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Novel Sulfonate Derivatives: Potent Antimitotic Agents

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Abstract—The synthesis and biological evaluation of novel sulfonate analogues of **E-7010** are reported. Several of the compounds are potent inhibitors of cell proliferation and tubulin polymerization. Importantly, these compounds are also active against P-glycoprotein positive (+) cancer cells, which are resistant to many other antitumor agents.

Microtubules are cellular structures formed by polymerization of the protein tubulin. Microtubules play an important role in many cellular processes, including mitosis. Various agents that modulate tubulin polymerization inhibit cancer cell proliferation.[1]

Three major classes of antimitotic agents, each with its own binding site on tubulin, act to disrupt tubulin dynamics. Compounds that bind to the taxane binding site[1,2] (e.g., paclitaxel and epothilone) act by preventing the depolymerization of tubulin, thus stabilizing microtubules. Compounds that bind to the vinca alkaloid domain (e.g., vincristine, dolastatins, and cryptophycins) and colchicine site binders (e.g., colchicine and combretastatins) inhibit the polymerization of tubulin.[1] Stabilization or destabilization of the microtubule structure leads to cell cycle arrest in the M phase and apoptosis.

Substantial efforts have been made to develop new antimitotic agents by preparing analogues of the natural products mentioned above or by screening compound libraries followed by traditional medicinal chemistry. Often, the goals of this research are to improve the therapeutic window (efficacy vs toxicity) of a compound class or to improve physical or pharmacological properties (such as aqueous solubility or pharmacokinetics). Of increasing clinical importance is the development of agents that are active against multidrug resistant tumor cell lines, since tumors composed of these cell types no longer respond to traditional chemotherapy. One mechanism responsible for the development of this resistance is over-expression of P-glycoprotein (multidrug resistant phenotype, MDR+).

E-7010 (Fig. 1) is an antitumor sulfonamide discovered at the Tsukuba Research Laboratories of Eisai

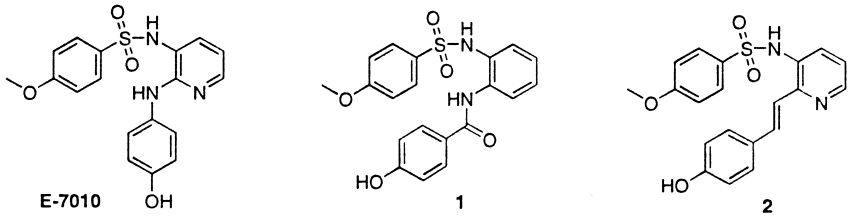

Figure 1. **E-7010** and analogues.

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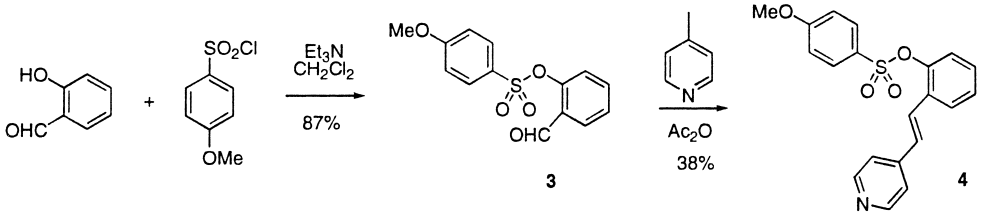
Company.[3] This compound inhibits tubulin polymerization by binding to tubulin at the colchicine binding site.[4] **E-7010** has shown good antitumor activity in vivo against both rodent tumors and human tumor xenografts.[5] Structurally related compounds **1**[6] and **2**[7] have also been reported and possess activity similar to that of **E-7010**.

As part of our program to identify novel antimitotic agents, we have synthesized some sulfonates related to the compounds discussed above. The synthesis of the first compound examined is shown in Scheme 1. Salicylaldehyde was treated with 4-methoxybenzenesulfonyl chloride under standard conditions[8] to provide sulfonate **3**. Condensation[7] of **3** with 4-picoline gave compound **4**.

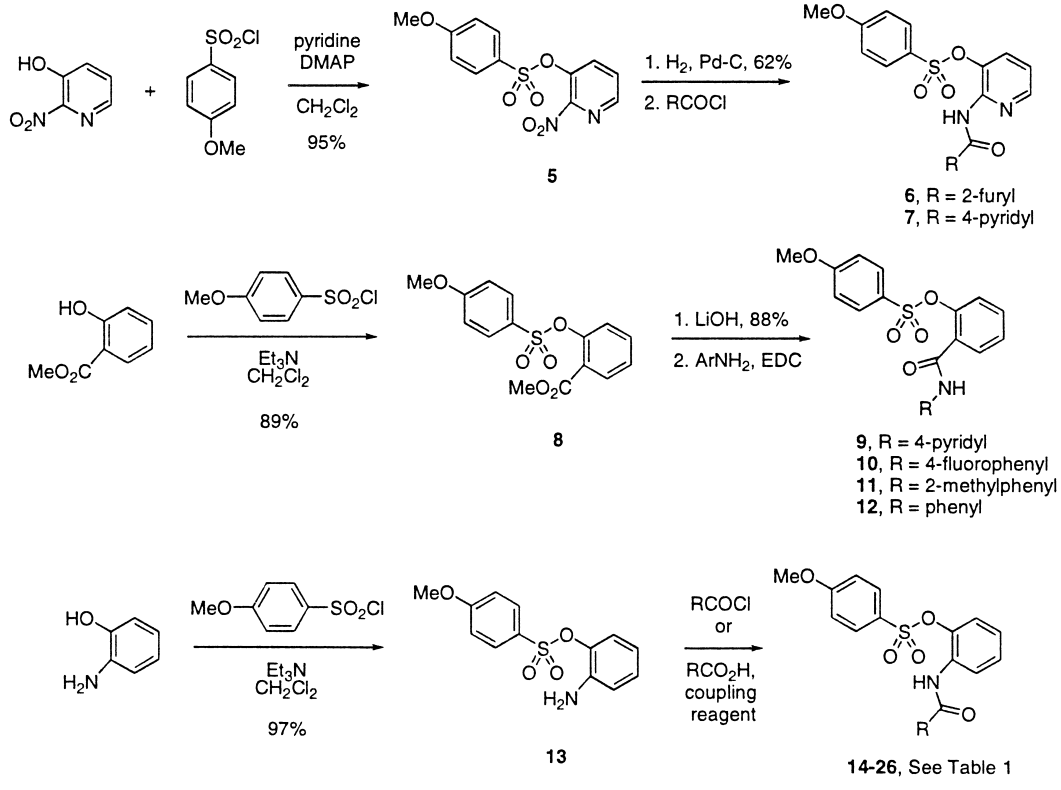
Compound **4** was tested for antiproliferative activity against two cancer cell lines: NCI-H460 and HCT-15. NCI-H460 is a human lung carcinoma that does not express P-glycoprotein, while HCT-15 is a human colon carcinoma that expresses a high level of this protein. Compound **4** inhibited the proliferation of these cell lines with IC_{50}'s of 130 nM and 56 nM, respectively. In contrast, **E-7010** inhibits these same cell lines with IC_{50}'s of approximately 350 nM. Importantly, both compound **4** and **E-7010** maintain activity against the MDR (+) cell line HCT-15, which indicates that they are not substrates for P-glycoprotein mediated transport.

We next prepared compounds where the olefin in compound **4** was replaced by an amide. The synthesis of these compounds is shown in Scheme 2. Sulfonylation of 3-hydroxy-2-nitropyridine gave sulfonate **5**. Reduction of the nitro group, followed by acylation gave target compounds **6** and **7**. Amides **9**–**12** could be prepared from methyl salicylate by sulfonylation, hydrolysis, and coupling to an aniline. Alternatively, the reverse amides **14**–**26** could be prepared by sulfonylation[8] of 2-aminophenol followed by acylation.

The pyridine-containing compounds **6** and **7** and benzamides **9**–**12** proved to be inactive ($IC_{50} > 10$ μM) against both cell lines tested. However, several of the anilides **14**–**26** showed good activity against these tumor cell lines (Table 1).



Scheme 1. Synthesis of compound **4**.



Scheme 2. Synthesis of sulfonate analogues of **E-7010**.

Table 1. Inhibition of cellular proliferation (IC_{50}) for sulfonate analogues of **E-7010**

Compd	R	IC_{50} (nM), HCT-15[a]	IC_{50} (nM), NCI-H460[b]
14	2-Furyl	19	24
15	4-Fluorophenyl	89	550
16	4-Pyridyl	89	55
17	2-Pyridyl	110	300
18	3-Pyridyl	>3000	>6000
19	Quinolin-4-yl	>10,000	>10,000
20	Quinolin-6-yl	>10,000	>10,000
21	4-(Dimethylamino)-phenyl	>10,000	>10,000
22	4-Pyridinylmethyl	600	720
23	Phenyl	310	410
24	NH-Phenyl	>10,000	>10,000
25	O-Phenyl	>10,000	>10,000
26	2-Pyrazinyl	68	250
E-7010	N.A.	340	350

[a]MDR (+), multidrug resistant.
[b]MDR (−), not multidrug resistant.

Table 2. Inhibition of tubulin polymerization (IC_{50}) for sulfonate analogues of **E-7010** and for **E-7010** itself

Compd	IC_{50} (μM)
4	3.46
16	3.73
17	4.06
26	5.20
E-7010	3.10

Examination of Table 1 reveals that several different types of aromatic substitutions at the amide site are well tolerated. The 2-furyl analogue (**14**) was quite potent; however, this compound proved relatively unstable and was not further examined. The 4-pyridyl group is well tolerated (**16**), and is better than either the 2- or 3-substituted compounds (**17** and **18**). Increasing chain length between the aromatic nucleus and the amide results in decreased potency (**22**).

Selected compounds that showed significant antiproliferative effects were also tested for their ability to inhibit the polymerization of tubulin[9] (Table 2). The results of this work demonstrate that the sulfonates tested are antimitotic agents with potency comparable to that of **E-7010.**

Since several of the sulfonate analogues above showed activity comparable to that of **E-7010**, the pharmacokinetic behavior of these compounds was examined. Sprague–Dawley rats were given an intravenous or oral 10 mg/kg dose of compounds **4**, **16**, **22**, and **26**. These compounds all exhibited short iv half-lives ($t_{1/2} < 1$ h) and poor oral bioavailability ($F \sim 0$).

In conclusion, we have synthesized sulfonate analogues of **E-7010** and have found several of these compounds to be potent in vitro inhibitors of the proliferation of two cancer cell lines. These compounds also inhibit the polymerization of tubulin. Further work to identify novel antimitotic agents is ongoing and will be reported in due course.

References and Notes

1. (a) Rowinsky, E. K.; Donehower, R. C. *Pharmacol. Ther.* **1991**, *52*, 35. (b) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207. (c) Shi, Q.; Chen, K.; Morris-Natschke, S. L.; Lee, K.-H. *Curr. Pharm. Des.* **1998**, *4*, 219. (d) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259. (e) Li, Q.; Sham, H.; Rosenberg, S. *Annu. Rep. Med. Chem.* **1999**, *34*, 139. (f) von Angerer, E. *Expert Opin. Ther. Pat.* **1999**, *9*, 1069.
2. Nicolau, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed.* **1994**, *33*, 15.
3. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitoh, K. *J. Med. Chem.* **1992**, *35*, 2496.
4. Yoshimatsu, K.; Yamaguchi, A.; Yoshino, H.; Koyanagi, N.; Kitoh, K. *Cancer Res.* **1997**, *57*, 3208.
5. Koyanagi, N.; Nagasu, T.; Fujita, F.; Watanabe, T.; Tsukahara, K.; Funahashi, Y.; Fujita, M.; Taguchi, T.; Yoshino, H.; Kitoh, K. *Cancer Res.* **1994**, *54*, 1702.
6. Yoshino, H.; Ueda, N.; Sugumi, H.; Niijima, J.; Kotake, Y.; Okada, T.; Koyanagi, N.; Watanabe, T.; Asada, M.; Yoshimatsu, K.; Iijima, A.; Nagasu, T.; Tsukahara, K.; Kitoh, K. U.S. Patent 5,610,320, 1997; *Chem. Abstr.* **1992**, *116*, 255492.
7. Hidaka, H.; Matsura, A.; Matsuda, M. International Patent WO 95/27699, 1995; *Chem. Abstr.* **1996**, *124*, 145916.
8. Kurita, K. *Chem. Ind.* **1974**, 345.
9. Gaskin, F.; Cantor, C. R.; Shelanski, M. L. *J. Mol. Biol.* **1974**, *89*, 737.