Supplementary file 1

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Marine fungal metabolites as antiviral agents: Computer-aided drug screening for selective inhibition of African swine fever virus dUTPase

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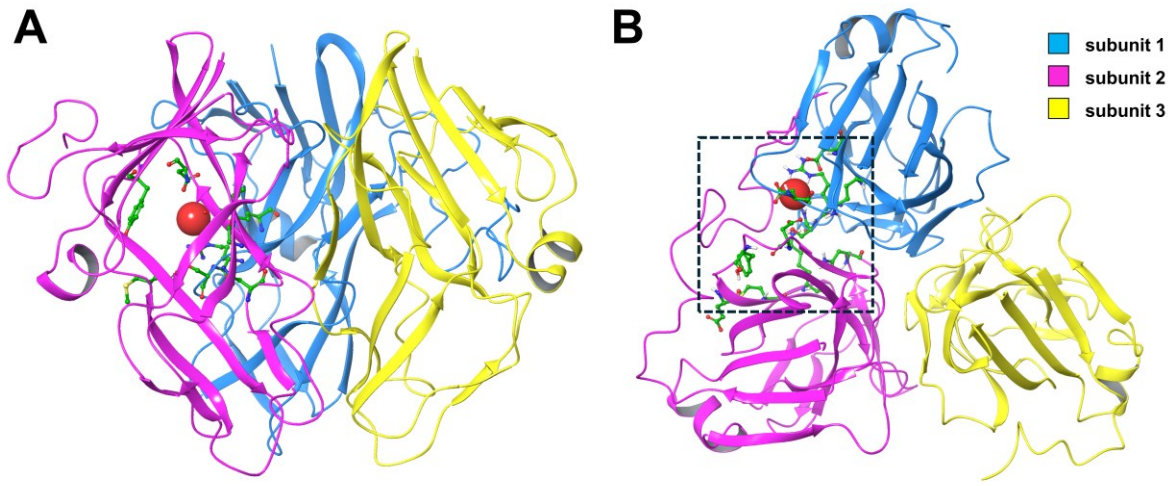

Fig. S1. 3D representation of trimeric ASFV dUTPase (PDB ID: 6LJ3). (A) Side view of ASFV dUTPase. (B) Top view of ASFV dUTPase. Also shown are the magnesium ion (red) and the location of some active site residues (green) within subunit 1 and subunit 2.

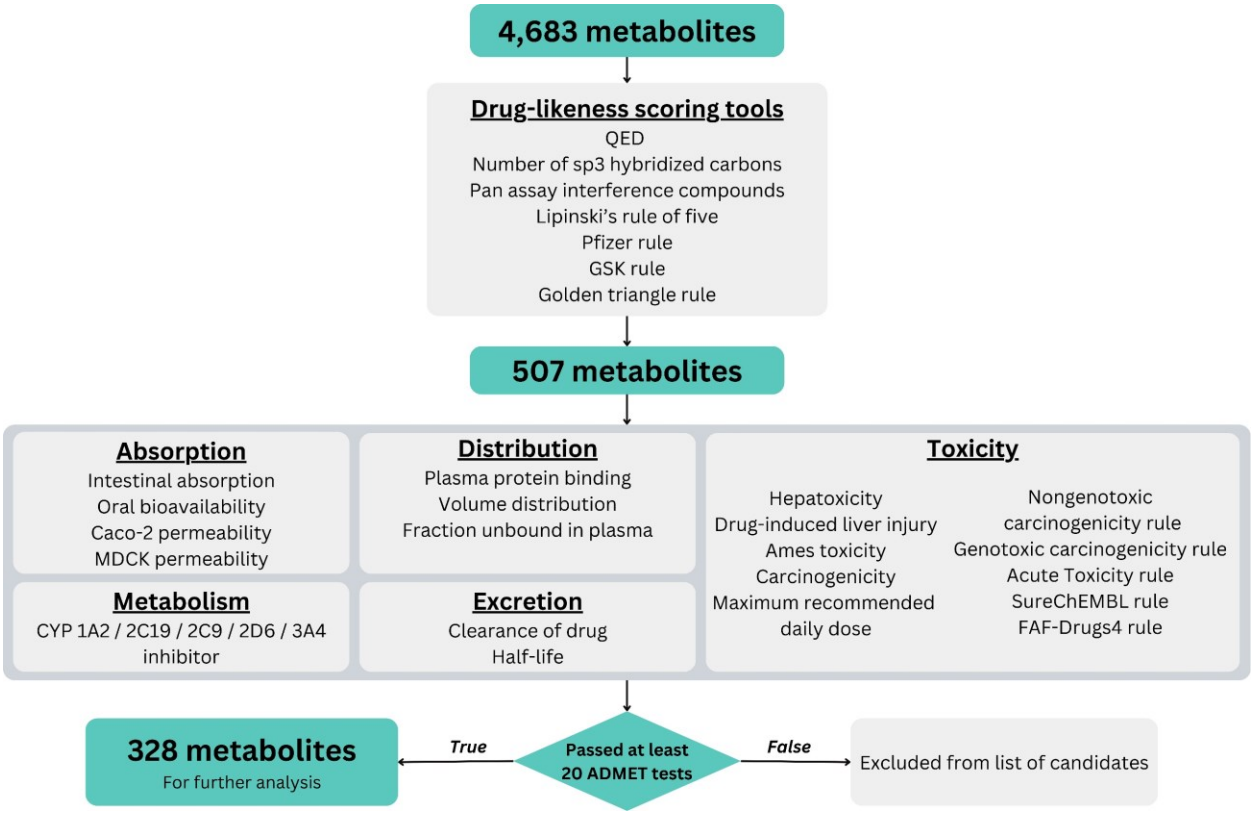

Fig. S2. ADMET filter used for the screening of the 4,683 metabolites. The compounds underwent initial screening using seven drug-likeness scoring tools and were subsequently refined using 24 ADMET tests. Only those that passed at least 20 ADMET tests were considered for further evaluation.

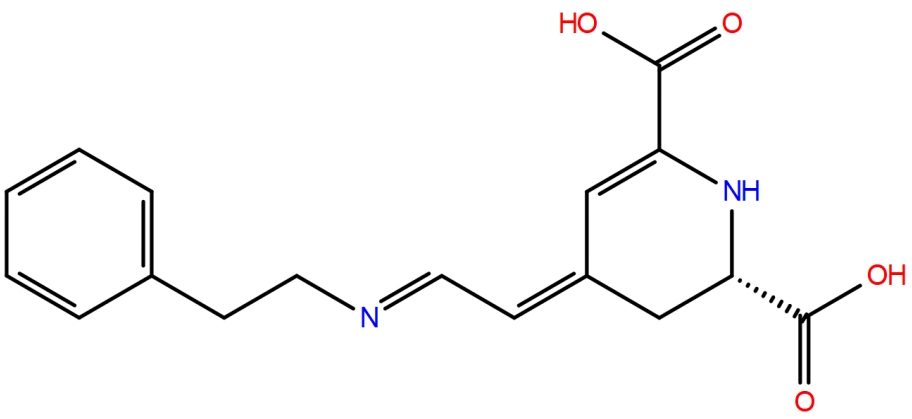

Fig. S3. 2D structure of the identified decoy ligand, CHEMBL554071

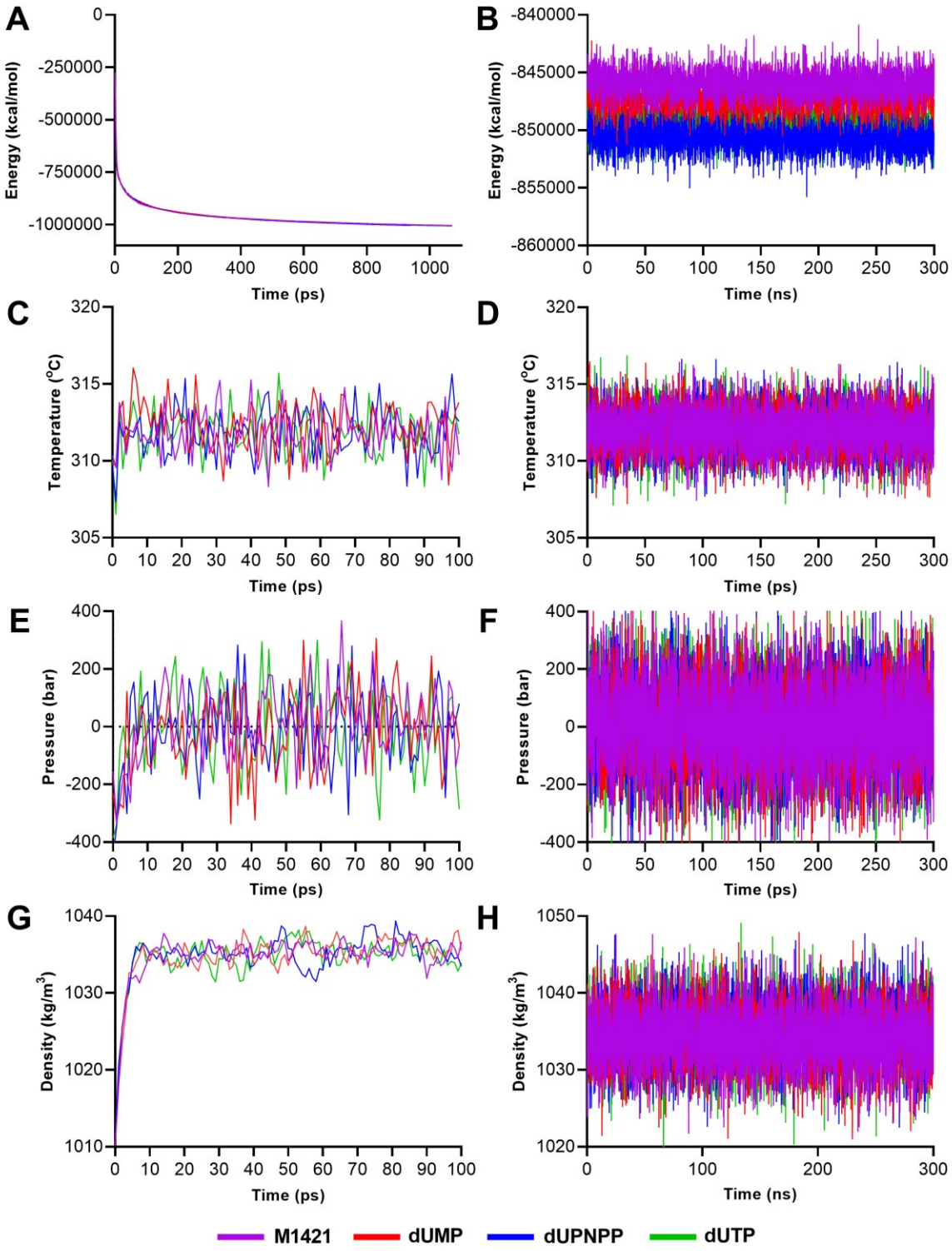

Fig. S4. System stability profiles throughout the simulation. (A–B) Potential energy during the equilibration phase (A) and MD production run (B). (C–D) Temperature profile during equilibration (C) and production (D). (E–F) Pressure profile during equilibration (E) and production (F). (G–H) Density profile during equilibration (G) and production (H).

Table S2. Grid box coordinates and the known active site residues of ASFV dUTPase and swine dUTPase

Protein	Grid Box Location	Active Site Residues
ASFV dUTPase	x = -9.633 y = 14.504 z = -7.145	Subunit 1: Asp 33, Arg 71, Arg 72, Ser 73, Gln 120 Subunit 2: Asn 85, Leu 89, Asp 91, Tyr 94, Met 99, Lys 101[11]
Swine dUTPase	x = 11.701 y = 16.666 z = -30.702	Subunit 1: Arg 210, Phe 215, Gly 216, Ser 217, Thr 218 Subunit 2: Asp 106, Pro 141, Arg 142, Ser 143, Gly 144, Gln 188 Subunit 3: Gly 154, Gly 156, Val 157, Asp 159, Gly 167, Val 169[11]

Table S3. Docking scores (kcal/mol) of the 328 metabolites against ASFV dUTPase

Rank	Ligand	AutoDock Vina	AutoDock 4.2	RMSD	Total

Control	*DUMP*	*-7.5*	*-7.68*	*0.732*	*-7.59*
Control	*DUTP*	*-7.4*	*-7.54*	*1.31*	*-7.47*
Control	*DUPNPP*	*-7.3*	*-7.34*	*1.604*	*-7.32*
1	M3120	-7.6	-8.78	1.489	-8.19
2	M1421	-6.9	-9.19	1.972	-8.045
3	M4555	-7.3	-8.31	0.892	-7.805
4	M0549	-7.6	-8	1.268	-7.8
5	M1231	-6.9	-8.7	1.235	-7.8
6	M0288	-7.7	-7.84	1.241	-7.77
7	M1628	-7.7	-7.72	1.159	-7.71
8	M2440	-6.9	-8.42	1.73	-7.66
9	M2989	-7.4	-7.88	1.694	-7.64
10	M2126	-6.3	-8.83		-7.565
11	M2837	-7	-8.05		-7.525
12	M0765	-6.9	-8.13		-7.515
13	M3006	-6.8	-8.19		-7.495
14	M0673	-7.1	-7.88		-7.49
15	M0913	-7	-7.97		-7.485
16	M0402	-7.5	-7.46		-7.48
17	M4203	-8.3	-6.64		-7.47
18	M2889	-6.9	-8		-7.45
19	M2464	-7	-7.89		-7.445
20	M1076	-6.8	-8.07		-7.435
21	M1640	-6.7	-8.13		-7.415
22	M3779	-6.6	-8.15		-7.375
23	M3030	-6.3	-8.44		-7.37
24	M3098	-7.1	-7.63		-7.365
25	M4511	-6.8	-7.9		-7.35
26	M3354	-6.8	-7.88		-7.34
27	M3810	-6.9	-7.78		-7.34
28	M1605	-6.9	-7.77		-7.335
29	M1164	-7	-7.66		-7.33
30	M3480	-6.6	-8.01		-7.305
31	M0323	-6.8	-7.78		-7.29
32	M3630	-6.3	-8.28		-7.29
33	M3570	-7.1	-7.47		-7.285
34	M1287	-7	-7.55		-7.275
35	M3526	-6.3	-8.22		-7.26
36	M3551	-7.3	-7.21		-7.255
37	M0381	-6.7	-7.81		-7.255
38	M1700	-6.7	-7.81		-7.255
39	M2817	-6.5	-8.01		-7.255
40	M2639	-6.6	-7.89		-7.245

41	M3032	-7	-7.48	-7.24
42	M4544	-6.8	-7.68	-7.24
43	M3382	-6.8	-7.67	-7.235
44	M1156	-7.1	-7.35	-7.225
45	M1524	-6.7	-7.75	-7.225
46	M0073	-7.1	-7.33	-7.215
47	M3385	-6.7	-7.73	-7.215
48	M4669	-6.8	-7.52	-7.16
49	M3635	-7	-7.31	-7.155
50	M1977	-6.4	-7.88	-7.14
51	M1815	-6.9	-7.38	-7.14
52	M3965	-6.8	-7.48	-7.14
53	M4063	-6.8	-7.47	-7.135
54	M2833	-6.9	-7.35	-7.125
55	M0183	-6.8	-7.43	-7.115
56	M0900	-6	-8.23	-7.115
57	M1870	-6.2	-8.03	-7.115
58	M0188	-6.7	-7.52	-7.11
59	M4073	-6.5	-7.72	-7.11
60	M3101	-6.4	-7.81	-7.105
61	M1159	-6.9	-7.29	-7.095
62	M1518	-6.6	-7.56	-7.08
63	M3413	-6.3	-7.86	-7.08
64	M0626	-6.6	-7.55	-7.075
65	M1276	-6.6	-7.53	-7.065
66	M1881	-6.8	-7.33	-7.065
67	M0776	-6.6	-7.51	-7.055
68	M1124	-6.7	-7.41	-7.055
69	M4257	-6.2	-7.91	-7.055
70	M1240	-6.3	-7.79	-7.045
71	M2538	-6.9	-7.19	-7.045
72	M0467	-6.5	-7.58	-7.04
73	M3261	-6.5	-7.57	-7.035
74	M1091	-6.6	-7.46	-7.03
75	M0296	-6.8	-7.23	-7.015
76	M0872	-6.8	-7.22	-7.01
77	M1044	-6.8	-7.22	-7.01
78	M2804	-6.4	-7.6	-7
79	M0985	-6.4	-7.57	-6.985
80	M2316	-6.5	-7.46	-6.98
81	M0930	-6	-7.94	-6.97
82	M3429	-6.6	-7.32	-6.96
83	M0355	-6.3	-7.61	-6.955

84	M1529	-6.1	-7.78	-6.94
85	M0839	-6.7	-7.17	-6.935
86	M0823	-6.6	-7.26	-6.93
87	M2757	-6.6	-7.26	-6.93
88	M0460	-6.4	-7.45	-6.925
89	M1535	-6.4	-7.45	-6.925
90	M1894	-6.5	-7.34	-6.92
91	M3111	-6.5	-7.32	-6.91
92	M0334	-6.6	-7.2	-6.9
93	M3164	-6.5	-7.3	-6.9
94	M4599	-6.7	-7.1	-6.9
95	M4356	-6.6	-7.18	-6.89
96	M0967	-6	-7.76	-6.88
97	M1008	-6.5	-7.22	-6.86
98	M1847	-6.5	-7.21	-6.855
99	M0358	-6.3	-7.4	-6.85
100	M1414	-6.5	-7.19	-6.845
101	M0925	-6.1	-7.57	-6.835
102	M1682	-7	-6.63	-6.815
103	M2326	-6.8	-6.8	-6.8
104	M0606	-5.8	-7.79	-6.795
105	M2475	-6.6	-6.98	-6.79
106	M3046	-6.5	-7.08	-6.79
107	M1648	-6.7	-6.84	-6.77
108	M2373	-6.7	-6.84	-6.77
109	M3586	-6	-7.54	-6.77
110	M4524	-6.4	-7.14	-6.77
111	M1194	-6.4	-7.13	-6.765
112	M1336	-6.4	-7.13	-6.765
113	M4145	-6	-7.53	-6.765
114	M3508	-6.3	-7.22	-6.76
115	M0821	-6.6	-6.91	-6.755
116	M3401	-6.6	-6.91	-6.755
117	M4142	-6.4	-7.09	-6.745
118	M0843	-6.3	-7.17	-6.735
119	M2253	-6.5	-6.97	-6.735
120	M0669	-6.5	-6.95	-6.725
121	M0974	-6.5	-6.95	-6.725
122	M2704	-6	-7.41	-6.705
123	M3740	-6.1	-7.31	-6.705
124	M4295	-6.2	-7.21	-6.705
125	M2231	-5.8	-7.59	-6.695
126	M2372	-6.1	-7.29	-6.695

127	M2630	-5.8	-7.59	-6.695
128	M4012	-6.2	-7.19	-6.695
129	M0337	-5.9	-7.48	-6.69
130	M1016	-6.1	-7.28	-6.69
131	M0709	-6.4	-6.97	-6.685
132	M0996	-6.2	-7.17	-6.685
133	M1498	-6.2	-7.17	-6.685
134	M3805	-5.8	-7.57	-6.685
135	M1037	-6.1	-7.27	-6.685
136	M1864	-5.9	-7.46	-6.68
137	M3016	-6.2	-7.1	-6.65
138	M3364	-6.3	-7	-6.65
139	M2076	-6.1	-7.18	-6.64
140	M2545	-6.1	-7.18	-6.64
141	M0803	-6.2	-7.07	-6.635
142	M2011	-6.2	-7.07	-6.635
143	M0408	-6.1	-7.14	-6.62
144	M1586	-6.1	-7.14	-6.62
145	M3865	-6.4	-6.81	-6.605
146	M2050	-6.1	-7.1	-6.6
147	M3037	-5.7	-7.5	-6.6
148	M2737	-6	-7.19	-6.595
149	M2561	-5.8	-7.38	-6.59
150	M2694	-5.9	-7.28	-6.59
151	M4010	-6.3	-6.86	-6.58
152	M3166	-6.5	-6.65	-6.575
153	M1388	-5.9	-7.22	-6.56
154	M1681	-5.9	-7.22	-6.56
155	M0527	-6.1	-7.02	-6.56
156	M0992	-5.9	-7.2	-6.55
157	M1486	-6	-7.1	-6.55
158	M0898	-6.1	-6.99	-6.545
159	M2836	-5.8	-7.29	-6.545
160	M1063	-6.4	-6.67	-6.535
161	M1304	-6	-7.07	-6.535
162	M3073	-6.4	-6.67	-6.535
163	M4157	-6.3	-6.76	-6.53
164	M0979	-6.1	-6.95	-6.525
165	M2539	-6.3	-6.75	-6.525
166	M2610	-6.1	-6.95	-6.525
167	M4611	-6.2	-6.85	-6.525
168	M2967	-5.7	-7.34	-6.52
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170	M1474	-6.3	-6.72	-6.51
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172	M3730	-6	-6.98	-6.49
173	M0207	-6.1	-6.86	-6.48
174	M1121	-6.1	-6.86	-6.48
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176	M3063	-5.9	-7.02	-6.46
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179	M4466	-5.8	-7.09	-6.445
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181	M1879	-6.4	-6.44	-6.42
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184	M0112	-6.1	-6.7	-6.4
185	M3973	-5.9	-6.9	-6.4
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190	M2928	-6.1	-6.65	-6.375
191	M1979	-6.1	-6.63	-6.365
192	M0130	-5.9	-6.83	-6.365
193	M4086	-5.7	-7	-6.35
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196	M1401	-6	-6.67	-6.335
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203	M2949	-5.7	-6.89	-6.295
204	M4103	-6.2	-6.39	-6.295
205	M1360	-6.1	-6.48	-6.29
206	M2799	-6.1	-6.48	-6.29
207	M4013	-6	-6.57	-6.285
208	M3273	-5.7	-6.8	-6.25
209	M4051	-5.4	-7.09	-6.245
210	M4226	-6.3	-6.18	-6.24
211	M2612	-5.8	-6.65	-6.225
212	M0600	-5.9	-6.54	-6.22

213	M3195	-5.8	-6.64	-6.22
214	M3332	-5.9	-6.54	-6.22
215	M1650	-5.6	-6.81	-6.205
216	M2454	-5.7	-6.7	-6.2
217	M2877	-5.7	-6.68	-6.19
218	M3369	-5.8	-6.56	-6.18
219	M4488	-5.7	-6.66	-6.18
220	M4363	-5.7	-6.62	-6.16
221	M3781	-5.7	-6.6	-6.15
222	M4155	-5.8	-6.5	-6.15
223	M1938	-6.1	-6.17	-6.135
224	M3815	-5.8	-6.44	-6.12
225	M2909	-5.7	-6.52	-6.11
226	M1587	-5.5	-6.69	-6.095
227	M3400	-5.8	-6.37	-6.085
228	M1808	-5.8	-6.33	-6.065
229	M3267	-5.5	-6.62	-6.06
230	M4223	-5.6	-6.5	-6.05
231	M1560	-6	-6.07	-6.035
232	M3955	-5.6	-6.47	-6.035
233	M0174	-5.7	-6.36	-6.03
234	M3397	-5.5	-6.52	-6.01
235	M0767	-5.7	-6.28	-5.99
236	M1984	-5.7	-6.11	-5.905
237	M2306	-5.4	-6.36	-5.88
238	M1011	-5.7	-6.05	-5.875
239	M2859	-5.9	-5.85	-5.875
240	M1872	-5.5	-6.25	-5.875
241	M1425	-5.5	-6.19	-5.845
242	M4015	-5.3	-6.36	-5.83
243	M2580	-5.7	-5.93	-5.815
244	M3265	-6.1	-5.51	-5.805
245	M0662	-6.1	-5.5	-5.8
246	M2491	-5.7	-5.9	-5.8
247	M4025	-5.3	-6.26	-5.78
248	M3118	-5.6	-5.92	-5.76
249	M2356	-5.7	-5.82	-5.76
250	M3762	-5.6	-5.91	-5.755
251	M2404	-5.2	-6.28	-5.74
252	M2767	-5.2	-6.28	-5.74
253	M3563	-5.6	-5.85	-5.725
254	M4100	-5.6	-5.85	-5.725
255	M4327	-6.1	-5.24	-5.67

256	M2953	-5.8	-5.5	-5.65
257	M2584	-5.1	-6.16	-5.63
258	M0744	-4.8	-6.35	-5.575
259	M3910	-5.2	-5.68	-5.44
260	M0440	-5.5	-5.37	-5.435
261	M1207	-4.7	-6.02	-5.36
262	M2681	-5	-5.69	-5.345
263	M3107	-5.1	-5.59	-5.345
264	M4549	-5.2	-5.48	-5.34
265	M3735	-5.5	-5.18	-5.34
266	M1152	-5.4	-5.25	-5.325
267	M1444	-5.7	-4.89	-5.295
268	M2289	-5.7	-4.89	-5.295
269	M2665	-5.4	-5.18	-5.29
270	M4496	-5.8	-4.77	-5.285
271	M2884	-4.8	-5.73	-5.265
272	M0076	-4.4	-6.06	-5.23
273	M3248	-4.6	-5.86	-5.23
274	M0121	-4.6	-5.85	-5.225
275	M2406	-4.9	-5.52	-5.21
276	M3690	-5.5	-4.89	-5.195
277	M2492	-4.4	-5.95	-5.175
278	M2622	-5.1	-5.19	-5.145
279	M2747	-4.5	-5.79	-5.145
280	M4361	-4.5	-5.76	-5.13
281	M1532	-5.1	-5.06	-5.08
282	M3599	-4	-6.15	-5.075
283	M4017	-4.9	-5.22	-5.06
284	M4397	-5.4	-4.68	-5.04
285	M1074	-4.8	-5.27	-5.035
286	M4217	-5.4	-4.62	-5.01
287	M0515	-4.7	-5.28	-4.99
288	M0332	-5.7	-4.28	-4.99
289	M3493	-5.7	-4.28	-4.99
290	M0268	-5.3	-4.64	-4.97
291	M3876	-4.9	-5.04	-4.97
292	M2078	-4.4	-5.49	-4.945
293	M3312	-4.7	-5.14	-4.92
294	M0868	-5.1	-4.54	-4.82
295	M1774	-5.8	-3.82	-4.81
296	M4346	-4.1	-5.36	-4.73
297	M2352	-4.3	-5.14	-4.72
298	M4206	-5.3	-4.03	-4.665

299	M1947	-3.9	-5.4	-4.65
300	M1041	-4.2	-5.02	-4.61
301	M4256	-4.2	-4.91	-4.555
302	M1299	-4.5	-4.59	-4.545
303	M4604	-4.1	-4.99	-4.545
304	M0847	-4.9	-4.13	-4.515
305	M0242	-4.2	-4.83	-4.515
306	M1935	-3.8	-5.05	-4.425
307	M0724	-4.8	-4.01	-4.405
308	M2141	-4.3	-4.47	-4.385
309	M1762	-4.3	-4.36	-4.33
310	M2778	-3.9	-4.53	-4.215
311	M2277	-3.3	-4.87	-4.085
312	M2535	-3.5	-4.62	-4.06
313	M1579	-3.8	-4.3	-4.05
314	M1330	-3.9	-4.2	-4.05
315	M3516	-3.7	-4.08	-3.89
316	M2162	-3.5	-4.15	-3.825
317	M1300	-2.9	-4.5	-3.7
318	M3141	-4.2	-3.1	-3.65
319	M2669	-3.1	-4.14	-3.62
320	M0392	-3	-4.21	-3.605
321	M0118	-3.8	-3.38	-3.59
322	M0145	-3.2	-3.93	-3.565
323	M4113	-3.2	-3.93	-3.565
324	M2484	-3	-4.03	-3.515
325	M3843	-3	-4.03	-3.515
326	M0309	-2.7	-3.97	-3.335
327	M4310	-3.5	-2.77	-3.135
328	M2644	-3	-2.57	-2.785

Table S4. Binding energies of the final candidate compound, tricycloalternarene C (M1421), and the three control compounds.

gmx_MMGBSA												
	M1421			dUMP			dUPNPP			dUTP		
van der Waals	-35.23	±	2.48	-26.44	±	2.73	-35.53	±	4.62	-37.16	±	3.49
Electrostatic	-13.43	±	3.43	-13.38	±	4.04	-22.27	±	12.65	-35.08	±	4.8
Polar Solvation	20.4	±	2.12	19.04	±	3.04	29.11	±	10.2	39.75	±	3.03
Nonpolar Solvation	-4.99	±	0.28	-4.05	±	0.32	-4.6	±	0.5	-5.85	±	0.21
Total Enthalpy	**-33.25**	**±**	**2.74**	**-24.84**	**±**	**3.2**	**-33.3**	**±**	**5.17**	**-38.34**	**±**	**3.12**
Entropy	**5.2**	**±**	**0.05**	**11.23**	**±**	**0.05**	**27.32**	**±**	**0.05**	**8.92**	**±**	**0.31**
Binding Energy	**-28.05**	**±**	**2.74**	**-13.61**	**±**	**3.2**	**-5.98**	**±**	**5.17**	**-29.43**	**±**	**3.24**

gmx_MMPBSA												
	M1421			dUMP			dUPNPP			dUTP		
van der Waals	-35.23	±	2.48	-26.44	±	2.73	-35.53	±	4.62	-37.16	±	3.49
Electrostatic	-13.43	±	3.43	-13.38	±	4.04	-22.27	±	12.65	-35.08	±	4.8
Polar Solvation	23.59	±	2.37	19.27	±	3.53	29.44	±	9.83	35.13	±	3.44
Nonpolar Solvation	-3.83	±	0.14	-2.88	±	0.13	-3.35	±	0.29	-3.99	±	0.12
Total Enthalpy	**-28.9**	**±**	**3.11**	**-23.43**	**±**	**3.18**	**-31.71**	**±**	**4.64**	**-41.11**	**±**	**3.27**
Entropy	**5.2**	**±**	**0.05**	**11.23**	**±**	**0.05**	**27.32**	**±**	**0.05**	**8.92**	**±**	**0.31**
Binding Energy	**-23.7**	**±**	**3.11**	**-12.21**	**±**	**3.17**	**-4.4**	**±**	**4.63**	**-32.19**	**±**	**3.28**