Supplementary information

Computational Identification of Blood-Brain Barrier permeant Microbiome Metabolites with Binding Affinity to Neurotransmitter Receptors in Neurodevelopmental Disorders

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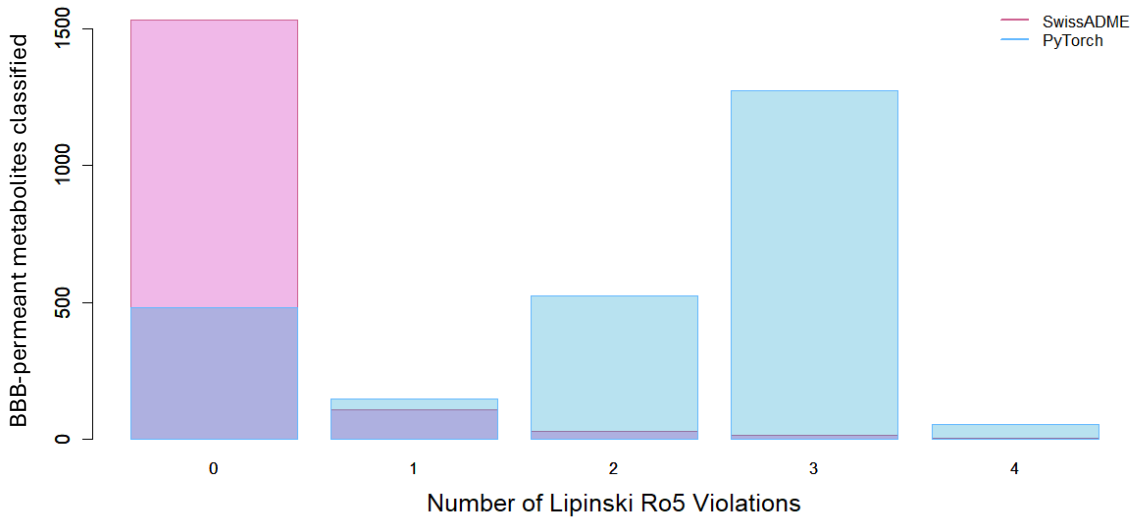


Figure S1. SwissADME (pink bars) versus PyTorch (blue bars) preferences for BBB-crossing metabolites classification according to Lipinski's Rule of Five (Ro5). Frequency overlap in bars is represented in transparency.

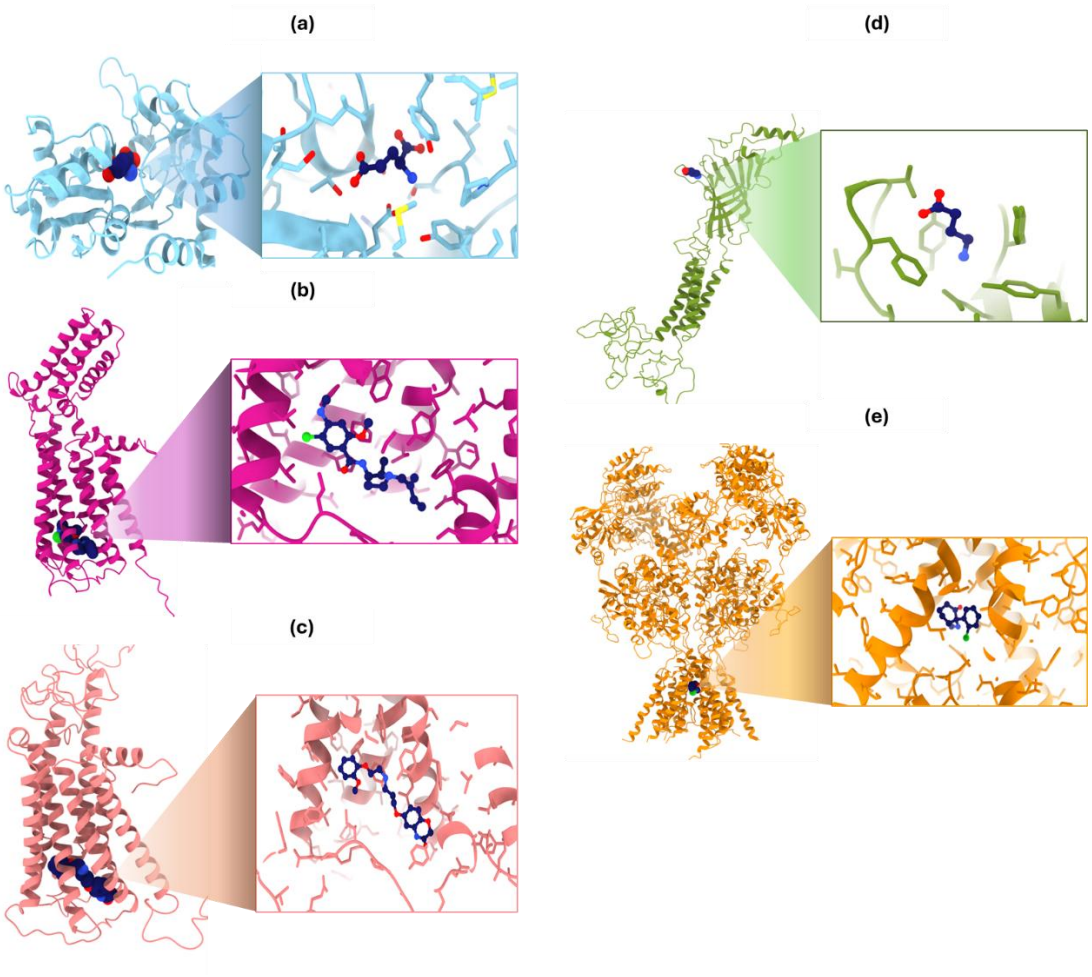


Figure S2. Crystallized ligands in their binding site for a) GRIA2 (PDB: 3RN8), b) DRD4 (PDB: 5WIU), c) HTR1A (PDB: 8PJK), d) GABRA2 (PDB: 9CRV) and e) GRIN2B (PDB: 9D3C).

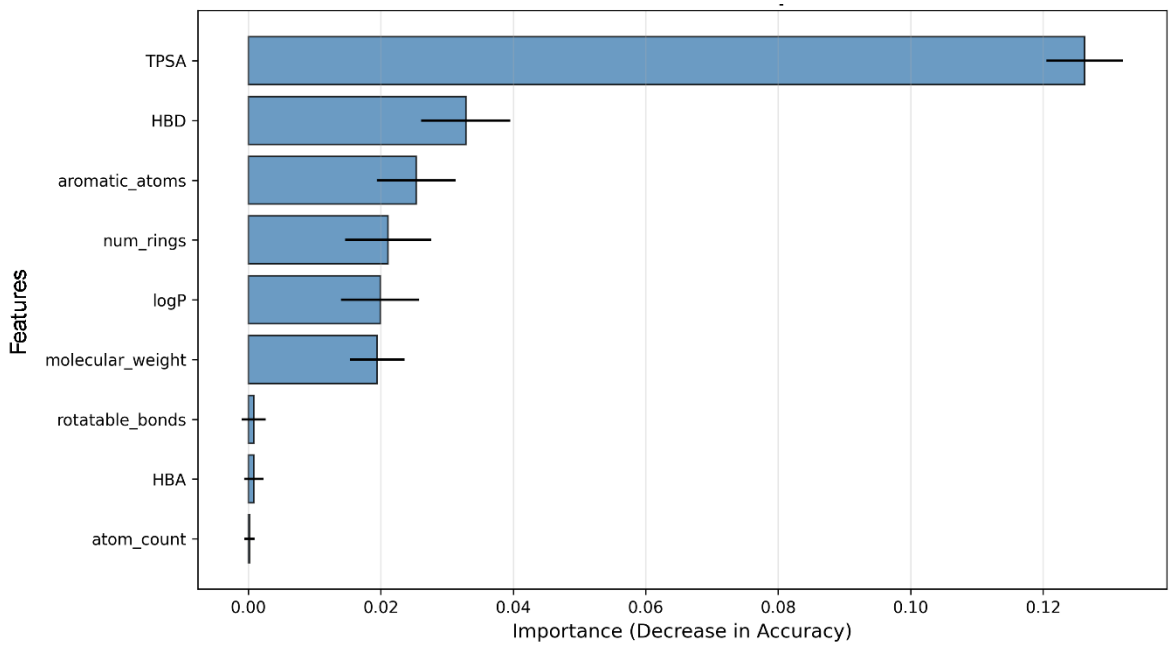


Figure S3. Permutation-based feature importance analysis for the PyTorch BBB permeability classifier. Bar plot showing the mean decrease in model accuracy when each molecular descriptor was randomly permuted in the test set (n = 10 permutations per feature). Error bars represent standard deviation across permutations.

Table S1. MiMeDB IDs from top 50 BBB-permeant metabolites and its common molecule name, the phylum of production origin, the BBB-permeant classifier that filtered them and their binding affinity across all 5 receptors evaluated by molecular docking.

ID	Name	*Phylum*	BBB Classifier	Affinity in kcal/mol				
				GABRA2	GRIA2	GRIN2B	DRD4	HTR1A
MMDBc0047901	Dehydroepiandrosterone	*Proteobacteria, Bacteroidetes, Firmicutes, Actinobacteria, Fusobacteria, Euryarchaeota, Planctomycetes*	Overlap	-7	1.7	-7.8	-10.1	-9
MMDBc0016397	Hesseltin E	*Ascomycota*	Overlap	-6.6	8.6	-7.6	-10.1	-9.6
MMDBc0030220	D-Urobilinogen	*Proteobacteria, Ascomycota*	PyTorch	-6.8	0.8	-6.9	-10.4	-9.9
MMDBc0004700	Penitrem B	*Ascomycota*	PyTorch	-6.4	32.6	9.2	-7.9	-11.2
MMDBc0006423	6-epiophiobolin	*Ascomycota*	SwissADME	-6.6	11.3	-8.1	-9.7	-9.7
MMDBc0055412	3-oxochola-4,6-dien-24-oic acid	*Firmicutes*	SwissADME	-7.8	2.5	-8.1	-9.5	-8.7
MMDBc0008319	Penicillipyrone B	*Ascomycota*	SwissADME	-6.6	2.2	-8.1	-10.3	-9.1
MMDBc0003850	4,4'-Oxybis(alpha,alpha,6-trimethyl-2,3-dihydrobenzofuran-2beta-methanol)	*Ascomycota*	SwissADME	-7.8	0.1	-7.3	-9.5	-9.5
MMDBc0002079	8-O-methylaverufin	*Ascomycota*	PyTorch	-6.9	1.1	-6.6	-10.6	-10
MMDBc0012635	Territrem B	*Ascomycota*	PyTorch	-6.4	15.1	2.7	-9.6	-9.6
MMDBc0047880	4Œ±-hydroxymethyl-5Œ±-cholesta-8,24-dien-3Œ≤-ol	*Ascomycota*	PyTorch	-7.6	2.9	-7.5	-9.4	-9.7
MMDBc0013469	Cyclotryprostatins A	*Ascomycota*	PyTorch	-7.5	11.8	-7	-10.3	-9.4
MMDBc0010769	Nigerasterol B	*Ascomycota*	SwissADME	-6.8	12.1	-8.9	-9.4	-9.1
MMDBc0019538	Eremoxylarin A	*Ascomycota*	PyTorch	-6.8	7.4	-8.6	-9.5	-9.4
MMDBc0017908	Aszonalenin	*Ascomycota*	SwissADME	-6.7	9.9	-8.7	-10	-9

MMDBc0024217	Asperversiamide D	*Ascomycota*	SwissADME	-7.6	21.4	-5.2	-10.5	-11.2
MMDBc0000417	Campesterol	*Firmicutes*	PyTorch	-7	3.1	-7.6	-9.6	-10.3
MMDBc0030039	Benzo[a]pyrene-4,5-oxide	*Proteobacteria*	Overlap	-7.6	-4.5	-9.1	-11.6	-10.4
MMDBc0011623	Hericenone B	*Basidiomycota*	SwissADME	-7.2	-7.2	-8.4	-10.4	-10
MMDBc0004479	6,8a-Seco-6,8a-deoxy-2,5-didehydroaverme	*Actinobacteria*	SwissADME	-7.2	108.4	27	7.3	-10.1
MMDBc0016230	Ergosterimide	*Ascomycota*	PyTorch	-6.6	8.1	-6.7	-10.3	-11
MMDBc0054593	N,N',N''-triacetylchitotriose	*Ascomycota*	PyTorch	-6.7	10.7	-6.5	-10.1	-11.4
MMDBc0015238	Demethoxyfumitremorgin C	*Ascomycota*	Overlap	-7	1.9	-7.2	-11	-9.5
MMDBc0010558	Brevianamide P	*Ascomycota*	SwissADME	-6.9	2.3	-8.4	-10	-9.6
MMDBc0008181	Schizine A	*Basidiomycota*	SwissADME	-6.3	27.5	-9	-9.8	-10.1
MMDBc0056394	(25S)-3-oxocholest-4-en-26-oate	*Actinobacteria*	SwissADME	-6.5	0.6	-8.3	-10.2	-10.3
MMDBc0024218	Asperversiamide E	*Ascomycota*	SwissADME	-7.7	13.8	-5.8	-10.5	-11.3
MMDBc0021505	Oxysporizoline	*Ascomycota*	SwissADME	-7.6	18.2	-9.3	-7.8	-10.6
MMDBc0019955	Chromoazepinone A	*Proteobacteria*	PyTorch	-6.4	2.1	-9.5	-9.8	-9.6
MMDBc0011274	YM-75518	*Proteobacteria*	Overlap	-7.3	16.4	-7.3	-10.8	-9.9
MMDBc0054496	glycodeoxycholic acid	*Actinobacteria, Firmicutes, Ascomycota, Proteobacteria, Bacteroidetes, Fusobacteria, Verrucomicrobia*	PyTorch	-6.6	1.4	-8.7	-10.6	-9.6
MMDBc0057082	4-Dimethyl-5a-cholesta-8,24-dien-3-b-ol	*Ascomycota*	PyTorch	-6.7	3.2	-7.9	-10.7	-10.3
MMDBc0019941	Benzomalvin B	*Ascomycota*	SwissADME	-6.9	18.2	-8.6	-10.2	-9.9

MMDBc0001025	Menaquinone MK-7	*Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, Spirochaetes, Thaumarcheota, Fusobacteria, Synergistetes, Euryarchaeota, Tenericutes*	Overlap	-6.8	8.3	-7.9	-10.7	-10.3
MMDBc0010086	Ditryptophenaline	*Ascomycota*	PyTorch	-7.3	41.2	3.7	-7	-12.5
MMDBc0018331	Marcfortine A	*Ascomycota*	SwissADME	-7.1	24.8	5.8	-9.1	-10.7
MMDBc0017045	Brevianamide S	*Ascomycota*	SwissADME	-7.1	16.1	6	-9.6	-10.3
MMDBc0055408	3-oxochol-4,6-dien-24-oyl-CoA	*Firmicutes*	PyTorch	-7.6	40.6	7.5	-8.2	-11.3
MMDBc0012256	Benzomalvin C	*Ascomycota*	SwissADME	-7.8	8.4	-7.7	-10.1	-10.6
MMDBc0022920	Lysiformine	*Firmicutes*	SwissADME	-8	-7.4	-9.1	-10.5	-10.3
MMDBc0012852	Asterriquinone	*Ascomycota*	PyTorch	-6.6	9.1	0.3	-10.2	-10.6
MMDBc0006370	Chromomycin A2	*Actinobacteria*	PyTorch	-6.7	65.8	15.7	4.4	-11.9
MMDBc0015280	Chaetominine	*Ascomycota*	PyTorch	-6.6	2.9	-10.7	-10.4	-9.6
MMDBc0054455	Digitoxin	*Actinobacteria*	SwissADME	-8.1	27.5	0.8	-10.1	-9.8
MMDBc0014365	Tryptoquivaline H	*Ascomycota*	PyTorch	-6.6	6.8	-9.7	-10.3	-11
MMDBc0004478	Benzomalvin A	*Ascomycota*	SwissADME	-7.3	6.8	-9.1	-11.2	-10.3
MMDBc0017260	Trisindoline	*Proteobacteria*	SwissADME	-7.8	1.5	-9.8	-10.5	-10.4
MMDBc0023129	2,2'-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione)	*Ascomycota*	PyTorch	-7.1	13	6.7	-10.8	-11.4
MMDBc0057265	Deoxycholyltyrosine	*Bacteroidetes, Firmicutes*	PyTorch	-9.2	2.6	-6.2	-11.6	-12.6
MMDBc0001332	Ergobine	*Ascomycota*	PyTorch	-8.3	11.3	-8.1	-13.3	-11.3

Table S2. Distribution of Phylum in MiMeDB.

Phylum	n	Percentage
Firmicutes	849	32.06
Proteobacteria	583	22.02
Actinobacteria	399	15.07
Ascomycota	251	9.48
Bacteroidetes	219	8.27
Basidiomycota	63	2.38
Euryarchaeota	46	1.74
Fusobacteria	36	1.36
Tenericutes	31	1.17
Bacillota	29	1.1
NULL	15	0.57
Spirochaetes	14	0.53
Uroviricota	13	0.49
Crenarchaeota	9	0.34
Cyanobacteria	8	0.3
Chlamydiae	7	0.26
Mucoromycota	6	0.23
Nematoda	6	0.23
Platyhelminthes	6	0.23
Synergistetes	6	0.23
Chlorobi	4	0.15
Peploviricota	4	0.15
Bacteroidota	3	0.11
Verrucomicrobia	3	0.11
Actinomycetota	2	0.08
Apicomplexa	2	0.08
Candidatus thermoplasmatota	2	0.08
Chloroflexi	2	0.08
Chlorophyta	2	0.08
Chytridiomycota	2	0.08
Deferribacteres	2	0.08
Deinococcus-thermus	2	0.08
Ignavibacteriae	2	0.08
Microsporidia	2	0.08
Planctomycetes	2	0.08
Thermotogae	2	0.08
Aquificae	1	0.04
Candidatus melainabacteria	1	0.04

Ciliophora	1	0.04
Cossaviricota	1	0.04
Cressdnaviricota	1	0.04
Euglenozoa	1	0.04
Fibrobacteres	1	0.04
Hofneiviricota	1	0.04
Negarnaviricota	1	0.04
Nitrososphaerota	1	0.04
Nitrospirae	1	0.04
Oomycota	1	0.04
Pseudomonadata	1	0.04
Thaumarchaeota	1	0.04