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Supplementary material

Identification of potential tubulin polymerization inhibitors by 3D-QSAR, molecular docking and molecular dynamics

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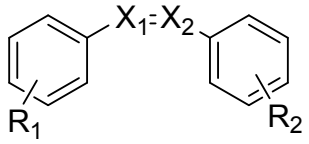
Table 1S Structures and inhibition activities of the CA-4 analogues in the training set and test set (* represents compounds in test set)



No.	R_1	X_1	X_2	R_2	IC_{50}(μM)	IC_{50}(μM) of CA-4	IC_{50}c[l] (μM)
1	3,4,5-OCH_3	CH	CH	3-OH,4- OCH_3	1.20	1.2[a]	1.00
2	3,4,5-OCH_3	CH	CH	4- OCH_3	1.30	1.2[a]	1.08
3	3,4,5-OCH_3	CH_2	CH_2	3-OH,4- OCH_3	2.10	1.2[a]	1.75
4*	3,4,5-OCH_3	CH_2	CH_2	4- OCH_3	3.20	1.2[a]	2.67
5	3,4,5-OCH_3	CH	CH	3-NO_2,4- OCH_3	2.60	1.2[b]	2.17
6	3,4,5-OCH_3	CH	CH	3-$O(CH_2)_3$OH,4-OCH_3	6.50	1.2[b]	5.42
7	3,4,5-OCH_3	CH	CH	3-$O(CH_2)_2$OH,4-OCH_3	2.80	1.2[b]	2.33
8	3,4,5-OCH_3	CH	CH	3-$O(CH_2)_2$O-imidazole,4-OCH_3	7.60	1.2[b]	6.33
9*	3-OCH_2O-4OCH_3	CH	CH	3-NH_2,4- OCH_3	3.10	2.1[c]	1.48
10	3,4,5-OCH_3	CH	CH	2,3-OH,4- OCH_3	1.90	1.2[d]	1.58
11	3,4,5-OCH_3	CH	CH	3,5- NO_2,4- OCH_3	7.40	1.2[d]	6.17
12	3,4,5-OCH_3	CH	CH	2-NH_2,4-OCH_3,5- NO_2	31.00	1.2[d]	25.83
13	3,4,5-OCH_3	CH	CH	2,3- NH_2,4- OCH_3	2.80	1.2[d]	2.33
14	3,4,5-OCH_3	CH	CH	3- NH_2,4- OCH_3	2.60	1.2[e]	2.17
15	3,4,5-OCH_3	CH	CH	2-NO_2,3-OH,4-OCH_3	1.50	1.2[e]	1.25
16	3,4,5-OCH_3	CH	CH	3-OH,4-OCH_3,5- NO_2	2.00	1.2[e]	1.67
17	3,4,5-OCH_3	CH	CH	2-NH_2,3-OH,4-OCH_3	2.50	1.2[e]	2.08
18*	3,4,5-F	CH	CH	3-OH,4-OCH_3	4.50	1.2[f]	3.75
19	3,4,5-OCH_3	CF	CF	3-OH,4-OCH_3	7.30	4.9[g]	1.49

20	3,4,5-OCH_3	CH	CF	3-OH,4-OCH_3	8.80	4.9[g]	1.80
21	3,4,5-OCH_3	CF	CF	3- NO_2,4-OCH_3	8.20	4.9[g]	1.67
22	3,4,5-OCH_3	CF	CH	3- NO_2,4-OCH_3	2.30	4.9[g]	0.47
23	3,4,5-OCH_3	CH	CF	3- NO_2,4-OCH_3	10.90	4.9[g]	2.22
24	3,4,5-OCH_3	CF	CH	3-NH_2,4-OCH_3	5.50	4.9[g]	1.12
25	3,4,5-OCH_3	CH	CF	3-NH_2,4-OCH_3	13.70	4.9[g]	2.80
26	3,4,5-OCH_3	CH	CH	3-N_3,4-OCH_3	1.40	1.2[h]	1.17
27	3,4,5-OCH_3	CH	CH	2-NH_2,4-OCH_3	1.40	1.2[e]	1.17
28*	3,4,5-OCH_3	CH	CH	2,3-OH,4-OCH_3	1.90	1.2[e]	1.58
29	3,4,5-OCH_3	CCHO	CH	4-OCH_3	4.00	4.0[h]	1.00
30	3,4,5-OCH_3	CCN	CH	4-OCH_3	6.00	4.0[i]	1.50
31	3,4,5-OCH_3	CCN	CH	3- NO_2,4-OCH_3	5.00	4.0[i]	1.25
32	3,4,5-OCH_3	CCN	CH	3-OH,4-OCH_3	5.00	4.0[i]	1.25
33*	-	CHCN	CH	3- NH_2,4-OCH_3	8.00	4.0[i]	2.00
34	3,4,5-OCH_3	CCN	CH	3- NH_2,4-CH_3	10.00	4.0[i]	2.50
35	3,4,5-OCH_3	CCN	CH	3- NH_2,4-Cl	6.00	4.0[i]	1.50
36	3,4,5-OCH_3	CCN	CH	3-NHAc,4-OCH_3	10.00	4.0[i]	2.50
***37**	4-OCH_3	CHCN	CH	3- NH_2,4-OCH_3	9.00	4.0[i]	2.25
38	3,4,5-OCH_3	CCON H_2	CH	3- NH_2,4-OCH_3	3.00	4.0[i]	0.75
39	3,4,5-OCH_3	CH	CH	3- NH_2,4- OCH_3	4.00	4.0[i]	1.00
40	3,4,5-OCH_3	CH	CH	3- NH_2,4- CH_3	4.00	4.0[i]	1.00
41*	3,4,5-OCH_3	CH	CH	3- NH_2,4- Cl	3.00	4.0[i]	0.75
42	3,4,5-OCH_3	CHCN	CH_2	3- NH_2,4-OCH_3	7.00	4.0[i]	1.75
43	3,4,5-OCH_3	CCN	CH	3- NH_2,4-OCH_3	10.00	4.0[i]	2.50
44	3,4,5-OCH_3	CH	CCN	3- NH_2,4-OCH_3	5.00	4.0[i]	1.25
45*	3,4-OCH_3	CHCN	CH	3- NH_2,4-OCH_3	7.00	4.0[i]	1.75
46	3,4,5-OCH_3	CH	CH	2-Cl,4-OCH_3	3.50	1.9[j]	1.84
47	3,4,5-OCH_3	CH	CH	4-Br	3.10	1.9[j]	1.63
48	3,4,5-OCH_3	CH	CH	4-NMe_2	3.40	1.9[j]	1.79
49	3,4,5-OCH_3	CH_2	CH_2	4-OCH_3	7.90	1.9[j]	4.16
50	3,4,5-OCH_3	CH_2	NH	4- OCH_3	23.00	1.9[j]	12.11
51*	3,5-OCH_3	CH_2	NH	4- OCH_3	29.00	1.9[j]	15.26
52	3,4,5-OCH_3	CH_2	NH	3-OH,4- OCH_3	100.00	3.9[k]	25.64
53	3,4,5-OCH_3	CH_2	NCH_3	3-OH,4- OCH_3	45.00	3.9[k]	11.54
54	3,4,5-OCH_3	CH_2	NEt	3-OH,4- OCH_3	15.00	3.9[k]	3.85
55*	3,4,5-OCH_3	CH_2	NAm	3-OH,4- OCH_3	20.00	3.9[k]	5.13
56	3,4,5-OCH_3	CH_2	NHex	3-OH,4- OCH_3	20.00	3.9[k]	5.13
57	3,4,5-OCH_3	CH_2	NBu-acid	3-OH,4- OCH_3	40.00	3.9[k]	10.26
58	3,4,5-OCH_3	CH_2	Npentanol	3-OH,4- OCH_3	20.00	3.9[k]	5.13
59	3,4,5-OCH_3	NH	CH_2	3-OH,4- OCH_3	100.00	3.9[k]	25.64
60	3,4,5-OCH_3	NCH_3	CH_2	3-OH,4- OCH_3	100.00	3.9[k]	25.64

[a]Ref. 38; [b]Ref. 39; [c]Ref. 40; [d]Ref. 41; [e]Ref. 42; [f]Ref. 12; [g]Ref.14; [h]Ref.13; [i]Ref.43; [j]Ref. 44; [k]Ref..45; $IC_{50}c$ [l] denotes the corrected IC_{50}.

Table 2S The experimental and predicted $pIC_{50}c$ values of all studied CA-4 analogues (* represents compounds in test set)

No.	$p(IC_{50})_c$	Predicted CoMFA	Residue CoMFA	Predicted CoMSIA	Residue CoMSIA
1(CA-4)	0.000	-0.189	-0.189	-0.181	-0.181
2	-0.033	-0.086	-0.053	-0.086	-0.053
3	-0.243	-0.295	-0.053	-0.221	0.022
4*	-0.427	-0.143	0.284	-0.087	0.340
5	-0.336	-0.286	0.050	-0.322	0.014
6	-0.734	-0.734	0.000	-0.711	0.023
7	-0.367	-0.362	0.005	-0.348	0.019
8	-0.801	-0.778	0.023	-0.782	0.019
9*	-0.170	-0.335	-0.165	-0.354	-0.184
10	-0.199	-0.248	-0.049	-0.178	0.021
11	-0.790	-0.803	-0.013	-0.795	-0.006
12	-1.412	-1.444	-0.032	-1.426	-0.014
13	-0.367	-0.339	0.028	-0.396	-0.029
14	-0.336	-0.341	-0.005	-0.278	0.059
15	-0.097	-0.134	-0.037	-0.098	-0.001
16	-0.223	-0.221	0.002	-0.176	0.047
17	-0.318	-0.317	0.001	-0.380	-0.062
18*	-0.574	-0.433	0.141	-0.502	0.072
19	-0.173	-0.182	-0.009	-0.260	-0.087
20	-0.255	-0.246	0.009	-0.234	0.021
21	-0.223	-0.181	0.042	-0.207	0.016
22	0.328	0.331	0.003	0.308	-0.020
23	-0.346	-0.305	0.041	-0.323	0.023
24	-0.049	-0.181	-0.132	-0.131	-0.082
25	-0.447	-0.377	0.070	-0.300	0.147
26	-0.068	-0.006	0.062	-0.099	-0.031
27	-0.068	-0.107	-0.039	-0.054	0.014
28*	-0.199	-0.075	0.124	-0.201	-0.002
29	0.000	0.036	0.036	0.005	0.005
30	-0.176	-0.275	-0.099	-0.217	-0.041
31	-0.097	-0.145	-0.048	-0.031	0.066
32	-0.097	-0.238	-0.141	-0.206	-0.109
33*	-0.301	-0.385	-0.084	-0.554	-0.253
34	-0.398	-0.289	0.109	-0.307	0.091
35	-0.176	-0.274	-0.098	-0.323	-0.148
36	-0.398	-0.300	0.099	-0.401	-0.003

37*	-0.352	-0.427	-0.075	-0.398	-0.046
38	0.125	0.136	0.011	0.118	-0.007
39	0.000	0.000	0.000	-0.044	-0.044
40	0.000	-0.064	-0.064	-0.026	-0.026
41*	0.125	-0.159	-0.284	-0.124	-0.249
42	-0.243	-0.195	0.048	-0.264	-0.021
43	-0.398	-0.222	0.176	-0.285	0.113
44	-0.097	-0.160	-0.063	-0.131	-0.034
45*	-0.243	-0.348	-0.105	-0.376	-0.133
46	-0.265	-0.166	0.099	-0.180	0.085
47	-0.212	-0.145	0.067	-0.139	0.073
48	-0.253	-0.152	0.101	-0.095	0.158
49	-0.619	-0.598	0.021	-0.607	0.012
50	-1.083	-1.149	-0.066	-1.105	-0.022
51*	-1.184	-0.983	0.201	-0.943	0.241
52	-1.409	-1.346	0.063	-1.293	0.116
53	-1.062	-1.113	-0.051	-1.105	-0.043
54	-0.585	-0.556	0.029	-0.616	-0.0313
55*	-0.710	-0.685	0.025	-0.705	0.005
56	-0.710	-0.686	0.024	-0.705	0.005
57	-1.011	-0.980	0.031	-1.052	-0.041
58	-0.710	-0.733	-0.023	-0.717	-0.007
59	-1.409	-1.407	0.002	-1.447	-0.038
60	-1.409	-1.399	0.010	-1.400	0.009

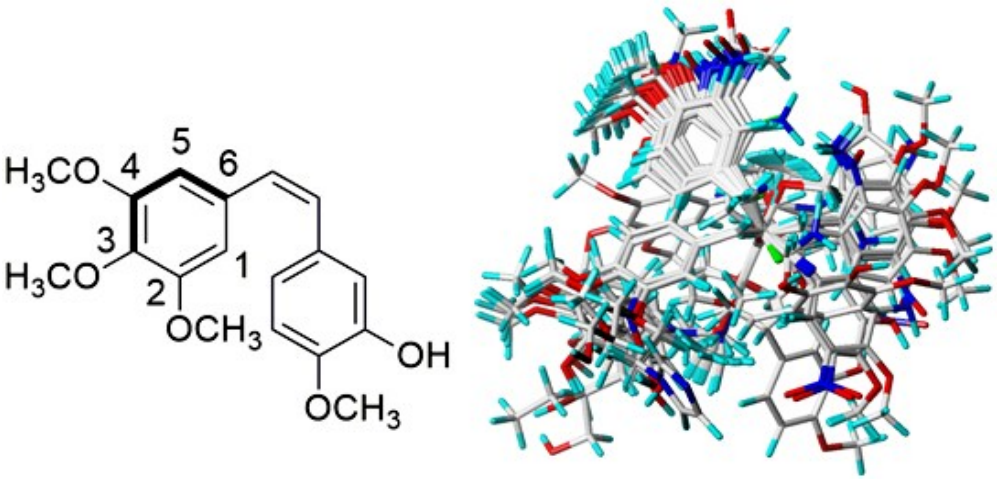


Fig. 1S Alignment of the training set and CA-4 used as a template for alignment, with the common substructure (atoms numbered from 3 to 6) shown in bold.

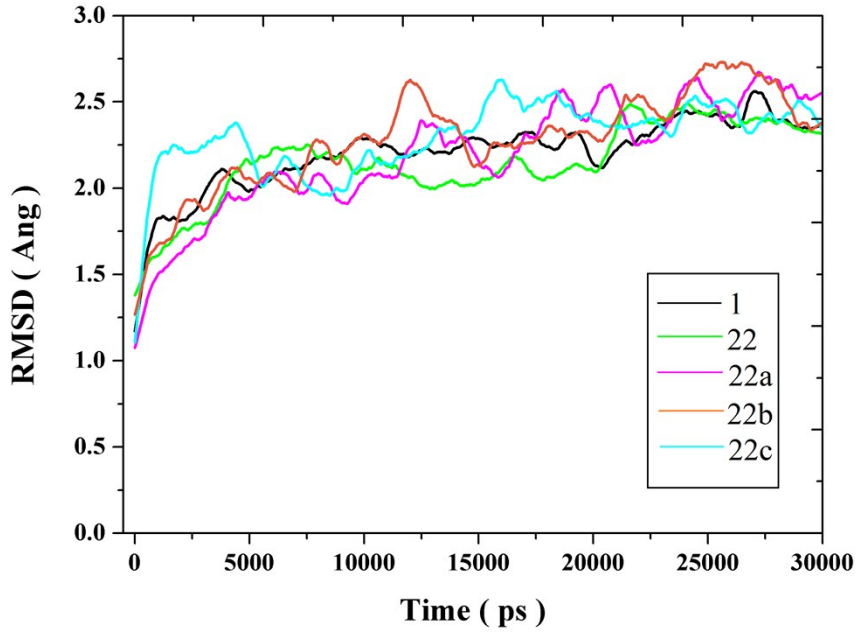


Fig. 2S Average root-mean-square displacement (RMSD) of the backbone (C, C_α, N, O) atoms of the ligands-3UT5 complexes (**1**, **22**, **22a- 22c**) versus time.

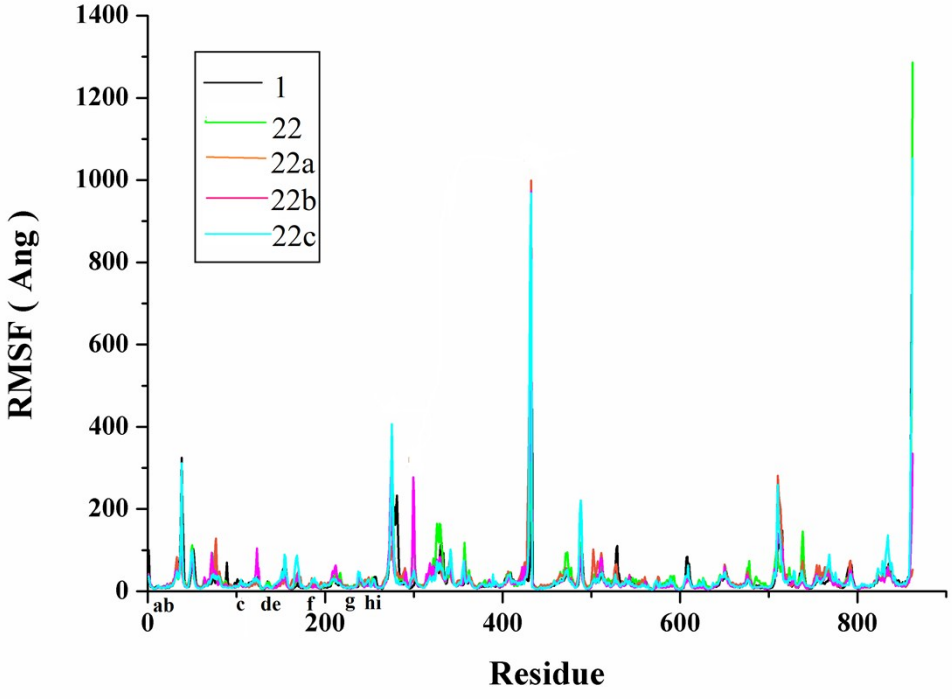


Fig. 3S Average root-mean-square fluctuation (RMSF) of the backbone (C, C_α, N, O) atoms of the ligands-3UT5 complexes (**1**, **22**, **22a- 22c**) versus residue numbers. The residues **a**, **b**, **c, d, e. f, g, h** and **i** are Gln11, Ala12, Asn101, Gly144, Thr145, Val177, Tyr224, Gys241 and Lys254, respectively.

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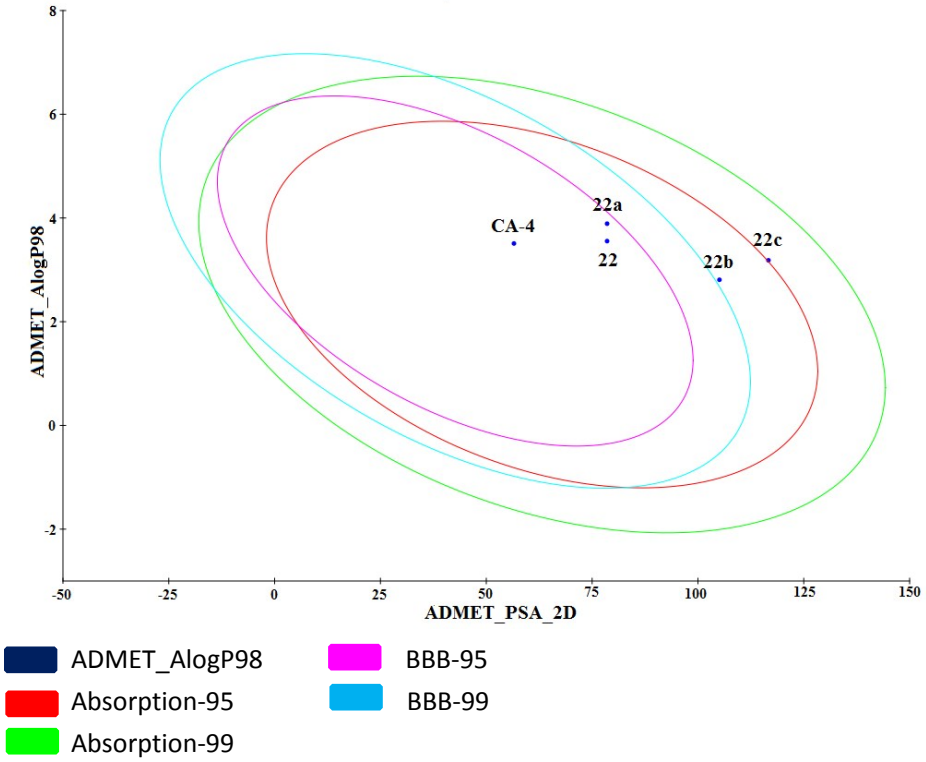

ADMET_AlogP98
Absorption-95
Absorption-99
BBB-95
BBB-99

Fig. 4S ADMET_AlogP98 versus ADMET_PSA_2D.