Supporting Information

Ligand and decoy sets for docking to G-Protein Coupled Receptors

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Table S1: Complete list of human GPCR targets and the number of their associated agonists and antagonists in the GLL.

Receptor Name	Primary Accession Number	Receptor Entry Name	Ligand	Number of Ligands
5-hydroxytryptamine receptor 1A	P08908	5HT1A_HUMAN	Agonist	952
5-hydroxytryptamine receptor 1A	P08908	5HT1A_HUMAN	Antagonist	506
5-hydroxytryptamine receptor 1B	P28222	5HT1B_HUMAN	Agonist	81
5-hydroxytryptamine receptor 1B	P28222	5HT1B_HUMAN	Antagonist	32
5-hydroxytryptamine receptor 1D	P28221	5HT1D_HUMAN	Agonist	558
5-hydroxytryptamine receptor 1D	P28221	5HT1D_HUMAN	Antagonist	315
5-hydroxytryptamine receptor 1E	P28566	5HT1E_HUMAN	Agonist	32
5-hydroxytryptamine receptor 1E	P28566	5HT1E_HUMAN	Antagonist	17
5-hydroxytryptamine receptor 1F	P30939	5HT1F_HUMAN	Agonist	131
5-hydroxytryptamine receptor 1F	P30939	5HT1F_HUMAN	Antagonist	11
5-hydroxytryptamine receptor 2A	P28223	5HT2A_HUMAN	Agonist	34
5-hydroxytryptamine receptor 2A	P28223	5HT2A_HUMAN	Antagonist	725
5-hydroxytryptamine receptor 2B	P41595	5HT2B_HUMAN	Agonist	30
5-hydroxytryptamine receptor 2B	P41595	5HT2B_HUMAN	Antagonist	197
5-hydroxytryptamine receptor 2C	P28335	5HT2C_HUMAN	Agonist	209
5-hydroxytryptamine receptor 2C	P28335	5HT2C_HUMAN	Antagonist	318
5-hydroxytryptamine receptor 4	Q13639	5HT4R_HUMAN	Agonist	235
5-hydroxytryptamine receptor 4	Q13639	5HT4R_HUMAN	Antagonist	241
5-hydroxytryptamine receptor 5A	P47898	5HT5A_HUMAN	Agonist	13
5-hydroxytryptamine receptor 5A	P47898	5HT5A_HUMAN	Antagonist	11
5-hydroxytryptamine receptor 6	P50406	5HT6R_HUMAN	Agonist	14
5-hydroxytryptamine receptor 6	P50406	5HT6R_HUMAN	Antagonist	33
5-hydroxytryptamine receptor 7	P34969	5HT7R_HUMAN	Agonist	12
5-hydroxytryptamine receptor 7	P34969	5HT7R_HUMAN	Antagonist	30
Adenosine receptor A1	P30542	AA1R_HUMAN	Agonist	138
Adenosine receptor A1	P30542	AA1R_HUMAN	Antagonist	280
Adenosine receptor A2a	P29274	AA2AR_HUMAN	Agonist	82
Adenosine receptor A2a	P29274	AA2AR_HUMAN	Antagonist	361
Adenosine receptor A2b	P29275	AA2BR_HUMAN	Agonist	85
Adenosine receptor A2b	P29275	AA2BR_HUMAN	Antagonist	370
Adenosine receptor A3	P33765	AA3R_HUMAN	Agonist	14
Adenosine receptor A3	P33765	AA3R_HUMAN	Antagonist	95
Muscarinic acetylcholine receptor M1	P11229	ACM1_HUMAN	Agonist	806
Muscarinic acetylcholine receptor M1	P11229	ACM1_HUMAN	Antagonist	78
Muscarinic acetylcholine receptor M2	P08172	ACM2_HUMAN	Agonist	13
Muscarinic acetylcholine receptor M2	P08172	ACM2_HUMAN	Antagonist	113
Muscarinic acetylcholine receptor M3	P20309	ACM3_HUMAN	Agonist	16
Muscarinic acetylcholine receptor M3	P20309	ACM3_HUMAN	Antagonist	295

Receptor Name	Primary Accession Number	Receptor Entry Name	Ligand	Number of Ligands
Muscarinic acetylcholine receptor M4	P08173	ACM4_HUMAN	Agonist	15
Muscarinic acetylcholine receptor M4	P08173	ACM4_HUMAN	Antagonist	51
Muscarinic acetylcholine receptor M5	P08912	ACM5_HUMAN	Agonist	7
Muscarinic acetylcholine receptor M5	P08912	ACM5_HUMAN	Antagonist	49
Alpha-1A adrenergic receptor	P35348	ADA1A_HUMAN	Agonist	20
Alpha-1A adrenergic receptor	P35348	ADA1A_HUMAN	Antagonist	588
Alpha-1B adrenergic receptor	P35368	ADA1B_HUMAN	Agonist	5
Alpha-1B adrenergic receptor	P35368	ADA1B_HUMAN	Antagonist	550
Alpha-1D adrenergic receptor	P25100	ADA1D_HUMAN	Agonist	12
Alpha-1D adrenergic receptor	P25100	ADA1D_HUMAN	Antagonist	568
Alpha-2A adrenergic receptor	P08913	ADA2A_HUMAN	Agonist	112
Alpha-2A adrenergic receptor	P08913	ADA2A_HUMAN	Antagonist	440
Alpha-2B adrenergic receptor	P18089	ADA2B_HUMAN	Agonist	105
Alpha-2B adrenergic receptor	P18089	ADA2B_HUMAN	Antagonist	437
Alpha-2C adrenergic receptor	P18825	ADA2C_HUMAN	Agonist	105
Alpha-2C adrenergic receptor	P18825	ADA2C_HUMAN	Antagonist	433
Beta-1 adrenergic receptor	P08588	ADRB1_HUMAN	Agonist	209
Beta-1 adrenergic receptor	P08588	ADRB1_HUMAN	Antagonist	211
Beta-2 adrenergic receptor	P07550	ADRB2_HUMAN	Agonist	206
Beta-2 adrenergic receptor	P07550	ADRB2_HUMAN	Antagonist	204
Beta-3 adrenergic receptor	P13945	ADRB3_HUMAN	Agonist	643
Beta-3 adrenergic receptor	P13945	ADRB3_HUMAN	Antagonist	170
Type-2 angiotensin II receptor	P50052	AG22_HUMAN	Antagonist	32
Type-1 angiotensin II receptor	P30556	AG2R_HUMAN	Antagonist	1502
B1 bradykinin receptor	P46663	BKRB1_HUMAN	Antagonist	114
B2 bradykinin receptor	P30411	BKRB2_HUMAN	Antagonist	131
Bombesin receptor subtype-3	P32247	BRS3_HUMAN	Antagonist	17
Cholecystokinin receptor type A	P32238	CCKAR_HUMAN	Agonist	38
Cholecystokinin receptor type A	P32238	CCKAR_HUMAN	Antagonist	360
C-C chemokine receptor type 5	P51681	CCR5_HUMAN	Antagonist	6
Cysteinyl leukotriene receptor 1	Q9Y271	CLTR1_HUMAN	Antagonist	333
Cannabinoid receptor 1	P21554	CNR1_HUMAN	Agonist	13
Cannabinoid receptor 2	P34972	CNR2_HUMAN	Agonist	13
D(1A) dopamine receptor	P21728	DRD1_HUMAN	Agonist	73
D(1A) dopamine receptor	P21728	DRD1_HUMAN	Antagonist	188
D(2) dopamine receptor	P14416	DRD2_HUMAN	Agonist	170
D(2) dopamine receptor	P14416	DRD2_HUMAN	Antagonist	529
D(3) dopamine receptor	P35462	DRD3_HUMAN	Agonist	6
D(3) dopamine receptor	P35462	DRD3_HUMAN	Antagonist	317
D(4) dopamine receptor	P21917	DRD4_HUMAN	Agonist	10
D(4) dopamine receptor	P21917	DRD4_HUMAN	Antagonist	665

Receptor Name	Primary Accession Number	Receptor Entry Name	Ligand	Number of Ligands
D(1B) dopamine receptor	P21918	DRD5_HUMAN	Agonist	11
D(1B) dopamine receptor	P21918	DRD5_HUMAN	Antagonist	12
Endothelin-1 receptor	P25101	EDNRA_HUMAN	Agonist	12
Endothelin-1 receptor	P25101	EDNRA_HUMAN	Antagonist	676
Endothelin B receptor	P24530	EDNRB_HUMAN	Agonist	12
Endothelin B receptor	P24530	EDNRB_HUMAN	Antagonist	561
Gastrin/cholecystokinin type B receptor	P32239	GASR_HUMAN	Agonist	5
Gastrin/cholecystokinin type B receptor	P32239	GASR_HUMAN	Antagonist	567
Putative G-protein coupled receptor 44	Q9Y5Y4	GPR44_HUMAN	Agonist	12
Gastrin-releasing peptide receptor	P30550	GRPR_HUMAN	Antagonist	17
Histamine H1 receptor	P35367	HRH1_HUMAN	Agonist	8
Histamine H1 receptor	P35367	HRH1_HUMAN	Antagonist	78
Histamine H2 receptor	P25021	HRH2_HUMAN	Agonist	8
Histamine H2 receptor	P25021	HRH2_HUMAN	Antagonist	123
Histamine H3 receptor	Q9Y5N1	HRH3_HUMAN	Agonist	34
Histamine H3 receptor	Q9Y5N1	HRH3_HUMAN	Antagonist	313
Histamine H4 receptor	Q9H3N8	HRH4_HUMAN	Agonist	11
Histamine H4 receptor	Q9H3N8	HRH4_HUMAN	Antagonist	15
Lutropin-choriogonadotropic hormone receptor	P22888	LSHR_HUMAN	Antagonist	230
Leukotriene B4 receptor 1	Q15722	LT4R1_HUMAN	Agonist	5
Leukotriene B4 receptor 1	Q15722	LT4R1_HUMAN	Antagonist	191
Leukotriene B4 receptor 2	Q9NPC1	LT4R2_HUMAN	Agonist	5
Leukotriene B4 receptor 2	Q9NPC1	LT4R2_HUMAN	Antagonist	191
Melatonin receptor type 1A	P48039	MTR1A_HUMAN	Agonist	136
Melatonin receptor type 1A	P48039	MTR1A_HUMAN	Antagonist	21
Melatonin receptor type 1B	P49286	MTR1B_HUMAN	Agonist	135
Melatonin receptor type 1B	P49286	MTR1B_HUMAN	Antagonist	24
Melatonin-related receptor	Q13585	MTR1L_HUMAN	Agonist	124
Melatonin-related receptor	Q13585	MTR1L_HUMAN	Antagonist	16
Substance-P receptor	P25103	NK1R_HUMAN	Antagonist	900
Substance-K receptor	P21452	NK2R_HUMAN	Antagonist	146
Neuromedin-K receptor	P29371	NK3R_HUMAN	Antagonist	118
Neuromedin-B receptor	P28336	NMBR_HUMAN	Antagonist	17
Neurotensin receptor type 1	P30989	NTR1_HUMAN	Antagonist	26
Neurotensin receptor type 2	O95665	NTR2_HUMAN	Antagonist	25
Delta-type opioid receptor	P41143	OPRD_HUMAN	Agonist	361
Delta-type opioid receptor	P41143	OPRD_HUMAN	Antagonist	16
Kappa-type opioid receptor	P41145	OPRK_HUMAN	Agonist	284
Kappa-type opioid receptor	P41145	OPRK_HUMAN	Antagonist	23
Mu-type opioid receptor	P35372	OPRM_HUMAN	Agonist	140

Receptor Name	Primary Accession Number	Receptor Entry Name	Ligand	Number of Ligands
Mu-type opioid receptor	P35372	OPRM_HUMAN	Antagonist	27
Nociceptin receptor	P41146	OPRX_HUMAN	Antagonist	9
Oxytocin receptor	P30559	OXYR_HUMAN	Antagonist	196
Platelet-activating factor receptor	P25105	PAFR_HUMAN	Antagonist	11
Prostaglandin D2 receptor	Q13258	PD2R_HUMAN	Agonist	19
Prostaglandin D2 receptor	Q13258	PD2R_HUMAN	Antagonist	5
Prostaglandin E2 receptor EP1 subtype	P34995	PE2R1_HUMAN	Agonist	18
Prostaglandin E2 receptor EP1 subtype	P34995	PE2R1_HUMAN	Antagonist	130
Prostaglandin E2 receptor EP2 subtype	P43116	PE2R2_HUMAN	Agonist	14
Prostaglandin E2 receptor EP2 subtype	P43116	PE2R2_HUMAN	Antagonist	128
Prostaglandin E2 receptor EP3 subtype	P43115	PE2R3_HUMAN	Agonist	16
Prostaglandin E2 receptor EP3 subtype	P43115	PE2R3_HUMAN	Antagonist	125
Prostaglandin E2 receptor EP4 subtype	P35408	PE2R4_HUMAN	Agonist	16
Prostaglandin E2 receptor EP4 subtype	P35408	PE2R4_HUMAN	Antagonist	129
Prostaglandin F2-alpha receptor	P43088	PF2R_HUMAN	Agonist	6
Prostaglandin F2-alpha receptor	P43088	PF2R_HUMAN	Antagonist	9
Prostacyclin receptor	P43119	PI2R_HUMAN	Agonist	23
Relaxin-3 receptor 2	Q8TDU9	R3R2_HUMAN	Antagonist	8
Somatostatin receptor type 1	P30872	SSR1_HUMAN	Antagonist	29
Somatostatin receptor type 2	P30874	SSR2_HUMAN	Antagonist	25
Somatostatin receptor type 3	P32745	SSR3_HUMAN	Antagonist	25
Somatostatin receptor type 4	P31391	SSR4_HUMAN	Antagonist	25
Somatostatin receptor type 5	P35346	SSR5_HUMAN	Antagonist	25
Thromboxane A2 receptor	P21731	TA2R_HUMAN	Agonist	12
Thromboxane A2 receptor	P21731	TA2R_HUMAN	Antagonist	725
Vasopressin V1a receptor	P37288	V1AR_HUMAN	Antagonist	225
Vasopressin V1b receptor	P47901	V1BR_HUMAN	Antagonist	225
Vasopressin V2 receptor	P30518	V2R_HUMAN	Antagonist	191

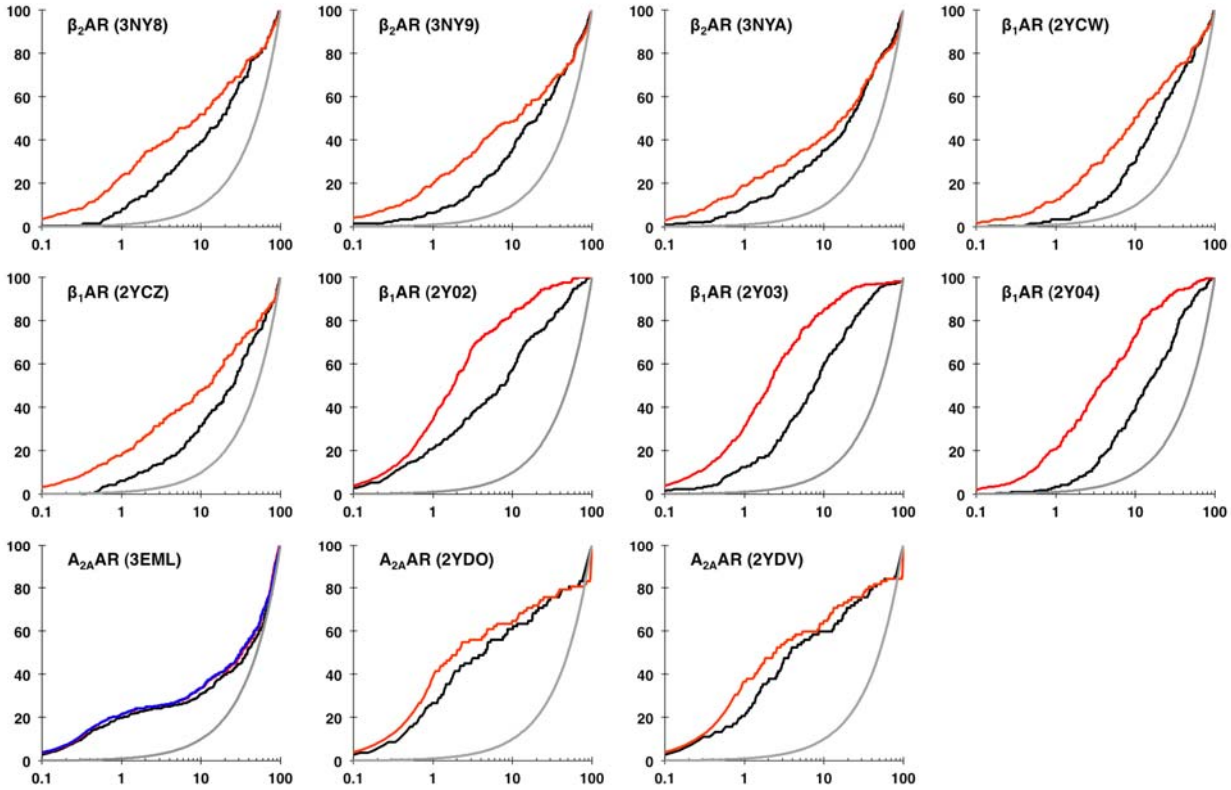

Figure S1. Eleven enrichment curves of the docking onto 19 GPCR targets, showing % of the screened database (x-axis) versus the % of ligands recovered (the rest of the curves are shown in Fig. 2). Ligands were taken from GLL. The GDD, and randomly selected sets from ZINC (RZ) and ChemBridge (RCB) were used as decoy sets, maintaining the 39 decoys per ligand ratio. The docking to A_{2A}AR (3EML) displayed was performed including eight crystallographic waters. Color code: GDD, black; RZ, red; RCB, blue; random selection, gray.

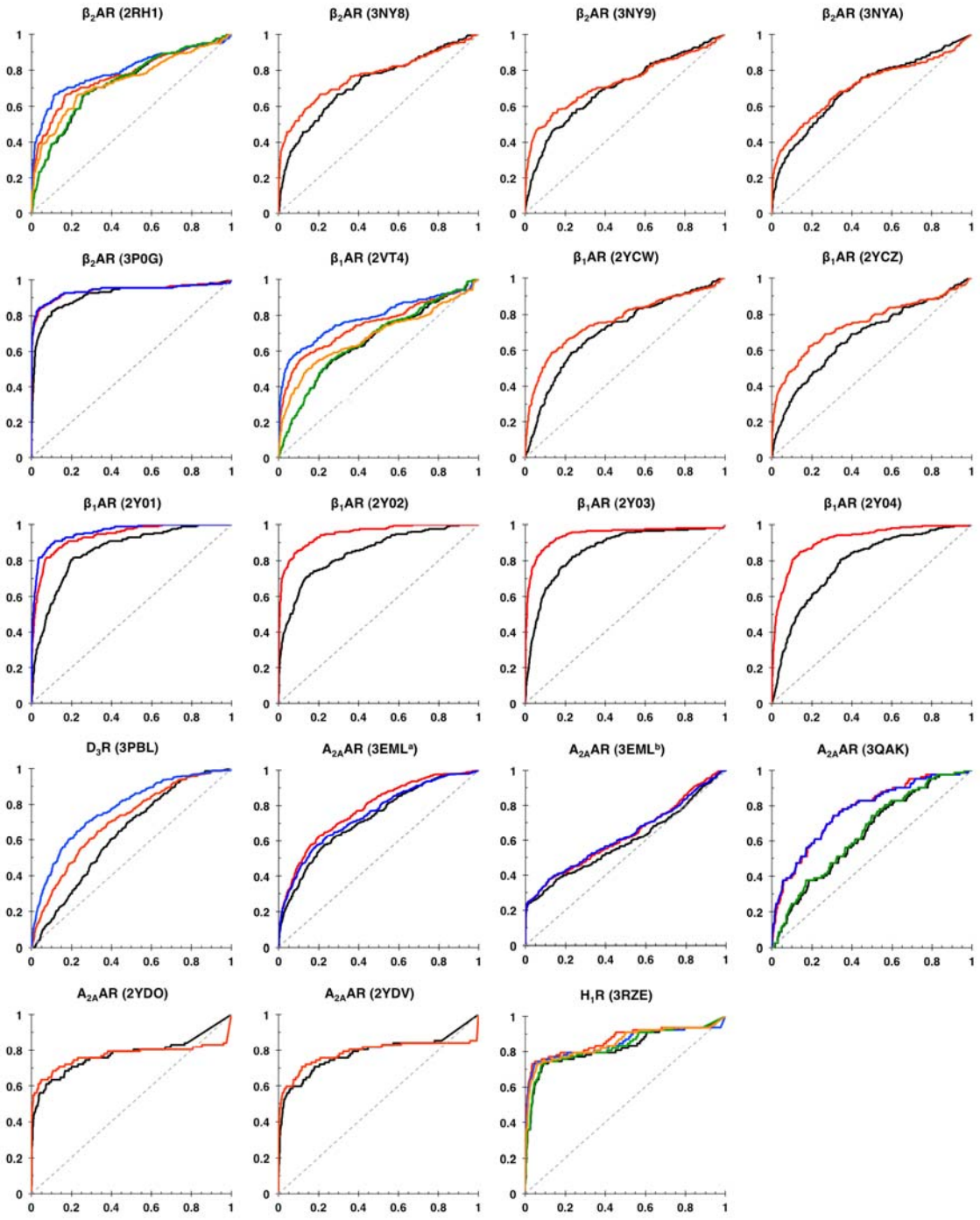

Figure S2: ROC curves corresponding to docking onto 19 GPCR targets, showing % of selected decoys (x-axis) versus the % of selected ligands. Ligands were taken from GLL. The GDD, and randomly selected sets from ZINC (RZ) and ChemBridge (RCB) were used as decoy sets, maintaining the 39 decoys per ligand ratio. In four structures, decoys from GDD* and a randomly selected set of molecules with a formal charge of +1 from ZINC (RZ1) were also docked. The docking to $A_{2A}AR$ was performed including eight crystallographic waters ($3EML^{b}$) and with no waters ($3EML^{a}$). Color code: GDD, black; RZ, red; RCB, blue; GDD*, green; RZ1, orange; random selection, gray.

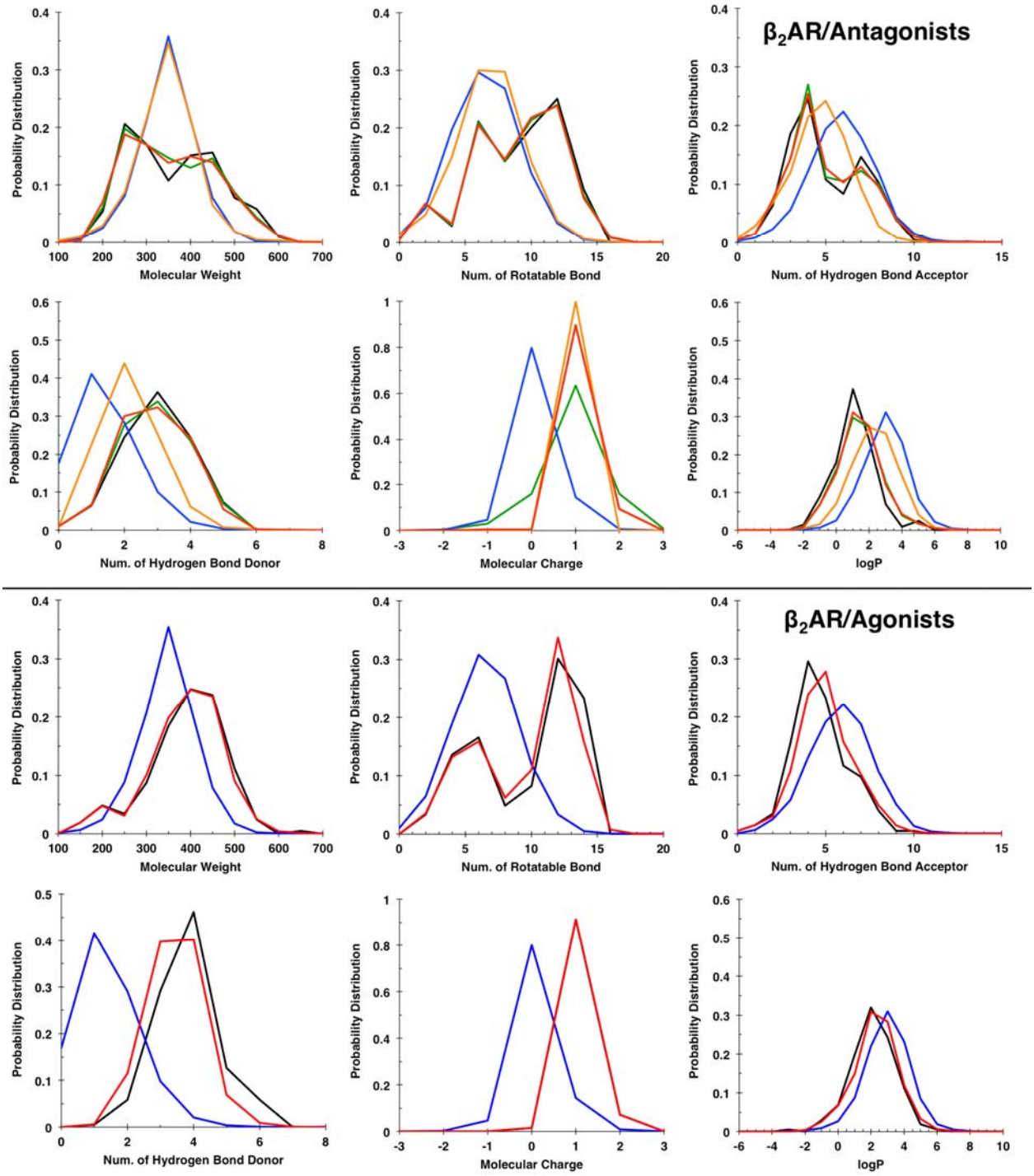

Figure S3: Physical property distributions for the ligand and decoy sets used in docking to each of the 8 GPCR target/ligand-activity (cf. Tables 1 and 2, and Figures 2 and S2). Color code: GLL, black; GDD, red; RZ, blue; GDD*, green; RZ1, orange. The distributions of formal charge for GLL and GDD perfectly overlap, thus the only red line is seen.

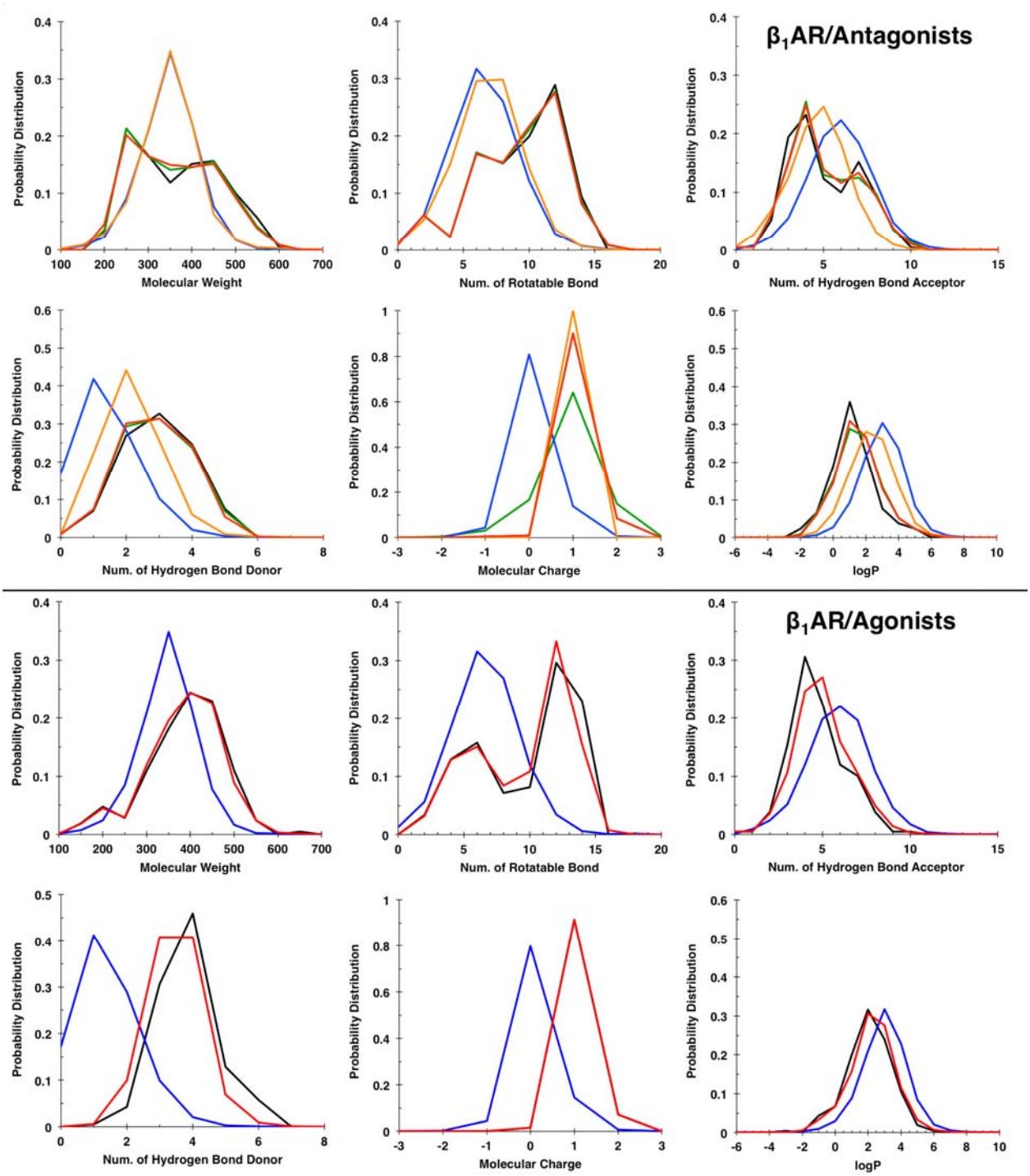

Figure S3 (cont.): Physical property distributions for the ligand and decoy sets used in docking to each of the 8 GPCR target/ligand-activity (cf. Table 1, and Figures 2 and S2). Color code: GLL, black; GDD, red; RZ, blue; GDD*, green; RZ1, orange. The distributions of formal charge for GLL and GDD perfectly overlap, thus the only red line is seen.

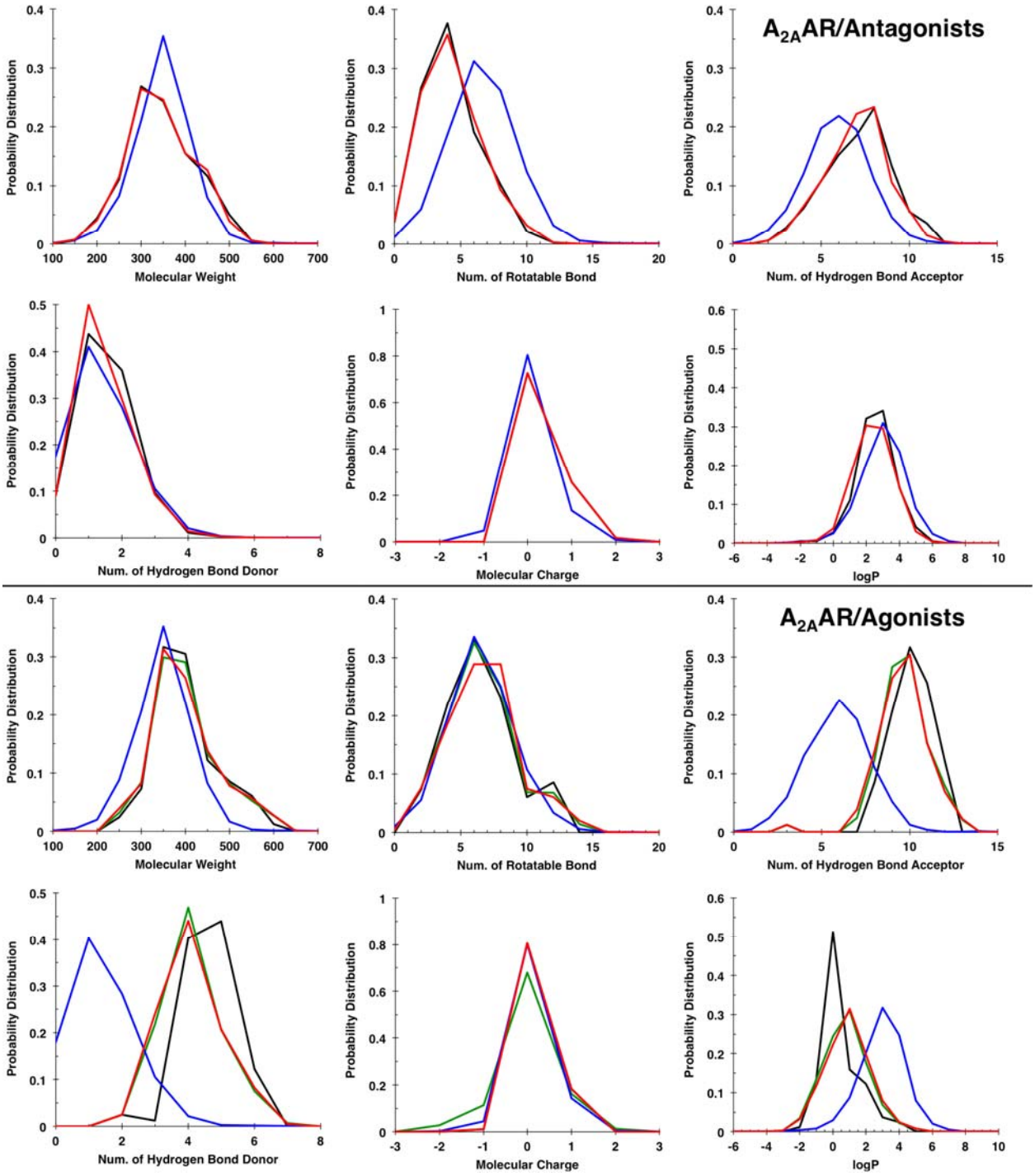

Figure S3 (cont.): Physical property distributions for the ligand and decoy sets used in docking to each of the 8 GPCR target/ligand-activity (cf. Table 1, and Figures 2 and S2). Color code: GLL, black; GDD, red; RZ, blue; GDD*, green; RZ1, orange. The distributions of formal charge for GLL and GDD perfectly overlap, thus the only red line is seen.

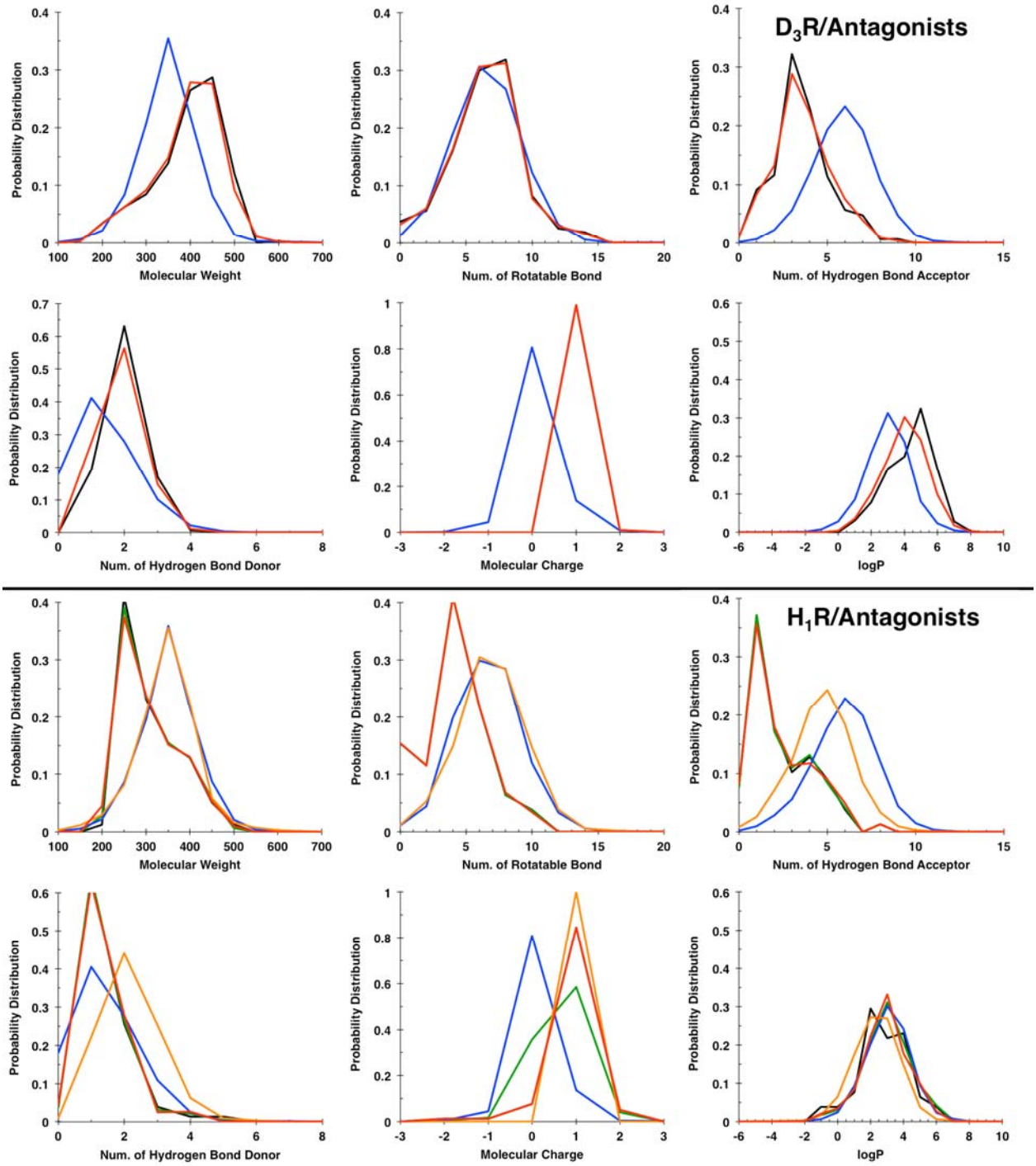

Figure S3 (cont.): Physical property distributions for the ligand and decoy sets used in docking to each of the 8 GPCR target/ligand-activity (cf. Table 1, and Figures 2 and S2). Color code: GLL, black; GDD, red; RZ, blue; GDD*, green; RZ1, orange. The distributions of formal charge for GLL and GDD perfectly overlap, thus the only red line is seen.

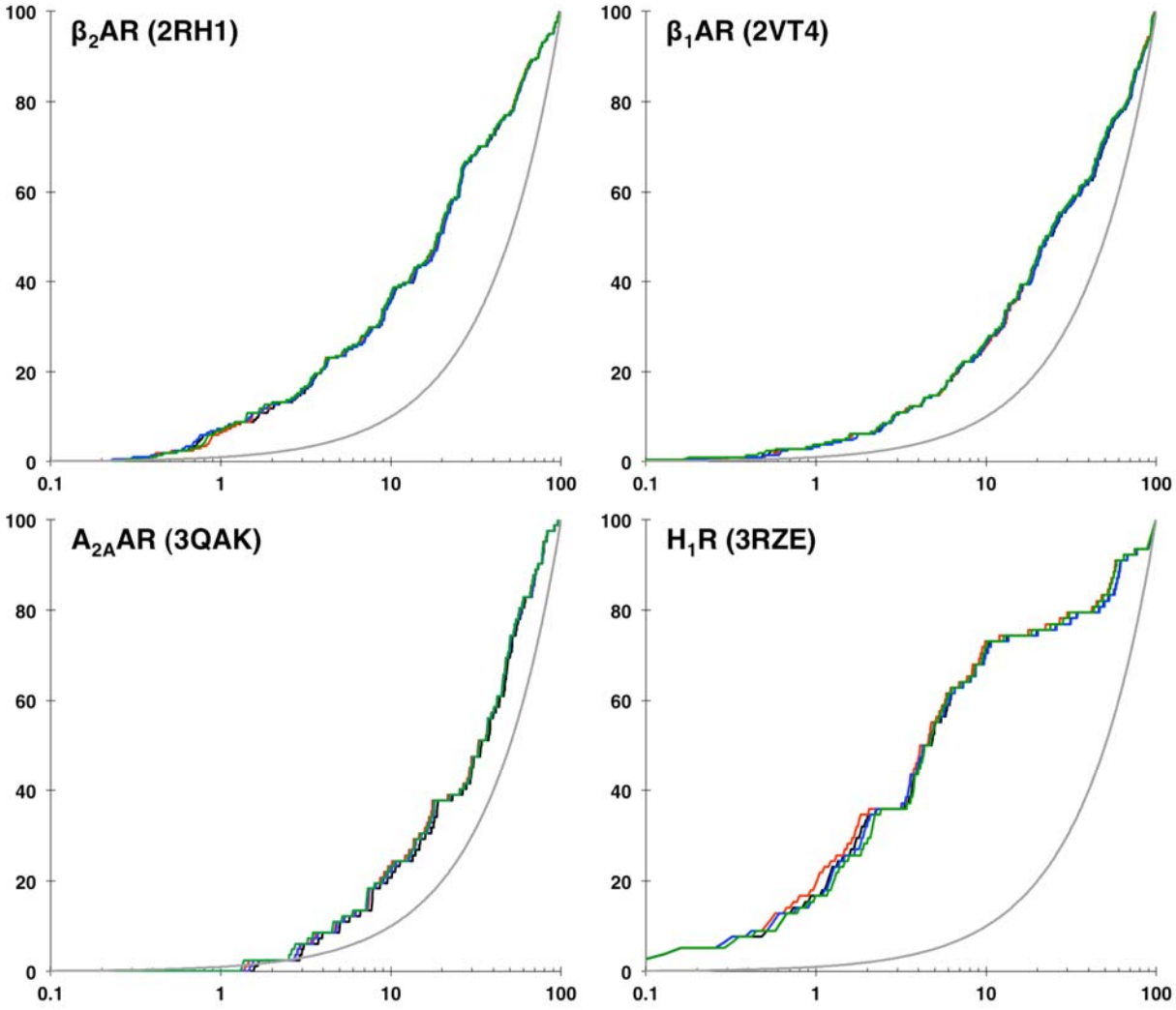

Figure S4. Enrichment curves for the docking on β_2AR, β_1AR, and H_1R antagonist bound, and A_{2A}AR agonist bound using ligands from GLL, and decoys from GDD, GDD*, GDD(p) and GDD*(p) (39 decoys per ligand). Color code: GDD, black; GDD*, red; GDD(p), blue; GDD*(p), green; random selection, gray.

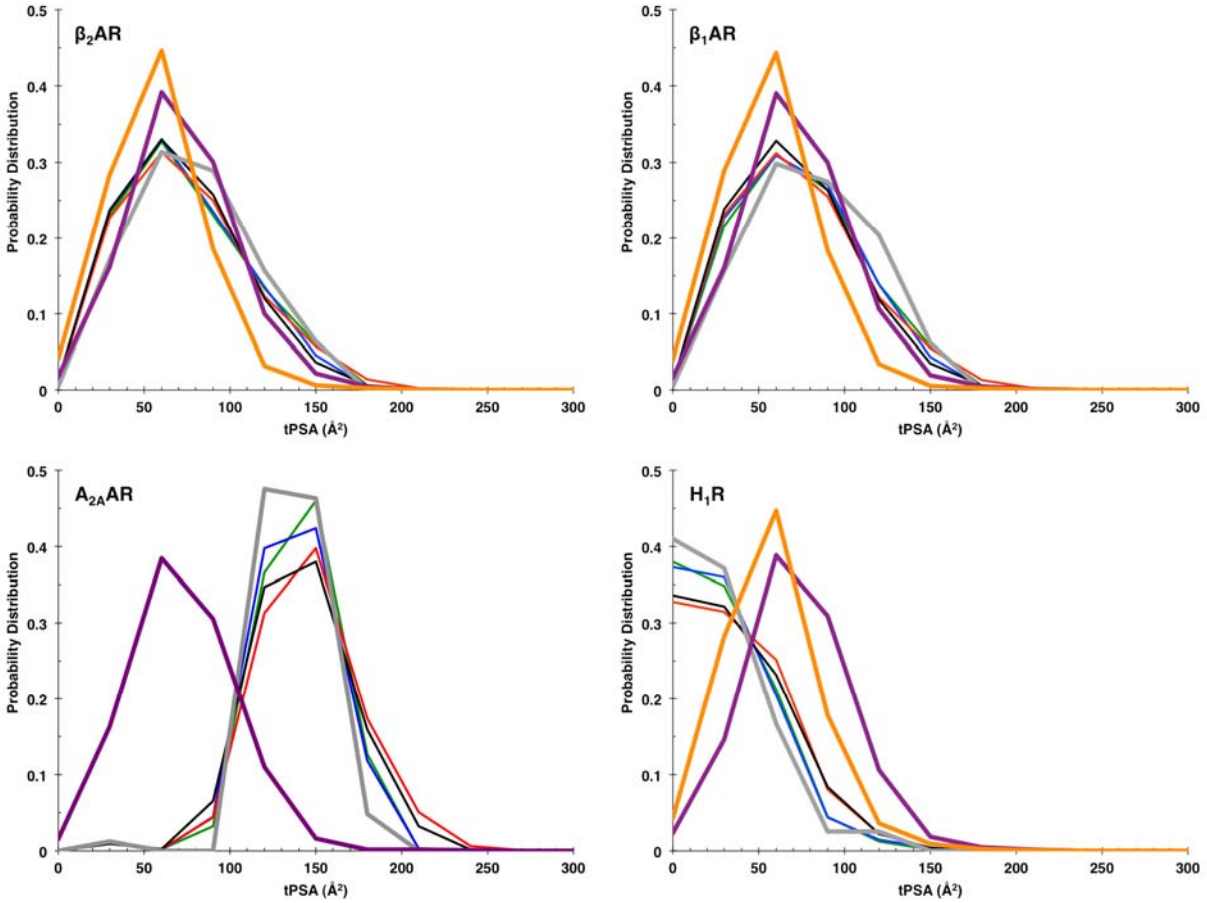

Figure S5: Distributions of tPSA for GLL, RZ1, GDD, GDD*, GDD(p) and GDD*(p) for β_2AR, β_1AR, and H_1R antagonist bound, and A_{2A}AR agonist bound. Color code: GLL, gray; GDD, black; GDD*, red; GDD(p), blue; GDD*(p), green; RZ, purple; RZ1, orange.