Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1013–1015

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Antitumor Agents. Part 3: Synthesis and Cytotoxicity of New *trans*-Stilbene Benzenesulfonamide Derivatives

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Received 17 December 2001; accepted 1 February 2002

Abstract—A new series of *trans*-stilbene benzenesulfonamide derivatives were designed and synthesized as potential antitumor agents. These new compounds were evaluated in the National Cancer Institute's 60 human tumor cell line in vitro screen. Compounds **9**–**13** were cytotoxic against several cell lines. Notably, two compounds, **9** and **12**, demonstrated selective cytotoxic activity against BT-549 breast cancer ($GI_{50} = 0.205$ μM) and HT–29 colon cancer ($GI_{50} = 0.554$ μM), respectively.

Resveratrol, a 3,5,4′-trihydroxy-*trans*-stilbene (Fig. 1) found in grapes and several plants, has been reported to show interesting biological properties,[1] especially antioxidant, anti-inflammatory,[2] and anticarcinogenic effects.[3] However, the mechanism by which resveratrol inhibits carcinogenesis has not yet been elucidated. As part of our continuing studies on new resveratrol analogues as potential cancer chemopreventive agents or cancer chemotherapeutic compounds, we have synthesized a series of *trans*-stilbene benzenesulfonamide derivatives (**9**–**15**) and evaluated their cytotoxicity in the National Cancer Institute's 60 human tumor cell line panel. Compounds **9**–**15** were designed by replacing the hydroxyl group in ring A of resveratrol with a sulfonamide moiety. A sulfonamide moiety[4] has recently been found to play a very important role in the potent antitumor activity of E7010, which is now in clinical trials as an anticancer drug.[5,6]

The synthesis of the target compounds (**9**–**15**) is outlined in Scheme 1. These new *trans*-stilbene benzenesulfonamide derivatives were synthesized from the commercially available sulfanilamide. Thus, diazotization of the sulfanilamide led to the diazonium salt **1**, which was then treated with potassium cyanide/copper sulfate pentahydrate (Sandmeyer reaction[7]) to yield benzonitrile **2** in 53% yield. Stephen reduction[8] of **2** with Raney nickel alloy in 75% aqueous formic acid gave benzaldehyde **3** in 86% yield. Sodium borohydride reduction of **3** furnished benzyl alcohol **4** in 92% yield. Treatment of alcohol **4** with phosphorous tribromide provided benzyl bromide **5**, which was then converted quantitatively to diethylphosphonium salt **6** using triethyl phosphite.[9] The Wittig–Horner condensation[10] of diethylphosphonium salt **6** with the appropriate nonphenolic benzaldehydes **7** or the benzyl-protected benzaldehydes **8** (obtained from the corresponding phenolic

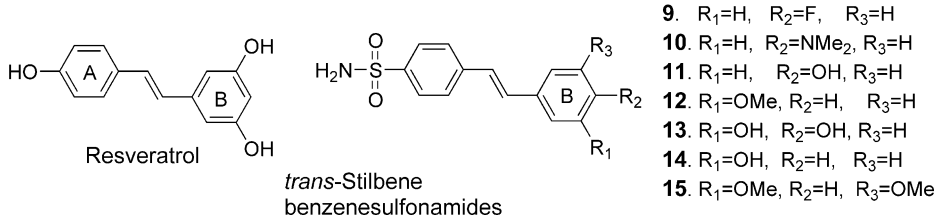

Figure 1.

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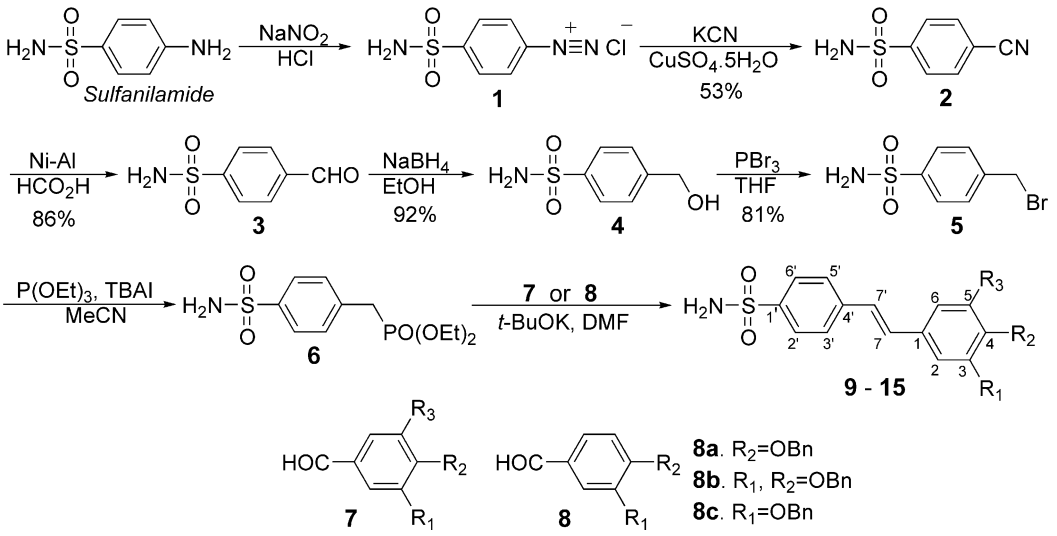
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00092-6



Scheme 1. Synthesis of *trans*-stilbene benzenesulfonamide derivatives **9**–**15**.

Table 1. Cytotoxicity of *trans*-stilbene benzenesulfonamide derivatives (GI_{50} values, μM)[a]

Tumor cell lines	Cytotoxicity (GI_{50} μM)[a]						
	9	**10**	**11**	**12**	**13**	**14**	**15**
Leukemia							
CCRF-CEM	62	46	4.5	13.6	4.79	16.1	19.9
HL-60	37.3	>100	4.35	10.4	16.3	41.4	18.6
K-562	14.9	>100	24.9	20.6	35.3	43.4	28.7
MOLT-4	12.9	>100	22.6	26.8	12.8	20	18.6
RPMI8226	42.3	11.6	7.09	3.81	9.16	18.9	14.3
SR	10.5	8.58	4.68	5.21	12.7	17.8	19.7
Non-small cell lung cancer							
A549	8.93	10.1	13.9	11	22.3	19.8	20.7
HOP-92	33.2	16.6	31.5	3.29	15.8	17.4	15
NCI-H226	7.97	12.1	11.1	2.91	14	25.8	12.3
NCI-H23	45.1	14.2	16.9	21	25.9	46.1	22.5
NCI-H522	4.81	6.88	13.8	NT	2.25	12.2	NT
Colon cancer							
HCT-15	9.98	17.14	24.6	3.6	13.9	22.8	17.4
HT-29	29.4	30.8	17.8	0.554	35.4	43.3	16.2
KM-12	16.3	8.28	11.1	12.2	18.2	35.4	20.8
CNS cancer							
SF-268	20.5	7.16	31.5	17.1	18.2	65.6	28.3
SF-539	29.1	11.7	7.4	16.8	14.2	36.7	18.8
U251	7.93	11.2	15	5.54	16.3	21.1	17.1
Melanoma							
LOXIMVI	26.7	18.7	19.1	30.7	29.9	43	18.2
UACC-62	NT	NT	3.4	14	23.3	18.6	15.4
Ovarian cancer							
IGROV1	20.9	13.4	20.3	2.5	4.49	30.2	23.1
OVCAR-4	34.4	3.34	36.9	25	11.6	27.8	21.2
OVCAR-8	15.2	4.95	4.81	31.6	16.7	25.2	37.9
Renal cancer							
ACHN	2.97	13.6	2.28	7.12	20.4	25.8	23.5
CAKI-1	36.3	50.3	5.59	14.7	29.1	50.2	19
Breast cancer							
HS-578T	23.7	3.03	28.9	25.5	25.6	61	20.1
MDAMB435	27	7.63	20.3	17.4	16.8	25.8	18.7
BT-549	0.205	2.14	NT	6.38	4.13	NT	10.7

[a]The GI_{50} values are the concentrations corresponding to 50% growth inhibition. Data are an average of at least two testings. NT, not tested.

benzaldehydes by reaction with benzyl bromide in ethanol) in the presence of potassium *tert*-butoxide at room temperature gave the *trans*-stilbene benzenesulfonamide derivatives **9**, **10**, **12** and **15**. The benzyl-protected stilbenes were subsequently *O*-debenzylated by boron tribromide-mediated to provide the target compounds **11**, **13** and **14**. The structures and stereochemistry of the new derivatives **9**–**15** were determined from spectroscopic data, which showed the (*E*)-isomers. This configuration was supported by the coupling constants of the olefinic protons, $J = 16$–17 Hz, in each ^{1}H NMR spectrum. The proposed structural assignments were confirmed by detailed ^{1}H, ^{13}C NMR (HMQC, HMBC, COSY) and HR-EIMS analyses.[11]

These derivatives were screened by the National Cancer Institute. All compounds were evaluated in vitro against a total of 60 human tumor cell lines derived from eight cancer types (leukemia, non-small cell lung cancer, colon cancer, CNS-cancer, melanoma, ovarian cancer, renal cancer and breast cancer) according to the standard protocol.[12] The dose–response curves for each cell line were measured with five different drug concentrations, and the molar concentration causing 50% cell growth inhibition (GI_{50}) was calculated. The results are shown in Table 1.

Various substituents were introduced into the B ring of the *trans*-stilbene benzenesulfonamide (**9**–**15**). These substituents included electron-donating groups, such as NMe_2, OH, and OMe, and electron-withdrawing groups, such as F. As seen in Table 1, compounds **9**–**13** were cytotoxic against several cell lines. Compound **9** was active against non-small cell lung cancer (NCI-H522), renal cancer (ACHN), and breast cancer (BT-549); compound **10** against ovarian cancer (OVCAR-4, OVCAR-8), and breast cancer (HS-578T, BT-549); compound **11** against leukemia (CCRF-CEM, HL-60, SR), melanoma (UACC-62), ovarian cancer (OVCAR-8), and renal cancer (ACHN); compound **12** against leukemia (RPMI8226, SR), non-small cell lung cancer (HOP-92, NCI-H226), colon cancer (HCT-15, HT-29), CNS cancer (U251), and ovarian cancer (IGROV1); and compound **13** against leukemia (CCRF-CEM), non-small cell lung cancer (NCI-H522), ovarian cancer (IGROV1), and breast cancer (BT-549). Additional mechanism studies are ongoing to better understand the results.

In conclusion, we have discovered a new series of *trans*-stilbene benzenesulfonamide derivatives as a novel class of antitumor agents. Among these compounds, only **9** and **12** displayed significantly selective cytotoxicity against BT-549 (GI_{50} 0.205 μM/mL) and HT-29 (GI_{50} 0.554 μM/mL), respectively. Thus, structure–activity investigations revealed that replacing the hydroxyl group in ring A of resveratrol with a sulfonamide moiety led to *trans*-stilbene benzenesulfonamide derivatives with enhanced cytotoxicity and selectivity. Compounds **9** and **12** deserve further development as potential clinical trials candidates. Further SAR studies will be undertaken to elucidate the antitumor mechanism of action involved.

Acknowledgements

This study was supported by grant NSC-89-2114-B-077-013 from the National Science Council of Republic of China. Thanks are due to the National Cancer Institute, Bethesda, MD, USA, for performing the antitumor screening of the synthesized compounds.

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