Selective structure-based virtual screening for full and partial agonists of the beta2 adrenergic receptor

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Supporting information

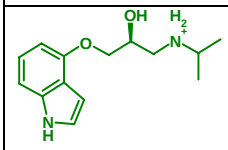
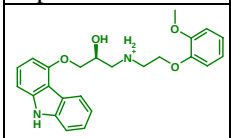
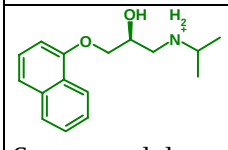
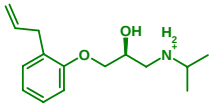
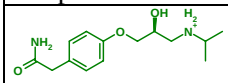
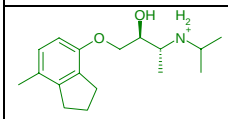
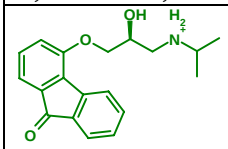
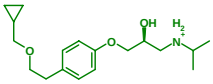
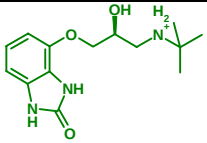
Contents:

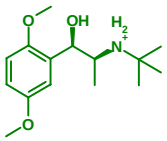
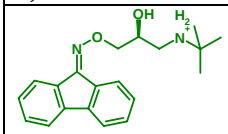
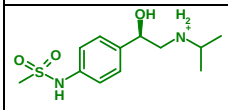
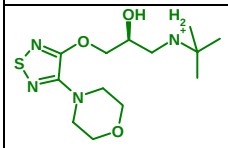
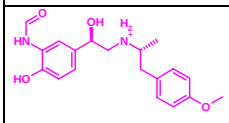
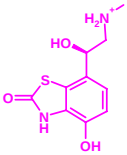
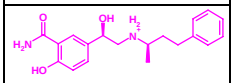
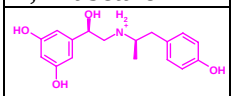
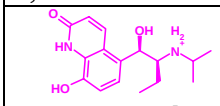
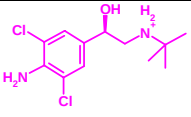
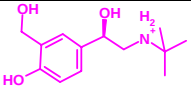
Appendices: zip file (appendix.jm-2008-00710x.zip) containing the following files:

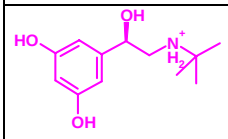
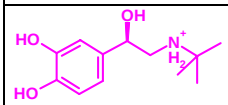
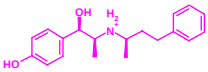
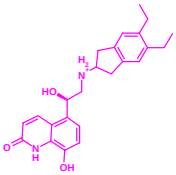
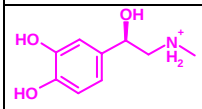
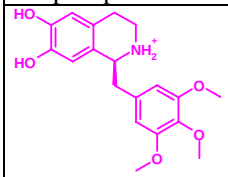
- *ADRB2_X-ray.mol2* (coordinates of the ADRB2 crystal structure used for automated docking studies)
- *ADRB2_custom.mol2* (coordinates of the customized ADRB2 crystal structure used for automated docking studies)
- *gold.conf* (Gold docking input file)
- *cavity_residues.lst* (list of residues to define binding cavity in Gold runs)
- *ADRB2_X-ray.protomol* (Surflex protomol file of ADRB2 crystal structure)
- *ADRB2_custom.protomol* (Surflex protomol file of customized ADRB2 structure)

- *ADRB2_database.mol2* (mol2 3-D database of 13 known inverse agonists/antagonists ("ADRB2_ANTAGONIST"), 13 known partial/full agonists ("ADRB2_AGONIST"), and 980 decoys).
- *ADRB2_database.sdf* (sdf 2-D database of 13 known inverse agonists/antagonists ("ADRB2_ANTAGONIST"), 13 known partial/full agonists ("ADRB2_AGONIST"), and 980 decoys).
- *carazolol_ref.mol2* (mol2 reference structure of *S*-carazolol)
- *isoproterenol_ref.mol2* (mol2 reference structure of *R*-isoproterenol)
- *carazolol_ref.IFP* (reference protein-ligand interaction fingerprint for analysis of docking poses in original ADRB2 crystal structure)
- *isoproterenol_ref.IFP* (reference protein-ligand interaction fingerprint for analysis of docking poses in customized ADRB2 structure)
- *cavity_ADRB2_X-ray.mol2* (original ADRB2 crystal structure binding cavity for IFP analysis (notice that for each Gold docking pose the coordinates of binding pocket hydroxyl hydrogen atoms were extracted from the Gold solution mol2 file)
- *cavity_ADRB2_custom_cavity.mol2* (customized ADRB2 crystal structure binding cavity for IFP analysis (notice that for each Gold docking pose the coordinates of binding pocket hydroxyl hydrogen atoms were extracted from the Gold solution mol2 file)

***Supporting Information Table 1*:** Ranking of antagonists (ANT), and inverse (iAGO), partial (pAGO), and full (fAGO) agonists of the beta2 adrenergic receptor in the hit lists of different virtual screening methods.

ligand[a]	**Virtual screening method**[b]												**pharmaco-logical activity class**[a]
	Gold-IFP ISP	**Surf-IFP ISP**	**ECFP-4 ISP**	**ROCS ISP**	**Gold-IFP CAZ**	**Surf-Surf ISP**	**Surf-IFP CAZ**	**Surf-Surf CAZ**	**ECFP-4 CAZ**	**ROCS CAZ**	**Gold-Gold ISP**	**Gold-Gold CAZ**	
 *S*-pindolol	58	21	35	16	1	8	28	10	1	3	321	258	**iAGO**[1-3], ANT[2,4,5]
 *S*-carvedilol	218	55	476	500	25	1	7	2	2	6	1	18	**ANT**[3,6]
 *S*-propranolol	232	47	25	25	2	58	13	4	3	8	487	280	**iAGO**[3,7,8], ANT[2,4,5,9,10], pAGO[7,8]
 *S*-alprenolol	316	67	18	19	524	14	5	18	4	7	634	718	**iAGO**[1,3], ANT[4,5,9,11], pAGO[7,8,10]
 *S*-atenolol	460	234	17	38	96	210	3	38	5	12	609	641	**iAGO**[2,3]
 *S,R*-ICI-118,551	56	90	33	138	124	348	27	77	18	59	718	445	**iAGO**[2,3,7,10,12], ANT[2]
 *S*-flisopolol	372	25	19	44	5	17	1	5	6	2	485	45	**ANT**[13]
 *S*-betaxolol	233	n.l.[c]	22	159	n.l.[c]	25	2	6	7	17	626	690	**iAGO**[7,8]
 *S*-CGP-12177	40	33	96	12	3	19	9	12	8	1	264	403	**ANT**[4]

ligand[a]	Virtual screening method[b]												pharmaco-logical activity class[a]
	Gold-IFP ISP	Surf-IFP ISP	ECFP-4 ISP	ROCS ISP	Gold-IFP CAZ	Surf-Surf ISP	Surf-IFP CAZ	Surf-Surf CAZ	ECFP-4 CAZ	ROCS CAZ	Gold-Gold ISP	Gold-Gold CAZ	
 *R,S*-butoxamine	n.l.[c]	34	13	10	9	74	14	373	23	330	886	953	**ANT**[14]
 *S*-IPS-339	443	196	31	151	62	154	8	1	46	5	691	290	**ANT**[15]
 *R*-sotalol	15	158	7	11	26	165	24	35	47	73	361	409	**iAGO**[1,10]
 *S*-timolol	371	104	174	22	6	29	4	16	54	4	617	239	**ANT**[7,8], iAGO[7,8,10]
 *R,R*-formoterol	13	2	8	8	83	3	n.l.[c]	47	61	243	6	347	**fAGO**[12]
 *R*-S1319	6	8	10	6	18	65	79	252	98	478	58	552	**fAGO**[16]
 *R,R*-labetalol	4	12	6	10	73	6	85	91	150	391	4	130	**pAGO**[7]
 *R,R*-fenoterol	2	5	2	66	35	4	50	52	192	400	85	474	**fAGO**[17]
 *R,S*-procaterol	7	11	15	5	4	192	6	549	270	220	741	878	**fAGO**[18,19]
 *R*-clenbutarol	14	15	12	3	49	136	18	309	286	113	137	661	**fAGO**[9,20]
 *R*-salbutamol	1	4	5	1	10	24	12	220	349	133	306	760	**pAGO**[2,3,12]

ligand[a]	Virtual screening method[b]												pharmaco-logical activity class[a]
	Gold-IFP ISP	Surf-IFP ISP	ECFP-4 ISP	ROCS ISP	Gold-IFP CAZ	Surf-Surf ISP	Surf-IFP CAZ	Surf-Surf CAZ	ECFP-4 CAZ	ROCS CAZ	Gold-Gold ISP	Gold-Gold CAZ	
 *R*-terbutaline	5	3	4	6	11	26	78	195	381	663	469	823	**pAGO**[21]
 *R*-colterol	3	1	1	2	12	36	51	179	405	153	414	832	**fAGO**[14]
 *R,S,R*-nylidrin	10	7	9	15	27	15	52	264	436	741	295	665	**fAGO**[22]
 *R*-indacaterol	9	22	11	17	206	92	61	14	302	311	130	597	**pAGO**[23]
 *R*-epinephrine	8	6	3	4	13	98	22	332	557	615	360	805	**fAGO**[3,4,9]
 *S*-trimethoquinol	57	16	29	140	226	78	n.l.[c]	186	598	271	113	440	**pAGO**[24]

[a)] Functional effects of some of these compounds may vary with the signalling pathway. Ligands considered as inverse agonists/antagonists and full/partial agonists in the current study are depicted in green and magenta, respectively.

[b)] *Gold-IFP*: Gold docking simulation[25] ranked with IFP Tc scoring function[26]; *Surf-IFP*: Surflex docking simulation[27] ranked with IFP Tc scoring function; *Gold-Gold*: Gold docking simulation ranked with Goldscore scoring function[25]; Surf-Surf: Surflex docking simulation ranked with Surflex scoring function[27]; *ECFP-4*: ECFP-4 Tc similarity score[28]; *ROCS*: ROCS run ranked with comboscore[29]; *CAZ*: Docking in original ADRB2 crystal structure and/or cazarolol used as IFP/ROCS/ECFP-4 reference; ISP: Docking in customized ADRB2 structure and/or isoproterenol used as IFP/ROCS/ECFP-4 reference.

[c)] Not listed: No ligand docking poses forming an H-bond and ionic interaction with D3.32.

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