Supplementary Materials: High throughput virtual screening to discover inhibitors of the main protease of the coronavirus SARS-CoV-2

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List of Figures

List of Tables

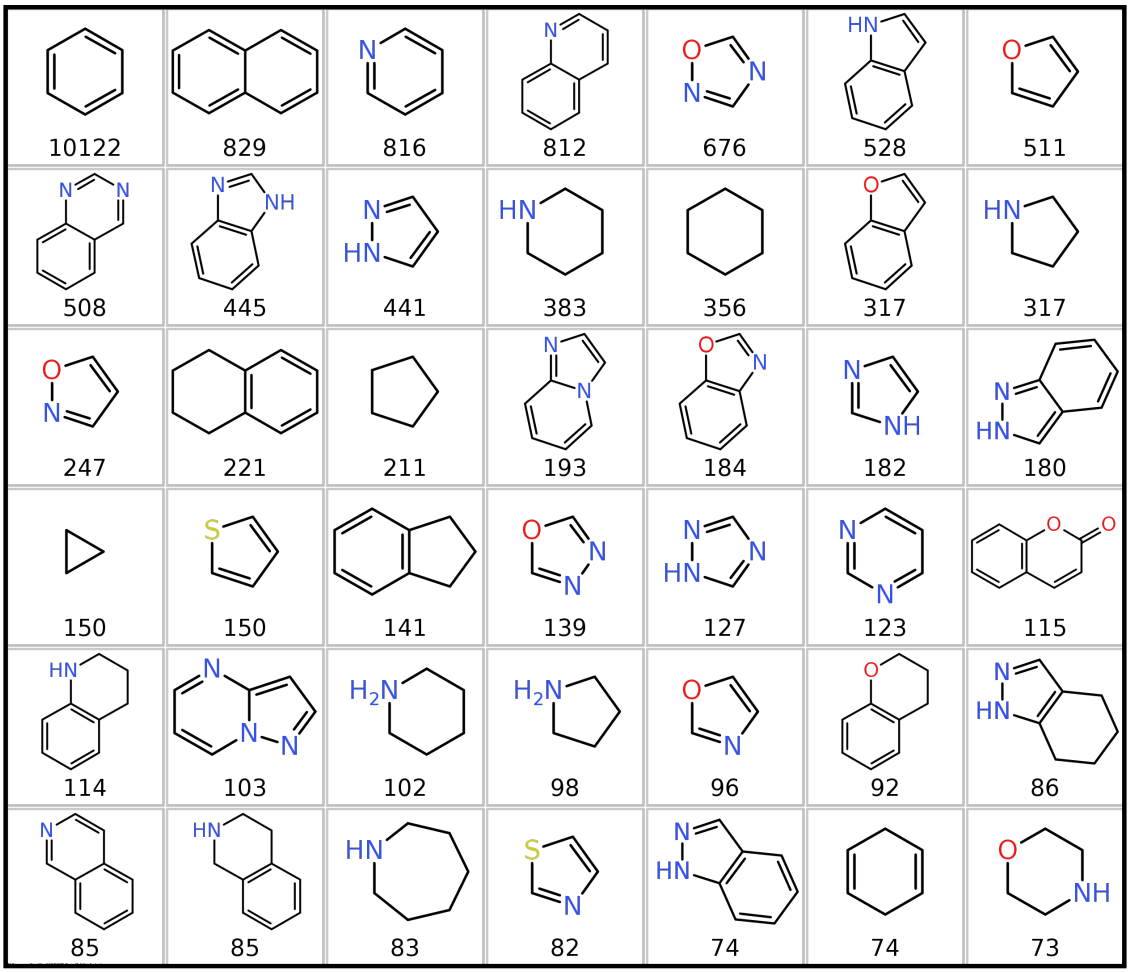

Figure S1: Chemical fragments majorly featured in the top performing 9,515 synthetic compounds obtained from screening against the crystal structure of the SARS-CoV-2 main protease 3CL^{pro}. The numbers represent the occurrence in absolute numbers.

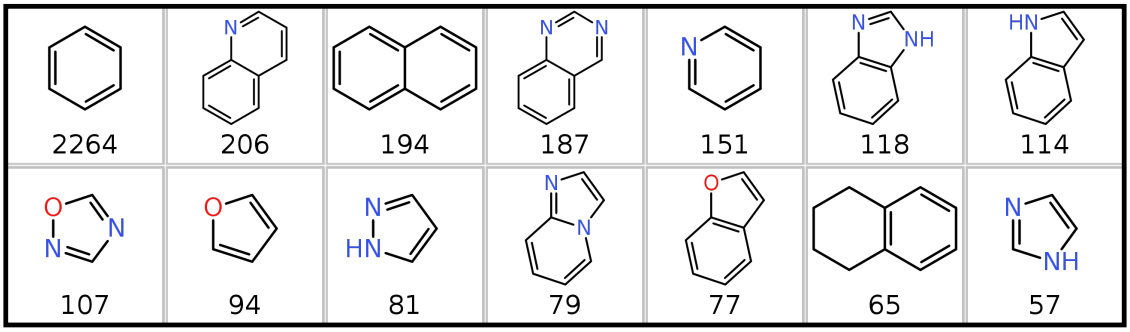

Figure S2: Chemical fragments majorly featured in the top 2,102 synthetic compounds obtained from ensemble docking and application of cutoff values of $\Delta G \leq -7.0$ kcal/mol and $d_{\text{dyad}} \leq 3.5$ Å. The numbers represent the occurrence in absolute numbers.

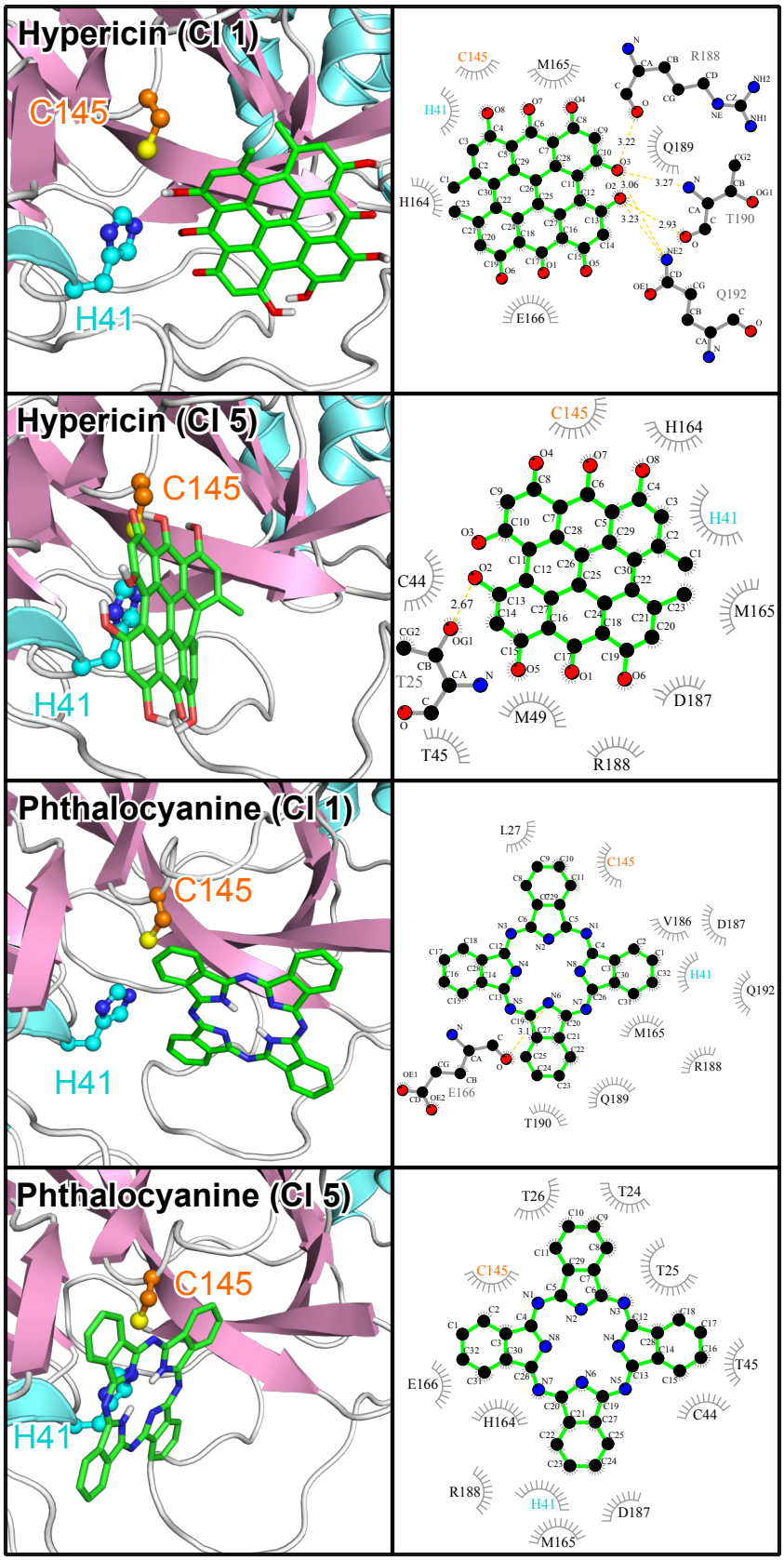

Figure S3: The poses and 3CL^{pro}–compound interactions of phthalocyanine and hypericin.

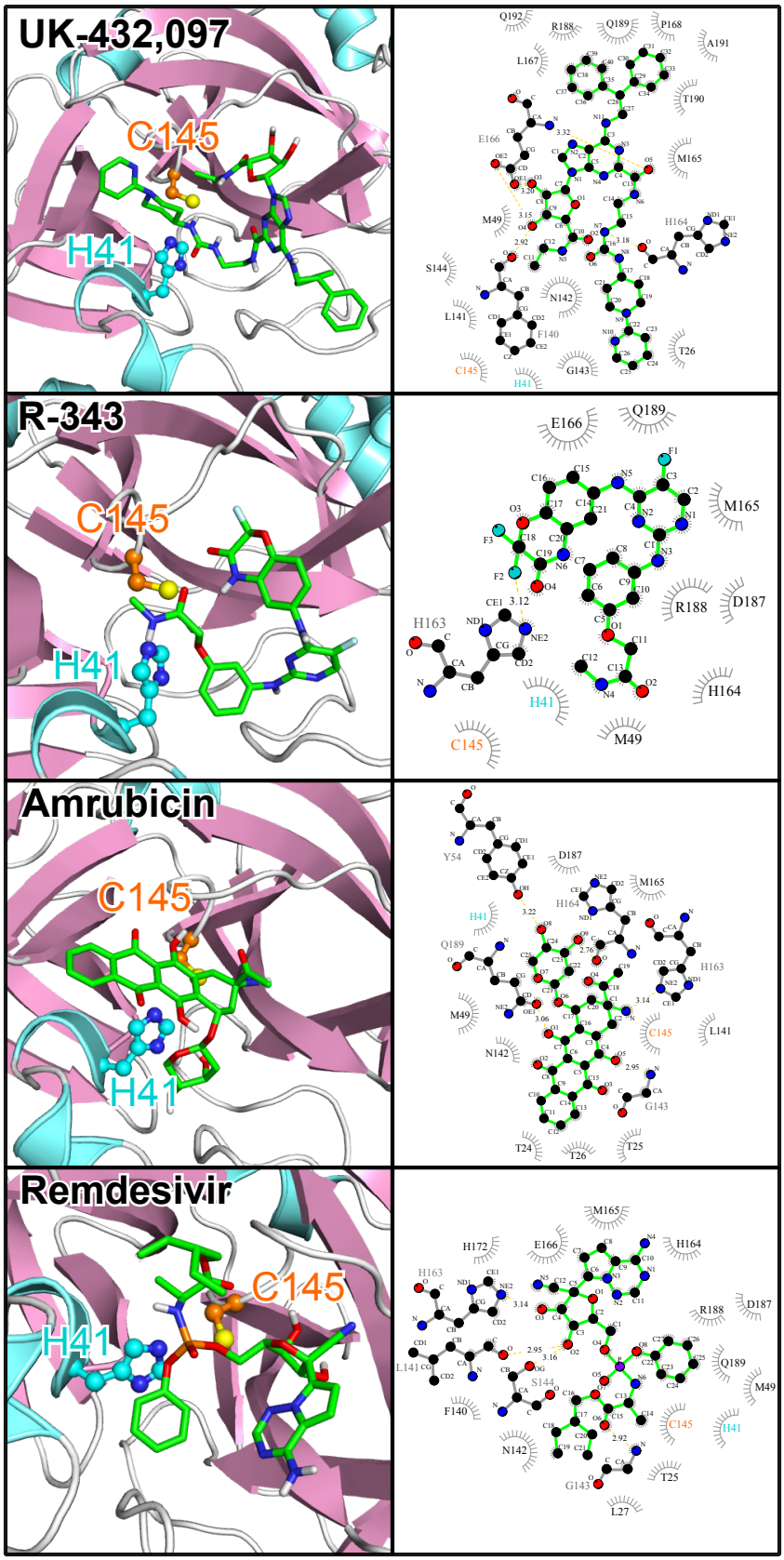

Figure S4: The poses and 3CL^{pro}–compound interactions of the four best non-FDA-approved and investigational drugs.

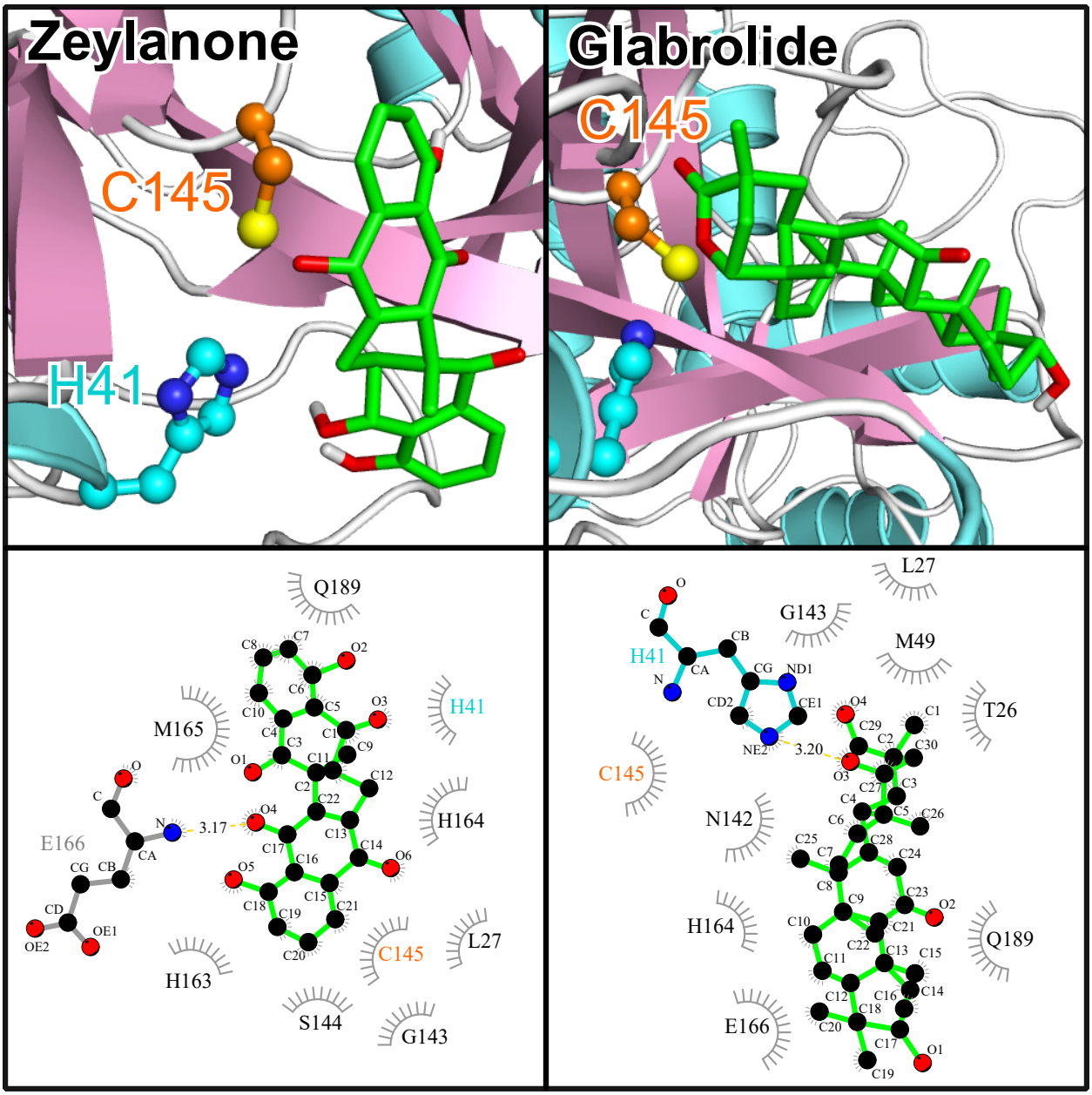

Figure S5: The poses and 3CL^{pro}–compound interactions of zeylanone and glabrolide.

Table S1: Names and properties of the compounds binding best to the active site of 3CL^{pro}. These compounds include FDA-approved drugs, other drugs, natural products, steroids, and eight reference compounds. The ΔG values and distances to the catalytic dyad (d_{dyad}) are average values obtained from ensemble docking agains five representative structures of 3CL^{pro} obtained from MD simulation. The compounds highlighted in bold are discussed in more detail in the text.

No.	Accession ID	Compound name	ΔG [kcal/mol]	d_{dyad} [Å]
		FDA drugs		
1	**ZINC000006716957**	**Nilotinib**	**−8.66**	**3.43**
2	ZINC000064033452	Lumacaftor	−8.36	3.36
3	ZINC000018324776	Dutasteride	−8.36	3.65
4	ZINC000003993855	Tadalafil	−8.28	3.42
5	ZINC000052955754	Ergotamine	−8.10	3.72
6	**ZINC000100378061**	**Naldemedine**	**−8.06**	**2.98**
7	ZINC000003920266	Idarubicin	−8.04	3.25
8	ZINC000001530788	Simeprevir	−8.02	3.68
9	ZINC000013831130	Raltegravir	−7.98	3.35
10	ZINC000014210642	Azilsartan	−7.90	3.27
11	ZINC000058581064	Dolutegravir	−7.88	3.73
12	ZINC000003927822	Lurasidone	−7.80	3.53
13	ZINC000004214700	Paliperidone	−7.78	3.58
14	**ZINC000222731806**	**Enasidenib**	**−7.76**	**2.89**
15	ZINC000012503187	Conivaptan	−7.76	3.33
16	ZINC000001530886	Telmisartan	−7.74	3.35
17	ZINC000003938684	Etoposide	−7.72	3.53
18	ZINC000029416466	Saquinavir	−7.70	3.32
19	ZINC000072318121	Abemaciclib	−7.70	3.65
20	ZINC000008101127	Indocyanine	−7.68	3.52
21	ZINC000011617039	Pazopanib	−7.66	3.58
22	ZINC000003938686	Palbociclib	−7.66	3.61
23	ZINC000004099008	Teniposide	−7.66	3.67
24	ZINC000035328014	Ibrutinib	−7.64	3.45
25	ZINC000253632968	Cromolyn	−7.64	3.68
26	ZINC000043100709	Trematinib	−7.60	3.42
27	ZINC000003831151	Montelukast	−7.58	3.41
28	ZINC000022448696	Indinavir	−7.54	3.29
29	ZINC000040430143	Olaparib	−7.52	3.86

30	ZINC000049036447	Suvorexant	−7.50	3.53
31	**ZINC000003976838**	**Afatinib**	**−7.44**	**3.04**
32	ZINC000003816514	Rolapitant	−7.44	3.40
33	ZINC000013986658	Idelalisib	−7.42	3.26
34	ZINC000013818943	Regadenoson	−7.38	3.20
35	ZINC000100003902	Maraviroc	−7.38	3.59
36	ZINC000019632618	Imatinib	−7.36	3.11
37	ZINC000003827556	Delafloxacin	−7.34	3.14
38	ZINC000003986735	Dasatinib	−7.32	3.46
39	ZINC000027990463	Lomitapide	−7.32	3.79
40	ZINC000003932831	Candesartan	−7.32	3.64
41	ZINC000035902489	Crizotinib	−7.30	3.57
42	ZINC000004175630	Pimozide	−7.30	3.73
43	ZINC000019796168	Sildenafil	−7.28	3.55
44	ZINC000043206370	Niraparib	−7.26	3.46
45	**ZINC000003918453**	**Ertapenem**	**−7.24**	**2.95**
46	ZINC000003860453	Fluorescein	−7.22	3.56
47	ZINC000001481815	Deferasirox	−7.22	3.59
48	ZINC000018324776	Vardenafil	−7.20	3.62
49	ZINC000060325170	Cobimetinib	−7.18	3.16
50	ZINC000000537791	Glimepiride	−7.18	3.51
51	ZINC000001489478	Sitagliptin	−7.18	3.60
52	ZINC000003812865	Olsalazine	−7.18	3.67
53	ZINC000011677837	Apixaban	−7.12	3.78
54	ZINC000005844788	Nebivolol	−7.04	3.43
55	ZINC000000897240	Azelastine	−7.04	3.45
56	ZINC000100022637	Tipranavir	−6.92	3.37
57	ZINC000001552174	Cilostazol	−6.86	3.45
58	ZINC000030691797	Perampanel	−6.82	3.67
59	ZINC000085537017	Cangrelor	−6.44	3.28
60	**ZINC000003944422**	**Ritonavir**	**−6.70**	**3.52**
61	ZINC000001530948	Thalidomide	−6.26	3.83
		Non-FDA and investigational drugs		
62	**ZINC000012358610**	**Phthalocyanine**	**−10.46**	**3.63**
63	**ZINC000003780340**	**Hypericin**	**−9.12**	**2.85**

64	ZINC000003922429	Adozelesin	−8.84	3.84
65	ZINC000003975327	Telomestatin	−8.80	3.34
66	ZINC000043203371	MK-3207	−8.74	3.54
67	ZINC000059749972	Radotinib	−8.68	3.43
68	ZINC000003812168	Ruboxistaurin	−8.56	3.55
69	ZINC000003950115	TMC647055	−8.50	3.77
70	ZINC000095092808	—	−8.48	3.86
71	ZINC000049888572	—	−8.42	3.55
72	**ZINC000095539256**	**UK-432,097**	**−8.34**	**3.18**
73	**ZINC000038576002**	**R-343**	**−8.30**	**2.71**
74	ZINC000014880002	Dihydroergotoxine	−8.30	3.43
75	ZINC000004215648	Dihydroergocornine	−8.30	3.80
76	ZINC000003817327	Ly2090314	−8.30	3.83
77	ZINC000003781738	Lestaurtinib	−8.26	3.53
78	ZINC000254071113	Ciluprevir	−8.26	3.64
79	ZINC000063933734	Rebastinib	−8.24	3.36
80	ZINC000059185874	GDC-0834	−8.24	3.58
81	ZINC000043133316	Tirilazad	−8.24	3.87
82	ZINC000098208742	Entospletinib	−8.20	3.57
83	ZINC000018710085	—	−8.20	3.97
84	ZINC000003930598	—	−8.18	3.71
85	ZINC000004215770	Elsamitrucin	−8.12	3.31
86	**ZINC000003780800**	**Amrubicin**	**−8.10**	**2.96**
87	ZINC000001539348	—	−8.10	3.39
88	ZINC000003978083	Tubocurarine	−8.10	3.56
89	ZINC000068250462	Tucatinib	−8.10	3.88
90	ZINC000001494900	Enzastaurin	−8.08	3.48
91	ZINC000003950115	Lonafarnib	−8.08	3.73
92	ZINC000019899628	Fenoverine	−8.06	4.06
93	ZINC000095535868	Rwj-58259	−8.04	3.55
94	ZINC000001490807	—	−8.04	3.60
95	ZINC000006717782	BMS-599626	−8.04	3.66
96	ZINC000100001820	PF-00477736	−8.02	3.49
97	ZINC000028827350	Telcagepant	−8.20	3.58
98	ZINC000003973984	Sotrastaurin	−8.02	3.68

99	ZINC000021290045	—	−8.00	3.32
100	ZINC000100029945	Zosuquidar	−8.00	3.45
101	CID121304016	Remdesivir	−6.44	2.84
	Natural products from ZINC database and flavonoids			
102	**ZINC000150352420**	**Theacitrin A**	**−9.82**	**3.31**
103	**ZINC000004098612**	**Corilagin**	**−9.58**	**3.22**
104	ZINC000008214976	Theasinensin B	−9.18	3.41
105	ZINC000169372863	Theasinensin A	−9.16	3.42
106	**ZINC000003978446**	**Theaflavin**	**−9.16**	**3.75**
107	ZINC000004235306	—	−9.18	3.52
108	ZINC000230071666	Theacitrin C	−8.96	3.54
109	**ZINC000003984030**	**Amentoflavone**	**−8.88**	**3.48**
110	ZINC000169333962	Theasinensin F	−8.78	3.43
111	ZINC000001531664	Ginkgetin	−8.76	3.68
112	ZINC000044351169	Proanthocyanidin A1	−8.76	3.74
113	ZINC000003978800	Rhoifolin	−8.70	3.56
114	ZINC000004098619	Proanthocyanidin A2	−8.68	3.69
115	ZINC000095619717	Proanthocyanidin A5’	−8.64	3.54
116	ZINC000003197535	Isoginkgetin	−8.54	3.67
117	**ZINC000014887561**	**Zeylanone**	**−8.44**	**3.56**
118	CID10077799	Isocorilagin	−8.28	3.81
119	**ZINC000003870412**	**Epigallocatechin gallate**	**−8.28**	**3.50**
120	ZINC000006624329	—	−8.28	3.77
121	ZINC000002148919	—	−8.26	3.63
122	ZINC000002107922	—	−8.24	3.82
123	ZINC000002161217	—	−8.22	3.48
124	ZINC000008297065	—	−8.20	3.67
125	ZINC000002125422	—	−8.18	3.50
126	ZINC000008764269	—	−8.16	3.50
127	ZINC000008789992	—	−8.12	3.56
128	ZINC000012296408	—	−8.10	3.59
129	ZINC000002147804	—	−8.08	3.55
130	ZINC000012881832	—	−8.06	3.46
131	ZINC000002158857	—	−8.06	3.46
132	CID5321811	Bavacoumestan A	−8.04	3.60

133	**ZINC000100828606**	**Neodiosmin**	**−8.04**	**3.12**
134	ZINC000011865175	—	−8.00	3.67
135	ZINC000002114470	—	−8.00	3.60
136	**ZINC000100777667**	**Glabrolide**	**−7.89**	**3.94**
137	CID12443227	Epitaraxerol	−7.00	3.79
138	ZINC000004098322	Homoeriodictyol	−6.64	3.42
139	ZINC000018847034	Daidzein	−6.04	3.75
		Steroids		
140	CID27125	Estetrol	−6.86	3.39
141	**ZINC000004340309**	**Cortisol**	**−6.80**	**3.62**
142	**CID5757**	**Estradiol**	**−6.74**	**3.41**
143	CID5994	Progesterone	−6.70	3.93
144	ZINC000004428526	Androstenedione	−6.66	3.65
145	CID91451	17-α-hydroxypregnanolone	−6.62	3.41
146	ZINC000003815419	2-Hydroxyestradiol	−6.46	3.67
147	ZINC000003807917	Dehydroepiandrosterone	−6.40	3.81
148	ZINC000004081043	Allopregnanolone	−6.34	3.88
149	**ZINC000118912393**	**Testosterone**	**−6.32**	**3.90**
		Reference compounds		
150	ZINC000013985228	Tideglusib	−6.64	3.71
151	PDB code 6LU7	N3	−6.00	3.23
152	ZINC000001714738	Cinanserin	−5.90	3.54
153	CID3194	Ebselen	−5.74	4.17
154	ZINC000001542916	Carmofur	−5.60	3.64
155	ZINC000013209429	PX-12	−3.84	3.97
156	ZINC000001529266	Disulfiram	−3.80	3.45
157	ZINC000002015152	Shikonin	−2.72	3.59