DRUG METABOLISM AND DISPOSITION

Identification and Validation of Novel hPXR Activators Amongst Prescribed Drugs via Ligand-Based Virtual Screening

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SUPPLEMENTAL DATA

This Supplemental Information includes 1) a discussion of the effects on Bayesian model predictive performance by using different descriptors. 2) Docking results of test set and SCUT database compounds to hPXR LBD. 3) Two tables with Bayesian, FlexX, and Surflex scores of test set (n = 145) and SCUT database (n = 550) compounds. 4) Good and bad fingerprints predicted by ECFP-2. 5) The Surflex docked (1NRL) conformations of newly identified PXR activators or an antagonist.

Supplemental Results 1. The effects of different descriptors on predictive performance of Bayesian models. The effects of using topological descriptors and different fingerprints, *i.e.,* ECFP_6 and FCFP_6 on the predictive performance of the Bayesian models are demonstrated in Table 1. Using fingerprint ECFP_6 is advantageous over FCFP_6 in terms of XV ROC AUC values, when comparing ECFP-1 and FCFP-1 (87.0 vs 85.2%) and ECFP-2 and FCFP-2 (87.7 vs. 86.4%). When it comes to the test set compounds, using ECFP_6 instead of FCFP_6 seemed to be favorable for specificity but unfavorable for sensitivity, when we compare ECFP-1 vs FCFP-1 (87.3 vs 82.5% for SP and 45.1 vs 58.5% for SE) and ECFP-2 vs FCFP-2 (92.1 vs 87.3% for SP and 35.4 vs

40.2% for SE). Using topological descriptors seems of no benefit to predictive performance validated by training set compounds, indicated with lower XV ROC AUC values of ECFP_1 than ECFP_2 (87.0 vs 87.7%) and FCFP_1 than FCFP_2 (85.2 vs 86.4%). In light of test set compounds, using more descriptors is helpful in improving SE, when comparing ECFP_1 and ECFP_2 (45.1 vs 35.4%) and FCFP_1 and FCFP_2 (58.5 vs 40.2%), but could be detrimental to SP, when comparing ECFP-1 vs ECFP-2 (87.3 vs 92.1%) and FCFP-1 vs FCFP-2 (82.5 vs 87.3%). In terms of overall predictive capacity, models built with more topological descriptors (ECFP-1 and FCFP1) demonstrated higher Q and C values than their counterparts with less descriptors, as shown in Table 1 when comparing ECFP-1 with ECFP-2 and FCFP-1 with FCFP-2.

Supplemental Results 2. Results of database filtering with FlexX and SurfleX. The docking programs were used to identify and exclude non-activators with bulky size or unfavorable binding energies. First, 82 hPXR activators and 63 hPXR nonactivators in the test set were docked into the active site of hPXR. The best poses selected based on the most favorable FlexX (binding energy, in kcal/mol) or Surflex score (-LogK_d) were generated. Since a binding score threshold for identifying hPXR activators and nonactivators did not work well previously (Ekins et al., 2008; Khandelwal et al., 2008; Yasuda et al., 2008; Kortagere et al., 2009), we applied only a standard filter of docked/undocked (FlexX) and a rather low cutoff score (Surflex) to identify hPXR nonactivators with unfavorable binding (Supplemental Information). Ten compounds failed to fit in the active site by FlexX, three compounds were docked outside of the binding pocket (some of them with positive binding energies), and one compound with positive binding energy docked inside the LBD. Since docking with FlexX only considers

residues within the defined active site, compounds docked outside of the active site should be regarded as unsuccessful. As a result, 14 drugs were discarded by FlexX. Surflex identified six compounds with scores below 2, indicating poor binding affinity, and all of these unsuccessfully docked with FlexX. The combined results from FlexX and Surflex indicate six molecules to be hPXR nonactivators. However, three are actually hPXR activators and another three are nonactivators. On the basis of data distribution, the probability of randomly selecting a PXR nonactivator is 63/(63+82) = 0.43, whereas the ratio of the nonactivators among the six compounds is 0.5. Thus, FlexX and Surflex appear to have some ability for initial exclusion of nonactivators, especially those with bulky or rigid structures and unfavorable binding energies. The fact that some activators failed to dock the LBD could be explained by the rigid treatment of the protein which is flexible in reality.

Among the 550 SCUT compounds that were docked into the hPXR-LBD, 31 failed to fit in the active site (FlexX). Additionally, 12 compounds were docked outside the active site (some with positive binding energies) and 3 had a positive FlexX score but were docked inside of the binding pocket. Overall, docking of 46 drugs was unsuccessful by FlexX. With Surflex, 17 compounds had scores below zero and 4 compounds had Surflex scores between 0 and 2. The low Surflex scores of these compounds indicated possible poor binding to hPXR. Among 17 compounds with negative Surflex scores, only two were docked successfully by FlexX. Nevertheless, all were excluded from the next screening step.

Supplemental Table S1 Test set compound (n = 145) scores based on Bayesian models, FlexX and Surflex.

Index *	Name	ECFP-1	FCFP-1	ECFP-2	FCFP-2	Activation **	FlexX (kcal/ mol)	FlexX Note** **	Surflex (-logKd)	Exclusion****
1	reserpine	-14.48	-17.78	-14.58	-17.88	a	1.58	o	-28.64	y
2	Structure6617	13.52	2.74	18.05	7.27	a	x		-17.06	y
3	Structure662	2.03	-4.13	5.84	-0.32		x		-7.49	y
4	Structure6625	27.01	17.88	31.67	22.54	a	4.12	o	-3.28	y
5	Structure2850	4.93	-0.20	8.89	3.75		14.01	o	-2.48	y
6	Structure1727	2.65	-1.55	6.36	2.17		x		1.49	y
7	Estriol	2.25	2.38	2.62	2.74	a	-15.78		2.23	
8	Structure3018	-2.36	-4.69	-1.17	-3.50	a	x		2.61	
9	Structure5033	-4.31	-10.42	-4.96	-11.06	a	-16.03		2.91	
10	Structure4226	-15.30	-15.29	-12.06	-12.05		-16.65		3.14	
11	Etiocholanolone	12.44	9.49	9.63	6.68	a	-9.44		3.44	
12	Structure1695	-3.07	-4.34	-5.28	-6.55		-17.3		3.47	
13	CDD3501	-3.37	-1.81	-1.85	-0.29	a	-12.21		3.47	
14	Structure2076	-3.22	-2.96	-3.89	-3.63		-19.83		3.49	
15	Structure5049	-2.59	-4.81	-2.39	-4.60		-11.66		3.55	
16	CDD3543	-2.92	0.72	-5.29	-1.64	a	-14.89		3.57	
17	Structure2013	-8.48	-11.25	-3.63	-6.40	a	-5.57		3.62	
18	Structure1441	-5.03	-4.92	-7.61	-7.49	a	-15.92		3.66	
19	Structure47	-4.97	-4.37	-0.51	0.10		-14.61		3.67	
20	Structure3479	-15.53	-18.04	-7.96	-10.46		-15.97		3.67	
21	forskolin	5.47	4.74	3.20	2.47	a	-6.92		3.82	
22	5_Pregnan_3_20_diol	8.90	7.20	5.07	3.37	a	x		3.83	
23	Structure2693	-8.59	-10.65	-5.75	-7.81	a	-13.72		3.9	
24	Structure4923	-26.53	-22.30	-24.12	-19.89	a	-17.55		3.93	
25	Estrone	7.91	6.11	9.06	7.27	a	-11.15		4.09	
26	Structure1280	-7.99	-5.28	-8.74	-6.02	a	-18.33		4.1	
27	CDD3532	1.23	2.30	-2.38	-1.31	a	-13.15		4.14	
28	Structure3360	-8.42	-7.42	-7.12	-6.13	a	-14.62		4.17	
29	Structure2937	-0.59	-1.98	2.37	0.99		-16.29		4.24	
30	petromyzonol	-29.65	-15.15	-31.68	-17.18		-0.93		4.32	
31	Structure7424	-12.62	-13.64	-8.41	-9.44		-15.18		4.4	
32	Structure4893	-11.09	-9.97	-7.72	-6.59		-11.12		4.45	
33	1-9-dideoxydorskolin	4.92	4.14	2.07	1.29	a	-11.21		4.48	
34	Structure4621	-20.93	-11.47	-21.31	-11.85	a	-29.13		4.49	
35	Structure7753	-33.52	-27.66	-30.47	-24.60	a	-17.52		4.56	
36	Structure5172	-3.35	-6.36	-2.66	-5.66		-16.93		4.61	
37	CDD3540	-1.63	1.75	-4.89	-1.51	a	-14.84		4.62	
38	Structure4308	-3.85	-5.04	-7.43	-8.62		-20.76		4.65	
39	CDD3530	2.34	1.49	-1.27	-2.12	a	-12.92		4.65	
40	phenylbutazone	-14.36	-12.13	-5.36	-3.12	a	-18.21		4.72	
41	Structure7565	-10.49	-8.38	-6.72	-4.61		-15.22		4.77	
42	Structure5608	-18.44	-10.25	-15.29	-7.11	a	-24.82		4.79	

43	Structure2326	-9.60	-10.94	-8.11	-9.46	a	-16.9		4.81	
44	Structure2616	3.05	2.97	-0.16	-0.24		x		4.83	
45	Structure7204	-10.00	-13.58	-7.54	-11.12		-14.17		4.85	
46	Structure7340	-6.14	-4.10	-6.48	-4.44		-21.64		4.92	
47	CDD3508	2.43	4.84	-0.82	1.59	a	-13.19		4.95	
48	Structure1115	-8.74	-9.06	-5.68	-6.00	a	-17.58		4.99	
49	Structure8134	-12.43	-14.66	-7.91	-10.14	a	-18.29		5	
50	Allocholicacid	-30.57	-14.30	-31.57	-15.30		-4.07		5.01	
51	CDD3538	-2.42	1.23	-5.80	-2.16	a	-14.91		5.04	
52	Muricholicacid	-2.80	-1.51	-5.12	-3.83	a	-6.72		5.07	
53	5beta-Cholan-3_7_12_24-tetrol	-29.65	-15.15	-31.68	-17.18		-7.62		5.08	
54	Structure4429	-5.90	-5.66	-11.40	-11.16	a	-18.11		5.09	
55	5beta_Androstan-3alph_ol	11.15	7.94	8.62	5.41	a	-10.7		5.12	
56	c2ba-11	-2.93	-6.60	-3.99	-7.65		-20.41		5.14	
57	Structure373	-35.53	-31.57	-23.98	-20.02		-15.1		5.19	
58	Structure1271	-6.90	-7.27	-3.53	-3.90		-17.74		5.19	
59	16_5a_Androsten-3b-ol	5.18	5.57	3.13	3.53	a	-11.06		5.22	
60	Structure3348	-7.24	-6.62	-7.53	-6.90	a	-14.19		5.26	
61	Structure5661	-4.19	-8.76	-5.63	-10.20		-15.3		5.31	
62	Structure5237	-13.26	-15.03	-8.27	-10.04		-15.64		5.32	
63	Structure7940	-6.86	-5.45	-2.86	-1.45	a	-9.24		5.33	
64	Structure3256	-20.52	-20.64	-12.48	-12.60		-15.2		5.35	
65	5alpha_Androstan-3beta_ol	11.15	7.94	8.62	5.41	a	-11.31		5.35	
66	Structure3695	-8.98	-6.55	-11.92	-9.49	a	-18.32		5.38	
67	Structure7627	-3.61	-2.33	-0.79	0.50		-21.11		5.38	
68	Structure2999	-20.97	-23.45	-12.02	-14.50		-12.92		5.4	
69	Structure3852	-5.73	-6.59	-2.26	-3.12		-11.39		5.42	
70	Structure6374	-13.28	-10.81	-9.48	-7.00		-21.34		5.46	
71	17beta-dihydroandrosterone	10.30	8.08	8.86	6.64	a	-11.49		5.47	
72	c2ba-10	-7.32	-6.24	-8.50	-7.42	a	-20.38		5.47	
73	Structure1639	-13.90	-14.59	-11.05	-11.74		-18.1		5.5	
74	Structure3532	-10.08	-8.03	-6.00	-3.95		-14.83		5.5	
75	CDD3536	2.36	5.35	-1.58	1.41	a	-14.57		5.52	
76	Structure3083	8.34	4.99	8.88	5.52	a	-18.78		5.55	
77	12_Ketolithocholica cid	-0.07	1.49	-1.71	-0.15	a	-14.8		5.58	
78	mevastatin	21.74	18.42	16.38	13.07	a	-7.72		5.65	
79	c2ba-251	-3.36	-3.38	-4.12	-4.14	a	-24.39		5.69	
80	c2ba-6	1.71	2.99	-3.63	-2.36	a	-20.65		5.74	
81	Structure2611	-36.45	-31.95	-23.42	-18.92		-20.49		5.75	
82	Estetrol	1.16	0.97	0.55	0.37	a	-16.71		5.75	
83	Epitestosterone_sulfate	17.32	14.43	12.08	9.19	a	-6.21		5.75	
84	Structure4196	-7.17	-3.83	-7.93	-4.59		-20.22		5.76	
85	Structure5533	-14.68	-15.06	-11.12	-11.51	a	-17.94		5.8	

86	Structure4360	-9.98	-7.33	-8.40	-5.75		-17.4		5.81	
87	dihydrotestosterone	17.90	12.65	16.32	11.07	a	-11.48		5.83	
88	Structure5110	-4.26	-7.96	-2.77	-6.47	a	-13.68		5.88	
89	Cortolone	6.79	4.28	3.11	0.60	a	-12.07		5.91	
90	Structure3058	-1.81	-4.50	-0.93	-3.61		-20.08		6.06	
91	Structure7343	-16.16	-18.28	-10.83	-12.95	a	-19.02		6.08	
92	Structure4879	-4.89	-6.70	-1.83	-3.64		-18.04		6.1	
93	c2ba-13	2.41	1.23	-2.33	-3.51	a	-23.84		6.14	
94	Structure5147	5.73	-1.84	0.75	-6.83	a	-12.84		6.16	
95	Structure2415	-13.02	-5.28	-15.75	-8.01	a	-16.5		6.18	
96	Structure1081	11.67	11.64	11.18	11.15	a	-12.53		6.2	
97	Structure5114	-16.52	-15.19	-9.36	-8.03		-17.87		6.2	
98	Structure4239	-12.96	-13.00	-13.90	-13.95	a	-17.47		6.21	
99	c2ba-3	-11.12	-9.08	-9.39	-7.34		-22.14		6.23	
100	Structure168	-11.04	-10.00	-6.78	-5.75		-11.5		6.29	
101	Structure3372	-10.40	-10.37	-13.18	-13.15	a	-15.4		6.34	
102	Structure377	8.98	6.60	5.29	2.90	a	-20.39		6.45	
103	Structure4563	-0.72	-3.98	-5.15	-8.41	a	-18.34		6.48	
104	Structure7655	-6.93	-8.39	-7.07	-8.52		-18.86		6.49	
105	Structure6521	-2.00	-2.76	-5.69	-6.45	a	-14.3		6.55	
106	Structure112	-7.79	-6.93	-4.82	-3.96		-13.45		6.58	
107	Structure2749	1.23	0.16	-1.71	-2.78		-15.55		6.59	
108	Structure5753	-8.40	-11.68	-6.43	-9.72		-16.75		6.6	
109	c2ba-7	-7.25	-3.77	-8.91	-5.43	a	-29.13		6.67	
110	c2ba-8	-3.96	-7.45	-4.07	-7.55	a	-14.61		6.68	
111	Structure2608	-9.56	-6.12	-8.48	-5.04		-20.54		6.7	
112	bergamottin	6.15	3.10	6.61	3.56	a	-12.46		6.71	
113	Structure2180	-42.77	-33.39	-32.99	-23.61		-13.51		6.76	
114	Structure5085	-10.53	-8.60	-4.48	-2.55		-13.67		6.78	
115	Structure7175	-14.60	-20.17	-10.60	-16.18		-20.57		6.84	
116	Structure1564	-46.40	-39.23	-38.77	-31.59		-16.82		6.91	
117	Structure6881	18.63	14.30	16.31	11.98	a	6.3		6.91	
118	Structure4151	-4.61	-4.91	0.78	0.47	a	-20.92		6.97	
119	Structure7965	-8.74	-10.91	-4.26	-6.43		-9.18		7.03	
120	Structure7687	-2.74	-3.67	-4.75	-5.69	a	-18.07		7.04	
121	Structure6704	0.73	-1.59	3.87	1.55	a	-23.34		7.07	
122	Taurochenodeoxycholicacid	-28.55	-17.72	-28.46	-17.64		x		7.12	
123	Lithocholicacid	6.77	6.96	2.45	2.64	a	x		7.21	
124	Structure6556	-12.35	-11.72	-9.57	-8.94		-17.57		7.27	
125	Tauro-b-muricholic acid	-23.23	-16.57	-22.10	-15.44		-10.39		7.31	
126	Structure583	-6.74	-9.06	-3.90	-6.22		-11.64		7.32	
127	Structure6490	-7.01	-5.07	-5.89	-3.95	a	-16.77		7.45	
128	c2ba-12	2.45	-0.83	-0.09	-3.37		-21.18		7.59	
129	Structure4376	-1.40	-3.32	-4.59	-6.51		-17.24		7.6	
130	7_Ketolithocholicacid	-0.97	0.70	-2.58	-0.91	a	-11.02		7.64	
131	Structure3194	-11.57	-9.31	-13.69	-11.43		x		7.66	

132	c2ba-9	-9.77	-14.22	-7.53	-11.99		-19.87		7.69	
133	Structure1574	6.07	9.45	0.58	3.96		x		7.73	
134	Structure6052	2.81	-0.27	4.71	1.63	a	-18.37		7.78	
135	Structure5251	6.40	2.69	5.15	1.45	a	-23.23		7.79	
136	Structure5528	-9.09	-10.95	-9.53	-11.39	a	-20.12		7.79	
137	c2ba-248	-1.44	-1.90	-1.22	-1.68	a	-19		7.85	
138	Lithocholicacidacetate	3.75	4.06	1.56	1.88	a	-7.1		7.9	
139	Structure6648	-14.10	-20.23	-14.38	-20.50		-16.14		8.03	
140	Structure6869	-9.01	-14.96	-10.70	-16.65	a	-17.66		8.06	
141	Structure8138	-15.63	-22.47	-7.84	-14.67		-17.45		8.15	
142	c2ba-5	-5.41	-5.65	-4.80	-5.04	a	-1.41		8.16	
143	Structure6541	-5.14	-13.67	-5.16	-13.68	a	-15.39		8.4	
144	Structure7944	-13.35	-8.57	-11.75	-6.97		-19.87		8.74	
145	Structure3577	-9.01	-3.72	-9.90	-4.61	a	-18.54		8.81	

*: Drug ranked according to Surflex scores.
**: “a” indicates an hPXR activator. Otherwise the compound is an hPXR nonactivator.
***: “o” indicates the drug was docked outside of binding pocket. “+” indicates the drug has a positive score.
****: “y” means the compound is predicted to be an hPXR nonactivator.

Supplemental Table S2 SCUT database compound (n = 550) scores based on Bayesian models, FlexX and Surflex.

Index*	scut ID	name	ECFP-2	FlexX	FlexX note**	Surflex	note2***	Exclusion****
1	scut0006623	rifampin	27.54	8.25	o	-19.29	b	y
2	scut0002209	dexamethasone	25.66	x		5.1	s	
3	scut0006992	spironolactone	25.20	-8.13		5.37	s	
4	scut0004451	lovastatin	24.01	-4.90		6.48	s	
5	scut0000714	beclometasone	21.20	x		3.91		
6	scut0004590	medroxyprogesterone	19.93	-9.96		4.26	c	
7	scut0006637	rimexolone	19.48	-12.35		5.04		
8	scut0002815	eplerenone	19.40	-16.74		6.67		
9	scut0006883	simvastatin	19.16	-3.63		6.9	s	
10	scut0007744	triamcinolone	19.05	x		4.46		
11	scut0004606	megestrol acetate	18.56	-10.89		5.91		
12	scut0004158	isradipine	17.22	-21.58		5.64	s	
13	scut0006657	ritonavir	17.14	x		7.68	s	
14	scut0003266	fludrocortisone	16.43	x		4.05		
15	scut0003362	fluticasone propionate	15.72	x		6.25		
16	scut0003324	fluoxymesterone	15.33	x		3.43		
17	scut0005882	permethrin	14.88	-14.27		7.26	b	
18	scut0002882	estramustine	11.65	-7.84		4.53		
19	scut0007237	tamoxifen	11.38	-18.96		8.07	s	
20	scut0001081	budesonide	10.75	-13.72		6.72	s	
21	scut0003205	finasteride	10.49	-15.09		6.47		
22	scut0006240	pravastatin	10.23	-5.62		7.32	b	
23	scut0005336	nisoldipine	10.14	-20.65		5.19		
24	scut0007137	sulfinpyrazone	9.89	-22.81		6.56	s	
25	scut0003295	flunisolide	9.85	-16.72		4.8		
26	scut0005252	nicardipine	9.76	-25.07		7.62	s	
27	scut0000377	amlodipine	9.70	-20.26		7.47	s	
28	scut0002872	estradiol	9.47	-11.16		5.78	b	
29	scut0003083	felodipine	8.78	-17.45		5.48	s	
30	scut0005928	phenobarbital	8.60	-18.03		5.09	s	
31	scut0004490	lopinavir	8.53	x		10.05		
32	scut0005839	pentobarbital	8.12	-16.53		5.87	s	
33	scut0004977	mitomycin	8.09	-16.19		4.1		
34	scut0005325	nimodipine	7.99	-20.96		7.63		
35	scut0000017	acarbose	7.68	2.39	+	7.66		
36	scut0001413	cefoxitin	7.52	-17.57		5.11		
37	scut0005149	naltrexone	7.36	-13.73		5.64		
38	scut0001867	clotrimazole	7.30	-16.21		3.34	s	
39	scut0000329	amikacin	7.23	-16.75		7.73		
40	scut0000341	aminoglutethimide	7.12	-18.58		6.63		
41	scut0005970	phenytoin	6.81	-16.98		4.71	s	
42	scut0007627	tobramycin	6.43	-15.93		7.78		
43	scut0007063	sufentanil	6.38	-16.04		6.85		

44	scut0007124	sulfasalazine	6.31	-26.28		6.81		
45	scut0001574	cholecalciferol	6.26	-1.58		4.61	s	
46	scut0001928	cortisone	6.16	-11.74		5.09	s	
47	scut0006816	secobarbital	6.09	-11.54		5.53		
48	scut0006788	saquinavir	5.94	x		9.35	s	
49	scut0007687	topiramate	5.89	x		5.62	s	
50	scut0001178	butorphanol	5.83	-11.96		4.7		
51	scut0001753	clindamycin	5.56	-12.85		6.93		
52	scut0001418	cefpodoxime	5.47	-20.80		4.85		
53	scut0005142	nalbuphine	5.41	-12.91		4.32		
54	scut0007037	streptomycin	5.38	-12.13		7.98		
55	scut0001429	ceftibuten	5.24	-18.25		5.81		
56	scut0004066	ipratropium bromide	5.17	-17.81		6.11		
57	scut0005148	naloxone	5.16	-12.95		4.8	s	
58	scut0004706	meropenem	5.06	-17.27		6.94		
59	scut0002616	doxorubicin	4.79	x		7.42	s	
60	scut0001433	ceftizoxime	4.65	-22.38		4.64		
61	scut0006350	propantheline bromide	4.46	-18.97		6.83		
62	scut0006548	ramipril	3.88	-18.09		9.59		
63	scut0000406	amprenavir	3.86	-19.91		9.02		
64	scut0005715	pancuronium bromide	3.82	10.33	o	-3.22		y
65	scut0004564	meclizine	3.74	-20.39		5.66	s	
66	scut0002618	doxycycline	3.67	x		3.59		
67	scut0001436	cefuroxime	3.57	-19.38		5.8		
68	scut0006059	pipecuronium bromide	3.55	x		-51.49		y
69	scut0001387	cefdinir	3.43	-21.60		4.75		
70	scut0000669	aztreonam	3.25	-14.58		6.7		
71	scut0000395	amoxicillin	3.23	-20.23		6.12		
72	scut0007961	vecuronium bromide	3.19	x		-3.5		y
73	scut0001895	colchicine	3.18	-16.37		5.14		
74	scut0001211	calcitriol	3.11	-11.33		5.94		
75	scut0002085	daunorubicin	3.09	-14.08		6.71		
76	scut0003420	fosphenytoin	2.97	-12.39		6		
77	scut0002850	erythromycin	2.96	x		-2.3	s	y
78	scut0008099	zidovudine	2.74	-18.78		6.81		
79	scut0006053	pioglitazone	2.71	-21.23		6.84	s	
80	scut0005877	perindopril	2.66	-16.76		7.62		
81	scut0002748	enalapril	2.66	-18.94		7.32	s	
82	scut0005279	nifedipine	2.65	-18.62		5.42	s	
83	scut0007502	tiagabine	2.45	-20.38		7.02		
84	scut0000847	bepridil	2.38	-14.32		8.06		
85	scut0002525	dirithromycin	2.29	x		-14.96		y
86	scut0003870	idarubicin	2.24	-18.55		5.13		
87	scut0001471	cetirizine	2.04	-17.67		6.93		
88	scut0005195	nedocromil	2.01	x		4		
89	scut0003217	flavoxate	2.00	-21.21		7.27		
90	scut0000190	alfentanil	2.00	-21.43		7.84		

91	scut0000595	atovaquone	1.68	-24.15		3.78		
92	scut0002572	dofetilide	1.64	-19.10		9.45		
93	scut0007389	tetracycline	1.59	-17.92		3.72		
94	scut0007526	ticarcillin	1.52	-15.44		5.61		
95	scut0003809	hydromorphone	1.52	-12.59		3.53		
96	scut0007239	tamsulosin	1.48	-21.38		8.46		
97	scut0000662	azithromycin	1.43	x		-18.62	s	y
98	scut0004246	latanoprost	1.38	-13.63		7.77		
99	scut0001370	cefadroxil	1.35	-22.59		5.98		
100	scut0002141	demeclocycline	1.30	x		3.97		
101	scut0007052	succinylcholine chloride	1.16	-9.54	+	7.84		
102	scut0007612	tirofiban	1.03	-12.23		8.15		
103	scut0004377	lisinopril	0.84	-19.41		8.41	s	
104	scut0001114	buprenorphine	0.66	x		5.94		
105	scut0006706	rosiglitazone	0.63	-22.38		6.86	s	
106	scut0003836	hydroxyzine	0.61	-17.88		6.68		
107	scut0003139	fenoprofen	0.56	-17.59		4.85		
108	scut0001409	cefotaxime	0.40	-19.76		6.96		
109	scut0000957	bitolterol	0.38	-13.35		9.29		
110	scut0001727	clarithromycin	0.34	x		-0.25	s	y
111	scut0001397	cefixime	0.21	-23.89		3.93		
112	scut0005657	oxybutynin	0.15	-10.82		8.39		
113	scut0003158	fentanyl	0.11	-20.43		7.71		
114	scut0002244	dexrazoxane	-0.13	-18.73		5.49		
115	scut0004971	misoprostol	-0.48	-8.98		7.08		
116	scut0003791	hydrochlorothiazide	-0.53	-14.59		2.87		
117	scut0005069	moxifloxacin	-0.62	-19.21		5.59		
118	scut0006972	sparfloxacin	-0.66	-21.28		7.71		
119	scut0007816	trimethobenzamide	-0.67	-16.45		8.1		
120	scut0006764	salmeterol	-0.75	-12.71		11.07		
121	scut0007056	sucralfate	-0.75	8.92	+	4.12		
122	scut0001311	carboplatin	-0.79	-12.79		3.85		
123	scut0004309	levofloxacin	-0.79	-20.76		4.35	s	
124	scut0005506	ofloxacin	-0.79	-20.76		4.8		
125	scut0005051	morphine	-0.85	-12.65		4.78	s	
126	scut0006866	sibutramine	-0.86	-9.82		5.66		
127	scut0002937	ethosuximide	-0.87	-16.30		4.13	s	
128	scut0000404	ampicillin	-0.94	-20.86		7.01		
129	scut0007041	streptozocin	-1.00	-16.63		4.37		
130	scut0005825	pentazocine	-1.06	-12.86		6.11		
131	scut0006543	raloxifene	-1.24	-22.92		7.31		
132	scut0001604	ciclopirox	-1.26	-10.90		5.02		
133	scut0001401	cefmetazole	-1.29	-21.32		5.34		
134	scut0002598	dorzolamide	-1.32	-13.86		5.07		
135	scut0001546	chlorothiazide	-1.32	-13.72		3.18		
136	scut0003018	etoposide	-1.34	x		4.75		
137	scut0004748	metaxalone	-1.34	-18.01		5.24		

138	scut0001962	cromolyn	-1.37	-19.62		7.12		
139	scut0005006	moexipril	-1.44	-13.39		6.98		
140	scut0003792	hydrocodone	-1.45	-12.58		5.27		
141	scut0000280	amantadine	-1.58	-4.76	o	4.01		
142	scut0006523	rabeprazole sodium	-1.59	-16.64		8.33		
143	scut0003058	famotidine	-1.67	-19.67		6.1		
144	scut0006375	propoxyphene	-1.67	-13.30		6.22		
145	scut0007706	trandolapril	-1.80	-14.20		7.35		
146	scut0005669	oxymorphone	-1.84	-13.41		4.86		
147	scut0004520	mannitol	-1.89	-8.71		3.64		
148	scut0004421	loperamide	-1.89	-21.07		4.83		
149	scut0007718	trazodone	-1.94	-17.81		8.34		
150	scut0003523	gatifloxacin	-1.99	-14.16		4		
151	scut0001886	codeine	-1.99	-12.99		5.45		
152	scut0007012	stavudine	-2.17	-13.14		4.14		
153	scut0001410	cefotetan	-2.27	-24.92		4.38		
154	scut0004359	lindane	-2.30	x		1.51		y
155	scut0001434	ceftriaxone	-2.31	-23.17		6.05		
156	scut0005079	mupirocin	-2.38	-13.59		10.15		
157	scut0005578	oxacillin	-2.48	-24.81		5.5		
158	scut0003219	flecainide	-2.53	-15.46		6.9		
159	scut0005788	penciclovir	-2.53	-15.32		5.8		
160	scut0004910	mezlocillin	-2.59	-18.40		5.09		
161	scut0001426	ceftazidime	-2.63	-15.00		4.41		
162	scut0005662	oxycodone	-2.69	x		5.3		
163	scut0001388	cefditoren	-2.73	-20.19		6.53		
164	scut0005362	nitrofurantoin	-2.74	-21.56		3.96		
165	scut0007688	topotecan	-2.74	-19.01		6.04		
166	scut0002589	dopamine	-2.74	-12.42		5.14		
167	scut0001123	buspirone	-2.76	-16.35		7.92		
168	scut0003320	fluorouracil	-2.79	-13.76		2.32		
169	scut0002076	dapsone	-2.80	-19.84		5.41		
170	scut0003260	fludarabine phosphate	-2.80	-10.78		6.53		
171	scut0001391	cefepime	-2.83	-19.42		4.91		
172	scut0003411	fosfomycin	-2.87	-7.47		3.28		
173	scut0007629	tocainide	-2.93	-22.15		4.05		
174	scut0000949	bisoprolol	-3.05	-16.31		8.66		
175	scut0006634	rimantadine	-3.15	-8.77		4.46		
176	scut0006388	propylthiouracil	-3.16	-11.71		3.83		
177	scut0004304	levocabastine	-3.16	-9.73		-2.61		
178	scut0002333	dicloxacillin	-3.22	-22.02		6.36		
179	scut0003695	haloperidol	-3.38	-17.20		5.73		
180	scut0002532	disopyramide	-3.39	-16.83		6.65		
181	scut0001124	busulfan	-3.44	-7.48		6.52		
182	scut0001706	cisplatin	-3.46	-		0.67		
183	scut0004113	isoetharine	-3.51	-15.35		7.16		
184	scut0002867	esmolol	-3.52	-17.10		6.37		

185	scut0006065	piperacillin	-3.56	-21.37		5.79		
186	scut0005173	naproxen	-3.57	-17.17		3.85		
187	scut0006871	sildenafil	-3.57	-18.94		7.09		
188	scut0004409	lomefloxacin	-3.61	-18.00		5.1		
189	scut0002508	dipivefrin	-3.61	-11.05		6.65		
190	scut0000271	altretamine	-3.63	-12.61		3.71		
191	scut0001380	cefazolin	-3.63	-23.92		4.6		
192	scut0004836	methylergonovine	-3.65	-20.26		5.83		
193	scut0004381	lithium carbonate	-3.68	-		1.98		
194	scut0006372	propofol	-3.71	-12.44		4.81		
195	scut0000886	bethanechol chloride	-3.83	-12.77		4.4		
196	scut0001736	clemastine	-3.87	-14.08		6.54		
197	scut0004746	metaraminol	-3.88	-15.63		4.24		
198	scut0004832	methyldopa	-3.88	-15.03		6.14		
199	scut0001694	ciprofloxacin	-3.90	-17.60		5.26		
200	scut0002259	dezocine	-3.92	-13.90		5.66		
201	scut0001440	celecoxib	-3.97	-16.42		5		
202	scut0004143	isosorbide mononitrate	-4.07	-15.46		4.44		
203	scut0004142	isosorbide dinitrate	-4.16	-14.96		5.39		
204	scut0003243	floxuridine	-4.18	-16.94		4.95		
205	scut0001325	carisoprodol	-4.21	-14.15		5.74		
206	scut0006227	pramipexole	-4.23	-10.92		4.97		
207	scut0006509	quinidine	-4.31	-18.08		5.3		
208	scut0002691	edrophonium chloride	-4.33	-14.58		4.17		
209	scut0001898	colestipol	-4.33	-16.29	o	3.55		
210	scut0004933	miglitol	-4.37	-14.16		4.63		
211	scut0005111	nabumetone	-4.37	-13.25		5.22		
212	scut0004790	methimazole	-4.42	-6.67		3.52		
213	scut0004671	meprobamate	-4.52	-12.34		4.64		
214	scut0005472	nitroglycerin	-4.55	-10.06		6.7		
215	scut0007151	sulindac	-4.55	-18.20		3.79		
216	scut0000480	anthralin	-4.56	-14.73		5.13		
217	scut0001572	chlorzoxazone	-4.57	-10.78		3.14		
218	scut0002915	ethambutol	-4.57	-14.33		6.75		
219	scut0004197	ketoprofen	-4.73	-23.77		5.85		
220	scut0004151	isotretinoin	-4.75	-21.27		6.72		
221	scut0007736	tretinoin	-4.75	-17.51		6.2		
222	scut0002978	etidronic acid	-4.75	-7.59		3.36		
223	scut0007704	tramadol	-4.75	-12.32		5.25		
224	scut0002816	epoprostenol	-4.77	-8.55		7.23		
225	scut0008072	zafirlukast	-4.81	-27.73		5.98		
226	scut0001494	chloral hydrate	-4.91	-4.89	o	1.78		y
227	scut0005954	phenylephrine	-4.91	-16.50		4.28		
228	scut0002380	diflunisal	-4.93	-16.54		3.38		
229	scut0005033	montelukast sodium	-4.95	-20.09		7.99		
230	scut0005410	norepinephrine	-4.97	-15.25		4.98		
231	scut0003194	fexofenadine	-4.98	-12.69		7.93		

232	scut0002806	epinephrine	-5.00	-14.01		4.62		
233	scut0001450	cephalexin	-5.02	-22.05		5.2		
234	scut0000046	acetaminophen	-5.02	-15.32		4.4		
235	scut0004942	milrinone	-5.06	-13.80		2.96		
236	scut0001301	carbidopa	-5.10	-12.29		5.43		
237	scut0004291	levamisole	-5.14	-12.14		4.98		
238	scut0003576	glimepiride	-5.16	-20.56		7.77		
239	scut0004427	loracarbef	-5.16	-23.73		6.09		
240	scut0007643	tolazoline	-5.17	-12.27		3.7		
241	scut0002634	dronabinol	-5.19	-15.96		6.61		
242	scut0002824	eprosartan	-5.20	-12.52		6.56		
243	scut0002798	ephedrine	-5.23	-14.62		4.23		
244	scut0006427	pseudoephedrine	-5.23	-14.61		4.28		
245	scut0006441	pyrazinamide	-5.27	-14.65		2.81		
246	scut0004880	metoprolol	-5.32	-17.11		6.46		
247	scut0005781	pemirolast	-5.41	-15.75		3.52		
248	scut0001369	cefaclor	-5.45	-22.16		4.98		
249	scut0006247	prazosin	-5.55	-25.72		5.86		
250	scut0000050	acetazolamide	-5.57	-14.93		3.62		
251	scut0001004	brimonidine	-5.64	-17.98		4.12		
252	scut0002427	dimenhydrinate	-5.66	-13.97		6.33		
253	scut0002500	diphenhydramine	-5.66	-13.91		5.6		
254	scut0007260	tazarotene	-5.67	-10.01		5.2		
255	scut0001404	cefonicid	-5.67	-22.19		5.36		
256	scut0006491	quinapril	-5.69	-21.04		9.42		
257	scut0006825	selegiline	-5.73	-18.66		4.54		
258	scut0007351	terconazole	-5.76	-9.57		7.26		
259	scut0002339	didanosine	-5.77	-14.62		7.06		
260	scut0000412	amrinone	-5.86	-12.89		4.47		
261	scut0004875	metolazone	-5.87	-24.91		6.21		
262	scut0000529	argatroban	-5.87	-25.33		9.7		
263	scut0003852	ibuprofen	-5.87	-13.90		5.45		
264	scut0005240	niacin	-5.95	-9.90		3.65		
265	scut0003136	fenofibrate	-5.99	-21.68		5.37		
266	scut0007081	sulfacetamide	-6.00	-17.76		4.21		
267	scut0001457	cephradine	-6.02	-18.02		5.49		
268	scut0003517	ganciclovir	-6.03	-11.83		6.5		
269	scut0005564	oseltamivir	-6.04	-20.97		7.93		
270	scut0004898	metyrosine	-6.04	-13.09		5.18		
271	scut0003398	formoterol	-6.09	-24.98		6.24		
272	scut0003835	hydroxyurea	-6.11	-9.46		2.09		
273	scut0004430	loratadine	-6.14	-18.20		5.65		
274	scut0004903	mexiletine	-6.21	-14.11		5.97		
275	scut0001405	cefoperazone	-6.22	-16.14		6.65		
276	scut0004561	mechlorethamine	-6.25	0.03	+	3.35		
277	scut0005124	nafcillin	-6.25	-18.02		6.6		
278	scut0000583	atenolol	-6.28	-19.86		7.4		

279	scut0005817	pentamidine	-6.31	-22.65		7.81		
280	scut0001616	cidofovir	-6.36	-8.94		7.69		
281	scut0005711	pamidronic acid	-6.39	-8.22		3.18		
282	scut0008023	voriconazole	-6.46	-14.61		4.64		
283	scut0000119	adefovir	-6.47	-12.07		7.52		
284	scut0007458	thioguanine	-6.47	-10.36		4.2		
285	scut0007342	terazosin	-6.56	-23.71		5.6		
286	scut0003530	gemcitabine	-6.64	-12.46		4.69		
287	scut0000884	betaxolol	-6.66	-10.26		7.9		
288	scut0005622	oxiconazole	-6.71	-15.00		4.87		
289	scut0006659	rivastigmin	-6.71	-13.81		4.92		
290	scut0007942	valproic acid	-6.72	-8.98		4.57		
291	scut0005912	phenelzine	-6.75	-14.03		4.01		
292	scut0006345	propafenone	-6.76	-20.57		7.16		
293	scut0004745	metaproterenol	-6.78	-13.20		4.49		
294	scut0000218	allopurinol	-6.81	-15.62		3.81		
295	scut0002573	dolasetron	-6.83	-17.61		4.83		
296	scut0005529	omeprazole	-6.84	-18.14		6.77		
297	scut0004195	ketoconazole	-6.86	-20.08		6.63		
298	scut0004712	mesalamine	-6.89	-15.76		3.96		
299	scut0003504	galantamine	-6.91	-15.14		4.35		
300	scut0005846	pentostatin	-6.92	-15.15		5.29		
301	scut0000070	acetylcysteine	-6.93	-11.42		3.63		
302	scut0003489	gabapentin	-6.96	-6.24	o	6.41		
303	scut0003405	foscarnet	-7.00	-7.75	o	2.81		
304	scut0007676	tolterodine	-7.02	-15.08		7.39		
305	scut0004087	irinotecan	-7.05	-2.81	o	-94.19		y
306	scut0007657	tolmetin	-7.05	-19.41		6.24		
307	scut0001271	captopril	-7.06	-17.95		3.9		
308	scut0004330	levorphanol	-7.15	-12.49		4.7		
309	scut0000830	benztropine	-7.16	-20.48		6.08		
310	scut0004917	miconazole	-7.17	-12.98		5.33		
311	scut0007349	terbutaline	-7.21	-14.75		5.43		
312	scut0005380	nizatidine	-7.21	-17.44		6.95		
313	scut0002521	dipyridamole	-7.32	x		6.76		
314	scut0004199	ketorolac	-7.33	-23.06		7.13		
315	scut0003348	flurbiprofen	-7.38	-19.63		4		
316	scut0007966	venlafaxine	-7.41	-9.08		5.07		
317	scut0006230	pramoxime	-7.42	-12.63		6.97		
318	scut0004808	methoxamine	-7.43	-17.51		5.47		
319	scut0008130	zoledronic acid	-7.49	-10.29		4		
320	scut0001251	candesartan	-7.54	-27.72		7.51		
321	scut0002637	droperidol	-7.56	-26.85		6.85		
322	scut0004761	metformin	-7.64	-13.65		3.78		
323	scut0004653	meperidide	-7.68	-22.76		9.15		
324	scut0002050	dacarbazine	-7.70	-18.93		4.98		
325	scut0007969	verapamil	-7.75	-17.06		8.56		

326	scut0000112	acyclovir	-7.87	-12.11		7.35		
327	scut0001903	colfosceril palmitate	-7.95	20.17	o	12.26		
328	scut0006969	sotalol	-7.96	-15.08		7.61		
329	scut0003359	flutamide	-8.00	-18.84		3.48		
330	scut0007820	trimetrexate	-8.08	x		7.24		
331	scut0000122	adenosine	-8.14	-13.72		5.55		
332	scut0004346	lidocaine	-8.20	-21.38		6.01		
333	scut0008079	zanamivir	-8.24	-18.51		5.14		
334	scut0000683	balsalazide	-8.27	-21.90		2.69		
335	scut0006305	procarbazine	-8.27	-21.93		4.49		
336	scut0007432	thiamine	-8.27	-13.15		5.04		
337	scut0005557	orphenadrine	-8.29	-12.08		6.19		
338	scut0001280	carbamazepine	-8.31	-18.33		3.64		
339	scut0000676	baclofen	-8.33	-14.33		4.68		
340	scut0004871	metoclopramide	-8.33	-14.97		6.83		
341	scut0007307	telmisartan	-8.34	-25.05		5.67		
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344	scut0001033	bromocriptine	-8.37	x		3.81		
345	scut0000536	aripiprazole	-8.38	-15.28		7.54		
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347	scut0005425	norgestrel	-8.44	-8.17		5.56		
348	scut0003858	ibutilide	-8.53	-10.40		8.48		
349	scut0004799	methocarbamol	-8.55	-17.56		5.79		
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351	scut0002693	efavirenz	-8.61	-14.37		4.34		
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353	scut0008104	zileuton	-8.69	-19.05		5.1		
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358	scut0001349	carteolol	-9.03	-16.44		7.31		
359	scut0001721	cladribine	-9.08	-13.44		4.44		
360	scut0001819	clonidine	-9.08	-17.70		4.63		
361	scut0000648	azathioprine	-9.13	-21.37		5.78		
362	scut0004085	irbesartan	-9.14	-26.25		6.45		
363	scut0002013	cyclophosphamide	-9.22	-5.90		3.21		
364	scut0003950	indomethacin	-9.25	-17.58		4.6		
365	scut0002680	econazole	-9.25	-14.66		4.47		
366	scut0004442	losartan	-9.27	-23.13		7.77		
367	scut0000331	amiloride	-9.27	-15.17		6.36		
368	scut0006049	pindolol	-9.30	-19.74		6.76		
369	scut0003579	glipizide	-9.33	-19.13		6.42		
370	scut0000020	acebutolol	-9.34	-22.38		6.52		
371	scut0001497	chlorambucil	-9.36	-6.51		5.84		
372	scut0006810	scopolamine	-9.41	-14.18		6.33		

373	scut0002608	doxazosin	-9.53	-22.56		5.94		
374	scut0005993	phytonadione	-9.54	-12.58		10.14		
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376	scut0004213	labetalol	-9.62	-21.56		6.68		
377	scut0006314	procyclidine	-9.63	-11.16		5.93		
378	scut0000603	atropine	-9.66	-10.85		5.12		
379	scut0001881	cocaine	-9.70	-15.94		5.79		
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383	scut0000167	albuterol	-9.79	-13.52		5.64		
384	scut0004288	levalbuterol	-9.79	-13.71		6.49		
385	scut0000088	acitretin	-9.83	-19.18		4.98		
386	scut0002011	cyclopentolate	-9.89	-9.03		5.49		
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389	scut0002071	dantrolene	-9.98	-27.10		5.22		
390	scut0004983	mitoxantrone	-10.01	-32.19		8.19		
391	scut0006303	procainamide	-10.02	-15.53		5.4		
392	scut0003931	indapamide	-10.02	-24.45		3.72		
393	scut0005722	pantoprazole	-10.04	-18.50		7.06		
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395	scut0004361	linezolid	-10.16	-17.71		5.4		
396	scut0002415	diltiazem	-10.17	-14.58		6.5		
397	scut0002327	diclofenac	-10.19	-17.11		4.79		
398	scut0003644	granisetron	-10.24	-21.88		5.25		
399	scut0003532	gemfibrozil	-10.36	-15.94		6.74		
400	scut0002787	entacapone	-10.45	-21.40		5.19		
401	scut0007567	timolol	-10.48	-15.37		5.82		
402	scut0001558	chlorpheniramine	-10.53	-11.44		5.97		
403	scut0001112	bupivacaine	-10.66	-19.72		6.38		
404	scut0006586	repaglinide	-10.67	-20.36		8.21		
405	scut0008121	ziprasidone	-10.74	-19.54		8.22		
406	scut0005754	paroxetine	-10.74	-16.92		6.62		
407	scut0005086	mycophenolic acid	-10.76	-13.31		7.4		
408	scut0003371	fluvastatin	-10.76	-15.53		7.02		
409	scut0000263	alprostadil	-10.76	-10.37		8.26		
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411	scut0004527	maprotiline	-10.81	-19.01		6.18		
412	scut0007529	ticlopidine	-10.85	-12.36		5.45		
413	scut0004302	levobunolol	-10.87	-16.85		7.64		
414	scut0006300	probenecid	-10.88	-12.54		5.7		
415	scut0004894	metronidazole	-10.91	-15.27		4.24		
416	scut0005165	naphazoline	-10.96	-16.96		5.14		
417	scut0001330	carmustine	-10.97	-6.31		3.81		
418	scut0001101	bumetanide	-10.98	-17.39		6.02		
419	scut0001268	capsaicine	-11.00	-15.19		7.15		

420	scut0004956	minoxidil	-11.13	-17.23		4.34		
421	scut0000738	benazepril	-11.15	-20.50		7.48		
422	scut0007177	sumatriptan	-11.23	-19.45		8.29		
423	scut0003914	imiquimod	-11.28	-17.16		4.84		
424	scut0000001	abacavir	-11.38	-12.80		6.28		
425	scut0002559	dobutamine	-11.49	-15.32		7.17		
426	scut0004239	lansoprazole	-11.52	-14.53		6.52		
427	scut0007692	torasemide	-11.73	-24.47		5.21		
428	scut0006558	ranitidine	-11.84	-18.03		8.75		
429	scut0005185	nateglinide	-12.00	-18.46		6.06		
430	scut0006104	pirbuterol	-12.06	-18.04		6.29		
431	scut0003138	fenoldopam	-12.07	-15.84		5.41		
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435	scut0003613	glyburide	-12.42	-19.77		6.93		
436	scut0005525	olsalazine	-12.45	-22.72		3.19		
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439	scut0007426	theophylline	-12.67	-15.19		4.61		
440	scut0008136	zolpidem	-12.67	-18.43		5.78		
441	scut0002241	dexpanthenol	-12.76	-12.41		4.14		
442	scut0007930	valacyclovir	-12.95	-16.80		6.77		
443	scut0004400	lodoxamide	-13.05	-20.91		3.39		
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446	scut0004165	itraconazole	-13.09	-13.47		3.87		
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455	scut0003057	famciclovir	-13.57	-14.26		5.72		
456	scut0001639	cimetidine	-13.60	-17.69		6.52		
457	scut0003479	furosemide	-13.82	-18.02		6.2		
458	scut0008074	zaleplon	-13.97	-24.03		4.31		
459	scut0004981	mitotane	-14.13	-8.28		2.34		
460	scut0008140	zomitriptan	-14.29	-18.43		8.71		
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464	scut0002302	dibucaine	-14.63	-16.68		7.6		
465	scut0006376	propranolol	-14.67	-20.51		5.83		
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467	scut0007658	tolnaftate	-14.69	-22.51		4.51		
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487	scut0004334	levothyroxine	-17.93	-10.79		4.46		
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490	scut0007207	tacrolimus	-18.22	12.56	o	-10.92		y
491	scut0004717	mesoridazine	-18.33	-14.85		7.79		
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516	scut0002832	eptifibatide	-25.70	-4.85	o	-1.98		y
517	scut0007312	temazepam	-26.13	-18.89		3.25		
518	scut0004924	midazolam	-26.75	-17.56		4.98		
519	scut0006308	prochlorperazine	-27.96	-16.14		6.22		
520	scut0000361	amiodarone	-28.24	-18.30		7.63		
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522	scut0005884	perphenazine	-28.57	-18.91		5.56		
523	scut0003323	fluoxetine	-29.24	-11.81		6.17		
524	scut0004806	methotrexate	-29.78	-28.26		7.94		
525	scut0004278	letrozole	-30.08	-11.82		4.68		
526	scut0005436	nortriptyline	-30.18	-18.96		5.9		
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533	scut0002611	doxepin	-31.85	-21.80		5.51		
534	scut0000373	amitriptyline	-32.14	-14.99		5.27		
535	scut0005510	olanzapine	-32.77	-14.39		4.82		
536	scut0002284	diazepam	-33.35	-17.69		4.99		
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538	scut0007755	triazolam	-33.65	-17.53		3.73		
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543	scut0007796	trifluoperazine	-37.25	-16.34		6.59		
544	scut0002180	desipramine	-37.57	-13.90		5.6		
545	scut0007822	trimipramine	-38.56	-13.61		5.29		
546	scut0001564	chlorpromazine	-41.00	-16.04		4.76		
547	scut0003330	fluphenazine	-41.58	-19.80		6.28		
548	scut0000260	alprazolam	-42.70	-18.33		3.18		
549	scut0008002	vinorelbine	-72.37	x		-27.34		y
550	scut0007984	vinblastine	-76.82	9.21	o	-9.87		y

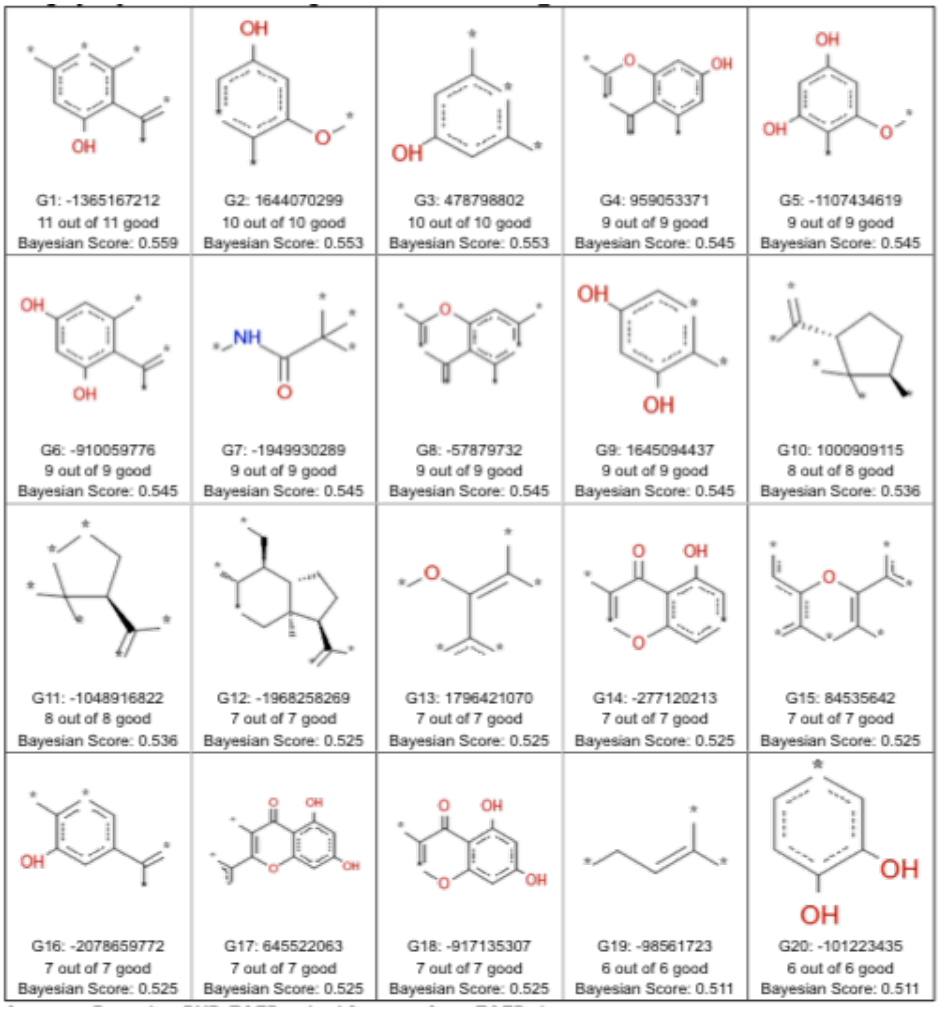
*: Drugs ranked according to ECFP-2 scores.

**: “o” indicates the drug was docked outside of binding pocket. “+” indicates the drug has a positive score.

***: “s” indicates the compound belongs to training or test set. “b” and “c” indicate the compound was reported as hPXR activator or nonactivator but not included in training or test set.

****: “y” means the compound is screened out from further virtual screening.

A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Bayesian Score: 0.559
G2: 1644070299
10 out of 10 good
Bayesian Score: 0.553
G3: 478798802
10 out of 10 good
Bayesian Score: 0.553
G4: 959053371
9 out of 9 good
Bayesian Score: 0.545
G5: -1107434619
9 out of 9 good
Bayesian Score: 0.545
G6: -910059776
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Bayesian Score: 0.545
G7: -1949930289
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Bayesian Score: 0.545
G8: -57879732
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Bayesian Score: 0.545
G9: 1645094437
9 out of 9 good
Bayesian Score: 0.545
G10: 1000909115
8 out of 8 good
Bayesian Score: 0.536
G11: -1048916822
8 out of 8 good
Bayesian Score: 0.536
G12: -1968258269
7 out of 7 good
Bayesian Score: 0.525
G13: 1796421070
7 out of 7 good
Bayesian Score: 0.525
G14: -277120213
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Bayesian Score: 0.525
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Bayesian Score: 0.525
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Bayesian Score: 0.525
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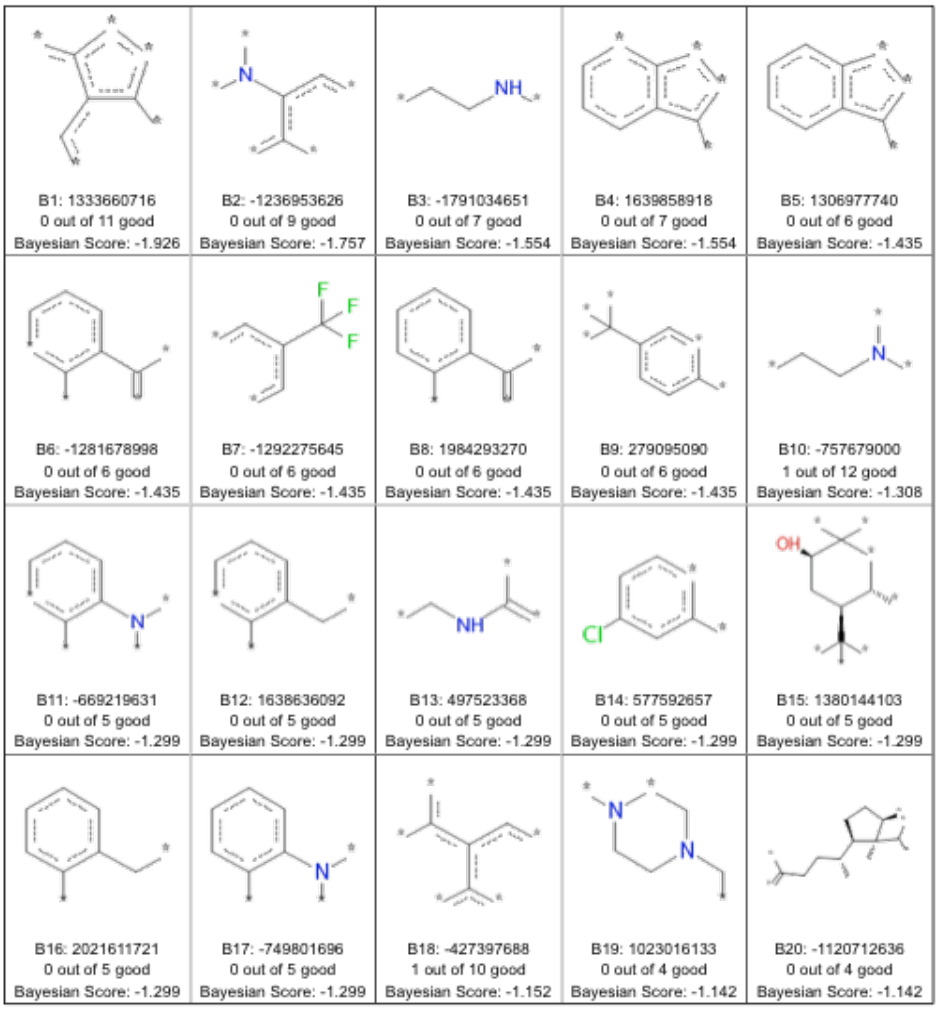
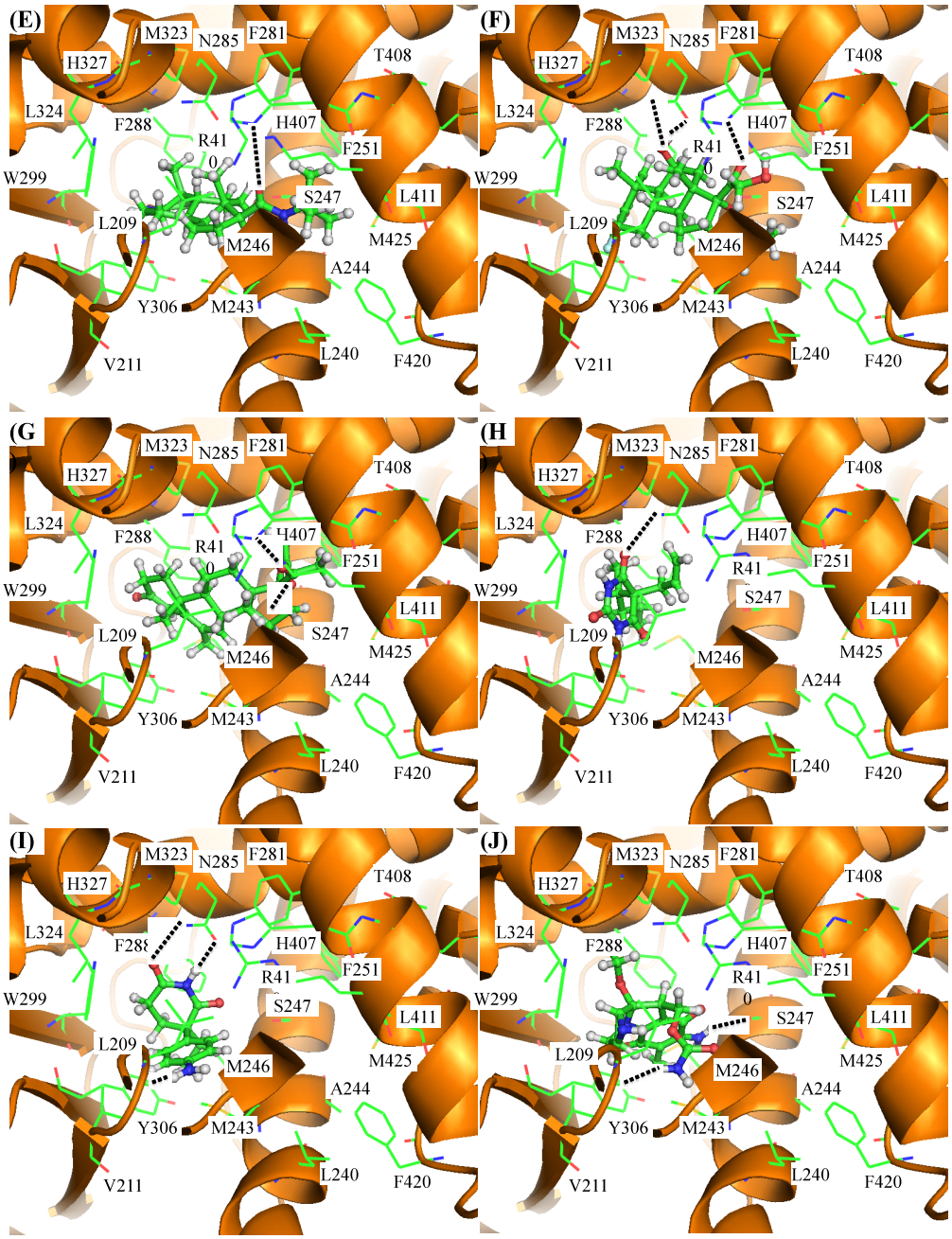
7 out of 7 good
Bayesian Score: 0.525
G18: -917135307
7 out of 7 good
Bayesian Score: 0.525
G19: -98561723
6 out of 6 good
Bayesian Score: 0.511
G20: -101223435
6 out of 6 good
Bayesian Score: 0.511

B



Supplemental Figure S1 Molecular features that contribute positively or negatively to a compound's PXR affinity identified by Bayesian model ECFP-2 using ECFP_6 fingerprints. **A.** Features that contributed positively to biological activity from ECFP-2 model. **B.** Features negatively impacting hPXR affinity from ECFP-2 model. Asterisks indicate that any atom can be represented. Numbers represent how many molecules out of the total number possessing the fingerprint are active (positive) or inactive (negative).



Supplemental Figure S2 The Surflex docked (1NRL) conformations of newly identified PXR activators or an antagonist finasteride (E), flunisolide(F), megestrol (G), secobarbital (H), aminoglutethimide (I) and mitomycin (J). The hydrogen bonding interaction is shown as black dotted lines. The protein backbone is shown as ribbon

(orange), amino acid residues are shown in the stick mode whereas the PXR activators are shown in the ball and stick mode. The images were created using Pymol.

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