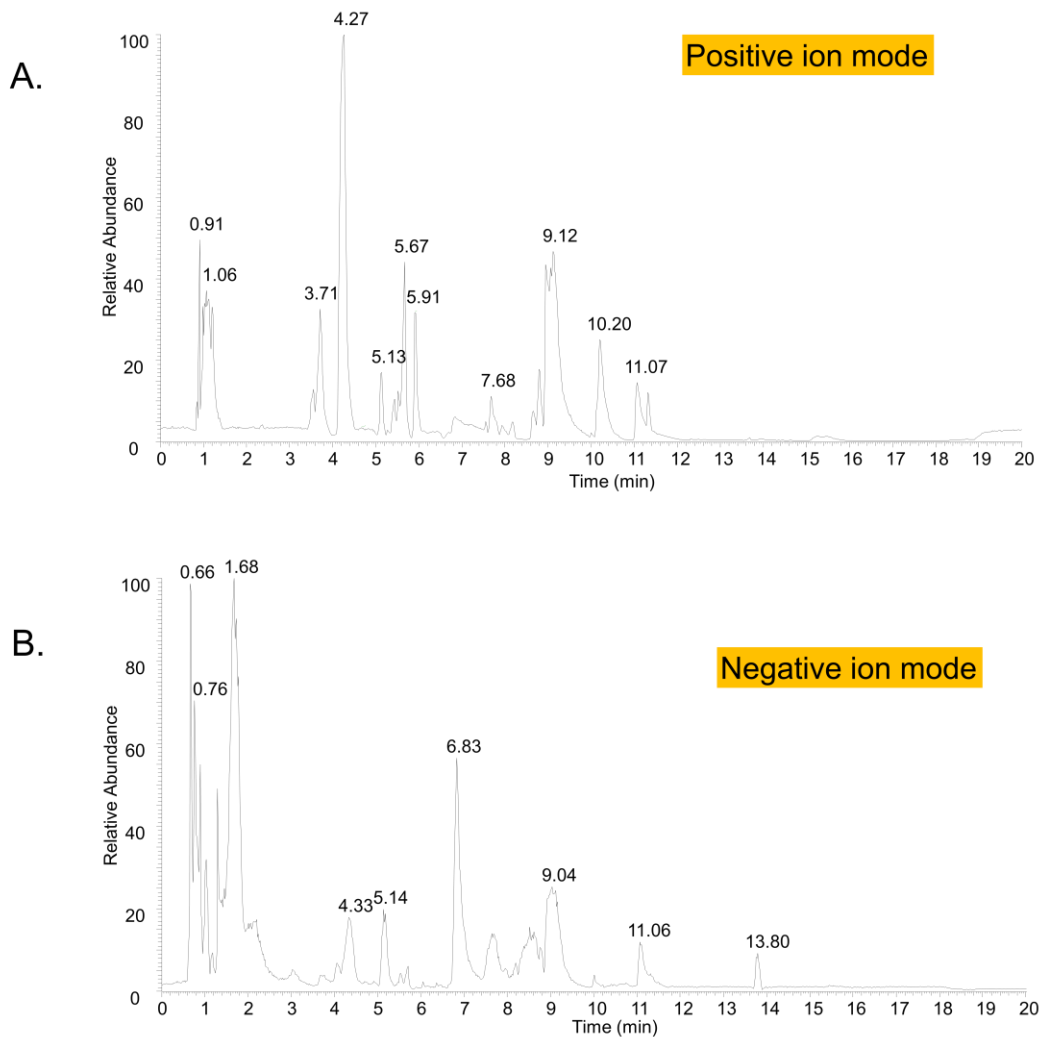


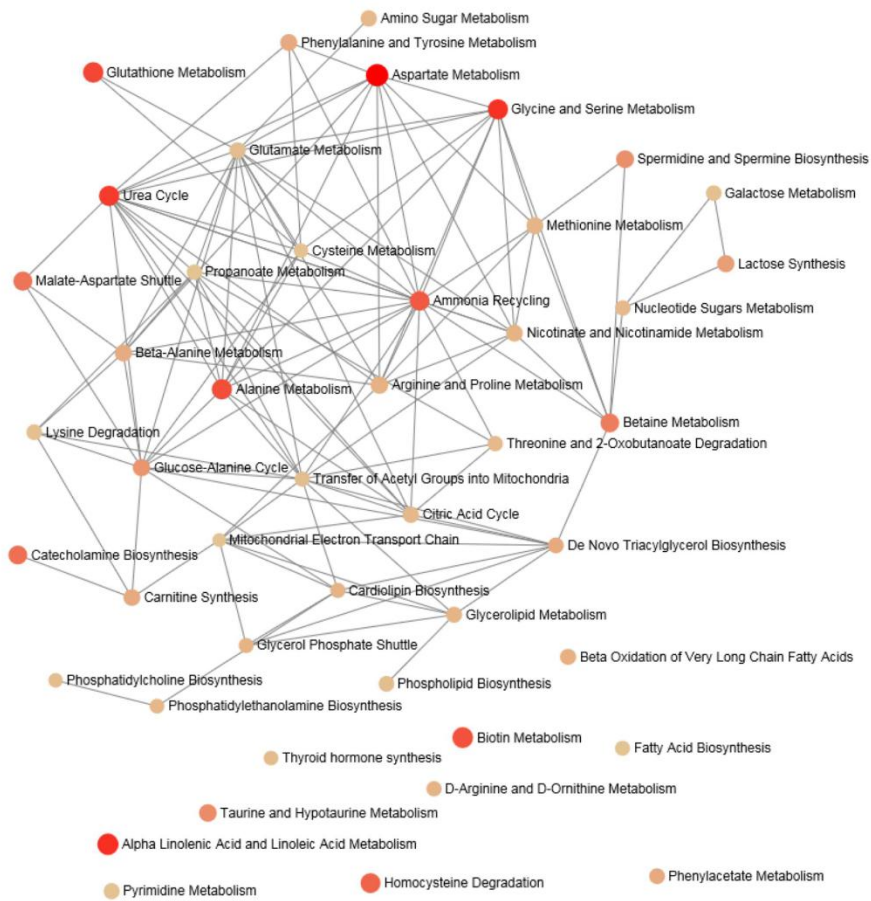
Comparative Metabolomic Effects of Herbal Dingkundan Versus Diane-35 in Polycystic Ovary Syndrome Treatment: A Clinical and Pharmacological Study

Dr. Élodie Laurent^{1*}, Dr. Marc Dubois¹

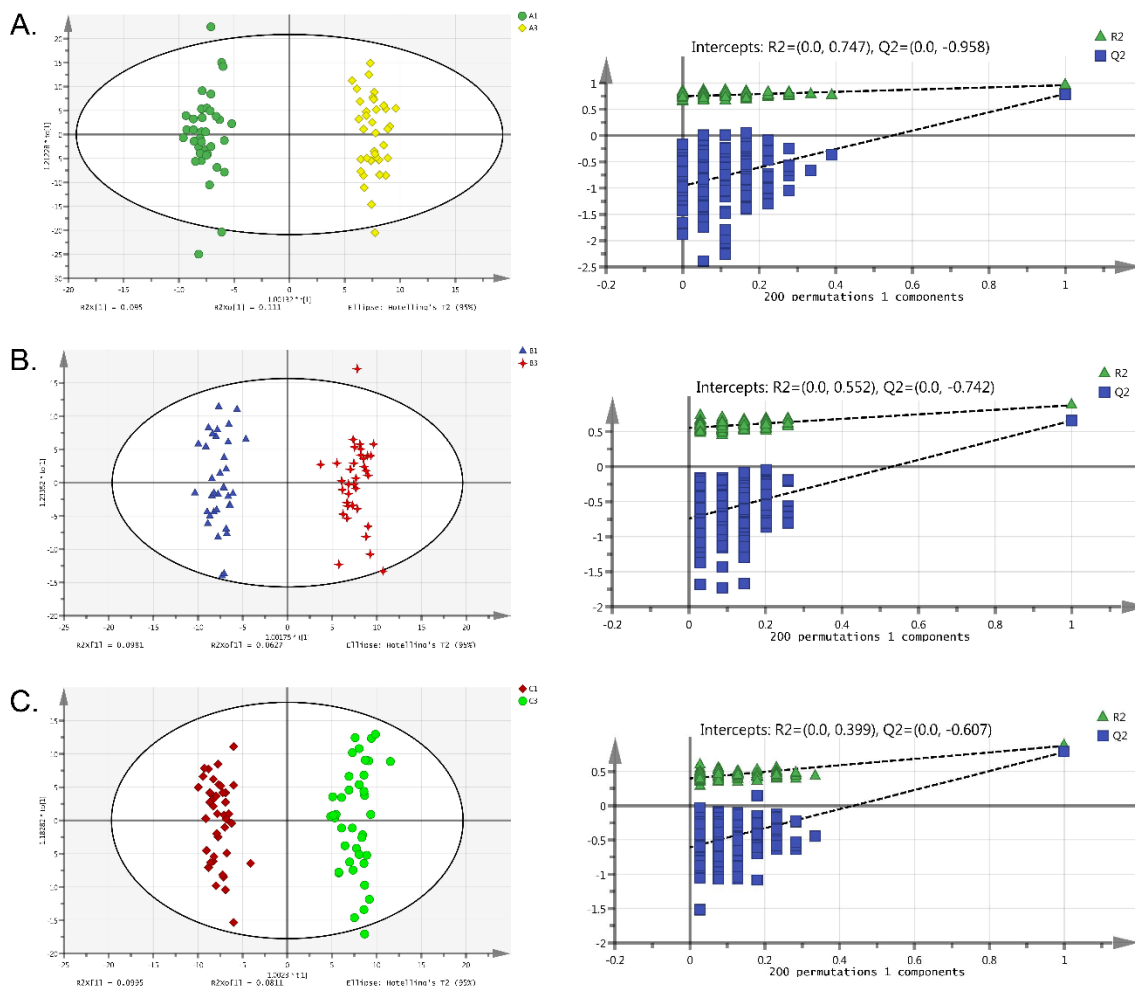
¹Université de Paris, Faculty of Medicine, Department of Reproductive Endocrinology and Clinical Pharmacology, Paris, France



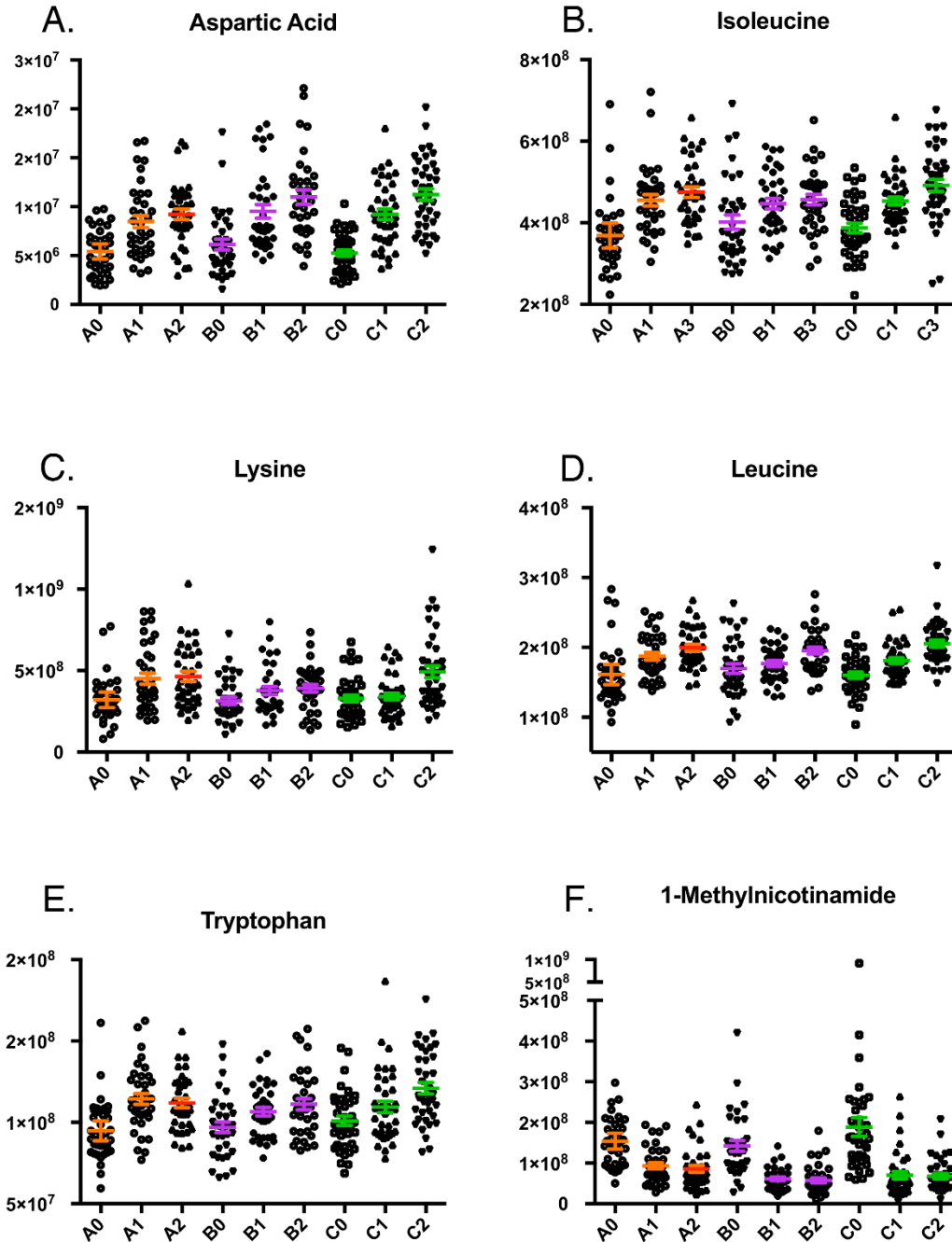
Supplemental Fig. S1. Representative chromatograms of metabolomics analysis in positive A) and negative B) ion mode respectively.



Supplemental Fig. S2. Pathway enrichment of metabolites using Metaboanalyst. The input metabolites were selected according to VIP values (> 1) in OPLSDA analysis.

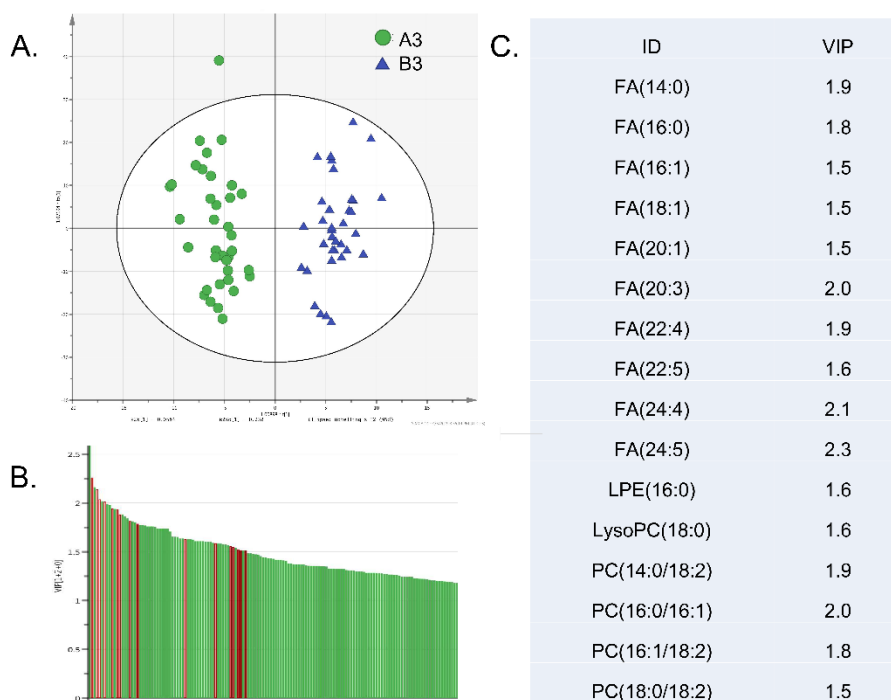


Supplemental Fig. S3. OPLSDA analysis and permutation of metabolic features to classify the patients prior to and after 3-month medication of A) herbal Dingkundan with $R2X=0.309$, $R2Y=0.983$, $Q2=0.906$; B) Diane-35 with $R2X=0.206$, $R2Y=0.973$, $Q2=0.866$; C) concomitant therapy with $R2X=0.232$, $R2Y=0.97$, $Q2=0.915$.

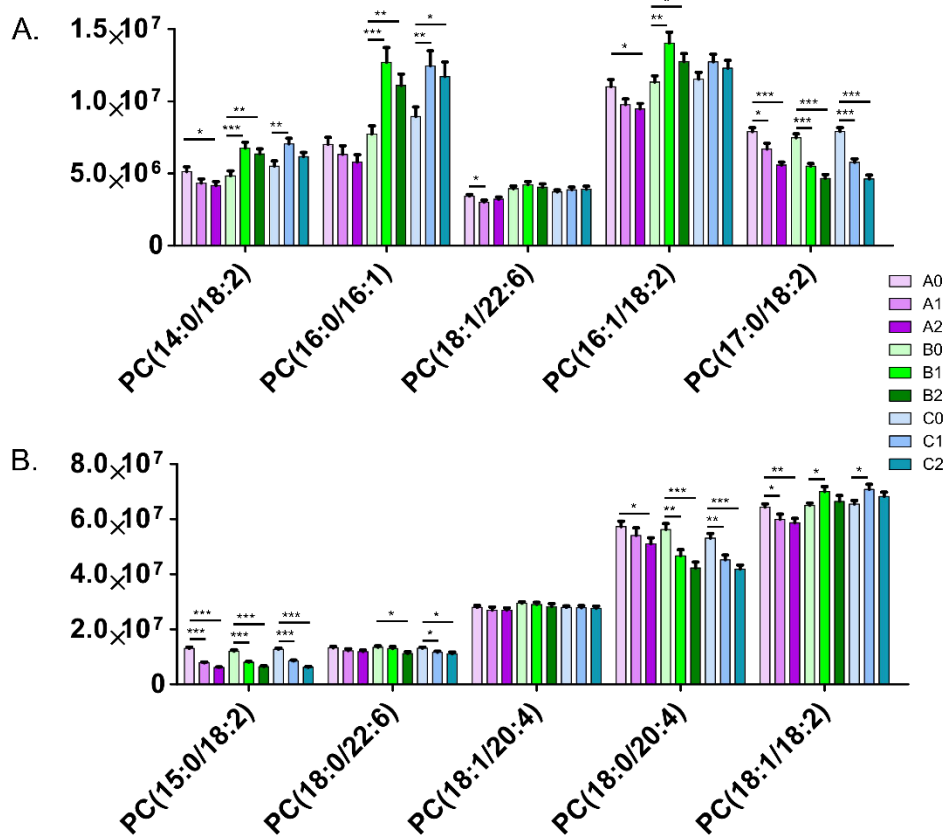


Supplemental Fig. S4. Scatter plots of A) Aspartic acid, B) Isoleucine, C) Lysine, D) Leucine, E) Tryptophan and F) 1-methylnicotinamide in Group A- Dingkundan treatment, B- Diane-35

treatment and C- concomitant treatment. Group A0, B0 and C0 include the patients prior to medication. Group A1, B1, C1 and A2, B2, C2 are patients after 2- and 3- month drug treatment respectively. Relative abundance was used in the analysis as Y-axis.



Supplemental Fig. S5. A) PLSDA analysis of metabolic features from patients after 3-month therapy of A3- Dingkundan and B3- Diane-35. In this analysis, the model was established with R2X- 0.337, R2Y- 0.916 and Q2- 0.757. B) VIP plot from PLSDA analysis. The red highlighted features were lipid molecules including free fatty acids and phosphatidylcholines. C) VIP list of free fatty acids and phosphatidylcholines highlighted in B).



Supplemental Fig. S6. Supplemental molecular abundance of PCs in Group A, B and C. The labeling of group A, B and C remains the same as introduced previously. Relative abundance was used in the analysis as Y-axis.

Supplemental Table S1. Clinical Characteristics and Biochemical Analysis at Baseline and Absolute Changes from Baseline to 3 Months

parameters	Group A n=35		Group B n=36		Group C n=39		P [†]	P [§]
	baseline	Absolute change	baseline	Absolute change	baseline	Absolute change		
age(year)	27.5 ± 3.4	—	27.2 ± 3.5	—	26.7 ± 6.4	—	0.783	—
BMI (kg/m ²)	26.1 ± 5.4	0.1 ± 0.9	25.5 ± 5.8	-0.0 ± 1.2	26.4 ± 5.9	-0.3 ± 0.9*	0.764	0.242
Hirsutism score	6.8 ± 4.7	-1.3 ± 3.9	6.1 ± 4.9	-0.9 ± 3.0	8.7 ± 5.6	-1.8 ± 2.5*	0.080	0.456
Acne score	6.3 ± 6.5	-2.8 ± 4.5*	5.9 ± 7.0	-1.8 ± 4.6*	6.2 ± 6.1	-4.1 ± 4.7*	0.957	0.107
Total T (ng/mL)	0.81 ± 0.27	-0.04 ± 0.24	0.72 ± 0.20	-0.14 ± 0.16*	0.74 ± 0.24	-0.14 ± 0.17*	0.220	0.033
DHEAS (µg/dL)	263.0 ± 96.9	-4.44 ± 71.06	246.9 ± 89.2	-43.29 ± 51.49*	242.2 ± 108.3	-31.01 ± 76.83*	0.641	0.005
LH(IU/L)	12.06 ± 6.89	-0.10 ± 5.33	9.04 ± 5.64	-4.93 ± 6.18*	10.31 ± 5.70	-5.23 ± 6.30*	0.116	0.001

Each value represents mean ± SD.

* P<0.05 for the comparison between baseline and 3 months.

† Baseline parameters among groups determined by one-way ANOVA.

§ Absolute changes among treatment groups determined by one-way ANOVA.

Group A: Dingkundan; Group B: Diane-35; Group C: Concomitant drugs.

BMI: Body mass index; Total T: Total testosterone; DHEAS: Dehydroepiandrosterone sulfate;
LH: Luteinizing Hormone

Supplemental Table S2. Information of 211 unique metabolites/candidates had VIP scores > 1 in OPLSDA analysis of Figure 3. 'RT' means the retention time of the metabolite. 'LS' shows the score of library search for MS/MS fragment match.

Metabolites	Polarity	m/z	RT	LS	Mass Tolerance (ppm)
Glycine	positive	76.04	10.59	49.00	(6.06)
beta-alanine	negative	88.04	10.01	48.00	(1.24)
lactate	negative	89.02	6.73	71.00	(1.40)
beta-Alanine	positive	90.06	10.01	35.00	(5.32)
Betaine aldehyde	positive	102.09	3.23	59.00	(0.17)
Tartronate semialdehyde	negative	103.00	3.18	29.00	0.52
N-Formiminoglycine	positive	103.05	10.24	NA	0.10
L-serine	negative	104.03	11.18	75.00	0.24
Glyceric acid	negative	105.02	6.05	67.00	(4.91)
L-Serine	positive	106.05	11.19	46.00	0.23
creatinine	negative	112.05	4.22	65.00	0.67
N-Methylhydantoin	negative	113.04	11.37	NA	(3.60)
2-Heptanone	negative	113.10	2.40	NA	(3.59)
maleamate	negative	114.02	11.36	30.00	0.89
Creatinine	positive	114.07	4.23	67.00	(4.87)
5,6-dihydrouracil	positive	115.05	1.80	41.00	(4.98)
guanidinoacetate	negative	116.05	10.33	38.00	1.62
5-aminopentanoate	negative	116.07	8.65	87.00	1.41
2-Hydroxy-3-methylbutyric acid	negative	117.06	4.29	40.00	(3.28)
L-threonine	negative	118.05	10.40	68.00	1.87
Guanidineacetic acid	positive	118.06	10.34	93.00	(4.70)
Betaine	positive	118.09	7.68	28.00	(4.96)
L-Valine	positive	118.09	8.66	72.00	(4.96)
L-Erythrulose	negative	119.03	8.60	93.00	(2.82)
hydroxybenzaldehyde	negative	121.03	2.90	40.00	1.69
Nicotinic acid	negative	122.02	1.55	NA	2.15
Hydroxybenzaldehyde	positive	123.04	8.87	60.00	(0.40)
3-methylhistamine	positive	126.10	8.83	20.00	(4.32)
Pyroglutamic acid	positive	130.05	11.07	47.00	(0.23)
Creatine	negative	130.06	10.16	99.00	2.49
L-Leucine	negative	130.09	7.66	50.00	2.46
L-Isoleucine	negative	130.09	7.93	50.00	2.46

L-Asparagine	negative	131.05	11.35	96.00	2.61
L-Ornithine	negative	131.08	15.53	90.00	(1.34)
L-aspartate	negative	132.03	12.69	90.00	2.76
Creatine	positive	132.08	10.13	84.00	(4.44)
L-Leucine	positive	132.10	7.67	45.00	(4.41)
L-Isoleucine	positive	132.10	7.93	50.00	(4.41)
L-Asparagine	positive	133.06	11.38	80.00	(4.58)
Ornithine	positive	133.10	15.48	90.00	(4.28)
L-Homocysteine	negative	134.03	8.78	NA	(0.95)
Aspartic Acid	positive	134.04	12.74	63.00	(0.23)
Adenine	negative	134.05	3.93	56.00	2.69
Aspartic Acid	positive	134.05	12.75	58.00	(4.19)
Adenine	positive	136.06	3.89	29.00	(4.47)
1-Methylnicotinamide	positive	137.07	1.24	36.00	(0.74)
Anthranilate	positive	138.06	8.13	50.00	(4.63)
1H-Indole-4-carboxaldehyde	negative	144.05	0.93	10.00	(0.09)
2-Keto-6-aminocaproate	negative	144.07	8.04	48.00	(0.25)
L-Glutamine	negative	145.06	11.07	100.00	3.72
L-lysine	negative	145.10	15.51	34.00	4.00
D-Glutamic acid	negative	146.05	12.33	43.00	3.97
Acetylcholine	positive	146.12	11.13	95.00	(0.08)
Spermidine	positive	146.17	11.12	10.00	(6.82)
L-Glutamine	positive	147.08	11.06	64.00	(4.48)
L-Lysine	positive	147.11	15.49	84.00	(4.34)
L-methionine	negative	148.04	8.30	53.00	3.48
L-Glutamic acid	positive	148.06	12.33	90.00	(4.31)
(RS)-Mevalonic Acid	positive	149.08	11.09	NA	(2.65)
L-Methionine	positive	150.06	8.29	90.00	(4.00)
Xanthine	negative	151.03	5.48	61.00	3.68
Phenylglyoxylic acid	positive	151.04	8.56	20.00	(0.73)
Arabitol	negative	151.06	2.43	32.00	(0.16)
Xylulose	positive	151.06	8.29	NA	9.63
3-sulfin-L-alanine	positive	154.02	11.79	NA	(4.20)
2-Aminomuconic acid	positive	158.04	7.70	NA	8.53
5-Acetamidovalerate	negative	158.08	6.04	19.00	0.36
DL-2-Aminooctanoic acid	negative	158.12	6.57	NA	(0.18)
2-Indolecarboxylic acid	negative	160.04	4.95	NA	0.38
N-methyl-L-glutamate	negative	160.06	8.06	50.00	3.03
3-hydroxy-3-methylglutarate	negative	161.05	8.55	43.00	3.34
L-Carnitine	positive	162.11	10.22	80.00	(1.09)
Benzenebutanoic acid	negative	163.08	1.74	15.00	(0.11)

5-hydroxylysine	positive	163.11	10.20	20.00	7.78
L-Phenylalanine	negative	164.07	7.56	68.00	2.99
7-Methylguanine	positive	166.07	4.86	62.00	(0.61)
L-cysteic acid	negative	168.00	11.21	NA	2.84
glycerol 2-phosphate	negative	171.01	7.70	34.00	11.51
3-dehydroshikimate	negative	171.03	8.93	43.00	(11.15)
cis-Aconitic acid	negative	173.01	11.29	77.00	(2.26)
Suberic acid	negative	173.08	6.10	NA	(0.35)
Gly-Val	negative	173.09	9.71	40.00	6.21
L-Arginine	negative	173.10	15.24	31.00	(0.06)
N-acetyl-L-aspartic acid	negative	174.04	12.22	46.00	3.05
Citrulline	negative	174.09	11.72	61.00	2.95
Ser-Ala	negative	175.07	10.36	80.00	6.36
indole-3-acetamide	positive	175.09	3.85	45.00	(3.33)
L-Arginine	positive	175.12	15.26	100.00	(3.17)
N-amidino-L-aspartate	positive	176.07	12.62	60.00	(7.47)
Citrulline	positive	176.10	11.71	100.00	(3.02)
4-Hydroxyphenylpyruvic acid	negative	179.03	2.75	NA	0.18
D-(+)-Glucose	negative	179.06	8.56	99.00	0.21
L-Tyrosine	positive	182.08	8.89	100.00	(2.83)
5-Hydroxyisourate	negative	183.02	8.11	21.00	(0.27)
Galactitol	positive	183.09	8.87	20.00	(9.84)
Phosphorylcholine	positive	184.07	5.41	40.00	(2.60)
5-Hydroxyisourate	positive	185.03	11.07	NA	9.24
Kynurenic acid	negative	188.04	6.01	30.00	0.17
Indoleacrylic acid	positive	188.07	7.70	100.00	(0.62)
Prenyl-L-cysteine	positive	190.09	4.10	NA	(3.82)
L-Homocitrulline	positive	190.12	11.39	NA	(3.41)
citrate	negative	191.02	16.17	96.00	3.07
5-Hydroxyindoleacetic acid	positive	192.07	8.41	NA	(0.99)
D-Glucuronic acid	negative	193.04	11.93	100.00	(0.02)
Gluconic acid	negative	195.05	11.32	89.00	2.95
methyl beta-D-galactoside	positive	195.09	10.14	24.00	(8.47)
3,4-Dihydroxy-L-phenylalanine	negative	196.06	8.91	26.00	(9.72)
Leu-Ala	negative	201.12	7.40	40.00	5.48
Asymmetric dimethylarginine	negative	201.14	14.00	NA	0.38
Glu-Gly	negative	203.07	13.32	82.00	8.61
Tryptophan	negative	203.08	7.68	90.00	2.86
Asymmetric dimethylarginine	positive	203.15	13.94	98.00	(0.44)
O-Acetyl-L-carnitine	positive	204.12	8.82	73.00	(0.87)
D-Glutamylglycine	positive	205.08	13.30	61.00	(0.45)

Tryptophan	positive	205.10	7.67	100.00	(3.47)
L-kynurenine	negative	207.08	7.77	NA	2.12
L-Kynurenine	positive	209.09	7.79	90.00	(3.73)
5-L-Glutamyl-L-alanine	negative	217.08	12.75	60.00	0.16
Pantothenic Acid	negative	218.10	8.03	96.00	0.16
Propionylcarnitine	positive	218.14	8.06	60.00	(0.82)
alpha-glutamylalanine	positive	219.10	12.75	52.00	(7.21)
Deoxycytidine	negative	226.08	8.39	20.00	2.35
Myristic acid	negative	227.20	0.93	30.00	2.60
Deoxycytidine	positive	228.10	8.39	NA	(3.51)
Ile-Pro	positive	229.16	8.70	22.00	(5.76)
Asn-Val	negative	230.11	10.23	48.00	4.78
Asn-Val	positive	232.13	10.27	21.00	(5.95)
L-Cystine	positive	241.03	15.04	70.00	(3.26)
Uridine	negative	243.06	4.10	97.00	1.83
Isopentenyl pyrophosphate	negative	245.00	4.26	20.00	(2.60)
Biotin	positive	245.10	2.92	NA	(1.39)
Gln-Thr	negative	246.11	11.15	74.00	4.57
Pivaloylcarnitine	positive	246.17	6.90	73.00	(1.39)
Palmitoleic acid	negative	253.22	0.93	21.00	0.26
Palmitic acid	negative	255.23	0.91	NA	0.16
Palmitic amide	positive	256.26	0.86	NA	(1.36)
Nicotinamide Ribose	positive	257.11	4.02	NA	(3.40)
Glycerophosphocholine	positive	258.11	11.32	80.00	(1.14)
AICAR	positive	259.10	11.35	30.00	13.70
L-gamma-glutamyl-L-leucine	positive	261.15	10.84	31.00	(2.69)
3-Methoxy-4-hydroxyphenylethyleneglycol sulfate	negative	263.02	1.43	80.00	(0.35)
FA(17:1)	negative	267.23	0.91	NA	1.39
Val-Arg	negative	272.17	11.14	40.00	4.82
Gln-Glu	negative	274.10	13.60	95.00	6.82
Gln-Glu	positive	276.12	13.60	58.00	(2.40)
Phe-Ile	negative	277.15	5.40	70.00	4.23
L-Aspartyl-L-phenylalanine	negative	279.10	10.86	61.00	0.44
Phe-Ile	positive	279.17	5.43	58.00	(5.33)
L-Aspartyl-L-phenylalanine	positive	281.11	10.86	95.00	(0.71)
Oleic Acid	negative	281.25	0.91	20.00	(0.48)
1-methyladenosine	positive	282.12	8.42	38.00	(2.74)
Oleamide	positive	282.28	0.88	100.00	(1.07)
Stearic acid	negative	283.26	0.91	20.00	(1.08)
5-Aminoimidazole ribonucleotide	positive	296.06	11.31	NA	5.05

N-Acetylaspartylglutamic acid	negative	303.08	4.12	14.00	0.40
FA(20:3)	negative	305.25	0.91	NA	0.41
N-Acetylneuraminic acid	negative	308.10	2.26	NA	2.55
Eicosanoic acid	negative	309.28	0.91	21.00	2.05
Phe-Phe	negative	311.14	4.96	100.00	4.35
Phe-Phe	positive	313.16	4.95	76.00	(4.99)
Uridine 5'-monophosphate	positive	325.04	8.89	NA	0.08
Docosahexaenoic acid	negative	327.23	0.91	84.00	0.23
FA(22:5)	negative	329.25	0.91	NA	0.77
FA(22:4)	negative	331.26	0.89	11.00	0.55
12(S)-HPETE	negative	335.22	2.48	NA	0.36
AICAR	negative	337.06	8.27	NA	(2.72)
8,9-DiHETrE	negative	337.24	2.29	NA	0.85
Inosine 5'-monophosphate	positive	349.05	4.25	10.00	12.83
Phe-Trp	negative	350.15	5.53	100.00	3.97
Phe-Trp	positive	352.17	5.52	82.00	(4.94)
FA(24:5)	negative	357.28	0.91	NA	0.36
FA(24:4)	negative	359.30	0.89	NA	(1.57)
Orotidylic acid	positive	369.03	7.00	NA	(13.94)
cis-5-Tetradecenoylcarnitine	positive	370.30	5.09	NA	(1.56)
Tetradecanoylcarnitine	positive	372.31	5.09	NA	(1.07)
FA(26:1)	negative	393.37	0.88	NA	0.39
trans-Hexadec-2-enoyl carnitine	positive	398.33	4.94	100.00	(1.09)
L-Palmitoylcarnitine	positive	400.34	4.93	100.00	(1.23)
Calcidiol	positive	401.34	4.93	NA	2.39
Linoleyl carnitine	positive	424.34	4.87	100.00	(1.28)
Elaidic carnitine	positive	426.36	4.81	100.00	(1.03)
DL-Stearoylcarnitine	positive	428.37	4.80	NA	0.48
Alpha-Tocopherol	positive	431.39	0.80	NA	(11.44)
dihydroxyvitamin D3	positive	445.29	1.01	NA	(14.18)
LPE(16:0)	negative	452.28	5.97	70.00	1.16
cholesterol sulfate	negative	465.30	0.71	30.00	0.17
LPE(18:0)	negative	480.31	5.69	70.00	(0.05)
LPE(20:2)	negative	504.31	5.64	80.00	(1.18)
N-Palmitoylsphingosine	positive	538.52	0.84	NA	(0.90)
uridine 5'-diphosphoglucose	negative	565.05	9.05	NA	1.52
Lutein	positive	569.44	0.82	NA	(8.49)
LPI(16:0)	negative	571.29	7.74	52.00	0.77
LysoPC(18:2)	negative	578.35	4.73	77.00	0.68
LysoPC(18:1)	negative	580.36	5.61	47.00	1.73
LysoPC(18:0)	negative	582.38	4.57	75.00	0.91

Bilirubin	positive	585.27	0.90	97.00	(1.90)
L-Urobilin	positive	595.35	2.05	NA	6.89
LPI(18:0)	negative	599.32	7.64	83.00	0.88
Uridine 5'-diphospho-N-acetylglucosamine	negative	606.07	8.91	NA	1.52
LPI(20:4)	negative	619.29	7.62	73.00	0.87
palmitoyl sphingomyelin	positive	703.58	5.16	NA	(3.23)
3-demethylubiquinol-9	positive	783.63	4.97	NA	9.80
PC(14:0/18:2)	negative	788.54	3.82	56.00	1.86
PC(16:0/16:1)	negative	790.56	3.78	77.00	1.65
ubiquinol-9	positive	797.64	4.94	NA	9.77
PC(15:0/18:2)	negative	802.56	3.73	43.00	(0.30)
PC(16:1/18:2)	negative	814.56	3.76	91.00	1.73
PC(16:0/18:2)	negative	816.58	3.74	100.00	1.14
PC(17:0/18:2)	negative	830.59	3.67	57.00	1.08
PC(18:0/18:2)	negative	844.61	3.63	70.00	0.69
PC(18:0/20:4)	negative	868.61	3.48	75.00	1.28

Supplemental Table S3. Information of 92 metabolites/candidates had VIP scores > 1 and FDR < 0.05 in OPLSDA analysis of Figure S3. P-value and FDR values were calculated from Metaboanalyst.

compound name	M S / M S	A				B				C			
		VIP	ratio (A3/A1)	p-value	FDR	VIP	ratio (B3/B1)	p-value	FDR	VIP	ratio (B3/B1)	p-value	FDR
5-Hydroxyindoleacetaldehyde	Y	1.41	0.29	0.0000	0.0001	1.36	0.24	0.0001	0.0004	1.05	0.42	0.0008	0.0029
N-Formiminoglycine	N	1.16	0.51	0.0006	0.0022	1.30	0.37	0.0003	0.0008	1.59	0.32	0.0000	0.0000
1-Methylnicotinamide	Y	1.53	0.54	0.0000	0.0000	1.76	0.37	0.0000	0.0000	1.37	0.35	0.0000	0.0000
L-Glutamic acid	Y	1.14	0.43	0.0004	0.0016	1.36	0.41	0.0001	0.0003	1.66	0.33	0.0000	0.0000
PC(15:0/18:2)	Y	2.02	0.40	0.0000	0.0000	2.23	0.45	0.0000	0.0000	1.94	0.44	0.0000	0.0000
Bilirubin	Y	1.39	0.58	0.0000	0.0000	1.71	0.45	0.0000	0.0000	1.32	0.46	0.0000	0.0001
FA(26:3)	N	1.06	0.47	0.0016	0.0050	1.29	0.49	0.0005	0.0017	1.15	0.51	0.0036	0.0101
3-Methoxy-4-hydroxyphenylethylenegativelycol sulfate	Y	1.84	0.55	0.0000	0.0000	1.80	0.49	0.0000	0.0000	1.64	0.50	0.0000	0.0000
Lutein	N	1.70	0.45	0.0000	0.0000	1.56	0.50	0.0000	0.0000	1.63	0.47	0.0000	0.0000
PC(17:0/18:2)	Y	1.62	0.61	0.0000	0.0000	1.99	0.51	0.0000	0.0000	1.81	0.53	0.0000	0.0000
Gln-Thr	Y	1.08	0.64	0.0017	0.0057	1.25	0.52	0.0006	0.0024	1.24	0.50	0.0001	0.0004
Drug	N	1.20	0.57	0.0004	0.0018	1.26	0.52	0.0007	0.0025	1.22	0.64	0.0063	0.0184
Pentacosylic acid	N	1.19	0.57	0.0004	0.0018	1.15	0.53	0.0022	0.0072	1.26	0.60	0.0041	0.0118
FA(26:2)	N	1.22	0.54	0.0003	0.0011	1.23	0.54	0.0009	0.0029	1.23	0.58	0.0022	0.0064
PC(18:0/18:2)	Y	1.30	0.72	0.0003	0.0016	2.01	0.54	0.0000	0.0000	1.70	0.63	0.0000	0.0000
N-alpha-Acetyl-L-Asparagine	N	1.05	0.74	0.0015	0.0050	1.48	0.56	0.0000	0.0001	1.36	0.62	0.0000	0.0001
3b,5a,6b-Cholestanetriol	N	1.03	0.61	0.0030	0.0095	1.28	0.56	0.0003	0.0013	1.17	0.58	0.0054	0.0153
FA(24:1)	N	1.34	0.53	0.0000	0.0002	1.39	0.56	0.0001	0.0005	1.27	0.57	0.0005	0.0019
Gamma-glutamyl-Threonine	N	1.30	0.58	0.0001	0.0004	1.30	0.57	0.0008	0.0036	1.39	0.52	0.0000	0.0001
Isopentenyl pyrophosphate	N	1.88	0.46	0.0000	0.0000	1.61	0.58	0.0000	0.0000	1.69	0.60	0.0000	0.0000

Androstenedione	N	1.05	0.68	0.0023	0.0079	1.51	0.58	0.0000	0.0000	1.09	0.64	0.0007	0.0027
Glu-Ile	Y	1.05	0.70	0.0015	0.0048	1.36	0.60	0.0001	0.0003	1.56	0.56	0.0000	0.0000
Leu-Glu	Y	1.05	0.70	0.0015	0.0048	1.36	0.60	0.0001	0.0003	1.56	0.56	0.0000	0.0000
PC(18:0/20:4)	Y	1.13	0.78	0.0032	0.0103	1.81	0.61	0.0000	0.0000	1.57	0.72	0.0000	0.0001
5-Tetradecenoylcarnitine	N	1.22	0.66	0.0005	0.0022	1.08	0.67	0.0016	0.0060	1.36	0.64	0.0000	0.0002
Butyrylcarnitine	Y	1.24	0.65	0.0009	0.0038	1.31	0.67	0.0002	0.0011	1.24	0.65	0.0002	0.0011
Orotidylic acid	N	1.79	0.63	0.0000	0.0000	1.80	0.68	0.0000	0.0000	1.95	0.65	0.0000	0.0000
PC(18:0/22:6)	Y	1.05	0.77	0.0088	0.0242	1.44	0.68	0.0001	0.0004	1.24	0.77	0.0032	0.0104
Linoleyl carnitine	Y	1.22	0.83	0.0002	0.0012	1.77	0.69	0.0000	0.0000	1.53	0.74	0.0000	0.0000
PC(16:0/18:2)	Y	1.72	0.70	0.0000	0.0000	1.90	0.69	0.0000	0.0000	1.60	0.74	0.0000	0.0000
L-Acetylcarnitine	Y	1.76	0.58	0.0000	0.0000	1.80	0.70	0.0000	0.0000	1.94	0.60	0.0000	0.0000
3-Hydroxycapric acid	Y	1.07	0.70	0.0013	0.0050	1.22	0.70	0.0015	0.0058	1.19	0.67	0.0002	0.0009
(25R)-5beta-Cholestane-3alpha,7alpha,12alpha,26-tetrol	N	1.17	0.61	0.0023	0.0082	1.17	0.72	0.0019	0.0068	1.27	0.71	0.0004	0.0016
DL-Stearoylcarnitine	N	1.01	0.80	0.0037	0.0111	1.44	0.74	0.0000	0.0001	1.33	0.75	0.0000	0.0002
Elaidic carnitine	Y	1.42	0.75	0.0000	0.0001	1.35	0.75	0.0001	0.0004	1.47	0.76	0.0000	0.0000
16-Hydroxypalmitic acid	Y	1.07	0.81	0.0021	0.0074	1.22	0.77	0.0002	0.0012	1.20	0.81	0.0001	0.0006
Asymmetric dimethylarginine	Y	1.65	0.80	0.0000	0.0000	1.91	0.77	0.0000	0.0000	1.81	0.79	0.0000	0.0000
Succinylcarnitine	Y	1.07	0.84	0.0030	0.0096	1.36	0.79	0.0026	0.0097	1.31	0.80	0.0018	0.0064
(RS)-Mevalonic Acid	N	1.37	0.89	0.0004	0.0018	1.77	0.80	0.0000	0.0000	1.66	0.80	0.0000	0.0000
PC(18:1/20:4)	Y	1.24	0.85	0.0016	0.0059	1.42	0.80	0.0011	0.0046	1.12	0.88	0.0205	0.0498
Inosine triphosphate	N	1.67	0.69	0.0000	0.0000	1.32	0.81	0.0019	0.0069	1.59	0.75	0.0000	0.0001
7-Methylguanine	Y	1.78	0.71	0.0000	0.0000	1.23	0.81	0.0002	0.0011	1.63	0.74	0.0000	0.0000
L-Glutamine	Y	1.32	0.90	0.0012	0.0048	1.78	0.81	0.0000	0.0000	1.82	0.80	0.0000	0.0000
Histamine	Y	1.54	0.78	0.0000	0.0000	1.52	0.82	0.0000	0.0000	1.63	0.79	0.0000	0.0000

Dantron	N	1.43	0.77	0.0000	0.0003	1.43	0.82	0.0001	0.0002	1.27	0.81	0.0005	0.0019
5-Hydroxyisourate	N	1.11	0.87	0.0033	0.0096	1.68	0.82	0.0000	0.0000	1.50	0.83	0.0000	0.0000
5-Oxo-proline	Y	1.27	0.91	0.0034	0.0108	1.79	0.83	0.0000	0.0000	1.82	0.81	0.0000	0.0000
Pyrrolidonecarboxylic acid	Y	1.27	0.91	0.0034	0.0108	1.79	0.83	0.0000	0.0000	1.82	0.81	0.0000	0.0000
4-Guanidinobutanoic acid	Y	1.40	0.76	0.0001	0.0005	1.33	0.83	0.0007	0.0030	1.53	0.77	0.0000	0.0001
Deoxycytidine	N	1.39	0.87	0.0072	0.0018	1.54	0.83	0.0054	0.0003	1.13	0.81	0.0014	0.0032
Deoxycytidine	N	1.06	0.87	0.0072	0.0018	1.12	0.83	0.0054	0.0003	1.08	0.81	0.0014	0.0032
N-Methylhydantoin	N	1.22	0.90	0.0137	0.0099	1.15	0.85	0.0156	0.0026	1.22	0.82	0.0001	0.0006
Deoxyuridine monophosphate	N	1.01	0.88	0.0041	0.0127	1.08	0.86	0.0023	0.0077	1.17	0.85	0.0010	0.0032
Arg-Val	N	1.44	0.92	0.4495	0.0000	1.08	0.87	0.2795	0.0278	1.35	0.94	0.5973	0.0000
Creatinine	Y	1.06	1.07	0.0049	0.0143	1.67	1.18	0.0000	0.0000	1.66	1.14	0.0000	0.0000
L-Tryptophan	Y	1.36	1.17	0.0002	0.0011	1.48	1.20	0.0000	0.0001	1.40	1.18	0.0001	0.0006
L-Leucine	Y	1.28	1.23	0.0001	0.0000	1.40	1.20	0.0000	0.0001	1.60	1.26	0.0000	0.0000
Indoleacrylic acid	Y	1.44	1.20	0.0001	0.0004	1.52	1.20	0.0000	0.0001	1.43	1.19	0.0001	0.0004
L-Lysine	Y	1.39	1.25	0.0028	0.0094	1.31	1.21	0.0105	0.0322	1.52	1.32	0.0002	0.0009
Phe-Phe	Y	1.53	1.10	0.4212	0.0000	1.54	1.21	0.1088	0.0000	1.80	1.20	0.1911	0.0000
L-Isoleucine	Y	1.58	1.28	0.0000	0.0001	1.36	1.21	0.0002	0.0009	1.53	1.25	0.0000	0.0001
N-Acetylneuraminic acid	N	1.96	1.06	0.3901	0.0000	2.03	1.23	0.0014	0.0000	1.98	1.30	0.6121	0.0000
3-Dehydroshikimate	Y	1.45	1.29	0.0000	0.0000	1.20	1.27	0.0002	0.0010	1.88	1.40	0.0000	0.0000
Amino adipic acid	Y	1.26	1.32	0.0023	0.0082	1.15	1.29	0.0022	0.0078	1.58	1.47	0.0000	0.0001
Glycerophosphocholine	Y	1.49	1.83	0.0000	0.0001	1.37	1.37	0.0008	0.0034	1.56	1.62	0.0000	0.0000
Prelyl-L-cysteine	N	1.86	1.86	0.0000	0.0000	1.19	1.37	0.0015	0.0060	1.28	1.38	0.0001	0.0005
Glyceric acid	Y	1.22	1.37	0.0003	0.0015	1.53	1.45	0.0000	0.0000	1.82	1.56	0.0000	0.0000
Ala-Asp	Y	1.48	1.87	0.0000	0.0003	1.27	1.46	0.0017	0.0067	1.47	1.71	0.0001	0.0005
4-Hydroxyphenyl pyruvic acid	N	1.28	1.76	0.0005	0.0020	1.07	1.47	0.0010	0.0040	1.20	1.76	0.0001	0.0005

Gly-Glu	Y	1.48	1.82	0.0000	0.0003	1.27	1.49	0.0002	0.0010	1.47	1.54	0.0005	0.0005
LPE(16:0)	Y	1.08	1.24	0.0069	0.0190	1.40	1.53	0.0002	0.0008	1.50	1.58	0.0000	0.0000
Phe-Trp	Y	1.52	1.08	0.3151	0.0001	1.55	1.54	0.0003	0.0000	1.84	1.29	0.0112	0.0000
5-Dehydro-4-deoxy-D-glucaric acid	Y	1.75	1.60	0.0000	0.0000	1.67	1.62	0.0000	0.0000	1.72	1.69	0.0000	0.0000
Citrate	Y	1.75	1.60	0.0000	0.0000	1.67	1.62	0.0000	0.0000	1.72	1.69	0.0000	0.0000
Isocitric acid	Y	1.75	1.60	0.0000	0.0000	1.67	1.62	0.0000	0.0000	1.72	1.69	0.0000	0.0000
Trans-Hexadec-2-enoyl carnitine	Y	1.58	1.60	0.0000	0.0000	1.61	1.64	0.0000	0.0000	1.72	1.68	0.0000	0.0000
Aconitic acid	Y	1.92	2.00	0.0000	0.0000	1.80	1.97	0.0000	0.0000	1.73	1.99	0.0000	0.0000
Phe-Leu	Y	1.33	1.76	0.0005	0.0004	1.61	1.98	0.0000	0.0000	1.25	1.75	0.0010	0.0001
Dehydroascorbic acid	Y	1.93	2.03	0.0000	0.0000	1.82	1.99	0.0000	0.0000	1.78	2.06	0.0000	0.0000
Aspartic Acid	Y	1.60	1.66	0.0000	0.0001	2.02	2.04	0.0000	0.0000	1.98	2.10	0.0000	0.0000
Adenine	N	2.03	2.14	0.0000	0.0000	2.01	2.06	0.0000	0.0000	2.10	2.26	0.0000	0.0000
AICAR	N	1.47	2.77	0.0000	0.0000	1.49	2.07	0.0000	0.0002	1.46	2.15	0.0000	0.0000
Palmitic amide	N	1.08	1.47	0.0016	0.0061	1.73	2.20	0.0000	0.0000	1.31	2.07	0.0000	0.0001
Indole-3-acetamide	Y	2.18	2.29	0.0000	0.0000	2.33	2.42	0.0000	0.0000	2.01	2.28	0.0000	0.0000
Pivaloylcarnitine	Y	1.39	2.30	0.0000	0.0001	1.57	2.87	0.0000	0.0000	1.75	3.98	0.0000	0.0000
3-Methylhistamine	Y	1.25	1.98	0.0001	0.0004	1.85	3.00	0.0000	0.0000	1.39	2.30	0.0000	0.0000
Dihydroxyvitamin D3	N	1.68	2.46	0.0000	0.0000	1.84	3.29	0.0000	0.0000	1.86	3.28	0.0000	0.0000
Nicotinic acid	N	1.56	3.36	0.0000	0.0000	1.75	3.59	0.0000	0.0000	1.72	4.12	0.0000	0.0000
Oleamide	Y	1.26	3.71	0.0001	0.0004	1.40	4.19	0.0000	0.0002	1.48	6.06	0.0000	0.0000
N-Palmitoylsphingosine	N	1.80	3.22	0.0000	0.0000	2.26	5.06	0.0000	0.0000	1.72	3.38	0.0000	0.0000
Asn-Val	N	1.36	3.37	0.0001	0.0005	1.72	7.49	0.0000	0.0000	1.72	6.81	0.0000	0.0000
Gly-Val	Y	1.19	3.83	0.0008	0.0024	1.44	9.30	0.0001	0.0002	1.55	8.41	0.0000	0.0000