7-Aroyl-aminoindoline-1-sulfonamides as a Novel Class of Potent Antitubulin Agents

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Abstract: A novel series of 7-aroyl-aminoindoline-1-benzenesulfonamides showed excellent activity as inhibitors of tubulin polymerization through binding with the colchicine binding site of microtubules. Compound **15** and **16** display IC_{50} values of 1.1 and 1.2 μM, respectively. Compound **15** inhibited the human cancer cell growth of KB, MKN45, H460, HT29, and TSGH, as well as one human-resistant cancer line of KB-vin 10, with an IC_{50} of 9.6, 8.8, 9.4, 8.6, 10.8, and 8.9 nM, respectively.

Microtubules are dynamic structures that play a crucial role in cellular division and are recognized as an important target for anticancer therapy.[1] A number of naturally occurring compounds, such as paclitaxel, epothilone A, vinblastine, combretastatin A-4, dolastatin 10, and colchicine, all exhibit their anticancer properties by interfering with the dynamics of tubulin polymerization and depolymerization, resulting in mitotic arrest. Recent research reported that drugs with binding to the colchicines domain are undergoing intensive investigation as vascular-discrupting agents for cancer therapy.[2] For example, some antitubulin clinical candidates, **3**, **4**, and **5**, act as vascular-discrupting agents, rapidly depolymerizing microtubules of newly formed vasculatures to shut down the blood supply to tumors.[3]

Because the antitubulin chemotherapy drugs have problems with toxicity and drug resistance, scientists have been actively exploring new antitubulin agents. A variety of synthetic small molecules have been reported as inhibitors of tubulin polymerization, which complete the colchicine-binding site to tubulin.[4] Structurally, they involve various heteroaromatic cores, for instance including the indole, benzothiophene,[5] benzofuran,[6] imidazole,[7] thiazole,[8] and oxadiazoline[9] moieties. A number of indole-based compounds, for example 2-aroylindoles,[10] 3-aroylindoles,[11] 3-aroyl-2-phenylindoles,[6] 3-arylthioindoles-2-carboxylate,[12] and indolyl-3- glyoxamides,[13] have shown strong antiproliferative and antitubulin activity, and some of them are being developed. (Figure 1).

The sulfonamide-containing compounds, such as *N*-pyridinyl sulfonamide **6**[14] and styryl-pyridine *N*-oxide sulfonamide **7**,[15] demonstrated effective inhibition of tubulin polymerization and were found to be potent antimitotic agents, respectively.

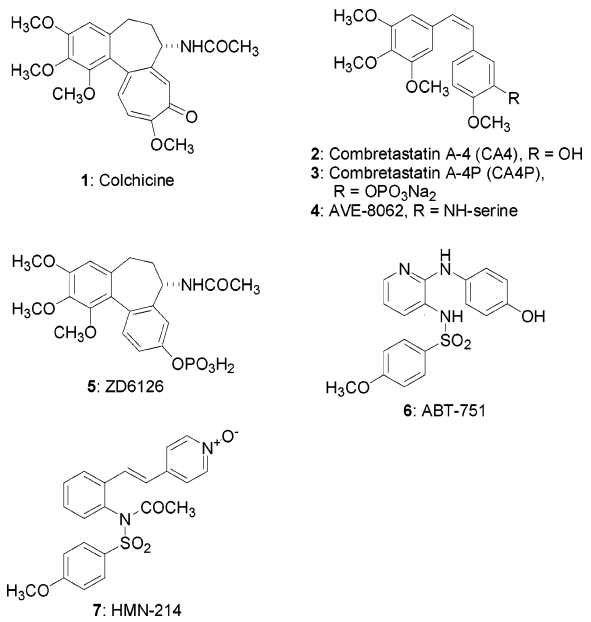
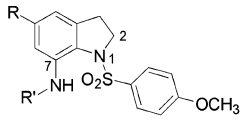


Figure 1.



8 : R, R' = H
9 : R = H; R' = benzoyl
10: R = H; R' = 4-fluorobenzoyl
11: R = H; R' = 4-nitrobenzoyl
12: R = H; R' = 4-cyanobenzoyl
13: R = H; R' = 4-methoxybenzoyl
14: R = H; R' = 4-(CH_3CO_2)benzoyl
15: R = H; R' = Isonicotinoyl
16: R = H; R' = 2-furoyl
17: R = H; R' = 2-thienoyl
18: R = H; R' = benzenesulfonyl
19: R = H; R' = 4-nitrobenzenesulfonyl
20: R = H; R' = 4-fluorobenzenesulfonyl
21: R = H; R' = $(CO)OC_6H_5$
22: R = H; R' = $(CO)N(CH_3)C_6H_5$
23: R = H; R' = benzyl
24: R = H; R' = acetyl
25: R = H; R' = pivaloyl
26: R = Br; R' = Isonicotinoyl
27: R = Br; R' = 2-furoyl

Figure 2.

Compounds **6** and **7** are now undergoing human clinical trial against various tumor types.[16,17] To our knowledge, there have been no reports on the inhibition of tubulin polymerization by indoline-sulfonamides. Therefore, here we describe the structure−activity relationships of a series of 7-aroylaminoindoline-1-sulfonamides as novel, highly potent inhibitors of tubulin polymerization. (Figure 2).

Indoline-sulfonamides **8**−**27** were synthesized as shown in Scheme 1. The preparation involved a straightforward reaction sequence with high yields (overall 48−56% in three or four steps). The commercially available 5-bromo-7-nitroindoline (**28**) was reacted with the 4-methoxybenzenesulfonyl chloride in pyridine to afford the 5-bromo-1-(4-methoxybenzenesulfonyl)-7-nitroindoline (**29**). The reduction of the 7-nitro group in **29** with Fe/NH_4Cl in isopropanol gave the corresponding **30**, 7-amino-5-bromo-1-(4-methoxybenzenesulfonyl)indoline, which was converted to the 7-amino-1-(4-methoxybenzenesulfonyl)-indoline (**8**) by a free radical-mediated debromination in the presence of AIBN and Bu_3SnH. Compound **30** or **8** was further reacted in pyridine with the corresponding electrophiles, such as aroyl chloride, heteroaroyl chloride, $ArSO_2Cl$, ArO(CO)Cl, $ArN(CH_3)(CO)Cl$, benzyl chloride, acetic anhydride, and pivaloyl chloride, to afford the desired 7-aminoindoline-1-sulfonamides (**9**−**14**, **16**−**25**, and **27**, respectively). 7-Isonicotinoyl-substituted indolines, **15** and **26**, were obtained by treatment of

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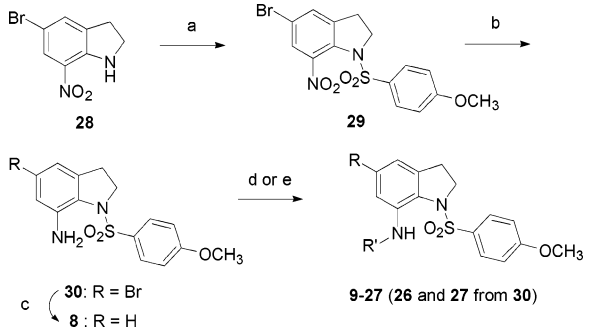
Scheme 1[a]



[a] Reagents and conditions: (a) 4-methoxyphenylsulfonyl chloride, pyridine, 85%; (b) Fe, NH_4Cl, isopropanol, 89%; (c) AIBN, Bu_3SnH, toluene, reflux, 90%; (d) aroyl chloride, heteroaroyl chloride, $ArSO_2Cl$, $ArO(CO)Cl$, $ArN(CH_3)(CO)Cl$, benzyl chloride, acetyl chloride, or pivoyl chloride, pyridine, 75−90%; (e) isonicotinoyl chloride hydrochloride, Cs_2CO_3, CH_3CN, reflux, 80−82%.

Table 1. IC_{50} Values (nM ± SD[a]) of Indoline-1-sulfonamides (**8**−**27**) and Colchicines

	cell type (IC_{50} nM ± SD[a])					
cmpd	KB	MKN45	H460	HT29	TSGH	KB-vin10
8	2800 ± 600	1200 ± 80				
9	297 ± 15	250 ± 18	257 ± 28	192 ± 32	201 ± 35	180 ± 23
10	93 ± 10	45 ± 2	95 ± 13	55 ± 7	100 ± 21	85 ± 12
11	102 ± 15	95 ± 7	122 ± 9	65 ± 8	116 ± 11	95 ± 14
12	105 ± 18	89 ± 12				
13	2600 ± 510	1600 ± 150				
14	376 ± 17	312 ± 14				
15	9.6 ± 1	8.8 ± 5	9.4 ± 2	8.6 ± 3	10.8 ± 1	8.9 ± 3
16	9.6 ± 4	10.7 ± 4	9.8 ± 2	9.5 ± 7	11.1 ± 4	9.2 ± 2
17	47 ± 9	31 ± 2	49 ± 7	37 ± 4	54 ± 6	43 ± 3
18	650 ± 21	562 ± 35				
19	1100 ± 150	933 ± 78				
20	1200 ± 60	890 ± 24				
21	>10 000	>10 000				
22	>10 000	>10 000				
23	>10 000	>10 000	>10 000	>10 000	>10 000	>10 000
24	89 ± 7	61 ± 6	75 ± 9	51 ± 11	103 ± 13	90 ± 9
25	359 ± 20	289 ± 38				
26	91 ± 8	86 ± 3				
27	89 ± 10	78 ± 2				
colch[b]	13.3 ± 4	15 ± 3				117 ± 8

[a] SD: standard deviation; all experiments were independently performed at least three times. [b] colch = colchicine.

8 and **30** with isonicotinoyl chloride hydrochloride in the presence of Cs_2CO_3 in anhydrous CH_3CN.

The synthesized indoline-sulfonamides **8**−**27** were evaluated for their cytotoxic activities against five types of human cancer cell lines, oral epidermoid carcinoma KB cells, colorectal carcinoma HT29 cells, non-small cell lung carcinoma H460 cells, and two stomach carcinoma TSGH, MKN45 cells, as well as one type of MDR-positive cell line: KB-VIN10 cells, overexpressed P-gp 170/MDR (Table 1).

We first evaluated the effect of the 7-amino group substitution on the indoline ring in the 1-(4-methoxybenzenesulfonyl)-indoline series for cytotoxic activity. Compounds **9**, **18**, **21**, **22**, and **23** with an amide, sulfonamide, carbamate, urea, and alkyl functionalities, respectively, on the 7-indoline were evaluated for their cell growth inhibitory activity. The SAR information indicates that amide **9**, with a benzoyl substitution on the 7-aminoindoline, showed the most potent activity, changing to 7-sulfonamide group (compound **18**), which resulted in moderate activity with 606 nM values of mean IC_{50} (KB and MKN-45), while changing to carbamate, urea, or alkyl functionalities decreased the activity drastically, even weaker than the unsubstituted 7-aminoindoline (**8**). On the basis of this result, of the benzoyl group in the 7-aminoindoline-core demonstrating substantial antiproliferative activity, aroyl-substituted 7-aminoindoline-sulfonamides, compounds **10**−**14**, were further synthesized and evaluated for the activity. The para -fluoro, nitro, and cyano-benzoyl compounds **10**, **11**, and **12**, respectively, showed strong cellular growth inhibitory activities with IC_{50} values of 45−105 nM against KB and MKN45 lines, apparently more potent than that of compound **9** and **13** with a benzoyl and 4-methoxybenzoyl substitutions, respectively. Compound **14** with a 4-(methoxycarbonyl)benzoyl substitution on the 7-aminoindoline ring also displayed a moderate cytotoxicity. This finding revealed that the inductive effect on the benzoyl substitution of the 7-aminoindoline-1-sulfonamides plays an important role for activity, which compounds with electron-withdrawing properties on the 7-aroylaminoindoline systems, is beneficial for potency. The substantial activity of 7-aroyl substitution in the aminoindoline-1-sulfonamides sparked us to investigate the effect of the 7-heteroaroyl substitutions. Compound **15** with an isonicotinoyl substitution, compound **16** with a 2-furoyl group, and compound **17** with a 2-thienoyl group on the 7-aminoindoline ring exhibit highly potent antiproliferative activities against human cancer cell lines. Notably, compounds **15** and **16** showed IC_{50} values of 8−11 nM in all six human cancer lines and are more potent than colchicine.

Table 2. Inhibition of Tubulin Polymerization and Colchicine Binding by Compounds **10**, **11**, **15**, **16**, **17**, **23**, **24**, Colchicine, and CA4

		colchicine binding[b] (% ± SD)	
cmpd	tubulin[a] IC_{50} ± SD (μM)	1μM inhibitor	5μM inhibitor
10	1.5 ± 0.2	65 ± 1	93 ± 2
11	1.9 ± 0.3	62 ± 2	91 ± 3
15	1.1 ± 0.1	78 ± 0.5	96 ± 2
16	1.2 ± 0.1	74 ± 1	95 ± 1
17	1.7 ± 0.3	75 ± 2	94 ± 1
23	> 5	-	-
24	1.9 ± 0.2	57 ± 3	86 ± 4
colchicine	3.3 ± 0.3		
CA4	1.2 ± 0.3	81 ± 0.2	97 ± 2

[a] Inhibition of tubulin polymerization.[18] [b] Inhibition of [^{3}H]colchicine binding.[18,19] Tubulin was at 1 μM; [^{3}H]colchicine was at 5 μM.

In an effort to further understand the substitution effect of the 7-aminoindoline ring, 7-alkylcarbonyl group, compounds **24** and **25** with an acetyl and pivaloyl moiety, respectively, were prepared. Compound **24**, with an acetyl group, displays substantial cytotoxicity, with IC_{50} values of 51−103 nM against cell lines, but a further increase in the bulkiness of substituent pivaloyl group in **25** resulted in a slight decrease in potency, thus revealing that the steric effect of the substitutions on the 7-aminoindoline ring influences cytotoxic activities. The bromo group at the C-5 position of 1-(4-methoxybenezenesulfonyl)-indolines **15** and **16**, gave **26** and **27**, respectively, with a 3−4-fold magnitude decreased cell growth inhibition as compared to that of the parent compounds.

To examine whether our indoline-1-sulfonamides were the tubulin inhibitors through the colchicines-binding domain, we selected compounds **10**, **11**, **15**, **16**, **17**, **23**, **24**, and references compounds (colchicine and combretastatin A-4) to evaluate for their antitubulin activities and determine their ability to compete for colchicine-binding sites (Table 2).

The results demonstrated that the drug cytotoxicity correlated with the inhibition of tubulin polymerization and colchicine-binding activities. As shown in Table 2, **10**, **11**, **15**, **16**, **17**, and **24** were effective in inhibiting tubulin assembly, with IC_{50} values of 1.5, 1.9, 1.1, 1.2, 1.7, and 1.9 μM, respectively, which were comparable or superior to the colchicine and combretastatin A-4

(IC_{50} = 3.3 and 1.2 μM, respectively). In the [^{3}H] colchicine-competing binding assay, our data indicate 7-heteroaroylcarbonyl-aminoindoline-1-sulfonamides (**15**−**17**), 7-aroylcarbonyl-aminoindoline-1-sulfonamides (**10** and **11**), and 7-alkylcarbonyl-aminoindoline-1-sulfonamides (**24**) were strongly bound to the colchicines binding site on the microtubules.

We have identified 7-aroylaminoindoline-1-benzenesulfonamides as a novel class of highly potent antitubulin agents acting through the binding with the colchicine binding site on the tubulin. The lead compound **15** (**J-30**) and **16** exhibit antiproliferative activity, with IC_{50} values ranging from 8.6 to 11.1 nM in a variety of human cancer cell lines from different organs, including the MDR-positive resistant cell line. (KB-vin 10) They also showed greater antitubulin activities than colchicines. The SAR information of the 7-aminoindoline-substitution pattern revealed that the 7-amide bond formation in the indoline-1-sulfonamides contributed to a significant extent for maximal activity rather than the carbamate, carbonate, urea, alkyl, and sulfonamide linkers. This amide bridge in the 7-aminoindoline-1-sulfonamides involves the substitutions of the 7-arylcarbonyl group (**9**−**14**), the 7-heteroarylcarbonyl group (**15**−**17**, **26**, and **27**), and the 7-alkylcarbonyl group (**24** and **25**). The 7-aroyl or 7-heteroaryl substitutions with an electron-withdrawing property are effectively improved for activity (**10**, **11**, **12**, and **15** vs **9**). These findings have encouraged us to extensively explore the novel indoline-sulfonamides and further investigate their mode of action and mechanism.

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Supporting Information Available: Spectral data of compounds **8**−**27**, **29**, and **30** and experimental procedures for synthesis and biological evaluations. This material is available free of charge via the Internet at http://pubs.acs.org.

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