

Discovery of Anti-Ebola Drugs: A Computational Drug Repositioning Case Study

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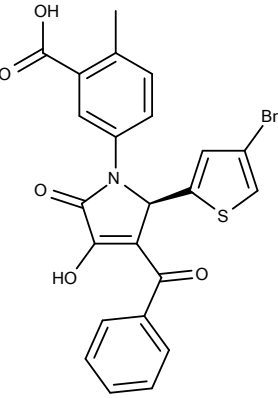
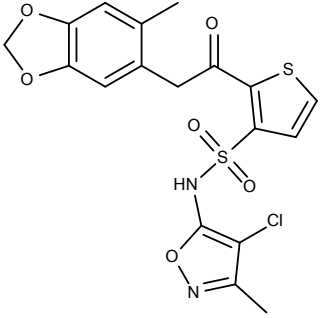
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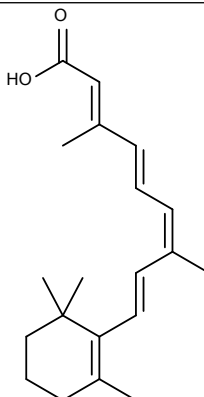
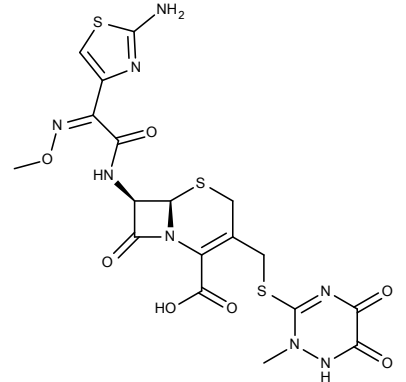
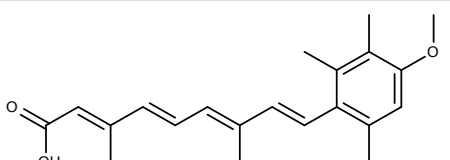
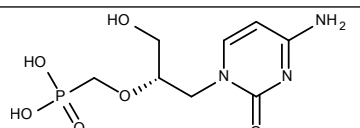
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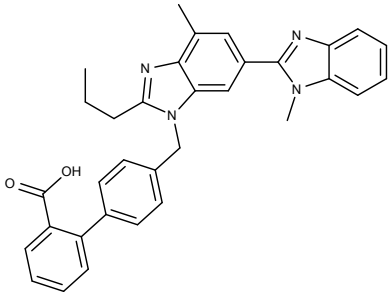
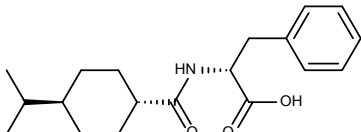
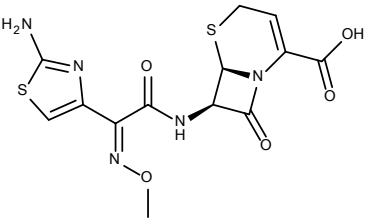
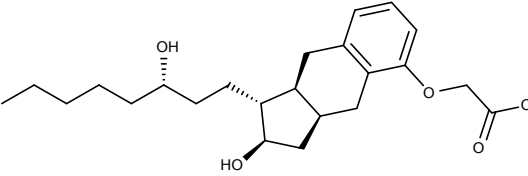
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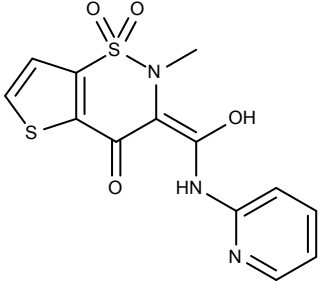
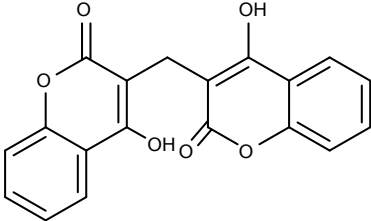
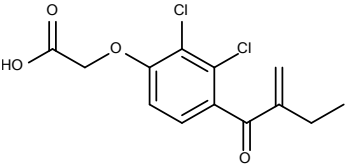
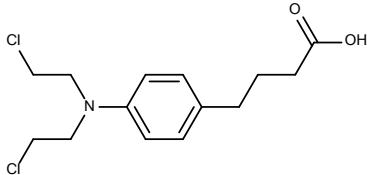
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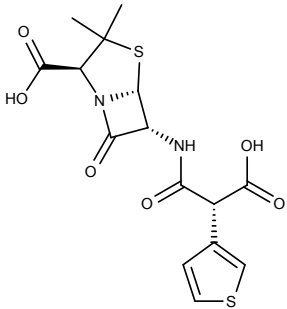
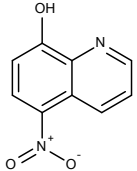
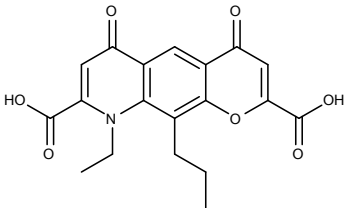
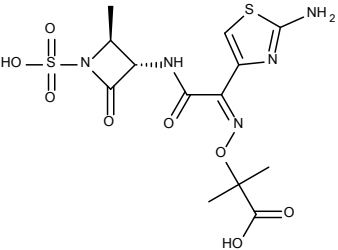
Table 1S. Top hits (#100) identified from EON screening using query 1

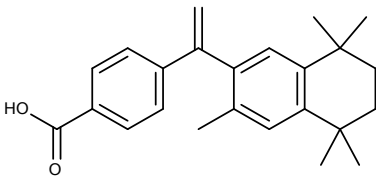
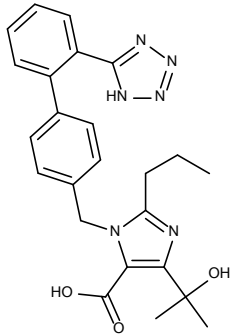
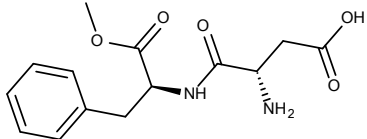
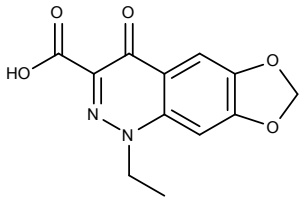
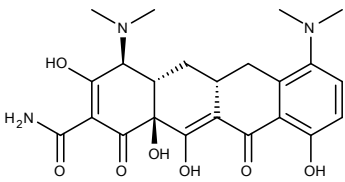
Sr. No.	Drug	Structure	ET_pb	ET_coul	ET_combo	EON_Shape Tanimoto	Rank	Estimated Free Energy of Binding (kcal/mol)
1	1							-9.88
2	Sitaxentan		0.633	0.914	0.926	0.294	1	-14.37

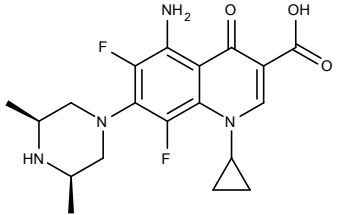
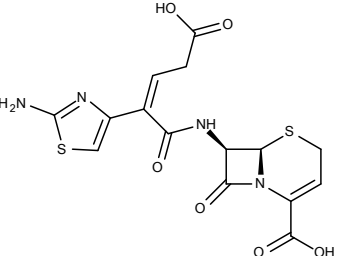
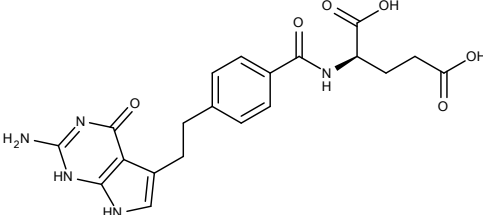
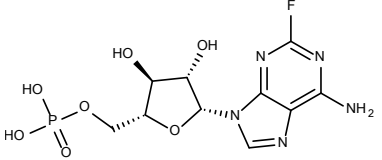
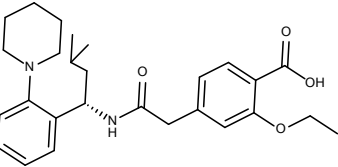
3	Alitretinoin ^a		0.66	0.91	0.906	0.246	2	-3.91
4	Ceftriaxone		0.606	0.937	0.823	0.217	3	-12.33
5	Acitretin ^a		0.637	0.936	0.809	0.172	4	-3.71
6	Cidofovir		0.473	0.633	0.783	0.31	5	-4.21

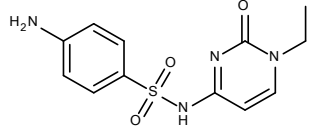
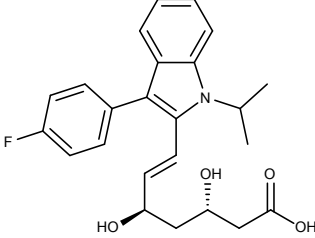
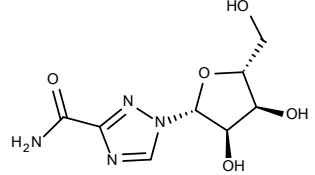
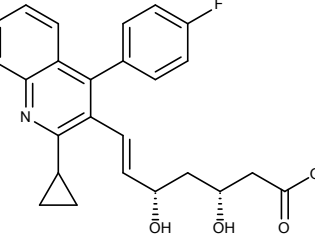
7	Telmisartan		0.601	0.908	0.775	0.174	6	-6.46
8	Nateglinide ^a		0.54	0.874	0.745	0.205	7	-3.78
9	Ceftizoxime		0.557	0.88	0.735	0.178	8	-11.35
10	Treprostinil		0.432	0.846	0.732	0.301	9	-3.41

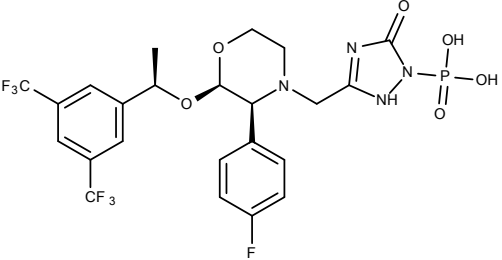
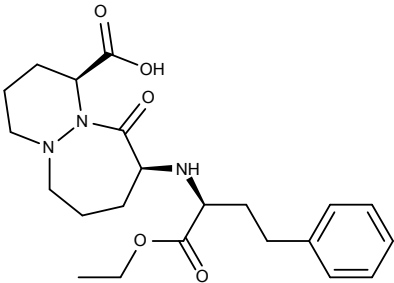
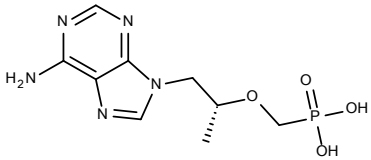
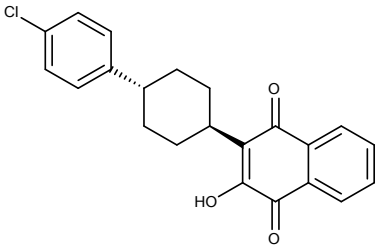
11	Tenoxicam		0.367	0.817	0.71	0.343	10	-7.86
12	Dicoumarol		0.368	0.615	0.663	0.295	11	-6.06
13	Ethacrynic acid		0.478	0.847	0.656	0.177	12	-4.13
14	Chlorambucil ^a		0.466	0.867	0.646	0.18	13	-3.14

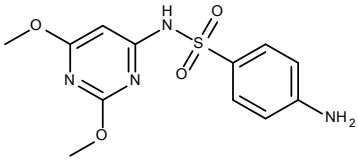
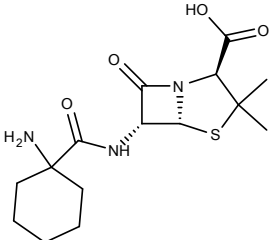
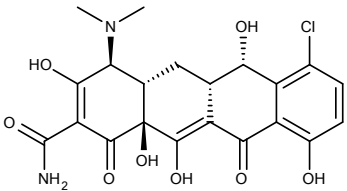
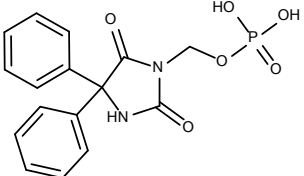
15	Ticarcillin		0.52	0.664	0.643	0.123	14	-17.89
16	Nitroxoline		0.41	0.824	0.641	0.232	15	-5.31
17	Nedocromil		0.321	0.603	0.637	0.316	16	-4.2
18	Aztreonam		0.417	0.609	0.636	0.219	17	-5.13

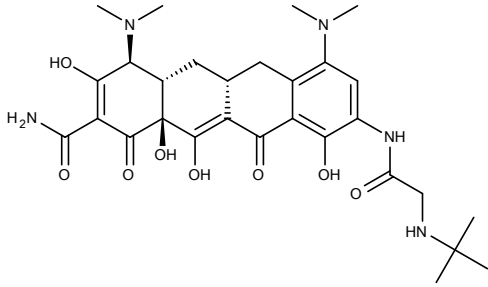
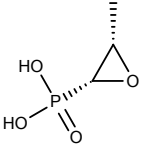
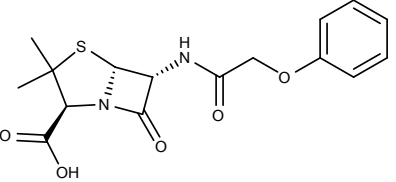
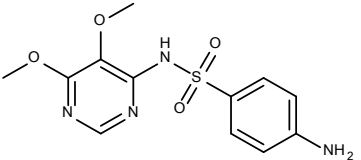
19	Bexarotene ^a		0.381	0.862	0.616	0.235	18	-4.58
20	Olmesartan		0.375	0.593	0.611	0.237	19	-6.28
21	Aspartame		0.284	0.118	0.605	0.32	20	-3.59
22	Cinoxacin		0.313	0.748	0.604	0.29	21	-5.66
23	Minocycline		0.346	0.602	0.594	0.248	22	-4.65

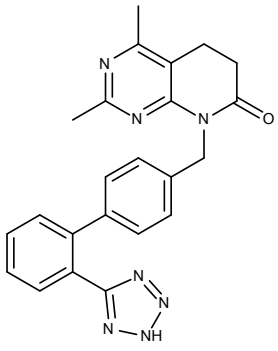
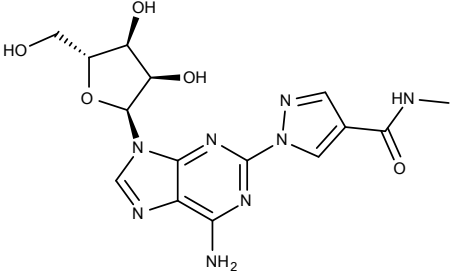
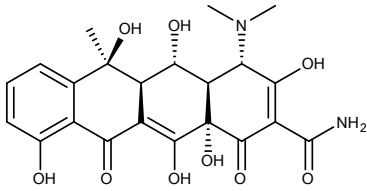
24	Sparfloxacin		0.156	0.061	0.591	0.435	23	-5.06
25	Ceftibuten		0.26	0.533	0.589	0.329	24	-14.71
26	Pemetrexed		0.538	0.609	0.588	0.051	25	-4.95
27	Fludarabine		0.365	0.58	0.588	0.223	26	-5.53
28	Repaglinide ^a		0.41	0.832	0.574	0.164	27	-5.61

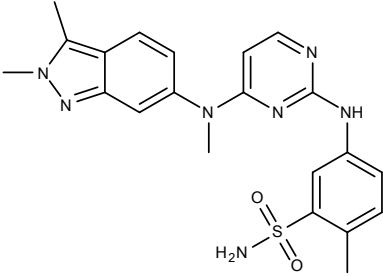
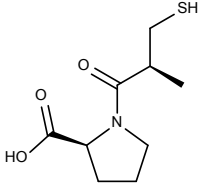
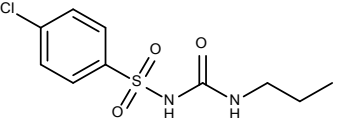
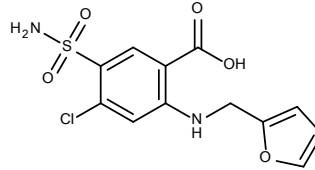
29	Sulfacytine		0.303	0.768	0.573	0.27	28	-4.09
30	Fluvastatin ^b		0.335	0.788	0.568	0.233	29	-3.53
31	Ribavirin		0.216	0.072	0.561	0.345	30	-4.52
32	Pitavastatin		0.46	0.861	0.558	0.098	31	-3.74

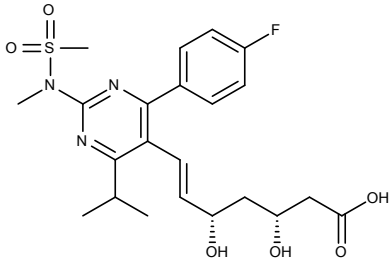
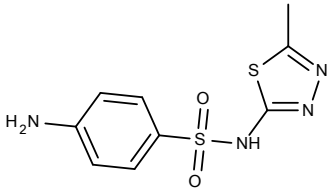
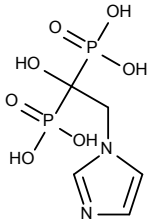
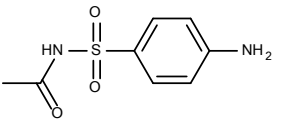
33	Fosaprepitant		0.43	0.743	0.552	0.121	32	-5.64
34	Cilazapril		0.276	0.144	0.544	0.268	33	-5.47
35	Tenofovir ^c		0.373	0.611	0.543	0.17	34	-5.65
36	Atovaquone		0.285	0.752	0.536	0.251	35	-5.07

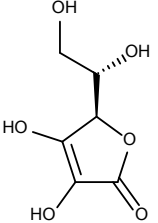
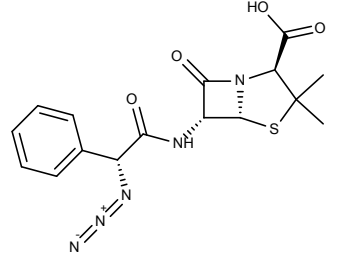
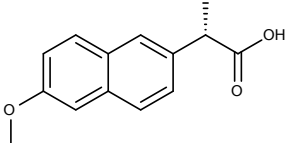
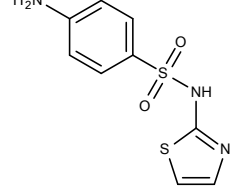
37	Sulfadimethoxine		0.28	0.746	0.536	0.256	36	-4.39
38	Cyclacillin		0.189	0.127	0.531	0.341	37	-14.26
39	Demeclocycline		0.223	0.523	0.53	0.306	38	-4.44
40	Fosphenytoin		0.395	0.593	0.529	0.134	39	-5.3

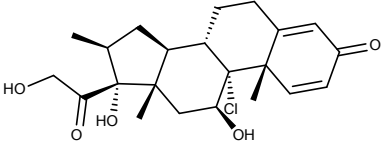
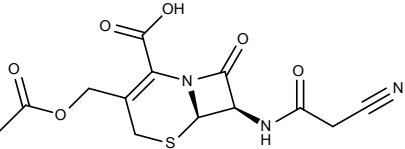
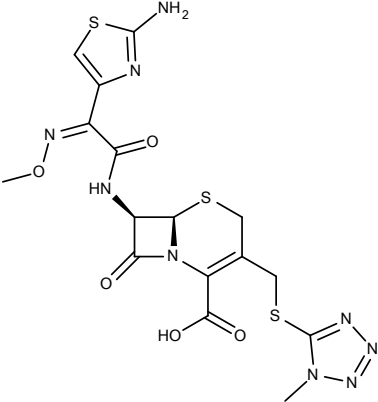
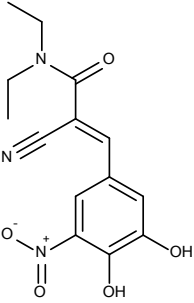
41	Tigecycline		0.314	0.688	0.528	0.214	40	-5.24
42	Fosfomicin		0.322	0.57	0.526	0.204	41	-4.1
43	Penicillin V		0.394	0.804	0.518	0.125	42	-8.79
44	Sulfadoxine		0.261	0.735	0.516	0.254	43	-4.37

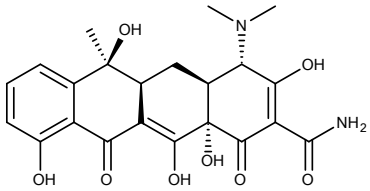
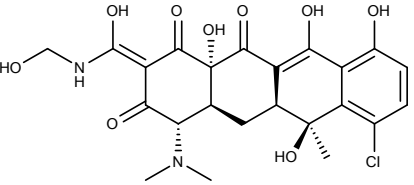
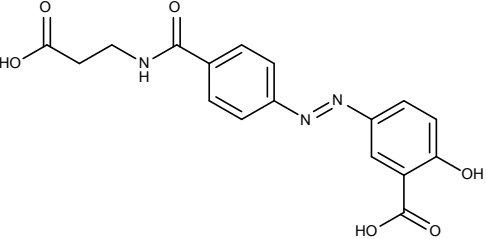
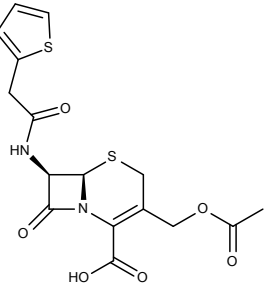
45	Tasosartan	 <p>The structure of Tasosartan consists of a 1,2,3,4-tetrahydroquinazolin-2(1H)-one ring system with methyl groups at positions 4 and 7. This is connected via a methylene bridge to a para-substituted benzene ring, which is further linked to a biphenyl system. The biphenyl system has a 1,2,4-triazole ring attached to the second phenyl ring.</p>	0.396	0.733	0.515	0.12	44	-7.76
46	Regadenoson	 <p>The structure of Regadenoson features a ribose sugar moiety attached to a 2,6-diaminopyrimidine ring. The pyrimidine ring is further substituted with a 1,2,4-triazole ring, which is in turn connected to a 5-methyl-1H-imidazole ring. A methylamino group is attached to the 4-position of the imidazole ring.</p>	0.168	0.054	0.514	0.346	45	-5.17
47	Oxytetracycline	 <p>The structure of Oxytetracycline is a tetracycline derivative. It features a tetracycline core with a dimethylamino group at the 4-position and a primary amide group at the 7-position. The molecule is highly substituted with hydroxyl groups at various positions, including the 2, 3, 4, 5, 6, and 7 positions.</p>	0.208	0.518	0.514	0.306	46	-3.83

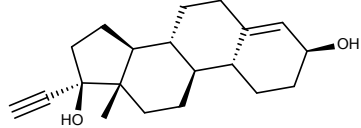
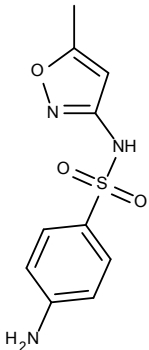
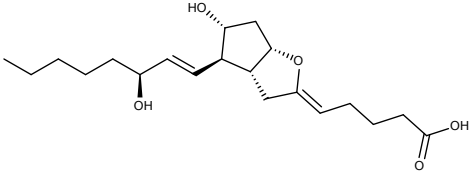
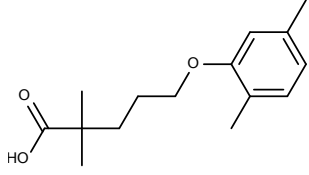
48	Pazopanib		0.25	0.081	0.506	0.257	47	-7.35
49	Captopril		0.331	0.8	0.506	0.175	48	-16.74
50	Chlorpropamide		0.263	0.7	0.503	0.24	49	-4.1
51	Furosemide		0.269	0.758	0.497	0.228	50	-4.58

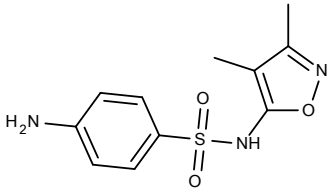
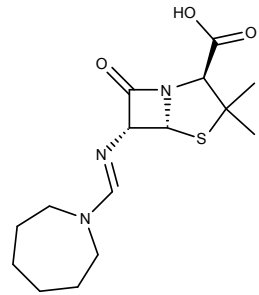
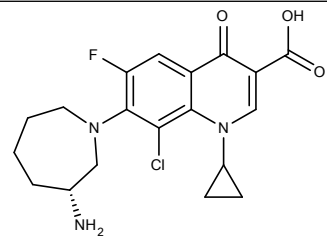
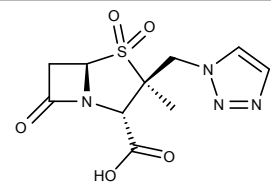
52	Rosuvastatin ^b		0.41	0.855	0.496	0.086	51	-3.05
53	Sulfamethizole		0.36	0.763	0.496	0.136	52	-5.27
54	Zoledronate		0.135	0.268	0.496	0.361	53	-4.38
55	Sulfacetamide		0.356	0.761	0.493	0.136	54	-4.1

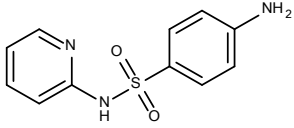
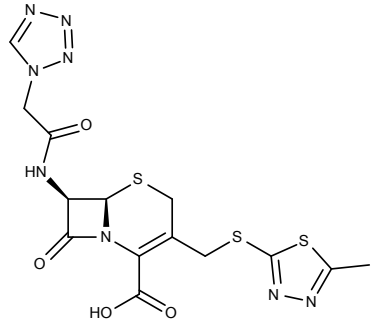
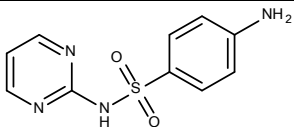
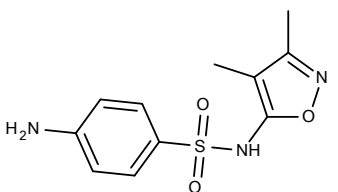
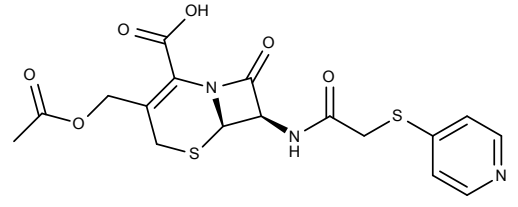
56	Ascorbic acid ^d		0.231	0.758	0.492	0.262	55	-2.86
57	Azidocillin		0.366	0.808	0.486	0.12	56	-13.11
58	Naproxen		0.28	0.77	0.486	0.206	57	-3.87
59	Sulfathiazole		0.343	0.75	0.48	0.138	58	-6.59

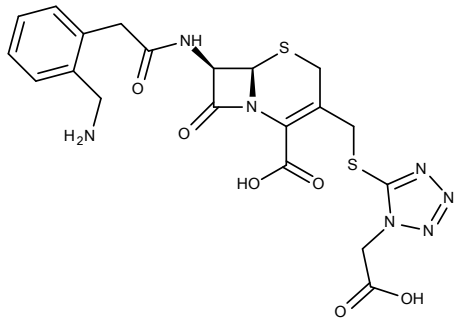
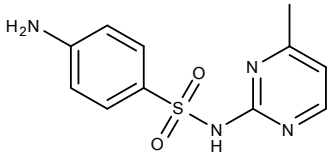
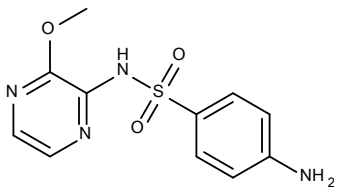
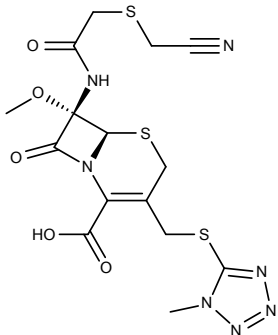
60	Beclomethasone ^a		0.139	0.011	0.479	0.341	59	-3.45
61	Cefacetrile		0.246	0.724	0.477	0.231	60	-8.14
62	Cefmenoxime		0.276	0.741	0.476	0.2	61	-8.23
63	Entacapone		0.301	0.748	0.473	0.172	62	-4.87

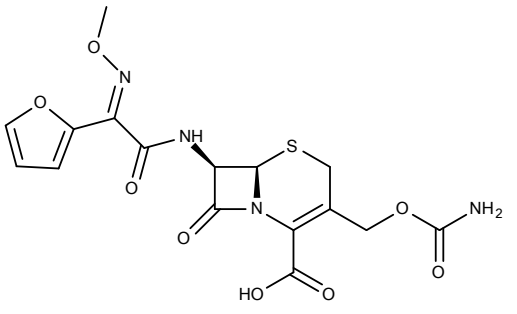
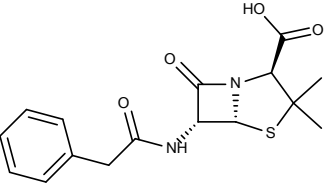
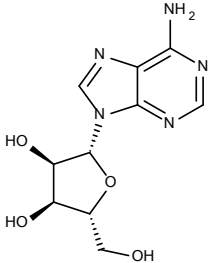
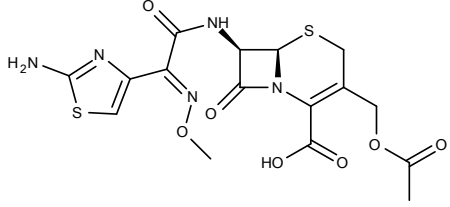
64	Tetracycline		0.212	0.514	0.472	0.26	63	-4.58
65	Clomocycline		0.224	0.525	0.472	0.248	64	-4.04
66	Balsalazide		0.34	0.602	0.472	0.132	65	-4.57
67	Cefalotin		0.258	0.735	0.471	0.214	66	-13.17

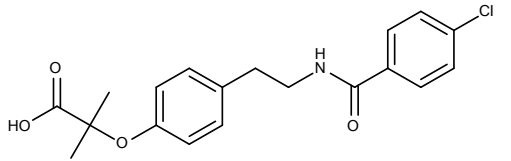
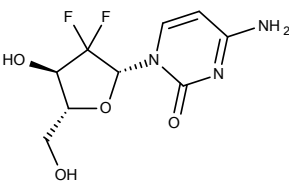
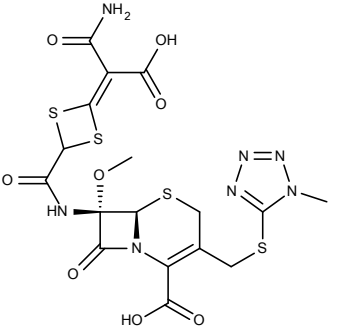
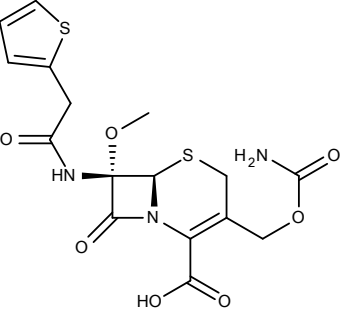
68	Ethynodiol ^a		0.071	0.011	0.471	0.4	67	-4.9
69	Sulfamethoxazole		0.348	0.761	0.469	0.121	68	-4.62
70	Epoprostenol ^a		0.123	0.599	0.468	0.345	69	-3.69
71	Gemfibrozil ^a		0.378	0.804	0.467	0.089	70	-3.29

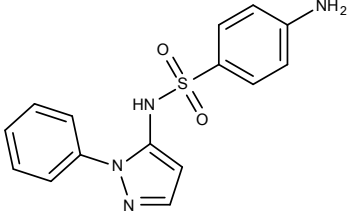
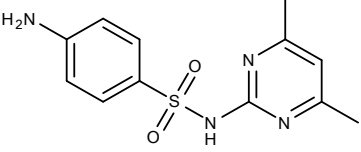
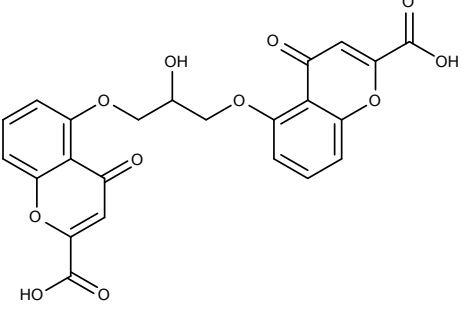
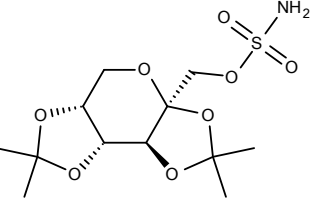
72	Sulfisoxazole		0.348	0.755	0.466	0.119	71	-5.03
73	Amdinocillin		0.246	0.102	0.466	0.219	72	-14.25
74	Besifloxacin		0.05	0.011	0.464	0.414	73	-4.99
75	Tazobactam		0.114	0.621	0.463	0.349	74	-4.91

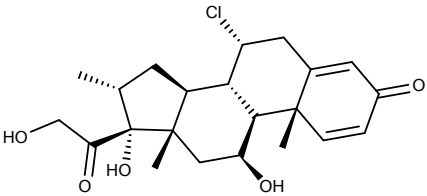
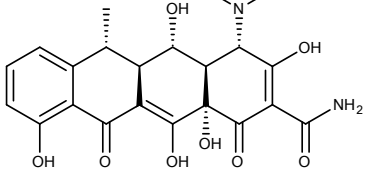
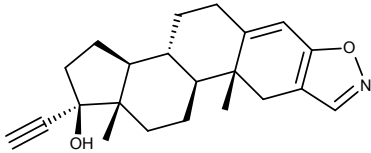
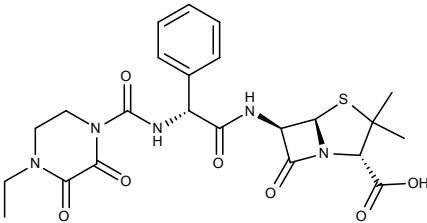
76	Sulfapyridine		0.338	0.751	0.462	0.124	75	-4.08
77	Cefazolin		0.262	0.741	0.462	0.2	76	-14.78
78	Sulfadiazine		0.206	0.688	0.46	0.254	77	-4.57
79	Sulfisoxazole		0.328	0.745	0.456	0.129	78	-4.76
80	Cefapirin		0.27	0.737	0.455	0.186	79	-13.38

81	Ceforanide		0.257	0.649	0.454	0.197	80	-13.58
82	Sulfamerazine		0.306	0.729	0.454	0.148	81	-4.81
83	Sulfametopyrazine		0.335	0.743	0.453	0.118	82	-4.82
84	Cefmetazole		0.236	0.731	0.451	0.215	83	-23.15

85	Cefuroxime		0.274	0.735	0.45	0.175	84	-6.87
86	Benzympenicillin ^e		0.32	0.792	0.448	0.128	85	-13.71
87	Adenosine ^f		0.089	0.034	0.445	0.356	86	-4.48
88	Cefotaxime		0.267	0.738	0.445	0.178	87	-13.25

89	Bezafibrate		0.351	0.752	0.443	0.092	88	-4.61
90	Gemcitabine		0.043	0.013	0.442	0.399	89	-3.54
91	Cefotetan		0.238	0.593	0.44	0.202	90	-5.73
92	Cefoxitin		0.233	0.722	0.439	0.206	91	-9.02

93	Sulfaphenazole		0.225	0.671	0.439	0.214	92	-5.05
94	Sulfamethazine		0.241	0.685	0.432	0.19	93	-4.94
95	Cromoglicic acid		0.198	0.559	0.426	0.228	94	-4.6
96	Topiramate		0.055	0.004	0.426	0.37	95	4.8

97	Alclometasone ^a		0.104	0.002	0.423	0.32	96	-4.26
98	Doxycycline ^g		0.117	0.456	0.423	0.307	97	-4.41
99	Danazol ^{a,b}		0.125	0.028	0.422	0.297	98	-5.85
100	Piperacillin		0.313	0.796	0.42	0.107	99	-10.16

^aApproved and experimental drugs selected as candidate for treatment of EVD [Veljkovic, V.; Loiseau, P.; Figadere, B. Virtual screen for repurposing approved and experimental drugs for candidate inhibitors of EBOLA virus infection. *F1000Research* **2015**, 4:34]

^b [US Pat. 8475804]

^c [<http://www.virology.ws/2014/10/09/treatment-of-ebola-virus-infection-with-brincidofovir/>]

^d [<http://scienceblogs.com/insolence/2014/09/05/high-dose-vitamin-c-can-cure-ebola-virus-disease-not-so-fast/>]

^e [<http://naturalsociety.com/ebola-scientists-discover-first-virological-penicillin-honeysuckle/>]

^f [Bray, M.; Driscoll, J.; Huggins, JW. Treatment of lethal Ebola virus infection in mice with a single dose of an S-adenosyl-L-homocysteine hydrolase inhibitor. *Antiviral Res.* **2000**, *5*, 135-147.]

^g [CDC Morbidity and Mortality Weekly Report (MMWR), June 27, 2014, Vol. 63(25)]

Property plots showing distribution of molecular and physicochemical properties in top-ranking hits (#100) obtained from EON screening

The property plots have been generated using Canvas version 1.6 as implemented in Schrödinger Suite 2013-1 (one-month trial version licensed to PSK).

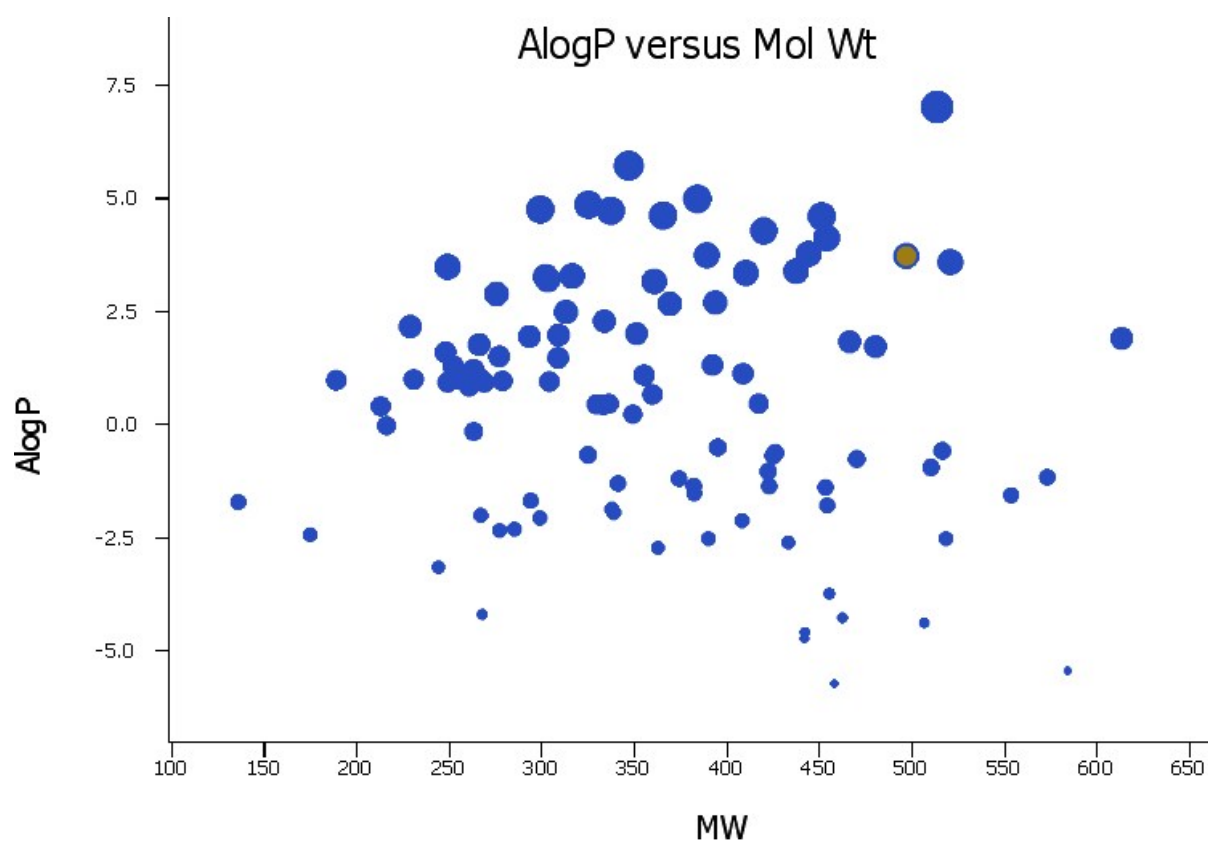


Figure 1S. Scatter plot of AlogP versus MW for top 100 hits obtained using Query 1 (brown circle). The size of the circle varies with AlogP value.

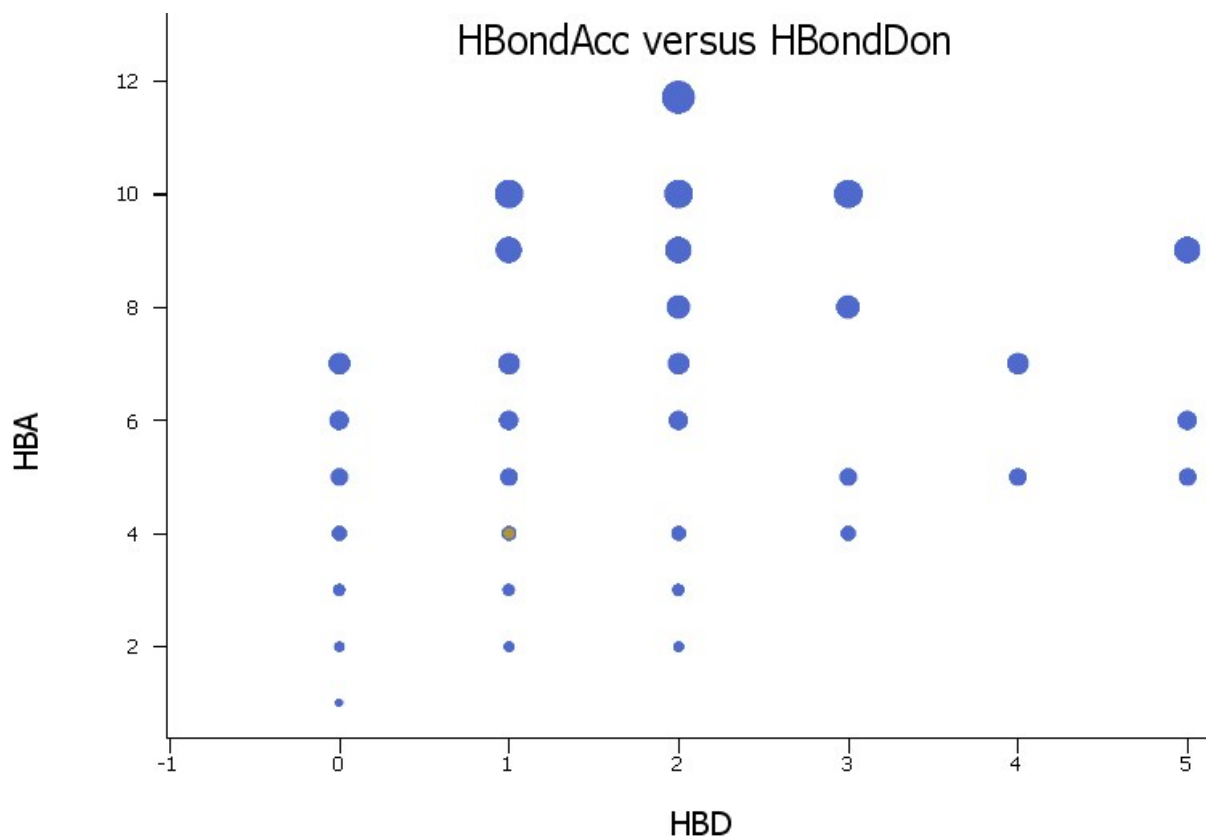


Figure 2S. Scatter plot of #HBondAcc (HBA) versus #HBondDon (HBD) for top 100 hits obtained using Query 1 (brown circle). The size of the circle varies with HBA value.

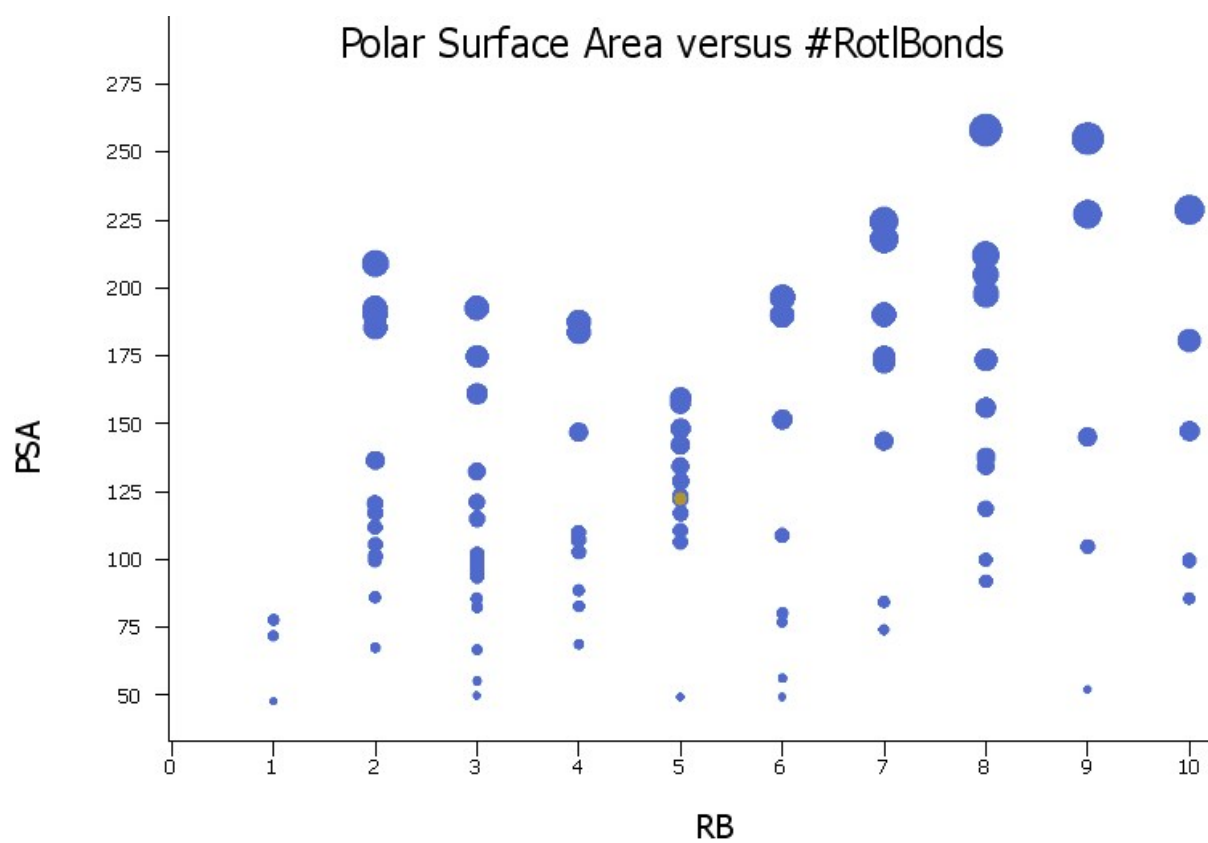


Figure 3S. Scatter plot of Polar Surface Area (PSA) versus #RotlBonds (RB) for top 100 hits obtained using Query 1 (brown circle). The size of the circle varies with PSA value.

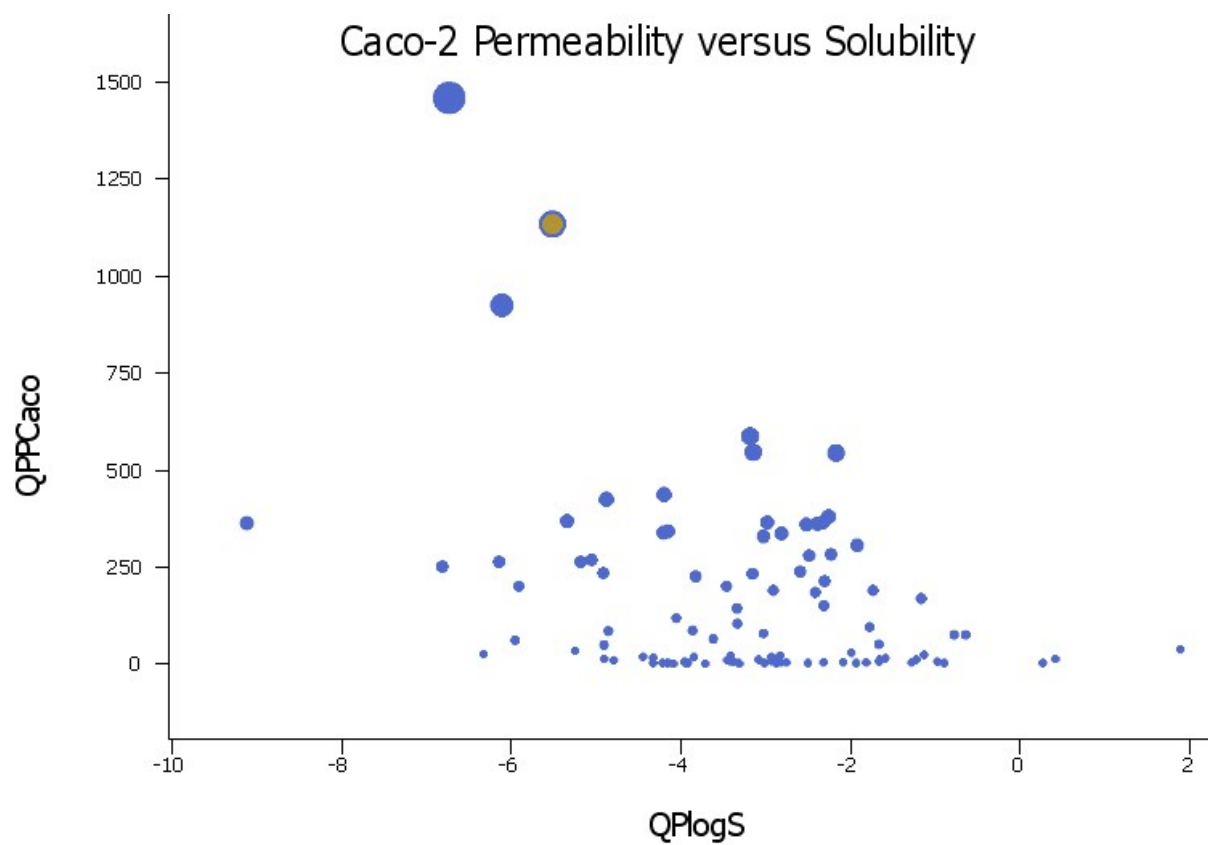


Figure 4S. Scatter plot of Predicted Caco-2 Permeability versus log Solubility for top 100 hits obtained using Query 1 (brown circle). The size of the circle varies with PSA value.

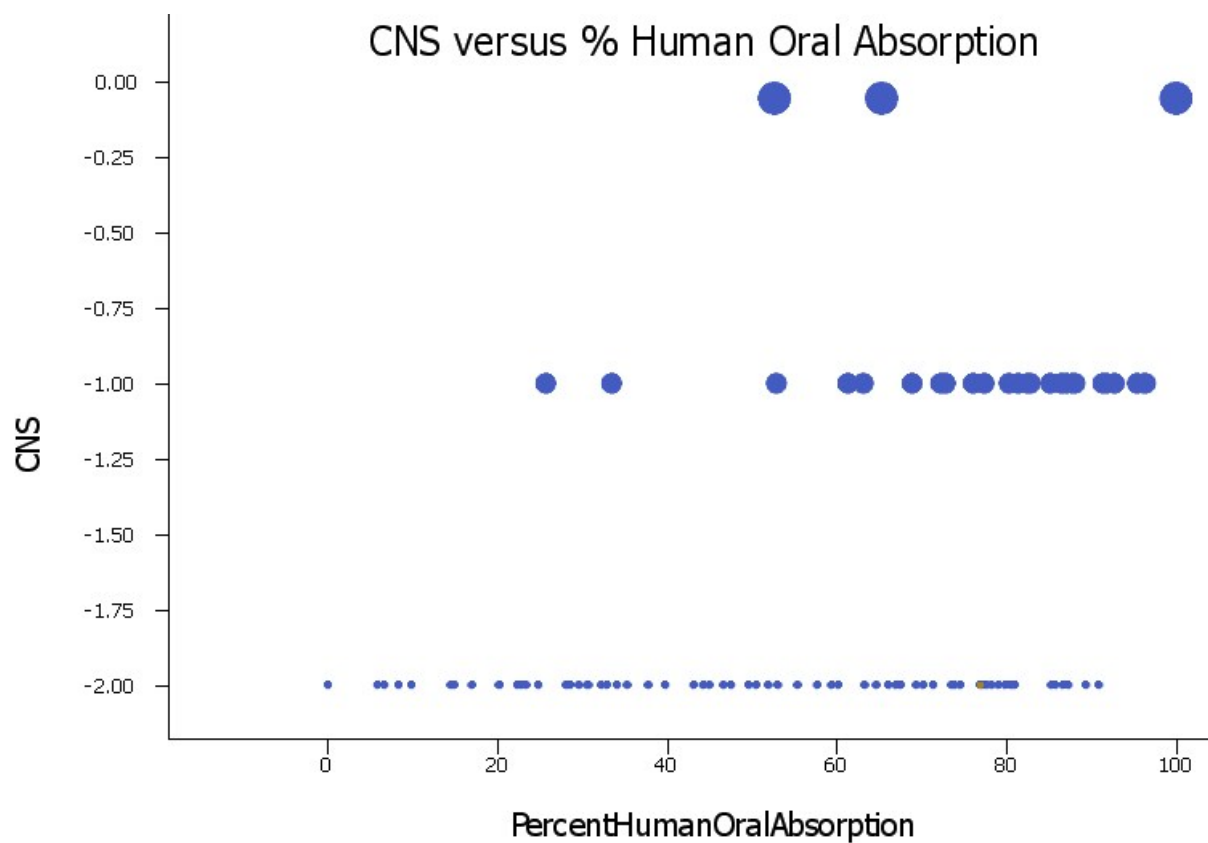


Figure 5S. Scatter plot of Predicted CNS Permeation versus % Human Oral Absorption for top 100 hits obtained using Query 1 (brown circle). The size of the circle varies with PSA value.