

Supplemental Data

Cystathionine-β-Synthase Inhibition for Colon Cancer: Enhancement of the Efficacy of Aminooxyacetic Acid via the Prodrug Approach

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Supplementary Table S1. Modulation of the metabolome of HCT116 cells by YD0171 and AOAA treatment (1 mM, 24 h). Numbers represent fold changes in metabolite concentrations; red backgrounds indicate increases, green backgrounds indicate decreases in the concentration of the metabolite compared to control.

Super Pathway	Sub Pathway	Analyte Name	AOAA vs. control	p	YD0171 vs. control	p
Amino Acid	Glycine, Serine and Threonine Metabolism	glycine	0.96	0.393	1.15	0.084
		dimethylglycine	1.06	0.602	1.26	0.017
		betaine	0.85	0.102	0.91	0.369
		serine	1.46	<0.01	1.42	0.016
		N-acetylserine	0.61	<0.01	0.9	0.182
		threonine	1.11	0.011	1.45	<0.01
		N-acetylthreonine	0.89	0.086	0.79	0.020
	Alanine and Aspartate Metabolism	alanine	0.62	<0.01	0.8	0.016
		N-acetylalanine	0.63	<0.01	0.59	<0.01
		aspartate	0.37	<0.01	0.36	<0.01
		asparagine	1.1	0.025	1.48	<0.01
		N-acetylaspargine	0.84	0.199	1.19	0.151
	Glutamate Metabolism	N-acetylaspargine	0.48	<0.01	0.34	<0.01
		glutamate	1.5	<0.01	1.49	<0.01
		glutamine	0.82	<0.01	0.72	<0.01
		N-acetylglutamate	0.96	0.7928	0.96	0.814
		N-acetylglutamine	0.76	<0.01	1.01	0.966
		N-acetyl-aspartyl-glutamate (NAAG)	1.28	0.169	0.82	0.106
		gamma-aminobutyrate (GABA)	0.26	<0.01	0.31	<0.01
		4-hydroxyglutamate	4.82	<0.01	2.49	<0.01
glutamate, gamma-methyl ester	0.84	0.423	0.41	<0.01		
pyroglutamine*	1.07	0.415	1.19	0.084		
S-1-pyrroline-5-carboxylate	5.7	<0.01	9.19	<0.01		

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Supplementary Table S1. *Continued.*

Histidine Metabolism	histidine	1.13	<0.01	1.24	0.025
	N-acetylhistidine	0.67	<0.01	0.68	<0.01
	1-methylhistidine	1.19	0.036	1.77	<0.01
	3-methylhistidine	1.16	0.052	2.21	<0.01
	imidazole propionate	0.51	<0.01	0.76	0.042
	imidazole lactate	0.5	<0.01	0.67	<0.01
	1-methylimidazoleacetate	1.19	0.079	1.57	<0.01
	4-imidazoleacetate	0.39	<0.01	0.72	0.020
	histidine methyl ester	1.02	0.831	0.94	0.552
Lysine Metabolism	lysine	0.92	0.135	0.79	0.075
	N6-acetyllysine	0.69	0.014	0.78	0.064
	N6,N6,N6-trimethyllysine	0.87	0.031	0.78	0.068
	5-hydroxylysine	1.6	<0.01	1.29	0.220
	saccharopine	1		1	
	2-aminoadipate	2.69	<0.01	2.4	<0.01
	glutarate (pentanedioate)	0.64	<0.01	1.23	0.072
	pipecolate	1.67	0.018	1.67	0.029
	5-aminovalerate	0.56	<0.01	0.49	<0.01
	6-oxopiperidine-2-carboxylic acid	1.14	0.401	1.37	0.063
Phenylalanine and Tyrosine Metabolism	phenylalanine	1.09	0.025	1.17	0.076
	N-acetylphenylalanine	0.66	0.186	1.15	0.7197
	phenyllactate (PLA)	0.42	<0.01	0.54	0.033
	phenylacetyl glycine	1.25	0.017	1.32	0.033
	tyrosine	1.16	0.012	1.23	0.065
	N-acetyltyrosine	1		1	
	3-(4-hydroxyphenyl)lactate	0.08	<0.01	0.14	<0.01
	phenol sulfate	0.91	0.295	0.97	0.652
	p-cresol sulfate	0.98	0.770	1.05	0.605
O-methyltyrosine	1.39	<0.01	1.25	0.086	
Tryptophan Metabolism	tryptophan	0.94	0.203	1.06	0.504
	indolelactate	0.26	<0.01	0.3	<0.01
	kynurenine	1.37	<0.01	1.8	<0.01
	serotonin	1		1	
	C-glycosyltryptophan	0.58	<0.01	0.32	0.012
Leucine, Isoleucine and Valine Metabolism	leucine	1.06	0.064	1.21	0.042
	N-acetylleucine	0.92	0.688	0.61	0.078
	4-methyl-2-oxopentanoate	0.89	0.391	0.89	0.391
	isovalerylcarnitine	1.88	<0.01	2.66	<0.01
	beta-hydroxyisovalerate	0.29	<0.01	0.27	<0.01
	beta-hydroxyisovalerylcarnitine	0.26	<0.01	0.26	<0.01
	3-methylglutaconate	0.57	<0.01	0.75	0.177
	alpha-hydroxyisovalerate	1.12	0.391	1	
	methylsuccinate	0.62	<0.01	0.95	0.608
	isoleucine	1.35	<0.01	1.68	<0.01
	3-methyl-2-oxovalerate	1		1	
	2-methylbutyrylcarnitine (C5)	0.92	0.145	1.36	0.013
	tiglylcarnitine	0.15	<0.01	0.15	<0.01
	2-hydroxy-3-methylvalerate	1		1	
	ethylmalonate	0.62	<0.01	1.03	0.946
	valine	1.16	<0.01	1.22	0.067
	N-acetylvaline	0.63	<0.01	0.6	<0.01
3-methyl-2-oxobutyrate	1		1		
isobutyrylcarnitine	0.71	<0.01	0.95	0.554	
3-hydroxyisobutyrate	0.49	<0.01	0.49	<0.01	
alpha-hydroxyisocaproate	1		1		

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Supplementary Table S1. *Continued.*

Methionine, Cysteine, SAM and Taurine Metabolism	methionine	0.91	0.039	0.94	0.337	
	N-acetylmethionine	0.78	0.011	0.7	0.014	
	N-formylmethionine	0.82	0.036	1	0.908	
	methionine sulfone	1.46	<0.01	1.97	<0.01	
	methionine sulfoxide	1.78	<0.01	1.99	<0.01	
	N-acetylmethionine sulfoxide	4.28	<0.01	3.09	<0.01	
	S-adenosylmethionine (SAM)	1.27	<0.01	1.32	0.086	
	S-adenosylhomocysteine (SAH)	1.1	0.049	1.12	0.191	
	homocysteine	1.41	<0.01	1.44	0.028	
	cystathionine	0.71	0.023	0.83	0.139	
	cysteine	0.67	<0.01	0.69	0.100	
	N-acetylcysteine	3.81	<0.01	1.95	0.020	
	S-methylcysteine	0.97	0.391	1.99	0.216	
	cysteine sulfinic acid	7.95	<0.01	8.68	<0.01	
	hypotaurine	0.93	0.298	1.11	0.529	
	taurine	1.1	0.209	1.26	0.030	
	N-acetyltaurine	0.54	0.042	0.92	0.575	
	2-hydroxybutyrate/2-hydroxyisobutyrate	1		1		
	Urea cycle; Arginine and Proline Metabolism	arginine	1.12	0.016	1.03	0.825
		ornithine	5.34	<0.01	5.1	<0.01
proline		1.47	<0.01	1.92	<0.01	
citrulline		2.45	<0.01	2.33	<0.01	
argininosuccinate		0.11	<0.01	0.22	<0.01	
homoarginine		1.2	0.122	1.58	0.024	
homocitrulline		1.07	0.290	1.19	0.033	
dimethylarginine (SDMA + ADMA)		0.73	<0.01	0.58	<0.01	
N-acetylarginine		0.95	0.709	0.8	0.102	
N-delta-acetylornithine		1.19	0.059	1.49	0<0.01	
N-methylproline		0.79	0.310	0.88	0.627	
trans-4-hydroxyproline		1.17	0.109	1.43	<0.01	
pro-hydroxy-pro		1.01	0.962	0.92	0.404	
N-monomethylarginine		1.13	0.033	0.94	0.562	
Creatine Metabolism	creatinine	1.13	0.04	1.19	0.024	
	creatinine	0.81	<0.01	0.88	0.131	
	creatinine phosphate	1.59	<0.01	1.86	<0.01	
Polyamine Metabolism	putrescine	0.08	<0.01	0.1	<0.01	
	spermine	44.41	<0.01	30.22	<0.01	
	N1,N12-diacetylspermine	0.76	<0.01	0.79	0.085	
	spermidine	6.46	<0.01	2.67	0.024	
	5-methylthioadenosine (MTA)	0.95	0.367	1.28	0.089	
	N-acetylputrescine	0.07	<0.01	0.1	<0.01	
	4-acetamidobutanoate	0.25	<0.01	0.24	<0.01	
Guanidino and Acetamido Metabolism	1-methylguanidine	0.7	0.149	1.1	0.681	
	4-guanidinobutanoate	1	0.945	1.38	<0.01	
Glutathione Metabolism	glutathione, reduced (GSH)	1.31	<0.01	1.34	<0.01	
	glutathione, oxidized (GSSG)	1.27	0.067	1.36	<0.01	
	cysteine-glutathione disulfide	0.35	0.027	0.43	0.086	
	S-methylglutathione	2.31	<0.01	2.26	<0.01	
	S-lactoylglutathione	1		1		
	cysteinylglycine	0.76	<0.01	0.88	0.205	
	5-oxoproline	1.08	0.087	1.43	<0.01	
	ophthalmate	0.27	<0.01	0.26	<0.01	
S-nitrosoglutathione (GSNO)	3	0.025	3.49	0.014		

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Supplementary Table S1. *Continued.*

Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylalanine	0.55	<0.01	0.69	0.017
		gamma-glutamylcysteine	1.61	<0.01	1.35	<0.01
		gamma-glutamylglutamate	2.76	<0.01	2.51	<0.01
		gamma-glutamylglutamine	0.9	0.27	0.71	<0.01
		gamma-glutamylglycine	0.84	0.199	0.85	0.364
		gamma-glutamylhistidine	0.74	0.019	0.72	0.017
		gamma-glutamylisoleucine	1.84	<0.01	1.9	<0.01
		gamma-glutamylleucine	2.33	<0.01	2.26	<0.01
		gamma-glutamyl-epsilon-lysine	1.35	0.013	1.33	0.134
		gamma-glutamylmethionine	1.05	0.534	0.93	0.333
		gamma-glutamylphenylalanine	0.9	0.489	0.86	0.285
		gamma-glutamyltyrosine	1		1	
		gamma-glutamylvaline	2.77	<0.01	2.28	<0.01
		Dipeptide Derivative	carnosine	0.99	0.893	1
	homocarnosine		1		1	
	anserine		1		1	
	Dipeptide	alanylleucine	0.42	<0.01	0.45	<0.01
		glycylisoleucine	1.41	0.019	1.51	0.032
		glycylleucine	1.18	0.057	1.48	0.051
		glycylvaline	0.85	0.057	0.84	0.224
		isoleucylglycine	0.68	<0.01	0.68	<0.01
		leucylalanine	2.07	0.206	0.73	0.315
		leucylglycine	1.13	0.281	1.02	0.874
		phenylalanylalanine	0.48	<0.01	0.52	<0.01
		phenylalanylglycine	0.48	<0.01	0.48	<0.01
		prolylglutamine	1	0.877	1	0.897
		prolylglycine	0.77	<0.01	0.75	0.0155
		threonylphenylalanine	0.52	0.183	0.52	0.183
		tryptophylglycine	0.28	<0.01	0.27	<0.01
		tyrosylglycine	0.8	0.028	0.76	0.058
valylglutamine		0.83	0.218	0.63	<0.01	
valylglycine		1.17	0.29	1.28	0.161	
valylleucine	0.67	0.121	0.47	0.021		
leucylglutamine	1.34	0.629	0.61	0.060		
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	glucose	1.82	<0.01	1.47	0.018
		glucose 6-phosphate	1.53	<0.01	1.55	<0.01
		fructose-6-phosphate	0.64	0.012	0.69	0.019
		Isobar: fructose 1,6-diphosphate, glucose 1,6-diphosphate, myo-inositol 1,4 or 1,3-diphosphate	2.56	<0.01	2.06	<0.01
		2,3-diphosphoglycerate	0.84	0.424	0.62	0.203
		dihydroxyacetone phosphate (DHAP)	1.87	0.059	0.86	0.591
		3-phosphoglycerate	1.89	0.139	2.36	0.018
		phosphoenolpyruvate (PEP)	3.07	0.022	3.31	0.017
		pyruvate	4.91	<0.01	3.83	0.083
		lactate	0.53	<0.01	0.62	<0.01
	glycerate	1.07	0.304	0.85	0.353	
	Pentose Phosphate Pathway	6-phosphogluconate	1.55	0.047	1.66	0.118
		ribose 1-phosphate	0.38	0.020	0.31	0.019
		5-phosphoribosyl diphosphate (PRPP)	3.42	<0.01	1.22	0.195
	Pentose Metabolism	sedoheptulose-7-phosphate	1.77	<0.01	2.08	<0.01
		ribose	1.28	0.022	1.3	0.028
		ribitol	2.69	<0.01	3.53	<0.01
		ribonate	0.63	<0.01	0.79	0.108

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Supplementary Table S1. *Continued.*

		adenosine-5'-diphosphoglucose	0.34	<0.01	0.34	<0.01
		arabitol/xylitol	0.92	0.400	1.02	0.901
		ribulose/xylulose	0.29	0.069	0.29	0.069
		arabonate/xylonate	0.32	0.058	0.83	0.590
	Glycogen Metabolism	maltotriose	0.22	<0.01	0.14	<0.01
	Fructose, Mannose and Galactose Metabolism	fructose	5.1	<0.015	5.22	<0.01
		mannitol/sorbitol	11.17	<0.01	14.66	<0.01
		galactitol (dulcitol)	4.48	<0.01	5.85	<0.01
		galactonate	2.16	0.016	3.27	<0.01
	Nucleotide Sugar	UDP-glucose	0.8	<0.01	0.47	<0.01
		UDP-galactose	0.62	0.042	0.47	0.044
		UDP-glucuronate	0.5	<0.01	0.37	<0.01
		guanosine 5'-diphospho-fucose	1		1	
		UDP-acetylglucosamine/galactosamine	5.89	<0.01	4.21	<0.01
		cytidine 5'-monophospho-N-acetylneuraminic acid	0.89	0.371	0.84	0.207
		glucuronate 1-phosphate	1.28	<0.01	1.11	0.196
	Aminosugar Metabolism	glucuronate	1.06	0.572	0.94	0.655
		N-acetylglucosamine 6-phosphate	1.34	0.540	0.65	0.492
		N-acetyl-glucosamine 1-phosphate	0.79	0.052	0.65	0.017
		N-acetylneuraminic acid	0.94	0.197	0.81	0.101
		N-acetylglucosaminylasparagine	1.01	0.995	0.75	<0.01
		erythronate	0.56	<0.01	0.64	0.017
		N-acetylglucosamine/N-acetylgalactosamine	1.27	0.030	0.9	0.310
Energy	TCA Cycle	citrate	1.52	<0.01	1.95	<0.01
		isocitrate	1.66	<0.01	3.02	<0.01
		alpha-ketoglutarate	2.04	<0.01	3.13	<0.01
		succinylcarnitine	0.38	<0.01	0.38	<0.01
		succinate	0.42	<0.01	0.56	<0.01
		fumarate	0.12	<0.01	0.19	<0.01
		malate	0.12	<0.01	0.27	<0.01
		2-methylcitrate/homocitrate	1.39	0.021	1.19	0.457
	Oxidative Phosphorylation	acetylphosphate	1.49	0.061	1.53	0.050
		phosphate	1.13	<0.01	1.07	0.310
Lipid	Medium Chain Fatty Acid	caprate (10:0)	1.76	<0.01	1.64	<0.01
		laurate (12:0)	1.64	<0.01	1.52	0.028
		5-dodecenoate (12:1n7)	2.36	<0.01	2.29	0.037
	Long Chain Fatty Acid	myristate (14:0)	0.97	0.856	1	0.752
		myristoleate (14:1n5)	1.64	<0.01	1.25	0.431
		pentadecanoate (15:0)	1.5	0.037	1.76	0.275
		palmitate (16:0)	1.17	0.231	1.2	0.775
		palmitoleate (16:1n7)	1.38	0.053	1.36	0.552
		margarate (17:0)	1.44	0.073	1.55	0.445
		10-heptadecenoate (17:1n7)	1.44	0.080	1.66	0.409
		stearate (18:0)	1.4	0.061	1.35	0.496
		nonadecanoate (19:0)	1.14	0.368	1.25	0.891
		10-nonadecenoate (19:1n9)	1.06	0.620	1.16	0.993
		arachidate (20:0)	0.56	<0.01	0.66	0.193
		eicosenoate (20:1)	0.7	0.173	0.76	0.325
		behenate (22:0)	0.65	0.058	0.78	0.35
		erucate (22:1n9)	0.68	0.073	0.84	0.374
		oleate/vaccenate (18:1)	1.18	0.230	1.28	0.703

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Supplementary Table S1. *Continued.*

Polyunsaturated Fatty Acid (n3 and n6)	stearidonate (18:4n3)	3.11	0.138	2.64	0.151
	eicosapentaenoate (EPA; 20:5n3)	3.74	<0.01	3.57	0.011
	docosapentaenoate (n3 DPA; 22:5n3)	2.06	0.018	2.32	0.135
	docosahexaenoate (DHA; 22:6n3)	1.99	<0.01	2.24	0.103
	linoleate (18:2n6)	2.07	<0.01	2.13	0.136
	linolenate (alpha or gamma; (18:3n3 or 6))	2.15	<0.01	2.02	0.094
	dihomo-linolenate (20:3n3 or n6)	2.06	<0.01	2.32	0.097
	arachidonate (20:4n6)	2.18	<0.01	2.3	0.072
	adrenate (22:4n6)	3.86	0.015	3.56	0.192
	docosapentaenoate (n6 DPA; 22:5n6)	1		1	
	docosadienoate (22:2n6)	1.18	0.357	1.43	0.725
	dihomo-linoleate (20:2n6)	1.17	0.357	1.37	0.668
	mead acid (20:3n9)	2.34	<0.01	2.4	0.070
	Fatty Acid, Branched	13-methylmyristate	1.09	0.668	1.31
15-methylpalmitate		1.08	0.535	1.11	0.971
17-methylstearate		0.79	0.228	0.89	0.481
Fatty Acid, Dicarboxylate	2-hydroxyglutarate	0.63	<0.01	0.9	0.340
	2-hydroxyadipate	0.75	0.391	0.75	0.39
	azelate (nonanedioate)	4.51	<0.01	1.28	0.856
Fatty Acid, Keto	1-dihomo-linoleoylglycerol (20:2)	0.32	0.022	0.55	0.189
Fatty Acid Metabolism	acetyl CoA	4.9	<0.01	2.43	0.030
	myristoyl CoA	0.46	<0.01	0.46	<0.01
Fatty Acid Metabolism (also BCAA Metabolism)	butyrylcarnitine	0.88	0.135	1.22	0.211
	propionyl CoA	0.1	<0.01	0.28	<0.01
	propionylcarnitine	0.35	<0.01	0.31	<0.01
	methylmalonate (MMA)	0.24	<0.01	0.36	<0.01
Fatty Acid Metabolism (Acyl Glycine)	N-palmitoyl glycine	0.9	0.391	0.9	0.391
Fatty Acid Metabolism (Acyl Carnitine)	acetylcarnitine	2.7	<0.01	1.16	0.237
	3-hydroxybutyrylcarnitine (1)	0.82	0.043	0.83	0.074
	3-hydroxybutyrylcarnitine (2)	0.7	<0.01	1.01	0.942
	hexanoylcarnitine	0.45	<0.01	0.41	<0.01
	octanoylcarnitine	0.73	0.224	0.72	0.214
	laurylcarnitine	0.87	0.354	0.76	0.155
	myristoylcarnitine	0.75	0.063	0.53	<0.01
	palmitoylcarnitine	1.31	0.084	0.87	0.406
	stearoylcarnitine	6.34	<0.01	4	<0.01
	linoleoylcarnitine	1		1	
	oleoylcarnitine	1.52	0.020	0.99	0.897
Carnitine Metabolism	deoxycarnitine	0.5	<0.01	0.56	<0.01
	carnitine	0.94	0.382	0.95	0.476
Ketone Bodies	3-hydroxybutyrate (BHBA)	2.47	<0.01	2.29	<0.01
Fatty Acid, Monohydroxy	4-hydroxybutyrate (GHB)	0.42	<0.01	0.46	<0.01
	2-hydroxypalmitate	1.82	<0.01	2.01	0.321
	2-hydroxystearate	2.38	<0.01	2.31	0.121
	3-hydroxyoctanoate	0.97	0.391	0.97	0.391
	3-hydroxylaurate	0.37	<0.01	0.27	<0.01
Endocannabinoid	oleoyl ethanolamide	1.6	<0.01	1.1	0.605
	palmitoyl ethanolamide	1.19	0.109	1.09	0.320
	N-oleoyltaurine	1		1	

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Supplementary Table S1. *Continued.*

	N-stearoyltaurine	1.43	0.182	1.88	0.381
	N-palmitoyltaurine	1		1	
Inositol Metabolism	myo-inositol	3.69	<0.01	4.22	<0.01
	inositol 1-phosphate (I1P)	1.7	<0.01	1.86	<0.01
Phospholipid Metabolism	choline	1.64	<0.01	1.66	<0.01
	choline phosphate	1.48	<0.01	1.59	<0.01
	cytidine 5'-diphosphocholine	1.15	0.264	0.82	0.118
	glycerophosphorylcholine (GPC)	1.27	<0.01	1.37	0.039
	phosphoethanolamine	2.55	<0.01	2.56	<0.01
	cytidine-5'-diphosphoethanolamine	0.58	<0.01	0.58	<0.01
	glycerophosphoethanolamine	0.66	<0.01	0.83	0.108
	glycerophosphoinositol	1	0.954	1.16	0.363
	1,2-dipalmitoyl-GPC (16:0/16:0)	0.73	<0.01	0.69	<0.01
	1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	1.23	<0.01	1.13	0.139
	1-stearoyl-2-arachidonoyl-GPC (18:0/20:4)	4.42	<0.01	3.79	<0.01
	1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)	1.52	<0.01	1.38	<0.01
	1-stearoyl-2-oleoyl-GPC (18:0/18:1)	1.25	<0.01	1.12	0.179
	1-stearoyl-2-oleoyl-GPI (18:0/18:1)	1.5	<0.01	1.62	<0.01
	1,2-dioleoyl-GPC (18:1/18:1)	1.07	0.188	0.97	0.635
	1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4)	3.04	<0.01	2.49	<0.01
	1-stearoyl-2-linoleoyl-GPC (18:0/18:2)	1.22	0.659	1.24	0.657
	1-palmitoleoyl-2-oleoyl-GPC (16:1/18:1)	1.21	<0.01	1.11	0.270
	1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)	1.15	0.024	1.05	0.536
	1,2-dipalmitoleoyl-GPC (16:1/16:1)	1.32	<0.01	1.09	0.360
	1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	2.43	<0.01	2.42	<0.01
	1-oleoyl-2-linoleoyl-GPC (18:1/18:2)	1.67	<0.01	1.6	<0.01
	1-palmitoyl-2-oleoyl-GPG (16:0/18:1)	0.38	<0.01	0.33	<0.01
	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	1.15	0.036	1.01	0.870
	1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)	2.12	<0.01	1.88	<0.01
	1-stearoyl-2-oleoyl-GPE (18:0/18:1)	1.25	<0.01	1.12	0.167
	1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)	1.82	<0.01	1.45	<0.01
	1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	1.12	0.880	1.41	0.283
	1-stearoyl-2-linoleoyl-GPE (18:0/18:2)	1.66	<0.01	1.43	0.013
	1,2-dioleoyl-GPG (18:1/18:1)	0.61	<0.01	0.68	<0.01
	1,2-dioleoyl-GPI (18:1/18:1)	1.05	0.401	0.96	0.604
	1-palmitoyl-2-stearoyl-GPC (16:0/18:0)	0.53	<0.01	0.5	<0.01
	1,2-dioleoyl-GPE (18:1/18:1)	1.01	0.834	0.87	0.085
	1-palmitoyl-2-oleoyl-GPI (16:0/18:1)	1.72	<0.01	1.58	<0.01
	1,2-dioleoyl-GPS (18:1/18:1)	1.54	<0.01	1.49	<0.01
	1-stearoyl-2-oleoyl-GPG (18:0/18:1)	1.65	<0.01	1.61	<0.01
	1-palmitoyl-2-linolenoyl-GPC (16:0/18:3)	1.34	<0.01	1.14	0.297
	1-palmitoleoyl-2-linoleoyl-GPC (16:1/18:2)	1.88	<0.01	1.55	<0.01
	1,2-dilinoeoyl-GPC (18:2/18:2)	1.99	<0.01	1.73	<0.01
	1-oleoyl-2-linoleoyl-GPE (18:1/18:2)*	1.3	<0.01	1.1	0.282
	1,2-distearoyl-GPC (18:0/18:0)	0.14	<0.01	0.11	<0.01
	1-palmitoyl-2-oleoyl-GPS (16:0/18:1)	1.57	<0.01	1.52	<0.01
	1-stearoyl-2-linoleoyl-GPS (18:0/18:2)	1.59	<0.01	1.33	0.028
Phosphatidylserine (PS)	1-stearoyl-2-arachidonoyl-GPS (18:0/20:4)	1.43	<0.01	1.12	0.263
	1-stearoyl-2-oleoyl-GPS (18:0/18:1)	3.61	<0.01	3.71	<0.01
Lysolipid	1-palmitoyl-GPC (16:0)	0.93	0.200	0.84	0.046
	2-palmitoyl-GPC (16:0)*	1.15	0.421	1.12	0.999
	1-palmitoleoyl-GPC (16:1)	1.13	0.114	0.95	0.533
	2-palmitoleoyl-GPC (16:1)	1.19	0.155	1.54	0.786
	1-stearoyl-GPC (18:0)	1.2	0.062	1.1	0.238

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Supplementary Table S1. *Continued.*

	1-oleoyl-GPC (18:1)	0.99	0.844	0.86	0.092
	1-linoleoyl-GPC (18:2)	1.58	0.0172	1.35	<0.01
	1-arachidonoyl-GPC (20:4n6)	2.26	<0.01	2.58	0.2057
	1-lignoceroyl-GPC (24:0)	0.63	0.014	0.48	<0.01
	1-palmitoyl-GPE (16:0)	1.73	0.748	2.15	0.615
	1-stearoyl-GPE (18:0)	0.98	0.743	0.81	0.025
	2-stearoyl-GPE (18:0)	1.05	0.817	1.12	0.649
	1-oleoyl-GPE (18:1)	1.36	0.782	1.99	0.646
	1-linoleoyl-GPE (18:2)	2.78	0.068	2.55	0.207
	1-arachidonoyl-GPE (20:4n6)	2.59	<0.01	2.87	0.070
	1-palmitoyl-GPI (16:0)	1.07	0.612	1.34	0.988
	1-stearoyl-GPI (18:0)	0.96	0.860	1.49	0.847
	1-oleoyl-GPI (18:1)	0.61	0.017	0.66	0.182
	1-linoleoyl-GPI (18:2)	0.66	0.027	0.87	0.4191
	1-arachidonoyl-GPI (20:4)	1.29	0.154	1.36	0.592
	1-stearoyl-GPS (18:0)	0.63	0.101	1.06	0.533
	1-oleoyl-GPS (18:1)	1.4	0.067	1.6	0.557
	1-palmitoyl-GPG (16:0)	0.62	0.072	0.84	0.436
	1-palmitoyl-GPS (16:0)	0.18	<0.01	0.25	0.04
	1-stearoyl-GPG (18:0)	0.55	0.139	0.6	0.234
	1-oleoyl-GPG (18:1)	1.03	0.712	1.37	0.515
Plasmalogen	1-(1-enyl-palmitoyl)-2-oleoyl-GPE (P-16:0/18:1)	0.93	0.076	0.86	0.064
	1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (P-16:0/18:2)	1.16	0.066	1.1	0.164
	1-(1-enyl-palmitoyl)-2-palmitoyl-GPC (P-16:0/16:0)	0.59	<0.01	0.54	<0.01
	1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)	0.73	<0.01	0.65	0.0129
	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)	1.52	<0.01	1.41	<0.01
	1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)	0.63	<0.01	0.57	<0.01
	1-(1-enyl-stearoyl)-2-oleoyl-GPE (P-18:0/18:1)	0.7	<0.01	0.64	<0.01
	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)	3.85	<0.01	3.75	<0.01
	1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)	1	0.935	1.08	0.542
	1-(1-enyl-stearoyl)-2-arachidonoyl-GPE (P-18:0/20:4)	1.21	<0.01	1.2	0.078
Lysoplasmalogen	1-(1-enyl-palmitoyl)-GPC (P-16:0)*	0.91	0.239	0.82	0.132
	1-(1-enyl-palmitoyl)-GPE (P-16:0)*	0.64	<0.01	0.55	<0.01
	1-(1-enyl-oleoyl)-GPE (P-18:1)*	0.82	0.175	1.55	0.978
	1-(1-enyl-stearoyl)-GPE (P-18:0)*	0.64	0.033	0.91	0.430
Glycerolipid	glycerol	0.8	0.033	0.78	0.070
Metabolism	glycerol 3-phosphate	2.65	<0.01	3.41	<0.01
	glycerophosphoglycerol	0.31	<0.01	0.4	<0.01
Monoacylglycerol	1-myristoylglycerol (14:0)	0.68	0.014	0.73	0.240
	2-myristoylglycerol (14:0)	0.39	<0.01	0.5	0.100
	1-pentadecanoylglycerol (15:0)	1.06	0.804	0.89	0.528
	1-palmitoylglycerol (16:0)	0.77	0.407	0.51	0.117
	2-palmitoylglycerol (16:0)	0.29	<0.01	0.36	0.052
	1-margaroylglycerol (17:0)	0.57	0.205	0.42	0.059
	1-oleoylglycerol (18:1)	0.84	0.554	0.8	0.418
	2-oleoylglycerol (18:1)	0.48	0.018	0.59	0.160
	1-linoleoylglycerol (18:2)	1.16	0.386	1.01	0.794
	2-linoleoylglycerol (18:2)	0.73	0.353	0.77	0.4239
	1-arachidonoylglycerol (20:4)	1.53	0.062	1.38	0.770
	2-arachidonoylglycerol (20:4)	0.99	0.945	0.95	0.572
	1-docosahexaenoylglycerol (22:6)	1.47	0.078	1.56	0.593
	2-docosahexaenoylglycerol (22:6)	0.87	0.971	1.15	0.805
	1-palmitoleoylglycerol (16:1)	0.72	0.122	0.68	0.223
	2-palmitoleoylglycerol (16:1)	0.45	<0.01	0.57	0.133

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Supplementary Table S1. *Continued.*

Diacylglycerol	1-oleoyl-3-linoleoyl-glycerol (18:1/18:2)	1.09	0.815	0.71	0.047	
	1-palmitoleoyl-3-oleoyl-glycerol (16:1/18:1)	0.78	<0.01	0.62	<0.01	
	1-palmitoyl-3-linoleoyl-glycerol (16:0/18:2)	1.09	0.276	0.88	0.159	
Sphingolipid Metabolism	N-palmitoyl-sphinganine (d18:0/16:0)	0.92	0.258	0.53	0.015	
	sphinganine	0.5	<0.01	0.41	<0.01	
	phytosphingosine	0.8	0.055	0.81	0.081	
	palmitoyl sphingomyelin (d18:1/16:0)	1.69	<0.01	1.48	<0.01	
	stearoyl sphingomyelin (d18:1/18:0)	1.55	<0.01	1.39	0.022	
	sphingomyelin (d18:1/18:1, d18:2/18:0)	1.43	<0.01	1.57	0.019	
	sphingosine	1.13	0.053	0.99	0.820	
	N-palmitoyl-sphingosine (d18:1/16:0)	2.38	<0.01	2.15	<0.01	
	sphingomyelin (d18:1/14:0, d16:1/16:0)	1.55	<0.01	1.31	0.025	
	sphingomyelin (d18:2/14:0, d18:1/14:1)	1.41	<0.01	1.09	0.333	
	sphingomyelin (d18:1/24:1, d18:2/24:0)	1.48	<0.01	1.32	0.034	
	sphingomyelin (d18:2/16:0, d18:1/16:1)	1.22	0.016	1.02	0.898	
	sphingomyelin (d18:1/20:1, d18:2/20:0)	1.17	0.156	1.15	0.243	
	behenoyl sphingomyelin (d18:1/22:0)	1.17	0.036	1.04	0.529	
	sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)	1.22	0.014	1.09	0.466	
	sphingomyelin (d18:1/20:0, d16:1/22:0)	1.27	0.015	1.06	0.535	
	palmitoyl dihydrosphingomyelin (d18:0/16:0)	0.64	<0.01	0.51	<0.01	
	sphingomyelin (d18:1/15:0, d16:1/17:0)	1.12	0.192	0.95	0.427	
	sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)	0.84	0.073	0.73	0.136	
	sphingomyelin (d18:2/23:0, d18:1/23:1, d17:1/24:1)	1.39	<0.01	1.25	0.079	
	sphingomyelin (d18:2/24:1, d18:1/24:2)	1.53	<0.01	1.25	<0.01	
tricosanoyl sphingomyelin (d18:1/23:0)	0.99	0.843	0.92	0.347		
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)	1.83	<0.01	1.59	<0.01		
glycosyl-N-stearoyl-sphingosine	3.53	<0.01	1.92	0.128		
glycosyl-N-palmitoyl-sphingosine	1.58	<0.01	1.44	<0.01		
lactosyl-N-palmitoyl-sphingosine	2.33	<0.01	2.09	<0.01		
Mevalonate Metabolism	3-hydroxy-3-methylglutarate	1.62	<0.01	1.55	<0.01	
Sterol	cholesterol	1.06	0.554	0.97	0.678	
	7-hydroxycholesterol (alpha or beta)	1.24	0.324	1.03	0.835	
Primary Bile Acid Metabolism	cholate	2.29	<0.01	1.9	<0.01	
	glycocholate	1.77	<0.01	1.58	0.031	
	taurocholate	1.66	<0.01	1.41	0.069	
	glycochenodeoxycholate	2	<0.01	2.05	<0.01	
	taurochenodeoxycholate	1.97	<0.01	1.63	0.070	
Secondary Bile Acid Metabolism	deoxycholate	1.58	0.014	1.69	<0.01	
	glycodeoxycholate	1.53	0.011	1.43	0.176	
	taurodeoxycholate	1.55	0.031	1.47	0.139	
Nucleotide	Purine Metabolism, (Hypo)Xanthine/ Inosine containing	AICA ribonucleotide	2.25	<0.01	0.35	<0.01
		inosine 5'-monophosphate (IMP)	1	0.852	0.68	0.160
		inosine	0.76	0.010	0.81	0.012
		hypoxanthine	0.78	<0.01	0.7	0.011
		xanthine	2.56	<0.01	1.97	<0.01
		xanthosine 5'-monophosphate (xmp)	1.45	0.058	0.7	0.159
		xanthosine	0.49	0.020	0.2	0.021
		2'-deoxyinosine	0.34	<0.01	0.28	<0.01
		urate	1.9	<0.01	2.76	<0.01
		allantoin	0.96	0.670	1.1	0.536
Purine Metabolism, Adenine containing	adenosine 5'-diphosphate (ADP)	1.08	0.632	1.49	0.039	
	adenosine 5'-monophosphate (AMP)	0.66	<0.01	0.7	<0.01	
	adenosine 3'-monophosphate (3'-AMP)	0.54	0.071	0.59	0.078	

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Supplementary Table S1. *Continued.*

		adenosine 2'-monophosphate (2'-AMP)	0.12	<0.01	0.11	<0.01
		adenosine 3',5'-cyclic monophosphate (cAMP)	0.47	<0.01	0.67	0.0367
		adenosine 3',5'-diphosphate	0.25	<0.01	0.2	<0.01
		adenylosuccinate	0.03	<0.01	0.07	<0.01
		adenosine	3.44	<0.01	2.04	<0.01
		adenine	2.44	<0.01	2.18	<0.01
		N1-methyladenosine	0.97	0.720	0.71	0.225
		N6-methyladenosine	19.72	<0.01	42.94	<0.01
		N6-carbamoylthreonyladenosine	1.52	<0.01	1.25	0.103
		2'-deoxyadenosine 5'-monophosphate	1.1	0.301	0.91	0.255
		2'-deoxyadenosine	0.67	0.278	0.63	0.222
		diadenosine triphosphate	1		1	
		N6-succinyladenosine	0.12	<0.01	0.15	<0.01
Purine Metabolism,		guanosine 5'-triphosphate	14.6	<0.01	8.5	<0.01
Guanine containing		guanosine 5'- diphosphate (GDP)	10.89	<0.01	6.85	<0.01
		guanosine 5'- monophosphate (5'-GMP)	1.4	<0.01	1.17	0.121
		guanosine	2.12	0.014	1.48	<0.01
		guanine	5.82	<0.01	2.43	<0.01
		7-methylguanine	0.99	0.898	0.93	0.384
		N2,N2-dimethylguanosine	1.02	0.832	0.71	0.043
		2'-deoxyguanosine 5'-monophosphate (dGMP)	1.18	0.358	0.69	0.026
		2'-deoxyguanosine	0.39	<0.01	0.29	<0.01
Pyrimidine Metabolism,		orotate	0.74	0.146	1.29	0.567
Orotate containing		orotidine	0.37	<0.01	0.23	<0.01
Pyrimidine Metabolism,		uridine 5'-triphosphate (UTP)	4.73	<0.01	2.76	<0.01
Uracil containing		uridine 5'-diphosphate (UDP)	3.3	<0.01	1.88	<0.01
		uridine 5'-monophosphate (UMP)	0.52	<0.01	0.34	<0.01
		uridine 3'-monophosphate (3'-UMP)	0.72	<0.01	0.54	0.163
		uridine-2',3'-cyclic monophosphate	1.04	0.391	1	
		uridine	1.09	0.291	0.53	<0.01
		uracil	0.72	<0.01	0.59	<0.01
		pseudouridine	0.72	<0.01	0.57	0.023
		5-methyluridine (ribothymidine)	0.61	<0.01	0.85	0.182
		2'-deoxyuridine	0.32	<0.01	0.32	<0.01
		beta-alanine	1	0.985	1.3	0.031
Pyrimidine Metabolism,		cytidine triphosphate	4.3	<0.01	1.88	0.135
Cytidine containing		cytidine diphosphate	5.09	<0.01	3.12	<0.01
		cytidine 5'-monophosphate (5'-CMP)	0.71	<0.01	0.52	<0.01
		cytidine 2',3'-cyclic monophosphate	1		1	
		cytidine	0.7	0.062	0.33	<0.01
		3-methylcytidine	0.77	0.016	0.61	<0.01
		5-methylcytidine	1		1	
		2'-deoxycytidine 5'-monophosphate	0.46	<0.01	0.5	<0.01
		2'-deoxycytidine	0.55	0.025	0.55	0.025
Pyrimidine Metabolism,		thymidine 5'-monophosphate	0.39	<0.01	0.49	<0.01
Thymine containing		thymidine	0.61	0.090	0.44	<0.01
		thymine	0.52	<0.01	0.95	0.563
		3-aminoisobutyrate	1.09	0.879	0.82	0.442
Purine and Pyrimidine		methylphosphate	0.61	0.032	0.39	<0.01
Metabolism						
Cofactors and	Nicotinate and	nicotinate ribonucleoside	2.77	<0.01	2.3	<0.01
Vitamins	Nicotinamide	nicotinamide	0.97	0.531	0.85	0.028
	Metabolism	nicotinamide ribonucleotide (NMN)	3.56	<0.01	2.59	<0.01

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Supplementary Table S1. *Continued.*

	nicotinamide riboside	7.87	<0.01	7.89	<0.01
	nicotinamide adenine dinucleotide (NAD ⁺)	3.29	<0.01	4.06	<0.01
	nicotinamide adenine dinucleotide reduced (NADH)	1.47	0.384	2.61	<0.01
	nicotinate adenine dinucleotide (NAAD ⁺)	1.18	0.448	0.73	<0.01
	1-methylnicotinamide	1		1	
	trigonelline (N ¹ -methylnicotinate)	0.52	<0.01	0.92	0.613
	adenosine 5'-diphosphoribose (ADP-ribose)	2.97	<0.01	4.5	<0.01
Riboflavin Metabolism	riboflavin (Vitamin B2)	1.45	0.036	1.06	0.582
	flavin adenine dinucleotide (FAD)	0.91	0.217	0.74	0.033
	flavin mononucleotide (FMN)	1.46	<0.01	0.88	0.403
Pantothenate and CoA Metabolism	pantothenate	1.41	<0.01	1.69	<0.01
	phosphopantetheine	2.81	<0.01	2.27	<0.01
	3'-dephosphocoenzyme A	0.55	<0.01	0.65	0.063
	coenzyme A	1.24	0.051	1.24	0.078
Ascorbate and Aldarate Metabolism	threonate	0.79	0.803	1.13	0.486
	gulonic acid	3.4	<0.01	4.25	<0.01
Tocopherol Metabolism	alpha-tocopherol	2.3	<0.01	2.29	<0.01
Biotin Metabolism	biotin	3.67	<0.01	4.69	<0.01
Folate Metabolism	5-methyltetrahydrofolate (5MeTHF)	0.04	<0.01	0.14	<0.01
Tetrahydrobiopterin Metabolism	biopterin	0.74	0.081	0.56	<0.01
	dihydrobiopterin	1.39	0.012	1.26	0.072
Pterin Metabolism	pterin	0.9	0.588	0.74	0.165
Hemoglobin and Porphyrin Metabolism	bilirubin	1		1	
Thiamine Metabolism	thiamin (Vitamin B1)	0.7	<0.01	0.64	0.014
	thiamin monophosphate	0.88	0.166	0.78	0.181
	thiamin diphosphate	1.03	0.867	1.15	0.240
Vitamin A Metabolism	retinol (Vitamin A)	1.13	0.056	0.97	0.672
Vitamin B6 Metabolism	pyridoxine (Vitamin B6)	1.53	0.089	1.56	0.107
	pyridoxamine	0.25	<0.01	0.23	<0.01
	pyridoxamine phosphate	0.03	<0.01	0.04	<0.01
	pyridoxal phosphate	0.7	0.079	0.7	0.079
	pyridoxal	0.32	<0.01	0.21	<0.01
	pyridoxate	0.75	0.391	2.93	0.436
Xenobiotics	hippurate	1.79	<0.01	2.01	<0.01
	O-methylcatechol sulfate	0.76	0.236	0.62	0.100
Food Component/Plant	gluconate	4.34	<0.01	5.73	<0.01
	ergothioneine	1.45	0.112	1.29	0.182
	erythritol	1.17	0.066	1.53	0.031
	N-glycolylneuraminatate	0.85	0.378	1.01	0.782
	stachydrine	0.81	0.040	0.83	0.048
Drug	penicillin G	1		1	
	O-sulfo-L-tyrosine	0.82	0.066	0.89	0.234
Chemical	lanthionine	0.31	<0.01	0.27	<0.01
	phenol red	1.66	<0.01	1.62	<0.01