN00269012	C13637	4-Ethylphenol
BM00311001	C00633	4-Hydroxybenzaldehyde/3-Hydroxybenzaldehyde
AN00477004	C00156	4-Hydroxybenzoic acid
AN00197005	C00989	4-Hydroxybutanoic acid
BM01229007		4-Hydroxyhippuric acid
AN00647002	C00642	4-Hydroxyphenylacetic acid
AN00396012	C00233	4-Methyl-2-oxopentanoic acid
BM00487001	C00870	4-Nitrophenol
AN00406002	C00430	5-Aminolevulinic acid
AN00277004	C00431	5-Aminopentanoic acid
AN01274001		5-Dodecenoic acid
AN00774001	C16741	5-Hydroxylysine
AN02059000		5-Methylcytidine
AN03836002		5beta-Cholanic acid-12alpha-ol-3-one
BM00410006	C02378	6-Aminohexanoic acid
AN00487003	C01020	6-Hydroxynicotinic acid
AN00743002		7-Hydroxyoctanoic acid
AN03968004	C04643	7-Ketodeoxycholic Acid
AN03836005		7-Ketolithocholic acid
AN03836001		7alpha-Hydroxy-3-oxo-5b-cholanoic acid
AN00014000	C00084	Acetaldehyde
AN00177002	C00164	Acetoacetic Acid
AN00026002	C00207	Acetone - isomer 1/Propanal

NovaMT Library No.	External Identifier	Compound
AN00060002	C00511	Acrylic Acid
AN00452000	C00147	Adenine
BM00573004	C06104	Adipic Acid
AN00124000	C00041	Alanine
AN00738000		Alanyl-Alanine
AN01346002		Alanyl-Aspartic Acid
AN01544002		Alanyl-Glutamic acid
AN01530001		Alanyl-Glutamine
AN00574007		Alanyl-Glycine
AN01660001		Alanyl-Histidine
AN01324000		Alanyl-Isoleucine
AN01534000		Alanyl-Lysine
AN01782000		Alanyl-Phenylalanine
AN01133002		Alanyl-Valine
AN01608003	C00542	Allocystathionine
AN00754003	C00956	Aminoadipic acid
AN00468006	C00108	Anthranilic acid
AN00945000	C00062	Arginine
AN00958000		Argininic acid
AN03117000		Arginyl-Arginine
AN01721000		Arginyl-Glycine
AN02122000		Arginyl-Serine
AN00419000	C00152	Asparagine
AN01902001		Asparaginyl-Asparagine
AN01922000		Asparaginyl-Aspartic acid
AN01146000		Asparaginyl-Glycine
AN02236000		Asparaginyl-Histidine
AN01563000		Asparaginyl-Serine
AN01742000		Asparaginyl-Threonine
AN00428000	C00049	Aspartic acid
AN01922001		Aspartyl-Asparagine
AN01933001		Aspartyl-Aspartic acid
AN01163001		Aspartyl-Glycine
AN02254000		Aspartyl-Histidine
AN01906003		Aspartyl-Isoleucine
AN02121002		Aspartyl-Lysine
AN01708000		Aspartyl-Proline
AN01757004		Aspartyl-Threonine
EF02406002		Aspartyphenylalanine
AN01132000	C08261	Azelaic acid
BM00208000	C00261	Benzaldehyde
AN00124003	C00099	Beta-Alanine
AN00410004	C02486	Beta-Leucine
AN01790000	C06313	Biopterin
AN00061006	C01412	Butanal
AN03850013	C02528	Chenodeoxycholic Acid
AN00594011	C02614, C02612	Citramalic acid
AN01194001	C00158	Citric acid/Isocitric acid
AN00958001	C00327	Citrulline
AN03543000	C00735	Cortisol
BP00108001	C01771	Crotonic Acid
AN02362001		Cysteinyl-Arginine
AN01965001		Cysteinyl-Glutamic acid
AN02070000		Cysteinyl-Histidine
AN01405000		Cysteinyl-Serine
AN02456000		Cysteinyl-Tyrosine
AN01818000	C00491	Cystine
AN01857000	C00475	Cytidine
AN00233000	C00380	Cytosine
AN01024016	C01487	D-Allose
AN02087000	C00352	D-Glucosamine 6-phosphate
AN01024001	C00031	D-Glucose
AN00207000	C00258	D-Glyceric acid
AN00315001	C16884	D-Threitol
AN00704003	C12307	Decanal/2-Decanone
AN00920000	C01571	Decanoic acid
AN01672000	C00881	Deoxycytidine
AN02208001	C00330	Deoxyguanosine

NovaMT Library No.	External Identifier	Compound
BM00823005	C01744	Desaminotyrosine
AN00108006	C00741	Diacetyl
AN00204000	C06772	Diethanolamine
AN01713000	C02678	Dodecanedioic acid
AN01300003	C02679	Dodecanoic acid
AN00037000	C00189	Ethanolamine
AN00513001	C00346	Ethanolamine phosphate
AN00418009		Ethylmalonic acid
BP01216007	C01494	Ferulic acid
AN00796000	C01019	Fucose
AN00265000	C00122	Fumaric Acid
AN01024000	C00984	Galactose
BM00887000	C01424	Gallic acid
AN03980000	C17649	Gamma-Muricholic acid
AN00583000	C00302	Glutamic Acid
AN00574000	C00064	Glutamine
AN02742002		Glutaminyl-Arginine
AN02118003		Glutaminyl-Aspartic Acid
AN02336002		Glutaminyl-Glutamic acid
AN02092001		Glutaminyl-Leucine
AN01742001		Glutaminyl-Serine/Seryl-Glutamine
AN01544000		Glutamyl-Alanine
AN02758001		Glutamyl-Arginine
AN02118004		Glutamyl-Asparagine
AN02135002		Glutamyl-Aspartic acid
AN02350001		Glutamyl-Glutamic acid
AN02336003		Glutamyl-Glutamine
AN01346004		Glutamyl-Glycine
AN02110005		Glutamyl-Isoleucine
AN02110000		Glutamyl-Leucine
AN02376000		Glutamyl-Methionine
AN02608004		Glutamyl-Phenylalanine
AN03154000		Glutamyl-Tryptophan
AN02849001		Glutamyl-Tyrosine
AN00418002	C00489	Glutaric Acid
AN01133007		Gly-Norleucine
AN00943007		Gly-Norvaline
AN00136000	C00116	Glycerol
AN00076000	C00037	Glycine
AN00080000	C00160	Glycolic Acid
AN00574005		Glycyl-Alanine
AN01721001		Glycyl-Arginine
AN01146001		Glycyl-Asparagine
AN01163002		Glycyl-Aspartic acid
AN01346005		Glycyl-Glutamic acid
AN01460000		Glycyl-Histidine
AN01133001	C02155	Glycyl-Leucine
AN01338000		Glycyl-Lysine
AN01612000		Glycyl-Phenylalanine
AN00914000		Glycyl-Proline
AN00972001		Glycyl-Threonine
AN00419004	C02037	Glycyl-glycine
BM00326004	C01502	Guaiacol
AN00274000	C00581	Guanidinoacetic acid
AN01006000	C01586	Hippuric Acid
AN00235000	C00388	Histamine
AN00684000		Histidine
AN01660002		Histidinyl-Alanine
AN02070001		Histidinyl-Cysteine
AN02459001		Histidinyl-Glutamic acid
AN01135000	C01924	Homoarginine
AN01150000	C02427	Homocitrulline
AN01061000	C16511	Homocysteic acid
AN00856000	C00544	Homogentisic acid
AN00291001	C00263	Homoserine
AN01052009	C05582	Homovanillic acid
AN00626000	C05629	Hydrocinnamic acid/3-Methylphenylacetic acid
AN00227003	C00530	Hydroquinone

NovaMT Library No.	External Identifier	Compound
AN00406000	C01157	Hydroxyproline
AN00218000	C00519	Hypotaurine
AN00459000	C00262	Hypoxanthine
AN00345002	C02835	Imidazole-4-acetic acid
AN00956003	C00954	Indole-3-acetic acid
BM00559000	C08493	Indole-3-carboxaldehyde
BM01147000	C22236	Indole-3-propionic acid
BM01113000		Indoleacrylic acid
AN00410002	C00407	Isoleucine
AN01324002		Isoleucyl-Alanine
AN01906006		Isoleucyl-Aspartic acid
AN01714000		Isoleucyl-Valine
AN00856010		Isovanillic acid
BM00392004	C00490	Itaconic acid
AN01408003	C01718	Kynurenine
AN00284000	C03283	L-2,4-Diaminobutanoic acid
AN01608000	C02291	L-Cystathionine /Allocystathionine
AN00277001	C01799	L-Norvaline
AN01024019	C00247	L-Sorbose
BM01168000	C00666	LL-2,6-Diaminoheptanedioic acid
AN00130001	C00186	Lactic Acid
AN03286003	C00243	Lactose
AN00410000	C00123	Leucine
AN01906007		Leucyl-Aspartic acid
AN02095001		Leucyl-Lysine
AN02941001		Leucyl-Tryptophan
AN01714001		Leucyl-Valine
AN00769003		Levoglucosan
AN00266005		Levulinic acid
AN02413000	C01595	Linoleic acid
AN00578000	C00047	Lysine
AN01534001		Lysyl-Alanine
AN02121003		Lysyl-Aspartic acid
AN02339002		Lysyl-Glutamic acid
AN02095003		Lysyl-Leucine /Leucyl-Lysine
AN02593000		Lysyl-Methionine sulfoxide
AN01861000		Lysyl-Proline
AN02840000		Lysyl-Tyrosine
AN01892000		Lysyl-Valine
AN00265001	C01384	Maleic acid
AN00435000	C00711	Malic Acid
AN00193001	C00383	Malonic Acid
AN00392001	C01732	Mesaconic Acid
AN00608000	C00073	Methionine
AN00810000	C02989	Methionine Sulfoxide
AN01586003		Methionyl-Alanine
AN02142003		Methionyl-Leucine
AN00102001		Methyl propenyl ketone
AN00060000	C00546	Methylglyoxal
AN00066000	C02294	Methylguanidine
AN00281003	C02170	Methylmalonic acid
AN00418007	C08645	Methylsuccinic acid
BM03850008	C15515	Murideoxycholic acid
AN01024005	C00137	Myoinositol
TA00952000	C01042	N-Acetyl-Aspartic acid
AN01597000	C01132	N-Acetyl-D-galactosamine
AN01597004	C00140	N-Acetyl-D-glucosamine
AN01597003	C00645	N-Acetyl-D-mannosamine
AN00583008		N-Acetyl-DL-serine
AN00273000		N-Acetyl-Glycine
TA00406009		N-Acetyl-alanine
AN02835000	C00270	N-Acetylneuraminic acid
AN01729001		N-Formyltryptophan
AN00583007		N-Methyl-D-aspartic acid
AN00124004	C00213	N-Methyl-Glycine
TA00943000	C00437	N-acetyl-Ornithine
AN01133000	C02727	N6-Acetyl-Lysine
AN02004003	C05926	Neopterin

NovaMT Library No.	External Identifier	Compound
AN00410003	C01933	Norleucine
AN01069002	C05589	Normetanephrine
AN03717001		Norursodeoxycholic Acid
AN00583002	C00979	O-Acetyl-L-serine
AN02466002	C01530	Octadecanoic acid
AN00376001	C01545	Octanal
AN02437000	C00712	Oleic Acid/Vaccenic Acid
BM03980010	C17727	Omega-Muricholic acid
AN00423000	C00077	Ornithine
BM00826012	C11924	Perillic acid
AN00307000	C05332	Phenethylamine
AN00145000	C00146	Phenol
AN00299005	C00601	Phenylacetaldehyde
AN00460002	C07086	Phenylacetic Acid
AN01210009	C05598	Phenylacetylglycine
AN00814000	C00079	Phenylalanine
AN02385000		Phenylalanyl-Leucine
AN02141000		Phenylalanyl-Proline
AN01996001		Phenylalanyl-Serine
AN00823016	C05607	Phenyllactic acid
BM00344002	C02183	Phloroglucinol
AN00318000	C10164	Picolinic Acid
AN00736000	C02656	Pimelic acid /3-Methyladipic Acid
AN00385000	C00408	Pipecolic acid
AN00259000	C00148	Proline
AN01106001		Prolyl-Alanine
AN02275001		Prolyl-Arginine/Arginyl-Proline
AN01708001		Prolyl-Aspartic acid
AN01874002		Prolyl-Glutamic acid
AN00914001		Prolyl-Glycine
AN01998001		Prolyl-Histidine
AN01688003		Prolyl-Leucine
AN01861001		Prolyl-Lysine
AN01904001		Prolyl-Methionine
AN01516001		Prolyl-Threonine
AN02725000		Prolyl-Tryptophan
AN02380001		Prolyl-Tyrosine
AN01489000		Prolyl-Valine
AN00026003	C00479	Propanal
AN00842000	C00250	Pyridoxal
BM00344003	C01108	Pyrogallol
AN00380000	C01879	Pyroglutamic acid
AN00117000	C00022	Pyruvic acid
AN02714000	C00777	Retinoic acid
AN02071002		Ribothymidine
AN00477006	C00805	Salicylic acid
BM01229005	C07588	Salicyluric acid
AN01323000	C08277	Sebacic Acid
AN01790003	C00835	Sepiapterin
AN00202000	C00065	Serine
AN00975002	C00780	Serotonin
AN01583002		Seryl-Aspartic acid
AN01405001		Seryl-Cysteine
AN01757006		Seryl-Glutamic acid
AN00770001		Seryl-Glycine
AN01852001		Seryl-Histidine
AN01744001		Seryl-Lysine
AN01779001		Seryl-Methionine
AN00565000	C00315	Spermidine
AN02696001	C00319	Sphingosine
AN00281002	C00042	Succinic Acid
AN00177003	C00232	Succinic semialdehyde
BM01266000	C10833	Syringic acid
AN00329000	C00245	Taurine
AN01690004	C06424	Tetradecanoic acid
AN00291000	C00188	Threonine
AN01608002		Threoninyl-Cysteine
AN01936001		Threoninyl-Glutamic acid

NovaMT Library No.	External Identifier	Compound
AN01735004		Threoninyl-Leucine
AN01927001		Threoninyl-Lysine
AN01516002		Threoninyl-Proline
AN00345001	C00178	Thymine
AN02296000		Thyroine
AN01687000	C16308	Traumatic Acid
BP01491000	C17076	Tridecylic Acid
AN01348000	C00078	Tryptophan
AN03834000		Tryptophyl-Tryptophan
AN01037004	C00082	Tyrosine
AN01801001		Tyrosyl-Glycine
AN03081001		Tyrosyl-Phenylalanine
AN01109004	C17715	Undecanoic acid
AN00240000	C00106	Uracil
AN00855000	C00366	Uric acid
AN01868000	C00299	Uridine
BM03850002	C07880	Ursodiol
AN00277003	C00183	Valine
AN01133006		Valyl-Alanine
AN01890005		Valyl-Glutamine
AN00943003		Valyl-Glycine
AN02180002		Valyl-Phenylalanine
AN01349002		Valyl-Serine
AN01548005		Valyl-Threonine
AN01522000		Valyl-Valine
BM00856008	C06672	Vanillic acid
AN00646000	C00385	Xanthine
AN00266001	C00141	a-Ketoisovaleric acid
AN00971000	C02504	alpha-Isopropylmalic acid
AN02387003	C06427	alpha-Linolenic acid
AN01024021	C02336	beta-D-Fructose
AN00406012	C03440	cis-4-Hydroxy-D-proline
AN00934000	C00417	cis-Aconitic acid
AN02350000	C05282	gamma-Glutamylglutamic acid
BM00216002	C01542	o-Cresol/4-Cresol
AN01037003		o-Tyrosine
AN00662000	C04227	p-Octopamine
AN01464000		prolyl-proline
BM00793002	C12621	trans-3-Hydroxycinnamic acid
BM00934003	C02341	trans-Aconitic acid

Table 3. 893 Metabolites that were high-confidence putative matched in tier 2 (LI Library)

NovaMT Library No.	External Identifier	Compound
AN01640006	C16318	(+)-7-Isomethyljasmonic acid
BM01755001	C16600	(-)-threo-Iso(homo)3-citric acid
AN02071000	C05131	(1-Ribosylimidazole)-4-acetic acid
BM00866018	C19083	(1R,4S)-1-Hydroxy-2-oxolimonene
AN00513000	C05678	(2-Amino-1-hydroxyethyl)phosphonate
BM02325001	C20278	(2R,3R)-3-Methylornithinyl-N6-lysine
AN00971001	C04411	(2R,3S)-3-Isopropylmalic acid
AN00423002	C03943	(2R,4S)-2,4-Diaminopentanoic acid
AN00578003	C05161	(2R,5S)-2,5-Diaminohexanoic acid
AN01371003	C04593	(2S,3R)-3-Hydroxybutane-1,2,3-tricarboxylic acid
BM01111001	C20258	(2S,4S)-4-Hydroxy-2,3,4,5-tetrahydrodipicolinic acid
BM00926005	C17366	(2S,5S)-trans-Carboxymethylproline
BM01083005	C11405	(3R)-3-Isopropenyl-6-oxoheptanoic acid
AN00578004	C01142	(3S)-3,6-Diaminohexanoic acid
AN00578005	C01186	(3S,5S)-3,5-Diaminohexanoic acid
AN05016000	C05786	(3Z)-Phycocyanobilin
AN01194003	C04575	(4R,5S)-4,5,6-Trihydroxy-2,3-dioxohexanoic acid
AN03088000	C06429	(4Z,7Z,10Z,13Z,16Z,19Z)-Docosahexaenoic acid
BM01706000	C20817	(5S)-3-(2-Aminoethylsulfanyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylic acid
AN02882006	C07354	(7S,8S)-DiHODE
AN03120001	C16513	(7Z,10Z,13Z,16Z,19Z)-Docosapentaenoic acid
AN02804003	C03242	(8Z,11Z,14Z)-Icosatrienoic acid
BM00638000	C04350	(E)-4-Hydroxyphenylacetaldehyde oxime
AN00956001	C03230	(Indol-3-yl)glycolaldehyde
AN00077000	C03194	(R)-1-Aminopropan-2-ol
AN00441003	C04272	(R)-2,3-Dihydroxy-3-methylbutanoic acid
AN00598000	C06007	(R)-2,3-Dihydroxy-3-methylpentanoic acid
AN00769008	C02488	(R)-2-Ethylmalic acid
AN01371001	C01251	(R)-2-Hydroxybutane-1,2,4-tricarboxylic acid
AN00769012	C01088	(R)-3,3-Dimethylmalic acid
AN00573009	C14463	(R)-3-Hydroxy-3-methyl-2-oxopentanoic acid
AN00422002		(R)-3-Hydroxyhexanoic acid
AN00573011	C01053	(R)-4-Dehydropantoic acid
AN00598002	C00418	(R)-Mevalonic acid
AN00598001	C00522	(R)-Pantoic acid
AN00360000	C00450	(S)-2,3,4,5-Tetrahydropyridine-2-carboxylic acid
AN00769011	C16390	(S)-2-(Hydroxymethyl)glutaric acid
AN00573008	C06006	(S)-2-Aceto-2-hydroxybutanoic acid
BM00606000	C03742	(S)-4-Hydroxymandelonitrile
AN00561008	C03656	(S)-5-Amino-3-oxohexanoic acid
AN00429000	C02091	(S)-Ureidoglycine
AN00184002	C20249	(Z)-3-Peroxyaminoacrylic acid
AN00981001		1,2-Dehydrosalsolinol
AN00767000	C15606	1,2-Dihydroxy-5-(methylthio)pent-1-en-3-one
BM01817000	C16196	1,2-Dihydroxynaphthalene-6-sulfonic acid
AN04326000	C04823	1-(5'-Phosphoribosyl)-5-amino-4-(N-succinocarboxamide)-imidazole
AN03221000	C04677	1-(5'-Phosphoribosyl)-5-amino-4-imidazolecarboxamide
BM01009002	C01214	1-Amino-1-deoxy-scyllo-inositol
AN00171002	C01234	1-Aminocyclopropane-1-carboxylic acid
AN01481002	C11437	1-Deoxy-D-xylulose 5-phosphate
AN02657000	C04545	1-Methylguanosine
AN00247003	C03564	1-Pyrroline-2-carboxylic acid
AN00380007	C04282	1-Pyrroline-4-hydroxy-2-carboxylic acid
AN00247000	C03912	1-Pyrroline-5-carboxylic acid
AN04478002	C00234	10-Formyltetrahydrofolic acid
AN02975002	C14780	11(R)-HETE
AN02975008	C14770	11,12-EET
AN03167002	C05949	12-Keto-leukotriene B4
AN03968003		12-Ketochenodeoxycholic acid
AN01465001	C16311	12-Oxo-9(Z)-dodecenoic acid
AN02955000	C14807	12-OxoETE
AN02857002	C04785	13(S)-HPOT
AN02615001	C14765	13-OxoODE
AN02931006	C14717	15-Deoxy-Delta12,14-PGJ2

NovaMT Library No.	External Identifier	Compound
AN03427008	C05960	15-Keto-prostaglandin F2alpha
AN02263001		15-Methylpalmitic acid
AN02955002	C04577	15-OxoETE
AN03196005	C14781	15H-11,12-EETA
AN02975010	C14778	16(R)-HETE
AN02744000	C05140	16alpha-Hydroxyandrost-4-ene-3,17-dione
AN02615006	C16346	17-Hydroxylinolenic acid
AN02975005	C14749	19(S)-HETE
AN02615005	C16342	2(R)-HOT
AN02857001	C16341	2(R)-HPOT
AN00162000		2,2,2-Trifluoroethanol
BM00903001	C03972	2,3,4,5-Tetrahydrodipicolinic acid
AN00887001		2,3,4-Trihydroxybenzoic acid
AN00355000	C03458	2,3,6-Trihydroxypyridine
AN00858000		2,3-Diaminosalicylic acid
BM01244007	C06580	2,3-Dihydroxy-p-cumic acid
AN03057000	C14794	2,3-Dinor-8-iso prostaglandin F2alpha
AN01906009	C19972	2,4-Bis(acetamido)-2,4,6-trideoxy-beta-L-altropyranose
BM00663001	C16399	2,4-Diamino-6-hydroxylaminotoluene
BM00317000	C14401	2,4-Diaminotoluene
AN00297002		2,4-Dihydroxybutanoic acid
AN01161001	C06201	2,4-Dihydroxyhept-2-enedioic acid
AN00732000	C20781	2,4-Diketo-3-deoxy-L-fuconic acid
PR01750000		2,5-Dihydroxybenzoate 2-O-sulfate
PR03108001		2,5-Dihydroxybenzoate 5-O-glucuronide
PR01750001		2,5-Dihydroxybenzoate 5-O-sulfate
AN00392002	C00433	2,5-Dioxopentanoic acid
AN01068000	C04744	2,6-Diamino-4-hydroxy-5-N-methylformamidopyrimidine
BM00843001	C16397	2,6-Diamino-4-nitrotoluene
AN00679002	C15523	2,6-Dihydroxynicotinic acid
AN00856004	C06207	2,6-Dihydroxyphenylacetic acid
AN02050000	C04441	2-(3-Carboxy-3-aminopropyl)-L-histidine
AN03566000		2-(acetylamino)-1,5-anhydro-2-deoxy-3-O-b-D-galactopyranosyl-D-arabino-Hex-1-enitol
AN00418000	C00900	2-Acetolactic acid/(S)-2-Acetolactic acid
AN01184000	C16850	2-Amino-3,7-dideoxy-D-threo-hept-6-ulosonic acid
ED00601000	C04075	2-Amino-4-chloro-4-pentenoic acid
BM01184001	C21247	2-Amino-5-epi-valiolone
AN00561006	C05825	2-Amino-5-oxohexanoic acid
AN00514000	C03824	2-Aminomuconate semialdehyde
AN01633000	C20653	2-Benzylmalic acid
AN01509000	C11434	2-C-Methyl-D-erythritol 4-phosphate
AN01229000	C05604	2-Carboxy-2,3-dihydro-5,6-dihydroxyindole
AN01214000	C06473	2-Dehydro gluconic acid
AN00594003	C03826	2-Dehydro-3-deoxy-D-xylonic acid
AN00769000	C03827	2-Dehydro-3-deoxy-L-fuconic acid
AN00993001	C01216	2-Dehydro-3-deoxy-galactonic acid
AN00993010	C06892	2-Deoxy-5-keto-D-gluconic acid
AN00796005	C02781	2-Deoxygalactopyranose
AN01385001	C05835	2-Formaminobenzoylacetic acid
BM00322000	C07103	2-Hydroxy-1,4-benzoquinone
BM00252002	C00596	2-Hydroxy-2,4-pentadienoic acid
PR02098001		2-Hydroxy-3-(4-hydroxyphenyl)propenoate O-sulfate
AN01019002	C05350	2-Hydroxy-3-(4-hydroxyphenyl)propenoic acid
AN00966006	C03217	2-Hydroxy-3-oxoadipic acid
AN00592000	C03459	2-Hydroxy-3-oxosuccinic acid
AN00793003	C02763	2-Hydroxy-3-phenylpropenoic acid
AN01288001	C04642	2-Hydroxy-5-carboxymethylmuconate semialdehyde
BM00909003	C07478	2-Hydroxy-5-methyl-cis,cis-muconic acid
AN01455000	C12624	2-Hydroxy-6-ketononatrienedioic acid
BM01987000	C06587	2-Hydroxy-6-oxo-6-(4'-chlorophenyl)-hexa-2,4-dienoic acid
AN01483000	C04479	2-Hydroxy-6-oxonona-2,4-diene-1,9-dioic acid
BM01606001	C14106	2-Hydroxy-7-hydroxymethylchromene-2-carboxylic acid
BM00371001	C11354	2-Hydroxy-cis-hex-2,4-dienoic acid
BM00254008	C01147	2-Hydroxycyclohexan-1-one
AN01137002		2-Hydroxydecanoic acid

NovaMT Library No.	External Identifier	Compound
AN00414001	C03981	2-Hydroxyethylenedicarboxylic acid
AN00909000	C05600	2-Hydroxyhepta-2,4-dienedioic acid
BM00525004	C00682	2-Hydroxymuconate semialdehyde
BM00711002	C02501	2-Hydroxymuconic acid
PR01724005		2-Hydroxyphenylacetic acid O-sulfate
AN00751001		2-Indolecarboxylic acid
AN00715001	C02631	2-Isopropylmaleic acid
BM00711000	C02222	2-Maleylacetic acid
AN00626002	C17883	2-Methoxy-4-vinylphenol
AN01032000	C06050	2-Methyl-3-hydroxy-5-formylpyridine-4-carboxylic acid
AN00532000		2-Methyl-4-heptanone
AN00725002		2-Methylbutyrylglycine
AN01371002	C02225	2-Methylcitric acid
BM00699000	C14099	2-Naphthaldehyde
BM00525005	C03586	2-Oxo-2,3-dihydrofuran-5-acetic acid
AN00583003	C05941	2-Oxo-4-hydroxy-5-aminovaleric acid
AN00995003	C20327	2-Oxo-4-phenylbutyric acid
AN00927000	C03771	2-Oxoarginine
AN00557000	C00940	2-Oxoglutaramic acid
AN00909001	C03063	2-Oxohept-3-enedioic acid
AN00971002	C05994	2-Propylmalic acid
AN00023000	C05985	2-Propynal
AN03075000	C16519	2-Succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylic acid
BM01757002	C22073	2-[(2-Aminoethylcarbamoyl)methyl]-2-hydroxybutanedioic acid
BM01198003	C17691	2-epi-5-epi-Valiolone
AN01592008	C03461	2-trans,6-trans-Farnesal
AN03326000	C00942	3',5'-Cyclic GMP
PR03664000		3,4-Dihydroxy-L-phenylalanine 3-O-glucuronide
AN00856003	C05577	3,4-Dihydroxymandelaldehyde
PR03312004		3,4-Dihydroxymandelaldehyde 3-O-glucuronide
PR01931004		3,4-Dihydroxymandelaldehyde 3-O-sulfate /3,4-Dihydroxymandelaldehyde 4-O-sulfate
PR01931005		3,4-Dihydroxymandelaldehyde 4-O-sulfate
PR03520002		3,4-Dihydroxymandelate 4-O-glucuronide
AN00647004	C04043	3,4-Dihydroxyphenylacetaldehyde
PR03312003		3,4-Dihydroxyphenylacetate 4-O-glucuronide
PR01931002		3,4-Dihydroxyphenylacetic acid 3-O-sulfate
AN00674004		3,4-Dihydroxyphenylethanol
AN01052011	C10447	3,4-Dihydroxyphenylpropanoic acid
AN01040000		3,4-Dimethoxyphenylethylamine
AN00823015	C01198	3-(2-Hydroxyphenyl)propanoic acid
AN01266003	C01207	3-(3,4-Dihydroxyphenyl)lactic acid
AN01241000	C04045	3-(3,4-Dihydroxyphenyl)pyruvic acid
PR03466000		3-(4-Hydroxyphenyl)pyruvate O-glucuronide
AN01019001	C01179	3-(4-Hydroxyphenyl)pyruvic acid
AN00255000		3-Amino-2-piperidone
AN01037005	C04368	3-Amino-3-(4-hydroxyphenyl)propanoic acid
BM01665000	C12469	3-Amino-4,7-dihydroxy-8-chlorocoumarin
BM00657002	C12115	3-Amino-4-hydroxybenzoic acid
AN00065001	C05665	3-Aminopropanal
AN01633001	C20654	3-Benzylmalic acid
AN00047000	C06145	3-Butynal
BM00253000	C02512	3-Cyano-L-alanine
AN01214006	C00618	3-Dehydro-L-gulonic acid
AN00435002	C03064	3-Dehydro-L-threonic acid
AN01161002	C00944	3-Dehydroquinic acid
AN00909002	C02637	3-Dehydroshikimic acid
AN02696000	C02934	3-Dehydrosphinganine
BM01169004	C12459	3-Dimethylallyl-4-hydroxybenzaldehyde
BM01379000	C12458	3-Dimethylallyl-4-hydroxybenzoic acid
BM01781000	C12457	3-Dimethylallyl-4-hydroxymandelic acid
AN00769009	C01989	3-Ethylmalic acid
AN00157000	C16310	3-Hexenal
AN00283003		3-Hydroxy-2-methyl-[S-(R,R)]-butanoic acid
AN00418003	C04181	3-Hydroxy-3-methyl-2-oxobutanoic acid
BM00573003	C16272	3-Hydroxy-5-oxohexanoic acid

NovaMT Library No.	External Identifier	Compound
AN01634002	C03227	3-Hydroxy-L-kynurenine
AN00406001		3-Hydroxy-L-proline
AN01353000	C01259	3-Hydroxy-N6,N6,N6-trimethyl-L-lysine
BM00711001	C03676	3-Hydroxy-cis,cis-muconic acid
PR03918001		3-Hydroxy-kynurenine O-glucuronide
BM00333002	C14602	3-Hydroxyaminophenol
PR01738000		3-Hydroxyanthranilate O-sulfate
BM01229006		3-Hydroxyhippuric acid
AN01029004	C05636	3-Hydroxykynurenamine
PR03469001		3-Hydroxykynurenamine O-glucuronide
AN01019004		3-Hydroxyphenylpyruvic acid
AN00487000	C18620	3-Hydroxypicolinic acid
AN00070002	C00969	3-Hydroxypropanal
AN01831000		3-Mercaptolactate-cysteine disulfide
AN00823014	C05581	3-Methoxy-4-hydroxyphenylacetaldehyde
PR03283000		3-Methoxy-4-hydroxyphenylacetaldehyde O-glucuronide
AN01079002	C05594	3-Methoxy-4-hydroxyphenylethyleneglycol
AN01052010	C05583	3-Methoxy-4-hydroxyphenylglycolaldehyde
BM00299001	C07209	3-Methylbenzaldehyde
BM00594000	C06029	3-Methylmalic acid/D-erythro-3-Methylmalic acid
BM00873002	C12477	3-Methylpyrrole-2,4-dicarboxylic acid
BM00460007	C14087	3-Methylsalicylaldehyde
BM00487002	C14418	3-Nitrophenol
AN01655000		3-Nitrotyrosine
AN01108002		3-Oxodecanoic acid
AN00396004	C02122	3-Oxohexanoic acid
AN00718001		3-Oxooctanoic acid
AN00117001	C00222	3-Oxopropanoic acid
BM01392003		3-Phenylpropionylglycine
AN00971003	C02123	3-Propylmalic acid
AN00814002		3-Pyridinebutanoic acid
AN00655000	C00606	3-Sulfino-L-alanine
BM01157000	C06336	3-Sulfocatechol
AN02127003		3-hydroxy-3-(3-hydroxyphenyl)propanoic acid-O-sulphate
AN04196001	C04554	3alpha,7alpha-Dihydroxy-5beta-cholestanic acid
AN04056003	C17333	3beta-Hydroxy-5-cholestenoic acid
AN03682004		3beta-Hydroxy-delta5-cholenic acid
AN00751003	C05639	4,6-Dihydroxyquinoline
AN00751004	C05637	4,8-Dihydroxyquinoline
AN01620000	C05652	4-(2-Amino-5-hydroxyphenyl)-2,4-dioxobutanoic acid
AN01385000	C01252	4-(2-Aminophenyl)-2,4-dioxobutanoic acid
AN03414000	C06118	4-(4-Deoxy-alpha-D-gluc-4-enuronosyl)-D-galacturonic acid
AN01694002	C04796	4-(L-Alanin-3-yl)-2-hydroxy-cis,cis-muconate 6-semialdehyde
AN02791000	C21107	4-(beta-D-Ribofuranosyl)phenol 5'-phosphate
AN01643000	C11355	4-Amino-4-deoxychorismic acid
AN00493001	C01279	4-Amino-5-hydroxymethyl-2-methylpyrimidine
AN00115001	C00555	4-Aminobutyraldehyde
BM00333000	C18351	4-Aminocatechol
AN01217000		4-Aminohippuric acid
BM01100002	C04484	4-Carboxy-2-hydroxymuconate semialdehyde
BM01026000	C22137	4-Chloro-L-lysine
BM00354000	C14450	4-Chloroaniline
BM00365000	C02124	4-Chlorophenol
AN00884000	C03077	4-Chlorophenylacetic acid
BM00368000	C16473	4-Fluorocatechol
AN00386000	C02647	4-Guanidinobutanal
AN00551000	C03078	4-Guanidinobutanamide
AN00256001		4-Heptanone
BM00418004	C03589	4-Hydroxy-2-oxopentanoic acid
PR03076004		4-Hydroxy-3-methoxy-benzaldehyde O-glucuronide
BM00979000	C06034	4-Hydroxy-4-methylglutamic acid
AN03933001		4-Hydroxy-5-(3',5'-dihydroxyphenyl)-valeric acid-O-glucuronide
AN01189000		4-Hydroxydebrisoquine
AN00703006		4-Hydroxynonenal

NovaMT Library No.	External Identifier	Compound
AN00460001	C03765	4-Hydroxyphenylacetaldehyde
PR02872001		4-Hydroxyphenylacetaldehyde O-glucuronide
AN00481000	C06044	4-Hydroxyphenylethanol
BM00818005	C03590	4-Hydroxyphenylglyoxylic acid
AN01288000	C01036	4-Maleylacetoacetic acid /4-Fumarylacetoacetic acid
BM00754000	C06234	4-Methyl-L-glutamic acid
BM00711003	C06035	4-Methylene-2-oxoglutaric acid
BM00722001	C00651	4-Methylene-L-glutamic acid
BM00716001	C01109	4-Methylene-L-glutamine
AN00593000	C01180	4-Methylthio-2-oxobutanoic acid
AN01076002		4-O-Methylgallic acid
AN00785001	C19567	4-Oxo-1-(3-pyridyl)-1-butanone
AN00380006	C01877	4-Oxoproline
AN02714004	C16683	4-Oxoretinol
AN00808002	C00971	4-Pyridoxolactone
BM01157001	C06674	4-Sulfocatechol
BM03412000	C18349	4-[2-(5-Carboxy-2-hydroxy-3-methoxyphenyl)-2-oxoethylidene]-2-hydroxy-2-pentenedioic acid
AN00505003	C20522	4-imidazolylpropanoic acid
AN01981001	C05198	5'-Deoxyadenosine
AN02975012	C04805	5(S)-HETE
AN00606002	C05578	5,6-Dihydroxyindole
AN02975006	C14768	5,6-EET
AN03167000	C14815	5,6-Epoxytetraene
AN01177000	C17938	5,6-Indolequinone-2-carboxylic acid
AN01668003	C05655	5-(2'-Carboxyethyl)-4,6-dihydroxypicolinic acid
AN02003000	C05641	5-(3'-Carboxy-3'-oxopropenyl)-4,6-dihydroxypicolinic acid
AN02031000	C05656	5-(3'-Carboxy-3'-oxopropyl)-4,6-dihydroxypicolinic acid
AN00725008	C03087	5-Acetamidopentanoic acid
AN00406003	C01110	5-Amino-2-oxopentanoic acid
AN00174001	C12455	5-Aminopentanal
AN00270000	C00990	5-Aminopentanamide
BM01455001	C18338	5-Carboxyvanillic acid
AN00966000	C04053	5-Dehydro-4-deoxy-D-glucuronic acid
AN01214010	C21644	5-Dehydro-L-gluconic acid
AN00993009	C16737	5-Deoxy-D-glucuronic acid
AN01314000	C12248	5-Hydroxy-2-oxo-4-ureido-2,5-dihydro-1H-imidazole-5-carboxylic acid
AN01992000	C05648	5-Hydroxy-N-formylkynurenine
AN00956002	C05634	5-Hydroxyindoleacetaldehyde
AN01180000	C05635	5-Hydroxyindoleacetic acid
AN01559000	C05646	5-Hydroxyindolepyruvic acid
AN01029003	C05638	5-Hydroxykynurenamine
PR03469000		5-Hydroxykynurenamine O-glucuronide
PR02102000		5-Hydroxykynurenamine O-sulfate
AN01634001	C05651	5-Hydroxykynurenine
PR03918000		5-Hydroxykynurenine O-glucuronide
AN02012000	C05844	5-L-Glutamyl-taurine
AN01360003	C05660	5-Methoxyindoleacetic acid
AN01186000		5-Methoxytryptophol
AN02955001	C14732	5-OxoETE
AN00266002	C03273	5-Oxopentanoic acid
AN01846000	C03366	5-Phosphooxy-L-lysine
AN01692000	C03090	5-Phosphoribosylamine
EF01663003		5-Tetradecenoic acid
AN03819001		5beta-Cholanic acid-3, 7-dione
AN01232000	C01300	6-(Hydroxymethyl)-7,8-dihydropterin
AN01114000	C05548	6-Acetamido-2-oxohexanoic acid
AN00561007	C03239	6-Amino-2-oxohexanoic acid
BM00422001	C06103	6-Hydroxyhexanoic acid
AN01356000	C05663	6-Hydroxykynurenic acid
PR04107000		6-Hydroxymelatonin O-glucuronide
AN03615002	C05962	6-Keto-prostaglandin E1
AN03641001	C05961	6-Keto-prostaglandin F1alpha
AN00514001	C04226	6-Oxo-1,4,5,6-tetrahydronicotinic acid
AN01790002	C03684	6-Pyruvoyltetrahydropterin
AN01811004	C02953	7,8-Dihydrobiopterin

NovaMT Library No.	External Identifier	Compound
AN02034000	C04874	7,8-Dihydroneopterin
AN01035001	C21065	7,8-Dihydroxanthopterin
AN01011000	C16675	7-Aminomethyl-7-carbaguanine
AN00954000	C15996	7-Cyano-7-carbaguanine
BM00550002	C16590	7-Oxoheptanoic acid
AN04160000	C17337	7alpha-Hydroxy-3-oxo-4-cholestenoic acid
PR04523004		7alpha-Hydroxydehydroepiandrosterone 3-O-glucuronide
AN02975001	C14776	8(S)-HETE
AN02975007	C14769	8,9-EET
AN00898021	C18202	8-Methyl-6-nonenoic acid
AN02615003	C04780	8-[(1R,2R)-3-Oxo-2-{(Z)-pent-2-enyl}cyclopentyl]octanoic acid
AN02650001	C14825	9(10)-EpOME
AN03819002		9(11), (5beta)-Cholenic acid-3alpha-ol-12-one
AN02650000	C14767	9(S)-HODE
AN02615002	C16326	9(S)-HOT
AN02912002	C14828	9,10-DHOME
AN02615000	C14766	9-OxoODE
AN00918000	C16322	9-Oxononanoic acid
AN02413001	C04056	9-cis,11-trans-Octadecadienoic acid
AN02464003	C16681	9-cis-Retinal
AN02714005	C15493	9-cis-Retinoic acid
AN00119000	C01769	Acetoin
BM00107001	C02659	Acetone cyanohydrin
AN03822000	C05993	Acetyl adenylic acid
BM00396001	C06102	Adipate semialdehyde
AN03151000	C16527	Adrenic acid
AN01036000		Adrenochrome o-semiquinone
AN04929000	C05554	Aerobactin
AN01320000		Alanyl-Hydroxyproline
AN02337000	C00806	Alanyl-Tryptophan/Tryptophyl-Alanine
AN00718002		Alpha-Ketooctanoic acid
AN00028000	C06735	Aminoacetaldehyde
AN00065000	C01888	Aminoacetone
AN00113000	C20253	Aminoacrylic acid
BM00333001	C14604	Aminohydroquinone
AN00287000	C00872	Aminomalonic acid
AN02776000	C00219	Arachidonic acid
AN02758000		Arginyl-Glutamic acid
AN02745000		Arginyl-Lysine
AN00966003	C00072	Ascorbic acid
AN02109000		Asparaginyl-Glutamine
AN01887000		Asparaginyl-Hydroxyproline
AN01720000		Asparaginyl-Valine
AN01708005		Aspartyl-L-proline
AN03174000	C04540	Aspartylglycosamine
BM02257001	C20942	Bacilysin
BM00344000	C02814	Benzene-1,2,4-triol
AN00818000		Benzoquinoneacetic acid
AN02899000		Beta-D-Glucopyranuronic acid
AN05473000	C16564	Bis(glutathionyl)spermine disulfide
AN04623000	C03646	Bis-gamma-glutamylcystine
AN00061003	C02845	Butanone
AN04155000	C05673	CMP-2-aminoethylphosphonate
AN05180000	C03691	CMP-N-glycoloylneuraminic acid
AN04469000	C05674	CMP-N-trimethyl-2-aminoethylphosphonate
AN05743000	C00323	Caffeoyl-CoA
AN00036000	C01563	Carbamic acid
BM01872001	C20818	Carbapenem biosynthesis intermediate 2
BM00842003	C20821	Carbapenem biosynthesis intermediate 6
AN01660003	C00386	Carnosine
BM00227000	C00090	Catechol
BM00903000	C21249	Cetoniacytone B
BM00086000	C06754	Chloroacetaldehyde
AN01654001	C00251	Chorismic acid
BM00898014	C16462	Citronellic acid
BM05307000	C12032	Clorobiocin
AN02387002	C07289	Crepenynic acid

NovaMT Library No.	External Identifier	Compound
AN00013000	C01417	Cyanic acid
BM00108000	C16267	Cyclopropanecarboxylic acid
AN01797000		Cystathionine sulfoxide
AN00304000	C00097	Cysteine
AN01608001		Cysteinyl-Threonine
PR03873000		Cysteinyldopa 3-O-sulfate
PR03873001		Cysteinyldopa 4-O-sulfate
AN00681001	C04122	D-1-Aminopropan-2-ol O-phosphate
AN01194002		D-Glucaro-1,4-lactone
AN02250000	C01726	D-Lombricine
AN01548006	C04020	D-Lysopine
AN01908000	C04137	D-Octopine
AN00594008	C06032	D-erythro-3-Methylmalic acid
BM01057002	C14113	Decahydro-2-naphthoic acid
AN00113001	C02218	Dehydroalanine
AN05236000		Dehydroisocoproporphyrinogen
AN03167003	C05958	Delta-12-Prostaglandin J2
AN00360001	C04092	Delta1-Piperideine-2-carboxylic acid
AN02287001	C18133	Deoxyshikonin
BM02863000	C05143	Dhurrin
BM00371002	C06719	Dihydrophloroglucinol
PR03639001		Dihydrotestosterone 17-O-sulfate
AN00592001	C00975	Dihydroxyfumaric acid
AN02485001		Diphenol glucuronide
AN03523001		Dityrosine
AN01229001	C00822	Dopaquinone
AN00528000	C06231	Ectoine
AN01696000		Endalin
AN02339000		Epsilon-(gamma-Glutamyl)-Lysine
AN02585003	C16319	Etherolenic acid
AN00256002		Ethyl isobutyl ketone
AN01784000	C16502	Farnesoic acid
AN01408002	C05647	Formyl-5-hydroxykynurenamine
PR03769000		Formyl-5-hydroxykynurenamine O-glucuronide
PR02520000		Formyl-5-hydroxykynurenamine O-sulfate
AN00808001	C05653	Formylanthranilic acid
AN00938000	C16674	Formylisoglutamine
AN02121000		Gamma-glutamyl-ornithine
AN00477005	C05585	Gentisate aldehyde
PR02900001		Gentisate aldehyde 2-O-glucuronide
PR02900002		Gentisate aldehyde 5-O-glucuronide
BM00866012	C16461	Geranic acid
AN02089000		Glutaminyl-Hydroxyproline
AN03144000		Glutaminyl-Tryptophan
AN01874000		Glutamyl-Proline
AN01144001		Glutaryl-Glycine
AN02808000	C00051	Glutathione
AN05115000	C00127	Glutathione disulfide
AN04193000	C05730	Glutathionylspermidine
AN01334004		Glycyl-Gamma-glutamic acid
AN02477000		Glycyl-Prolyl-Hydroxyproline
AN00029000	C17349	Guanidine
AN01242000	C00800, C00257	Gulonic acid
AN05127000		Harderoporphyrinogen
AN03196003	C14808	Hepoxilin A3
AN01945000	C16343	Heptadecatrienal
AN02184003	C16344	Heptadecatrienoic acid
AN01828000	C00517	Hexadecanal
AN02496000	C19615	Hexadecanedioic acid
AN02055000	C00249	Hexadecanoic acid
AN02050001		Histidinyl-Threonine
AN03270000		Histidinyl-Tryptophan
AN02951002		Histidinyl-Tyrosine
AN01826000	C00884	Homocarnosine
PR03312000		Homogentisic acid 2-O-glucuronide
PR03312001		Homogentisic acid 5-O-glucuronide
PR03489000		Homovanillate O-glucuronide
BM00219001	C02720	Hydroxylaminobenzene

NovaMT Library No.	External Identifier	Compound
AN00743001		Hydroxyoctanoic acid
AN01887001		Hydroxyprolyl-Asparagine
AN02089002		Hydroxyprolyl-Gamma-glutamic acid
AN02089001		Hydroxyprolyl-Glutamine
AN02226000		Hydroxyprolyl-Histidine
AN01684001		Hydroxyprolyl-Proline
AN01544003		Hydroxyprolyl-Serine
AN02608001		Hydroxyprolyl-Tyrosine
AN01711000		Hydroxyprolyl-Valine
AN00193002	C00168	Hydroxypyruvic acid
AN02004001		Hydroxysepiapterin
AN02827002	C16525	Icosadienoic acid
AN02804004	C16522	Icosatrienoic acid
AN00698000	C05568	Imidazole lactic acid
AN00671001	C03277	Imidazole pyruvic acid
AN00403001	C05840	Iminoaspartic acid
AN00064000	C15809	Iminoglycine
AN00582000	C05579	Indole-5,6-quinone
AN01360002	C02043	Indolelactic acid
AN01332000	C00331	Indolepyruvic acid
AN00431003	C05658	Indoxyl
AN01844001	C04299	Inositol cyclic phosphate
AN00561001		Isobutyrylglycine
AN01194007	C00311	Isocitric acid
AN01052002		Isohomovanillic acid
AN01876002		Isoleucyl-Hydroxyproline
AN01548000		Isoleucyl-Serine
AN01735001		Isoleucyl-Threonine
AN01640006	C16318	Isomer 1 of (+)-7-Isomethyljasmonic acid
BM01755001	C16600	Isomer 1 of (-)-threo-Iso(homo)3-citric acid
AN02027002	C08362	Isomer 1 of (9Z)-Hexadecenoic acid
AN00441003	C04272	Isomer 1 of (R)-2,3-Dihydroxy-3-methylbutanoic acid
AN00767000	C15606	Isomer 1 of 1,2-Dihydroxy-5-(methylthio)pent-1-en-3-one
BM01817000	C16196	Isomer 1 of 1,2-Dihydroxynaphthalene-6-sulfonic acid
BM01009002	C01214	Isomer 1 of 1-Amino-1-deoxy-scyllo-inositol
AN00171002	C01234	Isomer 1 of 1-Aminocyclopropane-1-carboxylic acid
AN02615001	C14765	Isomer 1 of 13-OxoODE
AN03427008	C05960	Isomer 1 of 15-Keto-prostaglandin F2alpha
AN00355000	C03458	Isomer 1 of 2,3,6-Trihydroxypyridine
BM01184001	C21247	Isomer 1 of 2-Amino-5-epi-valiolone
AN00726001		Isomer 1 of 2-Aminooctanoic acid
AN00796005	C02781	Isomer 1 of 2-Deoxygalactopyranose
BM01987000	C06587	Isomer 1 of 2-Hydroxy-6-oxo-6-(4'-chlorophenyl)-hexa-2,4-dienoic acid
AN00197004	C05984	Isomer 1 of 2-Hydroxybutyric acid
AN01137002		Isomer 1 of 2-Hydroxydecanoic acid
AN00177004	C00109	Isomer 1 of 2-Ketobutyric acid
AN00396002	C00902	Isomer 1 of 2-Ketohexanoic acid
AN00995003	C20327	Isomer 1 of 2-Oxo-4-phenylbutyric acid
AN00255000		Isomer 1 of 3-Amino-2-piperidone
AN00283003		Isomer 1 of 3-Hydroxy-2-methyl-[S-(R,R)]-butanoic acid
BM00460007	C14087	Isomer 1 of 3-Methylsalicylaldehyde
AN01108002		Isomer 1 of 3-Oxodecanoic acid
AN00718001		Isomer 1 of 3-Oxooctanoic acid
AN02127003		Isomer 1 of 3-hydroxy-3-(3-hydroxyphenyl)propanoic acid-O-sulphate
AN00751004	C05637	Isomer 1 of 4,8-Dihydroxyquinoline
BM01026000	C22137	Isomer 1 of 4-Chloro-L-lysine
AN00793000	C00811	Isomer 1 of 4-Coumaric acid
AN00785001	C19567	Isomer 1 of 4-Oxo-1-(3-pyridyl)-1-butanone
AN00380006	C01877	Isomer 1 of 4-Oxoproline
AN00808002	C00971	Isomer 1 of 4-Pyridoxolactone
AN00277004	C00431	Isomer 1 of 5-Aminopentanoic acid
AN01274001		Isomer 1 of 5-Dodecenoic acid
AN01180000	C05635	Isomer 1 of 5-Hydroxyindoleacetic acid
AN00774001	C16741	Isomer 1 of 5-Hydroxylysine
AN03836002		Isomer 1 of 5beta-Cholanic acid-12alpha-ol-3-one
BM00550002	C16590	Isomer 1 of 7-Oxoheptanoic acid

NovaMT Library No.	External Identifier	Compound
AN00918000	C16322	Isomer 1 of 9-Oxononanoic acid
AN00014000	C00084	Isomer 1 of Acetaldehyde
AN00119000	C01769	Isomer 1 of Acetoin
AN00026002	C00207	Isomer 1 of Acetone - isomer 1/Propanal
AN01036000		Isomer 1 of Adrenochrome o-semiquinone
AN01544002		Isomer 1 of Alanyl-Glutamic acid
AN00718002		Isomer 1 of Alpha-Ketooctanoic acid
AN00754003	C00956	Isomer 1 of Aminoadipic acid
AN02776000	C00219	Isomer 1 of Arachidonic acid
AN03174000	C04540	Isomer 1 of Aspartylglycosamine
AN01548006	C04020	Isomer 1 of D-Lysopine
AN00704003	C12307	Isomer 1 of Decanal/2-Decanone
AN05236000		Isomer 1 of Dehydroisocoproporphyrinogen
AN02287001	C18133	Isomer 1 of Deoxyshikonin
BM00371002	C06719	Isomer 1 of Dihydrophloroglucinol
PR03639001		Isomer 1 of Dihydrotestosterone 17-O-sulfate
AN02485001		Isomer 1 of Diphenol glucuronide
AN00418009		Isomer 1 of Ethylmalonic acid
AN01408002	C05647	Isomer 1 of Formyl-5-hydroxykynurenamine
AN02849001		Isomer 1 of Glutamyl-Tyrosine
AN01828000	C00517	Isomer 1 of Hexadecanal
AN02055000	C00249	Isomer 1 of Hexadecanoic acid
AN00684000		Isomer 1 of Histidine
AN01061000	C16511	Isomer 1 of Homocysteic acid
AN00291001	C00263	Isomer 1 of Homoserine
AN02004001		Isomer 1 of Hydroxysepiapterin
AN01360002	C02043	Isomer 1 of Indolelactic acid
AN00574004	C16673	Isomer 1 of Isoglutamine
AN01876002		Isomer 1 of Isoleucyl-Hydroxyproline
BM00392004	C00490	Isomer 1 of Itaconic acid
AN00291005	C05519	Isomer 1 of L-Allothreonine
AN00410000	C00123	Isomer 1 of Leucine
AN00578000	C00047	Isomer 1 of Lysine
AN02121003		Isomer 1 of Lysyl-Aspartic acid
BM00344001	C11918	Isomer 1 of Maltol
AN00608000	C00073	Isomer 1 of Methionine
AN00102001		Isomer 1 of Methyl propenyl ketone
AN00281003	C02170	Isomer 1 of Methylmalonic acid
PR00561005		Isomer 1 of N-Acetyl-(S)-2-Aminobutanoic acid
AN00583008		Isomer 1 of N-Acetyl-DL-serine
PR00189009		Isomer 1 of N-Acetyl-Ethanolamine
AN00938001	C00439	Isomer 1 of N-Formimino-L-glutamic acid
AN01778000	C02700	Isomer 1 of N-formylkynurenine
PR00943004		Isomer 1 of N5-Acetyl-L-Ornithine
AN00410003	C01933	Isomer 1 of Norleucine
AN00385000	C00408	Isomer 1 of Pipecolic acid
AN00259000	C00148	Isomer 1 of Proline
BM00344003	C01108	Isomer 1 of Pyrogallol
AN00596001	C17268	Isomer 1 of Pyruvophenone
AN00281002	C00042	Isomer 1 of Succinic acid
BM01168004	C20914	Isomer 1 of Tabtoxin biosynthesis intermediate 4
AN01711001		Isomer 1 of Valyl-Hydroxyproline
AN01892001		Isomer 1 of Valyl-Lysine
AN00934000	C00417	Isomer 1 of cis-Aconitic acid
AN01640006	C16318	Isomer 2 of (+)-7-Isomethyljasmonic acid
BM01755001	C16600	Isomer 2 of (-)-threo-Iso(homo)3-citric acid
BM01817000	C16196	Isomer 2 of 1,2-Dihydroxynaphthalene-6-sulfonic acid
BM00460007	C14087	Isomer 2 of 3-Methylsalicylaldehyde
AN00751004	C05637	Isomer 2 of 4,8-Dihydroxyquinoline
BM01026000	C22137	Isomer 2 of 4-Chloro-L-lysine
AN00277004	C00431	Isomer 2 of 5-Aminopentanoic acid
BM00550002	C16590	Isomer 2 of 7-Oxoheptanoic acid
AN00918000	C16322	Isomer 2 of 9-Oxononanoic acid
AN00014000	C00084	Isomer 2 of Acetaldehyde
AN01548006	C04020	Isomer 2 of D-Lysopine
AN01828000	C00517	Isomer 2 of Hexadecanal
AN00608000	C00073	Isomer 2 of Methionine
AN00281003	C02170	Isomer 2 of Methylmalonic acid

NovaMT Library No.	External Identifier	Compound
PR00943004		Isomer 2 of N5-Acetyl-L-Ornithine
AN00281002	C00042	Isomer 2 of Succinic acid
BM01168004	C20914	Isomer 2 of Tabtoxin biosynthesis intermediate 4
AN01548006	C04020	Isomer 3 of D-Lysopine
BM04636001	C00927	Isonocardicin A
AN00033000	C01845	Isopropanol
AN00929002		Isovalerylalanine
AN01440000	C08491	Jasmonic acid
AN00380005	C04281	L-1-Pyrroline-3-hydroxy-5-carboxylic acid
AN00273001	C03508	L-2-Amino-3-oxobutanoic acid
BM01144000	C03871	L-2-Amino-6-oxoheptanedioic acid
AN00583004	C05938	L-4-Hydroxyglutamate semialdehyde
BM00842002	C12323	L-4-Hydroxyphenylglycine
AN00291005	C05519	L-Allothreonine
AN00561000	C04076	L-Allysine
AN01671000	C00826	L-Arogenic acid
AN00273002	C00441	L-Aspartate 4-semialdehyde
AN00868000	C00506	L-Cysteic acid
AN01024003	C01720	L-Fuconic acid
AN01667000	C03287	L-Glutamyl 5-phosphate
AN00493000	C01929	L-Histidinal
AN01012005	C17235	L-Homophenylalanine
AN01260000	C05588	L-Metanephrine
AN00876002	C00547	L-Noradrenaline
PR01947000		L-Noradrenaline 3-O-sulfate
EF02022001		L-Pyridosine
BM02037000	C16138	L-Pyrrolysine
AN01024020	C01934	L-Rhamnonic acid
AN00769005	C02991	L-Rhamnono-1,4-lactone
AN02113000		L-Tyrosine O-sulfate
AN01900001		L-alpha-Aspartyl-L-hydroxyproline
AN02107001		L-alpha-glutamyl-L-hydroxyproline
BM00380002	C22141	L-beta-Ethynylserine
AN01933000		L-beta-aspartyl-L-aspartic acid
AN01163000		L-beta-aspartyl-L-glycine
AN01583001		L-beta-aspartyl-L-serine
AN01757003		L-beta-aspartyl-L-threonine
AN00782000	C05947	L-erythro-4-Hydroxyglutamic acid
ED02071001	C22140	L-gamma-Glutamyl-(3R)-L-beta-ethynylserine
AN01130001		L-glycyl-L-hydroxyproline
AN02380000		L-phenylalanyl-L-hydroxyproline
AN00583005	C03618	L-threo-3-Methylaspartic acid
AN01876003		Leucyl-Hydroxyproline
AN01688001		Leucyl-Proline
AN03196007	C02165	Leukotriene B4
AN05162000	C02166	Leukotriene C4
BM00344001	C11918	Maltol
AN04939000		Mesoporphyrin IX
PR03666000		Metanephrine O-glucuronide
PR03975000		Metatonin N-glucuronide
AN00009000	C00132	Methanol
AN01971000		Methionyl-Threonine
AN01939000		Methionyl-Valine
AN00130004		Methoxyacetic acid
AN00396003		Mevalonolactone
AN00951000	C01041	Monodehydroascorbic acid
BM03948000	C12221	Myxochelin B
AN00744000	C02728	N(6)-Methyllysine
AN00738001	C06442	N(gamma)-Acetyldiaminobutyric acid
AN01171000	C05933	N(omega)-Hydroxyarginine
BM01257001	C19715	N,N-Dihydroxy-L-phenylalanine
BM00609000	C20314	N,N-Dihydroxy-L-valine
AN02555000	C03406	N-(L-Arginino)succinic acid
PR00561005		N-Acetyl-(S)-2-Aminobutanoic acid
PR01065002		N-Acetyl-2-Aminomuconate semialdehyde
PR01789001		N-Acetyl-2-Carboxy-2,3-dihydro-5,6-dihydroxyindole
PR01144002		N-Acetyl-2-Oxo-4-hydroxy-5-aminovaleric acid
PR01809000		N-Acetyl-3,4-Dihydroxy-L-phenylalanine

NovaMT Library No.	External Identifier	Compound
PR01229010		N-Acetyl-3-Hydroxyanthranilic acid
PR02188000		N-Acetyl-4-(2-Amino-3-hydroxyphenyl)-2,4-dioxobutanoic acid
PR01949000		N-Acetyl-4-(2-Aminophenyl)-2,4-dioxobutanoic acid
TA02137001		N-Acetyl-5-Hydroxy-L-tryptophan
PR02604000		N-Acetyl-5-Hydroxy-N-formylkynurenine
PR02417003		N-Acetyl-6-(1'-Hydroxy-2'-oxopropyl)-tetrahydropterin
PR02417000		N-Acetyl-6-Lactoyl-5,6,7,8-tetrahydropterin
PR02392000		N-Acetyl-6-Pyruvoyltetrahydropterin
AN03398000	C04016	N-Acetyl-7-O-acetylneuraminic acid
AN03398001		N-Acetyl-9-O-acetylneuraminic acid
PR01006005		N-Acetyl-Anthranilic acid
PR00381000		N-Acetyl-Dehydroalanine
AN01234000		N-Acetyl-Dopamine
PR01789000		N-Acetyl-Dopaquinone
PR00189009		N-Acetyl-Ethanolamine
PR01970000		N-Acetyl-Formyl-5-hydroxykynurenamine
PR05241000		N-Acetyl-Glutathione disulfide
TA00926001		N-Acetyl-Hydroxyproline
PR01130004		N-Acetyl-Isoglutamine
PR00722000		N-Acetyl-L-2-Amino-3-oxobutanoic acid
PR01144003		N-Acetyl-L-4-Hydroxyglutamate semialdehyde
PR01646001		N-Acetyl-L-Adrenaline
TA02422000		N-Acetyl-L-Cystine
PR01766000		N-Acetyl-L-Dopachrome
PR00977002		N-Acetyl-L-Homocysteine
PR01449002		N-Acetyl-L-Noradrenaline
TA00708002		N-Acetyl-L-Proline
TA01623001		N-Acetyl-L-Tyrosine
TA01144004	C00624	N-Acetyl-L-glutamic acid
TA01130000		N-Acetyl-L-glutamine
PR01733000		N-Acetyl-N(omega)-Hydroxyarginine
PR01734001		N-Acetyl-N-Methylserotonin
PR00406011		N-Acetyl-Sarcosine
PR02392001		N-Acetyl-Sepiapterin
AN01013000		N-Acetyl-Tyramine
TA00938003		N-Acetyl-asparagine
AN00406005	C01073	N-Acetyl-beta-alanine
TA01392000	C03519	N-Acetyl-phenylalanine
PR02058000		N-Acetyl-sn-Glycero-3-phosphoethanolamine
PR00926003		N-Acetyl-trans-3-Hydroxy-L-proline
AN03567000	C17951	N-Acetylbialaphos
AN00956000	C02298	N-Acetylindoxyl
AN02590000	C02713	N-Acetylmuramic acid
AN00400000	C02714	N-Acetylputrescine
AN01546000	C00978	N-Acetylserotonin
PR03861000		N-Acetylserotonin O-glucuronide
AN00380003		N-Acryloylglycine
AN00561002		N-Butyrylglycine
AN00419003	C01043	N-Carbamoylsarcosine
AN00189006	C11735	N-Ethylglycine
AN00734001	C03409	N-Formimino-L-aspartic acid
AN00938001	C00439	N-Formimino-L-glutamic acid
AN00824000	C19872	N-Formyl-4-amino-5-aminomethyl-2-methylpyrimidine
AN00952001	C01045	N-Formyl-L-glutamic acid
AN00978002	C03145	N-Formylmethionine
BM00587000	C20310	N-Hydroxy-L-isoleucine
BM01037000	C19712	N-Hydroxy-L-phenylalanine
BM01257000	C03004	N-Hydroxy-L-tyrosine
BM00433000	C20313	N-Hydroxy-L-valine
AN00725003		N-Isovaleroylglycine
TM00754001	C01046	N-Methyl-L-glutamic acid
AN00277000		N-Methyl-a-aminoisobutyric acid
AN00681000	C01210	N-Methylethanolamine phosphate
AN00337000	C05127	N-Methylhistamine
PR03583000		N-Methylserotonin O-glucuronide
AN02508000		N-Ribosylhistidine
TA01903000		N-acetyl-Tryptophan

NovaMT Library No.	External Identifier	Compound
AN01778000	C02700	N-formylkynurenine
AN02336005		N-gamma-Glutamyl-Glutamine
PR02197000		N2'-Acetyl-5'-Hydroxykynurenine
PR04468000		N2'-Acetyl-CMP-2-aminoethylphosphonate
PR02454001		N2-Acetyl-5-Phosphooxy-L-lysine
PR04468001		N2-Acetyl-CMP-2-aminoethylphosphonate
PR03487001		N2-Acetyl-Cysteinyldopa
AN02172003		N2-Acetyl-L-Cystathionine
PR01349003		N2-Acetyl-L-Hydroxylysine
AN03710000	C20333	N2-Citryl-N6-acetyl-N6-hydroxy-L-lysine
PR01612003		N3-Acetyl-5'-Hydroxykynurenamine
PR04121001		N3-Acetyl-S-Adenosyl-L-homocysteine
PR03877001		N3-Acetyl-S-Adenosylmethioninamine
PR00943004		N5-Acetyl-L-Ornithine
PR04121000		N6'-Acetyl-S-Adenosyl-L-homocysteine
PR03877000		N6'-Acetyl-S-Adenosylmethioninamine
AN01138000	C03793	N6,N6,N6-Trimethyl-L-lysine
AN00774000	C01028	N6-Hydroxy-L-lysine
AN02416001		N6-Methyladenosine/N-Acetyl-6-(1'-Hydroxy-2'-oxopropyl)-tetrahydropterin
AN02121001		N6-beta-Aspartyl-Lysine
PR03487000		N7'-Acetyl-Cysteinyldopa
AN01117001	C01029	N8-Acetyl-spermidine
AN02207000	C06469	Neuraminic acid
AN00318001	C00253	Nicotinic acid
BM03780000	C17355	Nocardicin G
AN02772000	C01682	Nopaline
AN03865000		Norcholic acid
ED02962000		Norfloxacin
AN02336000		Norophthalmic acid
AN00814003		Norsalsolinol
BM05032000	C12473	Novclobiocin 104
AN00754002	C01077	O-Acetyl-L-homoserine
AN00433003		O-Methyl-L-threonine
AN01087000	C01005	O-Phospho-L-serine
AN01560000	C01118	O-Succinyl-L-homoserine
AN02912000		Octadecanedioic acid
AN02541000	C21016	Ophthalmic acid
AN00414000	C00036	Oxaloacetic acid
AN01159000	C05379	Oxalosuccinic acid
AN01565000	C00864	Pantothenic acid
BM00966008	C06033	Parapyruvic acid
AN02406001		Phenylalanyl-Aspartic acid
AN02644001		Phenylalanyl-Methionine
AN02198001		Phenylalanyl-Threonine
AN00619001	C02137	Phenylglyoxylic acid
AN00793004	C00166	Phenylpyruvic acid
AN02760000		Pimelylcarnitine
AN03880000	C18044	Pregnenolone sulfate
AN01654002	C00254	Prephenic acid
AN01860002		Prolyl-Gamma-glutamic acid
AN01860001		Prolyl-Glutamine
AN01684000		Prolyl-Hydroxyproline
AN01688002		Prolyl-Isoleucine
AN00406010		Propionylglycine
AN03167006	C05954	Prostaglandin B2
AN03196010		Prostaglandin C1(1-)
AN03167005	C05955	Prostaglandin C2
AN03427007	C00696	Prostaglandin D2
AN03427004	C00584	Prostaglandin E2
BM02625000	C00844	Prunasin
AN03162000	C20082	Pseudaminic acid
AN00745000		Putreanine
AN00122000	C00134	Putrescine
AN00863000	C00534	Pyridoxamine
AN01932000	C00647	Pyridoxamine phosphate
PR01947002		Pyridoxine O-sulfate
AN01948000	C00627	Pyridoxine phosphate

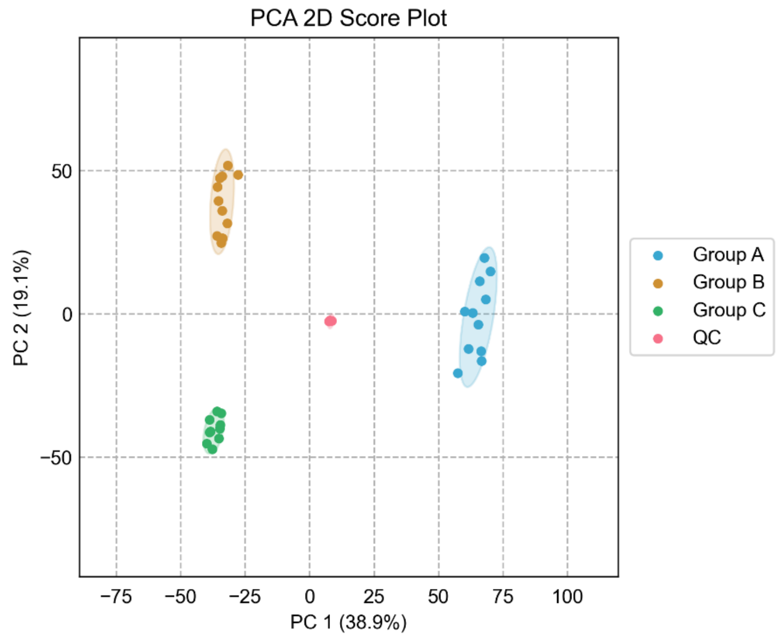
NovaMT Library No.	External Identifier	Compound
AN01599000	C02587	Pyrimidodiazepine
AN01157002		Pyrocatechol sulfate
AN02734000		Pyrogallol-2-O-glucuronide
BM00058000		Pyrrolidine
AN00596001	C17268	Pyruvophenone
BM00227001	C01751	Resorcinol
AN03521010	C01850	Rosmarinic acid
AN03771000	C00021	S-Adenosyl-L-homocysteine
AN03901000	C00019	S-Adenosyl-L-methionine
AN03446000	C01137	S-Adenosylmethioninamine
AN01786000		S-Cysteinosuccinic acid
AN04120000	C05526	S-Glutathionyl-L-cysteine
AN02206000	C03539	S-Ribosyl-L-homocysteine
AN01301000	C05824	S-Sulfo-L-cysteine
AN02354000	C00449	Saccharopine
BM00311002	C06202	Salicylaldehyde
AN02707000	C06046	Salidroside
AN01792000		Salsoline-1-carboxylic acid
AN01623000		Salsolinol 1-carboxylic acid
AN01544004		Serinyl-Hydroxyproline
PR03420000		Serotonin O-glucuronide
AN01563001		Seryl-Asparagine
AN01378000		Seryl-Threonine
AN02223000		Seryl-Tyrosine
AN01735000		Spermic acid 2
AN02358000	C16300	Stearidonic acid
AN03276000		Stearoylglycine
BM03284000	C01121	Streptidine 6-phosphate
AN01326001		Symmetric dimethylarginine
AN04966000	C09332	THF-L-glutamic acid
BM01757000	C20913	Tabtoxin biosynthesis intermediate 3
BM01168004	C20914	Tabtoxin biosynthesis intermediate 4
BM02567000	C20915	Tabtoxin biosynthesis intermediate 5
BM01130002	C20918	Tabtoxinine-beta-lactam
BM01130003	C20920	Tabtoxinine-delta-lactam
BM00818004	C06337	Terephthalic acid
AN03582000		Tetrahydropentoxyline
AN01924001		Threoninyl-Glutamine
AN02050002		Threoninyl-Histidine
AN02198002		Threoninyl-Phenylalanine
AN01378001		Threoninyl-Serine
AN01589001		Threoninyl-Threonine
AN03641000	C05963	Thromboxane B2
AN01849000	C00214	Thymidine
AN00708001		Tiglylglycine
AN01465000	C16309	Traumatin
AN02725001		Tryptophyl-Proline
AN02887000	C03033	Tyramine O-glucuronide
AN01996003		Tyrosyl-Alanine
AN03079000		Tyrosyl-Methionine sulfoxide
AN02223001		Tyrosyl-Serine
AN02430001		Tyrosyl-Threonine
AN05145000	C20359	UDP-2-acetamido-3-amino-2,3-dideoxy-alpha-D-glucuronic acid
AN04992000	C00167	UDP-glucuronic acid
AN01730004		Valyl-Aspartic acid
AN01711001		Valyl-Hydroxyproline
AN01714002		Valyl-Isoleucine
AN01892001		Valyl-Lysine
AN01432001		Vanilpyruvic acid
AN00536000		Vinylacetylglycine
BM03980004	C17650	Vulpecholic acid
AN02931009	C16679	all-trans-18-Hydroxyretinoic acid
BM00055001	C05714	alpha-Aminopropiononitrile
BM04110000	C17651	alpha-Phocaecholic acid
AN01534003	C05341	beta-Alanyl-Lysine
AN01173000		beta-Damascenone
BM00525003	C06603	cis,cis-4-Hydroxymuconic semialdehyde

NovaMT Library No.	External Identifier	Compound
BM01315000	C20581	cis-(Homo)2-aconitic acid
BM01375004	C14092	cis-1,2-Dihydroxy-1,2-dihydro-8-carboxynaphthalene
BM00892002	C06729	cis-1,2-Dihydroxy-4-methylcyclohexa-3,5-diene-1-carboxylic acid
BM01105002	C14112	cis-2-Carboxycyclohexyl-acetic acid
AN01052012	C12622	cis-3-(3-Carboxyethenyl)-3,5-cyclohexadiene-1,2-diol
AN01079003	C11588	cis-3-(Carboxy-ethyl)-3,5-cyclo-hexadiene-1,2-diol
BM00499000	C04431	cis-4-Carboxymethylenebut-2-en-4-olide
EF00898003		cis-4-Decenoic acid
BM00252000	C07091	cis-Acetylacrylic acid
AN01019008		cis-Caffeic acid
AN04001000	C00206	dADP
BM00373003	C05715	gamma-Amino-gamma-cyanobutanoic acid
AN00189003	C00334	gamma-Aminobutyric acid
AN02758002		gamma-Glutamyl-Arginine
AN01346001		gamma-Glutamyl-Glycine
AN02608000		gamma-Glutamyl-Phenylalanine
AN01757008		gamma-Glutamyl-Serine
AN01936002		gamma-Glutamyl-Threonine
BM01281000	C06114	gamma-Glutamyl-beta-aminopropiononitrile
BM01857001	C05711	gamma-Glutamyl-beta-cyanoalanine
AN01516000	C15700	gamma-Glutamyl-gamma-aminobutyraldehyde
AN02339003		gamma-Glutamyllysine
BM02198000	C20926	gamma-Glutamyltyramine
BM00460000	C07211	m-Methylbenzoic acid
BM00630000	C06576	p-Cumic alcohol
AN01417001	C05596	p-Hydroxyphenylacetylglycine
AN00847001	C04548	p-Synephrine
BM00299003	C06758	p-Tolualdehyde
AN01496000	C01233	sn-Glycero-3-phosphoethanolamine
AN01019003	C12623	trans-2,3-Dihydroxycinnamic acid
AN00414002	C03548	trans-2,3-Epoxysuccinic acid
BM00652032	C11942	trans-2-Methyl-5-isopropylhexa-2,5-dienal

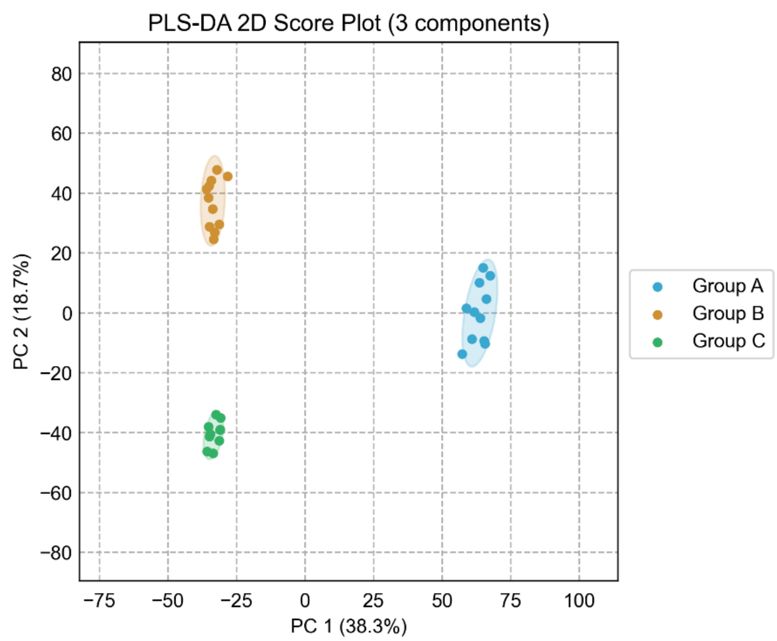
3.4 Multivariate Analysis

3.4.1 Comparison between 'Group A', 'Group B', and 'Group C' groups

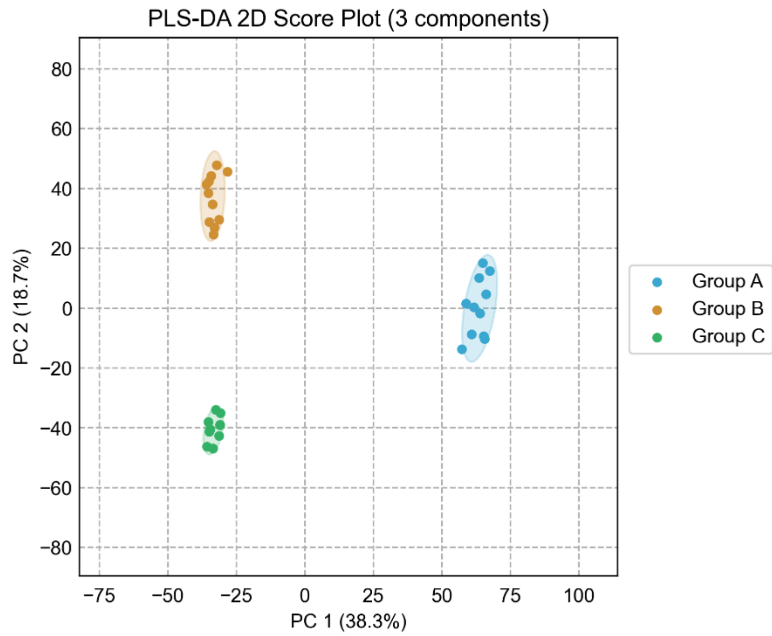
Principle component analysis (PCA) 2D scores plot (with QC) is shown below. .



Principle component analysis (PCA) 2D scores plot (without QC) is shown below.

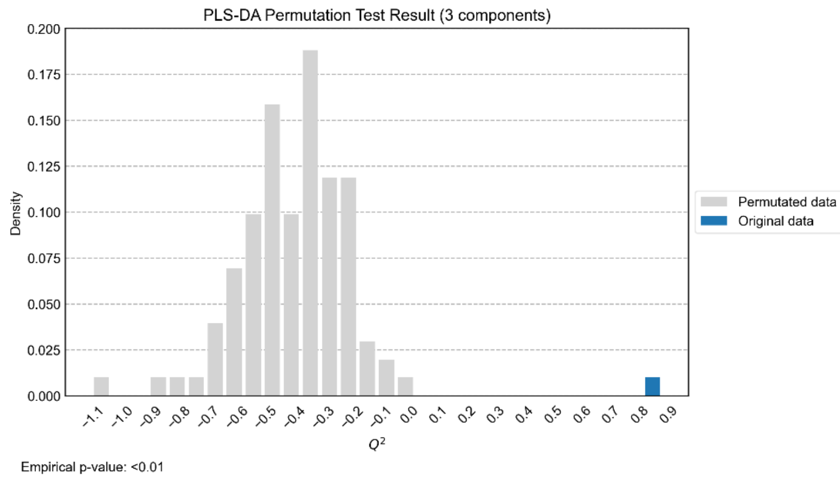


Partial least squares discriminant analysis (PLS-DA) scores plot (without QC) is below.

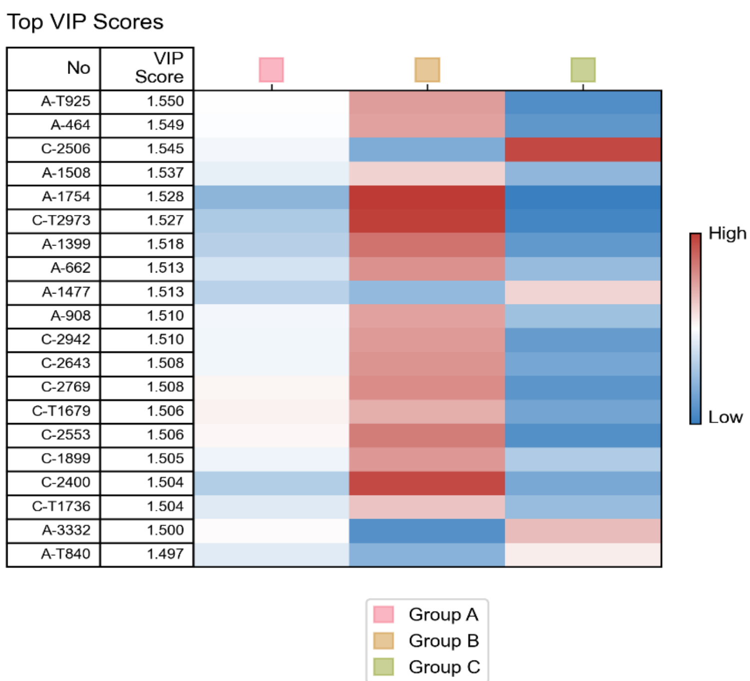


PLS-DA cross validation results are shown below (R^2=1.000, Q^2=0.294).

PLS-DA permutation test results are shown below. Empirical p-value: <0.01

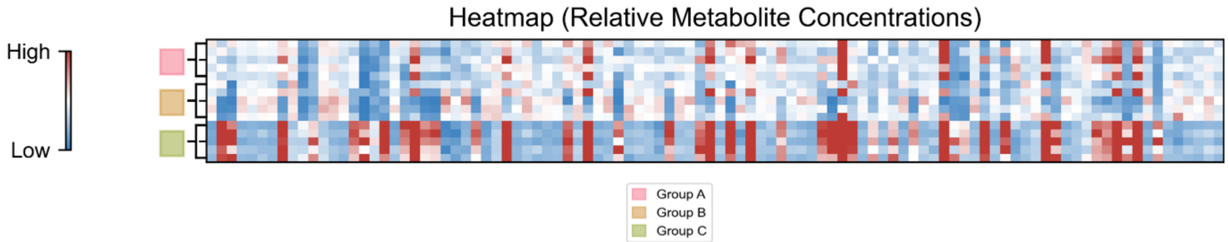


PLS-DA VIP Scores Heatmap is shown below.

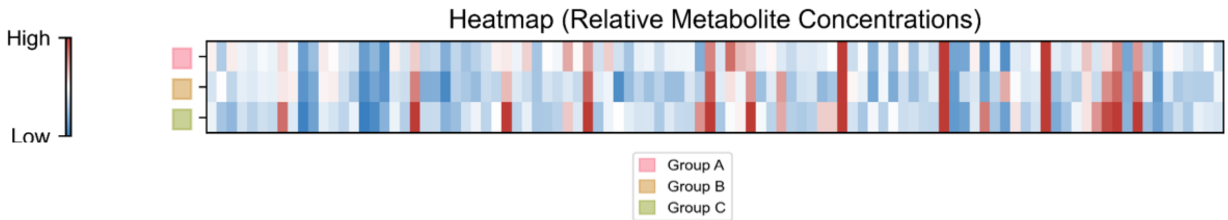


No	VIP Score
A-T925	1.550
A-464	1.549
C-2506	1.545
A-1508	1.537
A-1754	1.528
C-T2973	1.527
A-1399	1.518
A-662	1.513
A-1477	1.513
A-908	1.510
C-2942	1.510
C-2643	1.508
C-2769	1.508
C-T1679	1.506
C-2553	1.506
C-1899	1.505
C-2400	1.504
C-T1736	1.504
A-3332	1.500
A-T840	1.497

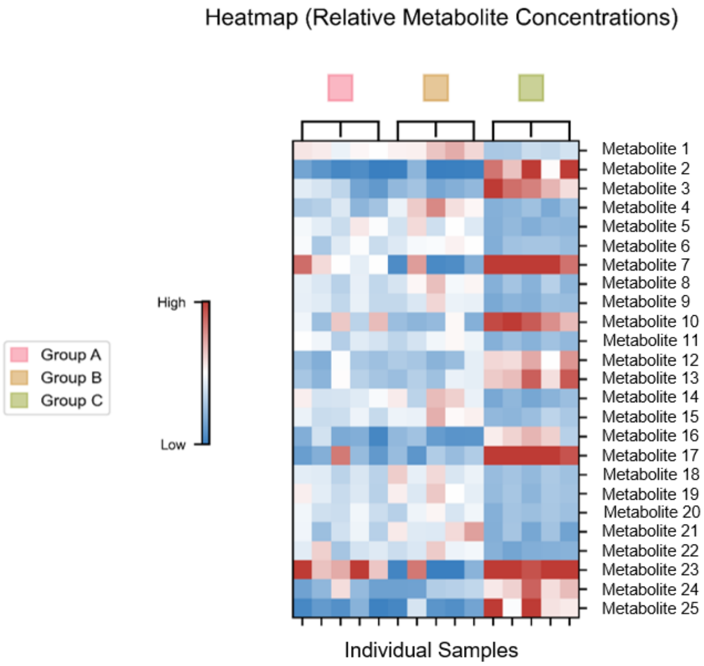
Heatmap (without QC) is shown below. Data for every sample is displayed, showing the top 100 high-confidence identified metabolites ranked by p-value.



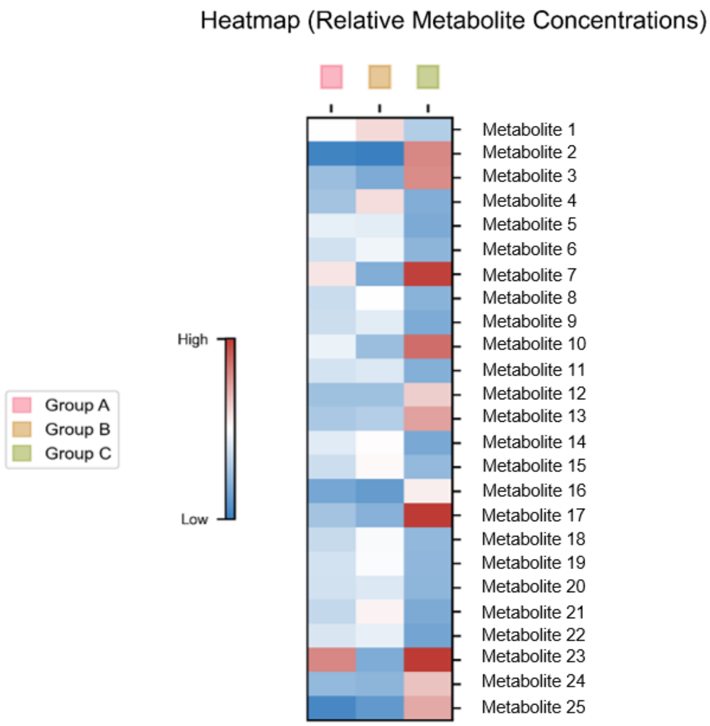
Heatmap (without QC) is shown below. Data for the average of each group is displayed, showing the top 100 high-confidence identified metabolites ranked by p-value.



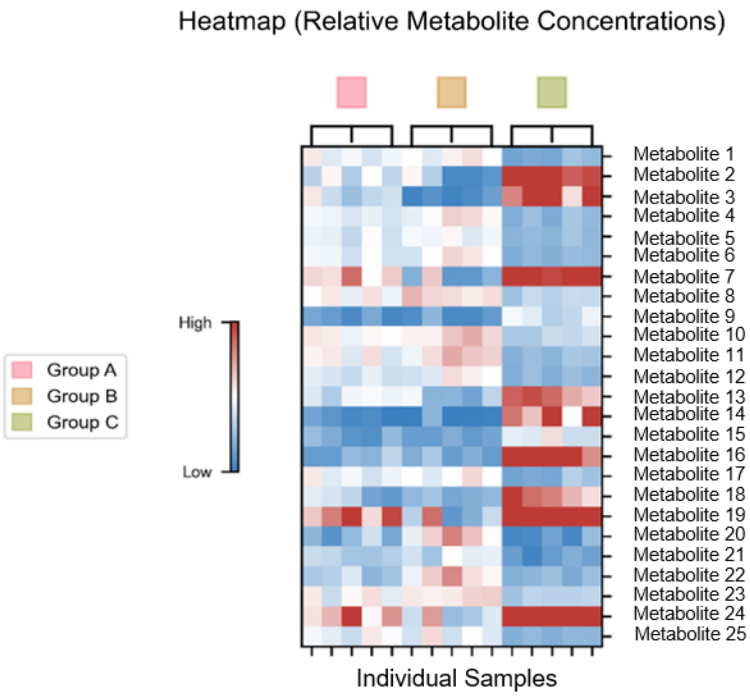
Heatmap (without QC) is show below. Data for every sample is displayed, showing the top 25 Tier 1 and Tier 2 identified metabolites ranked by p-value.



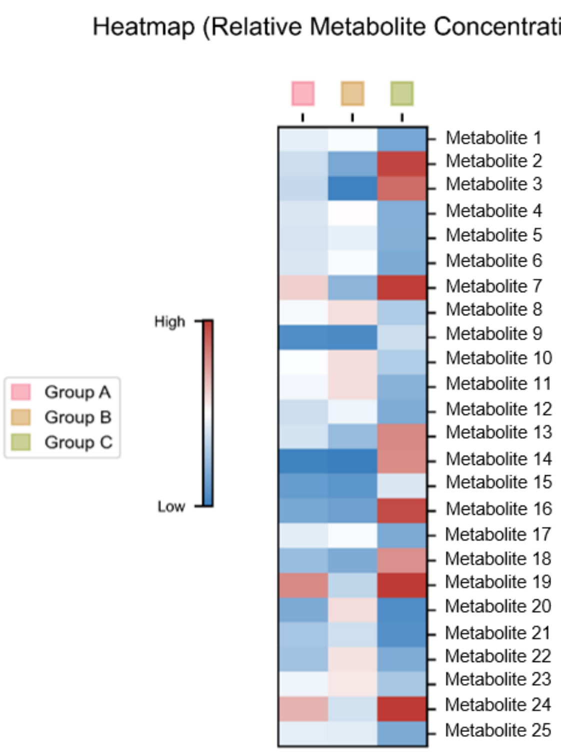
Heatmap (without QC) is shown below. Data for the average of each group is displayed, showing the top 25 Tier 1 and Tier 2 identified metabolites ranked by p-value.



Heatmap (without QC) is show below. Data for every sample is displayed, showing the top 25 Tier 1, Tier 2, and Tier 3 identified metabolites ranked by p-value.



Heatmap (without QC) is shown below. Data for the average of each group is displayed, showing the top 25 Tier 1, Tier 2, and Tier 3 identified metabolites ranked by p-value.



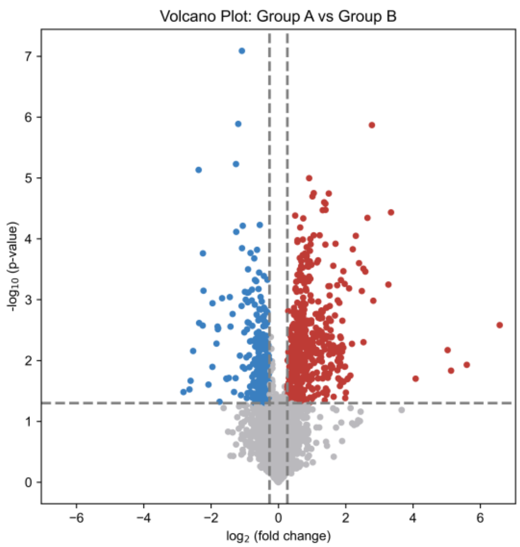
3.5 Univariate Analysis

3.5.1 Comparison between 'Group A' group and 'Group B' group

Volcano plot was constructed by plotting the fold change (FC) of each metabolite against p-value. The fold change was calculated as Mean(Group A) / Mean(Group B). The results of pathway/panel-related metabolites identified in tier 1 and tier 2 were shown in Supplemental Table 2.

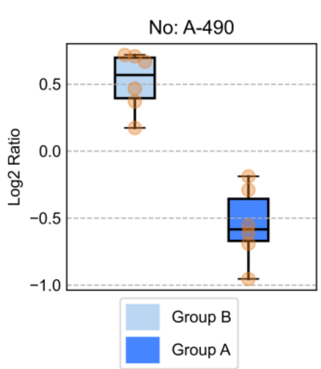
When using FC > 1.2 or < 0.83, p-value < 0.05, and q-value (or FDR-adjusted p-value) < 0.25 as criteria, the analysis showed that 1346 peak pairs with FC > 1.2, q-value < 0.25 and 1302 peak pairs with FC < 0.83, q-value < 0.25 (corresponding q-value threshold is 0.22).

Without considering FDR adjustment and using FC > 1.2 or < 0.83 and p-value < 0.05 as criteria, the analysis showed that 520 peak pairs with FC > 1.2, p-value < 0.05 (in red) and 333 peak pairs with FC < 0.83, p-value < 0.05 (in blue) (corresponding Storey's q-value threshold is 0.22). Among them, 67 peak pairs can be positively identified in tier 1 using CIL Library, 116 peak pairs can be high-confidence putative identified in tier 2 using LI Library and 600 peak pairs can be putatively identified in tier 3 using MCID library (Supplemental Table 3a).

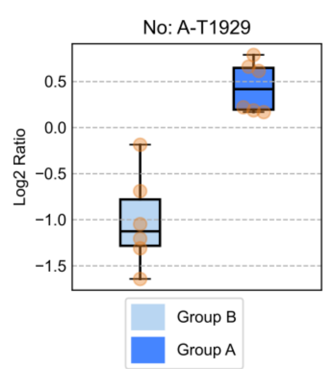


Shown below are the box plots of two identified significantly changed metabolites in tier 1, working as examples of metabolite concentration changes.

Ribothymidine
Fold Change = 0.48, p-value = 6.1e-05



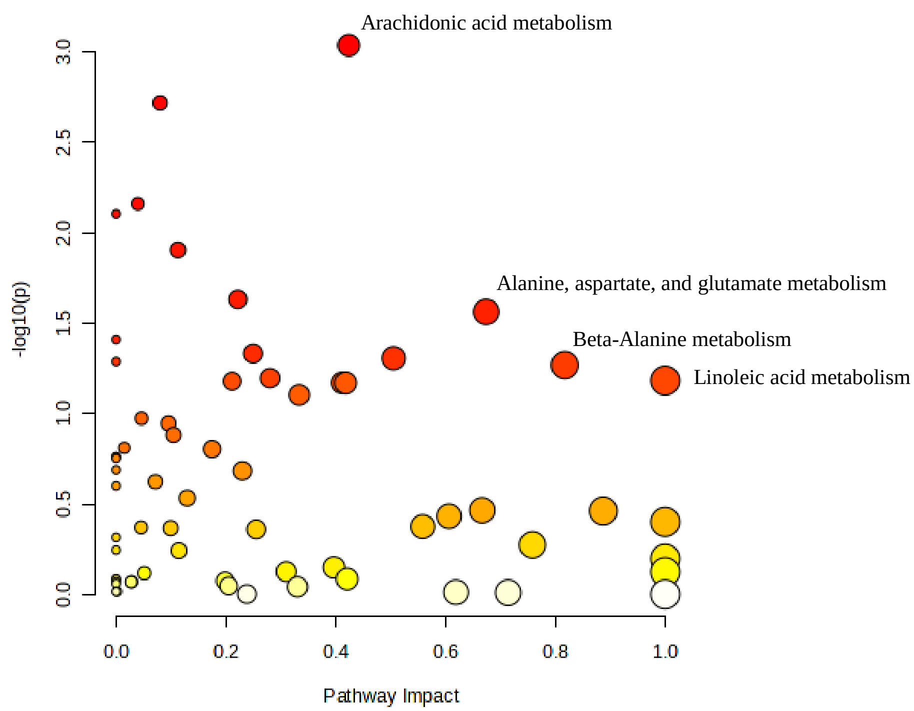
Asparaginyl-Histidine
Fold Change = 2.633, p-value = 0.00012



3.6 Pathway Analysis

3.6.1 Comparison between 'Group A' group and 'Group B' group (in Homo sapiens (KEGG) library)

Metabolites that were identified in tier 1 and tier 2 as high-confidence results were used for pathway analysis. The pathway analysis was performed using Global Test as enrichment analysis and Relative-betweeness Centrality as topology analysis in MetaboAnalyst (www.metaboanalyst.ca). The figure below shows the scatter plot of pathway analysis.



The table below shows the detailed information for each pathway.

Pathway Name	Total Cmpd	Hits	Raw p-value	Holm adjust p-value	FDR adjusted p-value	Impact
Arachidonic acid metabolism	44	15	0.000916	0.058622	0.058622	0.42364
Glycerophospholipid metabolism	36	4	0.001908	0.1202	0.061052	0.07982
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	32	2	0.006901	0.42788	0.12533	0.03947
Ether lipid metabolism	20	1	0.007833	0.47783	0.12533	0
Glycolysis or Gluconeogenesis	26	4	0.012414	0.74487	0.1589	0.11262
Retinol metabolism	17	4	0.023302	1	0.24855	0.22164
Alanine, aspartate and glutamate metabolism	28	17	0.027319	1	0.24978	0.67388
Biosynthesis of unsaturated fatty acids	36	8	0.038829	1	0.25436	0
Pyruvate metabolism	23	7	0.04651	1	0.25436	0.24932
Arginine biosynthesis	14	9	0.049356	1	0.25436	0.50532
Nicotinate and nicotinamide metabolism	15	3	0.051462	1	0.25436	0
beta-Alanine metabolism	21	10	0.053847	1	0.25436	0.81717
Lysine degradation	30	10	0.063605	1	0.25436	0.28015
Linoleic acid metabolism	5	2	0.065575	1	0.25436	1
Pyrimidine metabolism	39	9	0.066143	1	0.25436	0.21118
Citrate cycle (TCA cycle)	20	8	0.067479	1	0.25436	0.41209
Histidine metabolism	16	6	0.067564	1	0.25436	0.41802
alpha-Linolenic acid metabolism	13	2	0.078695	1	0.2798	0.33333
Propanoate metabolism	22	6	0.10626	1	0.35792	0.04616
Pantothenate and CoA biosynthesis	20	9	0.11316	1	0.36211	0.09524
Sphingolipid metabolism	32	4	0.13111	1	0.39957	0.10444

Pathway Name	Total Cmpd	Hits	Raw p-value	Holm adjust p-value	FDR adjusted p-value	Impact
Fatty acid biosynthesis	47	5	0.15477	1	0.43462	0.01473
Butanoate metabolism	15	5	0.15714	1	0.43462	0.17461
Fatty acid elongation	39	1	0.17316	1	0.43462	0
Fatty acid degradation	39	1	0.17316	1	0.43462	0
Biotin metabolism	10	1	0.17656	1	0.43462	0
Nitrogen metabolism	6	1	0.20463	1	0.47348	0
Purine metabolism	70	12	0.20715	1	0.47348	0.2299
Valine, leucine and isoleucine degradation	40	8	0.23803	1	0.5253	0.07143
D-Amino acid metabolism	15	7	0.25069	1	0.5348	0
Inositol phosphate metabolism	30	2	0.29289	1	0.60468	0.12939
Vitamin B6 metabolism	9	4	0.34249	1	0.66971	0.66667
Arginine and proline metabolism	36	21	0.34532	1	0.66971	0.8872
Tryptophan metabolism	41	21	0.36934	1	0.69523	0.60628
Taurine and hypotaurine metabolism	8	6	0.39703	1	0.71616	1
Glyoxylate and dicarboxylate metabolism	32	11	0.42121	1	0.71616	0.55834
Ubiquinone and other terpenoid-quinone biosynthesis	19	4	0.42597	1	0.71616	0.04545
Folate biosynthesis	27	4	0.42964	1	0.71616	0.09924
Amino sugar and nucleotide sugar metabolism	42	9	0.43641	1	0.71616	0.25496
Selenocompound metabolism	20	1	0.48384	1	0.77415	0
Cysteine and methionine metabolism	33	18	0.53181	1	0.83015	0.75832
Drug metabolism - cytochrome P450	55	1	0.56781	1	0.85149	0
Terpenoid backbone biosynthesis	18	2	0.57209	1	0.85149	0.11429
Phosphonate and phosphinate metabolism	6	2	0.63356	1	0.92155	1
Glutathione metabolism	28	8	0.70944	1	0.99228	0.39657
One carbon pool by folate	26	9	0.74843	1	0.99228	0.3096
Phenylalanine metabolism	8	8	0.75152	1	0.99228	1
Primary bile acid biosynthesis	46	6	0.76316	1	0.99228	0.05127
Starch and sucrose metabolism	18	1	0.82148	1	0.99228	0.4207
Neomycin, kanamycin and gentamicin biosynthesis	2	1	0.82148	1	0.99228	0
Pentose phosphate pathway	23	1	0.82462	1	0.99228	0
Galactose metabolism	27	5	0.84195	1	0.99228	0.19819
Thiamine metabolism	7	1	0.8513	1	0.99228	0
Porphyrin metabolism	31	2	0.85146	1	0.99228	0.02795
Steroid hormone biosynthesis	87	3	0.85274	1	0.99228	0.02707
Fructose and mannose metabolism	20	3	0.87421	1	0.99831	0
Pentose and glucuronate interconversions	19	3	0.89773	1	0.99831	0.20482
Glycerolipid metabolism	16	2	0.9076	1	0.99831	0.33022
Lipoic acid metabolism	28	2	0.96193	1	0.99831	0.0017
Valine, leucine and isoleucine biosynthesis	8	7	0.96384	1	0.99831	0
Tyrosine metabolism	42	29	0.97261	1	0.99831	0.61893
Glycine, serine and threonine metabolism	33	16	0.97758	1	0.99831	0.71399
Ascorbate and aldarate metabolism	9	3	0.99562	1	0.99831	0.2381
Phenylalanine, tyrosine and tryptophan biosynthesis	4	4	0.99831	1	0.99831	1

The profile suggested a perturbation in several pathways such as amino acid metabolism, and other pathways as summarized in the above table. The importance and biological functions of common metabolic pathways are listed in the references shown in the Appendix A in this report. The table that can be directly used in the Pathway Analysis Module in MetaboAnalyst (www.metaboanalyst.ca) was included with this report.

4 Conclusions

1) LC-MS data from 34 samples were processed. All data passed quality checks.
2) An average of 5707 ± 30 peak pairs per sample were detected.
3) Three-tier ID approach was used to perform metabolite identification. 5421 peak pairs were positively identified or putatively matched. Among them, 378 peak pairs were positively identified in tier 1 (CIL Library); 893 peak pairs were putatively identified with high-confidence in tier 2 (LI Library); 1124, 2311, and 715 peak pairs were matched in the zero-, one-, and two-reaction libraries, respectively.
4) Principal component analysis and partial least squares discriminant analysis as multivariate analysis tool, and volcano plot as univariate analysis tool, were used to analyze and view the data set.
5) Pathway analysis was performed to investigate the pathway perturbations.

5 Appendix A. Biological Functions of Common Metabolic Pathways

Pathway Name	Biological Roles	References
Glycolysis and Gluconeogenesis	Anaerobic component of cellular respiration that occurs in the cytosol of cells. Highly regulated pathway that catabolizes glucose and other hexoses to produce energy directly as ATP, and indirectly as pyruvate and NADH. Gluconeogenesis allows non-carbohydrate metabolites to replenish glucose [1] • In the "Warburg effect," glycolysis is dysregulated in tumor cells despite aerobic conditions, displacing glucose from healthy cells [2]	[1] Wünschiers et al. 2012 [2] Ganapathy-Kanniappan 2018
Tricarboxylic acid cycle (Krebs cycle, citrate cycle)	Aerobic component of cellular respiration that in eukaryotes, occurs in the mitochondrial matrices of cells. Plays a central catabolic role by oxidizing acetyl-CoA derived from carbohydrate, fatty acid, and amino acid sources to produce energy directly as ATP and indirectly as oxidative phosphorylation substrates NADH and $FADH_2$ [1] • In immune cells, functions in anti-inflammatory signalling via itaconate production from cis-aconitate [3]	[1] Wünschiers et al. 2012 [3] Williams and O'Neill 2018
Pentose phosphate pathway	Pathway branching from glycolysis that in the oxidative phase, produces NADPH, an anabolic cofactor that functions in fatty acid, steroid, and nucleotide biosynthesis, and the light reactions in plants [4]. The non-oxidative phase notably produces ribose-5-phosphate, the precursor to nucleic acids [1, 4] • 5-30% Of glucose is directed here, with higher rates occurring in erythrocytes and lipid-producing tissues [5] • Ameliorates oxidative stress via NADPH, which reduces glutathione into its antioxidant form [1]	[1] Wünschiers et al. 2012 [4] Ge et al. 2020 [5] Riganti et al. 2012
Pentose and glucuronate interconversions	• Helps form the extracellular matrix via production of glucuronate, a component of proteoglycans [1] • In plants, helps form cell walls via production of pentoses D-xylose and L-arabinose [1]	[1] Wünschiers et al. 2012
Fructose and mannose metabolism	• Provides substrates for energy production in glycolysis via conversions to glyceraldehyde-3-phosphate [1] • Unregulated fructose metabolism in the liver expends ATP and increases the by-product uric acid as hepatofructokinase produces fructose-1-phosphate [6] • Produces GDP mannose, a precursor to the N-glycans that facilitate protein folding [7]	[1] Wünschiers et al. 2012 [6] Helsley et al. 2020 [7] Sharma et al. 2014
Galactose metabolism	• Provides substrate for energy production in glycolysis via conversion to glucose-6-phosphate [1] • Inhibit glycolysis if galactose-1-phosphate accumulates [8]	[1] Wünschiers et al. 2012 [8] Liu et al. 2000
Ascorbate and aldarate metabolism	• In plants and some other organisms, allows for the biosynthesis of ascorbate (vitamin C), a potent antioxidant [1]	[1] Wünschiers 2012
Fatty acid biosynthesis	Use of acetyl-CoA as a principal substrate for the synthesis of fatty acids eventually involved in cell structure, energy storage, and signalling [1, 9] • Fatty acids form cell membranes as they are incorporated into the structures of phospholipids, sphingolipids, phosphosphingolipids, and gangliosides [9] • Fatty acids are energy storage molecules that after being converted to fatty acyl-CoA, undergo beta-oxidation to yield aerobic respiration substrates $FADH_2$, NADH, and acetyl-CoA [1, 9] • Fatty acids function as signal transduction molecules that help regulate metabolism [10]	[1] Wünschiers 2012 [9] de Carvalho and Caramujo 2018 [10] Papackova and Cahova 2015
Fatty acid elongation	Elongation of fatty acid acyl chains two carbons at a time, conferring new functional properties [9, 11] • Can produce myristic acid (1-tetradecanoic acid), an intracellular signalling molecule, from shorter fatty acids [12] • Can produce long-chain fatty acids that in plants, are used to synthesize protective structures [15]	[9] de Carvalho and Caramujo 2018 [11] Jump 2009 [12] Farazi et al. 2001 [15] Mazurek et al. 2017
Fatty acid degradation	Involves beta-oxidation. Shortening of fatty acid acyl chains two carbons at a time, producing the aerobic respiration substrates $FADH_2$, NADH, and acetyl-CoA [1, 9] • Helps meet the energy demands of cardiac and skeletal muscle, which require the high ATP yield of aerobic respiration [1, 13]	[1] Wünschiers 2012 [9] de Carvalho and Caramujo 2018

Pathway Name	Biological Roles	References
	• Imbalance with fatty acid uptake by muscles results in the accumulation of intramuscular lipids, which can cause localized insulin resistance [13]	[13] Zhang et al. 2010
Synthesis and degradation of ketone bodies	Pathway branching from fatty acid degradation that occurs mainly in hepatocytes during prolonged periods of fasting. Ketone bodies acetoacetate, beta-hydroxybutyrate, and acetone are water-soluble compounds that provide energy to the brain and other organs by converting to aerobic respiration substrate acetyl-CoA [1, 14] • Meets energy demands when carbohydrates are not available as energy sources via glycolysis. Instead, adipocytes provide fatty acids that are catabolized to form ketone bodies [1, 14] • Beta-hydroxybutyrate acts as a signalling molecule that can promote gene expression by inhibiting class I HDACs [14]	[1] Wünschiers 2012 [14] Newman and Verdin 2014
Cutin, suberine and wax biosynthesis	Biosynthesis of fatty acid polymers integral to the structure of specialized tissues in plants and other organisms that function in protection from the environment [15, 16, 17] • Cutin aids in protection as it forms the cell wall structures in the plant epidermis that create an extracellular cuticle layer [15] • Suberin aids in stem protection and wound sealing as it forms the cell wall structures of the periderm [16] • Wax esters have diverse functions such as water retention and buoyancy in plants and arthropods [17]	[15] Mazurek et al. 2017 [16] Graça 2015 [17] Patel et al. 2001
Steroid Biosynthesis	Biosynthesis of steroids from the terpenoid precursor squalene [1]. Produces cholesterol, which mediates membrane fluidity and permeability, and is a substrate for bile acid and steroid hormone biosynthesis [1, 18] • In the alternative pathway of plants, squalene converts to cycloartenol, which gives rise to the brassinosteroid phytohormones involved in growth, development, and abiotic stress responses [19]	[1] Wünschiers 2012 [18] Yang et al. 2016 [19] Li et al. 2021
Primary bile acid biosynthesis	Cholesterol-derived biosynthesis of bile acids, the major component of liver bile that aids in the digestion of lipids via emulsification. The classic (neutral) pathway occurs in hepatocytes while the alternative (acidic) pathway occurs in all tissues [1] • Bile acids function in toxin secretion, cholesterol homeostasis, and metabolic signalling [1, 20]	[1] Wünschiers 2012 [20] Vaz and Ferdinandusse 2017
Ubiquinone and other terpenoid-quinone biosynthesis	Biosynthesis of quinone cofactors involved in energy production, or injury prevention and repair [1, 21] • Ubiquinone facilitates ATP production as an electron carrier in the electron transport chain of aerobic respiration [1] • Menaquinone increases bone density by inhibiting osteoclast activity [21] • Phylloquinone (vitamin K_1) is a cofactor involved in blood coagulation [1]	[1] Wünschiers 2012 [21] Yamaguchi et al. 2003
Steroid hormone biosynthesis	Cholesterol-derived biosynthesis of corticosteroids (glucocorticoids and mineralocorticoids) and sex steroids (androgens, estrogens, and progestogens) involved in homeostasis and sexual development [1, 22] • Glucocorticoids such as cortisol diversely affect metabolism by increasing blood glucose, hepatic protein synthesis, and fatty acid catabolism, often in response to stress. They also suppress the immune system and inflammation [1, 22] • Mineralocorticoids such as aldosterone function to regulate salt and water balance by promoting sodium reabsorption at the kidneys. This causes water reabsorption, and thus an increase in blood volume and pressure [22] • Androgens such as testosterone develop male secondary sexual characteristics and masculinizing features in general [22] • Estrogens such as estradiol develop female primary and secondary sexual characteristics, and promote fat anabolism [1, 22] • Progestogens prepare the body for pregnancy by thickening the uterine lining and developing the breasts for lactation [22]	[1] Wünschiers 2012 [22] Holst et al. 2004
Purine metabolism	Biosynthesis, degradation, and interconversions of purines essential to the structure of DNA and RNA, the production of energy, and metabolism as a whole [1, 23]	[1] Wünschiers 2012 [23] Yin et al. 2018

Pathway Name	Biological Roles	References
	• Production of purine derivatives adenine and guanine, nucleobases used in DNA and RNA [1] • Production of the adenosine and guanosine phosphates, which act as crucial metabolic cofactors and signalling molecules [1] • Aberrations in purine metabolism are linked to cancers, with heightened inosine to adenosine ratios observed in tumor cells [23]	
Caffeine metabolism	Metabolism of the central nervous system stimulant caffeine, mainly in hepatocytes [24] • Stimulant effects of caffeine diminish as it is metabolized into paraxanthine, its major product [1, 24] • Two of the direct metabolic products of caffeine, theobromine and theophylline, are stimulants that are further metabolized [1, 24] • Anti-inflammatory and lipolytic effects as caffeine and its related metabolites elevate cAMP levels [25]	[1] Wünschiers 2012 [24] Cornelis et al. 2016 [25] Barcelos et al. 2020
Pyrimidine metabolism	Biosynthesis, degradation, and interconversions of pyrimidines essential to the structure of DNA, RNA, and nucleotide sugars involved in metabolism as a whole [1, 26] • Production of pyrimidine derivatives cytosine, thymine, and uracil, nucleobases used in DNA and RNA [1] • Production of glycosylating nucleotide sugars that facilitate protein and lipid modification, biosynthesis, and detoxifications [26]	[1] Wünschiers 2012 [26] Löffler et al. 2005
Glutathione metabolism	• Production and replenishment of reduced-form glutathione, an antioxidant and cytoprotective metabolite [1] • Hemolytic anemia may result from a surplus of oxidized-form glutathione in erythrocytes, due to inadequate NADPH [1]	[1] Wünschiers 2012
Arginine biosynthesis	Biosynthesis of the proteinogenic amino acid arginine, mainly via the intestinal-renal axis [1] • Involves the urea cycle, which eliminates toxic ammonia liberated from amino acid catabolism by converting it to urea for excretion in urine [1] • Arginine is a conditionally essential amino acid as biosynthesis may be inadequate in those with cancer or other pathologies [27]	[1] Wünschiers 2012 [27] Rodriguez et al. 2017
Alanine, aspartate and glutamate metabolism	• The alanine cycle allows for the elimination of toxic ammonia and the replenishment of glucose in muscles through alanine interconversion with pyruvate, and transport between skeletal muscle and the liver [1, 28] • Aspartate can be metabolized into signalling molecules such as N-acetyl-aspartate and beta-alanine [1] • Glutamate and its decarboxylation product gamma-aminobutyric acid (GABA) are excitatory and inhibitory neurotransmitters, respectively, that modulate the central nervous system [1] • Aspartate and glutamate metabolism promote cell proliferation by contributing to the production of purines and pyrimidines needed to make DNA and RNA [1, 29, 30] • Aspartate metabolizes into the proteinogenic amino acids glycine, serine, threonine, lysine, and cysteine. Glutamate, as a productive nitrogen donor, also aids in the biosynthesis of proteinogenic amino acids [1, 29, 30]	[1] Wünschiers 2012 [28] Felig 1973 [29] Alkan et al. 2018 [30] Walker and Donk 2015
Glycine, serine and threonine metabolism	• Drives the folate cycle, which promotes DNA and RNA biosynthesis, through the conversion of serine and glycine. Along with the methionine cycle, which promotes purine and polyamine biosynthesis, and methylation reactions, forms “one-carbon metabolism” needed for cell proliferation [1, 32, 34] • Essential to membrane synthesis as serine is a precursor to ceramides, glycerophospholipids, and sphingosines [1] • Helps maintain blood-glucose levels as serine is mainly catabolized to pyruvate, the principal substrate for gluconeogenesis [1] • Promotes muscle performance as glycine aids in the biosynthesis of creatine and thus phosphocreatine, which regenerates muscle ATP [1, 31]	[1] Wünschiers 2012 [31] Razak et al. 2017 [32] Wang et al. 2013

Pathway Name	Biological Roles	References
	• Exhibits anti-inflammatory and cytoprotective effects by contributing to glutathione production and decreasing pro-apoptotic events [31, 32]	
Cysteine and methionine metabolism	• Links with the folate cycle, which promotes RNA and DNA biosynthesis, to form "one-carbon metabolism" needed for cell proliferation [1, 33, 34] • Methionine converts to *S*-Adenosyl methionine (SAM), a methylating cofactor involved in polyamine biosynthesis and methylation reactions. The methionine cycle and methionine salvage regenerate methionine from SAM reactions [1, 33, 34] • Improves the digestion of lipids as cysteine is a substrate for the biosynthesis of taurine, a bile acid conjugation partner [1] • Helps maintain blood-glucose levels as cysteine catabolizes to pyruvate and favours its entry to gluconeogenesis over the TCA cycle or fatty acid synthesis [1, 35] • Reduces inflammation as cysteine is a substrate for glutathione biosynthesis [1, 35]	[1] Wünschiers 2012 [33] Affronti et al. 2020 [34] Sanderson et al. 2019 [35] Serpa 2020
Valine, leucine and isoleucine degradation	• Regulates leucine and isoleucine levels, which are positively correlated with insulin resistance [36] • Improves muscle performance and hypertrophy by stimulating protein synthesis through cell signalling (primarily by leucine), and inhibiting proteolysis (primarily by branched-chained keto acids and beta-hydroxy-beta-methylbutyrate) [37] • Contributes to energy production and lipid biosynthesis, as valine, leucine, and isoleucine catabolize into CoA substrates [1, 37] • Leucine contributes to energy production in a fasted state by catabolizing to aerobic respiration substrate acetyl-CoA [1]	[1] Wünschiers 2012 [36] Zhang et al. 2017 [37] Holeček 2018
Valine, leucine and isoleucine biosynthesis	Non-mammalian biosynthesis of the branched-chain proteinogenic amino acids from pyruvate and threonine [1]	[1] Wünschiers 2012
Lysine biosynthesis	Non-mammalian biosynthesis of the proteinogenic amino acid lysine via two mutually exclusive pathways [1, 38] • In plants, bacteria, and lower fungi, the diaminopimelate (DAP) pathway occurs, whereby aspartate is a precursor to lysine and DAP. In bacteria, these are incorporated into cell walls [1, 38] • In higher fungi and euglenoids, the alpha-aminoadipate (AAA) pathway occurs, whereby 2-oxoglutarate is the precursor to lysine [1, 32]	[1] Wünschiers 2012 [38] Xu et al. 2006
Lysine degradation	• Aids in fatty acid metabolism by producing carnitine, which shuttles fatty acids to the mitochondria for beta-oxidation [1] • Contributes to energy production in a fasted state by producing aerobic respiration substrate acetyl-CoA [1]	[1] Wünschiers 2012
Arginine and proline metabolism	• Production of nitric oxide (NO), a signalling molecule, from arginine. NO promotes vasodilation, cardiac muscle relaxation, and phagocytic immunity [1, 39, 40] • Production of urea cycle substrates ornithine and citrulline, which enable the conversion of toxic ammonia to urea for excretion in urine [1] • Promotes muscle performance as arginine aids in the biosynthesis of creatine and thus phosphocreatine, which regenerates muscle ATP [1, 41] • Enables cell proliferation via production of the polyamines spermidine and spermine, growth factors that stabilize DNA [1] • Proline cycling increases levels of reactive oxygen species, oxidative phosphorylation, and biomass precursors, implicating it in tumorigenesis and metastasis [42]	[1] Wünschiers 2012 [39] Ziolo et al. 2008 [40] Gogoi et al. 2016 [41] Paddon-Jones et al. 2004 [42] Tanner et al. 2019
Histidine metabolism	• Mainly results in the production of glutamate, which promotes neural functioning, cell proliferation, and the production of other amino acids [1, 43] • Production of histamine in mast and tissue cells in response to allergens, causing vasodilation and bronchoconstriction. Histamine also functions as a homeostatic neurotransmitter and aids in digestion by stimulating gastric HCl secretion [1, 43] • Exhibits anti-inflammatory and cytoprotective effects via production of carnosine, which scavenges free radicals and decreases protein glycation. This occurs mostly in skeletal muscle [1, 44]	[1] Wünschiers 2012 [43] Holeček 2020 [44] Mendelson 2008 [45] Brosnan 2020

Pathway Name	Biological Roles	References
	• Ameliorates DNA damage caused by UV radiation via production of urocanate in the skin [45]	
Tyrosine metabolism	• Production of the catecholamines and thyroid hormones that are crucial for stress responses and overall homeostasis [1] • In melanocytes, produces eumelanins responsible for skin pigmentation [1] • Exhibits anti-inflammatory effects through the production of antioxidants such as tocopherols and other anti-inflammatory compounds [46] • Contributes to energy production by forming the 4-hydroxybenzoate structure of coenzyme Q10 [47] • In plants, branches to phenolic secondary metabolic pathways involved in defense and pigmentation [46]	[1] Wünschiers 2012 [46] Schenck and Maeda 2018 [47] Turunen et al. 2004
Phenylalanine metabolism	• Mainly results in the production of tyrosine and its metabolic products [1] • Aberrant phenylalanine metabolism due to phenylketonuria, a hereditary disorder, can cause a buildup of phenylpyruvate and phenyllactate if dietary phenylalanine is too high. This impairs neuronal development [1] • In plants, branches to phenolic secondary metabolic pathways involved in defense and pigmentation [48]	[1] Wünschiers 2012 [48] Tohge et al. 2013
Tryptophan metabolism	• Production of serotonin, a neurotransmitter that functions in the regulation of mood, blood clotting, and smooth muscle in the circulatory and digestive systems [1, 49] • Production of melatonin, a hormone that functions in the regulation of the sleep-wake cycle, blood pressure, the immune system, and other physiological functions [1, 50] • Neurological effects via the kynurenine pathway, which yields compounds that affect glutamatergic neurotransmission [51] • In plants, produces the phytohormone indole acetate (auxin), which promotes growth [1]	[1] Wünschiers 2012 [49] Jonnakuty and Gragnoli 2008 [50] Pandi-Perumal et al. 2006 [51] Kadriu et al. 2020
Phenylalanine, tyrosine and tryptophan biosynthesis	Non-mammalian biosynthesis of the aromatic proteinogenic amino acids via the shikimate pathway. Mammalian tyrosine biosynthesis is derived from ingested phenylalanine [1] • In plants, the shikimate pathway branches to secondary metabolic pathways that produce folates (B vitamins), pigments, and defense compounds [1, 52]	[1] Wünschiers 2012 [52] Parthasarathy et al. 2018
beta-Alanine metabolism	• Exhibits anti-inflammatory and cytoprotective effects via production of carnosine, which scavenges free radicals and decreases protein glycation. This occurs mostly in skeletal muscle, where beta-Alanine is the rate-limiting precursor [1, 44] • Contributes to energy production and lipid biosynthesis via production of CoA substrates [1] • In plants, involved in defense against environmental stressors [53]	[1] Wünschiers 2012 [44] Mendelson 2008 [53] Parthasarathy et al. 2019
Taurine and hypotaurine metabolism	• Aids in the digestion of lipids as taurine conjugates with bile acids to form bile salts, which emulsify lipids [1] • Ameliorates oxidative stress as taurine decreases the mitochondrial production of superoxide radicals at the respiratory chain [54]	[1] Wünschiers 2012 [54] Jong et al. 2011
D-Glutamine and D-glutamate metabolism	• Can increase oxidative stress, as D-glutamate inhibits the production of potent antioxidant glutathione [1, 55] • In bacteria, helps form the peptidoglycan cell wall [56]	[1] Wünschiers 2012 [55] Ariyoshi et al. 2017 [56] Aliashkevich et al. 2018
D-Arginine and D-ornithine metabolism	• In bacteria, helps form the peptidoglycan cell wall [56]	[56] Aliashkevich et al. 2018
D-Alanine metabolism	• Neurological effects as D-alanine binds to NMDA receptors [57] • In bacteria, helps form the peptidoglycan cell wall [56]	[57] Kiriyama and Nochi 2016
Geraniol degradation	• Reduces cholesterol and isoprenoid biosynthesis by inhibiting the production of precursor mevalonate. This slows proliferation by decreasing the isoprenoid post-translational modifications of proteins utilized for cell growth [58]	[58] Polo and De Bravo 2006 [59] Babukumar et al. 2017

Pathway Name	Biological Roles	References
	• Geraniol supports glucose homeostasis by altering glycolytic and gluconeogenic enzyme activity in cases of insulin hypoactivity [59]	
Monobactam biosynthesis	Bacterial biosynthesis of monocyclic beta-lactam antibiotics [60] • Antibiotic activities of monobactams are weak against gram-positive bacteria [60] • Monobactams are not cleaved by metallo-beta-lactamases, bacterial enzymes that confer broad-spectrum antibiotic resistance [61]	[60] Sykes and Bonner 1985 [61] Li et al. 2017
Carbapenem biosynthesis	Bacterial biosynthesis of carbapenem beta-lactam antibiotics [62] • Carbapenems are not cleaved by extended spectrum beta-lactamases, bacterial enzymes that confer antibiotic resistance to penicillins and celphalosporins [62] • Carbapenem thienamycin is unstable and quickly metabolized by the dihydropeptidase enzyme in humans [62]	[62] Coulthurst et al. 2005
Starch and sucrose metabolism	• Dietary starch and sucrose are catabolized into simpler carbohydrates for energy production via glycolysis [1] • In plants, starch is synthesized from glucose polymers amylopectin and amylose for energy storage. Metabolism is tightly regulated to provide timely energy for development, nocturnal growth, and stress responses [63] • In plants, sucrose is a transport sugar that is synthesized at photosynthetic organs and translocated to non-photosynthetic organs for energy storage, conversion to starch, and/or metabolism [1, 64] • In plants, produces cellulose which is essential to cell wall integrity [1]	[1] Wünschiers 2012 [63] Skryhan et al. 2018 [64] Lemoine 2000
Amino sugar and nucleotide sugar metabolism	Biosynthesis, interconversions, and polymerizations of sugar derivatives that confer function to macromolecules, and play a role in carbohydrate and glycoconjugate formation [1, 65, 66] • Yields UDP-N-acetylglucosamine and UDP-N-acetylgalactosamine, glycosyl donors that help produce glycoproteins and glycolipids imperative to molecule activation, cell-cell interactions, and membrane functionality [1, 66] • Invertebrates, fungi, and algae polymerize N-acetylglucosamine to form chitin, which composes the structure of exoskeletons and cell walls [1, 66]	[1] Wünschiers 2012 [65] Mikkola 2020 [66] Skarbek and Milewska 2016
Glycerolipid metabolism	• Production, mainly by adipocytes, of energy-storing triacylglycerols from products of sugar metabolism. Triacylglycerols form intracellular lipid-regulating droplets and are the main component of adipose tissue [1] • Helps regulate glucose levels via metabolic flux between gluconeogenesis and triacylglycerol production. Adipose tissue liberates glycerol and fatty acids to muscle and liver tissue for glucose or energy production via beta-oxidation [1]	[1] Wünschiers 2012
Glycerophospholipid metabolism	• Production of various glycerophospholipids, the main structural component of cell membranes [1] • Glycerophospholipid properties such as head group, tail length, and tail saturation affect the topography and fluidity of cell membranes they form. This influences protein integration, transport, fusion, and other membrane activities [67] • Helps facilitate cellular responses by yielding diacylglycerol and inositol phosphates, second messengers involved in signal transduction, from phosphatidylinositol [1, 67]	[1] Wünschiers 2012 [67] Farooqui et al. 2007
Inositol phosphate metabolism	• Inositol phosphates are second messengers that facilitate signal transduction by regulating the intracellular release of calcium [1] • Deficiencies in myo-inositol are linked to diabetes complications in nerve, kidney, and eye tissues [68]	[1] Wünschiers 2012 [68] Croze and Soulage 2013
Arachidonic acid metabolism	• Production of prostaglandins and other eicosanoids that function in circulatory, respiratory, and digestive system regulation, immune cell activation, and neural transmission [69]	[69] Turman and Marnett 2010 [70] Duroudier et al. 2009 [71] Chandrasekharan and Sharma-Walia 2015

Pathway Name	Biological Roles	References
	• Mediates inflammation via production of leukotrienes and lipoxins. Leukotrienes promote and maintain inflammation, while lipoxins reduce inflammation by stimulating anti-inflammatory, and inhibiting pro-inflammatory, signalling pathways [70, 71]	
Linoleic acid metabolism	• Supports neuronal cell integrity via production of dihomo-gamma-linolenic acid, a membrane phospholipid component [72] • Production of signalling molecules such as 13(S)-HODE that activate receptors involved in lipid metabolism and other physiological functions [73, 74]	[72] Brownlee et al. 2016 [73] Whelan 2013 [74] Nagy et al. 1998
alpha-Linolenic acid metabolism	• In plants, produces jasmonic acids, a class of phytohormones involved in growth regulation and defense against biotic and abiotic environmental stressors [75]	[75] Pirbalouti et al. 2014
Sphingolipid metabolism	Biosynthesis, degradation, and interconversions of sphingolipids, a class of lipids with sphingosine backbones that contribute to membrane structure and cell signalling [76, 77] • Membrane component sphingomyelin is necessary for the survival of mammalian cells [76] • Accumulation of proapoptotic ceramides due to sphingomyelinase overactivity contributes to the pathogenesis of type 2 diabetes mellitus and Alzheimer's disease by decreasing insulin sensitivity and promoting neuronal death, respectively [77] • Mitigates or enhances tumorigenesis depending on the metabolic flux between ceramides (anti-proliferative metabolites) and sphingomyelin, glucosylceramide, and sphingosine-1-phosphate (pro-proliferative metabolites) [78]	[76] Gault et al. 2010 [77] Rao et al. 2013 [78] Ogretmen 2018
Pyruvate metabolism	Biosynthesis of pyruvate and its oxidative decarboxylation to the central metabolic substrate acetyl-CoA under aerobic conditions, and reduction to fermentation products under anaerobic conditions [1] • Links carbohydrate, lipid, and amino acid metabolism by providing substrates for the biosynthesis of glucose, fatty acids, ketone bodies, and amino acids [1] • Meets energy demands under aerobic conditions via production of tricarboxylic acid cycle substrates acetyl-CoA and oxaloacetate [1] • Meets energy demands under anaerobic conditions via the fermentation pathways, which replenish glycolysis cofactor NAD+ [1]	[1] Wünschiers 2012
Glyoxylate and dicarboxylate metabolism	Pathway in plants, bacteria, insects, and vertebrates that resembles the tricarboxylic acid cycle. In the glyoxylate cycle, fatty acid-derived acetyl-CoA combines with oxaloacetate to generate succinate for entry into gluconeogenesis, and malate for replenishment of oxaloacetate to restart the cycle [1] • In photosynthetic plants, supports glucose biosynthesis through energy-costly photorespiration. This replenishes Calvin cycle intermediate 3-phospho-D-glycerate from the phosphoglycolate by-product [1] • In bacteria, functions in acetate consumption as acetate is converted to acetyl-CoA [1]	[1] Wünschiers 2012

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