

SUPPORTING INFORMATION

Discovery of Guanfacine as a novel TAAR1 agonist: a combination strategy through molecular modeling studies and biological assays

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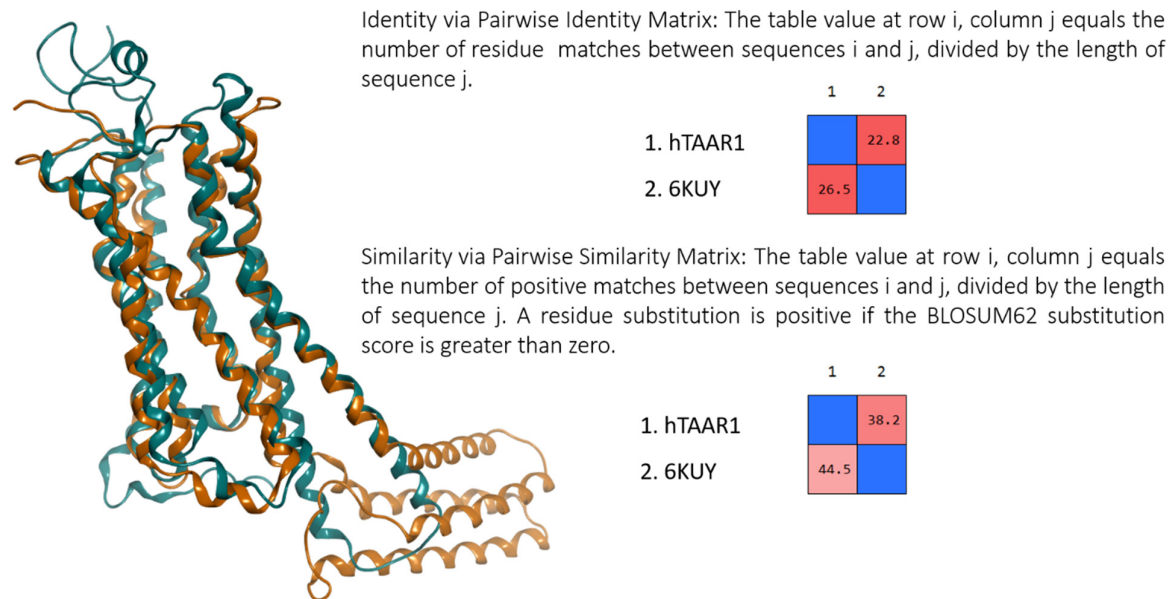


Figure S1. Pairwise Percentage Residue Identity (PPRI) and Similarity values as obtained by the *h*TAAR1 (shown as green ribbon) and α_2 -ADR (shown as gold ribbon) superposition.

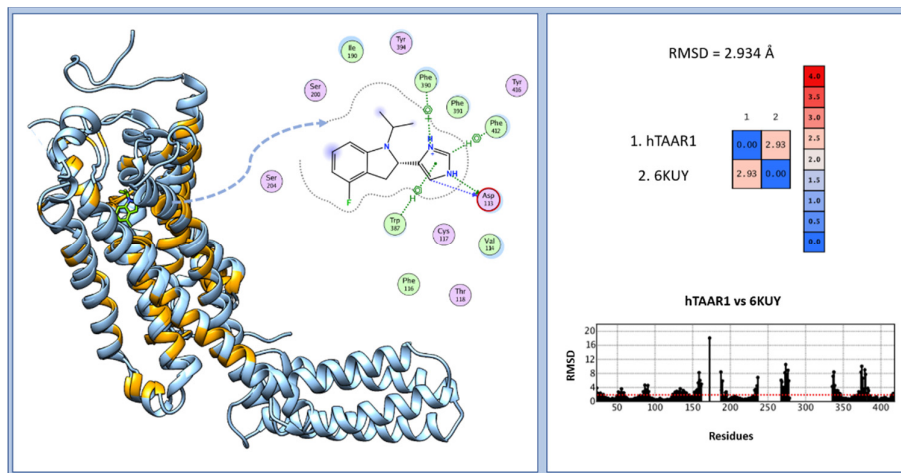


Figure S2. Superimposition of the hTAAR1 model and of the X-ray data about α_2 -ADR (left); the corresponding RMSD values are also reported (right).

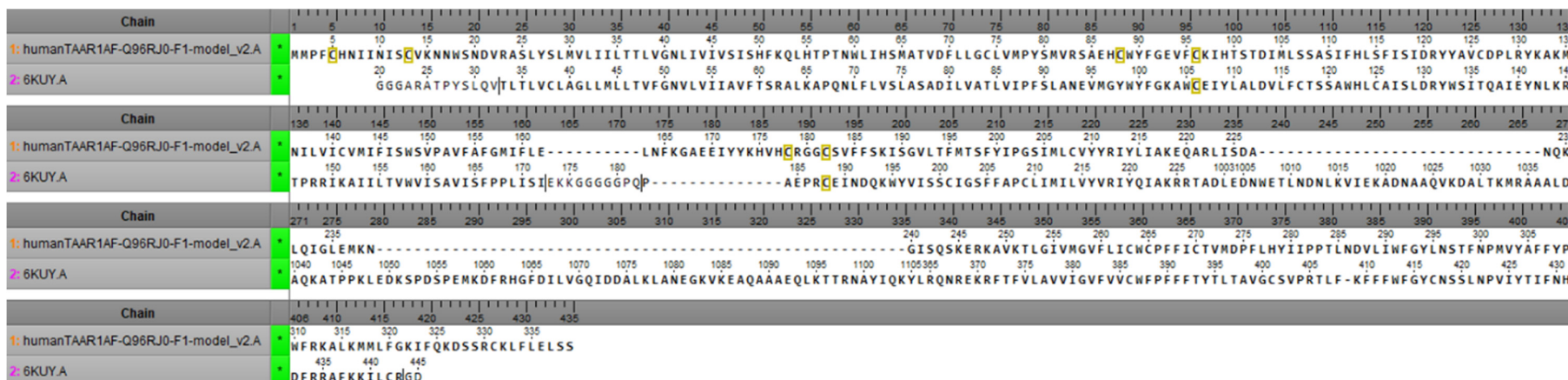


Figure S3. Alignment of the hTAAR1 and α_2 -ADR protein sequence.

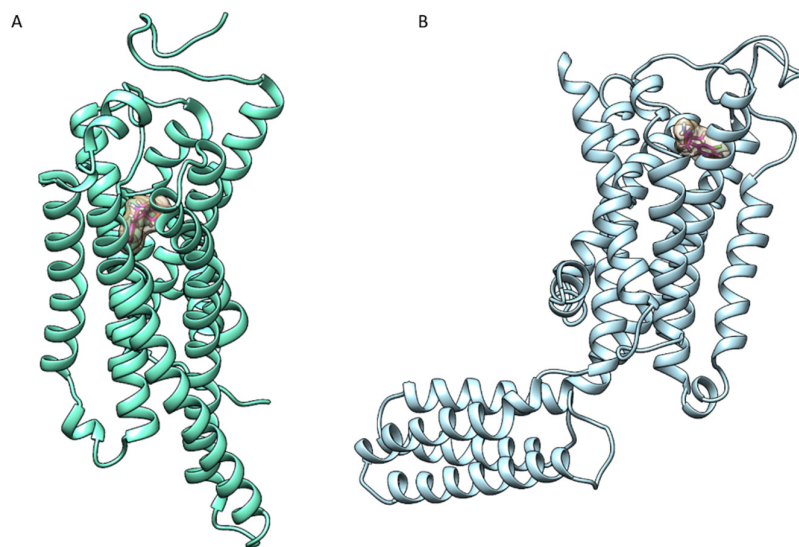


Figure S4. Full-view of the dual *h*TAAR1 (green) and α_2 -ADR (cyan) agonist **S18616** at the whole proteins. Ligand volume is highlighted in light brown.

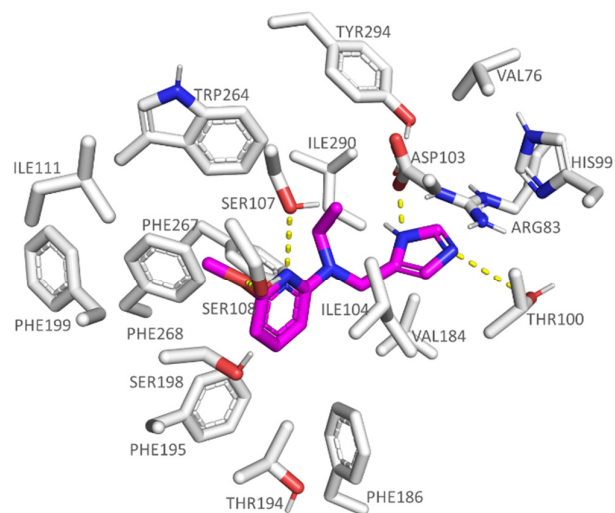


Figure S5. Docking positioning of **37** (C atom; magenta) at the *h*TAAR1 binding site. The most important residues involved in the agonist binding are labelled.

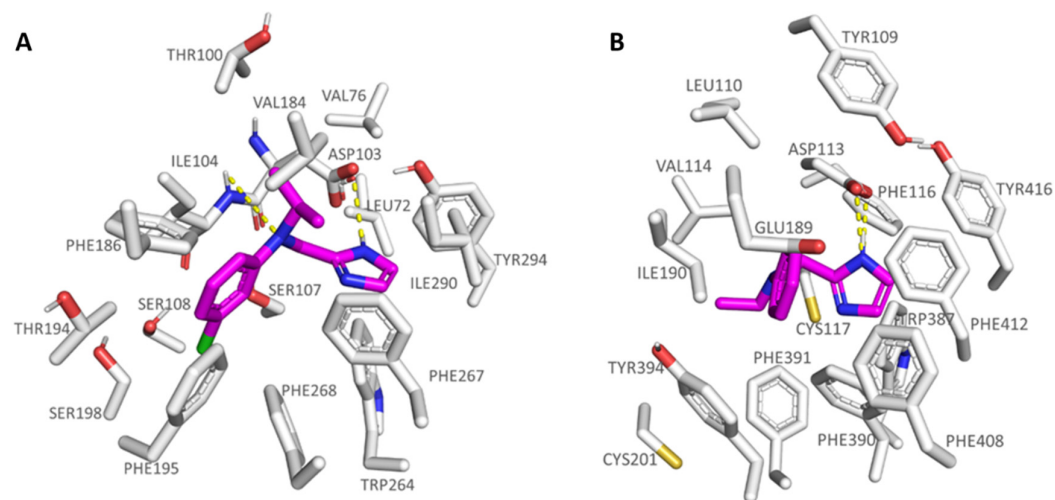


Figure S6. Docking positioning of **53** (C atom; magenta) at the *hTAAR1* binding site (A) and of **51** at the α_2 -ADR cavity (B). The most important residues involved in the agonist binding are labelled.

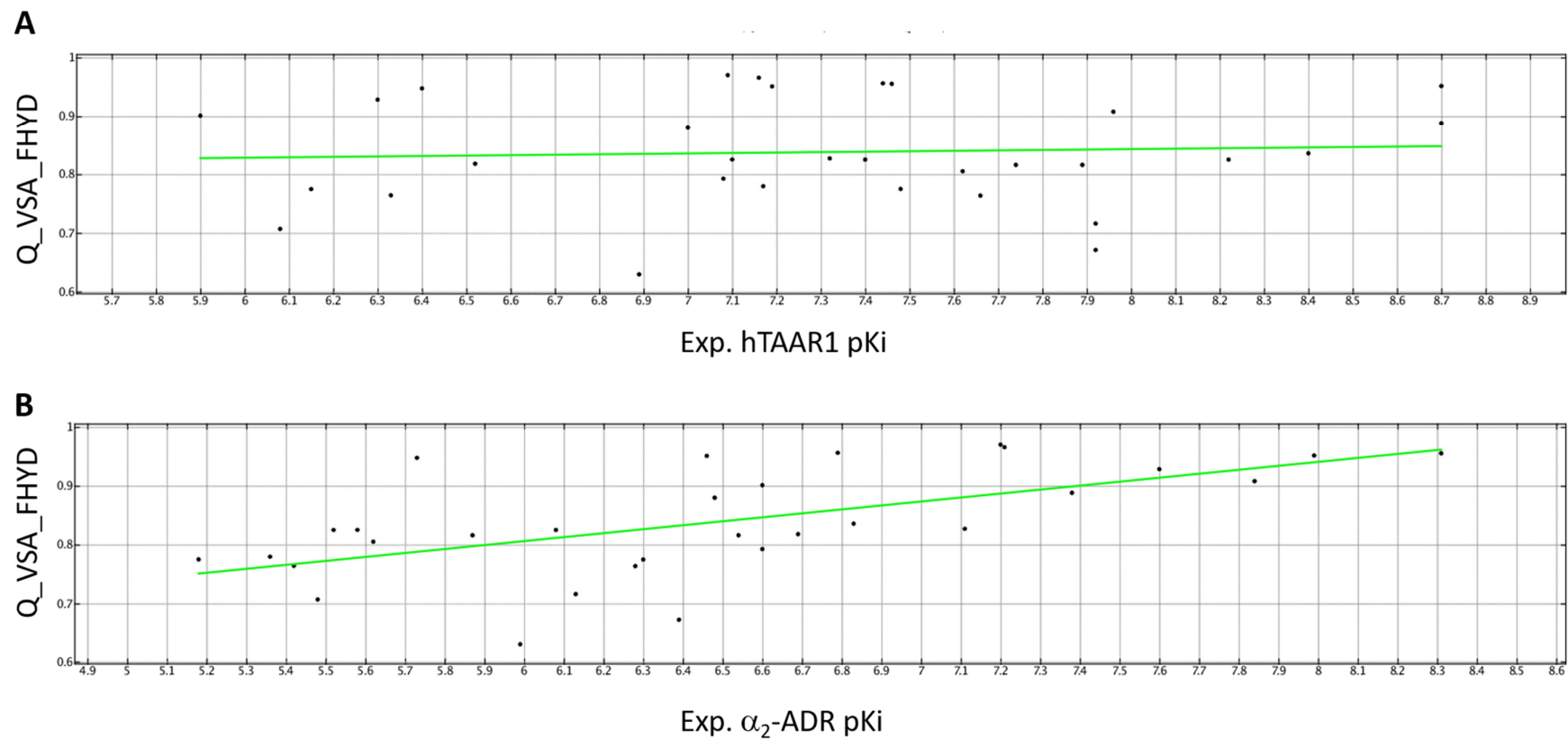


Figure S7. Schematic representation of the opposite role played by the Q_VSA_FHYD descriptor, shared by both models A and B, to influence the compound (*h*TAAR1 and α_2 -ADR) binding affinity values. Compounds are represented as dots.

Table S1. Five top scored docking positioning of **5a-5e**, **6a-6e**, **11-54** and the reference agonist **S18616** at the *h*TAAR1 (MOE software). The predicted ΔG value of each protein-ligand complex has been reported, as calculated in terms of final scoring function (S, as Kcal/mol).

Compound	S	E_conf	E_place	E_score1	E_refine	E_score2
5a	-5.1695	-18.2208	-15.3929	-7.7987	-11.6232	-5.1695
5a	-4.9402	-21.9155	-11.5622	-8.0304	-12.1832	-4.9402
5a	-4.7778	-21.0637	-16.6175	-7.5495	-18.4062	-4.7778
5a	-4.7573	-18.8261	-20.1722	-9.0459	-5.1190	-4.7573
5a	-4.5663	-14.8291	-15.6946	-8.0510	4.8254	-4.5663
5b	-5.7383	-14.1695	-19.3227	-7.0323	-4.9471	-5.7383
5b	-5.6052	-22.5438	-11.9454	-8.6970	-8.4442	-5.6052
5b	-5.5773	-23.7832	-22.1466	-8.3987	-10.3642	-5.5773
5b	-5.5106	-29.2996	-20.4277	-7.0394	-2.9662	-5.5106
5b	-5.4926	-12.3069	-17.7338	-7.0887	-7.1517	-5.4926
5c	-5.6357	-20.9581	-18.7912	-9.5620	-10.2463	-5.6357
5c	-5.5748	-25.0866	-14.4636	-9.5479	-11.3133	-5.5748
5c	-5.4536	-22.7922	-15.5140	-7.7365	3.8596	-5.4536
5c	-5.4508	-26.8145	-15.4513	-9.1423	-3.7877	-5.4508
5c	-5.4337	-20.2956	-15.6781	-8.1212	-7.7924	-5.4337
5d	-6.2309	-4.6525	-23.8586	-5.9309	-2.8928	-6.2309
5d	-6.2308	7.4696	-22.6422	-7.1454	13.1086	-6.2308
5d	-6.2161	-2.9400	-15.1797	-6.7809	1.6499	-6.2161
5d	-6.1771	-15.4006	-14.3756	-7.1999	8.1803	-6.1771
5d	-6.1644	-15.2244	-17.2960	-6.3838	3.0907	-6.1644
5e	-7.2043	6.5957	-16.4140	-4.6198	31.5089	-7.2043

5e	-5.9711	3.6161	-17.3355	-6.5913	16.9221	-5.9711
5e	-5.7338	-3.1095	-20.2515	-3.8649	25.5717	-5.7338
5e	-5.6962	15.5878	-27.9443	-6.8042	21.7943	-5.6962
5e	-5.6800	10.5990	-12.9053	-4.0603	24.0279	-5.6800
5f	-9.0759	84.1545	-20.2790	-6.3740	18.1892	-9.0759
5f	-8.6927	83.6578	-15.7717	-4.9193	5.3773	-8.6927
5f	-8.6000	86.7519	-13.4784	-5.8091	-0.5324	-8.6000
5f	-8.2305	99.6059	-25.1957	-6.6039	21.3119	-8.2305
5f	-8.0835	89.5961	-19.5672	-5.9362	11.4194	-8.0835
6a	-5.3953	5.7389	-18.6462	-8.3960	-15.9329	-5.3953
6a	-4.7282	3.3257	-16.5235	-8.5974	-10.0816	-4.7282
6a	-4.4469	2.5288	-13.6917	-8.3754	-16.2506	-4.4469
6a	-4.4362	4.3633	-17.8022	-8.3708	-14.5467	-4.4362
6a	-4.4188	3.5514	-22.1593	-9.0078	-16.2700	-4.4188
6b	-5.4092	3.2340	-22.2534	-7.7432	-5.3643	-5.4092
6b	-5.3233	-7.7289	-12.5484	-8.2110	-3.0144	-5.3233
6b	-5.3034	8.6078	-14.4162	-7.6342	-7.1388	-5.3034
6b	-5.2003	-6.8580	-14.9499	-8.0918	-2.7755	-5.2003
6b	-5.1916	-1.1206	-12.7061	-8.3744	-12.3165	-5.1916
6c	-5.9041	7.1270	-20.9191	-7.8765	-3.3152	-5.9041
6c	-5.5772	1.4818	-16.4811	-8.0756	-9.7957	-5.5772
6c	-5.2692	12.5013	-23.5135	-8.6044	-3.2450	-5.2692
6c	-5.2339	-0.8363	-12.1743	-7.8086	-3.2521	-5.2339
6c	-4.9241	2.2011	-24.1006	-8.8501	-10.9080	-4.9241
6d	-6.4847	13.5517	-18.7492	-8.0687	-2.7927	-6.4847
6d	-6.3261	17.2291	-12.2230	-7.2478	-6.8761	-6.3261
6d	-6.1090	13.6725	-18.2565	-7.0425	-4.6968	-6.1090
6d	-5.8187	22.6733	-27.8051	-8.3171	-3.0578	-5.8187
6d	-5.7408	17.1991	-21.4535	-5.9925	-5.8574	-5.7408
6e	-6.7232	14.0008	-12.2414	-4.7474	16.6205	-6.7232
6e	-6.4710	31.6233	-19.7940	-4.9765	9.7882	-6.4710

6e	-6.1201	29.3200	-23.5855	-6.0087	22.8018	-6.1201
6e	-5.8200	48.9085	-11.2518	-4.2977	19.7191	-5.8200
6e	-5.6230	33.2730	-13.4817	-4.6373	19.9673	-5.6230
6f	-8.5272	107.1073	-16.2378	-6.7236	-1.5848	-8.5272
6f	-8.3479	105.9284	-20.2435	-9.6098	8.5079	-8.3479
6f	-8.2120	122.5868	-15.4995	-5.4549	13.4576	-8.2120
6f	-8.2082	103.7487	-19.5016	-5.2509	-4.7198	-8.2082
6f	-8.0937	118.5481	-16.2313	-5.3252	8.4333	-8.0937
11	-5.7090	29.4435	-19.6682	-7.6979	-14.7501	-5.7090
11	-5.4144	25.7424	-20.7493	-7.4555	-11.6635	-5.4144
11	-5.3315	25.7919	-23.5614	-8.7031	-12.0477	-5.3315
11	-5.3078	26.5097	-15.8832	-7.5579	-11.8967	-5.3078
11	-5.2500	26.9098	-20.7082	-7.8863	-11.5234	-5.2500
12	-6.1454	4.5846	-19.2147	-7.4327	-18.0355	-6.1454
12	-5.8119	10.8324	-19.2887	-6.9958	-6.3611	-5.8119
12	-5.7567	6.1498	-20.1496	-7.0165	-8.8343	-5.7567
12	-5.7313	7.9706	-22.8352	-7.3023	-9.3164	-5.7313
12	-5.6702	7.6444	-23.9284	-7.3762	-9.2898	-5.6702
13	-5.4040	-7.5283	-21.3915	-7.9391	-11.8903	-5.4040
13	-5.2978	-7.7251	-21.1744	-8.0338	-17.0026	-5.2978
13	-5.2586	-7.3780	-15.3082	-7.9345	-15.5298	-5.2586
13	-4.9231	-9.3209	-15.5753	-7.9255	-15.6561	-4.9231
13	-4.8611	-6.8786	-21.1805	-7.4549	-7.8895	-4.8611
14	-6.4626	13.3278	-22.1317	-8.7533	-18.7278	-6.4626
14	-6.0362	10.5786	-24.7707	-7.9620	-10.7383	-6.0362
14	-5.9594	11.7547	-16.0253	-7.4753	-8.2048	-5.9594
14	-5.8320	20.3669	-15.2713	-7.5084	2.1454	-5.8320
14	-5.7888	15.5874	-17.4586	-7.4924	-4.7848	-5.7888
15	-6.7549	1.8752	-23.3285	-7.0698	-15.0008	-6.7549
15	-6.6118	-0.4646	-15.6514	-7.3002	-11.8436	-6.6118
15	-6.5809	2.5772	-17.2314	-6.4612	10.1483	-6.5809

15	-6.2528	0.9143	-19.1425	-6.7599	-12.9160	-6.2528
15	-6.2221	-2.2671	-23.5639	-6.5445	-6.2518	-6.2221
16	-7.1440	-11.4955	-17.7061	-6.4942	8.9249	-7.1440
16	-6.9392	-13.8669	-18.3291	-6.0322	-10.0654	-6.9392
16	-6.8404	-19.9071	-16.9745	-6.5779	-5.2914	-6.8404
16	-6.6698	-10.4167	-20.2815	-9.0931	0.9210	-6.6698
16	-6.3443	-6.7179	-18.7858	-6.6863	9.1221	-6.3443
17	-7.3907	52.5896	-16.6319	-3.7547	14.0191	-7.3907
17	-7.0762	41.0422	-13.9756	-5.7136	9.3760	-7.0762
17	-7.0090	40.6282	-23.6082	-5.9601	37.3648	-7.0090
17	-6.8208	51.5054	-20.9760	-4.6030	30.9254	-6.8208
17	-6.5617	32.6579	-17.5356	-4.1918	18.9843	-6.5617
18	-6.9658	20.8021	-15.6677	-3.5344	5.2737	-6.9658
18	-6.6448	20.7317	-16.3956	-4.5367	6.5673	-6.6448
18	-6.6294	31.5781	-11.2740	-3.7528	4.3735	-6.6294
18	-6.0415	33.6351	-14.6425	-4.9314	4.1108	-6.0415
18	-5.7984	31.3644	-18.9887	-4.2499	17.7233	-5.7984
19	-6.9677	87.2845	-21.5319	-5.9824	-8.0483	-6.9677
19	-6.6508	89.4113	-19.1190	-5.9106	-6.5768	-6.6508
19	-6.1856	106.2361	-22.8171	-5.7849	12.1217	-6.1856
19	-6.0403	96.5439	-18.3047	-6.6155	6.9887	-6.0403
19	-5.9968	91.8334	-22.6399	-7.8948	4.3238	-5.9968
20	-7.5258	11.2913	-21.8166	-7.9865	-11.8310	-7.5258
20	-7.1799	12.7587	-18.6011	-7.5269	-19.9563	-7.1799
20	-7.0693	13.0458	-22.4354	-8.3809	-17.6004	-7.0693
20	-6.6850	16.0688	-23.6803	-7.3477	-1.4379	-6.6850
20	-6.6562	12.4321	-25.1458	-8.0126	-7.6272	-6.6562
21	-6.8669	3.9646	-26.6164	-7.3751	5.1793	-6.8669
21	-6.7855	6.0261	-18.1630	-6.7628	-0.8237	-6.7855
21	-6.6724	7.6049	-15.6285	-6.6255	7.4249	-6.6724
21	-6.3927	2.3062	-23.9178	-6.9732	-1.9235	-6.3927

21	-6.2545	5.0963	-19.7187	-6.4777	24.6805	-6.2545
22	-6.9699	22.2918	-15.3753	-6.7936	-4.2195	-6.9699
22	-6.9692	26.3006	-14.1371	-6.2116	2.2323	-6.9692
22	-6.8174	49.5994	-17.2212	-6.4308	14.2583	-6.8174
22	-6.6597	33.7985	-18.8914	-5.7997	21.4677	-6.6597
22	-6.6221	27.1289	-21.4108	-6.3729	7.9265	-6.6221
23	-7.5642	-18.9900	-13.9996	-6.0764	13.4921	-7.5642
23	-7.4357	-10.5288	-14.4227	-6.1477	-13.7798	-7.4357
23	-7.4089	-25.5283	-18.0524	-6.9771	-6.1266	-7.4089
23	-7.2787	-15.9898	-13.9304	-6.0964	25.2386	-7.2787
23	-7.0379	-20.3794	-16.0643	-5.8960	23.9315	-7.0379
24	-7.3670	-2.4750	-17.3193	-5.4394	-12.8853	-7.3670
24	-6.9281	-17.7132	-20.3846	-5.8126	-9.8312	-6.9281
24	-6.3662	-14.6660	-17.3525	-5.6328	10.5366	-6.3662
24	-6.2868	-11.3076	-19.7575	-5.6213	8.0170	-6.2868
24	-6.2675	-16.7269	-20.3474	-6.1909	10.4787	-6.2675
25	-7.8486	3.2458	-18.8732	-5.9071	-7.5569	-7.8486
25	-7.5222	-15.9165	-22.7457	-6.5862	-0.3337	-7.5222
25	-6.8770	-9.6813	-19.5089	-6.9067	4.5640	-6.8770
25	-6.8578	25.4552	-17.4251	-5.2570	15.4274	-6.8578
25	-6.6790	-10.4764	-19.1989	-6.2277	18.0734	-6.6790
26	-6.9376	-9.3366	-18.5366	-5.8124	25.0962	-6.9376
26	-6.8056	2.3957	-23.0545	-8.7950	3.2299	-6.8056
26	-6.7563	-17.2014	-13.8468	-5.7417	-1.2804	-6.7563
26	-6.7378	-23.0396	-19.8893	-6.0405	23.0749	-6.7378
26	-6.7248	-21.0151	-13.3140	-5.0265	1.5234	-6.7248
27	-7.4888	17.0501	-21.2491	-6.1899	-4.8202	-7.4888
27	-7.3580	26.7535	-17.1392	-7.2857	-10.1628	-7.3580
27	-7.2921	27.8285	-12.7459	-6.4586	-8.3122	-7.2921
27	-6.8127	22.2414	-26.3685	-6.4341	3.8095	-6.8127
27	-6.5644	21.5504	-25.4835	-6.7994	-0.2655	-6.5644

28	-7.2976	-20.6007	-19.7241	-5.1740	-2.9507	-7.2976
28	-7.0139	-3.9735	-18.6085	-5.3661	-2.2493	-7.0139
28	-6.9897	-9.0595	-19.6567	-7.3524	0.0144	-6.9897
28	-6.7091	-15.1525	-21.1642	-5.7263	9.5314	-6.7091
28	-6.3743	-13.9352	-15.0619	-5.4695	6.7566	-6.3743
29	-7.1301	-14.0748	-16.4598	-7.5679	9.7341	-7.1301
29	-6.7880	-13.4198	-21.1735	-5.9730	-12.3510	-6.7880
29	-6.4256	-0.6906	-18.3878	-5.7179	7.6336	-6.4256
29	-6.3211	-10.6713	-20.4505	-7.8579	10.9515	-6.3211
29	-6.3114	-11.9885	-21.1278	-8.0907	8.9883	-6.3114
30	-6.9192	-21.2923	-12.7902	-7.4089	-12.7240	-6.9192
30	-6.8965	-19.1422	-10.0821	-5.5674	2.8830	-6.8965
30	-6.8485	-17.6830	-8.7993	-4.6989	9.1108	-6.8485
30	-6.6031	-7.6384	-16.1648	-6.4406	4.0124	-6.6031
30	-6.5161	1.5010	-22.4264	-5.5059	21.0534	-6.5161
31	-7.2516	-11.6325	-21.9350	-5.2964	13.7206	-7.2516
31	-7.1319	-8.8200	-12.8212	-5.8105	22.5673	-7.1319
31	-7.0846	2.2205	-10.7337	-6.1193	9.3931	-7.0846
31	-7.0687	-11.1753	-15.0521	-6.7364	20.6687	-7.0687
31	-7.0577	-17.5523	-22.4342	-7.2072	15.6324	-7.0577
32	-7.9356	27.6877	-17.6383	-4.1913	1.7178	-7.9356
32	-7.3214	33.7168	-14.6650	-4.2081	21.1119	-7.3214
32	-7.0113	50.0754	-18.5466	-4.2158	52.7006	-7.0113
32	-6.7946	30.6555	-22.1453	-4.9065	16.8809	-6.7946
32	-6.5793	37.2774	-23.1148	-7.4483	11.9846	-6.5793
33	-6.9640	6.9785	-18.3590	-7.0461	-19.1492	-6.9640
33	-6.7251	5.9511	-16.8946	-6.9217	-7.6307	-6.7251
33	-6.6629	9.9691	-18.4411	-6.9176	-13.6890	-6.6629
33	-6.6328	4.5592	-22.2054	-6.8794	-12.6632	-6.6328
33	-6.1540	16.1598	-14.7493	-7.0201	1.6893	-6.1540
34	-7.3067	2.4457	-18.9596	-6.6431	-18.2095	-7.3067

34	-6.8822	-6.0882	-19.1647	-6.7001	-8.4519	-6.8822
34	-6.6972	-7.5061	-22.5950	-7.4617	-11.3809	-6.6972
34	-6.6733	19.9712	-13.3194	-6.8019	23.3943	-6.6733
34	-6.6547	-1.7751	-19.0071	-6.8846	2.1441	-6.6547
35	-7.4790	-25.5311	-18.4569	-4.7887	35.3934	-7.4790
35	-6.6609	-29.8600	-17.1907	-6.1405	43.5066	-6.6609
35	-6.6300	-22.9587	-18.8594	-6.8698	21.6276	-6.6300
35	-6.5796	-40.8890	-17.2634	-5.7100	9.4792	-6.5796
35	-6.4968	-43.0403	-19.0494	-5.3069	15.4455	-6.4968
36	-6.1875	-49.3287	-16.0939	-6.3885	13.7182	-6.1875
36	-5.7137	-39.2731	-17.0539	-6.4438	-4.1801	-5.7137
36	-5.6017	-47.7943	-14.0281	-6.0964	-0.6161	-5.6017
36	-5.5020	-45.5616	-14.5369	-7.0523	13.8918	-5.5020
36	-5.4890	-52.1290	-15.1353	-7.0080	6.3151	-5.4890
37	-6.5851	-61.0472	-14.5192	-5.5712	10.2112	-6.5851
37	-6.4277	-25.4888	-19.7830	-6.5545	18.0433	-6.4277
37	-6.4246	-57.8340	-17.6521	-6.8929	1.4875	-6.4246
37	-6.4235	-56.8517	-12.2515	-7.5260	-13.4837	-6.4235
37	-6.3679	-59.2965	-18.7761	-7.4628	0.5092	-6.3679
38	-5.3083	-142.0945	-12.6841	-7.1155	-7.7869	-5.3083
38	-5.1815	-135.7909	-9.2237	-5.5435	-6.3058	-5.1815
38	-4.8488	-132.6850	-7.5954	-5.9117	8.1609	-4.8488
38	-4.8380	-127.0627	-14.1474	-6.0593	13.8880	-4.8380
38	-4.8256	-129.0628	-14.7706	-7.5835	9.6282	-4.8256
39	-5.3215	-105.9910	-15.6297	-7.6744	0.9608	-5.3215
39	-5.2457	-102.3219	-16.7335	-7.4557	-1.4090	-5.2457
39	-5.2107	-111.7456	-13.4833	-7.3193	-14.6700	-5.2107
39	-5.1875	-110.3807	-16.0767	-6.6105	18.9068	-5.1875
39	-5.0764	-105.3330	-12.8936	-7.9981	-6.1866	-5.0764
49	-5.2669	16.8708	-19.8830	-8.0641	-12.5071	-5.2669
49	-4.9535	20.4225	-16.6438	-7.6979	-14.7143	-4.9535

49	-4.9338	22.3600	-17.8494	-7.6705	-9.7148	-4.9338
49	-4.9077	20.8152	-16.6727	-7.6482	-13.4018	-4.9077
49	-4.7603	17.0036	-19.1916	-7.6223	-12.9514	-4.7603
50	-6.3263	36.8180	-23.8001	-7.4244	-1.8658	-6.3263
50	-6.2365	35.5761	-22.1739	-7.8108	-8.9523	-6.2365
50	-5.7440	43.2290	-11.9291	-7.0000	-9.5796	-5.7440
50	-5.3030	39.3780	-18.8912	-8.0380	-9.0851	-5.3030
50	-5.1336	36.6016	-19.1499	-8.8704	-8.0785	-5.1336
51	-6.4870	23.8828	-15.6876	-6.6502	2.0538	-6.4870
51	-6.2588	25.8877	-22.5323	-7.8278	-8.0515	-6.2588
51	-6.1905	30.2390	-11.5804	-6.8121	-5.4831	-6.1905
51	-5.9857	22.4576	-17.9261	-8.0817	-6.3433	-5.9857
51	-5.9833	26.1091	-23.4586	-6.7510	-8.4228	-5.9833
52	-6.9199	15.4097	-18.5293	-6.0291	22.3305	-6.9199
52	-6.5480	12.4628	-20.7098	-6.0875	17.7096	-6.5480
52	-6.3831	13.9484	-20.4280	-7.2490	4.9660	-6.3831
52	-6.2719	15.8614	-11.5977	-5.7030	9.3385	-6.2719
52	-6.2027	13.9959	-14.5955	-6.3727	1.0225	-6.2027
53	-6.8316	11.2652	-16.5366	-6.6175	-0.5447	-6.8316
53	-6.7944	21.8153	-17.7039	-7.4494	7.8954	-6.7944
53	-6.6836	3.3764	-16.9642	-5.6855	22.9776	-6.6836
53	-6.6380	12.2019	-17.2957	-6.1427	3.8562	-6.6380
53	-6.6294	7.7140	-18.3127	-5.7353	-2.3184	-6.6294
54	-7.4037	22.1949	-13.4854	-5.2514	0.6901	-7.4037
54	-6.9224	11.9278	-13.6312	-4.8080	11.5459	-6.9224
54	-6.4409	14.9964	-12.5669	-5.4748	2.2407	-6.4409
54	-6.2803	16.3959	-11.2060	-4.7610	18.5203	-6.2803
54	-6.2716	15.8469	-20.8939	-6.9144	3.7623	-6.2716
S18616	-7.2540	-78.9660	-20.1860	-6.6451	-3.8317	-7.2540
S18616	-6.5302	-80.7608	-24.7631	-8.4053	1.2911	-6.5302
S18616	-6.2843	-75.6964	-23.0394	-9.7113	0.1749	-6.2843

S18616	-6.0826	-67.0448	-21.8553	-8.3635	4.8944	-6.0826
S18616	-6.0375	-69.6867	-15.9147	-6.5721	6.7722	-6.0375

Table S2. Five top scored docking positioning of **5a-5e**, **6a-6e**, **11-54** and the reference agonist **S18616** at the α_2 -ADR (MOE software). The predicted ΔG value of each protein-ligand complex has been reported, as calculated in terms of final scoring function (S, as Kcal/mol).

Compound	S	E_conf	E_place	E_score1	E_refine	E_score2
5a	-4.8586	-24.6135	-16.3394	-8.4980	-28.3288	-4.8586
5a	-4.6276	-24.5541	-24.3329	-8.5346	-27.1076	-4.6276
5a	-4.5228	-24.7498	-14.0069	-8.4813	-24.3698	-4.5228
5a	-4.4926	-24.3935	-13.6725	-9.1069	-20.2049	-4.4926
5a	-4.3883	-23.1719	-16.4793	-8.4661	-22.3050	-4.3883
5b	-5.6235	-35.0779	-18.1036	-9.0295	-25.9453	-5.6235
5b	-5.6087	-35.0746	-15.8406	-9.8561	-25.9431	-5.6087
5b	-5.5957	-35.0741	-18.3770	-9.4665	-25.9385	-5.5957
5b	-5.5213	-34.9964	-20.7360	-9.5987	-29.9274	-5.5213
5b	-5.4698	-35.9122	-18.0356	-9.2531	-27.8051	-5.4698
5c	-5.6971	-33.9166	-21.4063	-9.4918	-29.9051	-5.6971
5c	-5.6018	-34.5350	-17.9618	-10.2308	-30.0033	-5.6018
5c	-5.5790	-34.3260	-17.8880	-9.7142	-29.9054	-5.5790
5c	-5.1553	-33.7042	-12.4049	-9.3017	-25.1663	-5.1553
5c	-5.1022	-34.8817	-19.8985	-9.8771	-26.3130	-5.1022
5d	-6.6975	-24.0750	-18.8442	-9.6650	-31.0271	-6.6975
5d	-6.6468	-27.0047	-27.9347	-9.4997	-29.5467	-6.6468
5d	-6.6046	-25.0672	-24.6577	-9.9896	-30.9893	-6.6046
5d	-6.4712	-26.6302	-27.2452	-9.9546	-31.1768	-6.4712
5d	-6.4128	-27.8938	-24.6200	-9.7864	-32.4074	-6.4128
5e	-7.7755	-27.0518	-30.8449	-9.5500	-30.2690	-7.7755

5e	-7.4451	-26.8237	-22.4104	-10.2015	-29.4374	-7.4451
5e	-7.2488	-22.0454	-27.3508	-10.1843	-26.4730	-7.2488
5e	-7.2126	-18.3991	-24.7323	-10.6521	-32.4382	-7.2126
5e	-6.9625	-28.2883	-22.8544	-9.0794	-28.2641	-6.9625
5f	-8.5205	67.0418	-22.9174	-9.0811	-19.9307	-8.5205
5f	-7.9588	66.6432	-25.5324	-8.7483	-22.6765	-7.9588
5f	-7.8949	67.4212	-26.1867	-8.6180	-23.2117	-7.8949
5f	-7.7658	69.0728	-21.7586	-9.1882	-21.8958	-7.7658
5f	-7.4667	70.6896	-26.0858	-8.6072	-24.0882	-7.4667
6a	-4.5923	1.3917	-16.0038	-8.7212	-22.6771	-4.5923
6a	-4.5848	1.8910	-13.5773	-9.6259	-18.8813	-4.5848
6a	-4.5240	0.6075	-18.4029	-9.0138	-27.3238	-4.5240
6a	-4.4712	0.7750	-13.1543	-9.1723	-22.9108	-4.4712
6a	-4.4480	1.5839	-19.6700	-9.0532	-28.8079	-4.4480
6b	-5.5751	-11.9718	-21.8407	-10.3889	-30.8106	-5.5751
6b	-5.3476	-11.0347	-15.4176	-9.2901	-28.0222	-5.3476
6b	-5.2181	-11.7669	-15.3975	-9.5230	-24.3644	-5.2181
6b	-5.0697	-11.6377	-14.2715	-9.2423	-21.3898	-5.0697
6b	-4.9603	-6.4500	-14.4135	-9.4583	-29.6776	-4.9603
6c	-5.6721	-8.3077	-21.9437	-9.5122	-31.3923	-5.6721
6c	-5.5861	-9.8174	-23.5658	-9.5916	-29.6594	-5.5861
6c	-5.4044	-9.0422	-13.5352	-9.1567	-24.4290	-5.4044
6c	-5.3778	-9.0981	-15.2839	-9.9294	-24.1277	-5.3778
6c	-5.3306	-7.9226	-13.1808	-9.0863	-25.2748	-5.3306
6d	-6.6008	-0.3248	-24.8208	-10.3116	-31.2008	-6.6008
6d	-6.4652	-0.9956	-20.6028	-9.6940	-29.2753	-6.4652
6d	-6.4627	0.9562	-28.1860	-10.4432	-31.7838	-6.4627
6d	-6.2677	-0.0595	-12.6899	-9.5491	-30.1310	-6.2677
6d	-6.2552	1.6043	-20.9041	-9.4861	-22.5559	-6.2552
6e	-7.4403	-3.4952	-19.8243	-8.9487	-27.0887	-7.4403
6e	-7.3642	-1.9331	-22.8069	-9.5952	-30.5953	-7.3642

6e	-7.1489	7.4743	-27.1922	-9.4821	-30.1815	-7.1489
6e	-7.1156	7.6250	-27.2737	-9.3741	-29.4376	-7.1156
6e	-7.0922	-4.5141	-26.7742	-9.1401	-30.4486	-7.0922
6f	-8.4565	95.5462	-21.9721	-8.8043	-19.7170	-8.4565
6f	-8.3076	95.6416	-23.0525	-9.5390	-20.1698	-8.3076
6f	-8.2740	99.0312	-22.9908	-9.4941	-21.2341	-8.2740
6f	-8.1691	97.1621	-26.3011	-9.4989	-23.8912	-8.1691
6f	-7.8912	96.0249	-22.8691	-8.8897	-21.7882	-7.8912
11	-5.2893	24.4764	-17.6885	-7.5478	-18.0551	-5.2893
11	-4.9647	24.4556	-16.1683	-7.4850	-18.2605	-4.9647
11	-4.8230	23.8081	-17.1736	-8.0563	-18.7143	-4.8230
11	-4.7963	23.9432	-21.2175	-8.3497	-19.3325	-4.7963
11	-4.7555	23.6229	-20.5758	-7.4879	-18.5984	-4.7555
12	-5.6061	4.1941	-28.3745	-7.6899	-20.9171	-5.6061
12	-5.4827	4.9921	-19.7117	-7.7559	-16.4729	-5.4827
12	-5.4537	5.5342	-17.0294	-7.6759	-17.4785	-5.4537
12	-5.3983	3.7078	-18.7093	-7.7303	-18.0687	-5.3983
12	-5.0632	4.7602	-20.5591	-8.2469	-19.3343	-5.0632
13	-5.0472	-10.6894	-17.0682	-7.9067	-19.5178	-5.0472
13	-4.6605	-8.5908	-19.0651	-7.8658	-22.1610	-4.6605
13	-4.5311	-9.6731	-21.6857	-8.0013	-18.9952	-4.5311
13	-4.3904	-10.2218	-19.0629	-9.1749	-21.2946	-4.3904
13	-4.3366	-12.0369	-14.5865	-8.5393	-20.6742	-4.3366
14	-5.9150	9.0452	-23.4623	-8.6325	-20.7938	-5.9150
14	-5.7216	8.3770	-25.7961	-8.0179	-22.1183	-5.7216
14	-5.6361	8.7530	-19.5716	-8.0999	-19.6382	-5.6361
14	-5.5880	9.4693	-17.8920	-8.6200	-19.8565	-5.5880
14	-5.5272	7.5691	-18.4660	-8.1814	-23.6766	-5.5272
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19	-6.1992	84.2436	-22.3513	-8.4652	-24.2098	-6.1992
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21	-6.4927	-0.6995	-19.1569	-9.0490	-22.0617	-6.4927

21	-6.4824	-3.7909	-26.1106	-9.2498	-26.1341	-6.4824
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24	-6.6353	-26.7619	-23.1236	-9.1385	-23.8164	-6.6353
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25	-7.1223	-24.3009	-26.0583	-8.7093	-22.7181	-7.1223
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25	-7.1073	-23.4272	-17.1189	-8.8531	-19.6431	-7.1073
26	-7.3091	-48.4599	-20.2525	-8.9794	-25.3975	-7.3091
26	-7.2557	-43.8436	-25.0952	-9.3903	-20.9577	-7.2557
26	-7.1310	-47.5892	-26.3670	-9.5929	-22.0982	-7.1310
26	-7.0794	-47.9655	-20.9768	-8.7592	-21.0231	-7.0794
26	-7.0100	-41.7263	-23.2032	-9.2199	-22.1466	-7.0100
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27	-6.6521	14.4414	-25.5952	-8.4380	-16.4351	-6.6521
27	-6.6221	9.3678	-19.5618	-8.3047	-21.5235	-6.6221
27	-6.5012	8.9346	-19.9677	-8.4928	-27.3237	-6.5012
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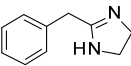
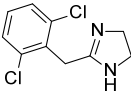
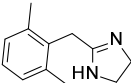
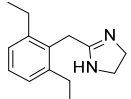
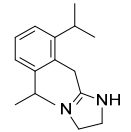
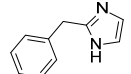
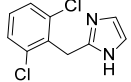
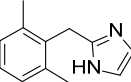
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28	-6.9778	-31.1672	-20.3190	-8.9944	-20.5990	-6.9778
28	-6.9118	-25.6494	-19.1445	-8.7814	-21.3153	-6.9118
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29	-7.1689	-23.6104	-26.1553	-9.3239	-23.1209	-7.1689
29	-7.0833	-25.2451	-17.7026	-9.4114	-26.3755	-7.0833
29	-6.9566	-22.4460	-20.4634	-9.1144	-23.7898	-6.9566
29	-6.9469	-19.8292	-25.8112	-8.9191	-24.9063	-6.9469
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31	-7.0555	-32.6103	-26.3370	-8.4073	-27.0119	-7.0555
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33	-5.8188	2.4838	-24.3193	-8.5676	-22.5270	-5.8188
33	-5.7877	2.9869	-18.0356	-8.5083	-20.5043	-5.7877
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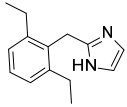
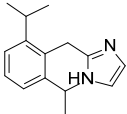
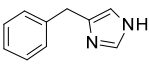
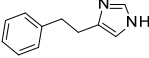
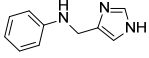
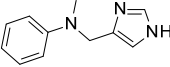
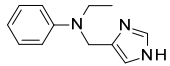
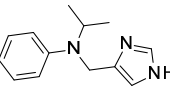
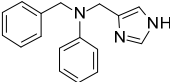
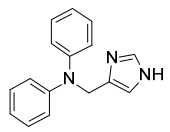
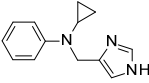
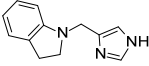
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34	-6.2867	-11.0908	-28.6052	-8.6405	-20.5439	-6.2867
34	-6.2282	-8.2014	-23.6725	-8.9825	-21.5663	-6.2282
35	-7.2505	-61.8967	-22.8761	-8.4210	-27.3701	-7.2505
35	-7.0719	-63.5825	-24.5839	-8.8749	-23.2964	-7.0719
35	-7.0673	-60.0247	-27.3402	-8.7845	-25.1516	-7.0673
35	-7.0603	-62.0371	-21.2994	-8.8864	-24.9197	-7.0603
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36	-5.3522	-57.0890	-28.8481	-8.4498	-21.7855	-5.3522
36	-5.3061	-58.7202	-17.9359	-8.3096	-24.3760	-5.3061
36	-5.2991	-56.3874	-18.8060	-8.4978	-21.5264	-5.2991
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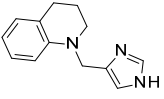
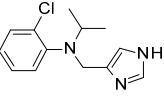
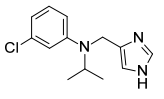
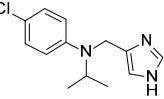
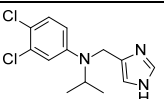
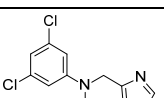
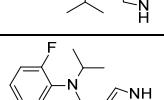
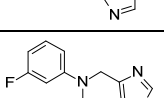
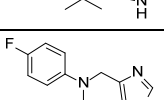
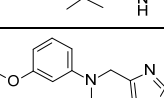
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49	-4.1912	20.5396	-15.3888	-8.1015	-19.5023	-4.1912
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50	-5.6173	37.6235	-19.1195	-7.8075	-21.5770	-5.6173
50	-5.4932	37.4128	-20.6806	-7.8797	-21.2514	-5.4932
50	-5.2406	35.5924	-15.8339	-7.9518	-20.3255	-5.2406
50	-5.2179	37.1503	-16.7410	-7.7157	-22.4346	-5.2179
51	-6.0491	19.7803	-19.0691	-8.1402	-23.1358	-6.0491
51	-6.0439	20.2981	-22.7599	-8.2127	-23.2525	-6.0439
51	-6.0204	21.9774	-20.6010	-8.8690	-21.8055	-6.0204
51	-5.8278	23.8223	-24.2422	-8.2092	-23.0137	-5.8278
51	-5.7679	23.6413	-15.0923	-8.5685	-21.6630	-5.7679
52	-6.3798	3.9218	-14.0076	-8.4794	-21.3763	-6.3798
52	-6.3741	-3.1675	-20.8488	-8.7941	-22.1811	-6.3741
52	-6.1751	-3.0134	-22.5094	-8.6615	-21.4697	-6.1751
52	-6.1436	2.3686	-18.8041	-8.8918	-23.5124	-6.1436
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53	-6.6388	-0.1960	-14.7378	-9.0941	-15.9828	-6.6388
53	-6.5780	-7.8056	-20.5304	-9.3202	-23.6089	-6.5780
53	-6.5190	-0.1792	-23.3101	-8.4270	-16.3114	-6.5190
53	-6.5175	-8.3566	-21.5743	-8.5800	-24.3277	-6.5175
53	-6.5070	-7.5486	-18.3678	-8.8382	-24.5050	-6.5070
54	-7.1372	-2.0929	-22.1443	-8.7294	-23.8655	-7.1372
54	-6.7926	4.8865	-15.2122	-9.0549	-21.4526	-6.7926
54	-6.5545	3.3080	-23.7167	-8.8303	-25.0563	-6.5545
54	-6.4753	-3.5967	-21.5505	-8.9400	-22.3819	-6.4753
54	-6.4619	-2.7573	-17.3143	-9.7629	-21.0312	-6.4619
S18616	-6.7109	-85.1541	-26.2111	-8.7237	-25.7039	-6.7109
S18616	-6.5137	-81.8289	-22.3768	-8.6693	-24.3697	-6.5137
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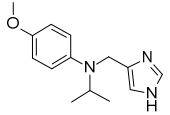
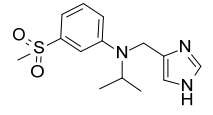
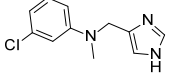
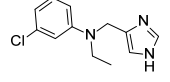
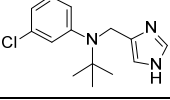
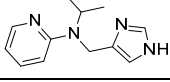
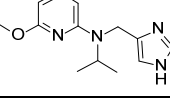
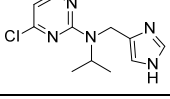
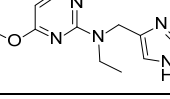
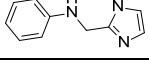
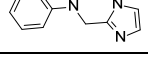
S18616	-6.3762	-81.4119	-19.1685	-9.1557	-23.2755	-6.3762
S18616	-6.3178	-76.6740	-22.7904	-9.8164	-15.2940	-6.3178

Table S3. Chemical structure of the dual acting *h*TAAR1 and α_2 ADR ligands. The corresponding binding affinity values are also reported.

Compound	TAAR1 Ki (nM)	α_2 -ADR / <i>h</i> TAAR1 Ki	α_2 -ADR Ki (nM)	Chemical Structure
5a	1640.00	0.06	98.40	
5b	500.00	0.05	25.00	
5c	82.00	0.77	63.14	
5d	300.00	0.68	204.00	
5e	825.00	4.00	3300.00	
6a	400.00	4.70	1880.00	
6b	1390.00	0.70	973.00	
6c	36.00	4.50	162.00	

6d	24.00	100.00	2400.00	
6e	630.00	14.00	8820.00	
11	20.00	2.50	50.00	
12	2.00	5.10	10.20	
13	65.00	5.30	344.50	
14	11.00	1.60	17.60	
15	48.00	1.60	76.80	
16	22.00	23.70	521.40	
17	32.00	4.00	128.00	
18	69.00	0.90	62.10	
19	100.00	3.30	330.00	
20	35.00	0.14	4.90	

21	12.00	4.00	48.00	
22	40.00	76.00	3040.00	
23	4.00	72.00	288.00	
24	6.00	140.00	840.00	
25	4.00	71.00	284.00	
26	4.00	37.00	148.00	
27	18.00	16.00	288.00	
28	12.00	34.00	408.00	
29	13.00	104.00	1352.00	
30	5.00	67.00	335.00	

31	80.00	33.00	2640.00	
32	128.00	8.00	1024.00	
33	11.00	1.30	14.30	
34	2.00	21.00	42.00	
35	33.00	200.00	6600.00	
36	195.00	12.00	2340.00	
37	12.00	62.00	744.00	
38	100.00	33.00	3300.00	
39	84.00	3.00	252.00	
49	4250.00	0.20	850.00	
50	1270.00	0.20	254.00	

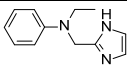
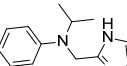
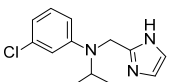
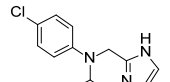
51	710.00	0.70	497.00	
52	470.00	8.00	3760.00	
53	68.00	64.00	4352.00	
54	138.00	22.00	3036.00	

Table S4. The predicted (Pred. pKi) and experimental (Exp. pKi) *h*TAAR1 binding affinity values of the compounds (Comp.) herein explored are reported, in tandem with the collected descriptors. The compounds included in the test set are underlined along the first column.

Comp.	Exp. hTAAR1 pKi	GCUT_SM R_0	E	dipoleY	dipoleZ	DCASA	Q_RPC-	Q_VSA_FHYD	SlogP_VSA4	vsurf_EDmin 1	vsurf_IW5	Pred. hTAAR1 pKi	Residual
<u>5a</u>	5.79	-0.5048	31.5871	-0.2109	0.1291	157.4579	0.1929	0.9660	3.1856	-2.5019	2.5918	5.81	0.02
5b	6.30	-0.5048	35.6559	-0.2837	0.0583	105.3684	0.2856	0.9300	3.1856	-2.8846	4.3883	6.43	0.13
5c	7.09	-0.5049	36.8534	-0.1856	0.1142	197.4412	0.1676	0.9717	9.5567	-2.4239	3.2398	6.65	-0.44
5d	6.52	-0.5164	40.9543	-0.1532	0.1450	309.1655	0.1460	0.8196	9.5567	-2.2841	3.4189	6.58	0.06
5e	6.08	-0.5222	51.2710	-0.1713	0.1310	420.1130	0.1252	0.7085	9.5567	-2.3425	3.5809	6.28	0.20
6a	6.40	-0.4721	17.4561	-0.3373	0.1267	39.2795	0.1286	0.9492	5.5135	-2.3605	3.1705	6.70	0.30
<u>6b</u>	5.86	-0.4719	22.6175	-0.4081	0.0531	7.5834	0.1471	0.9579	5.5135	-2.9112	4.4446	7.19	1.33
6c	7.44	-0.4847	22.7412	-0.2384	0.0291	77.0173	0.1077	0.9578	11.8846	-2.3530	3.5965	7.60	0.16
6d	7.62	-0.5164	27.2421	-0.2481	0.1213	187.1044	0.1024	0.8067	11.8846	-2.2929	3.8201	7.56	-0.06
<u>6e</u>	6.20	-0.5222	37.6495	-0.2553	0.0813	279.6188	0.0881	0.6968	11.8846	-2.3479	3.6272	7.19	0.99
11	7.70	-0.4682	19.6551	0.2232	0.3121	39.5252	0.1436	0.9484	5.9423	-2.7064	3.6205	8.35	0.65
12	8.70	-0.5062	19.8977	0.2076	0.3165	107.3042	0.1291	0.9532	5.9423	-2.8273	3.5625	8.22	-0.48
13	7.19	-0.4661	27.3867	0.2779	0.3305	118.9644	0.1727	0.9526	2.7567	-2.4910	3.1167	7.28	0.09
<u>14</u>	7.96	-0.4777	35.6927	0.2773	0.4286	129.5135	0.1664	0.9021	2.7567	-2.4044	4.3910	7.55	-0.41

15	7.32	-0.5075	34.0067	0.2784	0.4457	172.0687	0.1479	0.8286	2.7567	-2.4756	4.3415	7.70	0.38
16	7.66	-0.5159	36.9333	0.2558	0.3741	227.1855	0.1336	0.7652	2.7567	-2.4805	4.5911	7.58	-0.08
17	7.49	-0.4747	55.3304	0.2831	0.3820	172.2133	0.1204	0.9263	5.9423	-2.4080	5.0069	7.55	0.06
18	7.16	-0.4640	59.3388	0.3181	0.1707	121.0741	0.1098	0.9673	2.7567	-2.5218	4.9119	7.04	-0.12
19	7.00	-0.4690	38.1040	0.2488	0.4033	211.4028	0.1293	0.8814	2.7567	-2.6171	4.1916	7.34	0.34
20	7.46	-0.5048	37.7179	0.2324	0.3856	175.0137	0.1665	0.9569	5.9423	-2.4391	4.6835	7.73	0.27
21	7.92	-0.5144	35.4751	0.2615	0.4461	224.3391	0.1507	0.9603	5.9423	-2.6025	4.6638	7.88	-0.04
22	7.40	-0.5158	44.5035	0.1838	0.4414	57.1006	0.1647	0.8266	2.7567	-2.8280	4.0049	7.70	0.30
23	8.40	-0.5159	36.3419	0.1463	0.6620	32.7312	0.1450	0.8266	2.7567	-2.9375	4.0920	8.19	-0.21
24	8.22	-0.5159	37.2205	0.2702	0.5672	23.7212	0.1452	0.8266	2.7567	-2.8690	4.4702	8.44	0.22
25	8.40	-0.5158	39.0151	0.2055	0.8128	145.5844	0.1511	0.8373	2.7567	-3.1213	4.2703	8.21	-0.19
26	8.40	-0.5158	35.5056	0.2912	0.5749	144.4861	0.1490	0.8373	2.7567	-3.0699	4.5032	8.32	-0.08
27	7.74	-0.5159	40.8565	0.0533	0.4840	160.3320	0.1457	0.8176	2.7567	-2.5605	4.2162	7.19	-0.55
28	7.92	-0.5159	33.3279	0.1153	0.7269	159.9934	0.1355	0.6726	2.7567	-2.7422	4.0707	8.04	0.12
29	7.89	-0.5159	36.8043	0.2724	0.6086	155.0814	0.1441	0.8176	2.7567	-2.6938	4.3367	7.97	0.08
30	8.30	-0.5159	44.3150	0.3425	0.4258	281.6604	0.1247	0.6961	2.7567	-2.8822	3.7816	7.63	-0.67
31	7.10	-0.5159	48.0157	0.3007	0.2334	281.4287	0.1342	0.8267	2.7567	-2.8415	3.8066	7.04	-0.06
32	6.89	-0.5159	18.7812	-0.2198	0.7839	359.2455	0.1709	0.6311	2.7567	-2.6959	3.2562	6.97	0.08
33	7.96	-0.4776	35.0484	0.1958	0.6975	28.5787	0.1689	0.9096	2.7567	-2.8021	4.0481	8.06	0.10
34	8.70	-0.5074	36.6627	0.1293	0.5517	22.5185	0.1566	0.8898	2.7567	-2.5780	4.8064	7.93	-0.77
35	7.48	-0.5191	46.8478	0.0650	0.4660	23.7223	0.1375	0.7766	2.7567	-2.7308	4.8160	7.81	0.33
36	6.71	-0.5158	34.0791	0.2448	0.1901	212.0978	0.1190	0.6909	2.7567	-2.6528	3.2740	7.39	0.68
37	7.92	-0.5158	37.2112	0.3324	0.2404	268.9462	0.1117	0.7176	2.7567	-2.6913	4.0007	7.58	-0.34
38	7.00	-0.5157	29.1544	0.2132	0.3551	462.3309	0.1342	0.7344	2.7567	-2.9915	2.1633	6.69	-0.31
39	7.08	-0.5075	32.5707	0.4336	0.2463	331.3762	0.1314	0.7941	2.7567	-2.7324	2.4740	7.13	0.05
49	5.37	-0.4695	27.2743	-0.2927	0.1517	93.9851	0.1716	0.9073	2.3279	-2.4231	3.3491	6.10	0.73
50	5.90	-0.4781	35.1841	-0.3034	0.2338	104.3671	0.1657	0.9028	2.3279	-2.3549	3.8473	6.04	0.14
51	6.15	-0.5075	33.3358	-0.3183	0.2821	145.9252	0.1519	0.7763	2.3279	-2.3956	3.8095	6.26	0.11
52	6.33	-0.5159	35.9727	-0.3244	0.2784	177.5581	0.1383	0.7657	2.3279	-2.3224	3.4208	5.96	-0.37
53	7.17	-0.5159	35.7515	-0.0575	0.2377	14.3486	0.1402	0.7812	2.3279	-2.2991	4.0105	7.06	-0.11
54	6.86	-0.5159	36.6405	-0.2461	0.4066	8.5404	0.1409	0.8271	2.3279	-2.4028	3.9164	6.77	-0.09

Table S5. The predicted (Pred. pKi) and experimental (Exp. pKi) α_2 -ADR binding affinity values of the compounds (Comp.) herein explored are reported, in tandem with the collected descriptors. The compounds included in the test set are underlined along the first column.

Comp.	Exp. α_2 -ADR pKi	GCUT_SMR_1	balabanJ	E_tor	Q_VSA_FH_YD	Q_VSA_PN_EG	Q_VSA_P_OL	vsurf_oth_er	SlogP_VS_A3	vsurf_ID_1	vsurf_ID7	vsurf_IW_4	Pred. α_2 -ADR Ki	Residual
<u>5a</u>	7.01	-0.1920	1.7133	6.3513	0.9660	5.8195	5.8195	11.1906	36.8792	0.4434	0.6388	2.3317	7.05	7.01
<u>5b</u>	7.60	-0.1522	1.8792	6.2372	0.9300	5.8195	14.4385	11.1906	36.8792	0.3928	0.9248	3.3062	7.97	7.60
<u>5c</u>	7.20	-0.1506	1.8792	7.9738	0.9717	5.8195	5.8195	11.1906	36.8792	0.4681	0.7490	2.9026	7.07	7.20
<u>5d</u>	6.69	-0.1502	1.9471	7.9827	0.8196	43.3148	43.3148	11.1906	36.8792	0.4608	0.8987	2.9886	6.41	6.69
<u>5e</u>	5.48	-0.1487	2.0545	8.5903	0.7085	80.8102	80.8102	11.1906	36.8792	0.4280	0.9322	3.1916	5.58	5.48
<u>6a</u>	5.73	-0.2094	1.7159	3.9091	0.9492	0.0000	8.6190	11.1906	0.0000	0.4257	0.4994	2.6134	6.50	5.73
<u>6b</u>	6.01	-0.1759	1.8811	3.6180	0.9579	0.0000	8.6190	11.1906	0.0000	0.3239	0.6892	3.4183	6.69	6.01
<u>6c</u>	6.79	-0.1726	1.8811	5.2639	0.9578	0.0000	8.6190	11.1906	0.0000	0.4211	0.3080	3.1153	6.18	6.79
<u>6d</u>	5.62	-0.1717	1.9484	5.2933	0.8067	37.4954	46.1144	11.1906	0.0000	0.4083	0.5363	3.1678	5.60	5.62
<u>6e</u>	5.05	-0.1691	2.0555	5.8089	0.6968	74.9907	83.6097	11.1906	0.0000	0.3610	0.4533	3.3044	4.63	5.05
<u>11</u>	7.30	-0.2161	1.7164	3.3058	0.9484	0.1369	8.7559	24.7905	0.0000	0.5883	0.6782	3.4603	7.29	7.30
<u>12</u>	7.99	-0.2161	1.6145	0.0625	0.9532	0.1369	8.7559	24.7905	0.0000	0.5427	0.8767	3.3721	7.70	7.99
<u>13</u>	6.46	-0.2173	1.6145	3.6814	0.9526	0.2738	8.8928	24.7905	0.0000	0.6181	0.1463	2.5496	6.61	6.46
<u>14</u>	7.75	-0.1975	1.7368	4.1318	0.9021	12.3918	21.0108	24.7905	0.0000	0.6273	0.4429	4.0897	6.96	7.75
<u>15</u>	7.11	-0.1963	1.8018	4.0616	0.8286	31.1395	39.7585	24.7905	18.4396	0.5725	0.4914	4.1262	7.15	7.11
<u>16</u>	6.28	-0.1938	1.8802	4.9837	0.7652	49.8872	58.5062	24.7905	0.0000	0.6438	0.5367	4.3255	6.16	6.28
<u>17</u>	6.89	-0.2161	1.5574	5.3588	0.9263	12.3918	21.0108	24.7905	0.0000	0.5629	0.4175	4.8839	7.36	6.89
<u>18</u>	7.21	-0.2161	1.6255	8.8673	0.9673	0.1369	8.7559	24.7905	0.0000	0.5888	0.4177	4.6235	7.33	7.21
<u>19</u>	6.48	-0.2161	1.5695	12.1702	0.8814	17.5395	26.1585	24.7905	0.0000	0.5249	0.5755	4.0537	6.96	6.48
<u>20</u>	8.31	-0.1857	1.5747	7.4637	0.9569	0.1369	8.7559	24.7905	18.4396	0.5831	0.3270	4.4199	7.92	8.31
<u>21</u>	7.32	-0.1858	1.5975	4.4908	0.9603	0.1369	8.7559	24.7905	18.4396	0.5441	0.4096	4.4360	8.05	7.32
<u>22</u>	5.52	-0.1802	1.9531	15.3712	0.8266	37.6322	46.2513	24.7905	0.0000	0.4334	0.5836	3.9053	5.85	5.52
<u>23</u>	6.54	-0.1748	1.9124	7.3751	0.8266	37.6322	46.2513	24.7905	0.0000	0.4706	0.6459	3.8533	6.21	6.54
<u>24</u>	6.08	-0.1797	1.8776	7.4955	0.8266	37.6322	46.2513	24.7905	0.0000	0.4711	0.6446	4.2023	6.36	6.08
<u>25</u>	6.55	-0.1647	1.9273	7.4668	0.8373	37.6322	46.2513	24.7905	0.0000	0.4115	0.6399	4.0779	6.23	6.55
<u>26</u>	6.83	-0.1460	1.9562	7.3479	0.8373	37.6322	46.2513	24.7905	0.0000	0.4088	0.5248	4.2847	6.14	6.83

27	6.54	-0.1937	1.9531	9.6877	0.8176	37.6322	46.2513	24.7905	0.0000	0.8199	1.2406	3.5093	6.70	6.54
28	6.39	-0.1935	1.9124	9.2588	0.6726	74.3970	83.0160	24.7905	0.0000	0.9619	1.2894	3.4352	6.13	6.39
29	5.87	-0.1933	1.8776	8.9709	0.8176	37.6322	46.2513	24.7905	0.0000	0.7650	0.9268	2.9975	6.34	5.87
30	6.47	-0.1906	1.9154	9.2557	0.6961	66.9007	85.5197	24.7905	0.0000	0.5243	0.9115	3.0937	6.31	6.47
31	5.58	-0.1968	1.8571	7.2616	0.8267	40.1360	48.7550	24.7905	0.0000	0.2485	0.3474	2.5761	5.48	5.58
32	5.99	-0.1746	1.9757	46.6133	0.6311	94.5571	113.9543	31.3033	0.0000	0.7325	1.7489	3.0978	5.74	5.99
33	7.84	-0.1784	1.7688	4.1851	0.9096	12.3918	21.0108	24.7905	0.0000	0.4918	0.6669	3.8289	7.03	7.84
34	7.38	-0.1771	1.8347	5.5075	0.8898	18.8846	27.5036	24.7905	18.4396	0.5462	0.7210	4.6236	7.69	7.38
35	5.18	-0.1711	2.0002	11.2749	0.7766	56.3799	64.9989	24.7905	0.0000	0.4884	0.5347	4.5949	5.71	5.18
36	5.63	-0.1816	1.8802	5.3249	0.6909	67.8246	76.4436	35.9811	0.0000	0.7747	1.0942	3.1464	6.32	5.63
37	6.13	-0.1837	1.9154	6.6928	0.7176	70.3284	78.9474	51.4344	0.0000	0.4344	1.0296	2.4707	6.13	6.13
38	5.48	-0.1614	1.9124	4.3663	0.7344	61.2523	69.8713	49.4828	0.0000	0.5495	1.0985	1.9388	6.30	5.48
39	6.60	-0.1831	1.8388	6.0013	0.7941	45.0084	53.6274	55.9254	18.4396	0.1450	0.6994	1.1946	6.65	6.60
49	6.07	-0.2115	1.6141	35.4957	0.9073	0.6369	17.3749	11.1906	0.0000	0.6643	0.6669	2.6865	6.54	6.07
50	6.60	-0.1953	1.7365	5.9932	0.9028	12.2549	20.8739	11.1906	0.0000	0.4957	0.4490	3.3765	6.37	6.60
51	6.30	-0.1941	1.8015	5.9776	0.7763	43.2575	51.8765	11.1906	18.4396	0.4714	0.3470	3.4573	6.19	6.30
52	5.42	-0.1915	1.8800	6.6689	0.7657	49.7503	58.3693	11.1906	0.0000	0.4878	0.3623	3.2201	5.27	5.42
53	5.36	-0.1771	1.9122	6.5426	0.7812	49.7503	58.3693	11.1906	0.0000	0.4104	0.6361	3.7671	5.65	5.36
54	5.52	-0.1798	1.8774	6.5769	0.8271	37.4954	46.1144	11.1906	0.0000	0.4166	0.6571	3.6761	5.94	5.52

Abbreviation *BLOSUM62*: BLOcks SUBstitution Matrices; *RMSD*: Root-mean-square deviation

Denotation of the scoring functions for MOE molecular docking calculations

S: the final score, which is the score of the last stage of refinement; *E_conf*: the energy of the conformer - if there is a refinement stage, this is the energy calculated at the end of the refinement; *E_place*: score from the placement stage; *E_score1/2*: score from rescoring stages 1 and 2; *E_refine*: score from the refinement stage, calculated to be the sum of the van der Waals electrostatics and solvation energies, under the Generalized Born solvation model (GB/VI)

Denotation of QSAR molecular descriptors

GCUT_SMR_0: the GCUT descriptors using atomic contribution to molar refractivity; *E*: value of the potential energy; *dipoleY*: the y component of the dipole moment (external coordinates); *dipoleZ*: the z component of the dipole moment; *DCASA*: absolute value of the difference between *CASA+* (Positive charge weighted surface area, ASA^+ times $\max \{ q_i > 0 \}$) and *CASA-* (Negative charge weighted surface area, ASA^- times $\max \{ q_i < 0 \}$); *Q_RPC-*: relative negative partial charge; *Q_VSA_FHYD*: fractional hydrophobic van der Waals surface area; *SlogP_VSA4*: sum of v_i such that Li is in (0.1,0.15]; *vsurf_EDmin1*: lowest hydrophobic energy; *vsurf_IW5*: hydrophilic integy moment; *Q_VSA_PNEG*: fractional negative van der Waals surface area; *Q_VSA_POL*: total positive van der Waals surface area; *SlogP_VSA3*: sum of v_i such that Li is in (0,0.1]; *vsurf_ID7*: hydrophobic integy moment; *vsq_other*: approximation to the sum of VDW surface areas (\AA^2) of atoms typed as "other"; *E_tor*: torsion (proper and improper) potential energy; *balabanJ*: Balaban's connectivity topological index; *vsurf_ID1*: hydrophobic integy moment; *GCUT_SMR_1*: the GCUT descriptors using atomic contribution to molar refractivity.