Electronic Supplementary Material (ESI) for Molecular BioSystems

Molecular Dynamics and Tubulin Polymerization Kinetics Study on 1,14-Heterofused Taxanes: Evidences of Stabilization of the Tubulin Head-to-Tail Dimer-Dimer Interaction

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Supporting Informations

Table S1. MM-GB/PBSA Complex Absolute Energies and β-Tubulin/Ligand Binding Energies (kcal/mol) for the Obtained Poses. The pseudo-T-taxol conformation is referred as "csearch"

		GBSA				PBSA			
	pose_protocol	$E_{complex}$	St.Dev.	$\Delta E_{bind.}$	St.Dev.	$E_{complex}$	St.Dev.	$\Delta E_{bind.}$	St.Dev.
Paclitaxel (1)	1_1	-8016.9	57.2	-50.6	5.3	-7732.7	60.1	-31.9	5.5
	2_1	-8014.1	50.1	-45.0	4.4	-7720.2	52.0	-27.8	5.0
	3_1	-8001.4	51.6	-34.6	4.2	-7696.9	52.5	-28.3	4.6
	4_1	-7951.5	55.0	-46.1	4.5	-7652.5	54.7	-31.0	4.9
	5_1	-7954.5	61.3	-43.7	3.5	-7661.9	64.7	-27.2	4.1
	1_2	-8004.9	63.6	-54.0	5.9	-7709.4	63.9	-39.1	7.0
	2_2	-8027.5	55.9	-50.0	3.7	-7718.3	54.8	-31.8	4.2
	3_2	-7975.7	56.4	-48.0	3.4	-7671.2	61.9	-32.3	3.9
	4_2	-7998.0	68.9	-43.0	4.2	-7694.4	70.1	-32.5	5.2
	5_2	-8011.4	64.8	-40.0	4.4	-7712.3	67.4	-25.3	5.5
	t-taxol	-8038.5	62.2	-61.7	4.9	-7717.9	60.3	-39.7	5.6
IDN5109 (2)	1_1	-8069.7	55.0	-57.4	3.7	-7777.7	60.3	-40.1	5.0
	2_1	-8131.8	63.1	-35.1	3.5	-7844.3	67.2	-23.1	3.7
	3_1	-8051.7	59.0	-32.6	3.3	-7764.9	59.8	-25.5	4.0
	4_1	-8035.5	58.8	-44.1	3.4	-7727.8	59.1	-37.1	3.9
	5_1	-8087.9	54.9	-35.9	2.8	-7776.2	57.6	-24.7	4.0
	1_2	-8071.8	50.6	-28.5	2.9	-7778.3	57.1	-24.0	3.7
	2_2	-8136.5	55.7	-34.7	3.2	-7835.5	53.5	-26.4	3.6
	3_2	-8124.0	52.2	-40.7	5.3	-7818.2	55.2	-33.0	4.2
	4_2	-8077.5	65.5	-21.4	4.4	-7789.9	66.3	-22.3	3.9
	5_2	-8107.1	59.8	-38.9	2.7	-7823.7	66.2	-25.2	4.3
	pseudo-T-taxol	-8128.1	51.5	-49.2	5.4	-7832.7	56.2	-36.0	5.4
IDN5839 (3)	1_1	-8108.9	70.5	-36.5	3.8	-7824.6	71.3	-28.6	5.2
	2_1	-8064.2	52.9	-39.5	3.9	-7759.9	59.1	-31.7	4.5
	3_1	-8054.2	57.0	-43.9	6.5	-7757.2	59.5	-33.1	8.0
	4_1	-8043.5	53.7	-34.6	3.6	-7731.3	56.7	-22.2	5.4
	5_1	-8085.8	66.2	-43.8	3.0	-7795.0	69.6	-32.8	4.3
	1_2	-8118.0	57.3	-31.9	5.5	-7807.0	60.5	-21.3	4.4
	2_2	-8160.9	59.8	-27.8	5.0	-7886.2	64.4	-35.1	4.1
	3_2	-8106.7	63.7	-28.3	4.6	-7832.2	66.9	-26.2	3.7
	4_2	-8115.0	57.7	-31.0	4.9	-7818.2	61.9	-25.9	6.5
	5_2	-8137.1	54.9	-27.2	4.1	-7835.8	53.9	-29.8	3.9
	pseudo-T-taxol	-8178.0	49.9	-48.0	4.3	-7891.3	49.0	-36.6	5.4
IDN5798 (4)	1_1	-8029.7	48.1	-29.4	3.5	-7728.0	50.2	-25.8	3.9
	2_1	-8065.1	46.5	-43.9	3.0	-7754.9	49.9	-29.2	4.1
	3_1	-8014.7	56.7	-31.8	3.6	-7728.5	65.4	-28.5	3.2
	4_1	-8065.3	55.1	-29.0	3.2	-7779.1	57.7	-27.0	3.7
	5_1	-8020.8	63.3	-43.8	4.1	-7702.3	63.7	-34.5	4.2
	1_2	-8020.9	59.3	-35.8	4.2	-7741.9	62.4	-28.1	4.8
	2_2	-8060.1	53.2	-38.2	4.0	-7762.8	52.8	-33.0	4.1
	3_2	-8052.9	48.5	-33.9	3.6	-7729.5	49.8	-28.7	4.9
	4_2	-8054.4	57.8	-26.5	3.6	-7767.2	59.3	-24.1	3.8
	5_2	-8078.1	53.2	-31.7	7.2	-7797.0	48.9	-27.3	6.8
	pseudo-T-taxol	-8076.9	44.1	-44.3	3.2	-7761.2	47.8	-29.2	4.1

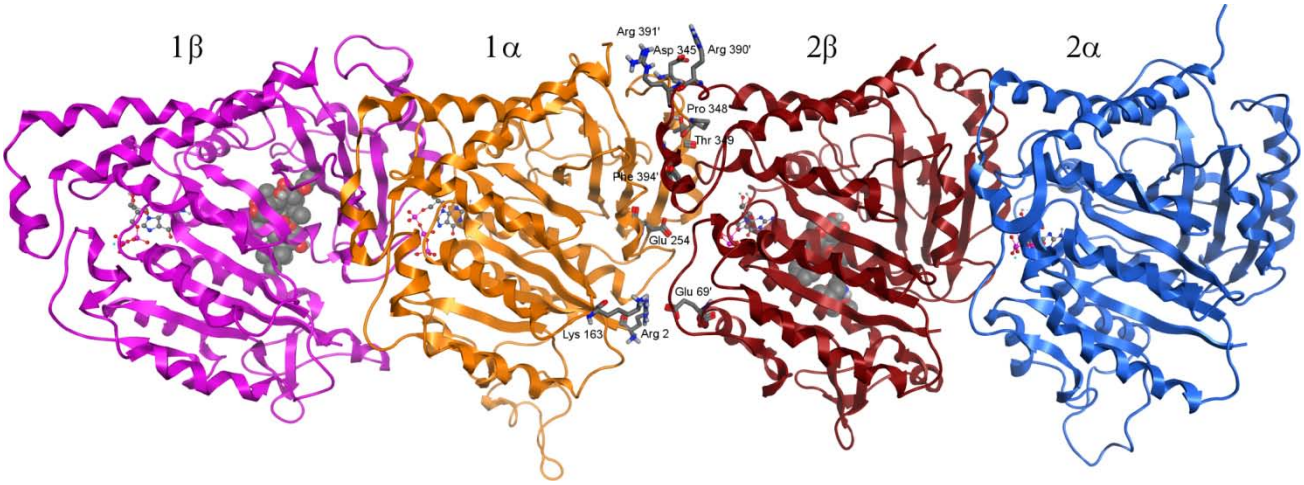

Figure 6. Structure of the simulated 1β,1α-2β,2α tubulin tetramer. Selected interfacial residues are evidenced accordingly to MM-PBSA per residue energy decomposition.

Table S2. MM-PBSA Per Residue Free Energy Decomposition Results. Contribution Higher Than 0.5 kcal/mol Are Reported.

Chain	Residue		Unbounded	Paclitaxel (1)	IDN5109 (2)	IDN5839 (3)	IDN5798 (4)
α1	ARG	2	-1.0	-1.4	-1.0	-4.7	-6.5
α1	ARG	123	-0.3	-0.5	-0.6	-0.5	-0.4
α1	ASP	127	0.3	0.5	0.5	0.4	0.4
α1	GLU	155	0.4	0.5	0.6	0.5	0.4
α1	ARG	156	-0.3	-0.5	-0.6	-0.4	-0.4
α1	ASP	160	0.3	0.6	0.6	0.5	0.5
α1	LYS	163	-0.8	-1.1	-1.0	-1.4	-5.0
α1	LYS	164	-0.5	-0.8	-0.8	-0.8	-0.6
α1	LYS	166	-0.4	-0.7	-0.8	-0.6	-0.6
α1	GLU	168	0.3	0.5	0.5	0.4	0.3
α1	HIP	192	-0.3	-0.5	-0.6	-0.4	-0.4
α1	GLU	196	0.4	0.5	0.7	0.5	0.4
α1	HIP	197	-0.4	-0.6	-0.7	-0.5	-0.5
α1	ASP	199	0.4	0.7	0.9	0.5	0.5
α1	ARG	243	-0.3	-0.6	-0.4	-0.4	-0.3
α1	GLU	254	2.2	0.1	2.9	2.0	0.2
α1	THR	257	0.3	0.1	0.1	-1.0	0.2
α1	ASN	258	-0.4	1.3	0.9	0.2	0.3
α1	PRO	261	-1.1	-2.3	-2.6	-1.4	-2.8
α1	TYR	262	-0.1	-0.9	-1.1	-0.1	-1.0
α1	PRO	263	-0.8	-1.4	-1.4	-1.8	-0.8
α1	ARG	264	-0.4	-0.6	-0.8	-0.6	-0.5
α1	LYS	326	0.5	-0.3	-0.1	-0.1	0.6
α1	LYS	336	1.6	-0.3	-0.1	2.4	-0.2
α1	ASP	345	0.7	-0.3	-0.9	0.4	-1.3
α1	TRP	346	-1.9	-1.4	-1.2	-2.3	-1.5
α1	CYS	347	-1.3	-0.4	-1.1	-0.6	-2.0
α1	PRO	348	-1.7	-4.0	-2.8	-2.9	-2.7
α1	THR	349	-0.8	-1.5	1.2	-0.7	-2.4
α1	GLY	350	-0.2	-0.4	-0.2	-0.5	-0.5
α1	LYS	352	-1.0	0.6	2.0	-0.3	0.5
α1	GLU	417	0.3	0.5	0.5	0.4	0.3
α1	GLU	420	0.3	0.4	0.5	0.4	0.3
α1	ASP	424	0.3	0.4	0.6	0.4	0.3
α1	VAL	435	0.0	-0.3	-1.4	-0.4	-0.5

Chain	Residue		Unbounded	Paclitaxel (1)	IDN5109 (2)	IDN5839 (3)	IDN5798 (4)
β2	GLU	69	0.1	0.4	0.1	0.0	-2.2
β2	SER	95	-0.1	-0.2	-0.1	-0.1	-0.5
β2	GLY	96	-0.1	-0.1	-0.1	-0.1	-0.5
β2	LYS	103	-0.8	-0.3	-0.5	-0.3	-0.2
β2	GLU	108	0.4	0.1	0.6	0.9	0.0
β2	LYS	174	0.3	-0.4	-0.1	-0.9	-0.3
β2	VAL	175	-1.1	-0.3	0.0	-1.2	-0.5
β2	SER	176	0.5	0.5	-0.1	-0.4	-0.1
β2	ASP	177	0.8	-0.2	0.1	0.0	0.6
β2	THR	178	-0.1	0.3	-0.1	0.0	0.8
β2	VAL	179	-0.5	-2.5	-1.3	-1.4	-2.5
β2	VAL	180	-0.1	-0.4	-0.1	-0.2	-0.6
β2	PRO	182	-0.2	-0.5	0.0	-0.3	-0.3
β2	ARG	380	-0.2	-0.4	-0.2	-0.5	-0.6
β2	GLU	383	0.2	0.7	0.2	0.6	0.5
β2	GLN	384	0.1	-0.1	-0.1	0.7	0.4
β2	ALA	387	0.7	-0.2	0.5	-1.1	-0.3
β2	MET	388	-0.9	-0.8	-1.0	-2.0	-1.6
β2	ARG	390	-4.7	-1.1	-2.3	-1.1	-1.1
β2	ARG	391	-6.3	-3.5	-4.7	-5.3	-6.4
β2	LYS	392	-1.1	-1.3	-1.7	-1.5	-1.8
β2	ALA	393	-1.4	0.1	-0.6	-1.1	-1.5
β2	PHE	394	-2.0	-3.4	-4.4	-2.9	-5.3
β2	LEU	395	-0.2	-0.3	-0.6	-0.3	-0.4
β2	HIE	396	-1.3	-1.8	-1.3	-1.6	-2.0
β2	TRP	397	-1.6	-2.6	-2.5	-1.7	-3.4
β2	GLU	401	0.6	0.4	0.7	0.4	0.3
β2	ASP	404	0.6	0.5	0.6	0.6	0.6
β2	GLU	405	0.6	0.7	0.9	0.8	0.7
β2	ASP	427	0.6	0.5	0.3	0.7	0.5

Cartesian coordinates (pdb) for the lowest energy conformations obtained from the conformational analysis of compounds **1**-**4**

Paclitaxel (1)

ATOM 1 0C11 PTX 869 47.473 29.811 57.568
ATOM 2 2C11 PTX 869 46.795 29.476 56.394
ATOM 3 8C10 PTX 869 47.254 29.077 58.734
ATOM 4 6C10 PTX 869 46.362 28.004 58.727
ATOM 5 4C10 PTX 869 45.681 27.666 57.555
ATOM 6 3C10 PTX 869 45.887 28.408 56.385
ATOM 7 1C10 PTX 869 45.190 28.077 55.111
ATOM 8 2O10 PTX 869 45.732 28.296 54.029
ATOM 9 N99 PTX 869 43.924 27.549 55.220
ATOM 10 C86 PTX 869 43.129 27.133 54.061
ATOM 11 C88 PTX 869 42.337 25.885 54.446
ATOM 12 C89 PTX 869 41.052 25.937 55.006
ATOM 13 C91 PTX 869 40.376 24.764 55.353
ATOM 14 C93 PTX 869 40.978 23.523 55.158
ATOM 15 C95 PTX 869 42.261 23.452 54.624
ATOM 16 C97 PTX 869 42.938 24.622 54.278
ATOM 17 C82 PTX 869 42.270 28.300 53.485
ATOM 18 O84 PTX 869 41.657 29.078 54.539
ATOM 19 C80 PTX 869 43.142 29.189 52.592
ATOM 20 O81 PTX 869 43.507 30.324 52.892
ATOM 21 O79 PTX 869 43.440 28.551 51.419
ATOM 22 C77 PTX 869 44.455 29.156 50.585
ATOM 23 C72 PTX 869 43.857 29.779 49.335
ATOM 24 C73 PTX 869 42.434 30.268 49.473
ATOM 25 C13 PTX 869 45.448 28.024 50.259
ATOM 26 C10 PTX 869 46.175 28.087 48.875
ATOM 27 O11 PTX 869 47.568 27.795 49.189
ATOM 28 C5 PTX 869 46.110 29.528 48.253
ATOM 29 C1 PTX 869 46.832 30.607 49.125
ATOM 30 C6 PTX 869 46.944 29.599 46.941
ATOM 31 C71 PTX 869 44.598 29.871 48.191
ATOM 32 C62 PTX 869 43.957 30.197 46.857
ATOM 33 O64 PTX 869 44.408 31.516 46.521
ATOM 34 C65 PTX 869 43.632 32.217 45.652
ATOM 35 O66 PTX 869 42.585 31.820 45.151
ATOM 36 C67 PTX 869 44.245 33.559 45.394
ATOM 37 C60 PTX 869 44.314 29.155 45.764
ATOM 38 O61 PTX 869 44.877 29.548 44.723
ATOM 39 C55 PTX 869 43.901 27.640 45.922
ATOM 40 C51 PTX 869 42.361 27.605 45.632
ATOM 41 C48 PTX 869 41.819 26.195 45.413
ATOM 42 C46 PTX 869 42.231 25.243 46.519
ATOM 43 C34 PTX 869 43.404 25.593 47.504
ATOM 44 O35 PTX 869 43.089 25.366 48.916
ATOM 45 C36 PTX 869 41.975 25.967 49.421
ATOM 46 O37 PTX 869 41.265 26.763 48.818
ATOM 47 C38 PTX 869 41.732 25.483 50.813
ATOM 48 C42 PTX 869 44.066 24.336 46.869
ATOM 49 O45 PTX 869 42.967 24.120 45.962
ATOM 50 O53 PTX 869 42.053 28.367 44.454
ATOM 51 C56 PTX 869 44.680 26.893 44.798
ATOM 52 C32 PTX 869 44.147 26.979 47.360
ATOM 53 C16 PTX 869 45.647 26.912 47.891
ATOM 54 O18 PTX 869 45.818 25.675 48.656
ATOM 55 C19 PTX 869 46.974 24.975 48.542
ATOM 56 O20 PTX 869 47.892 25.233 47.776
ATOM 57 C21 PTX 869 46.959 23.818 49.480
ATOM 58 C22 PTX 869 45.967 23.665 50.460
ATOM 59 C24 PTX 869 45.992 22.564 51.319
ATOM 60 C26 PTX 869 47.006 21.614 51.208
ATOM 61 C28 PTX 869 47.998 21.762 50.239
ATOM 62 C30 PTX 869 47.977 22.861 49.378
ATOM 63 0H10 PTX 869 43.497 27.438 56.136
ATOM 64 H85 PTX 869 42.405 29.369 55.108
ATOM 65 2H1 PTX 869 48.030 27.588 48.345
ATOM 66 H54 PTX 869 41.074 28.347 44.350

IDN5109 (2)

ATOM 1 C43 CP2 869 42.436 30.260 49.470
ATOM 2 C42 CP2 869 43.857 29.769 49.325
ATOM 3 C41 CP2 869 44.450 29.144 50.583
ATOM 4 O40 CP2 869 43.409 28.557 51.407
ATOM 5 C38 CP2 869 43.532 28.763 52.756
ATOM 6 C34 CP2 869 42.366 28.136 53.531
ATOM 7 C19 CP2 869 42.627 26.634 53.831
ATOM 8 N17 CP2 869 43.740 26.450 54.766
ATOM 9 C15 CP2 869 45.019 26.184 54.385
ATOM 10 O14 CP2 869 45.787 26.038 55.486
ATOM 11 C5 CP2 869 47.207 25.752 55.388
ATOM 12 C1 CP2 869 47.955 26.914 54.727
ATOM 13 C6 CP2 869 47.680 25.624 56.843
ATOM 14 C10 CP2 869 47.464 24.423 54.670
ATOM 15 O16 CP2 869 45.392 26.098 53.223
ATOM 16 C21 CP2 869 41.356 25.965 54.402
ATOM 17 C24 CP2 869 41.499 24.471 54.776
ATOM 18 C26 CP2 869 40.192 23.971 55.398
ATOM 19 C30 CP2 869 41.867 23.591 53.583
ATOM 20 O35 CP2 869 42.122 28.853 54.759
ATOM 21 O39 CP2 869 44.443 29.391 53.294
ATOM 22 C48 CP2 869 45.479 28.034 50.267
ATOM 23 O50 CP2 869 46.580 28.158 51.178
ATOM 24 C51 CP2 869 47.719 27.837 50.519
ATOM 25 O53 CP2 869 48.808 27.683 51.053
ATOM 26 O52 CP2 869 47.504 27.737 49.182
ATOM 27 C54 CP2 869 46.135 28.086 48.878
ATOM 28 C55 CP2 869 46.115 29.528 48.258
ATOM 29 C56 CP2 869 46.823 30.632 49.112
ATOM 30 C60 CP2 869 46.981 29.563 46.964
ATOM 31 C64 CP2 869 44.607 29.884 48.187
ATOM 32 C65 CP2 869 43.988 30.258 46.854
ATOM 33 O66 CP2 869 44.454 31.584 46.570
ATOM 34 C67 CP2 869 43.697 32.319 45.713
ATOM 35 O68 CP2 869 42.656 31.946 45.182
ATOM 36 C69 CP2 869 44.322 33.666 45.512
ATOM 37 C74 CP2 869 44.368 29.254 45.733
ATOM 38 O75 CP2 869 44.953 29.680 44.716
ATOM 39 C76 CP2 869 43.956 27.734 45.834
ATOM 40 C98 CP2 869 44.808 27.004 44.753
ATOM 41 C77 CP2 869 42.439 27.710 45.434
ATOM 42 O95 CP2 869 42.215 28.494 44.250
ATOM 43 C78 CP2 869 41.914 26.307 45.146
ATOM 44 C79 CP2 869 42.229 25.342 46.271
ATOM 45 O82 CP2 869 42.994 24.215 45.766
ATOM 46 C81 CP2 869 44.013 24.405 46.766
ATOM 47 C80 CP2 869 43.326 25.674 47.350
ATOM 48 O85 CP2 869 42.877 25.461 48.728
ATOM 49 C86 CP2 869 41.732 26.091 49.117
ATOM 50 O87 CP2 869 41.121 26.918 48.450
ATOM 51 C88 CP2 869 41.290 25.592 50.453
ATOM 52 C102 CP2 869 44.111 27.043 47.276
ATOM 53 C104 CP2 869 45.584 26.927 47.895
ATOM 54 O106 CP2 869 45.662 25.693 48.685
ATOM 55 C107 CP2 869 46.771 24.912 48.598
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ATOM 58 C110 CP2 869 45.621 23.677 50.487
ATOM 59 C112 CP2 869 45.599 22.631 51.412
ATOM 60 C114 CP2 869 46.648 21.712 51.456
ATOM 61 C116 CP2 869 47.720 21.836 50.573
ATOM 62 C118 CP2 869 47.745 22.880 49.645
ATOM 63 H18 CP2 869 43.579 26.514 55.768
ATOM 64 H36 CP2 869 42.954 28.763 55.279
ATOM 65 H96 CP2 869 41.245 28.479 44.076

IDN5839 (3)

ATOM 1 O51 CP3 869 48.552 26.687 50.926
ATOM 2 C49 CP3 869 47.573 27.229 50.440
ATOM 3 C118 CP3 869 46.366 27.618 51.159
ATOM 4 O50 CP3 869 47.461 27.619 49.140
ATOM 5 C52 CP3 869 46.103 28.054 48.865
ATOM 6 C53 CP3 869 46.128 29.495 48.254
ATOM 7 C54 CP3 869 46.869 30.552 49.141
ATOM 8 C58 CP3 869 46.991 29.510 46.963
ATOM 9 C48 CP3 869 45.530 28.142 50.257
ATOM 10 C41 CP3 869 44.396 29.074 50.588
ATOM 11 O40 CP3 869 43.369 28.318 51.252
ATOM 12 C38 CP3 869 42.881 28.879 52.404
ATOM 13 C34 CP3 869 41.768 28.024 53.026
ATOM 14 C19 CP3 869 42.356 26.885 53.902
ATOM 15 N17 CP3 869 42.934 27.408 55.145
ATOM 16 C15 CP3 869 44.247 27.713 55.315
ATOM 17 O14 CP3 869 44.433 28.174 56.571
ATOM 18 C5 CP3 869 45.743 28.594 57.037
ATOM 19 C1 CP3 869 46.734 27.424 57.033
ATOM 20 C6 CP3 869 46.262 29.788 56.230
ATOM 21 C10 CP3 869 45.516 29.041 58.489
ATOM 22 O16 CP3 869 45.105 27.591 54.452
ATOM 23 C21 CP3 869 41.262 25.852 54.256
ATOM 24 C24 CP3 869 41.760 24.616 55.036
ATOM 25 C26 CP3 869 40.569 23.731 55.412
ATOM 26 C30 CP3 869 42.779 23.794 54.243
ATOM 27 O35 CP3 869 40.856 28.829 53.801
ATOM 28 O39 CP3 869 43.245 29.954 52.881
ATOM 29 C42 CP3 869 43.861 29.775 49.333
ATOM 30 C43 CP3 869 42.450 30.304 49.462
ATOM 31 C62 CP3 869 44.625 29.905 48.201
ATOM 32 C63 CP3 869 44.023 30.331 46.880
ATOM 33 O64 CP3 869 44.565 31.629 46.607
ATOM 34 C65 CP3 869 43.856 32.409 45.749
ATOM 35 O66 CP3 869 42.798 32.099 45.210
ATOM 36 C67 CP3 869 44.558 33.720 45.557
ATOM 37 C72 CP3 869 44.345 29.307 45.766
ATOM 38 O73 CP3 869 44.951 29.702 44.750
ATOM 39 C74 CP3 869 43.851 27.811 45.870
ATOM 40 C96 CP3 869 44.629 27.066 44.742
ATOM 41 C75 CP3 869 42.320 27.867 45.529
ATOM 42 O93 CP3 869 42.090 28.700 44.380
ATOM 43 C76 CP3 869 41.714 26.500 45.222
ATOM 44 C77 CP3 869 42.059 25.466 46.276
ATOM 45 O80 CP3 869 42.776 24.357 45.670
ATOM 46 C79 CP3 869 43.850 24.472 46.624
ATOM 47 C78 CP3 869 43.210 25.708 47.321
ATOM 48 O83 CP3 869 42.840 25.384 48.700
ATOM 49 C84 CP3 869 41.704 25.944 49.200
ATOM 50 O85 CP3 869 41.068 26.849 48.672
ATOM 51 C86 CP3 869 41.330 25.253 50.471
ATOM 52 C100 CP3 869 44.001 27.078 47.297
ATOM 53 C102 CP3 869 45.470 26.916 47.904
ATOM 54 O104 CP3 869 45.516 25.678 48.694
ATOM 55 C105 CP3 869 46.532 24.799 48.499
ATOM 56 O106 CP3 869 47.420 24.907 47.665
ATOM 57 C107 CP3 869 46.406 23.655 49.444
ATOM 58 C108 CP3 869 47.269 22.563 49.288

ATOM 59 C110 CP3 869 47.182 21.469 50.154
ATOM 60 C112 CP3 869 46.236 21.462 51.178
ATOM 61 C114 CP3 869 45.376 22.547 51.340
ATOM 62 C116 CP3 869 45.460 23.644 50.479
ATOM 63 H18 CP3 869 42.338 27.564 55.953
ATOM 64 H36 CP3 869 41.404 29.213 54.522
ATOM 65 H94 CP3 869 41.114 28.737 44.246

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ATOM 1 O52 CP4 869 48.795 27.613 51.148
ATOM 2 C50 CP4 869 47.721 27.765 50.587
ATOM 3 N119 CP4 869 46.513 27.876 51.190
ATOM 4 O51 CP4 869 47.573 27.834 49.235
ATOM 5 C53 CP4 869 46.175 28.098 48.883
ATOM 6 C54 CP4 869 46.111 29.534 48.253
ATOM 7 C55 CP4 869 46.962 29.591 46.949
ATOM 8 C59 CP4 869 46.812 30.647 49.103
ATOM 9 C48 CP4 869 45.437 28.007 50.249
ATOM 10 C41 CP4 869 44.466 29.167 50.594
ATOM 11 O40 CP4 869 43.440 28.587 51.441
ATOM 12 C38 CP4 869 43.158 29.235 52.611
ATOM 13 C34 CP4 869 42.218 28.392 53.484
ATOM 14 C19 CP4 869 42.985 27.200 54.118
ATOM 15 N17 CP4 869 43.900 27.648 55.174
ATOM 16 C15 CP4 869 45.210 27.950 54.972
ATOM 17 O14 CP4 869 45.766 28.329 56.142
ATOM 18 C5 CP4 869 47.163 28.720 56.220
ATOM 19 C1 CP4 869 47.437 29.966 55.371
ATOM 20 C6 CP4 869 47.387 29.071 57.698
ATOM 21 C10 CP4 869 48.088 27.556 55.845
ATOM 22 O16 CP4 869 45.775 27.890 53.888
ATOM 23 C21 CP4 869 42.001 26.160 54.695
ATOM 24 C24 CP4 869 42.660 24.893 55.285
ATOM 25 C26 CP4 869 41.584 23.993 55.902
ATOM 26 C30 CP4 869 43.455 24.100 54.246
ATOM 27 O35 CP4 869 41.578 29.179 54.508
ATOM 28 O39 CP4 869 43.584 30.343 52.928
ATOM 29 C42 CP4 869 43.858 29.778 49.333
ATOM 30 C43 CP4 869 42.431 30.255 49.466
ATOM 31 C63 CP4 869 44.596 29.861 48.185
ATOM 32 C64 CP4 869 43.957 30.168 46.843
ATOM 33 O65 CP4 869 44.393 31.491 46.505
ATOM 34 C66 CP4 869 43.610 32.182 45.634
ATOM 35 O67 CP4 869 42.567 31.772 45.135
ATOM 36 C68 CP4 869 44.208 33.530 45.372
ATOM 37 C73 CP4 869 44.336 29.129 45.752
ATOM 38 O74 CP4 869 44.897 29.530 44.713
ATOM 39 C75 CP4 869 43.954 27.605 45.911
ATOM 40 C97 CP4 869 44.752 26.868 44.793
ATOM 41 C76 CP4 869 42.417 27.538 45.615
ATOM 42 O94 CP4 869 42.099 28.288 44.431
ATOM 43 C77 CP4 869 41.903 26.117 45.402
ATOM 44 C78 CP4 869 42.320 25.183 46.522
ATOM 45 O81 CP4 869 43.065 24.058 45.980
ATOM 46 C80 CP4 869 44.168 24.303 46.875
ATOM 47 C79 CP4 869 43.489 25.554 47.505
ATOM 48 O84 CP4 869 43.179 25.331 48.919
ATOM 49 C85 CP4 869 42.056 25.919 49.422
ATOM 50 O86 CP4 869 41.338 26.705 48.816
ATOM 51 C87 CP4 869 41.817 25.441 50.817
ATOM 52 C101 CP4 869 44.208 26.950 47.352
ATOM 53 C103 CP4 869 45.711 26.918 47.894
ATOM 54 O105 CP4 869 45.910 25.680 48.651
ATOM 55 C106 CP4 869 47.063 24.981 48.497
ATOM 56 O107 CP4 869 47.950 25.231 47.694
ATOM 57 C108 CP4 869 47.089 23.839 49.452
ATOM 58 C109 CP4 869 48.109 22.887 49.329
ATOM 59 C111 CP4 869 48.171 21.803 50.209
ATOM 60 C113 CP4 869 47.217 21.667 51.217
ATOM 61 C115 CP4 869 46.200 22.612 51.349
ATOM 62 C117 CP4 869 46.135 23.698 50.471
ATOM 63 H120 CP4 869 46.403 27.842 52.206
ATOM 64 H18 CP4 869 43.563 27.752 56.127
ATOM 65 H36 CP4 869 42.311 29.507 55.076
ATOM 66 H95 CP4 869 41.122 28.247 44.320

In vitro growth inhibition assay for compounds 2-4 according to reference 19. The inhibitory effects of compounds **2-4** on cell growth were assessed by use of sulforhodamine B (SRB) (Sigma Chemical Co.), a dye-based assay, which indirectly determines cell number by measuring membrane associate proteins. Briefly, $1x10^5$ exponentially proliferating cells were seeded on 96-well microtiter plates in complete growth medium and incubated at 37 °C for 15-18 h to allow the cells to attach to the substrate before drugs were added. For each drug tested, five 96-well microtiter plate were screened in parallel. The cell line was exposed to 10-12 different concentration of each drug, covering a 5- to 6-log range of concentrations, at 37 °C, 5% CO_2. MCF7 were expose to drug for 72 h. Cell were fixed in situ for 1 h at 4 °C with ice-cold 50% trichloroacetic acid. The plates were then washed six times with water, and 150 µL of 0.4% SRB were added to each well. After a 5 min. incubation at room temperature, the plates were rinsed with 0.1% acetic acid and air-dried. Bound SRB was solubilized by adding a 100 µL 10 mM Tris base (pH 10.5) per well and was allowed to stand at room temperature for 5 min. The optical density (OD) of each well was measured at 570 nm. Under this condition, cell number is proportional to OD. We determined the concentration of each compound that inhibit of 50% of cell growth (IC_{50}) using empirically determined concentrations of drug between 10 pM to 30 nM. The four-parameters Hill model was used as a structural model for the concentration-effect curve of each single agent. This model was used to determine the IC_{50} reported in Table S3.

Table S3. In vitro Growth Inhibitory Activity (IC_{50})[a] of **2-4** on MCF7 Human Cancer Cell Line, Accordingly to Reference 19.

Compound	IC_{50} (nM) ± S.E. MCF7
2	1.6 ± 0.10
3	0.4 ± 0.10
4	1.0 ± 0.04

[a] Concentration required for 50% reduction of cell growth compared with untreated controls after 72 h of exposure to the drug. Mean ± Standard Error (S.E.) values are reported from at least three experiments.

Full details for reference 23.

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