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Review

Recent advances in microtubule targeting agents for cancer therapy

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Table S1. New microtubule targeting agents reported since 2020.

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Comp.	*In vitro* antiproliferative activity in screening assays	Other effects observed *in vitro* assays	*In vivo* assays: Antitumor effects and toxicity	ADME studies	Ref
		MTAs targeting taxane binding site			
1	MCF-7: IC_{50} = 0.0031 μM MDA-MB-231: IC_{50} = 0.004 μM BT474: IC_{50} = 0.0314 μM BT549: IC_{50} = 0.0792 μM MDA-MB-453: IC_{50} = 0.0031 μM **MDR cancer cell lines:** MDA-MB-231R: IC_{50} = 0.1385 μM MCF-7R: IC_{50} = 0.0815 μM **Non-cancer cell lines**: 293T: IC_{50} = 0.0063 μM MCF-10A: IC_{50} = 0.0027 μM	**MDR cancer cell lines**: - Promoted tubulin polymerization in MCF-7R and MDA-MB-231R cells at 0.01 μM. - Induced G2/M cell cycle arrest in MCF-7R (0.005 μM), MDA-MB-231R (0.1 μM) as well as in their parental cell lines. - Triggered apoptosis and endoplasmic reticulum stress in MCF-7R and MDA-MB-231R cells at 0.005 μM.	**MDR cancers**: - Reduced tumor volume growth in MCF-7R and MDA-MB-231R xenograft mouse models at 10 mg/ kg.	ND	[1]
2	A549: IC_{50} = 5.99 μM PC-3: IC_{50} = 4.17 μM HepG2: IC_{50} = 3.36 μM NRK-52E: IC_{50} = 6.99 μM	- Caused microtubular aggregation and wrinkling of the cell nucleus in HepG2 cells (3 μM). - Stabilized tubulin assembly and promoted protofilament assembly at 20 μM. - Increased G2/M phase arrest in HepG2 cells at 24 μM. - Induced apoptotic effect in HepG2 cells at 6 μM. - Decreased A549 cell migration at 3 μM.	ND	ADMETLab 2.0 predictions: - predicted to have adequate absorption potency and an acceptable safety profile. - complied with all drug-likeness properties.	[2]

		MTAs targeting vinca alkaloids binding site			
3	MDA-MB-231: IC_{50} = 0.47 μM MDA-MB-468: IC_{50} = 0.06 μM HeLa: IC_{50} = 0.05 μM DLD-1: IC_{50} = 0.22 μM HCT-116: IC_{50} = 0.1 μM HH: IC_{50} = 0.08 μM HuT78: IC_{50} = 0.09 μM HL60: IC_{50} = 0.1 μM KG-1: IC_{50} = 0.12 μM MES-SA: IC_{50} = 0.13 μM YCC3/7, YCC11: IC_{50} < 1 μM **MDR cancer cell lines:** MES-SA/Dx5: IC_{50} = 9.54 μM	- Inhibited tubulin polymerization at 10 μM. - Induced G2/M cell cycle arrest in MDA-MB-231 cells at 2 μM. - Induced apoptosis in MDA-MB-231 cells at 4 μM. - Increased cellular levels of caspases-3 and -9 and reduced expression of anti-apoptotic proteins MCL-1 and Bcl-x, in MDA-MB-231 cells. **MDR cancer cell lines:** - Maintained antiproliferative activity in multidrug-resistant MES-SA/Dx5 cells comparable to the parental cell line.	ND	ND	[3]
4	MDA-MB-231: IC_{50} = 11.6 μM MCF-7: IC_{50} = 7 μM **Non-cancer cell lines**: MCF-10A: IC_{50} > 200 μM	- Selectivity for cancer cells. - Induced microtubule disorganization in MCF-7 cells at 7 μM. - Triggered apoptosis in MCF-7 cells at 7 μM.	ND	ND	[4]
		MTAs targeting colchicine binding site			
5, 6	**5:** A549: GI_{50} = 0.033 μM HCT-116: GI_{50} = 0.015 μM HepG2: GI_{50} = 0.027 μM SW620: GI_{50} = 0.008 μM HT29: GI_{50} = 0.0031 μM	**5**, **6**: - **5** (IC_{50} = 3.39 μM) and **6** (IC_{50} = 4.77 μM) inhibited tubulin polymerization. - Disrupted microtubule network in HCT116 cells at 0.02 μM. - Promoted 81% (**5**) and 87% (**6**) G2/M cell cycle arrest in HCT116 cells at 0.02 μM. - Triggered 17.4% (**5**) and 15.2% (**6**) accumulation of apoptotic HCT116 cells at 0.01 μM.	**5**,**6**: - Reduced tumour growth by 45.3% (**5**) and 58.9% (**6**) in a HCT116 xenograft mouse model at an oral dose of 25 mg/kg.	ND	[5]

	6: A549: GI_{50} = 0.065 μM HCT-116: GI_{50} = 0.041 μM HepG2: GI_{50} = 0.053 μM SW620: GI_{50} = 0.024 μM HT29: GI_{50} = 0.096 μM		- In a HCT116 xenograft mouse model at an oral dose of 25 mg/kg, both compounds caused no reduction in the animal weight.		
7-10	**7-10:** CA-4 sensitive MCF-7: IC_{50} = 0.005-0.044 μM CA-4 resistant HT-29: IC_{50} = 0.003-0.018 μM	**7-10:** - Inhibited tubulin polymerization at 10 μM. **7:** - Induced G2/M phase arrest in MCF-7 and HT-29 cells at 1 μM. - Downregulated the expression of anti-apoptotic proteins Mcl-1, Bcl-2 and survivin in MCF-7 cells at 0.1 μM.	ND	ND	[6]
11	MCF-7: IC_{50} = 27.22 μM MDA-MB-231: IC_{50} = 27.04 μM HeLa: IC_{50} = 18.08 μM Kyse150: IC_{50} = 62.82 μM	- 31% inhibition of tubulin polymerization at 10 μM. - Induced G2/M phase arrest in HeLa cells by26.93% at 9 μM.	ND	ND	[7]
12	Panel of human cancer cell lines, derived from lung, breast, liver, stomach, colon, prostate, and ovary: IC_{50} = 0.008-0.03 μM MR-90: IC_{50} = 0.326 μM A2780: IC_{50} = 0.012 μM HCT-8: IC_{50} = 0.019 μM **MDR cancer cell lines**: A549/CDPP: IC_{50} = 0.016 μM A2780/PTX: IC_{50} = 0.015 μM HCT-8/VCR: IC_{50} = 0.031 μM	- Inhibited tubulin polymerization by 88.9% at 10 μM. - Disrupted intracellular microtubule dynamics in A549 cells at 0.001 μM. - Induced cell cycle arrest at the G2/M phase in A549 cells (76.3% at 0.02 μM). - Promoted apoptosis in A549 cells (80% at 0.02 μM).	- Reduced tumor weight in A549 xenograft tumor models by 71.7% at 30 mg/kg.	ND	[8]

	Non-cancer cell lines: BJ: IC_{50} = 0.563 μM NCM-460: IC_{50} = 0.614 μM				
13	Panel of cancer cell lines of cervical, breast, leukemia, hepatoma, stomach, lung, prostate and skin cancers: IC_{50} = 0.2 to 0.4 μM K-562: IC_{50} = 0.386 μM MCF-7: IC_{50} = 7.95 μM **MDR cancer cell lines**: MCF-7/ADR: IC_{50} = 1.91 μM K562/ADR: IC_{50} = 0.326 μM	- Inhibited growth in 3D tumor spheroid cultures. - Increased the number of apoptotic HeLa cells at 1 μM. - Caused accumulation of PAPP, caspase-3, -7, -8, and - 9 at 10 μM. - Increased the number of G2/M cells as well as the levels of mitotic markers PLK1, cyclin B1, and CDC25C, in HeLa cells at 1 μM.	- Low toxicity against zebrafish models at 10 μM, causing no zebrafish death, morphological changes or significant neurotoxicity. - In a xenograft mouse model, it suppressed tumor size by approximately 20% at 50mg/kg. - In a skin cancer model decreased the average number of tumors by 50% at 0.5 μM.	ND	[9]
14-16	**14**: HT-29: GI_{50} = 2.9 μM A549: GI_{50} = 2.8 μM U251: GI_{50} = 1.7 μM **15**: HT-29: GI_{50} = 5.2 μM A549: GI_{50} = 7.9 μM U251: GI_{50} = 4.6 μM **16**: HT-29: GI_{50} = 2.1 μM A549: GI_{50} = 0.89 μM U251: GI_{50} = 0.27 μM	- **14**, **15**,**16:** - Inhibited tubulin polymerization at 10 μM. **16:** - Inhibited tubulin polymerization (IC_{50} = 2.1 μM) - Disrupted the microtubule network in A549 cells at 1 μM, resulting in its disassembly and fragmentation. - Promoted G2/M cell cycle arrest in A549 cells at 1 μM.	ND	ND	[10]

17	DU145: IC_{50} = 0.062 μM BGC823: IC_{50} = 0.051 μM MCF-7: IC_{50} = 0.039 μM HCT-116: IC_{50} = 0.023 μM A549: IC_{50} = 0.053 μM H1299: IC_{50} = 0.006 μM MX-1: IC_{50} = 0.01 μM **MDR cancer cell lines**: MX-1R: IC_{50} = 0.142 μM A549R: IC_{50} = 0.077 μM	- Showed antitumor efficacy on organoids derived from lung cancer (IC_{50} = 0.105 μM). - Blocked mitosis and inhibited the growth of a prostate cancer 3D tumor model (IC_{50} = 0.046 μM). - Disrupted and reduced microtubule networks and also induced cell shrinkage in DU145 cells at 0.1 μM. - Upregulated Cyclin B1, cleaved caspase 3 and poly (ADP-ribose) polymerase in DU145 cells. - Promoted DU145 (30.34%) and NCI–H1299 (40.2%) cell apoptosis at 0.03 μM. - Inhibited cancer cell migration in DU145 and NCI-H1299 at 0.03 μM. - Reduced cancer cell colony formation at 0.1 μM. - No neurotoxicity effects in PC12 cells treated with 0.1 μM.	- Inhibited tumor growth by 72.2% and 68.7% in DU145 and H1299 xenograft mouse models, respectively, at 20 mg/kg. **MDR cancers**: - Maintained antitumor efficacy in A549R xenograft mouse models.	- Demonstrated a bioavailability of 11.1 % and fast absorption in xenograft mouse model at an oral dose of 10mg/kg.	[11]
18	SCC-29B: GI_{50} < 0.1 Hep-G2: GI_{50} > 100 HT-29: GI_{50} = 51 μM	- Inhibited the growth of oral squamous cancer spheroids cells (GI_{50} = 0.96 μM). - Induced loss of polygonal shape, cell rounding, nuclear degradation, and apoptotic blebbing in SCC-29B cells at 2.5 μM.	- Tumor reduction (T/C % = 0.4) in AW13516 xenograft mouse model at 2.5 mg/kg. - Reduced angiogenesis and increased necrosis in AW13516 xenograft mouse model. - No toxicity in AW13516 xenograft mouse model. - Decreased proliferation and glycolysis metabolism in AW13516 xenograft mouse model. - Induced cell body shrinkages, shortening of cell migratory processes, and diffused microtubules.	ND	[12]

19-23	**19-23** MCF-7: IC_{50} = 0.012-4.21 μM HL-60: IC_{50} = 0.028-0.703 μM HCT-116: IC_{50} = 0.024-3.83 μM HeLa: IC_{50} = 0.028-1.151 μM **21**: **Non-cancer cell lines**: MCF-10A: IC_{50} > 35 μM	**19-23** - Tubulin polymerization inhibitory effect (IC_{50} = 35.64- 1.32 μM). **21:** - Selective towards cancer cells. - Increased G2/M phase arrest in MCF-7 cells at 0.05 μM. - Accumulation of apoptotic MCF-7 cells (12%) at 0.05 μM.	ND	ND	[13]
24-33	**24-33**: MDA-MB-435: IC_{50} = 0.0006-0.0124 μM HeLa: IC_{50} = 0.0006-0.0168 μM SK-OV-3: IC_{50} = 0.0008-0.0181 μM **MDR cancer cell lines**: WT β-III HeLa cells: IC_{50} = 0.0006-0.0131 SK-OV- 3-MDR- 1–6/6: IC_{50} = 0.001-0.0234 μM	**24-33**: - Depolymerization of microtubules in A-10 cells (EC_{50} = 0.0019-0.0234 μM). **25, 26** and **30**: - Inhibited tubulin polymerization (**25**: IC_{50} = 0.48 μM, **26**: IC_{50} = 0.64 μM, **30**: IC_{50} = 0.47 μM).	ND	ND	[14]
34	Panel of glioma cell lines (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251): IC_{50} = 0.023-0.069 μM MGG8: IC_{50} = 0.014 μM T98G: IC_{50} = 0.036 μM	- Inhibited tubulin polymerization (IC_{50} = 1.1 μM). - Inhibited microtubule assembly in HCT-116 cells at 0.2 μM. - Displayed IC_{50} values ranging from 0.047 to 0.024 μM against MGG8 cells and PD-glioma isolates that exhibit cancer stem cell properties.	- Reduced tumor growth by 200–300% in COLO205 xenograft model at 20 mg/kg. - No toxicity towards COLO205 xenograft model at 20 mg/kg. - Enhanced temozolide and radiation therapy effectiveness at 20 mg/kg.	- Plasma and brain concentration measurements of **34**, at 20 mg/kg in mice, revealed micromolar levels of **34**, a $T_{1/2}$ of approximately 6 h, and a brain/plasma ratio of 2.2, indicating blood-brain barrier penetraton.	[15]

35 – 49	**42, 44, 45, 48**: MCF-7: EC_{50} = 0.007-0.0175 μM **MDR cancer cell lines**: MCF-7 TUBB3 βIII-tubulin: EC_{50} = 0.0026-0.0168 μM **42-49**: OVCAR-8: IC_{50} = 0.002-0.880 μM **MDR cancer cell lines**: NCI/ADR-RES: IC_{50} = 0.004-0.800 μM	**35-49:** - Inhibited tubulin polymerization with IC_{50} values of 0.42-21 μM. **42-45:** - Inhibited tubulin polymerization at low micromolar concentrations (IC_{50} values of 0.42-0.49 μM).	**42**: - Reduced tumor volume by 79% in a mouse xenograft model of MCF-7 TUBB3 at 25 mg/kg. - No toxicity at 25 mg/kg in a mouse xenograft model of MCF-7 TUBB3 tumors.	ND	[16]
50	HCC-LM3: IC_{50} = 0.963 μM RKO: IC_{50} = 0.17 μM PANC-1: IC_{50} = 0.729 μM SK-BR-3: IC_{50} = 0.431 μM BT474: IC_{50} = 1.193 μM SW620: IC_{50} = 0.673 μM SW480: IC_{50} = 0.338 μM SGC-7901: IC_{50} = 0.617 μM	- Inhibited tubulin polymerization at 10 μM. - Caused cell shape to gradually turn from fusiform to round in RKO cells at 1 μM. - Promoted G2/M cell cycle arrest in RKO, SW620, and PANC-1 cell lines (< 1 μM). - Increased the percentage of total apoptotic cells in RKO and SW620 cell line at concentrations < 1 μM. - Increased ROS levels 1.5 times in both RKO and SW620 cells at 0.5 μM. - Disturbed HUVEC migration at 0.5 μM.	- Reduced tumor growth by 53.6% in SW620 xenograft mouse model at 25 mg/kg. - No toxicity in SW620 xenograft mouse model at 25 mg/kg.	ND	[17]
51 - 69	HepG2: IC_{50} = 0.23-11.57 μM HeLa: IC_{50} = 0.15-10.34 μM MCF-7: IC_{50} = 0.38-13.13 μM A549: IC_{50} = 0.3-8.55 μM **Non-cancer cell lines**: HEK-293T: IC_{50} = 126 μM	**51-69:** - Inhibited tubulin polymerization (IC_{50} = 2.1-35.79 μM). **57**: - Induced G2/M arrested in HeLa cells (37.19%) at 0.1 μM. - Decreased Cdc2, Cdc25c, and Cyclin B1 levels at 0.1 μM. - Increased apoptosis rates to 14% in HeLa cells at 0.1 μM. - Decreased the levels of anti-apoptotic proteins Bcl-2, Bcl-x1 and Mcl-1 at 0.1 μM. - Low toxicity against non-cancer cell lines such as HEK 293T (IC_{50} of 126 μM).	ND	ND	[18]

70	**70**: SGC-7901: IC_{50} = 0.09 μM A549: IC_{50} = 0.65 μM HeLa: IC_{50} = 0.268 μM	- Inhibited tubulin assembly at 2.5 μM. - Caused destruction of microtubules and their wrapping around the nucleus in SGC-7901 cell lines at 0.18 μM. - Caused G2/M cell cycle arrest in SGC-7901 cells at 0.18 μM.			[19]
71, 72	**71**: A549: IC_{50} = 11.7 μM MCF-7: IC_{50} = 14.85 μM HepG2: IC_{50} = 63.43 μM **MDR cancer cell lines**: MCF-7 MX: IC_{50} = 14.94 μM **72**: A549: IC_{50} = 7.05 μM MCF-7: IC_{50} = 9.88 μM HepG2: IC_{50} = 21.97 μM **MDR cancer cell lines**: MCF-7 MX: IC_{50} = 20.2 μM	**71, 72**: - Inhibited tubulin polymerization by 25% (**71**) and 42.85% (**72**), at 50 μM. - Increased G2/M phase arrest to 29.78% (**71**) and 34.9% (**72**) in A549 cells at 10 μM. **72**: - Induced accumulation of total apoptotic cells (11.54%) in A549 treated cells at 10 μM.	ND	ND	[20]
73-92	**73-92:** Panel of NCI-60 cell lines: GI_{50} <10 μM **73**: HeLa: IC_{50} = 3.2 μM	**73**: - Induced G2/M phase arrest (54%) in Hela cells at 5 μM - Induced microtubule depolymerization at 0.05 μM. - Co-administration with an efflux pump inhibitor significantly increased intracellular retention.	ND	ND	[21]

93, 94	**93:** MDA-MB-231: IC_{50} = 0.008 μM MDA-MB-453: IC_{50} = 0.004 μM SKBR3: IC_{50} = 0.0267 μM A375: IC_{50} = 0.0059 μM M14: IC_{50} = 0.0052 μM RPMI7951: IC_{50} = 0.0052 μM **94**: MDA-MB-231: IC_{50} = 0.0022 μM MDA-MB-453: IC_{50} = 0.0014 μM SKBR3: IC_{50} = 0.0048 μM A375: IC_{50} = 0.0018 μM M14: IC_{50} = 0.0019 μM RPMI7951: IC_{50} = 0.0024 μM **MDR cancer cell lines**: A375/TxR: IC_{50} = 0.0053 μM MDA-MB-231/TxR: IC_{50} = 0.0021 μM M14/LCC6MDR1: IC_{50} = 0.0049 μM	**94:** - Inhibited tubulin polymerization at 10 μM. **MDR cancer cell lines**: - Maintained its antiproliferative activity against A375/TxR, MDA-MB-231/TxR and M14/LCC6MDR1 cell lines showing resistance indices of 1.04, 0.36 and 1.8, respectively. - Reduced colony formation of A375/TxR cells, by 95% at 0.005 μM. - Induced G2/M phase arrest (62%) in A375/TxR cells at 0.01 μM. - Increased the proportion of apoptotic cells to 54.3% in A375/TxR cells at 0.01 μM.	**94:** **MDR cancers:** - Inhibited tumor growth by 44.4% in A375/TxR xenograft model at a dose of 10 mg/kg. - Induced necrosis and reduced metastasis of tumors in A375/TxR xenograft model tumors.	**94:** - Metabolic stability of 29.4 min in human liver microsomes.	[22]
95, 96	**95**: MCF-7: EC_{50} = 1.5 μM PANC-1: EC_{50} = 4.1 μM **MDR cancer cell lines** $NCI^{ADR/RES}$: EC_{50} = 1.5 μM **96**: NCI-60 Cell line EC_{50} < 2 μM MCF-7: EC_{50} = 0.73 μM PANC-1: EC_{50} = 1.1 μM **MDR cancer cell lines:**	**95,96:** - Inhibited tubulin polymerization.	ND	ND	[23]

	$NCI^{ADR/RES}$: EC_{50} = 0.81 μM				
97, **98**	**97**: MDA-MB-231: IC_{50} = 3.2 μM H1299: IC_{50} = 2.8 μM PC-3: IC_{50} = 7 μM HCC1806: IC_{50} = 8.4 μM **Non-cancer cell lines:** BJ tert: IC_{50} = 4 μM **98**: MDA-MB-231: IC_{50} = 4.8 μM H1299: IC_{50} = 3.1 μM PC-3: IC_{50} = 6.8 μM HCC1806 = 7.2 μM **Non-cancer cell lines**: BJ tert: IC_{50} = 4.2 μM	**97, 98**: - Inhibited tubulin polymerization. - Interfered with the microtubule network in HCC1806 cells at 10 μM. - Induced G_2/M phase arrest in HCC1806 cells (~50–60%) at 10 μM. - Increased apoptosis and apoptotic markers in HCC1806, MDA-MB-231, H1299 and PC-3 cells at 10 μM.	**97**, **98**: - Reduced tumor size in HCC1806 breast cancer xenograft model at 2 mg/kg.	ND	[24]
99	MCF-7: IC_{50} = 3.4 μM MDA-MB-23: IC_{50} = 12.2 μM **Non-cancer cell lines:** MCF-10A: IC_{50} = 23.6 μM	- Promoted microtubule disorganization in MCF-7 cells at 3.4 μM. - Triggered apoptosis at 3.4 μM. - Moderate toxicity against non-cancer cells.	ND	ND	[4]
100	A549: IC_{50} = 0.008 μM HeLa: IC_{50} = 0.021 μM MHCC-97H: IC_{50} = 0.006 μM HCT-8: IC_{50} = 0.029 μM A2780: IC_{50} = 0.018 μM MCF-7: IC_{50} = 0.035 μM **Non-cancer cell lines:**	- Inhibited tubulin polymerization (IC_{50} = 0.81 μM). - Caused disturbance and shrinking of microtubules as well as condensation of chromatin and nucleus shrinkage in MHCC-97H cells at 0.005 μM. - Promoted G2/M cell cycle arrest of MHCC-97H cells at 0.005 μM. - Increased MHCC-97H apoptotic cells at 0.005 μM. - Caused TrxR inhibition in MHCC-97H cells (IC_{50} = 10.24 μM) resulting in the accumulation of ROS and superoxide anions.	- Suppressed tumor growth by 75.4% in a cell line-derived xenograft mouse model at 30 mg/kg.	ND	[25]

	HUVECs: IC_{50} = 0.056 μM LO2: IC_{50} = 0.398 μM HLF: IC_{50} = 2.367 μM MCF-10A: IC_{50} = 0.723 μM **MDR cancer cell lines**: MCF-7/ ADR: IC_{50} = 0.018 μM HCT-8/VCR: IC_{50} = 0.045 μM A2780/TAX: IC_{50} = 0.02 μM	- Downregulated the expression of anti-apoptotic proteins such as Bcl-2, and Bcl-xl in MHCC-97H cells at 0.01 μM. - Upregulated the expression of pro-apoptotic proteins (Bax and Bad) in MHCC-97H cells at 0.01 μM. - Showed low toxicity against human normal HUVECs, L-O2, HLF, and MCF-10A cells.			
101, 102	**101, 102:** A549: IC_{50} = 0.094, 0.005 μM KB: IC_{50} = 0.0527, 6.3 μM K562: IC_{50} = 0.137, 7.8 μM **MDR cancer cell lines**: KB-VCR: IC_{50} = 0.0425, 0.0061 μM KB-V1: IC_{50} = 0.0517, 0.0063 μM K562-ADR: IC_{50} = 0.3052, 0.0071 μM **102:** HeLa: IC_{50} = 0.0042 μM 4T1: IC_{50} = 0.0077 μM HT1080: IC_{50} = 0.0063 μM RAW264.7: IC_{50} = 0.0076 μM HL60: IC_{50} = 0.0068 μM THP1: IC_{50} = 0.0074 μM KB: IC_{50} = 0.0063 μM **Non-cancer cell lines:** MRC-9: IC_{50} = 0.1664 μM	**101, 102**: - Inhibited tubulin polymerization by 23.9 % (**101**) and 75% (**102**) at 30 μM. **102**: - Disrupted microtubule network in A549 cells at 0.05 μM. - Arrested more than 90% of cells of A549 cells in G_2/M phase at 0.02 μM. - Selective towards cancer cells.	**102**: - Inhibited tumor growth (T/C value 29.9%) in a murine 4T1 breast cancer xenograft model at 5 mg/kg.	**102**: - Good metabolic stability, with a half-life of 60.3 h when incubated with human liver microsomes.	[26]

103 - 107	**103-107**: MDA-MB-435: IC_{50} = 0.009-0.088 μM HeLa: IC_{50} = 0.0135-0.146 μM SK-OV-3: IC_{50} = 0.0118-0.136 μM **MDR cancer cell lines**: HeLa WTβ3: IC_{50} = 0.0106-0.108 μM SK-OV-3 MDR1-M6/6: IC_{50} = 0.175-0.209 μM **103**: Panel of NCI-60 cell lines: IC_{50} = 0.0027 - 0.0175 μM	**103-107**: - Inhibited tubulin assembly (IC_{50} = 0.49-2.3 μM). - Rr values of ~1.0 in Hela and its βIII-tubulin expressing subline. - Rr values (between 1-1.5) in SK-OV-3 ovarian carcinoma and its P-gp-expressing subline.	**103:** - Antitumor effects in MDA-MB-435 xenograft model at 75 mg/kg. - Moderate weight loss in MDA-MB-435 xenograft model at 75 mg/kg	ND	[27]
108	MCF-7: IC_{50} = 0.009 μM HeLa: IC_{50} = 0.005 μM Raji: IC_{50} = 0.013 μM NCI-H460: IC_{50} = 0.014 μM A2780S: IC_{50} = 0.008 μM **MDR cancer cell lines**: A2780T: IC_{50} = 0.0131 μM A549T: IC_{50} = 0.0638 μM MCF7-AD: IC_{50} = 0.0135 μM	- Did not induce α,β-tubulin degradation when HeLa cells were pretreated with 0.01 μM of a proteasome inhibitor (MG-132). - Inhibited migration of HUVEC cells (76.21%) at 0.005 μM. - Inhibited microtubule polymerization and spindle formation in A2780S cells at 0.01 μM. **MDR cancer cell lines**: - Induced G2/M phase arrest in A2780S (79.54%) and A2780T (72.89%) at 0.3 μM. - Induced apoptosis in A2780S and A2780T cells at 0.3 μM.	- Inhibited tumor growth by 66.06% in A2780S xenograft mouse model at 10 mg/kg **MDR cancers**: - Inhibited tumor growth by 26.94% in A2780T xenograft mouse model at 10 mg/kg. - IV administration showed no signs of toxicity at 10 mg/kg or 20 mg/kg. - Oral administration showed signs of toxicity at 40mg/kg.	- Intravenous administration: $T_{1/2}$ = 3.57 hours -Oral administration: $T_{1/2}$ = 4.42 hours - Clearance rate for oral administration (5.06L/h/kg) higher than IV administration (1.52 L/h/kg). - Oral bioavailability of 30.70 % in mice.	[28]
109	A549: IC_{50} = 0.01 μM HeLa: IC_{50} = 0.02 μM A2780: IC_{50} = 0.02 μM HCT-8: IC_{50} = 0.04 μM MCF-7: IC_{50} = 0.05 μM	- Inhibited tubulin polymerization (IC_{50} = 0.58 μM). - Disrupted microtubule network in A549 cells at 0.005 μM. - Induced G2/M phase arrest in A549 cells at 0.005 μM. - Downregulated Cyclin B1 and consequently decreased Cdc2 and Cdc25C cells at 0.005 μM.	- Inhibited tumor growth by 78.63% (10 mg/kg) in A549 xenograft mouse models.	- Favorable oral (69.45%) bioavailability, fast absorption and a half-life of $T_{1/2}$ = 2.12 h for	[29]

	Non-cancer cell lines: HUVECs: IC_{50} = 0.04 μM LO2: IC_{50} = 1.45 μM HLF: IC_{50} = 1.32 μM MCF10-A: IC_{50} = 0.54 μM **MDR cancer cell lines**: A549/ADM: IC_{50} = 0.02 μM HCT-8/VCR: IC_{50} = 0.07 μM A2780/TAX: IC_{50} = 0.04 μM	- Triggered cell death in A549 cells mainly through cell ferroptosis at 0.005 μM. - Selective towards cancer cells.		PO, and $T_{1/2}$ = 0.62 h for IV.	
110 - 113	**110-113**: MDA-MB 231: IC_{50} = 0.43->10 μM HeLa: IC_{50} = 0.038-0.44 μM A549: IC_{50} = 0.043-0.76 μM HT-29: IC_{50} = 0.03-0.76 μM	**110 - 113**: - Inhibited tubulin polymerization (IC_{50} = 0.45-2.2 μM). **110**: - Promoted G2/M cell cycle arrest in HeLa cells at 0.01 μM. - Increased expression levels of Cyclin B and inhibited the phosphorylation of Cdc2 in HeLa cells at 0.01 μM. - Induced apoptosis in HeLa cells at 0.025 μM, with the appearance of cell necrosis at 0.050 μM (25% of cells became necrotic). - Decreased mitochondrial potential in HeLa cells at 0.025 μM.	**110**: - *In vivo*, zebrafish embryos showed no signs of toxicity after being exposed to 0.3 μM. - Decreased tumor cell dissemination and killed a significant portion of DiI-positive cancer cells.	ND	[30]
114	NCI-60 cell lines: GI_{50} ranging from > 100 to 0.0254 μM MCF-7: IC_{50} = 0.095 μM MDA-MB-231: IC_{50} = 0.62 μM **Non-cancer cell lines:** HEK-293T: IC_{50} > 50 μM	- Inhibited tubulin polymerization at 10 μM. - Selective towards cancer cells. - At 0.1 μM caused cell rounding, distinct abnormalities of the spindle formation as well as a loss of the structured tubulin in MCF-7 cells. - Induced cell apoptosis (14.2%) in MCF-7 cells at 0.1 μM. - Downregulated the expression of anti-apoptotic proteins Bcl2 and survivin in MCF-7 cells at 0.05 μM.	ND	ND	[31]

115	SW480: IC_{50} = 0.2 μM CT26: IC_{50} = 0.43 μM HT-29: IC_{50} = 0.28 μM HCT-116: IC_{50} = 0.13 μM HCT-15: IC_{50} = 0.31 μM A549: IC_{50} = 0.41 μM **Non-cancer cell lines:** HUEVC: IC_{50} = 32.76 μM L02: IC_{50} = 21.45 μM **MDR cancer cell lines**: A549/CDDP: IC_{50} = 0.85 μM HCT-116/OXA: IC_{50} = 0.2 μM	- Inhibited tubulin polymerization (IC_{50} = 11.68 μM).- Inhibited HCT-116 cell migration (healing rate of 28.7% at 5 μM). - Induced severe DNA damage in HCT-116/OXA cells at 5 μM. - Promoted apoptosis in HCT116/OXA cells (apoptotic ratio of 51.9% at 5 μM). - Increased intracellular ROS levels in HCT-116/OXA cells at 5 μM. - Decreased mitochondrial membrane potential at 5 μM in HCT-116/OXA cells. - Notable selectivity for cancer cell lines.	´ND	ND	[32]
116	HCT-116: IC_{50} = 0.023 μM B16-F10: IC_{50} = 0.02 μM HeLa: IC_{50} = 0.037 μM HepG2: IC_{50} = 0.041 μM	- Inhibited tubulin polymerization (IC_{50} = 1.5 μM) - B16-F10 cells after exposure to 0.025 μM displayed a lack of cellular structure and disrupted microtubule networks. - Promoted G2/M cell cycle arrest in B16-F10 cells at 0.05 μM. - Increased apoptotic cells in B16-F10 cells at 0.05 μM. - Inhibit 100% of colony formation in BF16-F10 cells at 0.05 μM.	- Caused no significant weight loss at 10 mg/kg indicating a good safety profile in melanoma B16-F10 tumor model. - B16-F10 tumor model treatment with a dose of 10 mg/kg caused tumor growth inhibition of 65.1 %, which was raised to 77.6% when combined with PD-L1 (10mg/kg) inhibitor.	ND	[33]
117–128	**117-128** MDA-MB-435: IC_{50} = 0.00244-0.62 μM HeLa: IC_{50} = 0.0279-2.6 μM SK-OV-3: IC_{50} = 0.0342-3.3 μM	**117-128**: Promoted microtubule depolymerization in A-10 cells (EC_{50} = 0.123-9.2 μM). **MDR cancer cell lines**: **125**:	**125**: - Decreased tumor volume in an MDA-MB-435 xenograft mouse model at 50 mg/kg.	ND	[34]

	MDR cancer cell lines: WTβIII: IC_{50} = 0.0338-2.6 μM SKOV-3 MDR-1- M6/6: IC_{50} = 0.0392-3 μM	- Promoted microtubule depolymerization activity (EC_{50} = 0.123 μM) in A-10 cells. - Overcame βIII tubulin-mediated drug resistance with a relative resistance value of 1.2 and was not affected by P-gp expression.			
129-131	**129-131:** A375: IC_{50} = 0.001-0.0136 μM M14: IC_{50} = 0.0006-0.0183 μM MDA-MB-231: IC_{50} = 0.0018-0.0258 μM MDA-MB-453: IC_{50} = 0.0006-0.0176 μM Mia PaCa-2: IC_{50} = 0.0029-0.0444μM PANC-1: IC_{50} = 0.0028-0.0562 μM PC-3: IC_{50} = 0.0005-0.0239 μM **MDR cancer cell lines**: PC-3/TxR : IC_{50} = 0.0002-0.0144 μM	**131:** - Inhibited tubulin polymerization at 5 and 10 μM. - Caused G2/M arrest in PC-3 cells at 0.003 μM. - Showed anti-angiogenic effect in HUVEC at 0.1 μM. - Inhibited cell migration of PC-3 cells at 0.005 μM. - Inhibited the growth of COS-7 cells without significant cytotoxicity. Cell viability of COS-7 cells after 3 μM treatment was above 50%. - Selective towards cancer cells.	**131:** **MDR cancers**: - Reduced tumor volume by 85.6% in PC-3/TxR xenograft mouse model, while also inhibiting angiogenesis by 44% at a well-tolerated dose of 2.5 mg/kg.	**131**: - Presented good stability and longer half-life than its parental compound ($T_{1/2}$ = >300 min) in liver microsomes.	[35]
132	MGC-803: IC_{50} = 0.0117 μM HGC-27: IC_{50} = 0.0146 μM SGC-7901: IC_{50} = 0.0211 μM DU-145: IC_{50} = 0.1066 μM PC-3: IC_{50} = 0.0299 μM A549: IC_{50} = 0.0624 μM NCI-H520: IC_{50} = 0.1107 μM MCF-7: IC_{50} = 0.0525 μM MDA-MB-231: IC_{50} = 0.3959 μM EC-109: IC_{50} = 0.0289 μM TE-1: IC_{50} = 0.2859 μM HCT-116: IC_{50} = 0.0377 μM SK-N-SH: IC_{50} = 0.0583 μM	- Induced G2/M arrest in MGC-803 and HGC-27 cell lines at 0.02 μM. - Downregulated the expression of cell cycle-related proteins p-cdc2, Cyclin B1, CDC25B, Wee1 in MGC-803 and HGC-27 at 0.02 μM. -Upregulated the expression of M−phase marker protein p-Histone H3 in MGC-803 and HGC-27 at 0.005 μM. - Inhibited ERK1/2 proteins, RSK1, and TGF-β/SMAD signaling pathway in MGC-803 and HGC-27 cells at 0.02 μM. - Increased apoptosis rate of MGC-803 and HGC-27 cells at 0.02 μM. - Downregulated anti-apoptotic proteins (Bcl-2, Mcl-1, c-IAP1) expression in MGC-803 and HGC-27, at 0.005 μM. Upregulated pro-apoptotic Noxa, and promoting cleavage of caspase-3/9 and PARP expression in MGC-803 and HGC-27 at 0.005 μM.	- Well tolerated at 20 mg/kg on mice bearing MGC-803 cells xenograft model, causing tumor growth inhibition of 85.9%, while downregulating the expression of c-myc, Ki67, and cyclinB1 and promoting PARP cleavage, indicating the induction of apoptosis.	ND	[36]

		- Reduced c-myc, Ki67, CyclinB1 expression and enhanced PARP cleavage in MGC-803 and HGC-27 at 0.005 μM. - Inhibited MGC-803 and HGC-27 cell migration at 0.005 μM. - Downregulated the expression levels of the cell migration-related proteins MMP2 and MMP9 at 0.003 μM. - Decreased colony formation in MGC-803 and HGC-27 cell lines at 0.003 μM.			
133	MDA-MB-468: IC_{50} = 0.225 μM MDA-MB-231: IC_{50} = 0.162 μM MDA-MB-361: IC_{50} = 0.637 μM MDA-MB-175-VII: IC_{50} = 0.43 μM BT-549: IC_{50} = 0.182 μM HCC70: IC_{50} = 0.352 μM **<u>Non-cancer cell lines</u>:** MCF10-A: IC_{50} = 4.409 μM 76N: IC_{50} = 4.156 μM	- Inhibited clonogenic viability in breast cancer cell lines (EC_{50} = 0.162-0.637 μM). - More effective against breast cancer cells with mutant p53. - Concentrations ≥ 1 μM caused G2/M phase arrest in both normal and cancer cells. - Induced apoptosis in MDA-MB175-VII cells at 1 μM. - Induced multi-micronuclei phenotype in MDA-MB-175-VII at 1 μM. - Exhibited over 10-fold greater potency in breast cancer cells compared to normal mammary epithelial cells.	ND	ND	[37]
134, **135**	**134**: A549: IC_{50} = 2.9 μM MCF-7: IC_{50} = 7.17 μM **<u>Non-cancer cell lines</u>:** MRC-5: IC_{50} = 16.87 μM **135**: A549: IC_{50} = 2.33 μM MCF-7: IC_{50} = 6.1 μM **<u>Non-cancer cell lines</u>:** MRC-5: IC_{50} = 12.1 μM	**134,135**: - Demonstrated selectivity for cancer cells: selectivity indexes of 5.81 (**134**) and 5.20 (**135**). - Stabilized tubulin polymerization at 20 μM. - Stabilized microtubule polymerization in A549 cells at 20 μM. - Induced in the G2/M phase arrest by 22% in A549 cells at 5 μM. - Inhibited cancer cell migration in A549 cells at 2.5 μM. - Inhibited the A549 cell colony formation at 5 μM. - Increased apoptosis in A549 cells by 78.2% (**134**) and 91.4% (**135**) at 5 μM. - Upregulated DeY-α-tubulin expression in A549 cancer cells. - Downregulated Ac-α-tubulin expression in A549 cancer cells.	ND	**134,135**: - *In silico* study showed agreement with the critical rules of drug-likeness and predicted poor oral bioavailability.	[38]

136-138	**<u>136-138</u>** HeLa, EC, T24, SHSY-5Y, HepG2, HEC: dose dependent growth inhibitory effect at 0.1-10 μM	**136**: - Restrained tubulin polymerization (IC_{50} = 16.12 μM). - Disrupted the microtubule network of HepG2 cells at 1 μM. - Induced G2/M phase arrest in HepG2 cells at 2 μM. - Promoted apoptosis in HepG2 cells at 2 μM.	**136**: - Tumor inhibitory ratios of 53.91% and 46.25% in H22 and S180 models, respectively, at 10 mg/kg. - Low toxicity in H22 and S180 at 10/mg/kg.	ND	[39]
139, 140	**139:** HT-29: IC_{50} = 2.2 μM HepG2: IC_{50} = 4.64 μM HeLa: IC_{50} = 2.84 μM MCF-7: IC_{50} = 7.52 μM **140:** HT-29: IC_{50} = 17.52 μM HepG2: IC_{50} = 11.51 μM HeLa: IC_{50} = 10.9 μM MCF-7: IC_{50} = 12.85 μM	**139, 140:** - Disrupted microtubule morphology in HT-29 cells. **139:** - Inhibited tubulin polymerization. - Induced G2/M phase arrest in HeLa cells at 4 μM.	ND	ND	[40]
141	A549: IC_{50} = 0.027 μM Huh-7: IC_{50} = 0.03 μM T24: IC_{50} = 0.046 μM **<u>MDR cancer cell lines</u>**: A549/Tax: IC_{50} = 0.033 μM	- Inhibited tubulin polymerization (IC_{50} = 1.75 μM). - Prevented microtubule aggregation and spindle formation in A549 cells at 0.0125 μM. - Induced G2/M phase accumulation in A549 cells at 0.0125 μM. - Increased apoptosis in A549 cells at 0.0125 μM. - Reduced A549 cell migration at 0.0125 μM.	- Reduced tumor volume by 64.1 % in A549 xenograft mouse models with no signs of toxicity after treatment with 25 mg/ kg.	ND	[41]
142-147	**142-147** A549, KP-4, HeLa, BxPC-3 and MCF-7: IC_{50} = 0.009-1.8 μM **143**: A2780: IC_{50} = 0.075 μM	**142-146**: - Inhibited tubulin polymerization with IC_{50} values of 4.2 (**142**), 1.3 (**143**), 8.8 (**144**), 1.6 (**145**), and 15.3 (**146**) μM. - Strong inhibitory activity against JAK2. **143**:	**143, 147**: Reduced tumor weight by 70% (**143**) and 91% (**147**), in an A549 xenograft mouse model at 50 mg/kg.	**143**: - *In Silico* testing showed favorable drug properties and stability.	[42]

	HCT-8: IC_{50} = 0.034 μM MCF-7: IC_{50} = 0.018 μM A549: IC_{50} = 0.08 μM **MDR cancer cells**: A2780/TAX: IC_{50} = 0.02 μM HCT-8/VCR: IC_{50} = 0.049 μM MCF-7/ADR: IC_{50} = 0.064 μM A549/DDP: IC_{50} = 0.036 μM	- Induced G2/M cell cycle arrest in A549 cells at 0.005 (15.6%) and 0.02 (91.5%) μM. - Selective towards cancer cells. - Increased proportion of apoptotic A549 cells by 8.9% at 0.005 μM and 80.7% at 0.02 μM. - Low resistance indices (0.3–0.36) when tested against drug-resistant cell lines (A2780/TAX, HCT-8/VCR, MCF-7/ADR, and A549/DDP) and their parental counterparts. - Increased ROS production in A549 cells at 0.005 μM. -Decreases mitochondrial membrane potential in A549 cells at 0.005 μM.		- Poor water solubility and limited oral bioavailability. **147**: Acceptable water solubility, oral bioavailability of 69.7%.	
148	HeLa: IC_{50} = 0.04 μM	- Disrupted tubulin polymerization at 4 μM. - Induced G2/M phase arrest in HeLa cells at 0.01 μM. - Inhibited Src signaling pathway, promoting a reduction in p-Src and p-FAK levels in HeLa cells at 0.05 μM. - Demonstrated no significant cytotoxic effects and unaltered cell morphologies against MCF-10A, human fibroblast (CCD-18Co and BJ) cell lines at concentrations below 4 μM.	ND	- Showed excellent oral bioavailability in animal models (oral AUC value of 4.0 mg h/mL). - Demonstrated good microsomal stability and a percentage of plasma protein binding within acceptable ranges in both mice and humans.	[43]
149	A549: IC_{50} = 3.12 μM Caski: IC_{50} = 2.93 μM MHCC-97H: IC_{50} = 1.09 μM PC-3: IC_{50} = 3.52 μM HCT-8: IC_{50} = 7.26 μM **MDR cancer cells**: MHCC-97H/CDDP: IC_{50} = 0.85 μM PC-3/ENZR: IC_{50} = 4.22 μM HCT-8/VCR: IC_{50} = 6.51 μM	- Inhibited tubulin polymerization (IC_{50} = 5.98 μM). - Disrupted microtubule network causing the disappearance of filamentous structures, shrinkage, and punctate distribution in MHCC-97H cells at 0.75 μM. - Increased G2/M arrest in MHCC-97H cells at 0.75 μM. - Increased apoptosis in MHCC-97H cells at 0.75 μM. - Elevated caspase-3 activity in MHCC-97H cells at 1.5 μM. - Decreased mitochondrial membrane potential in MHCC-97H cells at 0.75 μM. - Induced ROS accumulation in MHCC-97H at 0.75 μM.	ND	ND	[44]

	Non-cancer cell lines: L-02: IC_{50} = 10.26 μM RWPE-1: IC_{50} = 8.75 μM				
150	U87: IC_{50} = 0.9 μM A549: IC_{50} = 0.88 μM Huh7: IC_{50} = 1.19 μM	- Inhibited tubulin polymerization at 6 μM. - Degraded the intracellular tubulin skeleton at 0.5 μM. - Caused G2/M arrest in U87 (24.6%) at 1 μM. - Increased percentage of apoptotic cells in U87 cells (11.28%) at 0.3125 μM. - Downregulated TUBA1A and TUBA1B, as well as β-subunit related genes TUBB and TUBB4B. - Inhibited U87 cell migration at 0.25 μM.	- Inhibited tumor growth and lowered tumor microvessel density (5 mg/kg) in mice bearing orthotropic glioma. - No toxicity in mice bearing orthotropic glioma at doses up to 10 mg/kg. -Showed positive correlation between blood-brain barrier permeability and *in vivo* anti-glioblastoma activity.	ND	[45]
151, **152**	**151**: HCT-15: IC_{50} = 0.0037 μM NCI-H460: IC_{50} = 0.008 μM MDA-MB-231: IC_{50} = 0.0104 μM SUIT2: IC_{50} = 0.0154 μM MIA PaCa-2: IC_{50} = 0.0099 μM **152**: HCT-15: IC_{50} = 0.0042 μM NCI-H460: IC_{50} = 0.0083 μM MDA-MB-231: IC_{50} = 0.0078 μM SUIT2: IC_{50} = 0.0105 μM MIA PaCa-2: IC_{50} = 0.0074 μM	**151, 152**: - Induced cell cycle arrest in MIA PaCa-2 PDAC cells at 0.025 μM. - Retained nanomolar-range efficacy against hM1A patient-derived PDAC organoid line.	ND	ND	[46]

153	HeLa: IC_{50} = 0.05 μM HCT 116: IC_{50} = 0.03 μM MCF-7: IC_{50} = 0.02 μM K562: IC_{50} = 0.03 μM Molm 13: IC_{50} = 0.02 μM A2780S: IC_{50} = 0.018 μM A549 IC_{50} = 0.034 μM **MDR cancer cell lines**: A2780T: IC_{50} = 0.016 μM A549T: IC_{50} = 0.037 μM MCF-7/ADR: IC_{50} = 0.032 μM	- Caused tubulin degradation in HeLa cells at 1 μM. - Induced pro-apoptotic effects in A2780S cells at 0.3 μM. - Induced G2/M phase arrest in A2780S at 0.1 μM. **MDR cancer cell lines**: -Maintained antiproliferative potency against multidrug-resistant cell lines. - Induced G2/M phase arrest in A2780T cell lines at 0.1 μM.	- Inhibited tumor growth by 45.3% in A2780S xenograft mouse model at 10 mg/kg. **MDR cancers:** - Inhibited tumor growth by 52.2% in A2780T xenograft mouse model at 10 mg/kg.	- $T_{1/2}$ values of 1.93, 5.94 h, and Cmax values of 2885.77 and 77.92 μg/L for intravenous and oral administration, respectively, in rats at 10 mg/kg. - Bioavailability values for oral administration reached 10.47% in rats.	[47]
154-157	**154:** MDA-MB-231: IC_{50} = 30.4 μM **155:** MDA-MB-231: IC_{50} = 18.98 μM **156:** MDA-MB-231: IC_{50} = 34.97 μM **157:** MDA-MB-231: IC_{50} = 14.54 μM	ND	ND	- Favorable physicochemical features and pharmacokinetic profile in *in silico* studies.	[48]
158-167	**158-167:** K562: IC_{50} = 0.53-74.48 μM HCT-116: IC_{50} = 19.54-86.36 μM HL-60: IC_{50} = 0.35-37.91 μM H1299: IC_{50} = 0.3-18.03 μM **161:** K562: IC_{50} = 0.53 μM HCT-116: IC_{50} = 24.61 μM HL-60: IC_{50} = 0.35 μM	ND	ND	ND	[49]

	H1299: IC_{50} < 0.3 μM				
168	Panel of breast, ovarian, lung, stomach, cervical, pancreatic, prostate, colon and malignant glioma cancer cell lines: IC_{50} = 0.0005-0.015 μM MCF-7: IC_{50} = 0.0014 μM **MDR cancer cell lines**: A2780/T: IC_{50} = 0.0048 μM A549/T: IC_{50} = 0.0042 μM A2780/CDDP: IC_{50} = 0.0016 μM A549/CDDP: IC_{50} = 0.0020 μM	- Hindered tubulin polymerization (IC_{50} = 2 μM). - Disorganized fibrous microtubule structures and decreased their density in MCF-7 cells at 0.001 μM. - Induced G2/M phase arrest in MCF-7 cells (67%) after treatment with 0.01 μM. - Increased cyclin-B1, CDK-1, and P-Histone H3 proteins at 0.01 μM. - Increased apoptosis rates in MCF-7 cells (46%) at 0.01 μM. - Decreased colony formation of MCF-7 cells after at 0.005 μM. - Delayed cell migration of MDA-MB-231 cells and downregulated the expression of the metastasis-related proteins vimentin and MMP-9 at 0.01 μM. **MDR cancer cell lines**: - Maintained antiproliferative potency in multidrug resistant cell lines A2780/T, A549/T, A2780/CDDP and A549/CDDP with resistance indexes between 1.35-1.81.	- Reduced tumor weight by 63% in MDA-MB-231 xenograft mice model at 7.5 mg/kg. - Showed no significant signs of toxicity in MDA-MB-231 xenograft mice model at doses up to 15 mg/kg. - Caused development of necrosis in tumors. **MDR cancers:** - Reduced tumor weight by 74% in A549/T xenograft mode with no reduction in body weight at a dose of 15 mg/kg.	- Area under the concentration−time curve of 1335 ng/mL, $T_{1/2}$=1.92, maximum plasma concentration of 1196 ng/mL in mice. - Oral bioavailability of approximately 40% in mice.	[50]
169	NCI-60 cancer cell line panel: average GI_{50} values of 0.0219 μM HT-29: IC_{50} = 0.004 μM **Non-cancer cell lines:** PBMCs: IC_{50} = 14.064 μM MRC-5: IC_{50} = 23.256 μM	- Showed selectivity for cancer cell lines. - Induced disassembly of the microtubule network in A549 cells at 0.25 μM. - Induced G2/M cell cycle arrest in Jurkat T-cell leukemia cells at 0.002 μM. - Induced apoptosis in Jurkat T-cell leukemia cells at 0.01 μM	- Inhibited tumor growth in a HT-29 mouse xenograft model with a T/C ratio of 42% at 15 mg/kg. - Showed no significant signs of toxicity in a HT-29 mouse xenograft model at doses up to 30 mg/kg.		[51]
170	A549: IC_{50} = 0.023 μM **MDR cancer cell lines:** A549/T: IC_{50} = 0.057 μM	- Displayed a resistance index of 2.47 against A549/T its parental subline. - Inhibited tubulin polymerization (IC_{50} = 1.8 μM).	- Suppressed tumor growth in A549/T xenograft mouse		[52]

	Non-cancer cell lines: MCF-10A cells: inhibitory rate of 20% at 0.01 μM.	- Disrupted microtubule structures in A549 and A549/T cells at 0.05 and 0.1 μM, respectively. - Induced G2/M cell cycle arrest in A549 and A549/T at 0.025 μM. - Promoted apoptosis in A549 (15.47% at 0.025 μM) and A549/T (22.2% at 0.0625 μM) cells.	model at 15 mg/kg and 30 mg/kg.		
		MTAs targeting maytansine binding site			
171-180	**171-178:** A549: IC_{50} = 0.00007->1.030 μM A2780: IC_{50} = 0.000033-2.088 μM **MDR cancer cell lines**: A2780AD: IC_{50} between 0.0047->19.706 μM **173**: A549: IC_{50} = 0.00024 μM A2780: IC_{50} = 0.00011 μM **MDR cancer cell lines**: A2780AD: IC_{50} = 0.011 μM	**171-178:** - Inhibited tubulin assembly at 27.5 μM. **173:** - At 0.01 μM, disrupted microtubule networks in A549 cells, originating signs of depolymerization during interphase in irregular bi-nucleated cells.	ND	ND	[53]
		MTAs targeting laulimalide / peloruside A binding site			
181	HeLa: 36.7% of growth inhibition at 2 μM, HL-60: 59.67 % of growth inhibition at 2.5 μM	- Promoted tubulin polymerization at 0.025 μM. - Increased the density of microtubule networks and initiated bundling of microtubules in HeLa and HL-60 cells at 0.8 μM and 2.5 μM, respectively. - Increased of oblate and lobulated nuclei in HeLa cells and of lobulated nuclei in HL60-cells at 0.8 μM and 2.5 μM, respectively. - Promoted G2/M cell cycle arrest in HeLa (14%) and HL-60 (37.4%) cells at 1.5 μM.	ND	ND	[54]

CA-4: Combretastatin A4; MDR: multidrug resistance; ND: Not disclosed; ROS: Reactive oxygen species; T/C: Treated over control; Rr: Relative resistance; IV: Intravenous; DNA: Deoxyribonucleic acid; AUC: Area under curve; PO: Oral administration

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