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Recognition of the Importance of Imidazolidinone Motif for Cytotoxicity of 4-Phenyl-1-arylsulfonylimidazolidinones Using Thiadiazolidine-1,1-Dioxide Analogs

Il-Whan Kim and Sang-Hun Jung

College of Pharmacy, Chungnam National University, Daejeon 305-764, Korea

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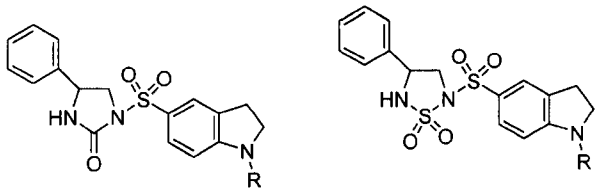
For probing the importance of planarity of imidazolidinone motif of 4-phenyl-1-(N-acylindoline-5-sulfonyl)imidazolidinones **1** for their cytotoxicity, 4-phenyl-1-(N-acylindoline-5-sulfonyl)[1,2,5]thiadiazolidine-1,1-dioxides **2** were prepared and their cytotoxicity were measured against human lung carcinoma (A549), human colon carcinoma (COLO205), human ovarian cancer (SK-OV-3), human leukemic cancer (K562), and murine colon adenocarcinoma (Colon26) cell lines *in vitro*. Although only carbonyl moiety of imidazolidinone ring was replaced with sulfonyl group, compounds **2** do not show any activity against all five cancer cell lines unlike 1. Therefore the planarity of imidazolidinone ring of **1** should be an important factor for their cytotoxic activity.

Key words: 4-Phenyl-1-(*N*-acylindoline-5-sulfonyl)imidazolidinones, Cytotoxicity, 4-Phenyl-1-(*N*-acylindoline-5-sulfonyl)[1,2,5]thiadiazolidine-1,1-dioxides

INTRODUCTION

Arylsulfonylimidazolidinones were reported (Jung, *et al.*, 1996; 1996; 1997; 1997; Hwang, *et al.*, 1999) as analogs possessing broad spectrum of potent activity against the various human cancer cell lines. Previous structure activity relationship study of **1** indicated that small aromatic motif at 4-positon of imidazolidinone ring is essential for their activity (Jung and Kwak., 1997). Phenyl moiety itself at this site is considered to be optimum size for binding to its putative receptor. All substituents at the various position on phenyl at 4-position reduce their activity (Jung, *et al.*, 1996). However their activity were varied on the kind of substitutent on phenyl group on sulfonyl function of **1** (Jung, *et al.*, 1996). Quantitative structure activity relationship study revealed that the enlargement of the substituents at 4-position of this phenyl enhance the activity regardless of their electronic or hydrophobic parameters (Lee, *et al*, 2000). Conformational study of **1** indicates that the necessity of two phenyl groups in certain distance, about 8.7Å between the centers of two phenyl rings (Jung, *et al.*, 2000). In addition, imidazolidinone ring is nearly planar, especially in urea region. This structural characteristics was proved by x-ray crystallography (Park, *et al.*, 2000). To determine whether this structural feature is essential for the activity of **1**, sp^2 carbonyl moiety was replaced with sp^3 sulfonyl group. This replacement obviously deviates the planarity of imidazolidinone ring. Accordingly 4-phenyl-2-arylsulfonyl[1,2,5]thiadiazolidine-1,1-dioxides **2** were designed (Fig. 1). These compounds were prepared along with their regioisomers **9** and diarylsulfonylated derivatives **10** (Scheme 1) and their cytotoxicities were measured against human and murine cancer cell lines to compare against those of **1**.

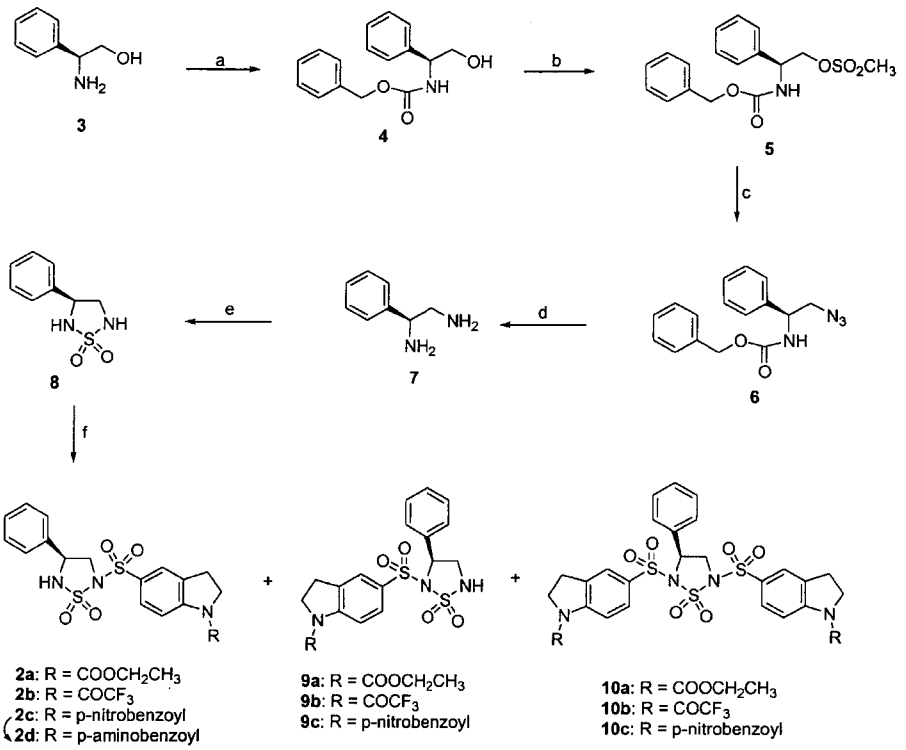


1a: R = $COOCH_2CH_3$
1b: R = $COCF_3$
1c: R = p-nitrobenzoyl
1d: R = p-aminobenzoyl

2a: R = $COOCH_2CH_3$
2b: R = $COCF_3$
2c: R = p-nitrobenzoyl
2d: R = p-aminobenzoyl

Fig. 1. Design of [1,2,5]thiadiazolidine-1,1-dioxides

Correspondence to : Sang-Hun Jung, Ph. D. College of Pharmacy Chungnam National University, Daejeon 305-764, Korea
E-mail: jungshh@cnu.ac.kr



a) benzyl chloroformate, $NaHCO_3$; b) CH_3SO_2Cl, triethylamine; c) NaN_3; d) H_2 (30 psi), Pd-C; e) catecholsulfate, triethylamine; f) NaH, and then arylsulfonyl chloride.

Scheme 1. Preparation of [1,2,5]thiadiazolidine derivatives

MATERIALS AND METHODS

Melting points (mp) were determined on Electrothermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use (Perrin and Armarego, 1982). Thin-layer chromatography was performed on E Merck silica gel GF-254 precoated plates and the identification was done with UV light and colorization with spray 10% phosphomolybdic acid followed by heating. Flash column chromatography was performed with E. Merck silica gel (230-400 mesh). IR spectra were recorded with Jasco IR-Report-100 IR spectrometer in cm-1 and corrected against peak at 1601 cm^{-1} of polystyrene. NMR spectra were measured against the peak of tetramethylsilane by JEOL JNM-EX90 NMR (89.45 MHz) and Varian Unity Inova 400NMR (400 MHz) spectrometers. Elemental analysis was performed with EA1110 elemental analyzer (CE Instrument).

Preparation of (*S*)-2-*N*-benzyloxycarbonylamino-2-phenylethanol 4

(S)-(+)-Phenylglycinol(2.19 g, 15.97 mmol) and sodium bicarbonate(2.00 g, 23.52 mmol) were dissolved in water (40 mL). Bnzyl chloroformate (2.72 g, 15.97 mmol) in tetrahydrofuran (10 mL) was dropped for ten minute. The resulting mixture was stirred for two hours. The white precipitate was filtered and dried. This product was very pure based on TLC and spectroscopic analyses and used in the next step without further purification.

yield 93.2%; R_f 0.23 (hexane : ethyl acetate=2:1); white solid; mp 103.3~104.5°C ; IR (KBr) 3300, 1690, 1540 cm^{-1}; ^{1}H-NMR (acetone-d_6 89.45 MHz) δ 3.82 (m, 2H), 4.80 (m, 1H), 5.05 (s, 2H), 7.23~7.41 (m, 10H); Anal. Calcd. for $C_{16}H_{17}NO_3$ C 70.83, H 6.32, N 5.16, Found: C 70.98, H 6.83, N 5.02.

Preparation of (*S*)-2-*N*-benzyloxycarbonylamino-2-phenylethyl methansulfonate 5

Compound **4** (2.493 g, 9.2 mmol) and triethylamine (3.717 g, 36.80 mmol) were dissolved in dichloromethane (30 mL) and the reaction mixture was cooled to 10°C. Methanesulfonyl chloride (1.049 g, 9.2 mmol) in dichloromethane (20 mL) was slowly added for twenty minutes under 10°C and the resulting mixture was stirred for 30 minutes. The reaction mixture was washed with 5% hydrochloric acid (50 mL) and water three times. The organic layer was dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The residue was recrystallized from methanol.

yield 85.7%; R_f 0.34 (hexane:ethyl acetate = 2 : 1); white solid; mp 131.9~132.1°C ; IR (KBr) 3330, 1690,

1540 cm^{-1}; ^{1}H-NMR (acetone-d_6 89.45 MHz) δ 3.04 (s, 3H), 4.45 (d, J = 5.9 Hz, 2H), 5.08 (m, 3H), 7.34~7.55 (m, 10H). Anal. Calcd. for $C_{17}H_{19}NO_5S$ C 58.44, H 5.48, N 4.01, Found: C 58.52, H 5.41, N 3.87.

Preparation of (*S*)-1-azido-2-*N*-benzyloxycarbonylamino-2-phenylethane 6

Compound **5** (3.81 g, 10.90 mmol) was dissolved in dimethylformamide (20 mL) and sodium azide (4.25 g, 65.38 mmol) was added and the resulting mixture was heated at 55°C for twelve hours. After removal of solvent, the residue was dissolved in ether (60 mL) and dehydrated with sodium sulfate. After evaporation of solvent, the crude product was purified by flash column chromatography.

yield 91.0%; R_f 0.74 (hexane:ethyl acetate = 2 : 1); colorless oil; IR (KBr) 3300, 2100, 1700 cm^{-1}; ^{1}H-NMR (acetone-d_6 89.45 MHz) δ 3.65 (d, J=6.8 Hz, 2H), 4.92 (m, 1H), 5.08 (s, 2H), 7.21~7.51(m, 10H); Anal. Calcd. for $C_{16}H_6N_4O_2$ C 64.85, H 5.44, N18.91, Found: C 64.53, H 5.53, N 18.90.

Preparation of (*S*)-2-phenyl-1,2-diaminoethane 7

Compound **6** (1.08 g, 3.64 mmol) was dissolved in methanol (20 mL) and 10% palladium-carbon (134 mg) was added. The reaction mixture was shaked under hydrogen gas (30 psi) for two hours at room temperature. After removal of catalyst by filtration with aid of celite, the filtrate was concentrated under vacuum to give very pure product 7. This compound was darkened after 10 minutes in the air. Therefore this product was immediately used in the next reaction without further purification.

yield 73.5%; R_f 0.08 (hexane : ethyl acetate=1 : 1); colorless oil; IR (KBr) 3300, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 89.45 MHz) δ 2.85 (m, 2H), 3.91 (dd, J = 5.8, 6.3 Hz, 1H), 7.22~7.51 (m, 5H).

Preparation of (*S*)-(+)-4-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 8

Compound **7** (1.06 g, 7.79 mmol) and triethylamine (1.57 g, 15.58 mmol) were dissolved in dichloromethane (20 mL) and the resulting solution was cooled to 0°C. Catecholsulfate (1.34 g, 7.79 mmol) in dichloromethane (5 mL) was slowly added and stirred for two hours. After removal of dichloromethane under vacuum, dioxane (30 mL) was added to the residue and the reaction mixture was refluxed for two hours. After removal of solvent, the residue was extracted with ethyl acetate (20 mL) two times. The organic layers combined were concentrated under vacuum to give the crude product, which was then purified by flash column chromatography.

yield 64%; R_f 0.37 (hexane : ethyl acetate = 1 : 1); white solid; mp 85.5~86.9 ; $[\alpha]_D^{18}$ =+ 36.66 (c = 1.2%, CH_3OH); IR (KBr) 3300, 1300, 1180 cm^{-1}; ^{1}H-NMR (Acetone-d_6 400 MHz) δ 3.42 (dd, J=7.4, 11.4 Hz, 1H), 3.90 (dd, J = 6.6, 11.4 Hz, 1H), 4.95 (dd, J=6.6, 7.4 1H), 7.29~7.51 (m, 5H); Anal. Calcd. for $C_8H_{10}N_2O_2S$ C 48.47, H 5.08, N 14.13, Found: C 48.58, H 4.96, N 13.87.

Preparation of compounds 2a, 9a, 10a

Compound **8** (307 mg, 1.55 mmol) in dry tetrahydrofuran (20 mL) was added to a suspension of sodium hydride (93 mg, 2.33 mmol) in dry tetarhydrofuran (10 mL) and the resulting mixture was cooled to 0°C. After 30 minute stirring of the reaction mixture, *N*-ethoxycarbonylindoline-5-sulfonyl chloride(448 mg, 1.55 mmol) in tetrahydrofuran (5 mL) was added and the mixture was stirred for one hour. After careful addition of water (10 mL) and then 5% hydrochloric acid (5 mL), the mixture was extracted with ethyl acetate three times. The organic layers combined were dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The crude product was separated by flash column chromatography.

(*S*)-(-)-2-[(*N*-ethoxycarbonyl)indoline-5-sulfonyl]-4-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 2a

yield 38.7%; R_f 0.54 (hexane : ethyl acetate=1 : 1); white solid; mp 171.0~172.5°C ; $[\alpha]_D^{18}$ = -15.49 (c=1 , CH_3OH); IR (KBr) 3200, 1700, 1320, 1180 cm^{-1}; ^{1}H-NMR (acetone-d_6 400 MHz) δ 1.34 (t, J=6.8 Hz, 3H), 3.22 (t, J= 8.4 Hz, 2H), 3.75 (dd, J=7.8, 9.6 Hz, 1H), 4.13 (t, J= 8.4 Hz, 2H), 4.30 (q, J=6.8 Hz, 2H), 4.36 (dd, J=8.8, 9.6 Hz, 1H), 4.98 (m, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.35 (m, 3H), 7.43 (m, 2H), 7.77 (m, 1H), 7.83 (m, 1H); Anal. Calcd. for $C_{19}H_{21}N_3O_6S_2$ C,50.54; H,4.69; N,9.31 Found: C,50.97; H,4.95; N,9.07.

(*S*)-2-[(*N*-ethoxycarbonyl)indoline-5-sulfonyl]-3-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 9a

yield 2.8%; R_f 0.42 (hexane:ethyl acetate=1 : 1); white solid; mp 213.5~215°C ; IR (KBr) 3190, 1700, 1320, 1190 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J=6.8 Hz, 3H), 3.09 (m, 2H) 3.30 (m, 1H), 3.77 (m, 1H), 4.07 (t, J=8.8 Hz, 2H), 4.31 (m, 2H), 5.07 (dd, J=3.6, 6.4 Hz, 1H), 5.87 (m, 1H), 7.287.31 (m, 6H), 7.56 (m, 1H), 7.66 (d, J=8.4 Hz, 1H); Anal. Calcd. for $C_{19}H_{21}N_3O_6S_2$ C,50.54; H,4.69; N,9.31 Found: C,50.75; H,4.78; N,9.58.

(*S*)-2,5-bis[(*N*-ethoxycarbonyl)indoline-5-sulfonyl]-3-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 10a

yield 25.1%; R_f 0.36 (hexane : ethyl acetate=1 : 1); white solid; mp 170.4~173.7°C; IR (KBr) 1710, 1320, 1180

cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.38 (m, 6H), 3.07 (t, J=8.4 Hz, 2H) 3.16 (t, J=8.4 Hz, 2H), 3.62 (dd, J=4.4, 10.4 Hz, 1H), 4.05 (dd, J=7.2, 10.4 Hz, 1H), 4.10 (m, 4H), 4.33 (m, 4H), 4.92 (dd, J=4.4, 7.2 Hz, 1H), 7.15~7.20 (m, 5H), 7.23~7.26 (m, 2H), 7.50 (m, 2H), 7.68 (m, 2H); Anal. Calcd. for $C_{30}H_{32}N_4O_{10}S_3$ C,51.12; H,4.58; N,7.95 Found: C,51.47; H,4.68; N,7.91.

Preparation of compounds 2b, 10b

The method employed for the preparation of **2a** was used for the preparation of **2b** and **10b** by the treatment of **8** (132.7 mg, 0.67 mmol) with *N*-trifluoroacetylindoline-5-sulfonyl chloride (219 mg, 0.67 mmol). The crude product was separated by flash column chromatography to give **2b** and **10b** without compound **9b**.

(*S*)-2-[(*N*-trifluoroacetyl)indoline-5-sulfonyl]-4-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 2b

yield 25.9%; R_f 0.34 (hexane : dichloromethane : methanol = 6 : 6 : 1); yellow solid; mp 216.7~217.9°C ; IR (KBr) 3200, 1700, 1350, 1150 cm^{-1}; ^{1}H-NMR (acetone-d_6, 400 MHz) δ 3.43 (t, J = 8.4 Hz, 2H), 3.81 (dd, J = 8.4, 9.6 Hz, 1H), 4.40 (dd, J = 6.4, 9.6 Hz, 1H), 4.50 (t, J = 8.4 Hz, 2H), 4.94 (m, 1H), 7.32~7.37 (m, 4H), 7.41~7.44 (m, 2H), 7.93~7.96 (m, 2H), 8.26 (d, J = 8.8 Hz, 1H); Anal. Calcd. for $C_{18}H_{16}F_3N_3O_5S_2$ C,45.47; H,3.39; N,8.84 Found: C,45.81; H,3.30; N,8.90.

(*S*)-2,5-bis[(*N*-trifluoroacetyl)indoline-5-sulfonyl]-3-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 10b

yield 24.2 %; R_f 0.49 (hexane : dichloromethane : methanol = 6 : 6 : 1); yellow solid; IR (KBr) 1700, 1390, 1150, 1130 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.22~3.36 (m, 4H), 3.68 (dd, J = 4.4, 10.6 Hz, 1H), 4.07 (dd, J = 7.2, 10.6 Hz, 1H), 4.38 (m, 4H), 4.97 (dd, J = 4.4, 7.2 Hz, 1H), 7.16~7.21 (m, 3H), 7.26 (m, 2H), 7.52 (m, 1H), 7.61 (m, 1H), 7.73 (m, 1H), 7.83 (m, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H);Anal. Calcd. for $C_{28}H_{22}F_6N_4O_8S_3$ C 44.68, H 2.95, N 7.44, Found: C 44.58, H 3.10, N 7.38.

Preparation of compounds 2c, 9c, 10c

The method employed for the preparation of **2a** was used for the preparation of **2c**, **9c**, and **10c** by the treatment of **8** (289 mg, 1.46 mmol) with N-(4-nitrobenzoyl)indoline-5-sulfonyl chloride (535 mg, 1.46 mmol). The crude product was separated by flash column chromatography to give **2c**, **9c**, and **10c**.

(*S*)-(-)-2-[(*N*-4-nitrobenzoyl)indoline-5-sulfonyl]-4-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 2c

yield 32.3;R_f 0.51 (hexane:ethyl acetate=2 : 1); white solid; mp 187.7~188.9°C ; $[\alpha]_D^{18}$ = -12.50 (c=0.8%, CH_3OH); IR (KBr) 3200, 1650, 1350, 1200, 1150 cm^{-1}; ^{1}H-NMR (acetone-d_6, 400 MHz) δ 3.27 (t, J = 8.4 Hz, 2H), 3.78 (dd, J = 8.4, 9.2 Hz, 1H), 4.20 (t, J = 8.4 Hz, 2H), 4.39 (dd, J = 6.4, 9.2 Hz, 1H), 4.95 (m, 1H), 7.32~7.40 (m, 3H), 7.43~7.46 (m, 2H), 7.86~7.89 (m, 2H), 7.94~7.97 (m, 3H), 8.40 (m, 2H); Anal. Calcd. for $C_{23}H_{20}N_4O_7S_2$ C,52.26; H,3.81; N,10.60 Found: C,51.94; H,3.71; N,10.60.

(*S*)-2-[*N*-(4-nitrobenzoyl)indoline-5-sulfonyl]-3-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 9c

yield 5.5%; R_f 0.32 (hexane:ethyl acetate = 2 : 1); white solid; mp 202.6~203.9°C;IR (KBr) 1660, 1520, 1350, 1200 cm^{-1}; ^{1}H-NMR (acetone-d_6, 400 MHz) 3.26 (m, 2H) 3.39 (m, 1H), 3.79 (m, 1H), 4.20 (t, J = 8.8 Hz, 2H), 5.29 (dd, J = 3.6, 6.8 Hz, 1H), 7.20 (m, 1H), 7.33~7.38 (m, 3H), 7.43~7.45 (m, 2H), 7.72 (m, 1H), 7.80 (m, 1H), 7.96 (m, 2H), 8.41 (m, 2H), 8.41 (m, 2H); Anal. Calcd. for $C_{23}H_{20}N_4O_7S_2$ C,52.26; H,3.81; N,10.60 Found: C,52.02; H,3.63; N,10.57;

(*S*)-2,5-bis[*N*-(4-nitrobenzoyl)indoline-5-sulfonyl]-3-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 10c

yield 28.7%; R_f 0.26 (hexane : ethyl acetate = 2 : 1); yellow solid; mp 211.8~212.7°C; IR (KBr) 1680, 1520, 1350, 1200, 1160 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 3.15~3.21 (m, 5H), 3.82 (dd, J=2.8, 11.2 Hz, 1H), 4.17 (m, 4H), 5.51 (dd, J=2.8, 6.8 Hz, 1H), 7.30 (m, 4H), 7.34 (m, 2H), 7.72 (m, 3H), 7.82 (m, 1H), 7.98 (m, 5H), 8.38 (m, 4H); Anal. Calcd. for $C_{38}H_{30}N_6O_{12}S_3$ C,53.14; H,3.52; N,9.78 Found: C,53.46; H,3.66; N,9.45.

Preparation of (*S*)-[*N*-(4-aminobenzoyl)indoline-5-sulfonyl]-4-phenyl[1,2,5]thiadiazolidine-1,1-dioxide 2d

Compound **2c** *(66 mg, 0.125 mmol)* was dissolved in tetrahydrofuran (10 mL) and 10% palladium-carbon (50 mg) was added. The reaction mixture was stirred under hydrogen gas (30 psi) for three hours at room temperature. After removal of catalyst by the filtration with *aid of celite, the filtrate was* concentrated under vacuum and the crude product was purified by flash column chromatography.

R_f 0.33 (hexane : ethyl acetate = 1 : 1); white solid; mp 287.0~288.2°C; yield 96.4; IR (KBr) 1650, 1350, 1180 cm^{-1}; ^{1}H-NMR (acetone-d_6, 400 MHz) δ 3.21 (m, 2H), 3.78 (dd, J =8.4, 9.2 Hz, 1H), 4.25 (m, 2H), 4.36 (dd, J = 6.4, 9.2 Hz, 1H), 4.93 (m, 1H), 6.73 (m, 2H), 7.34~7.38 (m, 3H), 7.43~7.47 (m, 4H), 7.81 (m, 3H); Anal. Calcd for $C_{23}H_{22}N_4O_5S_2$ C,55.41; H,4.45; N,11.24 Found: C,55.33; H,4.56; N,10.93.

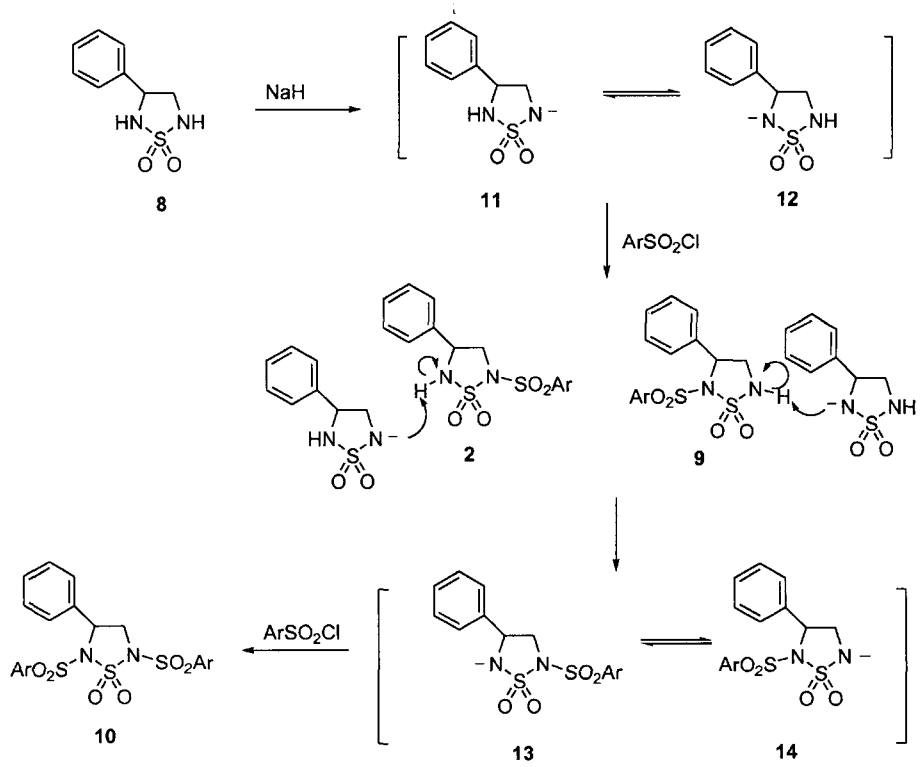
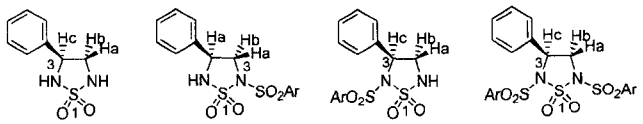


Fig. 2. Postulate mechanism for the formation of **10**

Table 1. The reaction of 8 with arylsulfonylchloride and select NMR data of **8**, **2**, **9**, **10**



Compd. No.	Yield (%)	Total yield (%)	Chemical shift (δ) and multiplicity[a]		
			Ha	Hb	Hc
8			3.42(dd, J=7.4, 11.4)	3.90(dd, J=6.6, 11.4)	4.95(dd, J=6.6, 7.4)
2a	38.7		3.75(dd, J=7.8, 9.6)	4.36(dd, J=8.8, 9.6)	4.98(m)
9a	2.8	66.6	3.30(m)	3.77(m)	5.07(dd, J=3.6, 6.4)
10a	25.1		3.62(dd, J=4.4, 10.4)	4.05(dd, J=7.2, 10.4)	4.92(dd, J=4.4, 7.2)
2b	25.9		3.81(dd, J=8.4, 9.6)	4.40(dd, J=6.4, 9.6)	4.94(m)
9b	0	50.1			
10b	24.2		3.68(dd, J=4.4, 10.6)	4.07(dd, J=7.2, 10.6)	4.97(dd, J=4.4, 7.2)
2c	32.3		3.78(dd, J=8.4, 9.2)	4.39(dd, J=6.4, 9.2)	4.95(m)
9c	5.5	66.5	3.39(m)	3.79(m)	5.29(dd, J=3.6, 6.8)
10c	28		3.21(overlapped with indoline CH_2 peak)	3.82(dd, J=2.8, 11.2)	5.51(dd, J=2.8, 6.8)

Biological assay

Cytotoxicities of compounds **1** (Jung, *et al.*, 1996), **2**, **9** and **10** were measured against human lung carcinoma (A549), Human colon carcinoma (COLO205), Human ovarian cancer (SK-OV-3), Human leukemic cancer (K562), and murine colon adenocarcinoma (Colon26) cell lines *in vitro* using MTT assay (Everitt *et al.*, 1987; Skehon *et al.*, 1990). The results from these tests are shown as IC_{50} values in Table 2, which are mean values from three times measurements.

RESULTS AND DISCUSSION

S-enantiomer of 4-phenyl-2-arylsulfonyl[1,2,5] thiadiazolidine-1,1-dioxides **2** were prepared along with their regioisomers **9** and diarylsulfonyl derivatives **10** as shown in scheme 1. Initially S-(+)-phenylglycinol (Abiko, *et al.*, 1992) was treated with benzyl chloroformate in the presence of sodium bicarbonate to give compound **4** in good yield. In the reaction of **4** with methanesulfonyl chloride, hydroxyl function was transformed to methanesulfonate as a good leaving group, which was then successfully replaced with azide group to generate **6** in the subsequent step. Employing catalytic hydrogenation (30 psi H_2, Pd-C) azide **6** was reduced to diamine **7**, which was quickly darkened in the air. Therefore diamine **7** was immediately treated with cathecholsulfate (Debois, 1980; Lee, *et al.*, 1993) to yield (S)-(+)-3-phenyl [1,2,5]thiadiazolidine-1,1-dioxide (**8**). In the next step, this compound was reacted with one equivqlent of the corresponding N-substituted indoline-5-sulfonyl chloride after treatment of 1.5 equivalent of sodium hydride. In these reactions, approximately equal amount of 4-phenyl-2-arylsulfonyl[1,2,5]thiadiazolidine-1,1-dioxides **2** and diarylsufonylated compounds **10** were formed along with compounds **9** as regioisomers of **2**. These results with the select NMR data are summarized in Table 1. Catalytic hydrogenation of **2c** gave aminobenzoyl derivative **2d**.

Formation of **2** and their regioisomers **9** was confirmed based on NMR spectra of **2** and **9**. Compound **2a** exhibits the absorption peaks at 3.75 (dd) for proton Ha, 4.36 (dd) for proton Hb, and 4.98 (m) for proton Hc. Proton Hc is coupled with NH proton at 5-position as well as Ha and Hb. Thus it shows multiplet. These coupling patterns are obvious in the spectra of **2b** and **2c**. However the regioisomer **9a** and **9c** shows the multiplet peaks for Ha and Hb. Therefore arylsulfonyl groups of **2** are located at 2 position. Chemical shift changes for protons Ha and Hb are another indication for the introduction of arylsulfonyl group at 2-position of **2**. Upon introduction of electron withdrawing group, arylsulfonyl function, at 5-position of **8**, chemical shifts for protons Ha and Hb are moved to downfield about 0.3-0.4 ppm for Ha and 0.4-0.5 ppm for Hb. However chemical shift for Hc remains at nearly same position. These changes obviously result from the effect of electron withdrawing group located to the closest position. In the spectra of regioisomers **9a** and **9c**, absorption peaks for Ha and Hb slightly shift to upfield but peaks for Hc shift downfield about 0.1 and 0.3 ppm upon the introduction of arylsulfonyl group at 2-position of **8**.

Production ratio of **2**, **9**, and **10** may be interpreted by the postulated mechanism shown in Fig. 2. Deprotonated species **11** and **12** undergo the reaction with arylsulfonyl chloride to form **2** and **9**. Compounds **2** are major product because nitrogen at 5-position of **8** is the less hindered side. NH potons of **2** or **9** become more acidic than those of **8**. Therefore proton exchange occurs between **11** and **2** to produce **13**, which was then reacted with remaining arylsulfonyl chloride to produce **10**. Since one equivalent of arylsulfonyl chloride was used, this pattern of product ratio was exhibited.

Cytotoxicities of **1**, **2**, **9**, and **10** were measured three times against measured against human lung carcinoma (A549), human colon carcinoma (COLO205), human ovarian cancer (SK-OV-3), human leukemic cancer (K562), and murine colon adenocarcinoma (Colon26) cell lines *in vitro* using MTT assay (Everitt *et al.*, 1987, Skehon *et al.*, 1990). The results from these tests are shown as mean IC_{50} values in table 2. Compounds **2**, **9**, and **10** do not show any activity against all five cancer cell lines. Although the activities of compounds **9** and **10** are expected when considering structure activity relationship of **1** (regioisomer of **1** and large substituent at 3 position of **1** shows very weak or no activity), the complete disappearance of activity of **2** are rather surprising. Because the structural difference between **1** and **2** are only sp^2 carbonyl function and sp^3 sulfonyl function in five membered ring. Carbonyl function of **1** has been considered as a hydrogen-bonding acceptor. In this point, sulfonyl of **2** may be able to perform the same role. Our model study of these two compounds shows very similar overall conformation. Therefore the planarity of imidazolidinone ring of **1** should be an important factor for their cytotoxic activity.

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