Electronic Supplementary Material (ESI) for RSC Advances.

Ligand Discrimination during Virtual Screening of CB1 Cannabinoid Receptor Crystal Structures following Cross-Docking and Microsecond Molecular Dynamics Simulations

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SUPPLEMENTARY INFORMATION

Table S1. Active ligands used in virtual screening datasets. Ligands were obtained from the ChEMBL database.

AGONISTS		ANTAGONISTS	
ChEMBL ID (name)	Ki (nM)	ChEMBL ID (name)	Ki (nM)
CHEMBL188 (WIN552122)	45	CHEMBL376700 (NESS0327)	0.00035
CHEMBL559612 (CP55940)	5.2	CHEMBL111 (rimonabant)	0.2
CHEMBL1950340	15	CHEMBL220360 (taranabant)	0.3
CHEMBL1223590	44.9	CHEMBL496507	0.7
CHEMBL442447	77	CHEMBL484929 (PF0514273)	0.8
CHEMBL244403	35	CHEMBL496091	0.8
CHEMBL232116	15	CHEMBL497557	0.2
CHEMBL1224631	15.6	CHEMBL520345	0.7
CHEMBL1224629	68	CHEMBL562668 (otenabant)	0.1
CHEMBL1223588	28.5	CHEMBL2063237	0.03
CHEMBL1223589	14.2	CHEMBL2063240	0.07
CHEMBL1223716	9	CHEMBL496508	0.9
CHEMBL1224689	51	CHEMBL496293	0.9
CHEMBL2029722	7.3	CHEMBL2063246	0.1
CHEMBL307696 (HU210)	0.2	CHEMBL3341898 (AM6545)	1
CHEMBL1224691	3.3	CHEMBL201602	1
CHEMBL1223592	19.3	CHEMBL498783	1.2
CHEMBL1223775	16.1	CHEMBL522720	1.7
CHEMBL1224630	6.4	CHEMBL189676 (surinabant)	3.2
CHEMBL1223591	32	CHEMBL482985	9.8
CHEMBL947 (Cesamet)	5.1	CHEMBL496555	1.6
CHEMBL1223778	4.7	CHEMBL568221	3.8
CHEMBL271158	12	CHEMBL568230	5.2
CHEMBL1828805	1.3	CHEMBL2063238	7.5
CHEMBL1828809	12.6	CHEMBL412262 (ibipinabant)	7.8
CHEMBL2218896 (Nabilone)	4.0	CHEMBL495892	2.8
CHEMBL1950335	56	CHEMBL2063252	6.5
CHEMBL1950348	36	CHEMBL522395	9.8
CHEMBL1950341	58	CHEMBL482741	4.8
CHEMBL1950344	34	CHEMBL579196	5
CHEMBL1950343	32	CHEMBL2296781	6.0
CHEMBL1828806	63.1	CHEMBL2296777	6
CHEMBL1950329	3	CHEMBL285932 (AM251)	7.5
CHEMBL1950357	51	CHEMBL577040	9
CHEMBL1950333	9	CHEMBL518982	11
CHEMBL1950353	31	CHEMBL476833	13.2
CHEMBL16901 (Honokiol)	6.5	CHEMBL519863	13
CHEMBL245876	3	CHEMBL2296784	11.7
CHEMBL2017678	6.3	CHEMBL495891	15.0
CHEMBL2177249	45	CHEMBL2296782	19.8
CHEMBL465 (Dronabinol)	41	CHEMBL2296786	18.2
CHEMBL2441251	77	CHEMBL484163	25
CHEMBL3323682	7.2	CHEMBL4956506	32.3
CHEMBL561013 (JWH018)	2.0	CHEMBL2296783	31.1
CHEMBL2029721	44.5	CHEMBL2296779	47.0
CHEMBL2029719	2.8	CHEMBL36250	60.4
CHEMBL1209573	12.6	CHEMBL2296780	63
CHEMBL1683648 (AM11542)	1.3	CHEMBL286188	76.7
CHEMBL2380416 (JWH073)	9.8	CHEMBL285259	81.9
CHEMBL3526578 (AM2201)	0.4	CHEMBL349955	81.5

Tables S2. Best ligand RMSD relative to crystal structures following IFD with corresponding ROC AUC and adjusted logAUCs following virtual screening. The ligand used for the antagonist dataset was taranabant, while the ligand used for the agonist dataset was AM11542. RMSD values were calculated following optimal superimposition of the receptor transmembrane backbone.

A) CB1-AM11542 simulations replicate 1

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.74	50.6	-0.9	3.02	80.5	17.7
50	7.75	42.1	-3.4	3.65	80.5	15.1
100	3.23	56.4	0.7	3.27	72.5	9.3
150	5.18	50.9	-1.3	4.10	71.6	13.6
200	5.79	68.8	7.8	3.67	74.5	10.7
250	6.60	43.4	-2.7	4.54	64.7	4.1
300	5.96	60.6	1.7	3.42	72.9	10.9
350	6.36	46.7	-2.1	4.03	78.5	21.6
400	2.78	47.3	-1.2	4.42	68.2	11.3
450	3.92	57.9	2.7	4.59	70.1	10.1
500	5.41	63.9	3.7	3.59	69.4	6.9
550	4.31	36.3	-5.6	3.74	71.8	16.9
600	6.63	45.1	-3.0	3.40	55.6	1.1
650	6.67	58.4	2.8	3.65	75.4	16.5
700	6.75	50.7	0.8	4.49	75.0	13.3
750	5.67	61.4	4.0	6.57	81.7	19.3
800	6.74	41.7	-4.3	4.04	82.7	28.3
850	6.52	44.7	-4.5	4.50	72.9	9.6
900	6.41	56.3	1.0	3.24	70.9	10.5
950	8.10	76.2	14.5	4.05	73.7	9.4
1000	6.88	46.7	-2.0	4.89	66.2	4.5

B) CB1-AM11542 simulations replicate 2

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.43	64.3	3.1	2.95	82.8	22.3
50	4.01	44.5	-2.5	4.15	71.1	7.6
100	5.13	46.1	-4.0	3.37	72.8	10.4
150	6.88	74.0	9.7	2.96	69.2	9.0
200	4.44	28.0	-8.5	4.92	60.4	1.6
250	8.85	61.5	2.5	7.20	84.9	20.6
300	6.73	62.7	2.3	3.10	68.1	8.0
350	6.21	64.3	3.1	4.62	75.8	11.5
400	6.63	54.1	-0.1	7.24	78.3	16.8
450	7.22	38.2	-6.2	3.75	75.8	13.1
500	5.61	49.1	-0.8	6.95	61.2	4.8
550	6.08	69.3	4.8	4.63	80.8	17.9
600	6.13	70.6	9.8	6.97	66.6	7.1
650	6.61	53.0	-1.5	5.17	68.4	15.9
700	6.02	60.8	2.1	5.11	74.0	13.4
750	6.46	44.4	-4.1	6.93	78.8	16.1
800	7.04	65.4	5.7	3.11	68.2	7.7
850	6.26	47.8	-2.8	4.53	74.5	10.6
900	6.16	73.9	12.5	3.46	72.5	11.8
950	9.39	47.1	-2.6	4.66	75.0	10.9
1000	9.55	48.9	-1.8	6.38	64.5	6.7

C) CB1-AM11542 simulations replicate 3

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.66	49.5	-0.9	2.95	84.1	23.3
50	6.52	66.1	4.3	2.73	68.9	5.5
100	5.46	57.1	0.5	3.66	71.0	8.4
150	6.61	79.3	14.6	3.00	76.2	11.7
200	4.58	44.4	-3.5	3.46	69.4	7.8
250	5.48	53.4	-1.1	3.41	75.3	13.2
300	5.63	67.0	6.8	3.59	75.3	13.3
350	6.92	40.7	-5.0	3.69	70.7	13.5
400	4.67	58.4	0.6	3.30	83.1	16.2
450	6.97	44.0	-2.2	3.43	73.1	7.9
500	8.74	54.7	3.0	3.35	80.2	14.7
550	5.76	48.7	-0.7	3.66	76.2	14.6
600	7.43	51.0	0.9	3.19	74.4	14.4
650	7.21	61.5	4.4	3.18	72.6	11.8
700	6.12	47.9	1.8	4.47	61.0	4.0
750	6.90	72.7	10.7	3.06	81.3	22.8
800	6.85	51.4	-0.7	3.16	68.3	12.4
850	6.52	36.8	-5.8	3.09	76.3	17.9
900	5.28	42.4	-2.3	2.43	72.9	16.0
950	6.82	49.4	0.5	3.71	77.7	14.4
1000	6.64	57.9	1.7	3.58	68.7	7.1

D) CB1*-taranabant simulations replicate 1

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	39.2	-5.3	0.89	77.5	22
50	6.21	55.3	3.6	0.66	76.8	21.3
100	6.61	48.2	-2.7	2.61	74.8	13.4
150	5.84	50.7	-2.0	1.59	73.6	12.6
200	6.27	50.2	-0.3	0.98	76.8	13.8
250	6.61	47.8	-1.9	1.26	75.9	13.4
300	6.98	33.3	-7.2	1.19	80.4	15.2
350	6.63	33.4	-7.2	0.92	74.7	10.7
400	6.17	44.2	-2.2	0.91	72.6	10.6
450	6.60	65.9	6.1	0.66	66.1	5.9
500	5.98	37.0	-6.1	0.92	82.6	17.4
550	6.24	51.0	-0.1	1.52	71.0	6.7
600	6.53	55.1	-0.1	1.14	77.7	13.2
650	6.35	31.3	-7.7	1.07	72.4	8.5
700	5.83	27.2	-8.3	2.23	75.0	10.7
750	6.33	44.5	-4.5	1.24	71.0	8.8
800	5.94	48.3	-2.0	1.53	75.0	11.3
850	6.12	57.4	0.7	0.66	71.4	8.6
900	6.31	50.3	-0.8	2.44	49.8	-0.9
950	6.02	53.4	-1.2	2.00	66.9	8.1
1000	6.05	37.0	-5.0	0.96	79.1	14.7

E) CB1*-taranabant simulations replicate 2

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	36.7	-5.9	0.84	77.2	16.2
50	7.67	52.5	2.7	0.58	76.7	13.9
100	6.77	54.4	0.5	0.86	78.1	12.1
150	6.62	56.0	2.2	1.03	72.3	12.6
200	6.38	54.7	-0.8	0.63	80.3	18.5
250	6.73	69.1	8.5	0.54	82.9	19.9
300	6.77	58.4	2.1	0.95	70.6	11.1
350	5.72	66.6	7.9	0.83	73.8	9.4
400	6.09	45.0	-3.4	0.63	78.3	16.7
450	6.03	52.8	0.4	0.87	78.7	15.9
500	6.66	60.9	3.5	2.50	71.8	7.6
550	6.23	48.9	-0.8	0.78	68.6	8.5
600	6.98	55.0	0.2	1.07	74.7	14.9
650	6.91	60.7	3.6	1.88	81.4	16.8
700	6.98	61.6	4.0	0.81	70.4	8.8
750	6.43	49.0	-2.0	0.70	75.9	15.0
800	6.90	61.8	1.2	1.20	78.1	15.8
850	6.99	47.7	-3.0	1.10	75.0	12.1
900	6.37	50.4	-0.5	2.86	76.6	16.1
950	6.76	50.2	-1.3	3.59	67.7	5.2
1000	6.88	56.5	-0.6	0.93	77.5	11.9

F) CB1*-taranabant simulations replicate 3

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	39.1	-5.3	0.89	80.4	21.1
50	6.70	58.3	3.3	0.66	85.0	24.2
100	6.19	49.8	-1.8	0.99	77.8	16.6
150	6.81	36.4	-6.5	2.68	74.8	10.4
200	6.08	57.5	1.8	4.38	77.4	14.5
250	6.62	55.5	0.8	0.45	80.0	18.3
300	6.95	50.3	-0.9	0.46	81.1	16.3
350	6.37	66.5	7.9	7.36	77.0	21.3
400	6.25	49.2	0.4	1.44	70.6	8.9
450	5.99	54.5	0.0	1.50	75.0	12.8
500	6.38	51.7	-0.3	1.34	75.6	13.5
550	6.99	47.4	-2.7	0.61	77.3	15.4
600	6.66	52.4	0.8	0.86	71.5	9.8
650	6.12	47.1	-2.6	0.86	74.6	14.5
700	5.94	43.5	-4.2	1.04	69.6	5.7
750	6.43	50.2	-0.7	2.86	73.7	10.2
800	6.90	61.8	1.2	1.37	68.9	5.9
850	6.48	46.6	-2.1	1.57	72.3	7.5
900	6.52	45.5	-3.5	1.29	73.0	8.7
950	6.47	46.5	-1.8	1.89	76.1	16.5
1000	6.00	41.7	-4.2	3.44	80.3	28.6

G) CB1-AM11542 simulations mean values

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	5.61 ± 0.13	54.8 ± 6.7	0.5 ± 1.9	2.98 ± 0.03	82.5 ± 1.5	21.1 ± 2.4
50	6.09 ± 1.56	50.9 ± 10.8	-0.5 ± 3.4	3.51 ± 0.59	73.5 ± 5.0	9.4 ± 4.1
100	4.61 ± 0.98	53.2 ± 5.0	-0.9 ± 2.2	3.43 ± 0.16	72.1 ± 0.8	9.4 ± 0.8
150	6.22 ± 0.75	68.1 ± 12.3	7.7 ± 6.7	3.35 ± 0.53	72.3 ± 2.9	11.4 ± 1.9
200	4.94 ± 0.60	47.1 ± 16.8	-1.4 ± 6.8	4.02 ± 0.65	68.1 ± 5.8	6.7 ± 3.7
250	6.98 ± 1.40	52.8 ± 7.4	-0.4 ± 2.2	5.05 ± 1.59	75.0 ± 8.2	12.6 ± 6.7
300	6.11 ± 0.46	63.4 ± 2.7	3.6 ± 2.3	3.37 ± 0.20	72.1 ± 3.0	10.7 ± 2.2
350	6.50 ± 0.31	50.6 ± 10.0	-1.3 ± 3.4	4.11 ± 0.39	75.0 ± 3.2	15.6 ± 4.4
400	4.69 ± 1.57	53.3 ± 4.6	-0.2 ± 0.7	4.99 ± 1.66	76.5 ± 6.2	14.8 ± 2.5
450	6.03 ± 1.50	46.7 ± 8.3	-1.9 ± 3.6	3.92 ± 0.49	73.0 ± 2.3	10.3 ± 2.1
500	6.58 ± 1.52	55.9 ± 6.1	2.0 ± 2.0	4.63 ± 1.64	70.3 ± 7.8	8.8 ± 4.3
550	5.38 ± 0.77	51.4 ± 13.6	-0.5 ± 4.2	4.01 ± 0.44	76.3 ± 3.7	16.5 ± 1.4
600	6.73 ± 0.53	55.6 ± 10.9	2.6 ± 5.3	4.52 ± 1.73	65.5 ± 7.7	7.5 ± 5.5
650	6.83 ± 0.27	57.6 ± 3.5	1.9 ± 2.5	4.00 ± 0.85	72.1 ± 2.9	14.7 ± 2.1
700	6.30 ± 0.32	53.1 ± 5.5	1.5 ± 0.6	4.69 ± 0.30	70.0 ± 6.4	10.2 ± 4.4
750	6.35 ± 0.51	59.5 ± 11.6	3.5 ± 6.0	5.52 ± 1.75	80.6 ± 1.3	19.4 ± 2.7
800	6.88 ± 0.12	52.8 ± 9.7	0.2 ± 4.1	3.44 ± 0.43	73.1 ± 6.8	16.1 ± 8.8
850	6.43 ± 0.12	43.1 ± 4.6	-4.4 ± 1.2	4.04 ± 0.67	74.6 ± 1.4	12.7 ± 3.7
900	5.95 ± 0.48	57.5 ± 12.9	3.7 ± 6.4	3.05 ± 0.44	72.1 ± 0.9	12.8 ± 2.3
950	8.10 ± 1.05	57.6 ± 13.2	4.1 ± 7.4	4.14 ± 0.39	75.5 ± 1.7	11.5 ± 2.1
1000	7.69 ± 1.32	51.2 ± 4.8	-0.7 ± 1.7	4.95 ± 1.14	66.5 ± 1.7	6.1 ± 1.2
Whole simulation	6.23 ± 1.26	54.1 ± 10.9	0.9 ± 4.9	4.08 ± 1.17	73.2 ± 6.1	12.3 ± 5.4

H) CB1*-taranabant simulations mean values

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	6.84 ± 0.00	38.3 ± 1.2	-5.5 ± 0.3	0.87 ± 0.02	78.4 ± 1.4	19.8 ± 2.5
50	6.86 ± 0.61	55.4 ± 2.4	3.2 ± 0.4	0.64 ± 0.04	79.5 ± 3.9	19.8 ± 4.3
100	6.52 ± 0.24	50.8 ± 2.6	-1.3 ± 1.3	1.49 ± 0.80	76.9 ± 1.5	14.0 ± 1.9
150	6.42 ± 0.42	47.7 ± 8.3	-2.1 ± 3.6	1.76 ± 0.68	73.6 ± 1.0	11.9 ± 1.0
200	6.24 ± 0.12	54.1 ± 3.0	0.2 ± 1.1	2.00 ± 1.69	78.2 ± 1.5	15.6 ± 2.1
250	6.65 ± 0.05	57.5 ± 8.8	2.5 ± 4.4	0.75 ± 0.36	79.6 ± 2.9	17.2 ± 2.8
300	6.90 ± 0.10	47.3 ± 10.5	-2.0 ± 3.9	0.87 ± 0.31	77.4 ± 4.8	14.2 ± 2.2
350	6.24 ± 0.38	55.5 ± 15.6	2.9 ± 7.1	3.04 ± 3.06	75.2 ± 1.3	13.8 ± 5.3
400	6.17 ± 0.07	46.1 ± 2.2	-1.7 ± 1.6	1.00 ± 0.34	73.8 ± 3.3	12.1 ± 3.3
450	6.21 ± 0.28	57.7 ± 5.8	2.2 ± 2.8	1.01 ± 0.36	73.3 ± 5.3	11.5 ± 4.2
500	6.34 ± 0.28	49.9 ± 9.8	-1.0 ± 3.9	1.58 ± 0.67	76.7 ± 4.5	12.8 ± 4.0
550	6.49 ± 0.36	49.1 ± 1.5	-1.2 ± 1.1	0.97 ± 0.40	72.3 ± 3.7	10.2 ± 3.7
600	6.72 ± 0.19	54.2 ± 1.2	0.3 ± 0.4	1.02 ± 0.12	74.6 ± 2.5	12.6 ± 2.1
650	6.46 ± 0.33	46.4 ± 12.0	-2.2 ± 4.6	1.27 ± 0.44	76.1 ± 3.8	13.3 ± 3.5
700	6.25 ± 0.52	44.1 ± 14.1	-2.8 ± 5.1	1.36 ± 0.62	71.7 ± 2.4	8.4 ± 2.1
750	6.40 ± 0.05	47.9 ± 2.5	-2.4 ± 1.6	1.60 ± 0.92	73.5 ± 2.0	11.3 ± 2.7
800	6.58 ± 0.45	57.3 ± 6.4	0.1 ± 1.5	1.36 ± 0.13	74.0 ± 3.8	11.0 ± 4.0
850	6.53 ± 0.35	50.6 ± 4.9	-1.5 ± 1.6	1.11 ± 0.37	72.9 ± 1.5	9.4 ± 2.0
900	6.40 ± 0.09	48.7 ± 2.3	-1.6 ± 1.3	2.19 ± 0.66	66.5 ± 11.9	8.0 ± 7.0
950	6.42 ± 0.31	50.0 ± 2.8	-1.4 ± 0.3	2.49 ± 0.78	70.2 ± 4.2	9.9 ± 4.8
1000	6.31 ± 0.40	45.1 ± 8.3	-3.3 ± 1.9	1.78 ± 1.17	79.0 ± 1.1	18.4 ± 7.3
Whole simulation	6.47 ± 0.38	50.2 ± 8.9	-0.9 ± 3.7	1.44 ± 1.11	74.9 ± 5.1	13.1 ± 5.1

Tables S3. ROC AUC and adjusted logAUCs following virtual screening *without* prior IFD.

A) CB1-AM11542 simulations replicate 1

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	34.6	-7.1	76.4	13.5
50	48.4	-2.2	75.5	12.7
100	39.8	-5.6	79.6	13.7
150	45.6	-3.8	69.3	7.3
200	45.2	-3.2	75.2	12.2
250	35.4	-7.3	72.1	8.0
300	50.8	-1.8	70.9	9.5
350	44.6	-4.5	78.0	16.6
400	41.4	-4.9	72.5	8.1
450	47.5	-2.2	81.3	16.6
500	54.8	1.1	71.3	8.0
550	56.8	1.7	76.2	12.0
600	63.8	5.0	82.5	21.6
650	40.4	-4.8	75.4	12.3
700	37.9	-6.1	69.9	8.0
750	40.7	-5.2	69.6	6.6
800	47.3	-3.4	76.5	13.9
850	40.5	-3.0	78.5	17.6
900	29.1	-7.7	77.9	17.8
950	35.7	-6.8	72.1	11.6
1000	40.3	-4.7	77.0	20.4

B) CB1-AM11542 simulations replicate 2

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	38.2	-6.6	74.5	15.2
50	35.3	-6.8	82.0	18.8
100	42.6	-4.0	80.6	22.4
150	60.0	1.6	72.5	9.8
200	58.1	1.0	78.2	13.8
250	49.8	-1.9	78.5	15.7
300	44.7	-4.3	78.3	13.9
350	57.7	1.4	77.4	13.9
400	56.0	0.1	81.9	18.1
450	59.2	1.4	77.5	13.3
500	52.1	-0.4	64.2	5.0
550	65.6	7.4	77.1	14.0
600	42.4	-4.3	72.7	10.4
650	49.3	-2.6	79.1	18.0
700	61.7	2.6	78.4	13.8
750	46.0	-2.6	74.2	11.8
800	62.4	2.8	74.4	17.5
850	60.7	4.7	76	11.6
900	52.8	-0.6	87.8	24.9
950	49.9	-1.8	74.5	11.6
1000	65.9	5.3	78.1	12.6

C) CB1-AM11542 simulations replicate 3

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	46.6	-3.7	74.6	14.5
50	37.1	-5.4	75.8	11.9
100	57.2	0.0	68.1	7.8
150	55.9	-0.9	72.9	9.7
200	36.6	-6.6	68.9	6.9
250	55.6	0.1	68.0	10.6
300	46.4	-3.2	78.3	16.9
350	60.2	3.1	78.2	13.5
400	39.5	-5.3	72.8	8.2
450	71.0	11.1	76.6	12.2
500	48.7	-2.0	74.8	9.5
550	45.6	-3.6	71.6	10.4
600	58.8	3.2	83.5	26.0
650	49.2	-2.0	75.1	14.2
700	47.4	-3.5	72.4	11.0
750	37.6	-6.4	79.2	14.8
800	57.1	1.4	76.0	21.7
850	66.8	10.3	70.2	13.5
900	54.1	3.4	77.1	16.0
950	40.5	-3.9	79.7	19.7
1000	43.0	-3.6	76.5	11.7

D) CB1*-taranabant simulations replicate 1

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	47.1	-2.5	78.7	14.6
50	59.3	0.8	72.3	11.4
100	54.4	0.2	73.5	11.9
150	50.6	-0.2	66.3	4.8
200	53.1	0.8	75.5	11.3
250	61.9	3.8	68.6	8.3
300	49.1	-2.9	67.3	6.3
350	39.0	-5.9	68.8	7.5
400	53.8	-0.2	72.1	8.5
450	58.3	2.9	73.8	11.0
500	50.7	-0.9	71.2	9.1
550	52.1	-0.5	77.2	13.8
600	54.5	0.2	68.9	10.6
650	47.2	-2.8	77.8	13.6
700	53.0	1.1	68.3	8.1
750	55.0	1.6	69.4	9.7
800	53.3	-1.3	67.6	9.2
850	55.9	0.0	74.7	12.4
900	59.0	1.3	65.6	5.6
950	56.9	2.1	73.5	10.3
1000	65.8	6.5	66.4	8.4

E) CB1*-taranabant simulations replicate 2

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	54.9	0.3	79.6	15.1
50	63.8	3.1	78.9	17.2
100	56.0	-0.7	76.0	13.6
150	64.5	3.0	77.3	11.7
200	57.3	0.5	75.1	12.0
250	58.4	1.1	80.0	16.1
300	60.2	4.8	84.7	20.0
350	52.7	-0.5	71.5	11.6
400	52.6	-1.2	76.5	11.3
450	57.4	0.5	74.4	11.4
500	55.4	-0.9	68.1	8.3
550	60.5	4.9	71.0	9.0
600	60.8	2.9	67.2	6.8
650	59.0	1.3	67.9	7.1
700	60.2	2.2	69.0	7.0
750	58.2	1.0	72.9	10.5
800	60.8	3.5	75.5	10.8
850	59.5	1.2	75.8	12.0
900	51.0	-2.0	74.7	10.8
950	48.2	-2.9	76.1	13.1
1000	53.6	0.4	73.0	11.3

F) CB1*-taranabant simulations replicate 3

	Antagonist Dataset		Agonist Dataset	
Time (ns)	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
0	42.1	-2.3	80.6	16.4
50	50.3	-1.3	77.5	13.2
100	51.9	-2.1	68.7	8.2
150	42.5	-4.4	73.7	10.6
200	57.4	0.4	77.1	14.1
250	56.9	1.2	76.9	10.1
300	49.0	-2.5	72.0	12.6
350	54.2	-0.5	71.5	9.9
400	51.1	-1.3	70.1	8.7
450	43.1	-4.3	73.2	9.1
500	52.0	-2.3	72.5	10.0
550	49.4	-2.8	77.6	12.1
600	42.9	-3.8	72.0	10.2
650	60.5	2.1	68.7	5.4
700	50.7	-1.0	78.5	14.7
750	57.0	2.0	67.6	10.0
800	65.4	4.0	65.5	4.8
850	58.9	2.2	74.2	9.9
900	57.4	1.8	70.2	7.1
950	56.2	1.3	67.8	8.0
1000	71.9	6.8	66.9	5.6

G) CB1-AM11542 simulations mean values

	Antagonist Dataset		Agonist Dataset	
Time (ns)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	39.8 ± 5.0	-5.8 ± 1.5	75.2 ± 0.9	14.4 ± 0.7
50	40.3 ± 5.8	-4.8 ± 1.9	77.8 ± 3.0	14.5 ± 3.0
100	46.5 ± 7.6	-3.2 ± 2.4	76.1 ± 5.7	14.7 ± 6.0
150	53.8 ± 6.1	-1.0 ± 2.2	71.6 ± 1.6	8.9 ± 1.2
200	46.6 ± 8.8	-2.9 ± 3.1	74.1 ± 3.9	10.9 ± 3.0
250	46.9 ± 8.5	-3.0 ± 3.1	72.9 ± 4.3	11.4 ± 3.2
300	47.3 ± 2.6	-3.1 ± 1.0	75.8 ± 3.5	13.4 ± 3.0
350	54.2 ± 6.8	0.0 ± 3.3	77.9 ± 0.3	14.7 ± 1.4
400	45.6 ± 7.4	-3.4 ± 2.4	75.7 ± 4.4	11.5 ± 4.7
450	59.2 ± 9.6	3.5 ± 5.6	78.5 ± 2.0	14.0 ± 1.9
500	51.9 ± 2.5	-0.4 ± 1.2	70.1 ± 4.4	7.5 ± 1.9
550	56.0 ± 8.2	1.8 ± 4.5	75.0 ± 2.4	12.1 ± 1.5
600	55.0 ± 9.1	1.3 ± 4.0	79.6 ± 4.9	19.3 ± 6.5
650	46.3 ± 4.2	-3.1 ± 1.2	76.5 ± 1.8	14.8 ± 2.4
700	49.0 ± 9.8	-2.3 ± 3.7	73.6 ± 3.6	10.9 ± 2.4
750	41.4 ± 3.5	-4.7 ± 1.6	74.3 ± 3.9	11.1 ± 3.4
800	55.6 ± 6.3	0.3 ± 2.6	75.6 ± 0.9	17.7 ± 3.2
850	56.0 ± 11.2	4.0 ± 5.4	74.9 ± 3.5	14.3 ± 2.5
900	45.3 ± 11.5	-1.6 ± 4.6	80.9 ± 4.9	19.6 ± 3.9
950	42.0 ± 5.9	-4.2 ± 2.1	75.4 ± 3.2	14.3 ± 3.8
1000	49.7 ± 11.5	-1.0 ± 4.5	77.2 ± 0.7	14.9 ± 3.9
Whole simulation	49.0 ± 9.5	-1.6 ± 4.2	75.6 ± 4.2	13.6 ± 4.5

H) CB1*-taranabant simulations mean values

	Antagonist Dataaset		Agonist Dataset	
Time (ns)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	48.0 ± 5.3	-1.5 ± 1.3	79.6 ± 0.8	15.3 ± 0.8
50	57.8 ± 5.6	0.9 ± 1.8	76.2 ± 2.8	14.0 ± 2.4
100	54.1 ± 1.7	-0.9 ± 1.0	72.7 ± 3.0	11.2 ± 2.3
150	52.5 ± 9.1	-0.6 ± 3.0	72.4 ± 4.6	9.0 ± 3.0
200	55.9 ± 2.0	0.6 ± 0.2	75.9 ± 0.9	12.5 ± 1.2
250	59.1 ± 2.1	2.0 ± 1.3	75.2 ± 4.8	11.5 ± 3.3
300	52.8 ± 5.3	-0.2 ± 3.5	74.7 ± 7.3	13.0 ± 5.6
350	48.6 ± 6.8	-2.3 ± 2.5	70.6 ± 1.3	9.7 ± 1.7
400	52.5 ± 1.1	-0.9 ± 0.5	72.9 ± 2.7	9.5 ± 1.3
450	52.9 ± 7.0	-0.3 ± 3.0	73.8 ± 0.5	10.5 ± 1.0
500	52.7 ± 2.0	-1.4 ± 0.6	70.6 ± 1.8	9.2 ± 0.7
550	54.0 ± 4.7	0.6 ± 3.2	75.3 ± 3.0	11.6 ± 2.0
600	52.7 ± 7.4	-0.3 ± 2.8	69.4 ± 2.0	9.2 ± 1.7
650	55.6 ± 5.9	0.2 ± 2.1	71.5 ± 4.5	8.7 ± 3.5
700	54.6 ± 4.0	0.8 ± 1.3	71.9 ± 4.7	9.9 ± 3.4
750	56.7 ± 1.3	1.5 ± 0.4	70.0 ± 2.2	10.0 ± 0.3
800	59.8 ± 5.0	2.1 ± 2.4	69.5 ± 4.3	8.3 ± 2.6
850	58.1 ± 1.6	1.2 ± 0.9	74.9 ± 0.7	11.4 ± 1.1
900	55.8 ± 3.5	0.4 ± 1.7	70.2 ± 3.7	7.8 ± 2.2
950	53.8 ± 3.9	0.2 ± 2.2	72.5 ± 3.5	10.5 ± 2.1
1000	63.8 ± 7.6	4.6 ± 2.9	68.8 ± 3.0	8.4 ± 2.3
Whole simulation	54.9 ± 6.1	0.3 ± 2.5	72.8 ± 4.4	10.5 ± 3.1

Tables S4. ROC AUC and adjusted log AUC values for virtual screenings using only active ligands (for the antagonist dataset the agonist ligands were considered as the only inactives and vice versa). Decoy molecules were excluded from calculations.

A) Crystal structures

	Antagonist Dataset		Agonist Dataset	
Crystal structure	ROC AUC (%)	Adj LogAUC (%)	ROC AUC (%)	Adj LogAUC (%)
Inactive state (5U09)	67.5	13.9	32.5	-7.5
Active state (5XRA)	23.7	-7.7	76.3	11.4

B) CB1-AM11542 simulations replicate 1

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.74	8.7	-12.6	3.02	91.2	28
50	7.75	30.4	6.0	3.65	69.6	7.4
100	3.23	47.4	-2.3	3.27	52.6	2.5
150	5.18	53.2	0.0	4.10	46.8	-0.1
200	5.79	50.8	0.2	3.67	49.2	-0.7
250	6.60	22.4	-9.1	4.54	77.6	15.2
300	5.96	9	-12.9	3.42	91	32.4
350	6.36	20.3	-10.1	4.03	79.7	21.8
400	2.78	61.6	4.1	4.42	38.4	-4.1
450	3.92	43.5	-2.8	4.59	56.5	2.8
500	5.41	78.3	16.6	3.59	21.7	-10.1
550	4.31	44	-4.0	3.74	56	6
600	6.63	65.4	8.6	3.40	34.6	-6.5
650	6.67	23.5	-9.6	3.65	76.5	22.1
700	6.75	25.7	-7.2	4.49	74.3	9.9
750	5.67	32.4	-6.7	6.57	67.6	9.4
800	6.74	11	-12.5	4.04	88.9	26.5
850	6.52	42.4	-3.5	4.50	57.6	3.5
900	6.41	24.4	-8.6	3.24	75.6	14
950	8.10	24.3	-7.6	4.05	75.7	10.6
1000	6.88	56.9	9.9	4.89	43.1	-5.6

C) CB1-AM11542 simulations replicate 2

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.43	13.20	-11.9	2.95	86.8	25.3
50	4.01	8.60	-12	4.15	91.4	27.5
100	5.13	57.00	2.2	3.37	43	-2.6
150	6.88	32.40	-7.3	2.96	67.6	11.4
200	4.44	54.7	6.0	4.92	45.3	-4.3
250	8.85	11.7	-11.6	7.20	88.3	26.2
300	6.73	47.8	-2.5	3.10	52.2	2.4
350	6.21	34.9	-5.7	4.62	65.1	6.6
400	6.63	31.6	-6.9	7.24	68.4	9.2
450	7.22	15.3	-11.6	3.75	84.7	24.3
500	5.61	40.2	-4.5	6.95	59.8	5.9
550	6.08	25.5	-9.7	4.63	74.5	17.9
600	6.13	31.9	-7.1	6.97	68.1	10.5
650	6.61	77.3	10.3	5.17	22.7	-7.8
700	6.02	56.8	2.0	5.11	43.2	-2.1
750	6.46	13.7	-11.6	6.93	86.3	21.1
800	7.04	45.0	-1.8	3.11	55.0	1.5
850	6.26	31.7	-5.9	4.53	68.3	7.6
900	6.16	30.9	-6.3	3.46	69.1	8.2
950	9.39	47.0	-0.8	4.66	53.0	0.4
1000	9.55	45.3	-1.8	6.38	54.7	1.5

D) CB1-AM11542 simulations replicate 3

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	5.66	10.7	-12.0	2.95	89.3	22.5
50	6.52	56.5	3.2	2.73	43.5	-3.2
100	5.46	48.6	-0.1	3.66	51.4	-0.3
150	6.61	65.9	7.8	3.00	34.1	-6.0
200	4.58	44.6	-1.2	3.46	55.4	0.9
250	5.48	36.1	-6.2	3.41	63.9	8.7
300	5.63	42.4	-3.9	3.59	57.6	4.9
350	6.92	40.6	-4.7	3.69	59.4	6.6
400	4.67	18.4	-11.0	3.30	81.6	22.1
450	6.97	39.6	-1.8	3.43	60.4	1.4
500	8.74	23.7	-7.0	3.35	76.3	10.1
550	5.76	18.9	-9.9	3.66	81.1	17.7
600	7.43	45.2	0.0	3.19	54.8	-0.3
650	7.21	61.8	11.2	3.18	38.2	-6.8
700	6.12	34.6	-2.5	4.47	65.4	2.9
750	6.90	58.3	3.5	3.06	41.7	-3.6
800	6.85	29.0	-8.7	3.16	71.0	15.5
850	6.52	14.4	-11.1	3.09	85.5	27.5
900	5.28	14.4	-11.1	2.43	85.6	23.4
950	6.82	30.7	-5.2	3.71	69.3	5.9
1000	6.64	52.0	1.9	3.58	48.0	-2.0

E) CB1*-taranabant simulations replicate 1

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	24.6	-9.5	0.89	75.4	17.0
50	6.21	14.0	-11.5	0.66	86.0	25.3
100	6.61	16.2	-11.5	2.61	83.8	22.3
150	5.84	31.6	-7.6	1.59	68.4	10.6
200	6.27	39.4	-2.9	0.98	60.6	2.9
250	6.61	27.3	-7.6	1.26	72.7	10.1
300	6.98	10.9	-11.9	1.19	89.1	29.0
350	6.63	14.2	-11.1	0.92	85.8	23.3
400	6.17	21.2	-9.2	0.91	78.8	14.9
450	6.60	42.8	-2.5	0.66	57.2	2.4
500	5.98	5.8	-12.8	0.92	94.2	37.8
550	6.24	32.0	-4.9	1.52	68.0	6.5
600	6.53	28.0	-8.8	1.14	72.1	13.9
650	6.35	26.1	-7.1	1.07	73.9	9.5
700	5.83	10.2	-11.6	2.23	89.8	23.5
750	6.33	39.4	-5.0	1.24	60.6	6.0
800	5.94	28.3	-7.2	1.53	71.7	10.1
850	6.12	27.8	-7.8	0.66	72.2	10.5
900	6.31	54.7	1.4	2.44	45.3	-1.7
950	6.02	41.0	-4.6	2.00	59.0	5.4
1000	6.05	18.3	-9.6	0.96	81.7	15.9

F) CB1*-taranabant simulations replicate 2

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	15.5	-11.1	0.84	84.5	20.9
50	7.67	13.4	-9.8	0.58	86.6	19.6
100	6.77	24.6	-7.8	0.86	75.4	11.6
150	6.62	41.1	-3.7	1.03	58.9	3.7
200	6.38	19.6	-10.8	0.63	80.4	21.8
250	6.73	34.9	-5.5	0.54	65.1	7.0
300	6.77	58.0	2.8	0.95	42.0	-2.8
350	5.72	33.8	-3.6	0.83	66.2	4.3
400	6.09	35.1	-5.2	0.63	64.9	6.1
450	6.03	39.6	-3.2	0.87	60.4	3.3
500	6.66	67.0	10.5	2.50	33.0	-6.7
550	6.23	30.2	-6.7	0.78	69.8	8.9
600	6.98	41.6	-4.2	1.07	58.4	4.7
650	6.91	47.1	-0.4	1.88	52.9	0.0
700	6.98	57.2	3.8	0.81	42.8	-3.8
750	6.43	25.1	-8.5	0.70	74.9	12.7
800	6.90	57.6	-0.1	1.20	42.4	1.1
850	6.99	34.6	-7.0	1.10	65.4	10.8
900	6.37	36.3	-5.3	2.86	63.7	7.3
950	6.76	36.3	-4.0	3.59	63.6	4.2
1000	6.88	42.1	-4.2	0.93	57.9	4.9

G) CB1*-taranabant simulations replicate 3

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)	Best Ligand RMSD (Å)	ROC AUC (%)	Adj LogAUC (%)
0	6.84	16.9	-11.1	0.89	83.1	21.4
50	6.70	11.0	-12.6	0.66	89.0	27.8
100	6.19	60.0	3.7	0.99	40.0	-3.4
150	6.81	21.8	-9.6	2.68	78.2	14.9
200	6.08	52.8	2.0	4.38	47.2	-2
250	6.62	38.3	-5.4	0.45	61.7	7.5
300	6.95	40.7	-2.5	0.46	59.3	22.8
350	6.37	53.3	0.1	7.36	46.7	-0.1
400	6.25	38.9	-0.5	1.44	61.1	1.5
450	5.99	61.7	6.0	1.50	38.3	-4.6
500	6.38	34.6	-5.5	1.34	65.4	5.9
550	6.99	55.0	2.7	0.61	45.0	-2.6
600	6.66	28.8	-6.8	0.86	71.2	8.9
650	6.12	29.9	-7.4	0.86	70.1	9.9
700	5.94	51.6	3.0	1.04	48.4	-2.4
750	6.43	36.3	-4.3	2.86	63.7	4.7
800	6.90	67.0	8.4	1.37	33.0	-6.1
850	6.48	27.4	-7.2	1.57	72.6	10.7
900	6.52	56.3	8.5	1.29	43.7	-4.8
950	6.47	34.9	-5.1	1.89	65.1	5.8
1000	6.00	45.6	-1.5	3.44	54.4	0.8

H) CB1-AM11542 simulations mean values

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	5.61 ± 0.13	10.9 ± 1.8	-12.2 ± 0.3	2.98 ± 0.03	89.1 ± 1.8	25.3 ± 2.2
50	6.09 ± 1.56	31.8 ± 19.6	-0.9 ± 7.9	3.51 ± 0.59	68.2 ± 19.6	10.6 ± 12.7
100	4.61 ± 0.98	51.0 ± 4.3	-0.1 ± 1.8	3.43 ± 0.16	49.0 ± 4.3	-0.1 ± 2.1
150	6.22 ± 0.75	50.5 ± 13.8	0.2 ± 6.2	3.35 ± 0.53	49.5 ± 13.8	1.8 ± 7.2
200	4.94 ± 0.60	50.0 ± 4.2	1.7 ± 3.1	4.02 ± 0.65	50.0 ± 4.2	-1.4 ± 2.2
250	6.98 ± 1.40	23.4 ± 10.2	-9.0 ± 2.2	5.05 ± 1.59	76.6 ± 10.0	16.7 ± 7.2
300	6.11 ± 0.46	33.1 ± 17.2	-6.4 ± 4.6	3.37 ± 0.20	66.9 ± 17.2	13.2 ± 13.6
350	6.50 ± 0.31	31.9 ± 8.5	-6.8 ± 2.3	4.11 ± 0.39	68.1 ± 8.5	11.7 ± 7.2
400	4.69 ± 1.57	37.2 ± 18.1	-4.6 ± 6.4	4.99 ± 1.66	62.8 ± 18.1	9.1 ± 10.7
450	6.03 ± 1.50	32.8 ± 12.5	-5.4 ± 4.4	3.92 ± 0.49	67.2 ± 12.5	9.5 ± 10.5
500	6.58 ± 1.52	47.4 ± 22.9	1.7 ± 10.6	4.63 ± 1.64	52.6 ± 22.9	2.0 ± 8.7
550	5.38 ± 0.77	29.5 ± 10.6	-7.9 ± 2.7	4.01 ± 0.44	70.5 ± 10.6	13.9 ± 5.6
600	6.73 ± 0.53	47.5 ± 13.8	0.5 ± 6.4	4.52 ± 1.73	52.5 ± 13.8	1.2 ± 7.0
650	6.83 ± 0.27	54.2 ± 22.9	4.0 ± 9.6	4.00 ± 0.85	45.8 ± 22.6	2.5 ± 13.9
700	6.30 ± 0.32	39.0 ± 13.1	-2.6 ± 3.8	4.69 ± 0.30	61.0 ± 13.1	3.6 ± 4.9
750	6.35 ± 0.51	34.8 ± 18.3	-4.9 ± 6.3	5.52 ± 1.75	65.2 ± 18.3	9.0 ± 10.1
800	6.88 ± 0.12	28.3 ± 13.9	-7.7 ± 4.4	3.44 ± 0.43	71.6 ± 13.8	14.5 ± 10.2
850	6.43 ± 0.12	29.5 ± 11.5	-6.8 ± 3.2	4.04 ± 0.67	70.5 ± 11.5	12.9 ± 10.5
900	5.95 ± 0.48	23.2 ± 6.8	-8.7 ± 2.0	3.05 ± 0.44	76.8 ± 6.8	15.2 ± 6.3
950	8.10 ± 1.05	34.0 ± 9.6	-4.5 ±2.8	4.14 ± 0.39	66.0 ± 9.6	5.6 ± 4.2
1000	7.69 ± 1.32	51.4 ± 4.8	3.3 ± 4.9	4.95 ± 1.14	48.6 ± 4.8	-2.0 ± 2.9
Whole simulation	6.23 ± 1.26	36.7 ± 17.6	-3.7 ± 6.9	4.08 ± 1.17	63.3 ± 17.6	8.3 ± 10.9

I) CB1*-taranabant simulations mean values

	Antagonist Dataset			Agonist Dataset		
Time (ns)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)	Mean Best Ligand RMSD (Å ± SD)	Mean ROC AUC (% ± SD)	Mean Adj LogAUC (% ± SD)
0	6.84 ± 0.00	19.0 ± 4.0	-10.6 ± 0.8	0.87 ± 0.02	81.0 ± 4.0	19.8 ± 2.0
50	6.86 ± 0.61	12.8 ± 1.3	-11.3 ± 1.2	0.64 ± 0.04	87.2 ± 1.3	24.2 ± 3.4
100	6.52 ± 0.24	33.6 ± 19.0	-5.2 ± 6.5	1.49 ± 0.80	66.4 ± 19.0	10.2 ± 10.5
150	6.42 ± 0.42	31.5 ± 7.9	-7.0 ± 2.4	1.76 ± 0.68	68.5 ± 7.9	9.7 ± 4.6
200	6.24 ± 0.12	37.3 ± 13.6	-3.9 ± 5.3	2.00 ± 1.69	62.7 ± 13.6	7.6 ± 10.3
250	6.65 ± 0.05	33.5 ± 4.6	-6.2 ± 1.0	0.75 ± 0.36	66.5 ± 4.6	8.2 ± 1.4
300	6.90 ± 0.10	36.5 ± 19.5	-3.9 ± 6.1	0.87 ± 0.31	63.5 ± 19.5	16.3 ± 13.8
350	6.24 ± 0.38	33.8 ± 16.0	-4.9 ± 4.7	3.04 ± 3.06	66.2 ± 16.0	9.2 ± 10.2
400	6.17 ± 0.07	31.7 ± 7.6	-5.0 ± 3.6	1.00 ± 0.34	68.3 ± 7.6	7.5 ± 5.6
450	6.21 ± 0.28	48.0 ± 9.8	0.1 ± 4.2	1.01 ± 0.36	52.0 ± 9.8	0.4 ± 3.5
500	6.34 ± 0.28	35.8 ± 25.0	-2.6 ± 9.7	1.58 ± 0.67	64.2 ± 25.0	12.3 ± 18.7
550	6.49 ± 0.36	39.1 ± 11.3	-3.0 ± 4.1	0.97 ± 0.40	60.9 ± 11.3	4.3 ± 5.0
600	6.72 ± 0.19	32.8 ± 6.2	-6.6 ± 1.9	1.02 ± 0.12	67.2 ± 6.2	9.2 ± 3.8
650	6.46 ± 0.33	34.4 ± 9.1	-5.0 ± 3.2	1.27 ± 0.44	65.6 ± 9.1	6.5 ± 4.6
700	6.25 ± 0.52	39.7 ± 21.0	-1.6 ± 7.1	1.36 ± 0.62	60.3 ± 21.0	5.8 ± 12.6
750	6.40 ± 0.05	33.6 ± 6.1	-5.9 ± 1.8	1.60 ± 0.92	66.4 ± 6.1	7.8 ± 3.5
800	6.58 ± 0.45	51.0 ± 16.5	0.4 ± 6.4	1.36 ± 0.13	49.0 ± 16.5	1.7 ± 6.6
850	6.53 ± 0.35	29.9 ± 3.3	-7.3 ± 0.3	1.11 ± 0.37	70.1 ± 3.3	10.7 ± 0.1
900	6.40 ± 0.09	49.1 ± 9.1	1.5 ± 5.6	2.19 ± 0.66	50.9 ± 9.1	0.3 ± 5.1
950	6.42 ± 0.31	37.4 ± 2.6	-4.6 ± 0.4	2.49 ± 0.78	62.6 ± 2.6	5.1 ± 0.7
1000	6.31 ± 0.40	35.3 ± 12.1	-5.1 ± 3.4	1.78 ± 1.17	64.7 ± 12.1	7.2 ± 6.4
Whole simulation	6.47 ± 0.38	35.0 ± 15.1	-4.6 ± 5.5	1.44 ± 1.11	65.0 ± 15.1	8.8 ± 9.7

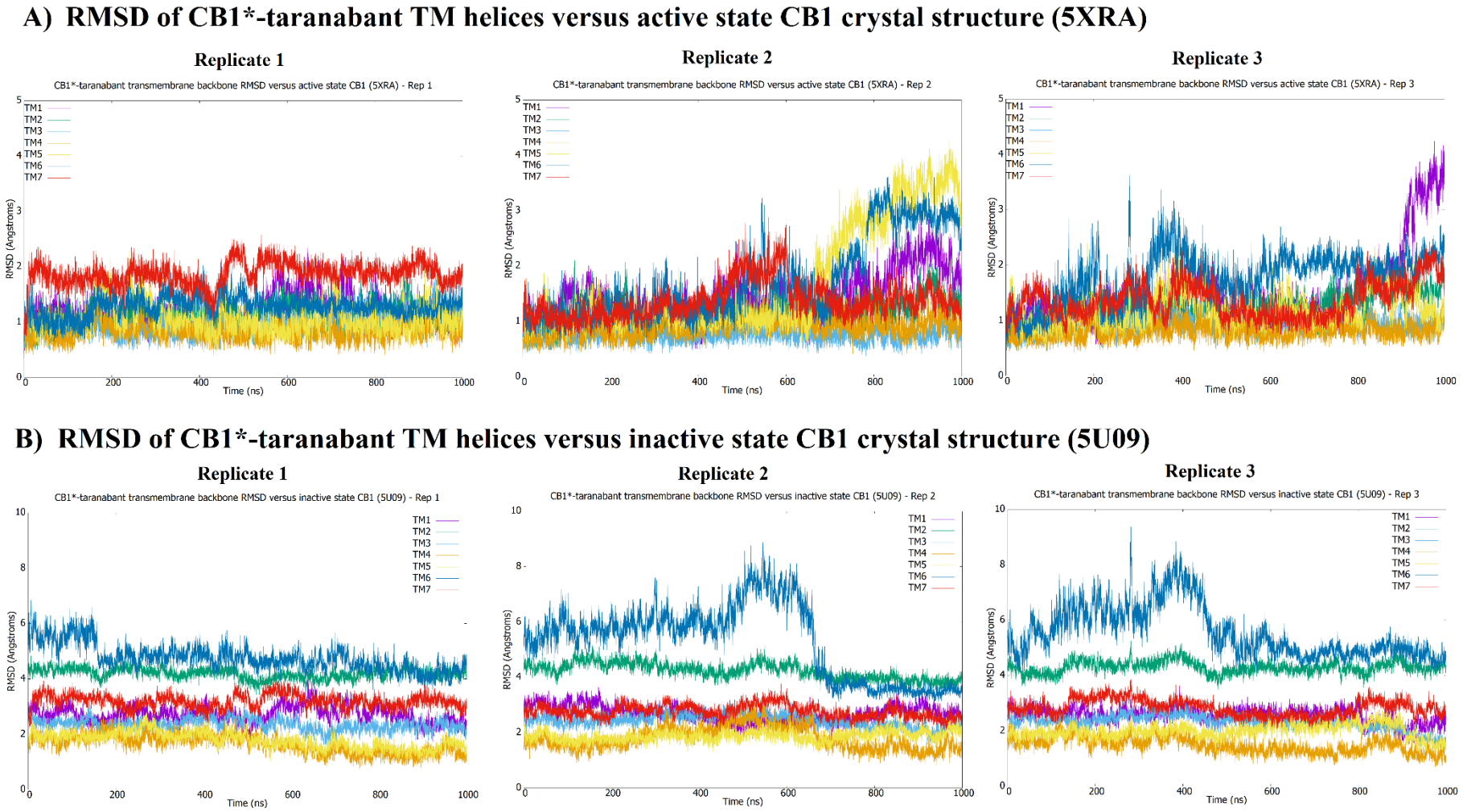

Figure S1. Individual TM helix RMSDs of CB1*taranabant versus the original active-state crystal structure (5XRA) and the inactive-state crystal structure (5U09).

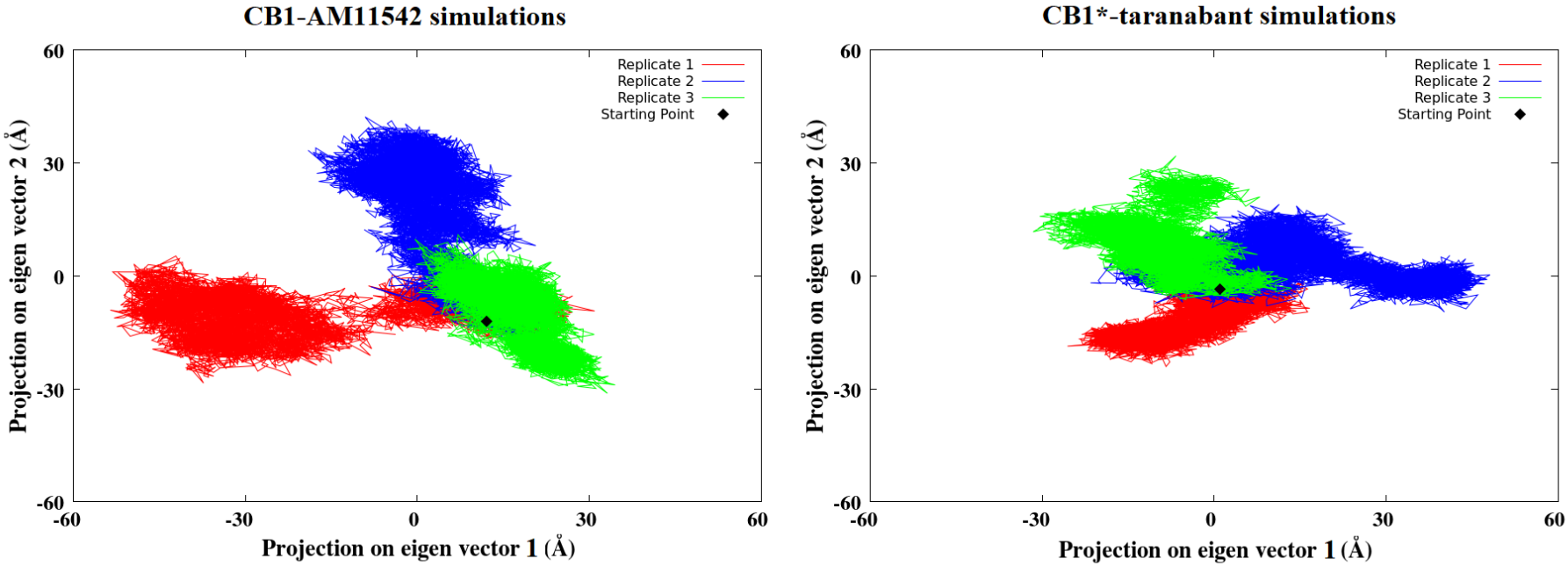

Figure S2. Principal components analysis of CB1-AM11542 and CB1*-taranabant simulations based on movement of receptor transmembrane backbone atoms. Plots are based on the the two principal components with the highest eigenvector values, which therefore represent most of the observed intermolecular movements. All three replicates in both simulations are observed to sample different regions of phase space.

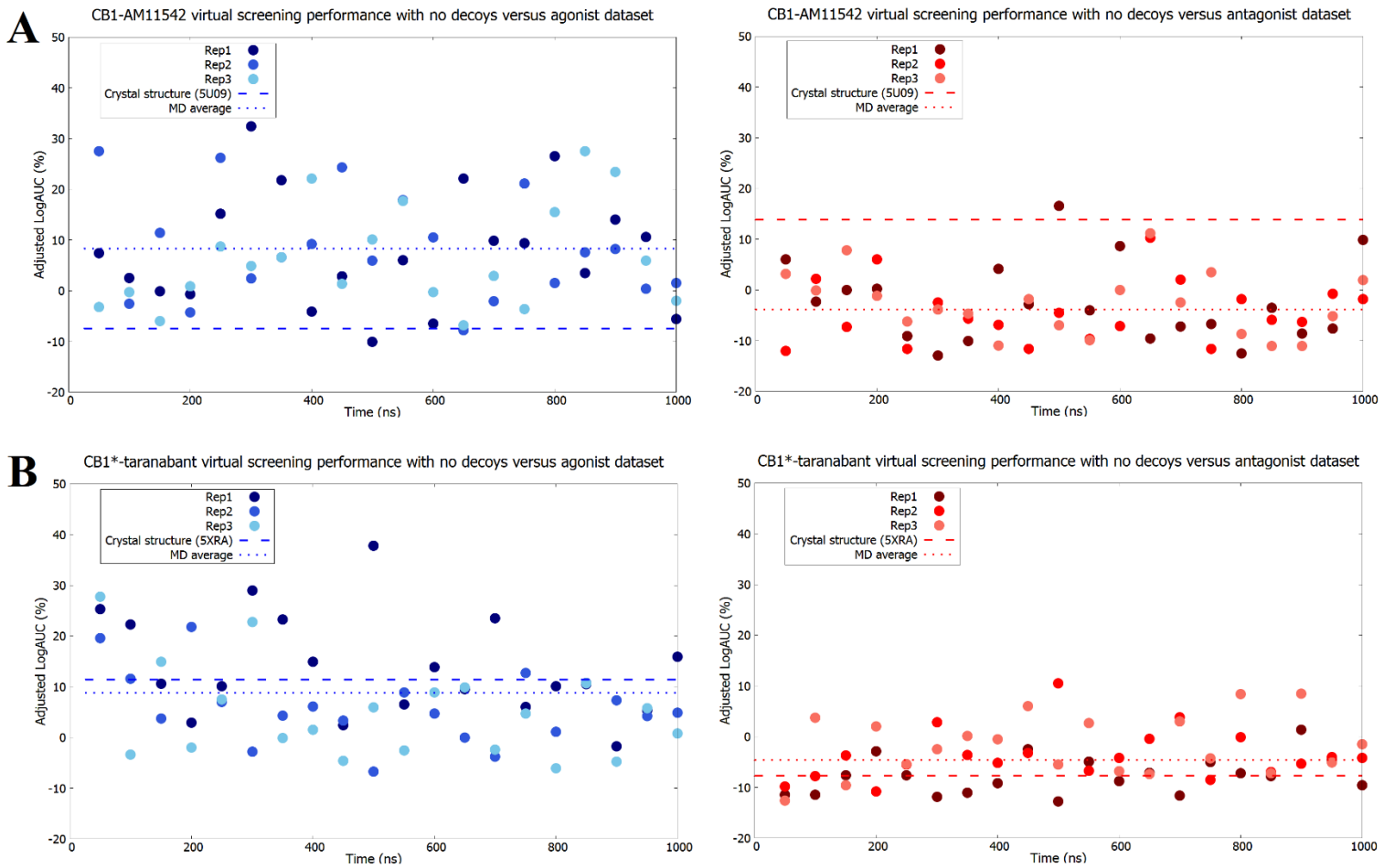

Figure S3. Comparison of direct agonist/antagonist discrimination (no decoy molecules) throughout molecular dynamics simulations of (A) CB1-AM11542 structures and (B) CB1*-taranabant structures. Adjusted logAUC values with agonists designated as actives are shown as blue dots, while values using antagonist as actives are shown as red dots. The performance of the original crystal structures and the average across all replicates are shown as dashed lines.