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NOVEL ANTINEOPLASTIC AGENTS WITH EFFICACY AGAINST MULTIDRUG RESISTANT TUMOR CELLS

Julio C. Medina,* Bei Shan, Holger Beckmann, Robert P. Farrell, David L. Clark, R. Marc Learned, Daniel Roche, Angela Li, Vijay Baichwal, Casey Case, Patrick A. Baeuerle, Terry Rosen, and Juan C. Jaen

Tularik Inc., Two Corporate Drive, South San Francisco, CA 94080, U.S.A.

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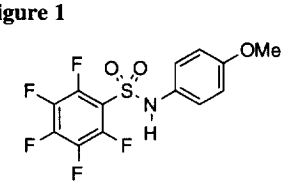
Abstract A novel series of pentafluorobenzenesulfonamides has been shown to inhibit the growth of a variety of human tumor cell lines. Among the cell types against which these agents were evaluated were the multidrug resistant (MDR) cell lines MCF-7/ADR and P388/ADR. The cytotoxic activity of members of this series of compounds was not affected by the multidrug resistant pump in MCF-7/ADR or P388/ADR cells.

Introduction

The emergence of multidrug resistant (MDR) tumors following initially successful chemotherapy is one of the major causes of treatment failure in cancer chemotherapy and represents a significant clinical problem.[1] MDR tumor cells often become simultaneously resistant to a variety of functionally and structurally unrelated cytotoxic agents, such as vinblastine, paclitaxel, colchicine, actinomycin D and doxorubicin.[2] Therefore, there is a great deal of interest in cytotoxic agents that are efficacious against tumor cells that exhibit the MDR phenotype.[3] In this report, we describe a novel series of pentafluorobenzenesulfonamides with broad antitumor activity. A representative set of these compounds (Figure 1) was evaluated against a wide range of human tumor cells including those that express the MDR phenotype.

With the exception of compound **6**, all of these molecules are pentafluorobenzenesulfonamide derivatives of a diverse group of anilines. Compounds **1** through **5** were readily synthesized by reacting pentafluorobenzenesulfonyl chloride with the appropriate aniline. Compound **6** was prepared in a similar manner by reacting 2,3,4-trifluorobenzenesulfonyl chloride with *p*-anisidine.[4]

Figure 1



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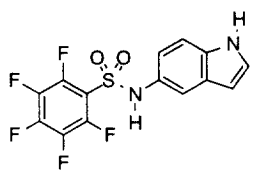

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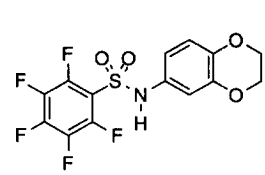

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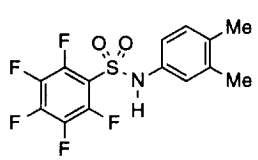

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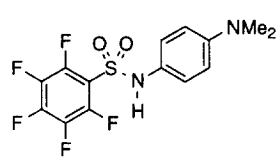

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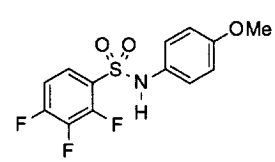

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Biology

The abilities of compounds **1–6** to arrest the in vitro growth of cancer cells derived from human leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast tumors was evaluated at the National Cancer Institute (NCI, Cancer Drug Discovery and Development Program) is summarized in Table 1.[5] Each compound was evaluated at five different concentrations. The growth rate at each concentration was determined using a standard sulforhodamine B assay (SRB) to measure total protein content 48 hours after treatment.[5] The concentrations at which the compounds reduced the growth rate of treated cells by 50%, relative to the growth rate of untreated cells, are shown as GI_{50} values.

Table 1.
Growth inhibition of cultured cells derived from a variety of human tumor types.[a]

	Cell Line[b] (GI_{50}, nM)								
Compd	CCRF-CEM	NCI-522	COLO 205	SF 295	SK-MEL-5	OVCAR-8	CAKI-1	PC 3	MDA-N
1	< 10	< 10	< 10	11	< 10	50	56	< 10	41
2	< 10	< 10	14	40	13	50	72	35	21
3	51	26	19	54	20	91	63	62	40
4	68	49	220	479	151	437	479	468	123
5	320	58	220	501	183	372	417	525	30
6	600	371	1.3×10^3	2.7×10^3	1.0×10^3	5.0×10^3	5.5×10^3	3.2×10^3	1.4×10^3

a These studies were performed at the NCI as part of their drug screening program. The compounds were tested at 10, 100, 1.0×10^3, 1.0×10^4 and 1.0×10^5 nM.
b Tumor type: CCRF-CEM (Leukemia), NCI-522 (Non-small Cell Lung), COLO 205 (Colon), SF 295 (CNS), SK-MEL-5 (Melanoma), OVCAR-8 (Ovarian), CAKI-1 (Renal), PC 3 (Prostate), MDA-N (Breast).

Table 2. Growth inhibition in culture of cell lines that exhibit the MDR phenotype and their parental cell lines.[a]

	Cell type (GI_{50}, nM)			
Compd	MCF-7[b]	MCF-7/ADR[c]	P388[d]	P388/ADR[c]
1	29 ± 23	58 ± 28	12 ± 7	34 ± 21
2	28 ± 24	115 ± 80	12 ± 7	32 ± 19
3	430 ± 355	410 ± 242	140 ± 62	340 ± 204
4	120 ± 87	320 ± 204	37 ± 20	110 ± 71
5	34 ± 25	96 ± 64	27 ± 13	36 ± 23
paclitaxel	1.1 ± 0.2	>15,000	16 ± 11	>15,000
vinblastine	2.3 ± 0.5	350 ± 71	4.1 ± 1.4	470 ± 300

a Compounds were tested at concentrations of 1.5, 5, 15, 50, 150, 500, 1.5×10^3, 5×10^3 and 1.5×10^4nM.
b Human breast cancer cells.
c Cells that exhibit the MDR phenotype.
d Murine leukemic cells.

The abilities of these compounds to inhibit the growth rate of cells that exhibit the MDR phenotype was studied using MCF-7 and P388 cell lines and their MDR sublines. MCF-7 and MCF-7/ADR cells are derived from a human breast tumor. P388 cells and their multidrug resistant subline, P388/ADR are murine leukemic cells. Compounds **1–5** were tested in triplicate at nine different concentrations, and the cellular growth rate at each concentration was determined 72 hours after treatment, using an Alamar Blue metabolic dye assay.[6,7] The concentration at which 50% growth inhibition (GI_{50}) is observed was determined using a curve fitting program, and the results are shown in Table 2.

Results and Discussion

In this publication, we report the discovery of a series of pentafluorobenzenesulfonamides that display cytotoxicity against a broad variety of tumor cells. The compounds were evaluated against eight different human tumor types, as shown in Table 1. The GI_{50} values for a given compound across the cell lines evaluated typically were within one order of magnitude of each other, regardless of the tumor type. Compound **1** was the most potent cytotoxic agent.

It can also be observed from the structural differences of the compounds that a variety of modifications at the aniline ring are tolerated. In contrast, compound **6**, which lacks the pentafluoro substitution pattern common to sulfonamides **1–5**, was generally at least two log units of magnitude less potent than **1** in reducing the growth rate of the tumor cells. This indicates that the pentafluorophenyl ring plays a critical role in the biological activity of this series.

The cytotoxic properties of the compounds were also evaluated in MCF-7/ADR and P388/ADR cells. These cells are derived from MCF-7 and P388 cells, respectively, and exhibit the MDR phenotype.[1,8] Both sublines have been generated to be doxorubicin- resistant, with cross-resistance to structurally diverse chemotherapeutic agents such as vinblastine, etoposide and paclitaxel. In Table 2, it can be observed that, while MCF-7/ADR and P388/ADR cells show resistance to vinblastine and paclitaxel, they show sensitivity (GI_{50} values) to the pentafluorobenzenesulfonamide agents that is essentially equivalent to that of the corresponding parental cell lines.

In summary, we report the discovery of a new family of pentafluorobenzenesulfonamides that inhibit the growth of a broad variety of tumor cells, including those that exhibit the MDR phenotype. Further characterization of the structure–toxicity relationship and mechanism of action of these compounds will be published elsewhere.

References and Notes

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4. All new compounds were characterized by ^{1}H NMR, and EI mass spectrometry. Elemental analysis values (C, H, N) were within 0.4% of the theoretical values. Pentafluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (**1**): ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1H), 6.96 (d, J = 4 Hz, 2H), 6.88 (d, J = 4 Hz, 2H), 3.83 (s, 3H); 5-pentafluorophenylsulfonamidoindole (**2**): ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1H), 7.43 (s, 1H), 7.3 (d, J = 8 Hz, 1H), 7.22(s, 1H), 6.98 (d, J = 8 Hz, 1H), 6.92 (s, 1H), 6.50 (s, 1H); pentafluoro-*N*-(3,4-ethylenedioxyphenyl)benzenesulfonamide (**3**): ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.6, 2.6 Hz, 1H), 4.2 (s, 4H); pentafluoro-*N*-(3,4-dimethylphenyl)benzenesulfonamide (**4**): ^{1}H NMR ($CDCl_3$) δ 7.03 (d, J = 7.9 Hz, 1H), 6.92 (s, 1H), 6.85–6.82 (m, 2H), 2.18 (s, 3H), 2.16 (s, 3H); pentafluoro-*N*-(4-*N*,*N*-dimethylaminophenyl)benzenesulfonamide (**5**): ^{1}H NMR ($CDCl_3$) δ 7.01 (d, J = 8.9 Hz, 2H), 6.77 (s, 1H), 6.59 (d, J = 8.3 Hz, 2H), 2.92 (s, 6H); 2,3,4,-trifluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (**6**): ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 1H), 7.02 (m, 3H), 6.78 (dd, J = 9, 2 Hz, 2H), 6.65 (br s, 1H), 3.76 (s, 3H).
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