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Supporting Information for:

A Multiple-step Screening Protocol to Identify Norepinephrine and Dopamine Reuptake Inhibitors for Depression

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TABLES

Table S1. ADME/T and medicinal chemistry friendliness properties of 85 identified NDRIs with good druglikeness.

No	Absorption	Distribution			Metabolism							Excretion	Toxicity			Medicinal chemistry			
					2D6	3A4	1A2	2C19	2C9	2D6	3A4								
	HIA[a]	VDss[b]	BBB	CNS	substrate		inhibitor					CLtot[c]	AMES	Hepato toxicity	Skin Sensitization	PAINS[d]	Brenk[e]	Leadlikeness violations	SA[f]
10198901	85.98	-0.153	-0.062	-2.974	No	No	No	No	No	No	No	0.371	No	No	No	0	0	0	3.66
11529806	97.93	0.21	-0.134	-2.958	No	Yes	No	No	No	No	No	0.769	No	No	No	0	0	0	3.5
15462961	94.054	0.268	-0.122	-2.945	No	Yes	No	No	No	No	No	0.752	No	No	No	0	0	0	2.89
2252698	93.303	-0.25	-0.122	-2.913	No	Yes	No	No	No	No	No	0.48	No	No	No	0	0	0	3.69
2830426	93.303	-0.25	-0.122	-2.913	No	Yes	No	No	No	No	No	0.48	No	No	No	0	0	0	3.69
2830427	92.884	-0.19	-0.138	-2.912	No	Yes	No	No	No	No	No	0.514	No	No	No	0	0	0	3.83
740411	92.884	-0.19	-0.138	-2.912	No	Yes	No	No	No	No	No	0.514	No	No	No	0	0	0	3.83
4439548	93.249	-0.178	-0.12	-2.906	No	Yes	No	No	No	No	No	0.52	No	No	No	0	0	0	3.83
694296	93.249	-0.178	-0.12	-2.906	No	Yes	No	No	No	No	No	0.52	No	No	No	0	0	0	3.83
16863753	85.092	-0.172	-0.093	-2.892	No	No	Yes	No	No	No	No	0.245	No	No	No	0	0	0	1.67
9179017	94.055	0.209	0.05	-2.866	No	No	Yes	No	No	No	No	0.261	No	No	No	0	0	0	2.92
9179018	94.055	0.209	0.05	-2.866	No	No	Yes	No	No	No	No	0.261	No	No	No	0	0	0	2.92
4463768	89.75	-0.13	-0.085	-2.855	No	No	No	No	No	No	No	0.389	No	No	No	0	0	0	3.18
2854801	93.917	0.399	0.113	-2.82	No	No	Yes	No	No	No	No	0.938	No	No	No	0	0	0	3.48
7310282	93.917	0.399	0.113	-2.82	No	No	Yes	No	No	No	No	0.938	No	No	No	0	0	0	3.48
7310284	93.917	0.399	0.113	-2.82	No	No	Yes	No	No	No	No	0.938	No	No	No	0	0	0	3.48
773655	93.917	0.399	0.113	-2.82	No	No	Yes	No	No	No	No	0.938	No	No	No	0	0	0	3.48
CHEMBL1542304	94.874	0.413	0.149	-2.81	No	No	Yes	No	No	No	No	0.72	No	No	No	0	0	0	3.63
11694773	93.945	0.359	-0.035	-2.77	No	No	No	No	No	No	No	0.915	No	No	No	0	0	0	2.99

755204	95.003	0.023	0.192	-2.765	No	Yes	Yes	Yes	No	No	No	0.509	No	No	No	0	0	0	2.4
12152606	98.663	0.393	0.255	-2.741	No	Yes	No	No	No	No	No	1.714	No	No	No	0	0	0	3.51
17792486	94.03	-0.302	0.081	-2.558	No	Yes	No	No	No	No	No	0.545	No	No	No	0	0	0	2.36
CHEMBL1194927	92.139	0.387	0.478	-2.541	No	No	No	No	No	No	No	0.859	No	No	No	0	0	0	2.87
3664120	92.022	-0.208	0.201	-2.517	No	No	No	No	No	No	No	0.287	No	No	No	0	0	0	2.69
16243951	91.052	-0.443	0.079	-2.516	Yes	No	No	No	No	No	No	0.352	No	No	No	0	0	0	2.39
10199019	94.422	0.261	0.202	-2.398	No	No	No	No	No	No	No	0.736	No	No	No	0	0	0	3.41
16243946	92.316	-0.387	0.043	-2.389	Yes	No	No	No	No	No	No	0.286	No	No	No	0	0	0	2.44
17163712	93.574	0.09	0.369	-2.358	No	No	Yes	No	No	No	No	0.212	No	No	No	0	0	0	1.72
4309781	94.01	-0.66	0.063	-2.351	Yes	Yes	No	No	No	No	No	0.426	No	No	No	0	0	0	2.74
7023523	94.01	-0.66	0.063	-2.351	Yes	Yes	No	No	No	No	No	0.426	No	No	No	0	0	0	2.74
7094962	94.01	-0.66	0.063	-2.351	Yes	Yes	No	No	No	No	No	0.426	No	No	No	0	0	0	2.74
7094966	94.01	-0.66	0.063	-2.351	Yes	Yes	No	No	No	No	No	0.426	No	No	No	0	0	0	2.74
17683253	91.31	0.199	0.32	-2.336	No	No	No	Yes	No	No	No	0.131	No	No	No	0	0	0	1.73
9178384	93.919	0.195	-0.103	-2.328	No	Yes	Yes	Yes	Yes	No	No	1.282	No	No	No	0	0	0	3
9173641	93.827	0.067	0.373	-2.328	No	No	Yes	No	No	No	No	0.254	No	No	No	0	0	0	2.54
9173642	93.827	0.067	0.373	-2.328	No	No	Yes	No	No	No	No	0.254	No	No	No	0	0	0	2.54
9178809	93.91	0.342	-0.126	-2.316	No	Yes	No	Yes	No	No	No	1.323	No	No	No	0	0	0	3.04
9178810	93.91	0.342	-0.126	-2.316	No	Yes	No	Yes	No	No	No	1.323	No	No	No	0	0	0	3.04
9179019	93.462	0.27	0.039	-2.316	No	Yes	Yes	Yes	Yes	No	No	0.287	No	No	No	0	0	0	3.04
9179020	93.462	0.27	0.039	-2.316	No	Yes	Yes	Yes	Yes	No	No	0.287	No	No	No	0	0	0	3.04
4332128	88.189	0.01	0.293	-2.314	No	No	No	No	No	No	No	0.464	No	No	No	0	0	0	2.77
2872324	92.355	0.02	0.339	-2.314	No	No	Yes	Yes	No	No	No	1.2	No	No	No	0	0	0	2.53
738726	92.355	0.02	0.339	-2.314	No	No	Yes	Yes	No	No	No	1.2	No	No	No	0	0	0	2.53

738728	92.355	0.02	0.339	-2.314	No	No	Yes	Yes	No	No	No	1.2	No	No	No	0	0	0	2.53
705668	92.537	0.017	0.345	-2.314	No	No	Yes	Yes	No	No	No	0.333	No	No	No	0	0	0	2.34
705671	92.537	0.017	0.345	-2.314	No	No	Yes	Yes	No	No	No	0.333	No	No	No	0	0	0	2.34
5136595	91.267	-0.192	0.137	-2.311	No	No	No	No	No	No	No	0.282	No	No	No	0	0	0	2.84
16488658	94.216	0.035	0.386	-2.282	No	No	Yes	No	No	No	No	0.251	No	No	No	0	0	0	2.44
16243943	91.078	-0.189	0.326	-2.28	Yes	No	No	No	No	No	No	0.369	No	No	No	0	0	0	2.28
3303426	89.435	0.048	0.27	-2.255	No	No	No	No	No	No	No	0.245	No	No	No	0	0	0	2.82
17823867	89.701	0.426	0.408	-2.245	No	Yes	No	No	No	Yes	No	0.603	No	No	No	0	0	0	2.8
11097354	93.23	0.079	0.269	-2.243	No	Yes	No	No	No	No	No	0.188	No	No	No	0	0	0	2.97
10879888	93.294	0.053	0.278	-2.243	No	Yes	No	No	No	No	No	0.253	No	No	No	0	0	0	2.98
9178915	93.678	0.176	0.133	-2.221	No	Yes	No	Yes	Yes	No	No	-0.002	No	No	No	0	0	0	2.85
9178916	93.678	0.176	0.133	-2.221	No	Yes	No	Yes	Yes	No	No	-0.002	No	No	No	0	0	0	2.85
3153078	92.936	0.057	0.36	-2.217	No	No	Yes	Yes	No	No	No	0.226	No	No	No	0	0	0	2.17
9178917	93.049	0.22	0.092	-2.202	No	Yes	Yes	Yes	Yes	No	No	0.025	No	No	No	0	0	0	2.97
9178918	93.049	0.22	0.092	-2.202	No	Yes	Yes	Yes	Yes	No	No	0.025	No	No	No	0	0	0	2.97
2885047	93.369	-0.185	-0.492	-2.201	No	Yes	No	No	No	No	No	-0.014	No	No	No	0	0	0	3.56
714580	93.369	-0.185	-0.492	-2.201	No	Yes	No	No	No	No	No	-0.014	No	No	No	0	0	0	3.56
3719810	100	-1.305	0.034	-2.191	No	No	No	No	No	No	No	0.543	No	No	No	0	0	0	3.09
7389842	100	-1.305	0.034	-2.191	No	No	No	No	No	No	No	0.543	No	No	No	0	0	0	3.09
4654013	88.564	-0.004	0.3	-2.179	No	No	No	No	No	No	No	0.393	No	No	No	0	0	0	2.85
9179135	91.458	0.291	0.107	-2.146	No	Yes	Yes	Yes	Yes	No	No	0.189	No	No	No	0	0	0	3.08
9179136	91.458	0.291	0.107	-2.146	No	Yes	Yes	Yes	Yes	No	No	0.189	No	No	No	0	0	0	3.08
3784742	92.931	0.034	0.38	-2.145	No	No	Yes	Yes	No	No	No	0.192	No	No	No	0	0	0	2.28
5018994	90.225	0.017	0.3	-2.133	No	No	No	No	No	No	No	0.359	No	No	No	0	0	0	2.68

7312550	94.181	0.228	-0.032	-2.115	Yes	Yes	No	Yes	No	No	No	0.197	No	No	No	0	0	0	4.23
7312551	94.181	0.228	-0.032	-2.115	Yes	Yes	No	Yes	No	No	No	0.197	No	No	No	0	0	0	4.23
851745	94.181	0.228	-0.032	-2.115	Yes	Yes	No	Yes	No	No	No	0.197	No	No	No	0	0	0	4.23
1236294	94.181	0.228	-0.032	-2.115	Yes	Yes	No	Yes	No	No	No	0.197	No	No	No	0	0	0	4.23
17984994	92.636	0.121	0.276	-2.115	No	Yes	No	No	No	No	No	0.459	No	No	No	0	0	0	3.49
11601549	92.791	-0.022	0.234	-2.105	No	Yes	No	No	No	No	No	0.265	No	No	No	0	0	0	3.36
4013319	94.469	-0.228	0.178	-2.081	No	No	No	No	No	No	No	0.267	No	No	No	0	0	0	2.82
17980455	93.844	-0.341	-0.056	-1.898	No	Yes	No	No	No	No	No	0.285	No	No	No	0	0	0	3.14
4672791	93.006	0.185	-0.068	-1.886	No	Yes	Yes	Yes	No	No	No	0.258	No	No	No	0	0	0	3.66
9548016	95.297	0.354	0.225	-1.786	No	Yes	No	No	No	Yes	No	0.859	No	No	No	0	0	0	3.58
9548004	95.01	0.338	0.228	-1.786	No	Yes	No	No	No	Yes	No	0.79	No	No	No	0	0	0	3.58
9993413	92.459	0.436	0.405	-1.775	Yes	Yes	No	Yes	No	No	No	1.147	No	No	No	0	0	0	3.44
11821937	95.555	-0.315	0.545	-1.556	No	Yes	Yes	Yes	Yes	No	No	0.388	No	No	No	0	0	0	3.07
5772986	96.165	0.373	0.135	-1.433	No	Yes	Yes	Yes	Yes	No	Yes	0.335	No	No	No	0	0	0	3.46
10491654	94.908	0.095	0.13	-1.413	No	Yes	No	No	No	No	No	0.458	No	No	No	0	0	0	4.06
6044288	95.529	0.421	0.094	-1.255	No	Yes	Yes	Yes	Yes	No	No	0.317	No	No	No	0	0	0	3.29
5962259	95.817	0.428	0.105	-1.248	No	Yes	Yes	Yes	Yes	No	Yes	0.306	No	No	No	0	0	0	3.34
11616151	97.106	0.139	0.323	-1.079	No	Yes	Yes	Yes	No	No	No	0.171	No	No	No	0	0	0	3.61

[a] HIA: human intestine absorption.

[b] VDss: volume of distribution at steady state.

[c] CLtot: Total Clearance.

[d] PAINS: pan assay interference compounds.

[e] Brenk: Brenk filter.

[f] SA: synthetic accessibilities.

Table S2. Distances and angles between acceptor···donor atoms and the occupancies calculated in hydrogen bond analysis for hNET and hDAT.

Drugs	Target	H-Bond	Acceptor	Donor	Distance (Å)[a]	Angle (°)[a]	Occupancy (%)[b]	Round No.
3719810	hNET	HB1	Asp75 (OD1)	3719810 (N1-H1)	2.76	154.81	63.41	Round 1
		HB2	Asp75 (OD2)	3719810 (N1-H1)	2.76	154.62	22.03	
		HB1	Asp75 (OD1)	3719810 (N1-H18)	2.82	156.71	38.52	Round 2
		HB2	Asp75 (OD2)	3719810 (N1-H18)	2.83	150.52	25.15	
		HB1	Asp75 (OD1)	3719810 (N1-H18)	2.80	157.22	5.20	Round 3
		HB2	Asp75 (OD2)	3719810 (N1-H18)	2.83	153.67	5.17	
	hDAT	HB1	Asp79 (OD2)	3719810 (N1-H1)	2.84	153.60	72.89	Round 1
		HB1	Asp79 (OD2)	3719810 (N1-H18)	2.77	163.98	97.15	Round 2
		HB1	Asp79 (OD2)	3719810 (N1-H18)	2.78	158.55	85.97	Round 3
3719810B	hNET	HB1	Asp75 (OD2)	3719810B (N1-H23)	2.82	151.91	73.52	Round 1
		HB1	Asp75 (OD1)	3719810B (N1-H1)	2.80	153.35	44.56	Round 2
		HB2	Asp75 (OD2)	3719810B (N1-H1)	2.78	155.98	37.55	
		HB1	Asp75 (OD1)	3719810B (N1-H1)	2.80	157.02	48.39	Round 3
		HB2	Asp75 (OD2)	3719810B (N1-H1)	2.80	156.23	41.58	
	hDAT	HB1	Asp79 (OD1)	3719810B (N1-H1)	2.85	150.21	19.94	Round 1
		HB2	Asp79 (OD2)	3719810B (N1-H23)	2.84	155.60	17.89	
		HB1	Asp79 (OD1)	3719810B (N1-H23)	2.79	148.14	42.05	Round 2
		HB2	Asp79 (OD2)	3719810B (N1-H23)	2.79	149.07	13.54	
		HB1	Asp79 (OD1)	3719810B (N1-H23)	2.86	152.07	33.89	Round 3
3719810D	hNET	HB1	Asp75 (OD1)	3719810D (N1-H1)	2.76	154.18	52.97	Round 1
		HB2	Asp75 (OD2)	3719810D (N1-H1)	2.74	153.98	39.40	
		HB1	Asp75 (OD2)	3719810D (N1-H1)	2.82	156.45	66.39	Round 2
		HB2	Asp75 (OD1)	3719810D (N1-H1)	2.79	155.10	13.38	
		HB1	Asp75 (OD2)	3719810D (N1-H1)	2.80	153.75	43.09	Round 3
		HB2	Asp75 (OD1)	3719810D (N1-H1)	2.79	154.38	41.24	
	hDAT	HB1	Asp79 (OD2)	3719810D (N1-H1)	2.78	145.56	17.58	Round 1
		HB2	Asp79 (OD1)	3719810D (N1-H1)	2.82	144.15	11.72	
		HB1	Asp79 (OD1)	3719810D (N1-H22)	2.77	151.81	79.44	Round 2
		HB1	Asp79 (OD1)	3719810D (N1-H22)	2.79	146.73	29.59	Round 3
3719810E	hNET	HB1	Asp75 (OD2)	3719810E (N1-H1)	2.77	144.72	66.80	Round 1
		HB1	Asp75 (OD2)	3719810E (N1-H1)	2.81	149.25	75.52	Round 2
		HB1	Asp75 (OD1)	3719810E (N1-H1)	2.80	156.23	51.58	Round 3
		HB2	Asp75 (OD2)	3719810E (N1-H1)	2.79	156.39	29.39	
	hDAT	HB1	Asp79 (OD2)	3719810E (N1-H1)	2.74	150.52	96.56	Round 1
		HB1	Asp79 (OD2)	3719810E (N1-H1)	2.77	153.35	96.19	Round 2
		HB1	Asp75 (OD1)	3719810E (N1-H1)	2.73	153.51	82.58	Round 3
		HB2	Asp75 (OD2)	3719810E (N1-H1)	2.78	154.42	13.51	

3719810N1	hNET	HB1	Asp75 (OD2)	3719810N1 (N1-H25)	2.84	144.35	28.07	Round 1
		HB1	Asp75 (OD1)	3719810N1 (N1-H17)	2.87	142.14	1.52	Round 2
		HB1	Asp75 (OD1)	3719810N1 (N1-H17)	2.87	157.06	61.09	Round 3
		HB2	Asp75 (OD2)	3719810N1 (N1-H17)	2.87	147.00	32.48	
	hDAT	HB1	Asp79 (OD1)	3719810N1 (N1-H17)	2.87	155.86	50.81	Round 1
		HB2	Asp79 (OD2)	3719810N1 (N1-H17)	2.85	149.58	39.19	
		HB1	Asp79 (OD2)	3719810N1 (N1-H17)	2.85	150.53	66.98	Round 2
		HB1	Asp79 (OD2)	3719810N1 (N1-H17)	2.82	145.08	68.29	Round 3
3719810N2	hNET	HB1	Asp75 (OD1)	3719810N2 (N1-H14)	2.80	156.26	29.80	Round 1
		HB2	Asp75 (OD2)	3719810N2 (N1-H14)	2.85	162.35	24.77	
		HB1	Asp75 (OD2)	3719810N2 (N1-H14)	2.86	156.92	55.28	Round 2
		HB1	Asp75 (OD2)	3719810N2 (N1-H14)	2.81	158.62	48.82	Round 3
		HB2	Asp75 (OD1)	3719810N2 (N1-H14)	2.81	160.46	39.11	
	hDAT	HB1	Asp79 (OD1)	3719810N2 (N1-H22)	2.82	145.54	25.99	Round 1
		HB2	Asp79 (OD2)	3719810N2 (N1-H22)	2.83	147.65	23.02	
		HB1	Asp79 (OD2)	3719810N2 (N1-H22)	2.86	155.48	69.52	Round 2
		HB1	Asp79 (OD2)	3719810N2 (N1-H22)	2.85	150.63	34.58	Round 3

[a] The hydrogen bonds are determined by the acceptor···donor atom distance of less than 3.5Å and acceptor···H-donor angle of greater than 120º.

[b] Occupancy (%) represents the stability and strength of the hydrogen bonds.

Table S3. Detailed energy terms of calculated binding energies for 3719810 and its optimized compounds in hNET and hDAT (ΔG are in $kcal/mol$).

Drugs	Targe	ΔE_{ele}	ΔE_{vdw}	ΔG_{pol}	ΔG_{nonpol}	$\Delta G_{cacl(MM/GBSA)}$[a]	Round No.
3719810	hNET	-66.70±0.15	-39.21±0.12	69.58±0.14	-5.10±0.01	-41.43±0.12	Round 1
		-68.69±0.18	-38.95±0.12	71.97±0.17	-4.95±0.01	-40.63±0.10	Round 2
		-66.32±0.26	-38.11±0.12	70.14±0.22	-4.83±0.01	-39.13±0.14	Round 3
	hDAT	-113.25±0.17	-45.91±0.12	113.20±0.15	-5.41±0.00	-51.37±0.17	Round 1
		-103.61±0.19	-31.93±0.11	104.66±0.17	-4.69±0.01	-35.56±0.09	Round 2
		-93.49±0.20	-32.99±0.11	97.77±0.20	-4.68±0.01	-33.39±0.10	Round 3
3719810B	hNET	-76.40±0.17	-43.55±0.10	78.73±0.15	-5.76±0.01	-46.97±0.09	Round 1
		-68.95±0.41	-37.78±0.12	71.70±0.41	-5.33±0.01	-40.37±0.11	Round 2
		-82.51±0.22	-38.94±0.12	83.16±0.20	-5.21±0.01	-43.50±0.11	Round 3
	hDAT	-91.78±0.21	-38.85±0.11	94.16±0.19	-5.31±0.01	-41.78±0.10	Round 1
		-87.58±0.45	-39.32±0.10	87.71±0.49	-5.30±0.01	-44.49±0.11	Round 2
		-88.52±0.19	-36.16±0.08	87.72±0.18	-4.87±0.01	-41.83±0.09	Round 3
3719810D	hNET	-78.66±0.23	-41.05±0.13	77.98±0.24	-5.51±0.01	-47.24±0.12	Round 1
		-70.42±0.30	-40.68±0.11	73.46±0.25	-5.30±0.01	-42.95±0.12	Round 2
		-75.77±0.41	-39.79±0.13	77.06±0.37	-5.40±0.01	-43.89±0.14	Round 3
	hDAT	-88.43±0.27	-40.98±0.18	92.52±0.26	-5.26±0.02	-42.15±0.20	Round 1
		-104.74±0.16	-43.40±0.10	104.09±0.14	-5.57±0.00	-49.62±0.09	Round 2
		-95.93±0.16	-40.84±0.11	95.35±0.16	-5.32±0.01	-46.74±0.10	Round 3
3719810E	hNET	-73.69±0.18	-47.16±0.13	73.19±0.15	-5.68±0.01	-53.34±0.13	Round 1
		-79.22±0.17	-47.21±0.13	77.53±0.14	-5.65±0.00	-55.56±0.12	Round 2
		-75.11±0.30	-47.32±0.13	77.18±0.23	-5.75±0.01	-51.00±0.15	Round 3
	hDAT	-110.07±0.16	-47.17±0.12	107.08±0.14	-5.92±0.00	-56.08±0.11	Round 1
		-112.48±0.22	-47.96±0.12	108.94±0.20	-6.11±0.00	-57.60±0.11	Round 2
		-110.13±0.18	-47.52±0.12	109.88±0.14	-5.98±0.00	-53.75±0.13	Round 3
3719810N1	hNET	-76.95±0.16	-47.16±0.11	76.43±0.15	-6.17±0.01	-53.85±0.11	Round 1
		-76.21±0.19	-49.48±0.10	77.34±0.18	-6.35±0.01	-54.71±0.12	Round 2
		-86.82±0.22	-48.69±0.11	86.14±0.21	-5.99±0.01	-55.36±0.10	Round 3
	hDAT	-107.02±0.17	-48.70±0.13	106.75±0.14	-5.79±0.01	-54.77±0.11	Round 1
		-113.53±0.17	-47.37±0.11	111.50±0.16	-6.08±0.00	-55.47±0.10	Round 2
		-109.08±0.20	-46.82±0.11	105.28±0.17	-6.21±0.01	-56.72±0.12	Round 3
3719810N2	hNET	-78.38±0.35	-38.07±0.14	81.15±0.28	-5.10±0.01	-40.40±0.18	Round 1
		-76.41±0.26	-43.52±0.11	77.91±0.23	-5.55±0.01	-47.58±0.12	Round 2
		-71.04±0.32	-40.34±0.13	72.87±0.33	-5.23±0.01	-43.74±0.16	Round 3
	hDAT	-109.37±0.17	-45.56±0.11	111.30±0.15	-5.52±0.00	-49.15±0.11	Round 1
		-109.18±0.16	-46.99±0.11	112.06±0.15	-5.52±0.00	-49.62±0.11	Round 2
		-105.66±0.22	-43.93±0.10	108.61±0.19	-5.42±0.00	-46.41±0.10	Round 3

[a] Calculated binding energy in this work.

FIGURES

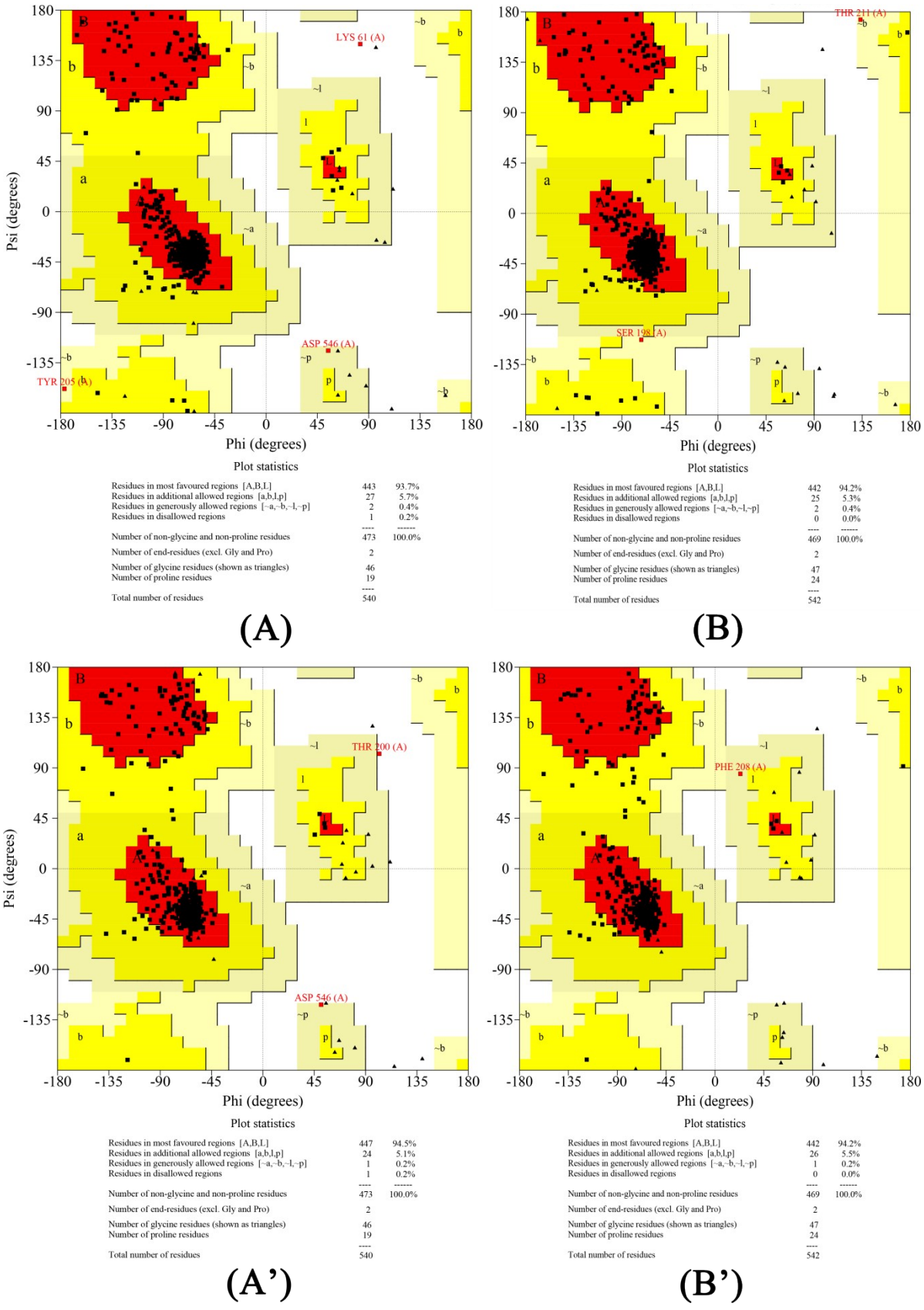


Figure S1. Ramachandran plots of the homology models for hNET and hDAT. (A) and (B) were Ramachandran plots of models constructed based on the crystalized templets of dDAT 4XNX by SWISS-MODEL, (A') and (B') were that of obtained from AlphaFold 2.

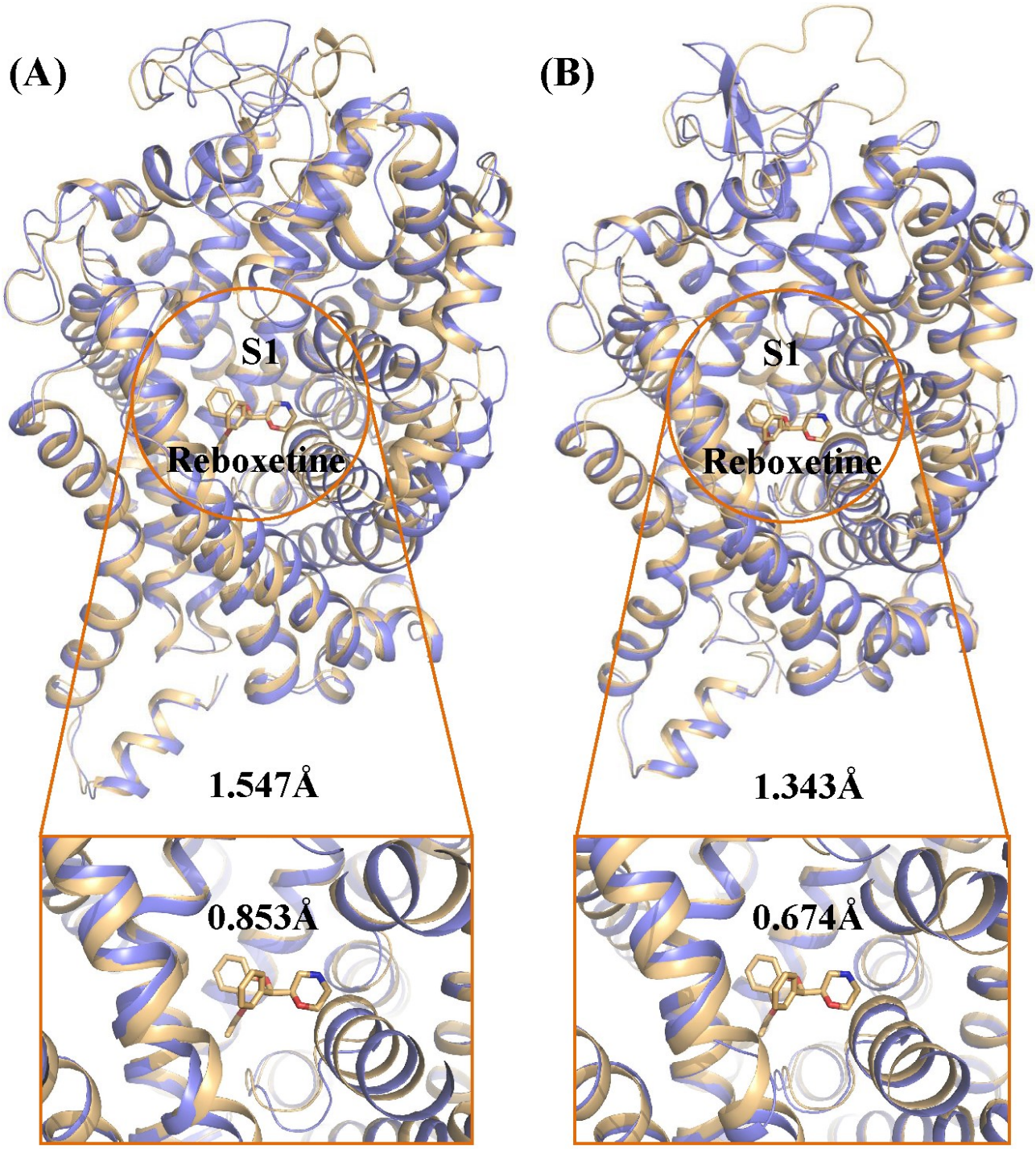


Figure S2. Structural superimposition of homology models constructed by SWISS-MODEL (blue) and AlphaFold 2 (brown) for hNET (A) and hDAT (B).

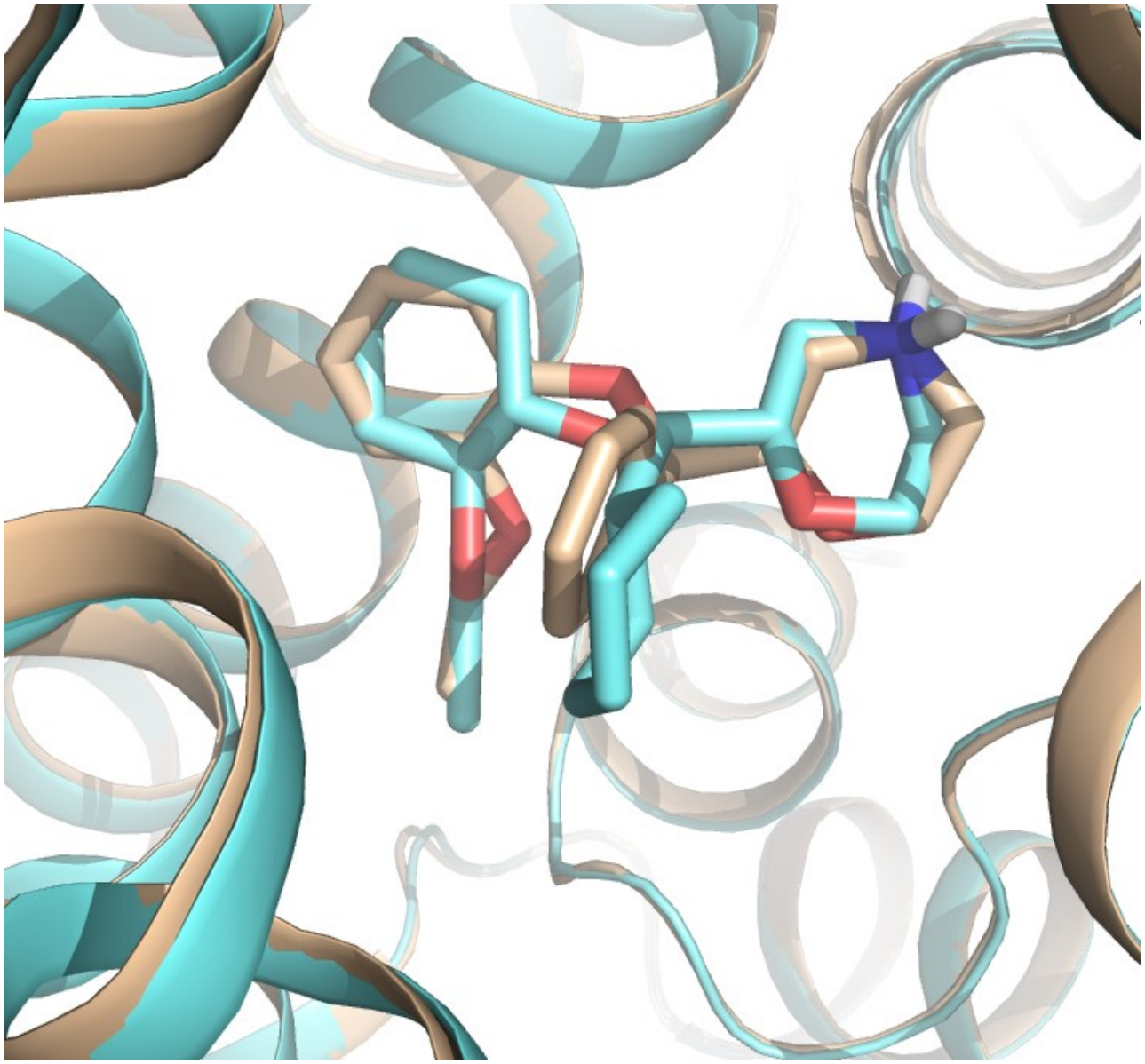


Figure S3. Structural superimposition of re-docking pose of Mavoglurant (cyan) with its co-crystallized pose (light brown).

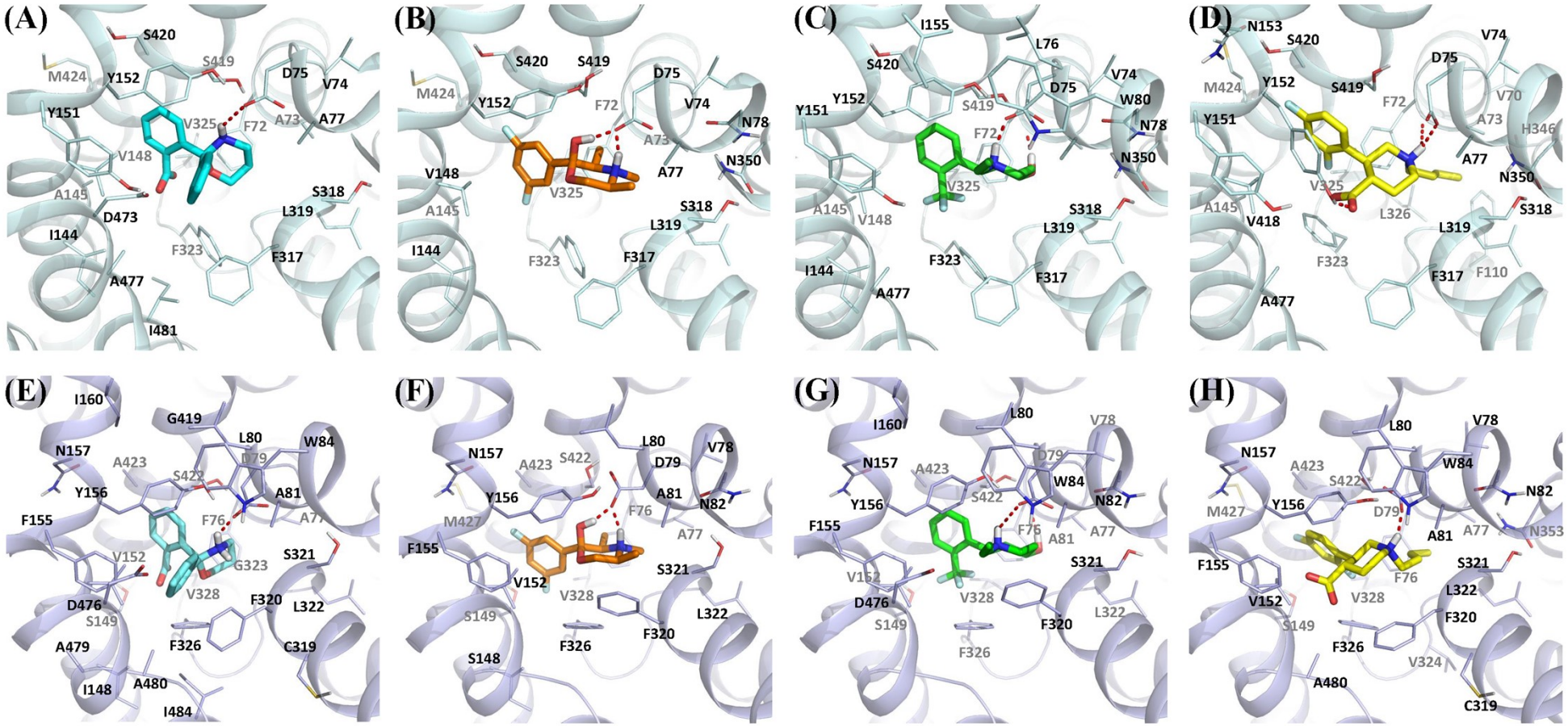
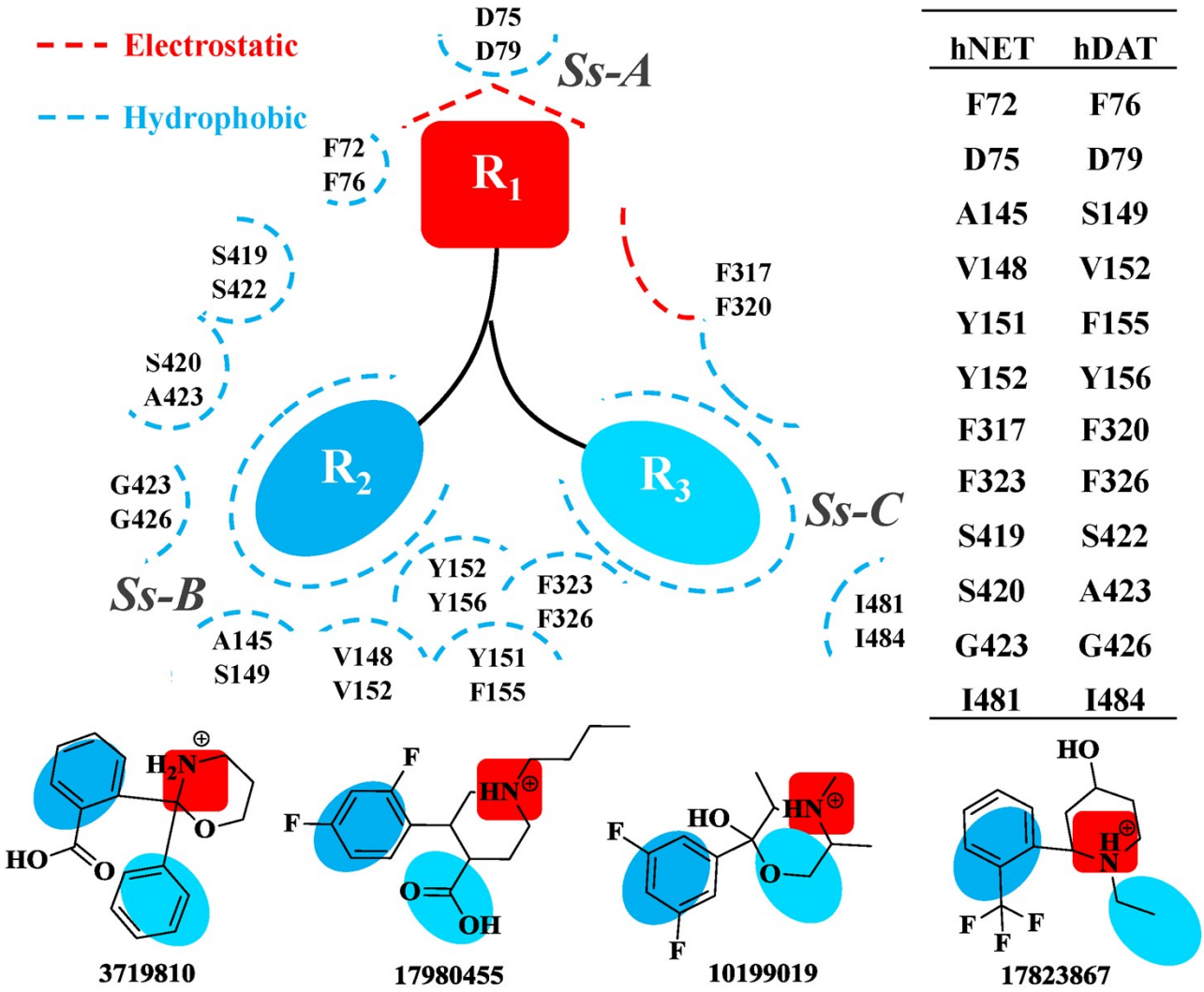


Figure S4. The docking poses of 4 obtained NDRIs compounds in the binding site of hNET (palecyan) and hDAT (slateblue) shown in ribbon representation. A-D and E-H were 3719810 (cyan), 10199019 (brown), 17823867 (green), 17980455 (yellow) in hNET and hDAT. Palecyan and slateblue cartoon representation was used for the backbone atoms of hNET and hDAT. Residues and drugs were shown in stick representation, and only polar hydrogen atoms were displayed for clarity. Salt bridges and hydrogen bonds were depicted as red dotted lines and residues located out and in the visual plane were illustrated in black and gray color, respectively.



hNET	hDAT
F72	F76
D75	D79
A145	S149
V148	V152
Y151	F155
Y152	Y156
F317	F320
F323	F326
S419	S422
S420	A423
G423	G426
I481	I484

Figure S5. Schematic representation of the binding mode between obtained NDRIs and reported sensitive residues in hNET and/or hDAT. The electrostatic and hydrophobic interactions were depicted in red and light blue dashed lines respectively. *Ss-A*, *Ss-B* and *Ss-C* were subsite A, subsite B and subsite C respectively. R_1 (red) were ammonium groups with electrostatic interaction to residues in the vicinity; R_2 (blue) were aromatic moieties with only hydrophobic interaction to its nearby residues, and R_3 (lightblue) groups perfomed hydrophobic and/or electrostatic interaction with nearby residues.

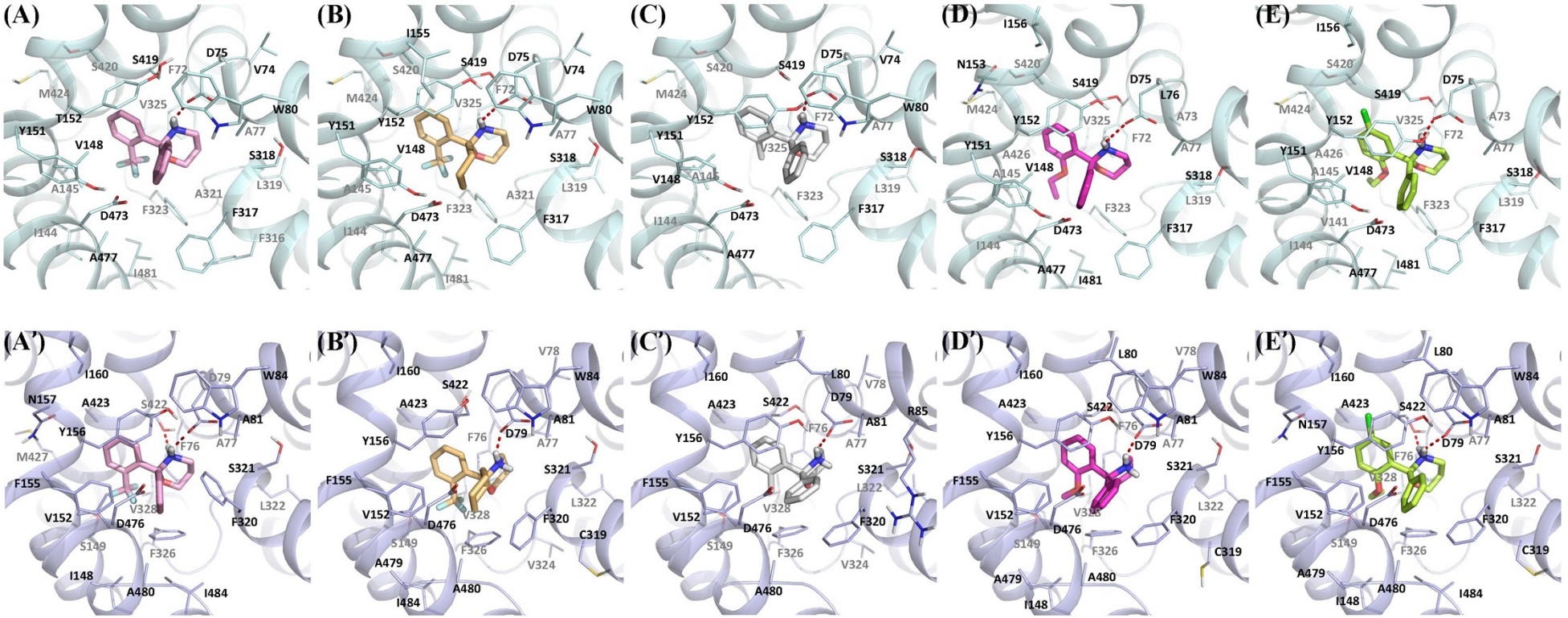


Figure S6. The docking poses of 5 analogs for 3719810 in the binding site of hNET (palecyan) and hDAT (slateblue) shown in ribbon representation. A-E and A'-E' were 3719810A (pink), 3719810B (lightbrown), 3719810C (gray), 3719810D (magenta) and 3719810E (limon) in hNET and hDAT. Palecyan and slateblue cartoon representation was used for the backbone atoms of hNET and hDAT. Residues and drugs were shown in stick representation, and only polar hydrogen atoms were displayed for clarity. Salt bridges and hydrogen bonds were depicted as red dotted lines and residues located out and in the visual plane were illustrated in black and gray color, respectively.

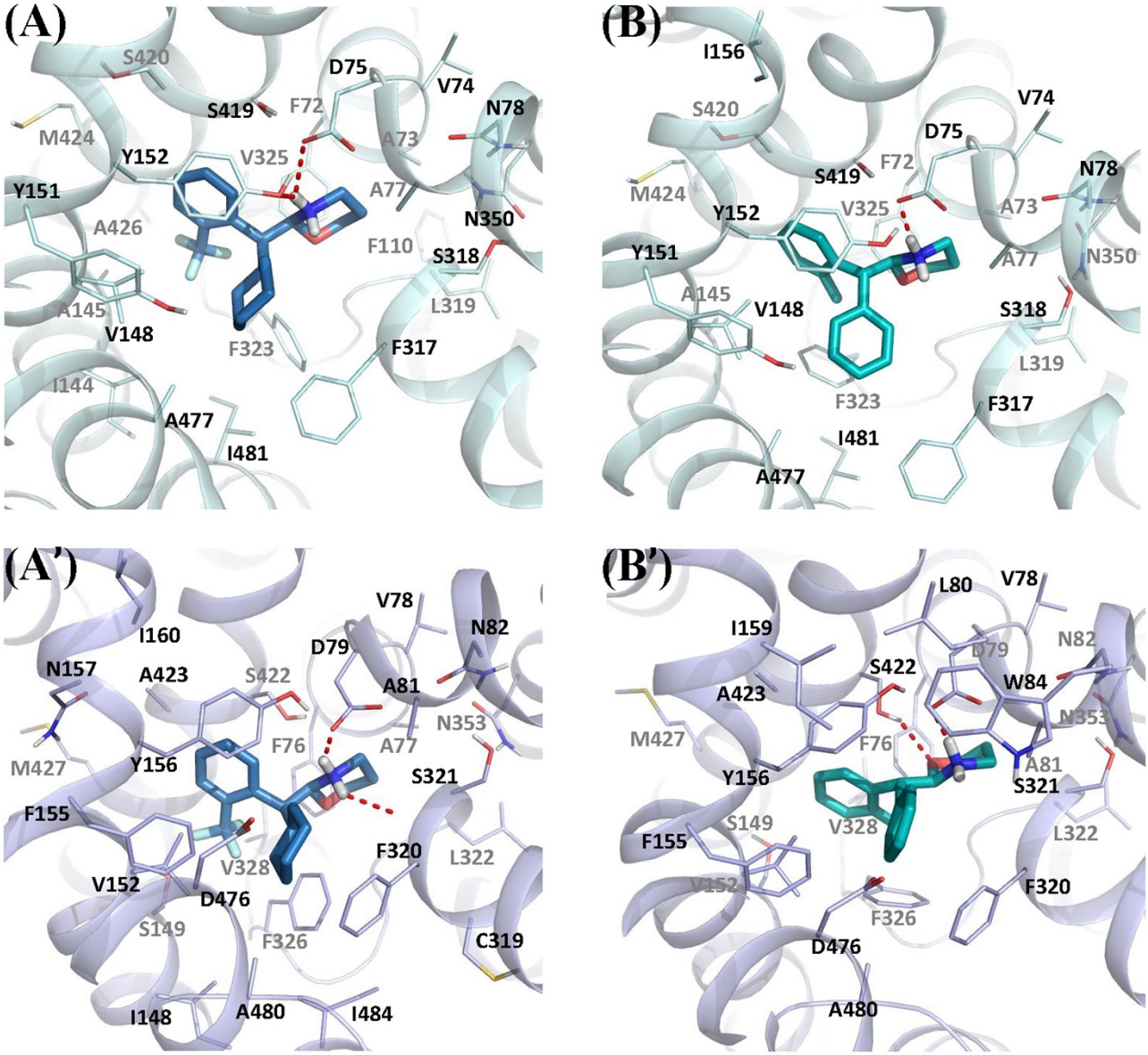


Figure S7. The docking poses of 2 novel designed compounds based on 3719810B and 3719810C in the binding site of hNET (palecyan) and hDAT (slateblue) shown in ribbon representation. A-B and A'-B' were 3719810N1 (skyblue), 3719810N2 (teal) in hNET and hDAT. Palecyan and slateblue cartoon representation was used for the backbone atoms of hNET and hDAT. Residues and drugs were shown in stick representation, and only polar hydrogen atoms were displayed for clarity. Salt bridges and hydrogen bonds were depicted as red dotted lines and residues located out and in the visual plane were illustrated in black and gray color, respectively.

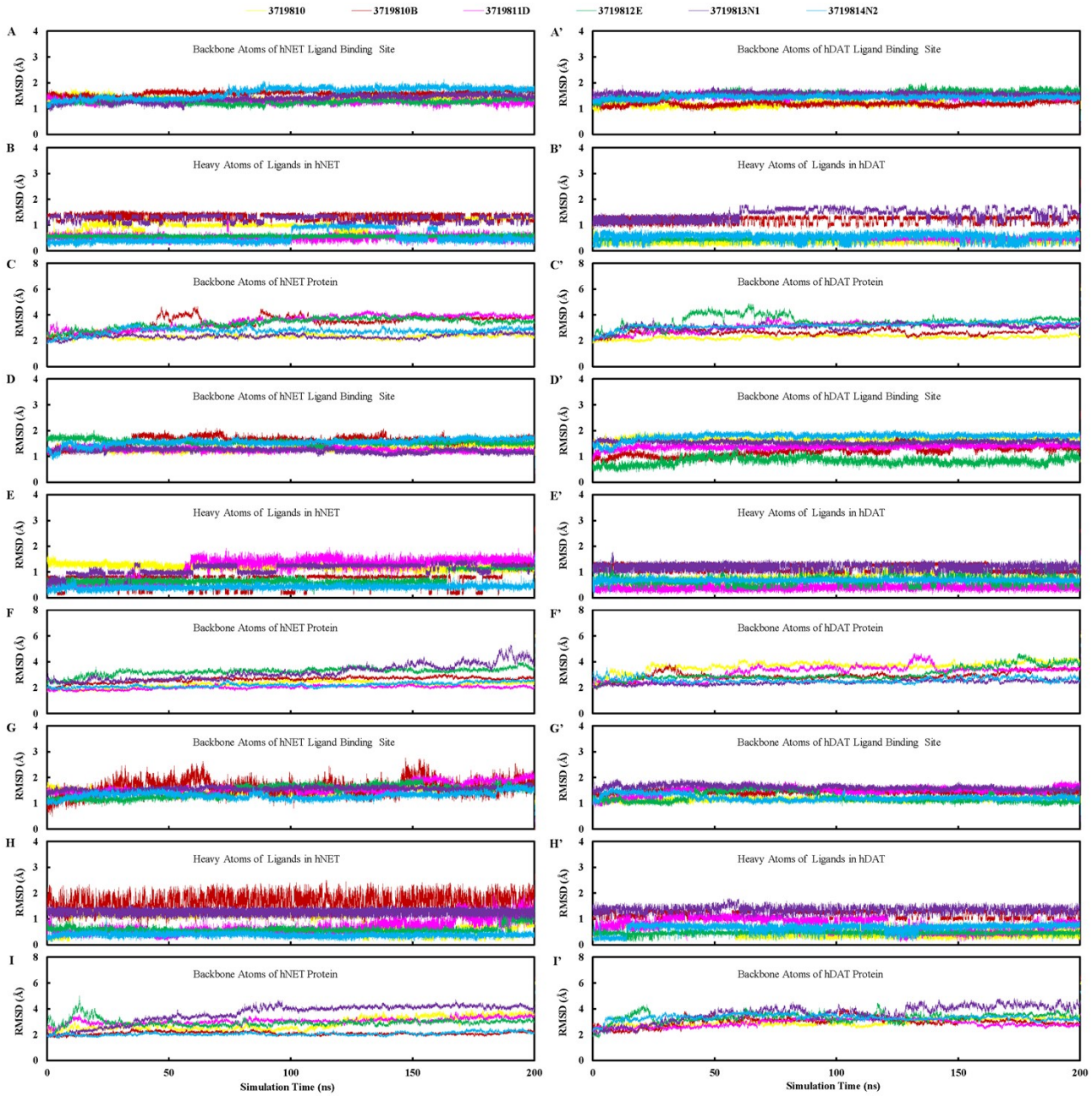


Figure S8. RMSDs plot of ligand binding site backbone, ligand heavy atoms and protein backbone in hNET (A-I) and hDAT (A'-I') as a function of MD simulations time. All 12 systems were simulated by three independent repetitions, A-C, D-F and E-I were the RMSDs plots for hNET simulated round 1, 2 and 3 respectively; A'-C', D'-F' and E'-I' were the plots for 3 hDAT simulated rounds. All systems reached equilibration state after 150 ns with only little fluctuation (within 1Å) in monitored RMSDs.

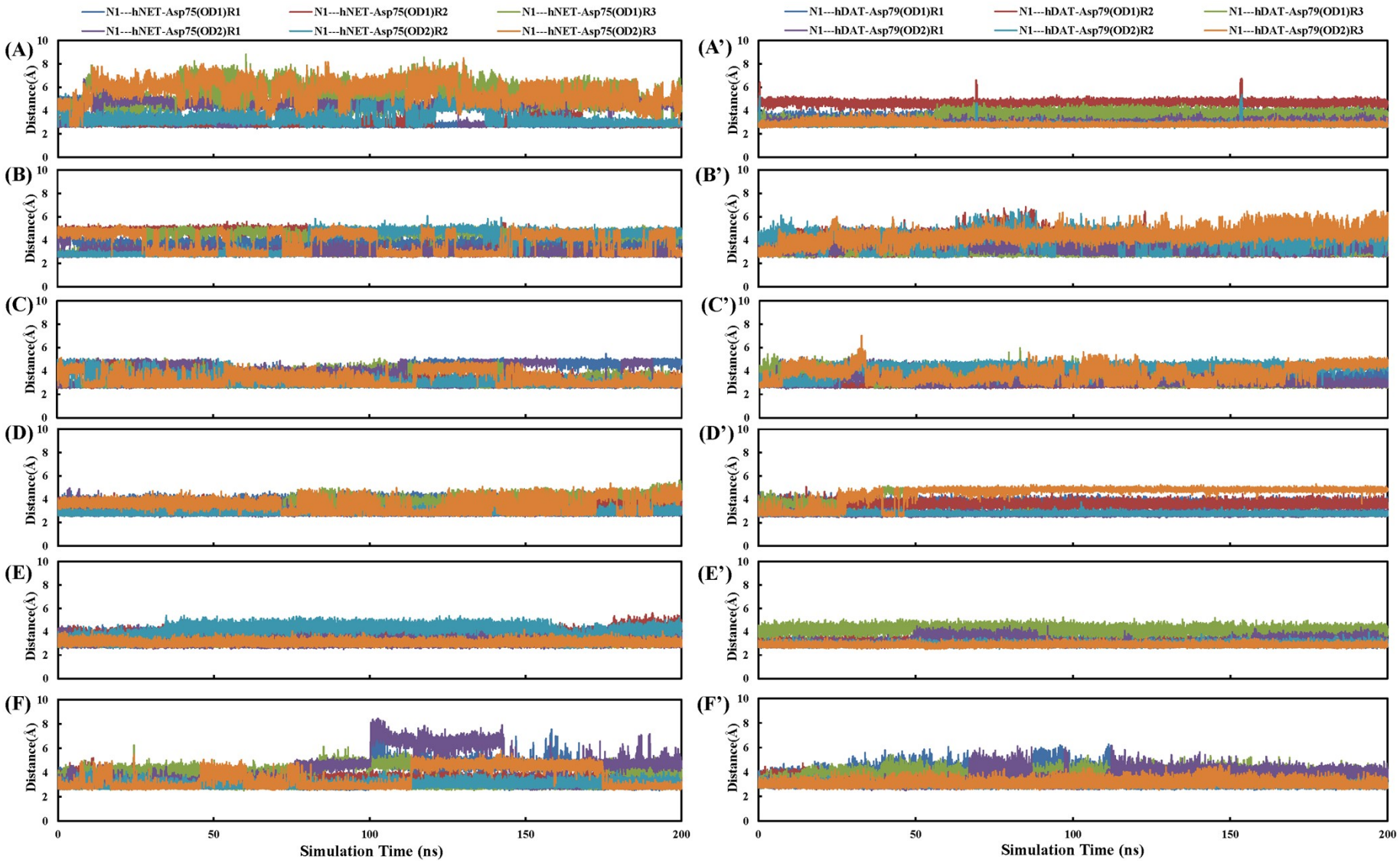


Figure S9. Distance of salt bridge between the negative oxygen atoms of Asp75 (hNET)/Asp79 (hDAT) and the positive nitrogen atoms of all obtained NDRIs compounds monitored as a function of simulation time. A-F illustrated the distance of salt bridge for 3719810, 3719810B, 3719810D, 3719810E, 3719810N1 and 3719810N2 in hNET respectively, and A'-F' were that of in hDAT. Each system was monited by three repetited simulstions, which were distinguished by round 1, 2 and 3 respectively.