Integrated LC-MS/MS and network pharmacology approach for predicting active ingredients and pharmacological mechanisms of *Tribulus terrestris* L. against cardiac diseases

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Supplementary Table 1. Results of high-performance liquid chromatography electrospray ionization tandem mass spectrometry (HPLC-QTOF-MS/MS) analysis of *Tribulus terrestris* L. plant extract

Retention time	Observed mass	Theoretical mass	Error (PPM)	Adducts	Molecular formula	Score (max=10)	Putative compound	Fragments	Ontology
6.543	118.0866	118.086255	5.4	$[M+H]^+$	$C_5H_{11}NO_2$	8.95	Betaine	118.0867, 59.0732	Alpha amino acids
5.678	118.1204	118.122640	7.95	$[M+H]^+$	$C_6H_{15}NO$	6.38	2-Diethylaminoethanol	118.1201, 102.0859, 59.0475	1,2-aminoalcohols
8.978	124.0405	124.039304	3.19	$[M+H]^+$	$C_6H_5NO_2$	8.35	Nicotinic acid	124.0402, 78.0348	Pyridinecarboxylic acids
13.804	130.0865	130.086255	1.88	$[M+H]^+$	$C_6H_{11}NO_2$	7.32	Pipecolic acid	130.0873, 112.0765, 84.0819	Alpha amino acids
7.035	136.0622	136.060434	12.97	$[M+H]^+$	$C_4H_9NO_4$	7.18	(+)-threo-2-Amino-3,4-dihydroxybutanoic acid	136.0625	L-alpha-amino acids
7.503	137.045	137.045787	5.74	$[M+H]^+$	$C_5H_4N_4O$	8.61	Hypoxanthine	137.0469, 94.0395, 73.0291	Hypoxanthines
6.625	138.0558	138.054954	6.12	$[M+H]^+$	$C_7H_7NO_2$	8.69	2-Aminobenzoic acid	138.0561, 94.066	Aminobenzoic acids
8.956	152.0575	152.056686	5.35	$[M+H]^+$	$C_5H_5N_5O$	7.73	Guanine	152.0569, 135.0332, 110.0382	Purines and purine derivatives
22.7	154.0866	154.086255	2.23	$[M+H]^+$	$C_8H_{11}NO_2$	7.21	Dopamine	154.0869	Catecholamines and derivatives

6.4	159.077	159.076418	3.65	$[M+H]^+$	$C_6H_{10}N_2O_3$	8.02	5-hydroxyectoine	159.0768, 113.0708, 83.0615	Alpha amino acids and derivatives
5.819	162.1129	162.112469	2.65	$[M+H]^+$	$C_7H_{15}NO_3$	9.2	L-Carnitine	162.112, 103.0387, 60.0802	Carnitines
57.095	163.0763	163.078727	14.88	$[M+H]^+$	$C_7H_{14}O_2S$	7.57	Methyl cinnamate	163.0761, 105.0339, 77.0392	Carboxylic acid esters
27.61	165.1273	165.127391	0.55	$[M+H]^+$	$C_{11}H_{16}O$	6.17	trans-Jasmone	165.1283, 121.1014, 109.105	Cyclic ketones
11.842	166.0743	166.072336	11.82	$[M+H]^+$	$C_6H_7N_5O$	5.92	7-Methylguanine	166.0742, 149.0466, 96.045	Hypoxanthines
15.739	166.0867	166.086255	2.67	$[M+H]^+$	$C_9H_{11}NO_2$	7.57	L-Phenylalanine	166.085, 149.0519, 120.0804	Phenylalanine and derivatives
45.889	204.1269	204.123034	18.93	$[M+H]^+$	$C_9H_{17}NO_4$	6.6	L-Acetylcarnitine	204.1273, 160.9976	Acyl carnitines
61.007	209.154	209.153606	1.88	$[M+H]^+$	$C_{13}H_{20}O_2$	7	3-Hydroxy-beta-ionone	209.1546, 135.0784, 55.0545	Sesquiterpenoids
18.702	220.1187	220.117949	3.41	$[M+H]^+$	$C_9H_{17}NO_5$	7.53	Pantothenic acid	220.1178, 202.1065, 184.0952, 116.034, 90.0547, 69.0698	Secondary alcohols
5.005	233.198	233.201225	13.82	$[M+H]^+$	$C_{15}H_{24}N_2$	7.2	Aloperine	233.197, 162.1212, 72.0805	Aloperine and related alkaloids

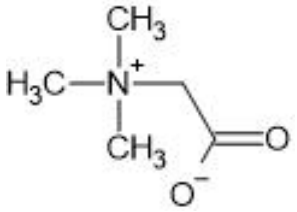
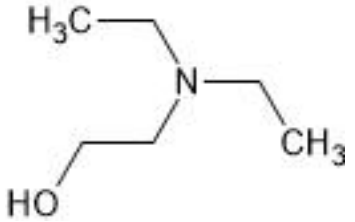
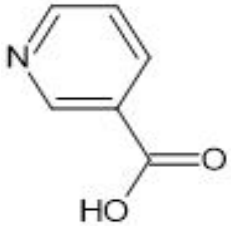
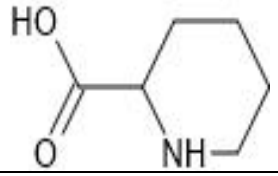
57.458	261.1122	261.112135	0.24	$[M+H]^+$	$C_{15}H_{16}O_4$	7.28	Hemigossypol	261.1103	Sesquiterpenoids
55.011	264.2347	264.232191	9.49	$[M+H]^+$	$C_{17}H_{29}NO$	7.89	Victoxinine	264.2311, 219.175	Sesquiterpenoids
25.749	265.1557	265.154669	3.88	$[M+H]^+$	$C_{14}H_{20}N_2O_3$	8.16	Subaphylline	265.1548, 219.1487	Hydroxycinnamic acids and derivatives
44.445	287.0572	287.055014	7.61	$[M+H]^+$	$C_{15}H_{10}O_6$	8.46	Kaempferol	287.0554, 145.0558	Flavonols
31.229	299.2096	299.211789	7.31	$[M+H]^+$	$C_{19}H_{26}N_2O$	6.97	Astrophylline	299.2068, 231.1452, 196.1089, 72.0804	Cinnamic acids and derivatives
54.018	314.1412	314.138684	8.0	$[M+H]^+$	$C_{18}H_{19}NO_4$	6.63	Moupinamide	314.1407, 177.0548, 106.0652	Hydroxycinnamic acids and derivatives
56.422	316.2869	316.284620	7.2	$[M+H]^+$	$C_{18}H_{37}NO_3$	7.45	Dehydrophytosphingosine	316.2866, 95.0852, 60.0448	1,3-aminoalcohols
57.307	318.3042	318.300270	12.34	$[M+H]^+$	$C_{18}H_{39}NO_3$	7.57	Phytosphingosine	318.3016, 60.0447	1,3-aminoalcohols
59.494	327.1631	327.159085	12.27	$[M+H]^+$	$C_{20}H_{22}O_4$	6.25	Uncinatone	327.1621, 203.1065, 151.0765, 71.0852	Phenanthrenes and derivatives
31.068	328.1983	328.201951	11.12	$[M+NH_4]^+$	$C_{19}H_{22}N_2O_2$	5.6	Sarpagine	311.1589, 283.1759, 205.1006, 177.1123, 133.0853, 89.0601	Macroline alkaloids

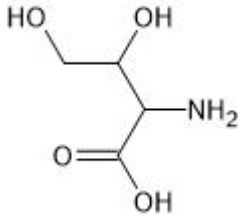
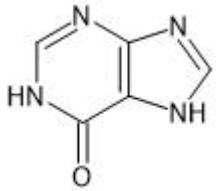
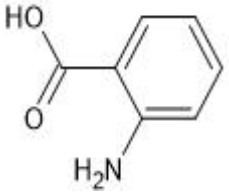
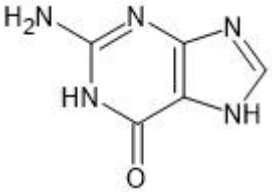
27.037	344.2303	344.233251	8.57	$[M+NH_4]^+$	$C_{20}H_{26}N_2O_2$	7.86	Ajmaline	327.2036, 239.1503, 177.1125, 133.0865, 89.0603	Ajmaline-sarpagine alkaloids
33.667	372.2251	372.228166	8.23	$[M+NH_4]^+$	$C_{21}H_{26}N_2O_3$	6.64	Yohimbine	327.2004, 283.1779, 177.1115, 133.0863, 89.06	Yohimbine alkaloids
31.04	377.148	377.145560	6.46	$[M+H]^+$	$C_{17}H_{20}N_4O_6$	8.05	Riboflavin	377.1569, 243.088, 99.0385	Flavins
59.257	387.182	387.180215	4.61	$[M+H]^+$	$C_{22}H_{26}O_6$	7.77	Gingerenone B	105.0709	Linear diarylheptanoids
57.879	403.2035	403.201619	4.66	$[M+H]^+$	$C_{25}H_{26}N_2O_3$	6.09	Aurantiamide	385.1907, 224.1052, 152.1066, 105.0332	Phenylalanine and derivatives
60.179	412.3256	412.321006	11.14	$[M+H]^+$	$C_{27}H_{41}NO_2$	7.53	Cyclopamine	412.3227, 271.2062, 72.0811	Jerveratrum-type alkaloids
48.735	435.1798	435.180215	0.95	$[M+H]^+$	$C_{26}H_{26}O_6$	6.68	Auriculin	417.1699, 132.0443, 93.0555	6-prenylated isoflavanones
44.443	449.1115	449.107837	8.15	$[M+H]^+$	$C_{21}H_{20}O_{11}$	7.49	Quercetin-3-O-α-rhamnoside	287.0576, 133.0863, 89.06	Flavonoid-3-O-glycosides
44.896	479.1224	479.118402	8.34	$[M+H]^+$	$C_{22}H_{22}O_{12}$	6.53	Isorhamnetin 3-galactoside	317.0647, 85.0283	Flavonoid-3-O-glycosides
55.402	535.2682	535.270367	4.04	$[M+H]^+$	$C_{33}H_{34}N_4O_3$	6.73	Pyrophaeophorbide a	517.2564, 459.2125,	Chlorins

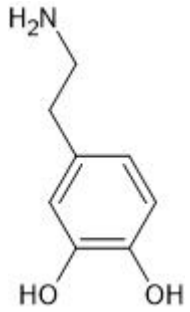
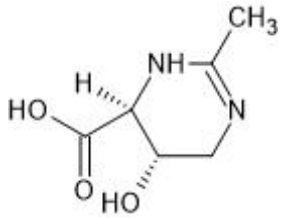
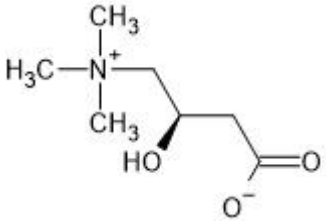
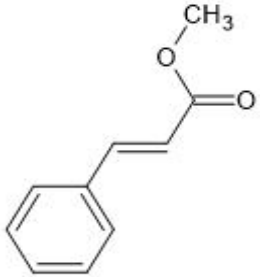
								343.1287, 269.0921	
49.767	577.378	577.373495	7.8	$[M+H]^+$	$C_{33}H_{52}O_8$	6.44	Collettiside I	577.3721, 415.3212, 273.2202, 115.0739	Steroidal saponins
49.502	579.3931	579.389145	6.82	$[M+H]^+$	$C_{33}H_{54}O_8$	7.25	Asparagoside A	579.3954, 417.3383, 273.2221, 115.0748	Steroidal saponins
55.953	593.3108	593.310894	0.15	$[M+H]^+$	$C_{35}H_{44}O_8$	6.93	Yungensin F	517.2548, 401.1731, 251.187, 157.1221, 99.0803	2,2-dimethyl-1-benzopyrans
40.803	593.373	593.368409	7.73	$[M+H]^+$	$C_{33}H_{52}O_9$	6.34	Agavoside A	593.3735, 431.3188, 287.0573, 85.031	Steroidal saponins
54.841	595.1508	595.144617	10.38	$[M+H]^+$	$C_{30}H_{26}O_{13}$	7.02	Tribuloside	287.0578, 147.0452	Flavonoid 3-O-p-coumaroyl glycosides
38.564	611.1645	611.160661	6.28	$[M+H]^+$	$C_{27}H_{30}O_{16}$	7.59	Rutin	303.05, 85.0285	Flavonoid-3-O-glycosides
55.822	615.2928	615.301118	13.51	$[M+H]^+$	$C_{30}H_{46}O_{13}$	6.95	Forskoditerpenoside B	615.295, 273.1685, 59.0494	Triterpenoids
42.592	625.1803	625.176311	6.38	$[M+H]^+$	$C_{28}H_{32}O_{16}$	6.18	Keioside (Isorhamnetin 3-robinobioside)	317.068, 85.0284	Flavonoid-3-O-glycosides
38.861	652.4145	652.422114	11.67	$[M+NH_4]^+$	$C_{40}H_{50}N_4O_3$	7.1	Capuvosine	635.3896, 89.0602	Vobasan alkaloids

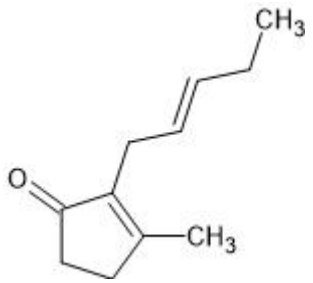
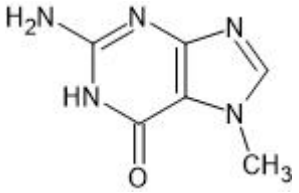
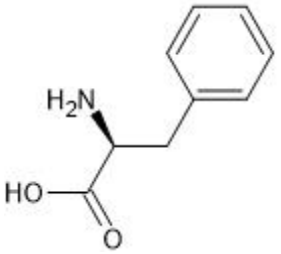
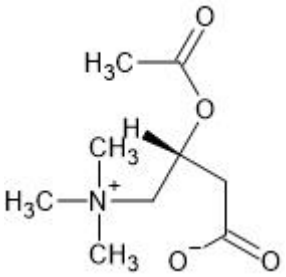
55.08	723.4433	723.431403	16.44	$[M+H]^+$	$C_{39}H_{62}O_{12}$	5.84	Ophiopogonin C'	723.424, 577.3749, 397.3106, 269.1921, 85.0295	Steroidal saponins
41.002	740.4697	740.477852	11.0	$[M+NH_4]^+$	$C_{40}H_{68}O_7P_2$	7.04	Octaprenyl diphosphate	723.4381, 89.0601	Tetraterpenoids
56.288	741.1842	741.181396	3.78	$[M+H]^+$	$C_{39}H_{32}O_{15}$	7.93	3",6"-Di-O-p-coumaroyltrifolin	287.0572, 147.0448	Flavonoid 3-O-p-coumaroyl glycosides
49.51	741.4465	741.441968	6.11	$[M+H]^+$	$C_{39}H_{64}O_{13}$	6.56	Capsicoside B2	741.4463, 579.3912, 435.2772, 255.2117, 115.0755	Steroidal saponins
56.296	771.1915	771.197834	8.21	$[M+H]^+$	$C_{33}H_{38}O_{21}$	7.02	Kaempferol 3-rutinoside-7-glucuronide	317.0672, 147.0445	Flavonoid-7-O-glucuronides
47.803	903.2389	903.243603	5.2	$[M+H]^+$	$C_{56}H_{38}O_{12}$	5.38	Upunaphenol B	745.1841	2-arylbenzofuran flavonoids
58.894	941.4765	941.474056	2.59	$[M+H]^+$	$C_{47}H_{72}O_{19}$	7.86	Amaranthussaponin III	941.4729, 779.4164	Diterpene glycosides

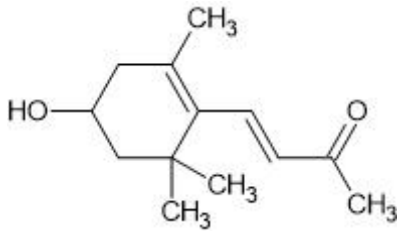
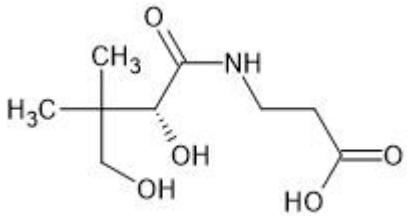
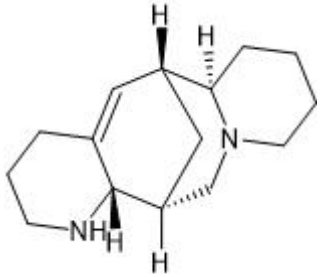
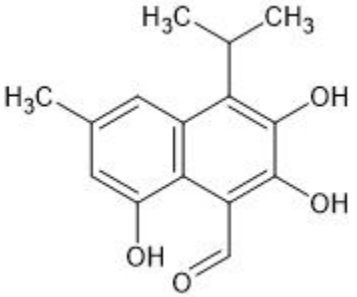
Supplementary Table 2. 2D structures of putative compounds with their PubChem CIDs

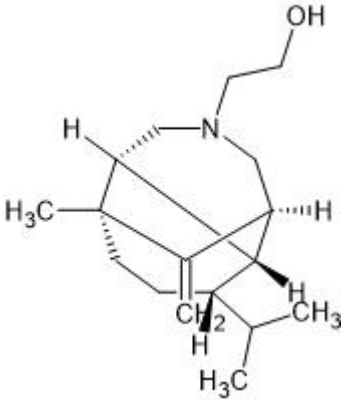
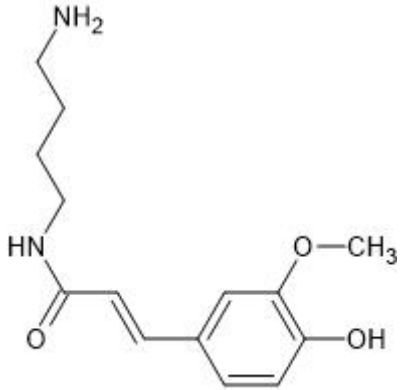
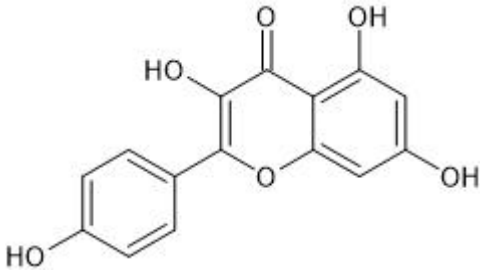
Sl No.	Putative compound	PubChem CID	2D structure
1	Betaine	247	
2	2-Diethylaminoethanol	7497	
3	Nicotinic acid	938	
4	Pipecolic acid	849	

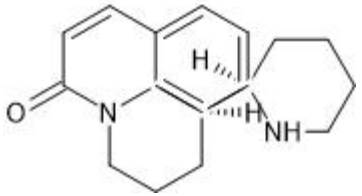
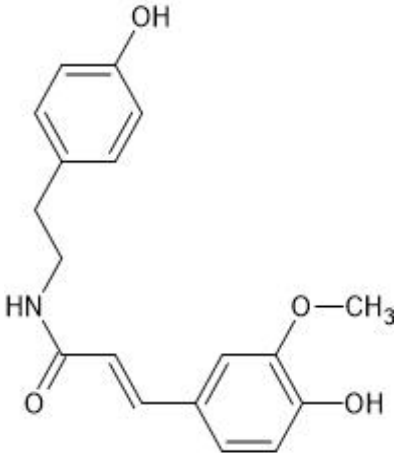
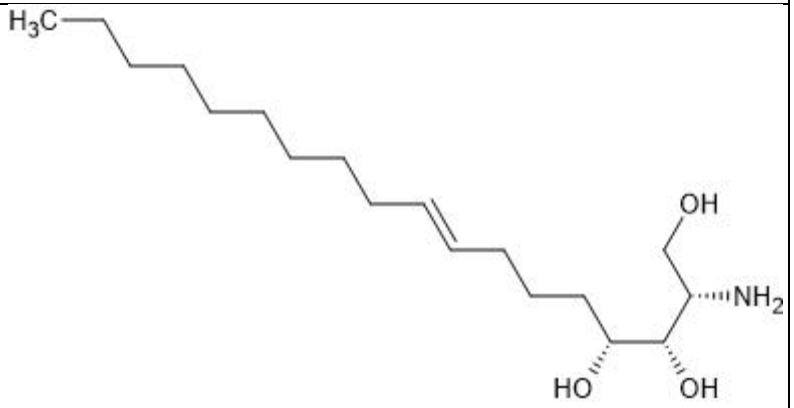
5	(+)-threo-2-Amino-3,4-dihydroxybutanoic acid	3914727	
6	Hypoxanthine	135398638	
7	2-Aminobenzoic acid	227	
8	Guanine	135398634	

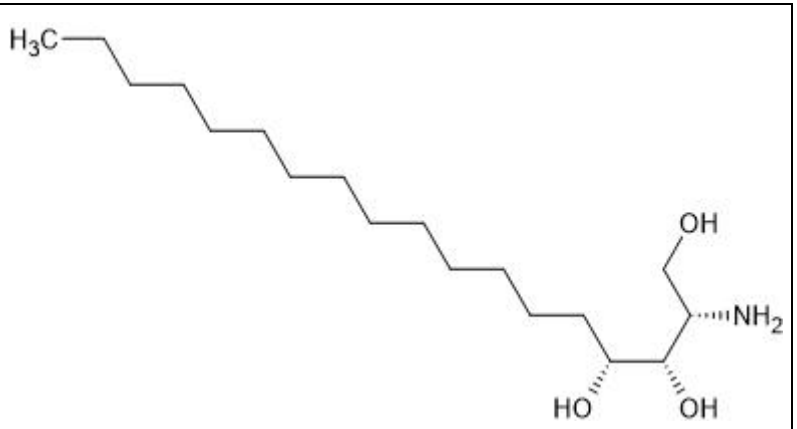
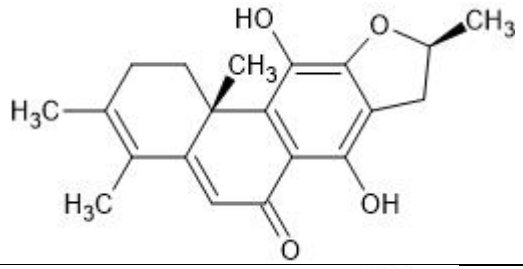
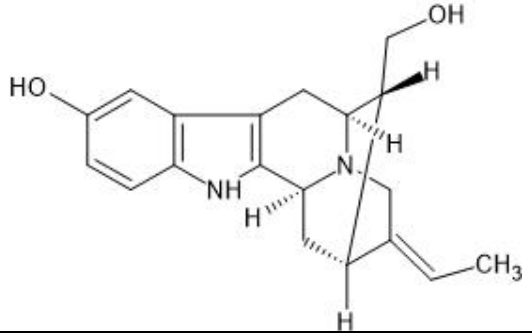
9	Dopamine	681	
10	5-hydroxyectoine	12011795	
11	L-Carnitine	10917	
12	Methyl cinnamate	637520	

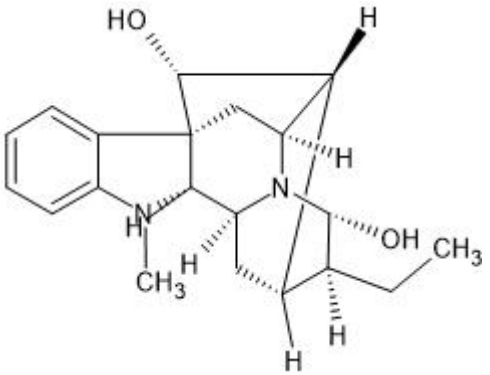
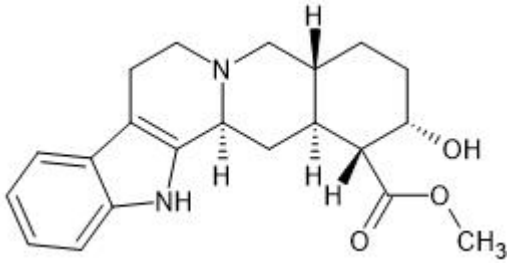
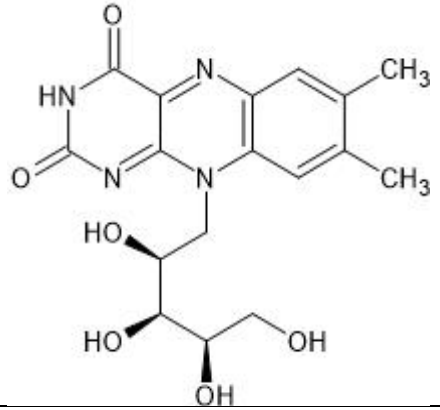
13	trans-Jasmone	1549019	
14	7-Methylguanine	135398679	
15	L-Phenylalanine	6140	
16	L-Acetylcarnitine	7045767	

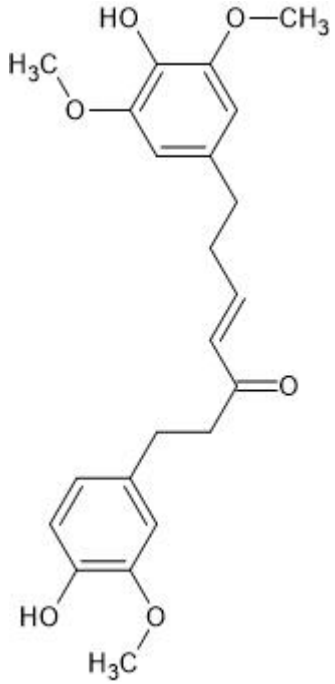
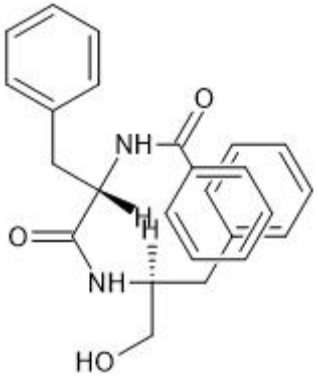
17	3-Hydroxy-beta-ionone	5363700	
18	Pantothenic acid	6613	
19	Aloperine	162147	
20	Hemigossypol	115300	

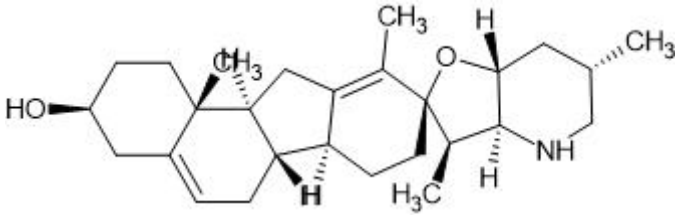
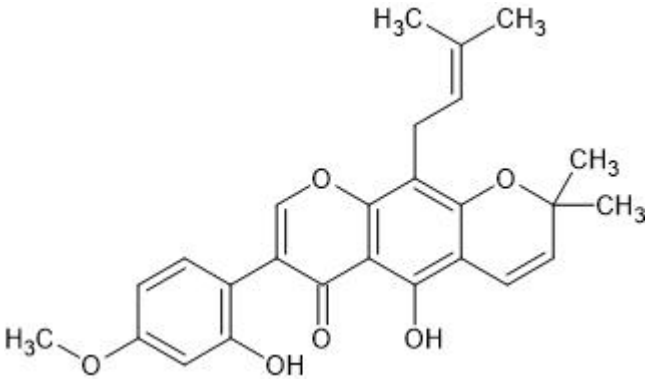
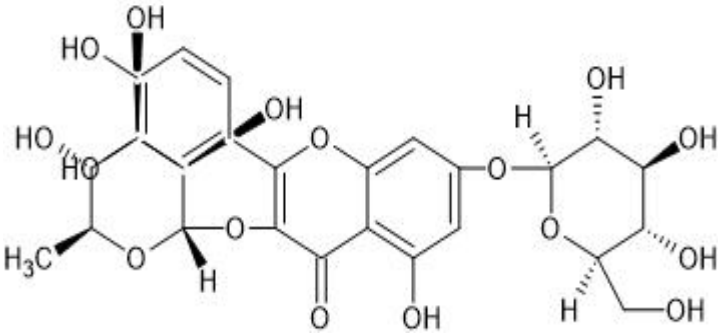
21	Victoxinine	181648	
22	Subaphylline	5281796	
23	Kaempferol	5280863	

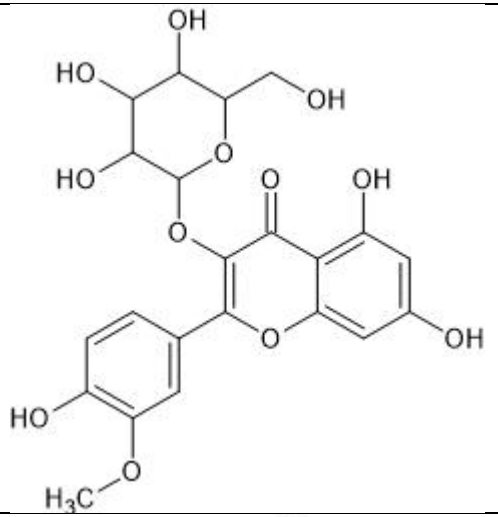
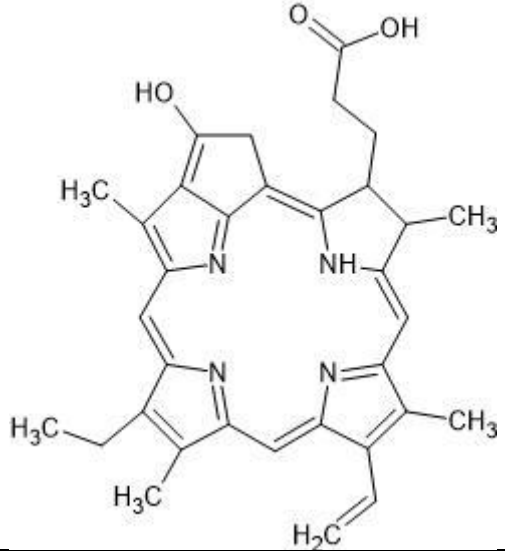
24	Astrophylline	11150687	
25	Moupinamide	5280537	
26	Dehydrophytosphingosine	14757418	

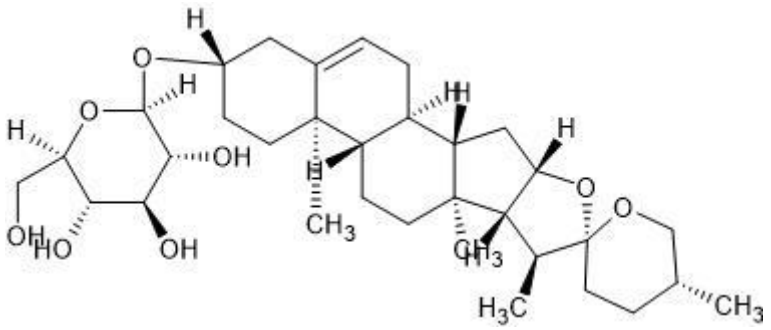
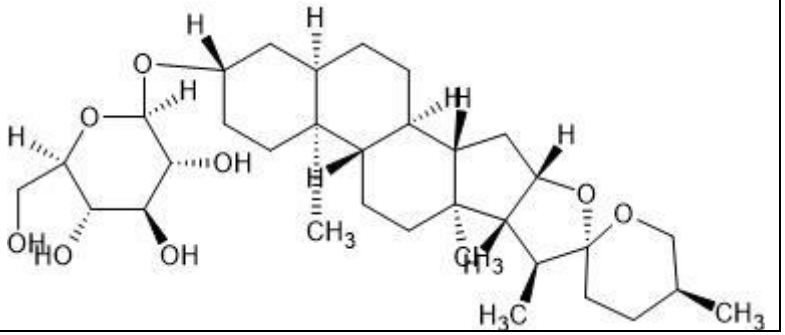
27	Phytosphingosine	122121	
28	Uncinatone	442547	
29	Sarpagine	12314884	

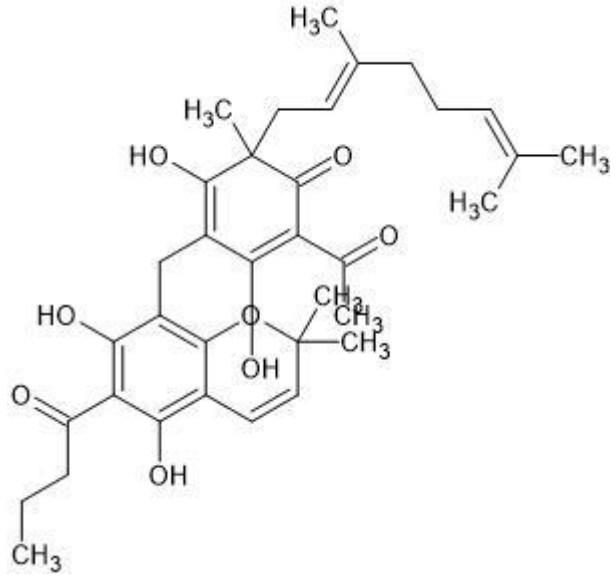
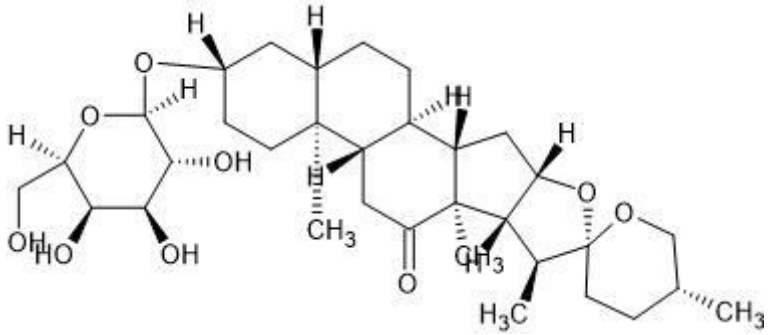
30	Ajmaline	6100671	
31	Yohimbine	8969	
32	Riboflavin	493570	

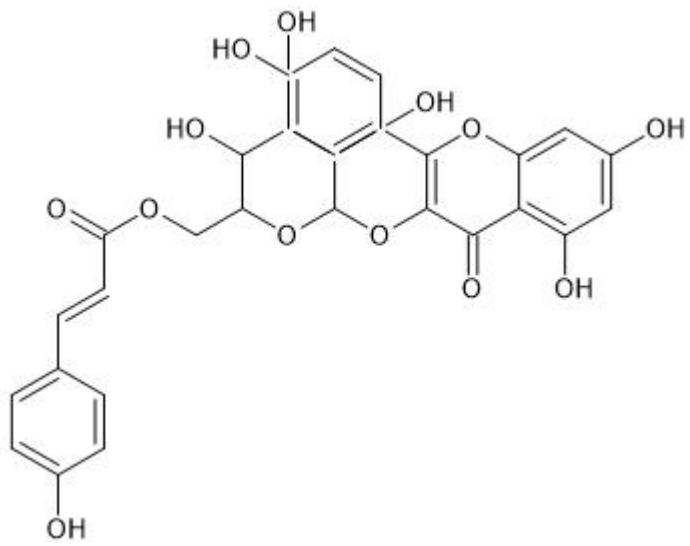
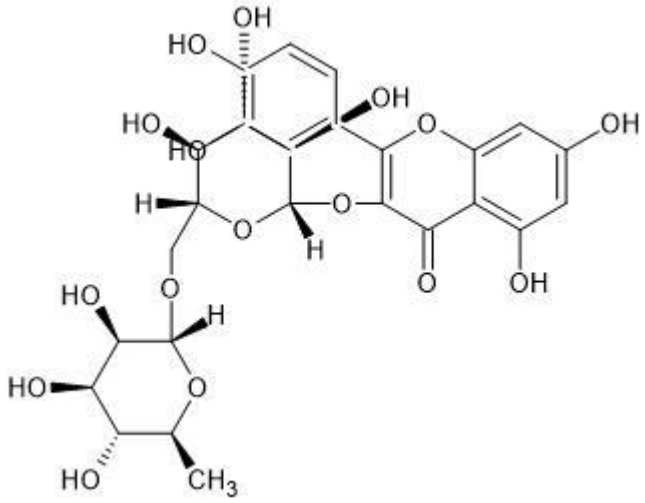
33	Gingerenone B	5317592	
34	Aurantiamide	185904	

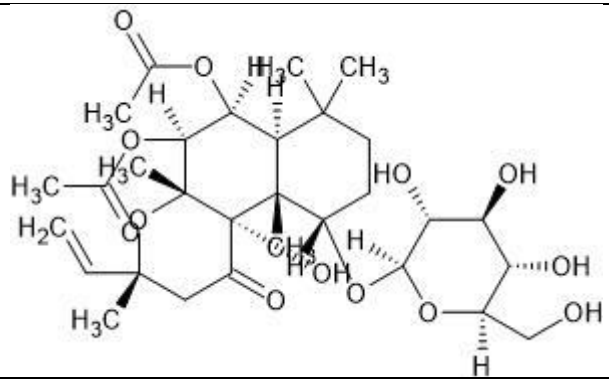
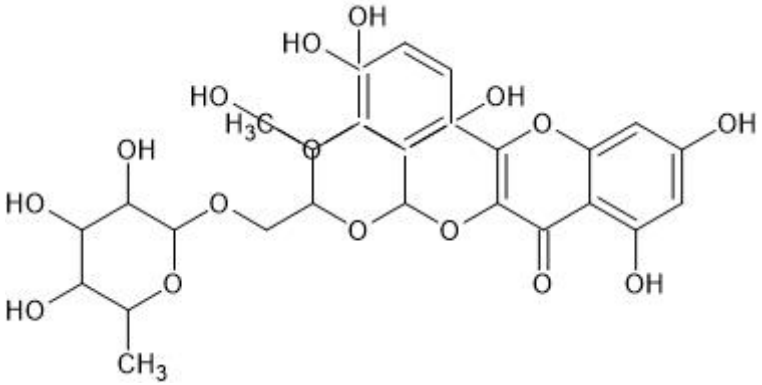
35	Cyclopamine	442972	
36	Auriculin	5491651	
37	Quercetin-3-O-α-rhamnoside	5280459	

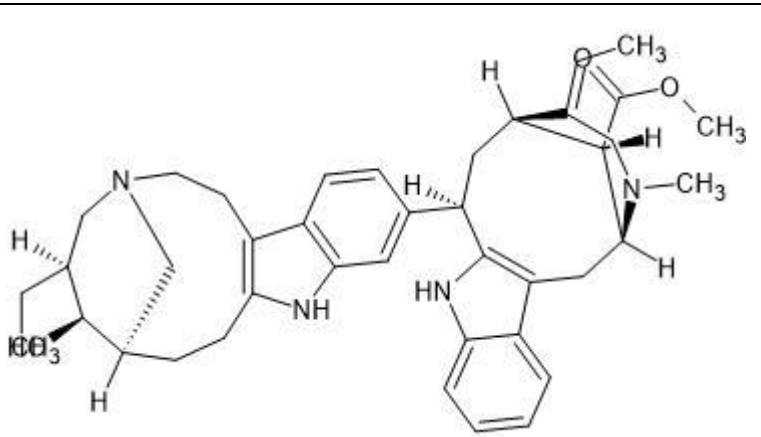
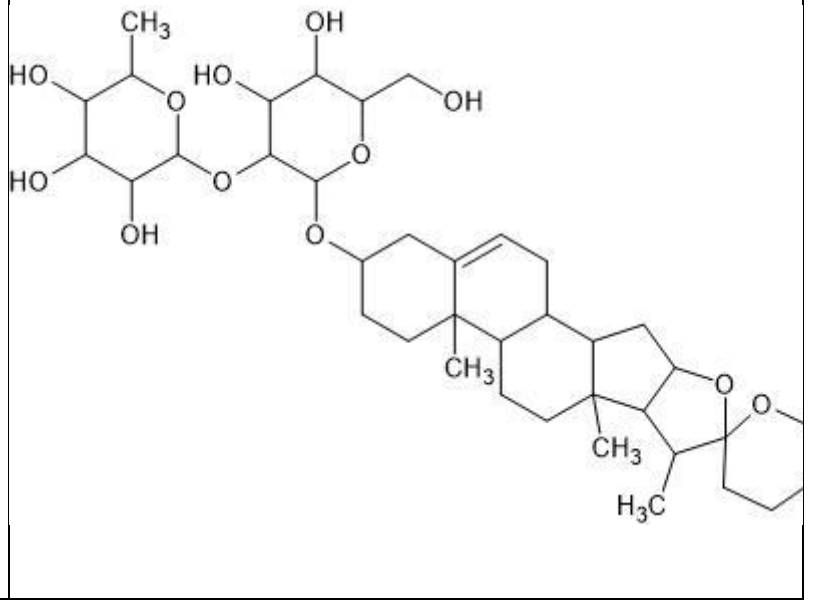
38	Isorhamnetin 3-galactoside	13245586	
39	Pyrophaeophorbide a	3819540	

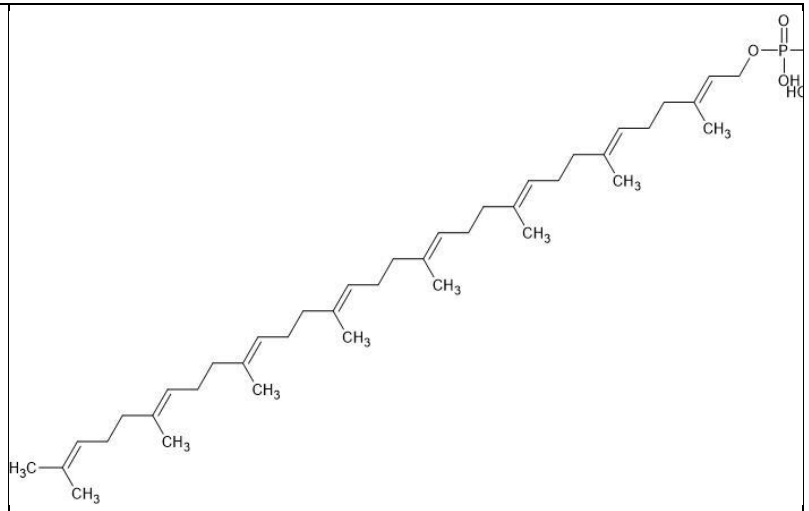
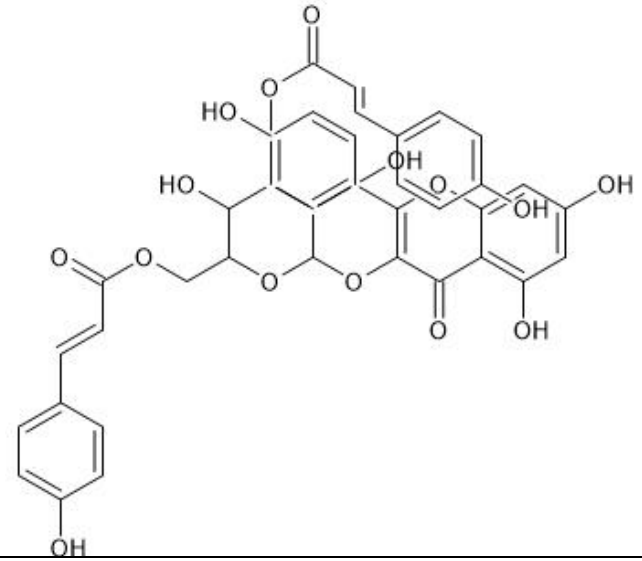
40	Collettiside I	11827970	
41	Asparagoside A	440454	

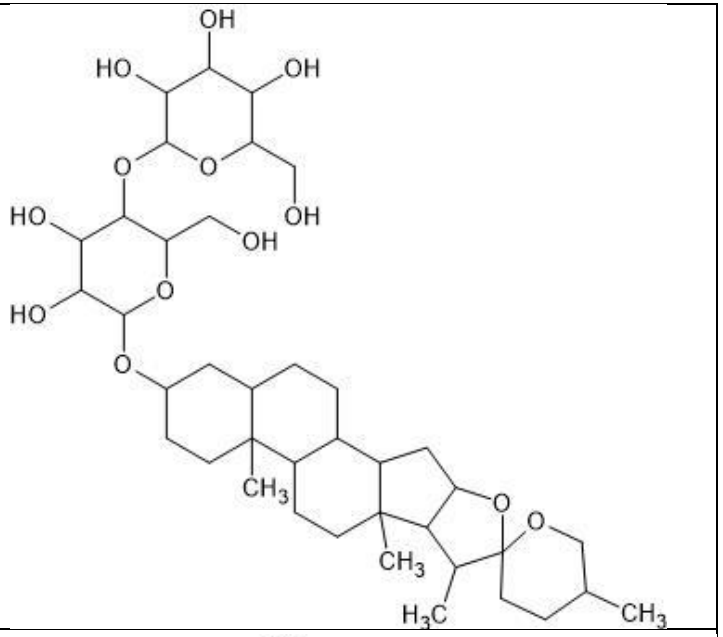
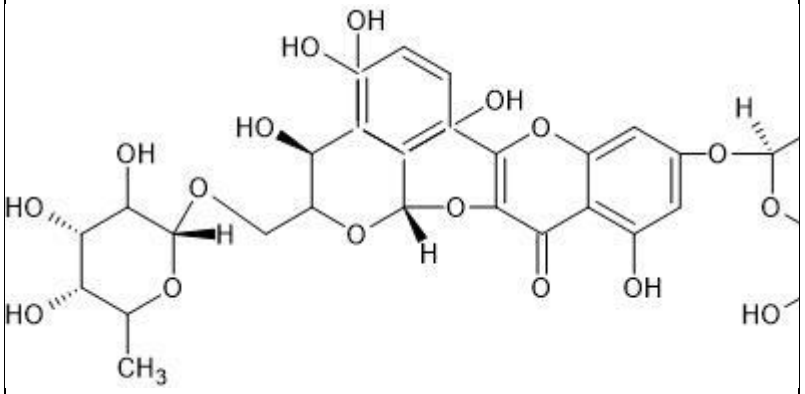
42	Yungensin F	50900664	
43	Agavoside A	441876	

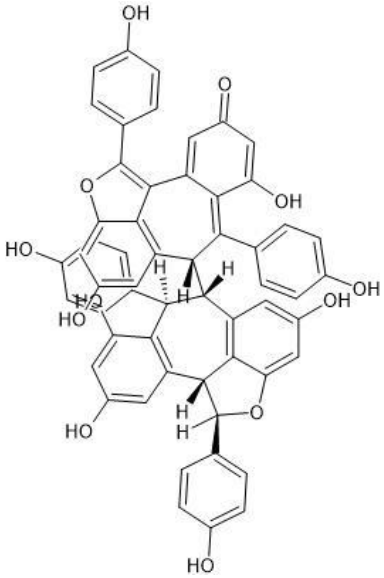
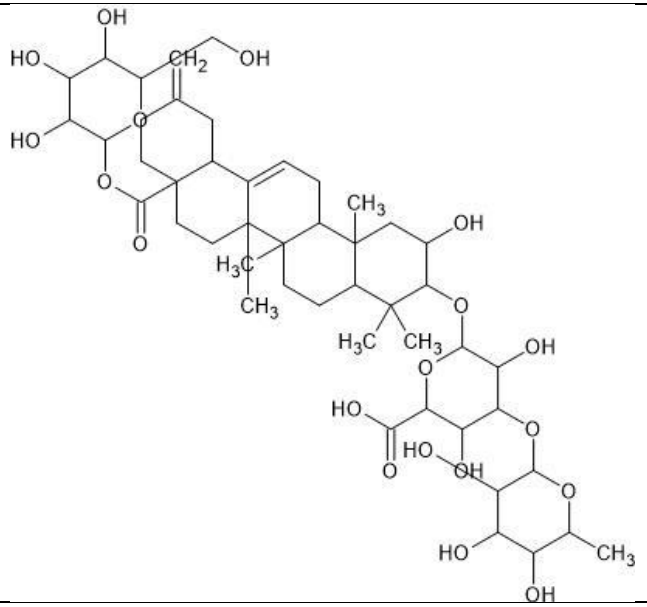
44	Tribuloside	10175330	
45	Rutin	5280805	

46	Forskoditerpenoside B	16215884	
47	Keioside	6223069	

48	Capuvosine	101277359	
49	Ophiopogonin C'	4483248	

50	Octaprenyl diphosphate	5280651	
51	3",6"-Di-O-p-coumaroyltrifolin	131753000	

52	Capsicoside B2	3437856	
53	Kaempferol 3-rutinoside-7-glucuronide	44258841	

54	Upunaphenol B	25082685	
55	Amaranthussaponin III	131753078	

Supplementary Table 3. Gene ontology includes biological processes (BP), cellular components (CC) and molecular functions (MF) of overall targets related to cardiac disease.

Biological processes (BP)				
GO ID	**Description**	**P-value**	**Gene count**	**Associated genes**
GO:0007187	G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger	6.04E-15	12	*OPRL1, ADRA1A, DRD2, DRD1, ADRA2C, ADRB1, ADRA1D, CHRM5, ADRA1B, ADRB2, HTR1A, HTR2B*
GO:0015844	monoamine transport	2.39E-14	9	*SLC6A2, DRD2, DRD1, ADRA2C, ITGB3, CHRM5, MAOB, HTR1A, SLC18A2*
GO:0055074	calcium ion homeostasis	1.88E-10	11	*OPRL1, AVPR1A, ADRA1A, DRD2, DRD1, F2R, TACR1, F2, ADRA1B, HTR2B, EPHX2*
GO:0048871	multicellular organismal homeostasis	8.25E-08	9	*MET, DRD2, DRD1, F2R, ADRB1, ITGB3, CA2, ADRB2, EGFR*
GO:0033555	multicellular organismal response to stress	1.47E-07	5	*SLC6A2, DRD1, TACR1, ADRB1, HTR1A*
GO:0007202	activation of phospholipase C activity	2.16E-07	4	*AVPR1A, ADRA1A, EGFR, HTR2B*
GO:0060402	calcium ion transport into cytosol	2.52E-07	6	*ADRA1A, DRD2, DRD1, F2R, F2, HTR2B*
GO:0060401	cytosolic calcium ion transport	4.02E-07	6	*ADRA1A, DRD2, DRD1, F2R, F2, HTR2B*
GO:0007190	activation of adenylate cyclase activity	5.04E-07	4	*DRD1, ADORA3, ADRB1, ADRB2*
GO:0042417	dopamine metabolic process	5.60E-07	4	*DRD2, DRD1, MAOB, HTR1A*

GO:0015893	drug transport	1.49E-06	6	*SLC6A2, DRD2, DRD1, CA2, CHRM5, SLC18A2*
GO:0007625	grooming behavior	4.35E-06	3	*AVPR1A, DRD2, DRD1*
GO:0032147	activation of protein kinase activity	1.89E-05	6	*DRD2, ADRA2C, F2R, ITGB3, ADRB2, EGFR*
GO:0098664	G protein-coupled serotonin receptor signaling pathway	2.64E-05	3	*CHRM5, HTR1A, HTR2B*
GO:0035690	cellular response to drug	3.36E-05	6	*MET, DRD1, KCNH2, CHRM5, KDR, EGFR*
GO:0060249	anatomical structure homeostasis	8.59E-05	6	*SLC6A2, F2R, ITGB3, CA2, ADRB2, EGFR*
GO:0035264	multicellular organism growth	0.000109	4	*DRD2, ADRB1, AR, ADRB2*
GO:0007588	Excretion	0.000169	3	*AVPR1A, ADRA1A, DRD2*
GO:0006914	Autophagy	0.000172	6	*ADRA1A, MET, DRD2, KDR, ADRB2, HTR2B*
GO:0002024	diet induced thermogenesis	0.000186	2	*ADRB1, ADRB2*
GO:0009914	hormone transport	0.000203	5	*DRD2, ADRA2C, EGFR, HTR1A, TTR*
GO:0042711	maternal behaviour	0.000219	2	*AVPR1A, DRD1*
GO:0007599	Homeostasis	0.000265	5	*PROC, ADRA2C, F2R, F2, ITGB3*
GO:0033604	negative regulation of catecholamine secretion	0.000295	2	*DRD2, ADRA2C*
GO:0008306	associative learning	0.000319	3	*OPRL1, DRD2, DRD1*
GO:0007626	locomotory behaviour	0.00035	4	*OPRL1, DRD2, DRD1, SLC18A2*
GO:0048708	astrocyte differentiation	0.000356	3	*DRD1, F2, EGFR*
GO:0048148	behavioural response to cocaine	0.00053	2	*DRD2, DRD1*
GO:0007631	feeding behaviour	0.00068	3	*OPRL1, DRD2, DRD1*

GO:0007628	adult walking behaviour	0.001123	2	*DRD2, DRD1*
GO:0050482	arachidonic acid secretion	0.001283	2	*ACE, DRD2*
GO:0003382	epithelial cell morphogenesis	0.001543	2	*MET, AR*
GO:0050890	Cognition	0.001569	4	*OPRL1, DRD2, DRD1, EGFR*
GO:0002209	behavioural defence response	0.001925	2	*DRD1, HTR1A*
GO:0007618	Mating	0.002131	2	*AVPR1A, DRD1*
Cellular components (CC)				
GO ID	**Description**	**P-value**	**Gene count**	**Associated genes**
GO:0098691	dopaminergic synapse	1.10E-06	3	*ADRA1A, DRD2, SLC18A2*
GO:0097060	synaptic membrane	4.84E-06	7	*ADRA1A, SLC6A2, DRD2, DRD1, ADRA2C, F2R, CHRM5*
GO:0045121	membrane raft	1.01E-05	6	*ADRA1A, SLC6A2, F2R, KDR, ADRA1B, EGFR*
GO:0098857	membrane microdomain	1.03E-05	6	*ADRA1A, SLC6A2, F2R, KDR, ADRA1B, EGFR*
GO:0045211	postsynaptic membrane	1.17E-05	6	*ADRA1A, DRD2, DRD1, ADRA2C, F2R, CHRM5*
GO:0099699	integral component of synaptic membrane	0.000103	4	*ADRA1A, DRD2, DRD1, ADRA2C*
GO:0098982	GABA-ergic synapse	0.000206	3	*ADRA1A, DRD2, DRD1*
GO:0098978	glutamatergic synapse	0.000229	5	*ADRA1A, DRD2, DRD1, ADRA2C, ITGB3*
GO:0005769	early endosome	0.000233	5	*F2R, ADRB1, KDR, ADRB2, EGFR*
GO:0005901	Caveola	0.000293	3	*ADRA1A, F2R, ADRA1B*
GO:0030665	clathrin-coated vesicle membrane	0.000847	3	*ADRB2, EGFR, SLC18A2*
GO:0043679	axon terminus	0.000936	3	*DRD2, ADRA2C, SLC18A2*
GO:0009925	basal plasma membrane	0.001386	2	*MET, EGFR*
Molecular functions (MF)				

GO ID	Description	P-value	Gene count	Associated genes
GO:0008227	G protein-coupled amine receptor activity	4.63E-18	10	*ADRA1A, DRD2, ADRA2C, ADRB1, ADRA1D, CHRM5, ADRA1B, ADRB2, HTR1A, HTR2B*
GO:0042562	hormone binding	3.30E-05	4	*AVPR1A, AR, EGFR, TTR*
GO:0015378	sodium: chloride symporter activity	0.000141	2	*SLC6A2, SLC18A2*
GO:0043176	amine binding	0.000141	2	*HTR1A, HTR2B*
GO:0051378	serotonin binding	0.000141	2	*HTR1A, HTR2B*
GO:0004714	transmembrane receptor protein tyrosine kinase activity	0.000189	3	*MET, KDR, EGFR*
GO:0031690	adrenergic receptor binding	0.000531	2	*ADRA2C, ADRB1*

Supplementary Table 4. KEGG pathway enrichment of overall targets related to cardiac diseases. ($p<0.01$)

ID	Pathways	P-value	Gene count	Associated genes
hsa04080	Neuroactive ligand-receptor interaction	7.48E-16	17	*OPRL1, AVPR1A, ADRA1A, DRD2, DRD1, ADRA2C, ADORA3, F2R, TACR1, F2, ADRB1, ADRA1D, CHRM5, ADRA1B, ADRB2, HTR1A, HTR2B*
hsa04020	Calcium signaling pathway	4.57E-14	14	*AVPR1A, ADRA1A, MET, DRD1, F2R, TACR1, ADRB1, ADRA1D, CHRM5, KDR, ADRA1B, ADRB2, EGFR, HTR2B*
hsa04022	cGMP-PKG signaling pathway	2.39E-06	7	*ADRA1A, ADRA2C, ADORA3, ADRB1, ADRA1D, ADRA1B, ADRB2*
hsa04540	Gap junction	1.82E-05	5	*DRD2, DRD1, ADRB1, EGFR, HTR2B*
hsa04970	Salivary secretion	2.38E-05	5	*ADRA1A, ADRB1, ADRA1D, ADRA1B, ADRB2*
hsa05030	Cocaine addiction	3.28E-05	4	*DRD2, DRD1, MAOB, SLC18A2*
hsa04015	Rap1 signaling pathway	0.00012	6	*MET, DRD2, F2R, ITGB3, KDR, EGFR*
hsa04024	cAMP signaling pathway	0.000159	6	*DRD2, DRD1, F2R, ADRB1, ADRB2, HTR1A*
hsa04261	Adrenergic signaling in cardiomyocytes	0.000233	5	*ADRA1A, ADRB1, ADRA1D, ADRA1B, ADRB2*

Supplementary Table 5. Drug likeness and ADME prediction of 25 secondary metabolites with various parameters

Compounds	Dipole	QPlogPo/w	QPlogS	QPlogHERG	QPPCaco	QPlogBB	PSA	% Human Oral Absorption	Rule of Five
2-Aminobenzoic acid	4.932	1.501	-0.382	-1.567	97.391	-0.689	71.906	71.323	0
Dopamine	2.682	-0.98	0.379	-4.361	65.474	-0.693	71.935	53.713	0
3-Hydroxy-beta-ionone	4.133	2.134	-2.985	-3.412	1154.019	-0.515	51.601	94.249	0
Subaphylline	4.308	1.117	-1.904	-5.987	55.196	-1.416	96.364	64.663	0
Kaempferol	4.456	1.034	-3.138	-5.175	51.241	-1.887	121.64	63.596	0
Astrophylline	4.881	3.472	-3.925	-5.849	795.575	0.29	41.301	100	0
Moupinamide	5.013	2.834	-4.381	-6.18	278.32	-1.696	91.346	87.294	0
Sarpagine	5.478	2.104	-3.034	-5.276	151.599	-0.382	65.449	78.297	0
Yohimbine	5.592	3.499	-4.731	-5.994	279.299	-0.141	71.642	91.212	0
Aurantiamide	4.625	4.362	-5.381	-6.29	677.717	-1.184	89.318	100	0
Quercetin-3-O-α-rhamnoside	6.762	-0.583	-2.664	-4.772	9.428	-2.879	198.104	15.055	2
Isorhamnetin 3-galactoside	7.338	-0.583	-2.736	-5.211	16.202	-2.981	200.003	19.261	2
Collettiside I	5.25	3.891	-6.749	-5.041	370.204	-1.465	110.95	82.739	1
Asparagoside A	4.203	3.801	-7.027	-5.11	250.24	-1.71	116.646	79.168	1
Agavoside A	4.89	2.886	-6.39	-5.045	137.804	-1.988	143.411	69.174	1
Tribuloside	7.035	0.914	-4.584	-7.176	3.069	-4.445	228.978	2.135	3
Rutin	11.956	-2.419	-2.081	-5.099	1.883	-4.179	269.544	0	3
Forskoditerpenoside B	10.868	0.516	-2.949	-3.727	54.995	-2.206	191.524	35.196	2
Keioside	7.1	-1.744	-2.055	-4.943	5.226	-3.632	256.051	0	3
Capuvosine	2.03	6.444	-8.006	-7.935	82.468	0.129	79.12	73.057	2
Ophiopogonin C'	3.565	2.461	-4.975	-4.595	170.868	-1.952	165.118	42.439	3
3",6"-Di-O-p-coumaroyltrifolin	3.953	2.907	-6.779	-8.674	1.33	-5.674	263.146	7.304	3

Capsicoside B2	7.488	1.674	-6.023	-5.614	30.632	-3.376	196.205	24.472	3
Kaempferol 3-rutinoside-7-glucuronide	9.254	-3.378	-2.222	-4.442	0.035	-6.48	355.563	0	3
Amaranthussaponin III	1.132	-0.242	-4.44	-4.05	0.334	-5.398	315.612	0	3

#QPlogPo/w-octonol/water partition coefficient; QPlogS-Predicted aqueous solubility; QPlogHERG-Predicted IC_{50} value for blockage of HERG K+ channels; QPPCaco Predicted Caco-2 cell permeability in nm/s; QPlogBB-Predicted brain/blood partition coefficient; PSA-Polar surface area; % Human oral absorption-Percentage of human oral absorption; Rule of five-Number of violation to Lipinski's rule of five

Supplementary Table 6. Binding sites with site score and D-score values predicted by sitemap for hub targets

Sl No.	Hub targets	Top site score	Top D-score	Binding site residues
1	TACR1	1.059	1.105	Chain A: 89, 92, 93, 96, 108, 109, 112, 113, 116, 165, 181, 182, 183, 184, 185, 186, 187, 190, 191, 192, 193, 194, 196, 197, 200, 201, 204, 261, 264, 265, 267, 268, 271, 272, 280, 283, 284, 287, 291
2	CHRM5	1.166	1.229	Chain A: 79, 87, 90, 91, 95, 106, 107, 110, 111, 114, 115, 118, 162, 182, 183, 184, 185, 188, 189, 190, 191, 194, 197, 198, 201, 202, 455, 458, 459, 462, 465, 470, 471, 472, 473, 474, 477, 478, 481, 484, 485
3	F2R	1.095	1.15	Chain A: 95, 162, 183, 187, 229, 233, 234, 236, 237, 240, 255, 256, 257, 258, 260, 261, 262, 263, 264, 265, 267, 268, 269, 270, 271, 274, 332, 333, 336, 337, 338, 340, 341, 342, 343, 344, 345, 349, 350, 352, 353, 354, 3004
4	F2	1.060	1.080	Chain H: 57, 60A, 60C, 60D, 96, 97, 97A, 98, 99, 146, 174, 189, 190, 191, 192, 195, 213, 214, 215, 216, 217, 219, 220, 221, 221A, 224, 226, 2236, 2252, 2275, 2276
5	ADRA1B	1.088	1.123	Chain A: 76, 78, 80, 81, 84, 139, 143, 146, 150, 151, 153, 154, 285, 288, 289, 291, 292, 293, 295, 296, 348, 351, 352, 353, 354, 355
6	HTR2B	1.153	1.197	Chain A: 110, 111, 113, 114, 117, 118, 119, 120, 121, 122, 131, 132, 135, 136, 139, 140, 143, 186, 206, 207, 208, 209, 210, 211, 212, 214, 215, 217, 218, 221, 222, 225, 337, 340, 341, 344, 347, 348, 355, 359, 362, 363, 366, 367, 370, 2020
7	ADRA1A	1.122	1.175	Chain A: 57, 61, 62, 65, 68, 117, 120, 124, 127, 128, 131, 134, 207, 266, 267, 269, 270, 271, 273, 274, 277, 280, 281, 318, 322, 325, 326, 329, 330, 331, 332, 333
8	AVPR1A	1.078	1.044	Chain B: 25, 26, 27, 28, 29, 53, 54, 55, 56, 57, 58, 59, 75, 76, 77, 79, 80, 125, 167, 168, 169, 170, 244, 276, 344, 351, 354, 355, 358, 534, 622, 740, 815, 1034
9	ADRA1D	1.2	1.236	Chain A: 169, 170, 173, 174, 176, 177, 180, 181, 184, 227, 231, 232, 236, 247, 248, 249, 254, 255, 258, 262, 357, 361, 364, 365, 368, 388

Supplementary Table 7. Molecular docking of co-crystallized ligands with hub targets

Hub target: TACR1 (PDB ID: 6HLP)			
Sl No.	**Ligand number**	**Co-crystallized ligand**	**Docking score**
1	12	1-Oleoyl-R-glycerol (OLC-A-1513)	-8.146
2	38	1-Oleoyl-R-glycerol (OLC-A-1539)	-6.991
3	13	1-Oleoyl-R-glycerol (OLC-A-1514)	-6.991
4	14	1-Oleoyl-R-glycerol (OLC-A-1515)	-6.991
5	11	1-Oleoyl-R-glycerol (OLC-A-1512)	-6.8
6	15	1-Oleoyl-R-glycerol (OLC-A-1516)	-6.477
7	11	1-Oleoyl-R-glycerol (OLC-A-1512)	-6.252
8	39	1-Oleoyl-R-glycerol (OLC-A-1540)	-5.933
9	1	2-[3,5-bis(trifluoromethyl)phenyl]-~{N},2-dimethyl-~{N}-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl) pyridin-3-yl] propenamide (GAW-A-1501)	-5.799
10	38	1-Oleoyl-R-glycerol (OLC-A-1539)	-5.328
11	13	1-Oleoyl-R-glycerol (OLC-A-1514)	-5.328
12	3	Oleic acid (OLA-A-1504)	-5.238

13	4	Oleic acid (OLA-A-1505)	-4.906
14	39	1-Oleoyl-R-glycerol (OLC-A-1540)	-4.313
15	15	1-Oleoyl-R-glycerol (OLC-A-1516)	-4.204
16	10	Oleic acid (OLA-A-1511)	-3.866
17	20	Di(hydroxyethyl)ether (PEG-A-1521)	-3.465
18	21	Di(hydroxyethyl)ether (PEG-A-1522)	-3.465
19	22	Di(hydroxyethyl)ether (PEG-A-1523)	-3.465
20	23	Di(hydroxyethyl)ether (PEG-A-1524)	-3.465
21	24	Di(hydroxyethyl)ether (PEG-A-1525)	-3.465
22	25	Di(hydroxyethyl)ether (PEG-A-1526)	-3.465
23	26	Di(hydroxyethyl)ether (PEG-A-1527)	-3.465
24	27	Di(hydroxyethyl)ether (PEG-A-1528)	-3.465
25	28	Di(hydroxyethyl)ether (PEG-A-1529)	-3.465
26	29	Di(hydroxyethyl)ether (PEG-A-1530)	-3.465
27	16	Di(hydroxyethyl)ether (PEG-A-1517)	-3.465
28	17	Di(hydroxyethyl)ether (PEG-A-1518)	-3.465
29	18	Di(hydroxyethyl)ether	-3.465

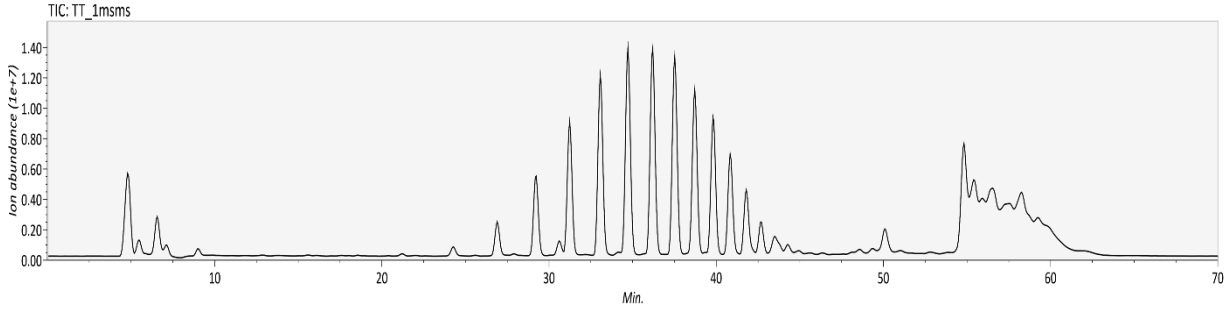
		(PEG-A-1519)	
30	19	Di(hydroxyethyl)ether (PEG-A-1520)	-3.465
31	30	Di(hydroxyethyl)ether (PEG-A-1531)	-3.465
32	31	Di(hydroxyethyl)ether (PEG-A-1532)	-3.465
33	32	Di(hydroxyethyl)ether (PEG-A-1533)	-3.465
34	33	Di(hydroxyethyl)ether (PEG-A-1534)	-3.465
35	34	Di(hydroxyethyl)ether (PEG-A-1535)	-3.465
36	40	Di(hydroxyethyl)ether (PEG-A-1541)	-3.465
37	41	Di(hydroxyethyl)ether (PEG-A-1542)	-3.465
38	35	Di(hydroxyethyl)ether (PEG-A-1536)	-3.465
39	36	Di(hydroxyethyl)ether (PEG-A-1537)	-3.465
40	37	Di(hydroxyethyl)ether (PEG-A-1538)	-3.465
41	2	Oleic acid (OLA-A-1503)	-3.41
42	8	Oleic acid (OLA-A-1509)	-3.383
43	7	Oleic acid (OLA-A-1508)	-3.293
44	5	Oleic acid (OLA-A-1506)	-3.12
45	1	2-[3,5-bis(trifluoromethyl)phenyl]-	-2.974

		~{N},2-dimethyl-~{N}-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl) pyridin-3-yl] propenamide (GAW-A-1501)	
46	9	Oleic acid (OLA-A-1510)	-2.754
47	1	2-[3,5-bis(trifluoromethyl)phenyl]-~{N},2-dimethyl-~{N}-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl) pyridin-3-yl] propenamide (GAW-A-1501)	-2.423
48	1	2-[3,5-bis(trifluoromethyl)phenyl]-~{N},2-dimethyl-~{N}-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl) pyridin-3-yl] propenamide (GAW-A-1501)	-2.148
49	6	Oleic acid (OLA-A-1507)	-1.743
Hub target: CHRM5 (PDB ID: 6OL9)			
Sl No.	**Ligand number**	**Co-crystallized ligand**	**Docking score**
1	3	Tiotropium (0HK-A-1203)	-14.336
2	3	Tiotropium (0HK-A-1203)	-14.138
3	3	Tiotropium (0HK-A-1203)	-13.941
4	3	Tiotropium (0HK-A-1203)	-13.785

5	5	1-Oleoyl-R-glycerol (OLC-A-1205)	-11.925
6	5	1-Oleoyl-R-glycerol (OLC-A-1205)	-10.201
7	2	Oleic acid (OLA-A-1202)	-7.512
8	4	3,6,9,12,15,18-Hexaoxaicosane-1,20-diol (P33-A-1204)	-6.272
9	1	Oleic acid (OLA-A-1201)	-5.426
Hub target: F2R (PDB ID: 3VW7)			
Sl No.	**Ligand number**	**Co-crystallized ligand**	**Docking score**
1	2	1-Oleoyl-R-glycerol (OLC-A-2002)	-12.823
2	10	1-Oleoyl-R-glycerol (OLC-A-2010)	-12.823
3	3	1-Oleoyl-R-glycerol (OLC-A-2003)	-12.823
4	4	1-Oleoyl-R-glycerol (OLC-A-2004)	-12.823
5	5	1-Oleoyl-R-glycerol (OLC-A-2005)	-12.823
6	7	1-Oleoyl-R-glycerol (OLC-A-2007)	-12.823
7	9	1-Oleoyl-R-glycerol (OLC-A-2009)	-12.823
8	2	1-Oleoyl-R-glycerol (OLC-A-2002)	-12.787
9	10	1-Oleoyl-R-glycerol (OLC-A-2010)	-12.787
10	3	1-Oleoyl-R-glycerol (OLC-A-2003)	-12.787

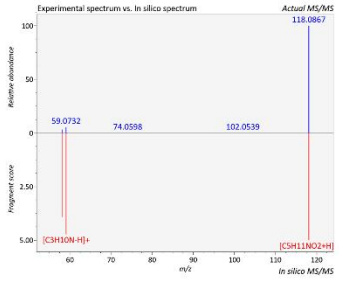
11	4	1-Oleoyl-R-glycerol (OLC-A-2004)	-12.787
12	5	1-Oleoyl-R-glycerol (OLC-A-2005)	-12.787
13	6	1-Oleoyl-R-glycerol (OLC-A-2006)	-12.787
14	7	1-Oleoyl-R-glycerol (OLC-A-2007)	-12.787
15	8	1-Oleoyl-R-glycerol (OLC-A-2008)	-12.787
16	9	1-Oleoyl-R-glycerol (OLC-A-2009)	-12.787
17	1	Vorapaxar (VPX-A-2001)	-11.031
18	1	Vorapaxar (VPX-A-2001)	-10.905
Hub target: AVPR1A (PDB ID: 1YTV)			
Sl No.	**Ligand number**	**Co-crystallized ligand**	**Docking score**
1	2	Composite ligand, containing glucose (GLC-D-1)	-14.618
2	1	Composite ligand, containing glucose (GLC-C-1)	-14.618

Supplementary Figure 1. Total ion chromatogram of HPLC-QTOF-MS/MS for *Tribulus terrestris* L. plant extract in positive ionization mode

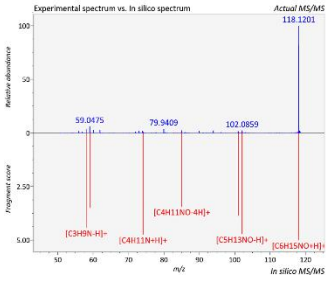


Supplementary Figure 2. Spectra matching of putative compounds from *Tribulus terrestris* L. using MS-DIAL integrated MS-Finder software.

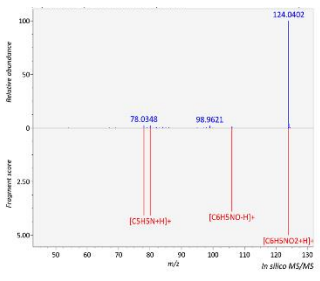
Betaine
(m/z: 118.08)



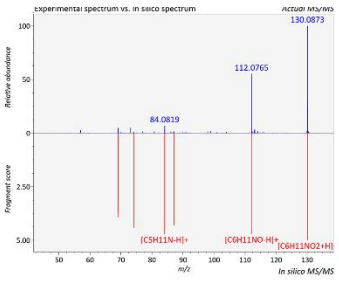
2-Diethylaminoethanol
(m/z: 118.12)



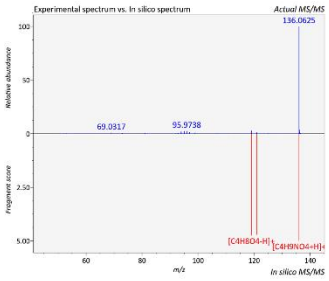
Nicotinic acid
(m/z: 124.04)



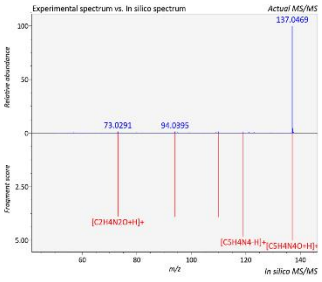
Pipecolic acid
(m/z: 130.08)



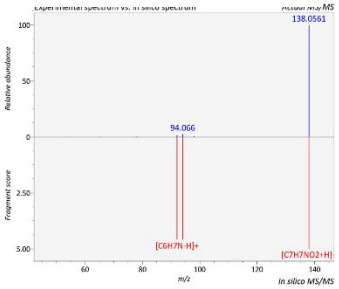
(+)-threo-2-Amino-3,4-dihydroxybutanoic acid
(m/z: 136.06)



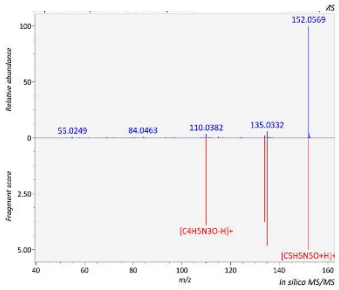
Hypoxanthine
(m/z: 137.04)



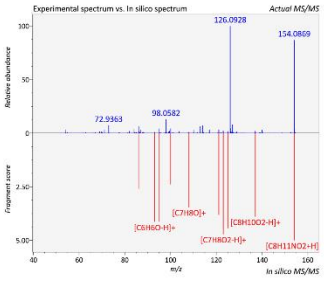
2-aminobenzoic acid
(m/z: 138.05)



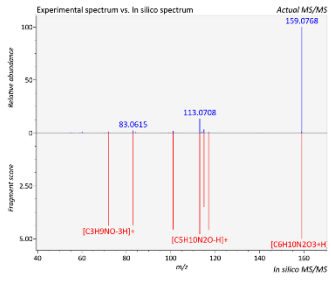
Guanine
(m/z: 152.05)



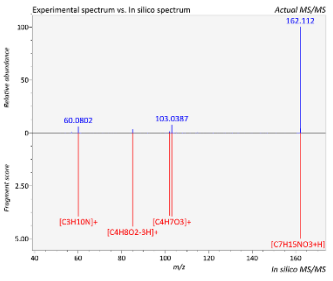
Dopamine
(m/z: 154.08)



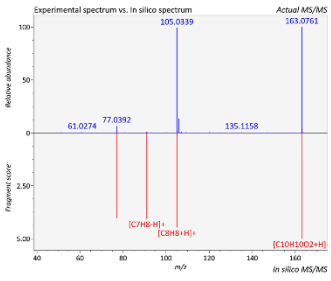
5-hydroxyectoine
(m/z: 159.07)



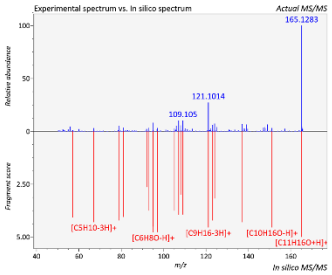
L-carnitine
(m/z: 162.11)



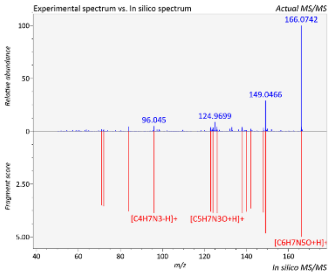
Methyl cinnamate
(m/z: 163.07)



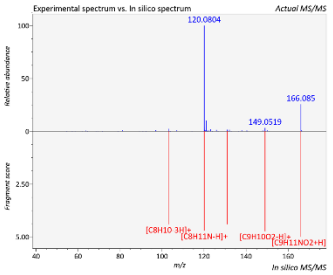
Trans-jasmone
(m/z: 165.12)



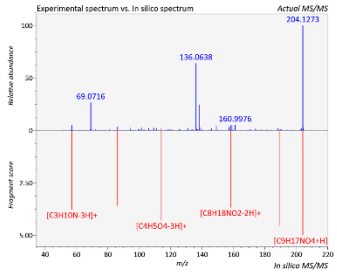
7-Methylguanine
(m/z: 166.07)



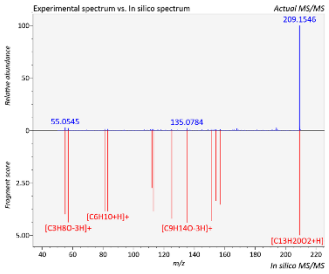
Phenylalanine
(m/z: 166.08)



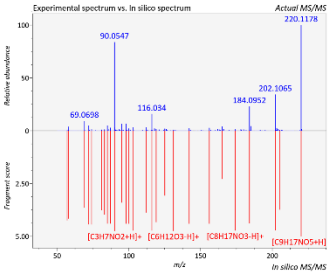
L-Acetylcarnitine
(m/z: 204.12)



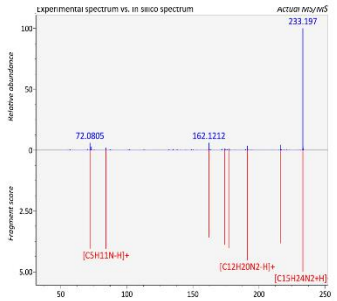
3-Hydroxy-beta-ionone
(m/z: 209.15)



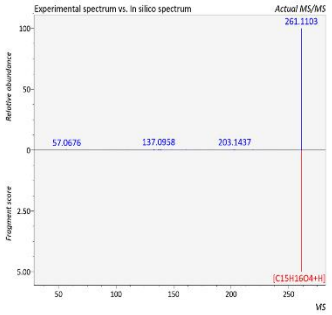
Pantothenic acid
(m/z: 220.11)



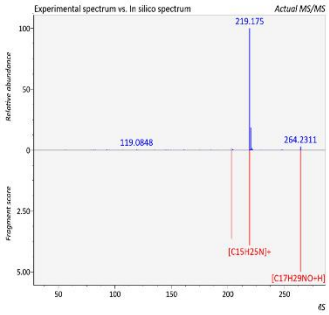
Aloperine
(m/z: 233.19)



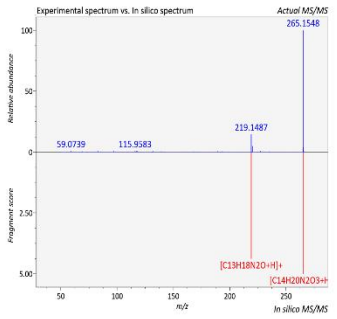
Hemigossypol
(m/z: 261.11)



Victoxinine
(m/z: 264.23)



Subaphylline
(m/z: 265.15)



Kaempferol
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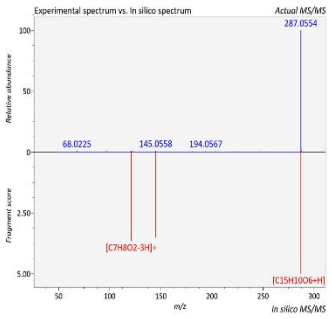
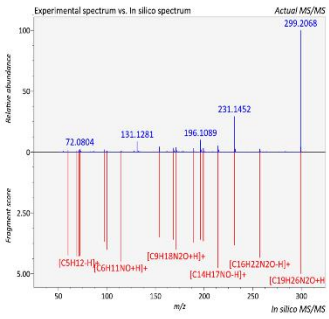
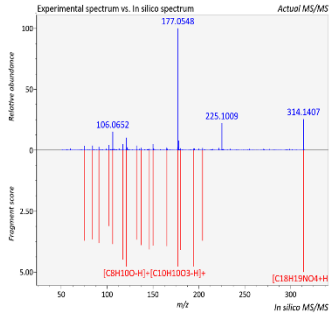


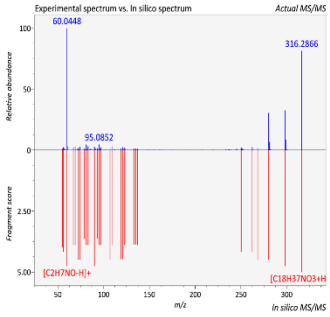
Astrophylline
(m/z: 299.20)



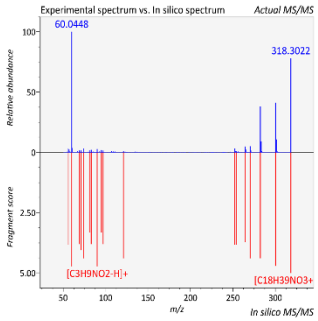
Moupinamide
(m/z: 314.14)



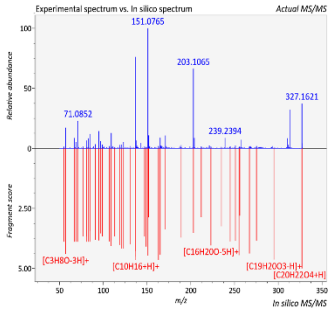
Dehydrophytosphingosine
(m/z: 316.28)



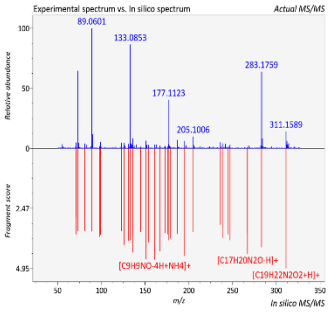
Phytosphingosine
(m/z: 318.30)



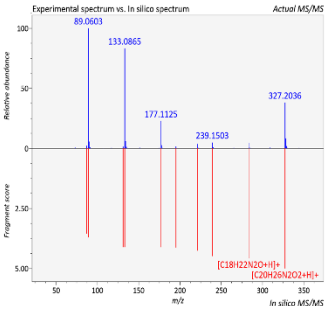
Uncinatone
(m/z: 327.16)



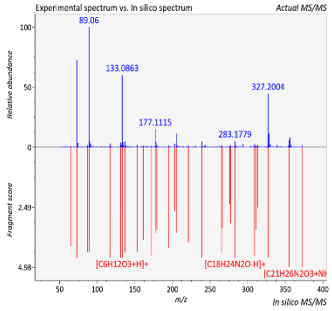
Sarpagine
(m/z: 328.19)



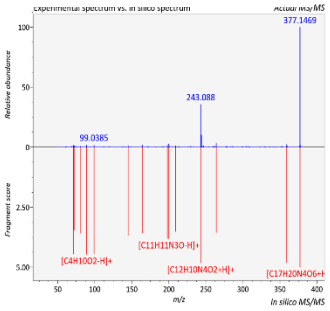
Ajmaline
(m/z: 344.23)



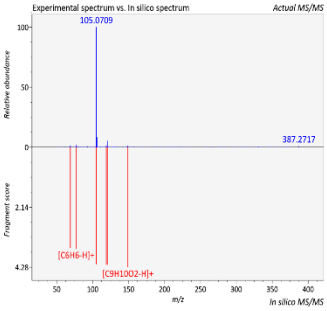
Yohimbine
(m/z: 372.22)



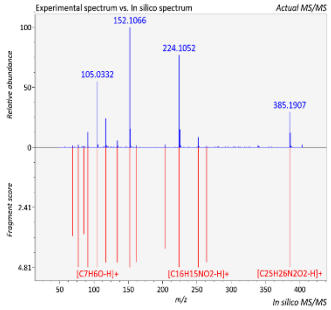
Riboflavin
(m/z: 377.14)



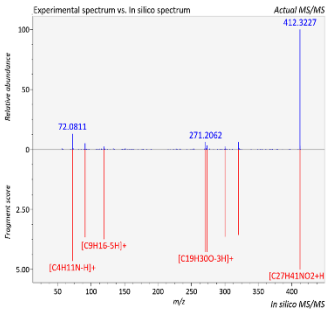
Gingerenone B
(m/z: 387.18)



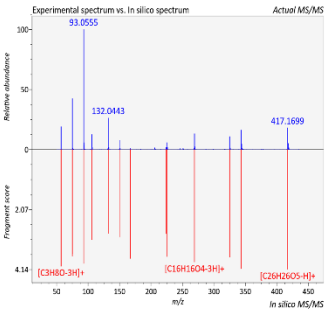
Aurantiamide
(m/z: 403.20)



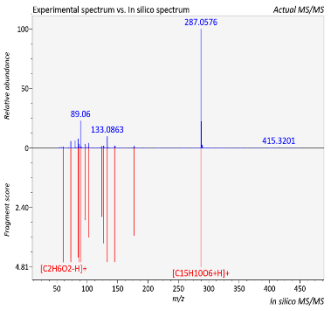
Cyclopamine
(m/z: 412.32)



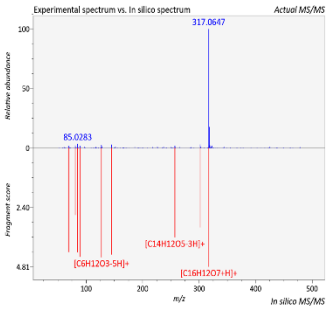
Auriculin
(m/z: 435.17)



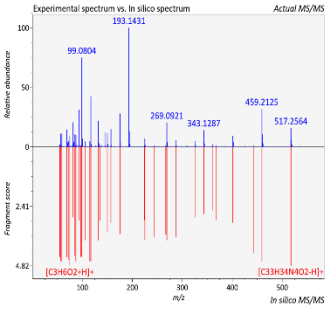
Quercetin-3-O-α-rhamnoside
(m/z: 449.11)



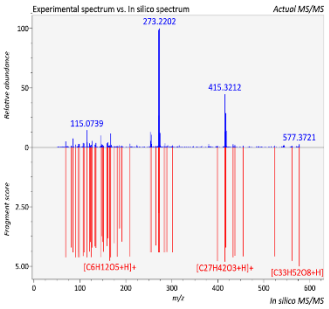
Isorhamnetin 3-galactoside
(m/z: 479.12)



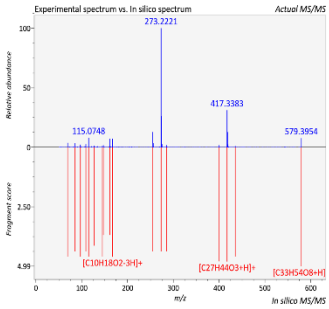
Pyrophaephorbide a
(m/z: 535.36)



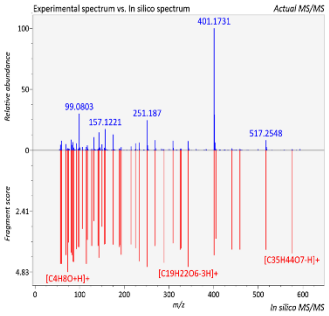
Collettiside I
(m/z: 577.37)



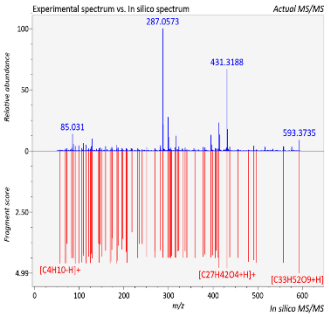
Asparagoside A
(m/z: 579.39)



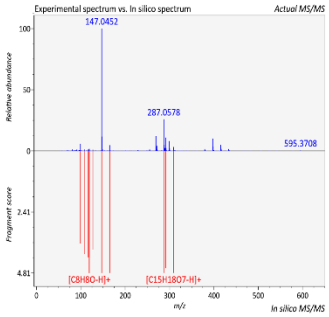
Yungensin F
(m/z: 593.31)



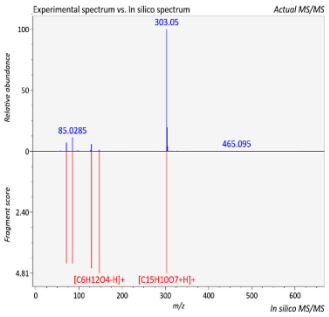
Agavoside A
(m/z: 593.37)



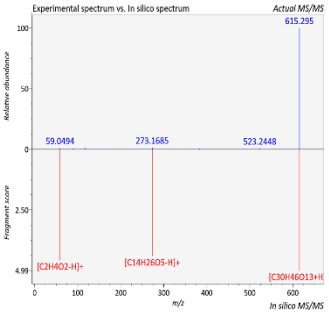
Tribuloside
(m/z: 595.15)



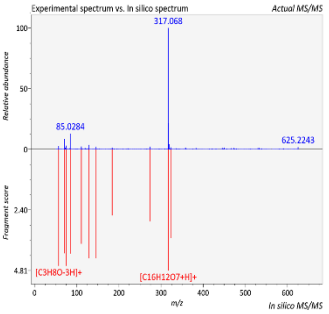
Rutin
(m/z: 611.16)



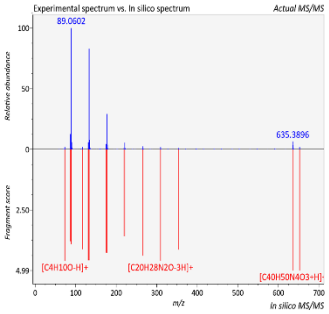
Forskoditerpenoside B
(m/z: 615.29)



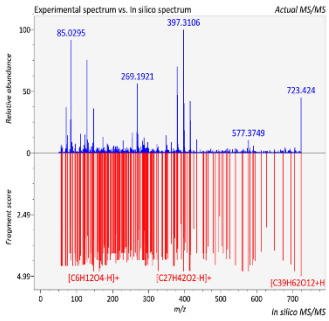
Keioside
(m/z: 625.18)



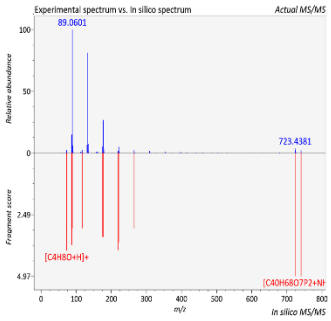
Capuvosine
(m/z: 652.41)



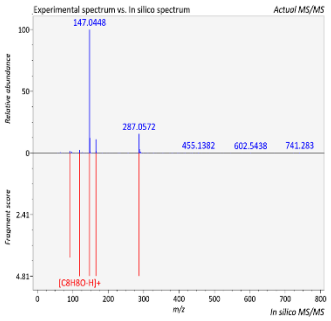
Ophiopogonin C’
(m/z: 723.44)



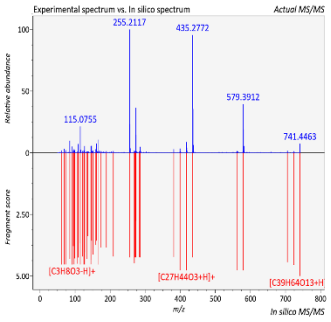
Octaprenyl diphosphate
(m/z: 740.46)



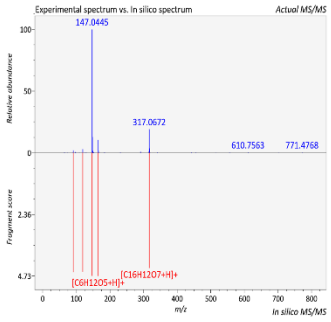
3”,6”-Di-O-p-coumaroyltrifolin
(m/z: 741.18)



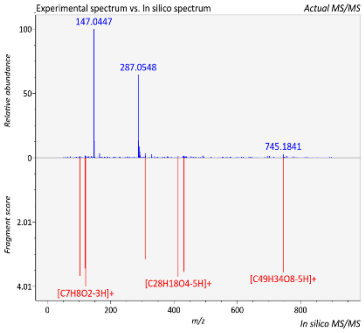
Capsicoside B2
(m/z: 741.44)



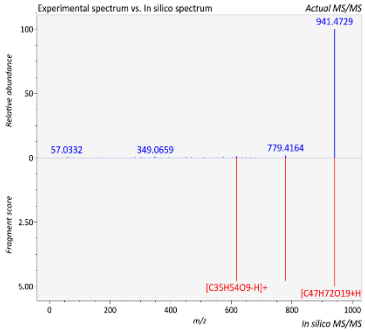
Kaempferol 3-rutinoside-7-glucoronide
(m/z: 771.19)



Upunaphenol B
(m/z: 903.23)

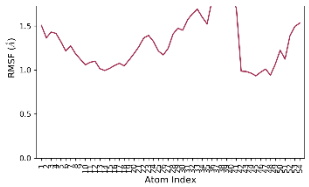


Amaranthussaponin III
(m/z: 941.47)

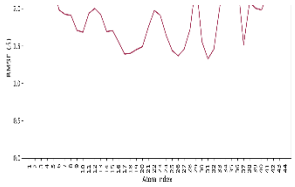


Supplementary Figure 3. (A) RMSF plots for top three hit ligands against different hub target proteins (TACR1, CHRM5, F2R, F2).

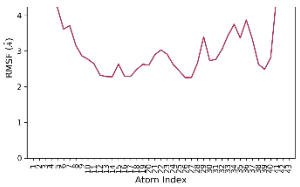
Complex 1A. TACR1 with Kaempferol 3-rutinoside 7-glucoronide



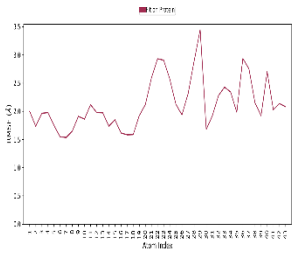
Complex 1B. TACR1 with Keioside



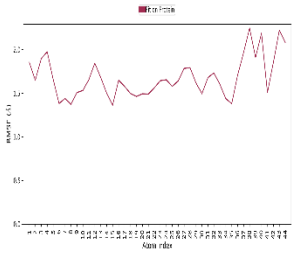
Complex 1C. TACR1 with Rutin



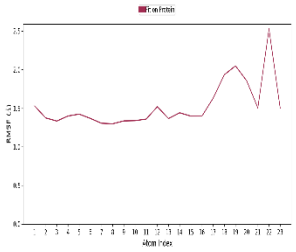
Complex 2A. CHRM5 with Rutin



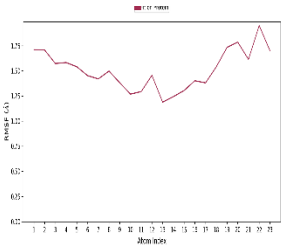
Complex 2B. CHRM5 with Keioside



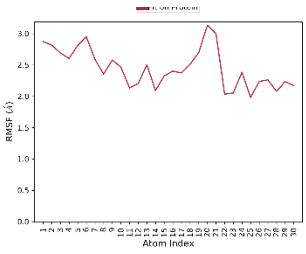
Complex 2C. CHRM5 with Moupinamide



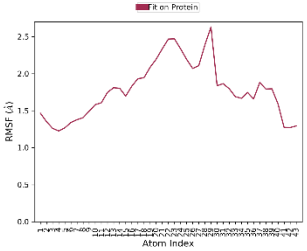
Complex 3A. F2R with Moupinamide



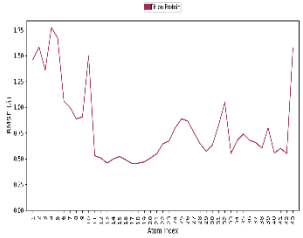
Complex 3B. F2R with Aurantiamide



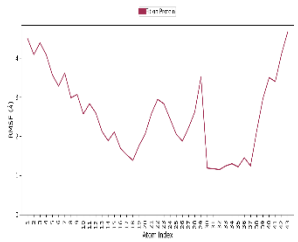
Complex 3C. F2R with Rutin



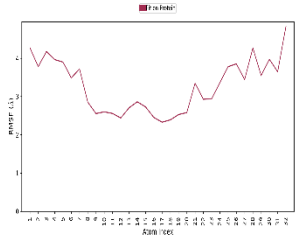
Complex 4A. F2 with Tribuloside



Complex 4B. F2 with Rutin

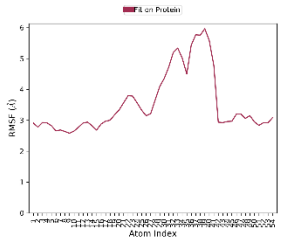


Complex 4C. F2 with Quercetin-3-O-α-rhamnoside

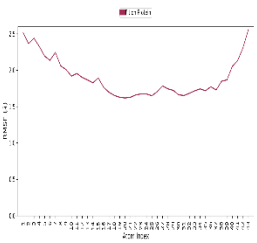


Supplementary Figure 3. (B) RMSF plots for top three hit ligands against different hub target proteins (ADRA1B, HTR2B, ADRA1A, AVPR1A)

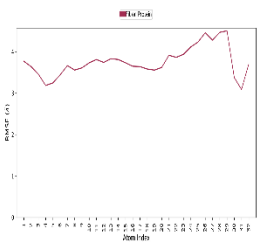
Complex 5A. ADRA1B with Kaempferol 3-rutinoside 7-glucoronide



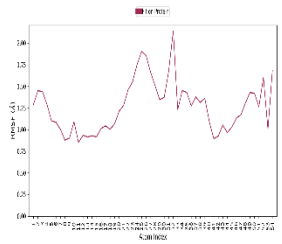
Complex 5B. ADRA1B with Rutin



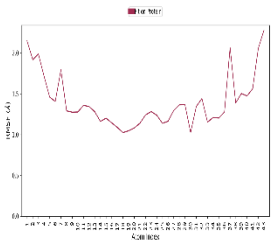
Complex 5C. ADRA1B with Quercetin-3-O-α-rhamnoside



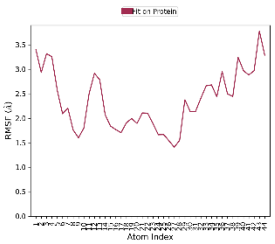
Complex 6A. HTR2B with 3’’,6’’-Di-O-p-coumaroyltrifolin



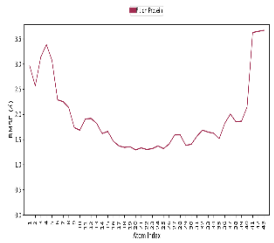
Complex 6B. HTR2B with Rutin



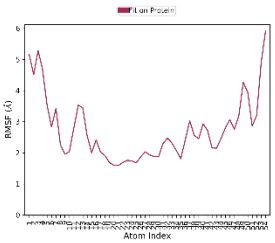
Complex 6C. HTR2B with Keioside



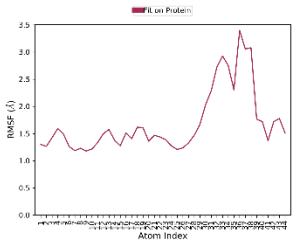
Complex 7A. ADRA1A with Rutin



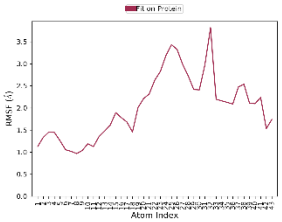
Complex 7B. ADRA1A with Kaempferol 3-rutinoside 7-glucoronide



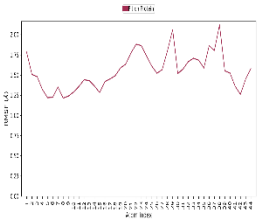
Complex 7C. ADRA1B with Keioside



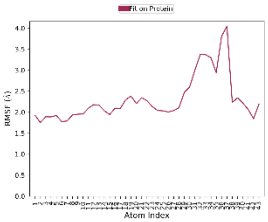
Complex 8A. AVPR1A with Tribuloside



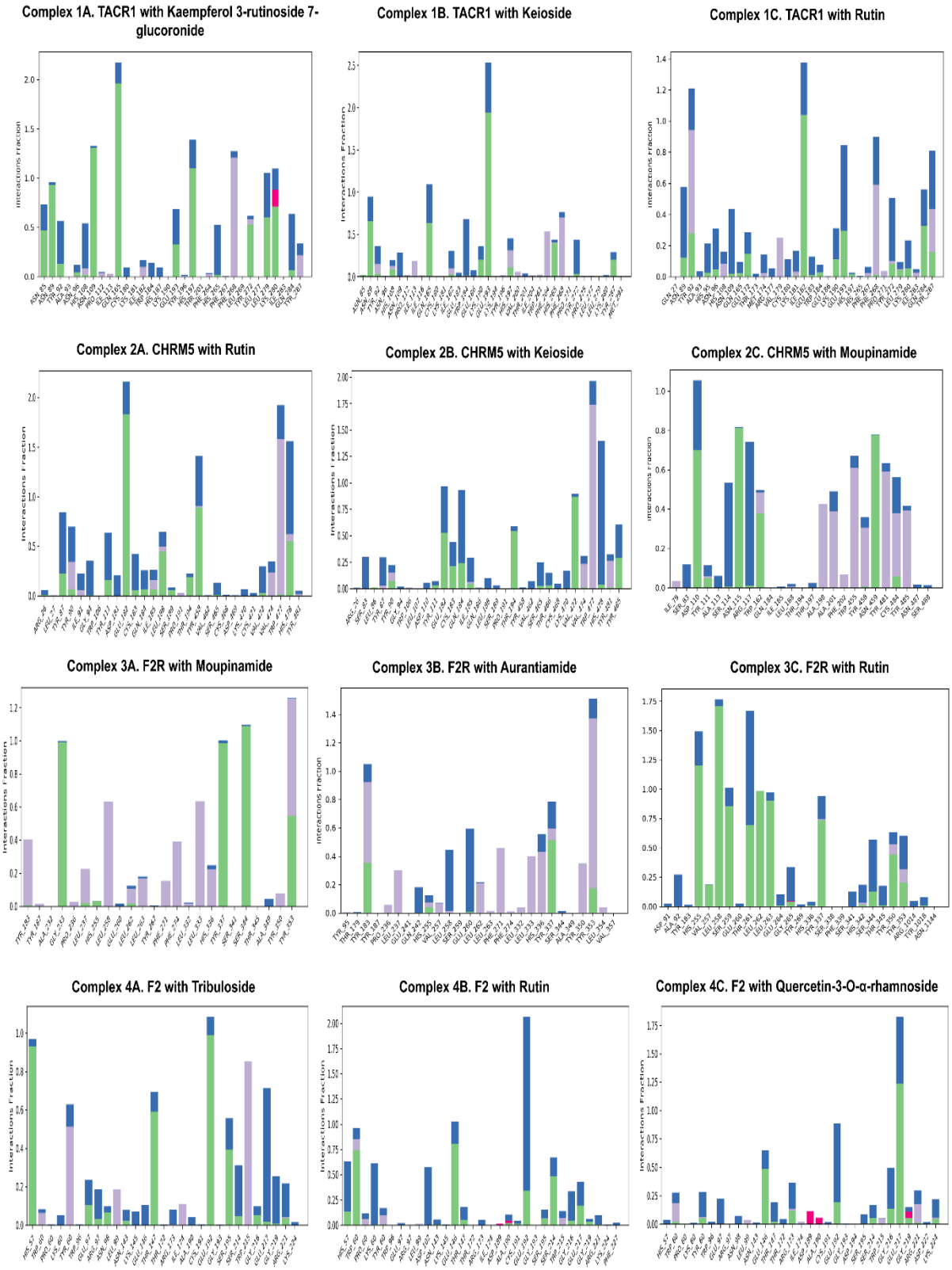
Complex 8B. AVPR1A with Keioside



Complex 8C. AVPR1A with Rutin



Supplementary Figure 4. (A) Protein-ligand interaction plot for top three hit ligands against different hub target proteins (TACR1, CHRM5, F2R, F2).



Supplementary Figure 4. (B) Protein-ligand interaction plot for top three hit ligands against different hub target proteins (ADRA1B, HTR2B, ADRA1A, AVPR1A)