

Table S1: Annotation and identification of relevant metabolites selected according to the SUS-plot, modulated by the pharmaceutical mixture exposure in male mussels either at the low concentration (SCvsLD), high concentration (SCvsHD), or both.

Metabolic pathway / Class compound	Annotation	HMDB/KEGG IDs	Molecular ion species detected	Retention Time (min)	Calculated mass	Observed mass	Mass difference (ppm)	RSD QC % ^b	SC vs LD			SC vs HD			Annotation level ^a
									Modulation amplitude %	p-value	adjusted p-value ^c	Modulation amplitude %	p-value	adjusted p-value ^c	
Purine metabolism	Adenine	HMDB0000034/C00147	[M+H] ⁺	2,93	136,06177	136,06123	-4	9	+37	5,02E-02	6,96E-02	+26	1,35E-01	1,87E-01	1
Purine metabolism	Adenosine	HMDB0000050/C00212	[M+H] ⁺	3,22	268,10403	268,10288	-4	9	+80	2,40E-02	5,06E-02	+102	7,27E-02	1,17E-01	1
			[M+FA-H] ⁻	3,22	312,09495	312,09565	2	6	+86	1,15E-02	3,69E-02	+104	4,68E-02	8,65E-02	1
Purine metabolism	Guanosine	HMDB0000133/C00387	[M+H] ⁺	2,12	284,09894	284,09774	-4	11	+3	8,68E-01	8,68E-01	+61	3,54E-02	7,19E-02	1
Purine metabolism	Hypoxanthine	HMDB0000157/C00262	[M+H] ⁺	1,95	137,04579	137,04525	-4	9	+7	7,14E-01	7,39E-01	+130	1,51E-04	2,31E-03	1
Purine metabolism	Inosine	HMDB0000195/C00294	[M+H] ⁺	1,95	269,08805	269,08698	-4	12	+13	4,20E-01	4,50E-01	+181	5,52E-05	1,12E-03	1
Purine metabolism	Xanthosine 5'-triphosphate	HMDB0000293/C00700	[M-H ₂ O-H] ⁻	2,07	504,95629	504,95509	-2	21	+134	3,48E-02	5,59E-02	+28	4,81E-01	5,24E-01	2
Purine metabolism	Adenosine monophosphate	HMDB0000045/C00020	[M-H] ⁻	1,32	346,05581	346,05640	2	18	+69	4,22E-02	6,43E-02	+66	9,00E-02	1,37E-01	1
Pyrimidine metabolism	Uridine	HMDB0000296/C00299	[M+H] ⁺	1,92	245,07681	245,07595	-4	13	+53	7,15E-02	9,09E-02	+452	6,67E-06	2,04E-04	1
Pyrimidine metabolism	4,5-Dihydroorotic acid or L-Dihydroorotic acid	HMDB0000528 or HMDB0003349/C00337	[M-H] ⁻	6,70	157,02548	157,02575	2	24	+103	4,05E-04	1,23E-02	+91	3,26E-02	7,66E-02	2
Oxidized nucleosides	4,6-Diamino-5-(formylamino)pyrimidine	HMDB0004816/C06502	[M+H] ⁺	2,22	154,07234	154,07302	4	7	+33	1,51E-02	4,40E-02	+65	1,50E-03	9,14E-03	2
Dipeptides; Protein catabolism	Cysteinyl-Gamma-glutamate or Cysteinyl-Glutamine	HMDB0002879 or HMDB00028773	[M-H ₂ O-H] ⁻	2,62	230,05994	230,06080	4	14	-27	6,84E-03	3,48E-02	-7	5,39E-01	5,77E-01	2
				2,95		230,06081	4	15	-32	4,26E-03	4,33E-02	-14	2,52E-01	3,14E-01	2
Glycine, serine and threonine metabolism	L-threonine or L-allothreonine	HMDB0000167/C00188 or HMDB0004041/C05519	[M-H] ⁻	1,43	118,05097	118,05124	2	3	-16	1,01E-01	1,26E-01	-20	1,01E-01	1,50E-01	1
Lysine metabolism	L-lysine	HMDB0000182/C00047	[M-H] ⁻	2,44	145,09825	145,09845	1	17	-27	1,09E-01	1,33E-01	-42	1,09E-01	1,58E-01	1
Glutathione metabolism	Oxidized glutathione	HMDB0003337/C00127	[M+2H] ²⁺	2,23	307,08326	307,08193	-4	12	+17	1,85E-01	2,13E-01	+62	5,33E-03	2,03E-02	1
			[M-H] ⁻	2,23	611,14469	611,14596	2	9	+13	3,67E-01	4,00E-01	+59	5,62E-03	2,02E-02	1
Glutathione metabolism; Cysteine and methionine metabolism	Reduced glutathione	HMDB0000125/C00051	[M-H] ⁻	2,33	306,07653	306,07711	2	12	+36	5,86E-02	7,94E-02	+58	2,57E-02	6,53E-02	2
Cysteine and methionine metabolism	S-Adenosylhomocysteine	HMDB0000939/C00021	[M-H] ⁻	3,65	383,11431	383,11496	2	17	+21	2,85E-01	3,22E-01	+45	1,03E-02	3,15E-02	2
Cysteine and methionine metabolism	Methionine sulfoxide	HMDB0002005/C02989	[M-H] ⁻	1,40	164,03869	164,03878	1	14	-44	1,08E-02	3,89E-02	-31	7,01E-02	1,16E-01	2
Methionine derivatives	N-Propionylmethionine	HMDB0094704	[M-H] ⁻	9,08	204,06999	204,07025	1	22	+82	6,43E-02	8,53E-02	+23	4,19E-01	4,82E-01	2
Cysteine and methionine metabolism; Taurine and hypotaurine metabolism	Cysteic acid	HMDB0002757/C00506	[M-H] ⁻	1,12	167,99722	167,99751	2	5	-39	2,25E-02	5,27E-02	-13	4,22E-01	4,77E-01	2
			[M+H] ⁺	1,08	170,01177	170,01109	-4	6	-41	3,68E-02	5,75E-02	-15	4,44E-01	4,93E-01	2
Valine, leucine and isoleucine degradation	L-isoleucine or L-leucine	HMDB0000172/C00407 or HMDB0000687/C00123	[M-H ₂ O+H] ⁺	4,88	114,09190	114,09083	-9	12	+12	1,10E-01	1,31E-01	+24	2,89E-04	3,53E-03	1
Tyrosine metabolism	Dopamine	HMDB0000073/C03758	[M-H] ⁻	5,52	152,07170	152,07198	2	27	+50	6,72E-03	3,73E-02	-2	8,97E-01	9,12E-01	2
			[M+H] ⁺	5,53	154,08625	154,08553	-5	7	+40	4,11E-03	5,01E-02	-5	6,85E-01	7,08E-01	2
Tryptophan metabolism	5-Hydroxytrypturenamine	HMDB0004076/C05638	[M-H] ⁻	9,00	179,08260	179,08286	1	11	+18	1,37E-01	1,61E-01	+36	8,04E-03	2,58E-02	2
Nicotinate and nicotinamide metabolism	Nicotinic acid	HMDB0001488/C00253	[M-H] ⁻	2,00	122,02475	122,02500	2	8	+28	2,31E-03	4,69E-02	+47	7,27E-04	5,54E-03	1
			[M+H] ⁺	2,00	124,03930	124,03882	-4	5	+29	1,11E-02	3,75E-02	+61	2,80E-03	1,32E-02	1
Nicotinate and nicotinamide metabolism	Niacinamide	HMDB0001406/C00153	[M+H] ⁺	2,57	123,05529	123,05474	-4	11	+66	2,23E-02	5,43E-02	+63	4,76E-02	8,53E-02	1
Pantothenate and CoA biosynthesis	Pantothenol	HMDB0304820/C05944	[M+H] ⁺	2,75	206,13868	206,13790	-4	10	+33	3,48E-02	5,74E-02	+52	3,72E-02	7,31E-02	2
Vitamin C metabolism	Ascorbic acid 2-sulfate	HMDB00060649	[M-H ₂ O-H] ⁻	2,13	236,97051	236,96898	-6	9	+199	2,38E-02	5,18E-02	+82	1,90E-01	2,52E-01	2
Citrate cycle (TCA cycle); Lysine degradation; Tyrosine metabolism; Pyruvate metabolism; Glyoxylate and dicarboxylate metabolism; Nicotinate and nicotinamide metabolism	Succinic acid	HMDB0000254/C00042	[M-H] ⁻	2,08	117,01933	117,01956	2	8	+208	2,09E-02	5,32E-02	+102	1,13E-01	1,61E-01	1
Glyoxylate and dicarboxylate metabolism	Phosphoglycolic acid	HMDB0000816/C00988	[M+Na] ⁺	2,08	178,97159	178,97094	-4	7	+160	1,29E-02	3,93E-02	+38	3,35E-01	4,01E-01	2
			[M+K] ⁺	2,08	194,94553	194,94492	-3	10	+176	8,57E-03	3,74E-02	+38	3,28E-01	4,00E-01	2
Galactose metabolism	Lactose 6-phosphate	HMDB0006789 /C05396	[M-H] ⁻	2,97	421,07527	421,07422	-2	18	+84	6,69E-03	4,08E-02	+53	3,30E-02	7,46E-02	2
Galactose metabolism; Inositol metabolism; Inositol phosphate metabolism	myo-inositol	HMDB0000211/C00137	[M-H] ⁻	1,33	179,05611	179,05643	2	8	+37	3,11E-02	5,93E-02	+14	3,87E-01	4,54E-01	2
Pyruvate metabolism	S-Lactoylglutathione	HMDB0001066/C03451	[M-H] ⁻	2,56	378,09766	378,09832	2	10	+125	3,40E-02	6,09E-02	+268	3,40E-02	7,40E-02	2
Pentose phosphate pathway	Deoxyribose	HMDB0003224/C01801	[M-H ₂ O+H] ⁺	1,97	117,05520	117,05412	-9	17	+24	6,59E-02	8,55E-02	+54	3,88E-04	3,95E-03	2
Pentose and glucuronate interconversions; Ascorbate and aldarate metabolism	D-Glucuronic acid 1-phosphate	HMDB0003976/C05385	[M-H] ⁻	2,08	273,00171	273,00229	2	7	+390	1,68E-02	4,65E-02	+136	1,99E-01	2,58E-01	2
Glycolysis; Glycerolipid metabolism; Glycerophospholipid metabolism	Glycerol 3-phosphate	HMDB0000126/C00093	[M+H] ⁺	1,95	173,02095	173,02054	-2	24	+4	7,60E-01	7,73E-01	-44	1,12E-03	7,60E-03	2
Glycerophosphoinositols	Glycerophosphoinositol	HMDB0011649/C01225	[M-H] ⁻	0,98	333,05922	333,06001	2	7	+44	4,57E-02	6,79E-02	+59	2,43E-02	6,44E-02	2
Glycerophospholipid metabolism; Sphingolipid metabolism	O-Phosphoethanolamine	HMDB0000224/C00346	[M+Na] ⁺	2,03	164,00831	164,00763	-4	13	+194	2,27E-02	5,12E-02	0	9,95E-01	9,95E-01	2
Lysophospholipids	LysoPC(18:4(6Z,9Z,12Z,15Z))	HMDB0010389	[M+H] ⁺	14,62	516,30847	516,30558	-6	30	+131	3,86E-06	2,35E-04	+115	2,84E-03	1,24E-02	2
Phosphatidylcholines	ADP-ribose 1"-2" cyclic phosphate	HMDB0011671	[M-2H] ²⁻	0,88	309,50644	309,50702	2	6	+28	3,36E-02	6,22E-02	+64	2,00E-03	1,01E-02	2

Methyl-branched fatty acids	2-Methylglutaric acid	HMDB0000422	[M-H]-	5,33	145,05063	145,05092	2	16	+27	9,58E-03	3,65E-02	+28	1,67E-02	4,85E-02	1
Oxidation of branched chain fatty acids; Beta oxidation of very long chain fatty acids	L-Acetylcarnitine	HMDB0000201/CO2571	[M]+	6,32	204,12358	204,12219	-7	8	+73	3,41E-02	5,94E-02	+66	2,31E-02	6,40E-02	1
Acylcarnitines	Glutaryl carnitine	HMDB0013130	[M]+	11,74	276,14416	276,14288	-5	13	+177	4,89E-02	7,11E-02	+84	2,07E-01	2,63E-01	2
Acylcarnitines	Hydroxypropionyl carnitine	HMDB0013125	[M+FA-H]-	2,17	278,12452	278,12494	2	10	+106	2,91E-02	5,92E-02	+103	6,48E-02	1,10E-01	2
Acylcarnitines	Succinyl carnitine	HMDB0061717	[M+H]+	7,00	262,12851	262,12741	-4	6	+17	4,72E-01	4,96E-01	+48	3,98E-02	7,59E-02	1
Acylglycines	Capryloylglycine	HMDB0000832	[M-H]-	12,97	200,12922	200,12960	2	12	+32	1,92E-02	5,10E-02	+69	7,16E-03	2,43E-02	2
Acylglycines	N-Lauroylglycine	HMDB0013272	[M+H]+	15,45	258,20637	258,20493	-6	18	+61	8,91E-03	3,62E-02	+108	1,63E-03	9,06E-03	2
Acylglycines	Suberylglycine	HMDB0000953	[M-H]-	10,02	230,10340	230,10374	1	14	+260	2,94E-02	5,79E-02	+101	3,53E-02	7,43E-02	2
			[M+H]+	10,02	232,11795	232,11697	-4	8	+231	3,45E-02	5,85E-02	+95	5,79E-02	1,01E-01	2
Cholesterol biosynthesis; Fatty acid metabolism	(R)-Mevalonic acid-5-pyrophosphate	HMDB0001981	[M+K]+	2,07	346,96938	346,96865	-2	8	+165	5,01E-02	7,11E-02	+28	5,99E-01	6,30E-01	2
Prostaglandin metabolism or Thromboxane metabolism	2,3-dinor, 6-keto-PGF1alpha or 2,3-Dinor-TXB2	HMDB0062618 or HMDB0002904	[M+H]+	14,38	343,21151	343,20732	-12	14	-5	3,57E-01	3,96E-01	-36	1,94E-06	1,18E-04	2
Steroid hormone biosynthesis	4-Methylpentanal	HMDB0001318/CO2373	[M+ACN+H]+	10,52	142,12264	142,12202	-4	9	+39	7,90E-03	3,71E-02	+62	4,62E-04	4,03E-03	2
3-alkylindoles	5-Methoxytryptophol	HMDB0001896	[M+H]+	6,98	192,10190	192,10112	-4	12	+56	5,68E-03	3,85E-02	+86	3,49E-03	1,42E-02	2
Sulfuric acid monoesters	2-Ethylhexyl sulphate	HMDB0033373	[M-H]-	12,12	209,08530	209,08568	2	6	+446	3,12E-03	4,76E-02	+111	7,36E-02	1,15E-01	2
				12,82	209,08530	209,08576	2	10	+50	4,90E-03	3,74E-02	+20	1,83E-01	2,49E-01	2
o-glycosyl compounds	N2-Galacturonyl-L-lysine	HMDB0033105	[M+2ACN+H]+	10,15	405,19799	405,19627	-4	27	+75	4,40E-03	3,83E-02	+55	3,14E-02	7,66E-02	2

Annotation level 1: metabolite identity confirmed by injection of the corresponding analytical standard in the same analytical conditions.

Annotation level 2: putative annotation, based on physicochemical properties and/or spectral similarity with public spectral libraries.

Annotation level 3: putatively characterized compound classes based on characteristic physicochemical properties of a chemical class of compounds.

Colours allow the classification of compound classes and metabolic pathways within principal metabolism (orange: amino acid metabolism; red: nucleic acid metabolism; purple: metabolism of cofactors and vitamins; green: lipid metabolism; blue: carbohydrate metabolism; black: biosynthesis of other secondary metabolites)

^a Based on the recommendation of the Compound Identification work group of the Metabolomics Society (Blaženović et al., 2018).

^b RSD: Relative Standard Deviation calculated for each feature detected in Quality Control (QC) sample injected throughout the analytical sequence (analytical variability).

^c adjusted p-value provided after Benjamini-Hochberg FDR correction