**Supplementary Table 5. Differential metabolites of** [**mild**](javascript:;)[**cognitive**](javascript:;)[**impairment**](javascript:;) **and their reported frequencies in previous studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number** | **Metabolites’ Name** | **HMDB ID** | **Frequencya** | **Number** | **Metabolites’ Name** | **HMDB ID** | **Frequencya** | |
| 1 | L-Tryptophan | HMDB0000929 | 3[27,29,30] | 148 | 10-hydroxy-8E-Decene-2,4,6-triynoic acid | / | 1[29] |
| 2 | 5'-Methylthioadenosine | HMDB0001173 | 2[33,51] | 149 | 1a,1b-dihomo-PGJ2 | / | 1[29] |
| 3 | L-Valine | HMDB0000883 | 2[29,59] | 150 | VALERYL SALYCILATE | / | 1[29] |
| 4 | 5-Hydroxyindoleacetic acid | HMDB0000763 | 2[29,30] | 151 | VD 2656 | / | 1[29] |
| 5 | L-Methionine | HMDB0000696 | 2[29,30] | 152 | Visnagin | / | 1[29] |
| 6 | L-Arginine | HMDB0000517 | 2[29,51] | 153 | 1-Aminocyclohexanecarboxylic acid | / | 1[29] |
| 7 | 5-Hydroxy-L-tryptophan | HMDB0000472 | 2[29,30] | 154 | Tyr Pro | / | 1[29] |
| 8 | L-Phenylalanine | HMDB0000159 | 2[27,29] | 155 | 1-eicosanoyl-rac-glycerol | / | 1[29] |
| 9 | epsilon-Caprolactam | METPA0843 | 1[29] | 156 | 1-Hydroxyvitamin D3 3-D-glucopyranoside | / | 1[29] |
| 10 | Benzene-1,2,4-triol | METPA0328 | 1[29] | 157 | 1-Phenyl-2-(diethylamino)-1-propanol | / | 1[29] |
| 11 | (R)-Citronellal | HMDB0035820 | 1[29] | 158 | 2,5-Dimethoxycinnamic acid | / | 1[29] |
| 12 | Isoquinoline | HMDB0034244 | 1[29] | 159 | 20-oxo-heneicosanoic acid | / | 1[29] |
| 13 | 2-Amino-4-hydroxy-6-pteridinecarboxylic acid | HMDB0033136 | 1[29] | 160 | 2-Amino-3-methyl-1-butanol | / | 1[29] |
| 14 | Citropten | HMDB0032952 | 1[29] | 161 | Thr Ser Gln | / | 1[29] |
| 15 | Succinic anhydride | HMDB0032523 | 1[29] | 162 | 2-Hydroxy-3-(4-methoxyethylphenoxy)-propanoic acid | / | 1[29] |
| 16 | Acetamide | HMDB0031645 | 1[29] | 163 | 3-(a-Naphthoxy)lactic acid | / | 1[29] |
| 17 | 4-Hydroxybenzeneacetonitrile | HMDB0029757 | 1[29] | 164 | 3,6-octadecadiynoic acid | / | 1[29] |
| 18 | Glutamylglutamine | HMDB0028817 | 1[26] | 165 | TEGASEROD | / | 1[29] |
| 19 | Dimercaprol | HMDB0015677 | 1[29] | 166 | 3beta,4beta-Dihydroxy-5beta-cholan-24-oic Acid | / | 1[29] |
| 20 | Acenocoumarol | HMDB0015487 | 1[29] | 167 | 3-dodecynoic acid | / | 1[29] |
| 21 | Bepridil | HMDB0015374 | 1[29] | 168 | 4-dodecynoic acid | / | 1[29] |
| 22 | Penicillin G | HMDB0015186 | 1[29] | 169 | 4-hydroxy enanthoic acid | / | 1[29] |
| 23 | Netilmicin | HMDB0015090 | 1[29] | 170 | 4'-Hydroxyminoxidil | / | 1[29] |
| 24 | Aciclovir | HMDB0014925 | 1[29] | 171 | 4-undecynoic acid | / | 1[29] |
| 25 | Nalidixic Acid | HMDB0014917 | 1[29] | 172 | Trp Ala Ile | / | 1[29] |
| 26 | Azatadine | HMDB0014857 | 1[29] | 173 | 5,7-nonadienoic acid | / | 1[29] |
| 27 | Pirenzepine | HMDB0014808 | 1[29] | 174 | 5beta-Androstan-3alpha-ol-17-one sulfate | / | 1[29] |
| 28 | Ethosuximide | HMDB0014731 | 1[29] | 175 | TUBAIC ACID | / | 1[29] |
| 29 | Ethopropazine | HMDB0014536 | 1[29] | 176 | 5-NITRO-2-PHENYLPROPYLAMINOBENZOIC ACID [NPPB] | / | 1[29] |
| 30 | Tranexamic Acid | HMDB0014447 | 1[29] | 177 | 5-octadecylenic acid | / | 1[29] |
| 31 | Lidocaine | HMDB0014426 | 1[29] | 178 | 5-oxo-7-decynoic acid | / | 1[29] |
| 32 | Pyrimethamine | HMDB0014350 | 1[29] | 179 | 6-hydroxy-2-hexynoic acid | / | 1[29] |
| 33 | Lorazepam | HMDB0014332 | 1[29] | 180 | 7,12-Dioxo-5beta-cholan-24-oic Acid | / | 1[29] |
| 34 | N-Nonanoylglycine | HMDB0013279 | 1[33] | 181 | 7,8-Didehydroastaxanthin | / | 1[29] |
| 35 | 3-Dehydroquinate | HMDB0012710 | 1[29] | 182 | 8R-hydroxy-9Z-octadecenoic acid | / | 1[29] |
| 36 | SM(d18:1/14:0) | HMDB0012097 | 1[14] | 183 | 9,12-dioxo-dodecanoic acid | / | 1[29] |
| 37 | MG(18:0/0:0/0:0) | HMDB0011131 | 1[29] | 184 | 9-lauroleic acid | / | 1[29] |
| 38 | SM(d18:1/16:0) | HMDB0010169 | 1[14] | 185 | 9-pentadecen-1-ol | / | 1[29] |
| 39 | PE(16:0/18:0) | HMDB0008925 | 1[14] | 186 | Adriamycinone | / | 1[29] |
| 40 | PC(22:5(4Z,7Z,10Z,13Z,16Z)/14:1(9Z)) | HMDB0008657 | 1[20] | 187 | Ala Ala Asp | / | 1[29] |
| 41 | PC(20:0/18:3(6Z,9Z,12Z)) | HMDB0008271 | 1[20] | 188 | Ala Leu | / | 1[29] |
| 42 | PC(18:1(9Z)/22:5(4Z,7Z,10Z,13Z,16Z)) | HMDB0008121 | 1[20] | 189 | Ala Met Lys | / | 1[29] |
| 43 | PC(16:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z)) | HMDB0008023 | 1[14] | 190 | Ala Thr Pro | / | 1[29] |
| 44 | PC(16:0/20:3(5Z,8Z,11Z)) | HMDB0007980 | 1[14] | 191 | AMBELLINE | / | 1[29] |
| 45 | PC(16:0/18:2(9Z,12Z)) | HMDB0007973 | 1[14] | 192 | Anandamide (20:2, n-6) | / | 1[29] |
| 46 | PC(14:0/20:4(8Z,11Z,14Z,17Z)) | HMDB0007884 | 1[20] | 193 | Asn Gln Gln | / | 1[29] |
| 47 | Docosapentaenoic acid | HMDB0006528 | 1[29] | 194 | Asp Asn Glu | / | 1[29] |
| 48 | Loratadine | HMDB0005000 | 1[29] | 195 | BERGENIN | / | 1[29] |
| 49 | Guaifenesin | HMDB0004998 | 1[29] | 196 | bicyclo-PGE2 | / | 1[29] |
| 50 | Ceramide (d18:1/16:0) | HMDB0004949 | 1[14] | 197 | Bifemelane (M4) | / | 1[26] |
| 51 | 13,14-Dihydro-15-keto PGF2a | HMDB0004685 | 1[29] | 198 | C10:0-carnitine | / | 1[26] |
| 52 | Phytosphingosine | HMDB0004610 | 1[27] | 199 | C8-carnitine | / | 1[6] |
| 53 | Imidazolone | HMDB0004363 | 1[29] | 200 | cholesteryl ester 32:0 | / | 1[6] |
| 54 | Tryptophanol | HMDB0003447 | 1[29] | 201 | cholesteryl ester 32:4 | / | 1[6] |
| 55 | Diacetyl | HMDB0003407 | 1[29] | 202 | cholesteryl ester 33:6 | / | 1[6] |
| 56 | Acetoin | HMDB0003243 | 1[29] | 203 | cholesteryl ester 34:0 | / | 1[6] |
| 57 | Isoacitretin | HMDB0003039 | 1[29] | 204 | cholesteryl ester 34:6 | / | 1[6] |
| 58 | Testosterone sulfate | HMDB0002833 | 1[29] | 205 | cholesteryl ester 40:4 | / | 1[29] |
| 59 | Desmosterol | HMDB0002719 | 1[31] | 206 | cis-3-(6-Hydroxy-7-methoxy-5-benzofuranyl)acrylic acid | / | 1[29] |
| 60 | 6-Hydroxynicotinic acid | HMDB0002658 | 1[29] | 207 | clavulone I | / | 1[29] |
| 61 | Sumiki's acid | HMDB0002432 | 1[29] | 208 | cyclohexylammonium | / | 1[54] |
| 62 | N-Acetylcadaverine | HMDB0002284 | 1[29] | 209 | d18:1/16:0 | / | 1[54] |
| 63 | 27-Nor-5b-cholestane-3a,7a,12a,24,25-pentol | HMDB0002126 | 1[29] | 210 | d18:1/24:0 | / | 1[54] |
| 64 | Oleamide | HMDB0002117 | 1[14] | 211 | d18:1/24:1 | / | 1[29] |
| 65 | N-Acetylputrescine | HMDB0002064 | 1[51] | 212 | DALBERGIONE, 4-METHOXY-4'-HYDROXY- | / | 1[29] |
| 66 | 2-Pyrrolidinone | HMDB0002039 | 1[29] | 213 | DIALLYL SULFIDE | / | 1[29] |
| 67 | D-threo-Isocitric acid | HMDB0001874 | 1[29] | 214 | dihydro-alpha-ergocryptine | / | 1[29] |
| 68 | Progesterone | HMDB0001830 | 1[27] | 215 | Dihydrolevobunolol | / | 1[29] |
| 69 | Asymmetric dimethylarginine | HMDB0001539 | 1[29] | 216 | dodecanamide | / | 1[29] |
| 70 | Glucosamine | HMDB0001514 | 1[29] | 217 | EB 1213 | / | 1[29] |
| 71 | Queuine | HMDB0001495 | 1[29] | 218 | Embelin | / | 1[29] |
| 72 | Pyridoxamine | HMDB0001431 | 1[29] | 219 | EMODIC ACID | / | 1[29] |
| 73 | Putrescine | HMDB0001414 | 1[51] | 220 | Estradiol valerate | / | 1[29] |
| 74 | p-Aminobenzoic acid | HMDB0001392 | 1[29] | 221 | Furafylline | / | 1[29] |
| 75 | Diaminopimelic acid | HMDB0001370 | 1[29] | 222 | GlcAbeta-Cer(d18:1/18:0) | / | 1[29] |
| 76 | Purine | HMDB0001366 | 1[29] | 223 | Gln Pro Lys | / | 1[29] |
| 77 | SM(d18:1/18:0) | HMDB0001348 | 1[14] | 224 | Glu Ser | / | 1[29] |
| 78 | N1-Acetylspermidine | HMDB0001276 | 1[26] | 225 | GPA(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)) | / | 1[29] |
| 79 | Spermidine | HMDB0001257 | 1[51] | 226 | GPEtn(18:1(11Z)/18:1(9Z))[U] | / | 1[29] |
| 80 | Spermine | HMDB0001256 | 1[51] | 227 | GPEtn(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z))[U] | / | 1[29] |
| 81 | N-Acetylarylamine | HMDB0001250 | 1[29] | 228 | GPEtn(O-16:0/22:5(4Z,7Z,10Z,13Z,16Z)) | / | 1[29] |
| 82 | (S)-Succinyldihydrolipoamide | HMDB0001177 | 1[29] | 229 | GPSer(16:0/18:1(11Z)) | / | 1[29] |
| 83 | 4-Aminophenol | HMDB0001169 | 1[29] | 230 | Granisetron metabolite | / | 1[29] |
| 84 | Pyruvaldehyde | HMDB0001167 | 1[29] | 231 | Gualenate | / | 1[29] |
| 85 | 3-Aminopropionaldehyde | HMDB0001106 | 1[29] | 232 | Gummiferol | / | 1[14] |
| 86 | 4-Aminobutyraldehyde | HMDB0001080 | 1[51] | 233 | Hex-CER(d18:1/16:0) | / | 1[14] |
| 87 | Glyceraldehyde | HMDB0001051 | 1[29] | 234 | Hex-CER(d18:1/18:0) | / | 1[29] |
| 88 | Biliverdin | HMDB0001008 | 1[29] | 235 | Ile Ser Lys | / | 1[14] |
| 89 | Trehalose | HMDB0000975 | 1[29] | 236 | inoleyl-carnitine | / | 1[29] |
| 90 | Traumatic acid | HMDB0000933 | 1[29] | 237 | KARANJIN | / | 1[14] |
| 91 | Stearoylcarnitine | HMDB0000848 | 1[14] | 238 | Lac-CER(d18:1/14:0) | / | 1[14] |
| 92 | Phenylacetylglycine | HMDB0000821 | 1[14] | 239 | Lac-CER(d18:1/16:0) | / | 1[14] |
| 93 | Indoleacrylic acid | HMDB0000734 | 1[29] | 240 | Lac-CER(d18:1/16:1) | / | 1[29] |
| 94 | Hippuric acid | HMDB0000714 | 1[29] | 241 | L-Alanine n-butyl ester | / | 1[29] |
| 95 | L-Kynurenine | HMDB0000684 | 1[30] | 242 | Leu Glu Gln | / | 1[29] |
| 96 | Citraconic acid | HMDB0000634 | 1[29] | 243 | Leu Leu Ala | / | 1[29] |
| 97 | Cytosine | HMDB0000630 | 1[60] | 244 | L-Glutamic acid dibutyl ester | / | 1[29] |
| 98 | Ethylmalonic acid | HMDB0000622 | 1[29] | 245 | Loroxanthin ester/ Loroxanthin dodecenoate | / | 1[27] |
| 99 | 2-Furoic acid | HMDB0000617 | 1[29] | 246 | LPC C 18:0 | / | 1[27] |
| 100 | PC(16:0/16:0) | HMDB0000564 | 1[14] | 247 | LPC C 18:1 | / | 1[27] |
| 101 | Creatinine | HMDB0000562 | 1[29] | 248 | LPC C 18:2 | / | 1[27] |
| 102 | Caproic acid | HMDB0000535 | 1[33] | 249 | LPC C 20:4 | / | 1[20] |
| 103 | Aminoadipic acid | HMDB0000510 | 1[29] | 250 | lysoPC a C18:2 | / | 1[29] |
| 104 | 3-Methylhistidine | HMDB0000479 | 1[29] | 251 | Mebeverine | / | 1[29] |
| 105 | 3,4-Dihydroxyhydrocinnamic acid | HMDB0000423 | 1[29] | 252 | Met Trp Gln | / | 1[29] |
| 106 | 3-Hydroxydodecanedioic acid | HMDB0000413 | 1[29] | 253 | Methoxsalen Metabolite | / | 1[29] |
| 107 | 2-Methyl-3-ketovaleric acid | HMDB0000408 | 1[29] | 254 | METHYL 7-DESHYDROXYPYROGALLIN-4-CARBOXYLATE | / | 1[33] |
| 108 | 2-Hydroxy-3-methylbutyric acid | HMDB0000407 | 1[29] | 255 | methyl-salsolinol | / | 1[51] |
| 109 | 3-Hydroxybutyric acid | HMDB0000357 | 1[59] | 256 | N1 or N8-acetyl-spermidine | / | 1[51] |
| 110 | 2-Methylbutyrylglycine | HMDB0000339 | 1[29] | 257 | N1,N12-diacetlyspermine | / | 1[29] |
| 111 | Urocanic acid | HMDB0000301 | 1[29] | 258 | N4-Acetylsulfapyridine | / | 1[29] |
| 112 | Uric acid | HMDB0000289 | 1[30] | 259 | SM(OH) C14:1 | / | 1[14] |
| 113 | Sphingosine 1-phosphate | HMDB0000277 | 1[14] | 260 | N-arachidonoyl D-serine | / | 1[29] |
| 114 | Sphinganine | HMDB0000269 | 1[27] | 261 | N-Didesethylquinagolide | / | 1[29] |
| 115 | Pyroglutamic acid | HMDB0000267 | 1[29] | 262 | N-methyl-Gabapentin | / | 1[14] |
| 116 | Taurine | HMDB0000251 | 1[29] | 263 | oleylcarnitine | / | 1[29] |
| 117 | Tetrahydrofuran | HMDB0000246 | 1[29] | 264 | Ophiobolin A | / | 1[20] |
| 118 | Pyruvic acid | HMDB0000243 | 1[29] | 265 | PC aa C40:5 | / | 1[7] |
| 119 | Ornithine | HMDB0000214 | 1[51] | 266 | PC aaC32:0 | / | 1[7] |
| 120 | Oxoglutaric acid | HMDB0000208 | 1[29] | 267 | PC aeC32:2 | / | 1[7] |
| 121 | Indoleacetic acid | HMDB0000197 | 1[30] | 268 | PC aeC34:1 | / | 1[43] |
| 122 | L-Lactic acid | HMDB0000190 | 1[59] | 269 | PC(32a:0) | / | 1[43] |
| 123 | L-Asparagine | HMDB0000168 | 1[26] | 270 | PC(38a:5) | / | 1[43] |
| 124 | Hypoxanthine | HMDB0000157 | 1[30] | 271 | PC(38a:6) | / | 1[26] |
| 125 | Fumaric acid | HMDB0000134 | 1[29] | 272 | Phe Phe | / | 1[29] |
| 126 | D-Glucose | HMDB0000122 | 1[59] | 273 | Phe Val Val | / | 1[14] |
| 127 | Gamma-Aminobutyric acid | HMDB0000112 | 1[51] | 274 | PPC(16:0/18:2) | / | 1[29] |
| 128 | Choline | HMDB0000097 | 1[26] | 275 | Pro Pro | / | 1[29] |
| 129 | Dimethylglycine | HMDB0000092 | 1[29] | 276 | Propionylglycine methyl ester | / | 1[43] |
| 130 | Cholesterol | HMDB0000067 | 1[6] | 277 | PS(38a:6) | / | 1[29] |
| 131 | Creatine | HMDB0000064 | 1[51] | 278 | PURPUROGALLIN | / | 1[29] |
| 132 | L-Carnitine | HMDB0000062 | 1[26] | 279 | PYROGALLIN | / | 1[29] |
| 133 | Acetoacetic acid | HMDB0000060 | 1[29] | 280 | QUERCETIN TETRAMETHYL (5,7,3',4') ETHER | / | 1[29] |
| 134 | Bilirubin | HMDB0000054 | 1[29] | 281 | Rimiterol | / | 1[29] |
| 135 | Acetic acid | HMDB0000042 | 1[59] | 282 | Ritodrine glucuronide | / | 1[29] |
| 136 | Biotin | HMDB0000030 | 1[29] | 283 | S-(p-Azidophenacyl)glutathione | / | 1[14] |
| 137 | 4-Pyridoxic acid | HMDB0000017 | 1[29] | 284 | SM(d18:1/18:1) | / | 1[7] |
| 138 | (17Z)-1alpha,25-dihydroxy-26,27-dimethyl-17,20,22,22,23,23-hexadehydrovitamin D3 / (17Z)-1alpha,25-d | / | 1[29] | 285 | 1alpha,25-dihydroxy-11beta-phenylvitamin D3 / 1alpha,25-dihydroxy-11beta-phenylcholecalciferol | / | 1[29] |
| 139 | (22E,24E)-1alpha,25-dihydroxy-22,23,24,24a-tetradehydro-24a-homovitamin D3 / (22E,24E)-1alpha,25-dih | / | 1[29] | 286 | 1alpha,25-dihydroxy-22-oxavitamin D3 3-hemiglutarate/ 1alpha,25-dihydroxy-22-oxacholecalciferol 3-he | / | 1[29] |
| 140 | (22R)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 / (22R)-1alpha,22,2 | / | 1[29] | 287 | 1alpha,25-dihydroxy-3-deoxy-3-thiavitamin D3 / 1alpha,25-dihydroxy-3-deoxy-3-thiacholecalciferol | / | 1[29] |
| 141 | (22R)-1alpha,22,25-trihydroxy-26,27-dimethyl-23,24-tetradehydro-24a-homo-20-epivitamin D3 / (22R)-1a | / | 1[29] | 288 | 1beta,25-dihydroxy-2beta-(3-hydroxypropoxy)vitamin D3 / 1beta,25-dihydroxy-2beta-(3-hydroxypropoxy)c | / | 1[29] |
| 142 | (22S)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 / (22S)-1alpha,22,2 | / | 1[29] | 289 | 5-(4-hydroxy-2,5-dimethylphenoxy)-2,2-dimethyl-Pentanoic acid (Gemfibrozil M1) | / | 1[29] |
| 143 | (23R)-1alpha,23,25-trihydroxy-24-oxovitamin D3 / (23R)-1alpha,23,25-trihydroxy-24-oxocholecalciferol | / | 1[29] | 290 | 5H-Oxireno[4,5]furo[3,2-g][1]benzopyran-5-one, 1a,8b-dihydro-3-methoxy- | / | 1[29] |
| 144 | (23R,25R)-1alpha,25-dihydroxyvitamin D3 26,23-lactone / (23R,25R)-1alpha,25-dihydroxycholecalciferol | / | 1[29] | 291 | 3alpha,6alpha,12alpha-Trihydroxy-7-oxo-5beta-cholan-24-oic Acid | / | 1[29] |
| 145 | (24S)-1alpha,24-dihydroxy-22-oxa-20-epivitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxa-20-epicholecalc | / | 1[29] | 292 | N'-5Z,8Z,11Z,14Z-eicosatetraenoyl-N''-diethyl-ethylenediamine | / | 1[29] |
| 146 | (24S)-1alpha,24-dihydroxy-22-oxavitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxacholecalciferol | / | 1[29] | 293 | 2H-1-Benzopyran-6-acetic acid, 7-hydroxy-8-methoxy-2-oxo- | / | 1[29] |
| 147 | 1,3-DIPROPYL-8-CYCLOPENTYLXANTHINE [DPCPX] | / | 1[29] |  |  |  |  |

areference number are same as in Supplementary Table 2.