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Effect of Substituents on Benzenesulfonyl Motif of 4-Phenyl-1-arylsulfonylimidazolidinones for Their Cytotoxicity

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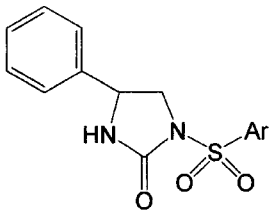
To explore the effect of substituents' on phenyl motif on sulfonyl function of novel anticancer 4-phenyl-1-benzenesulfonylimidazolidinones (**1**), electron donating or withdrawing substituents were introduced at 3 or 4-position and the analogs were tested against human lung (A549) and colon (HCT-15) cancer cell lines. Quantitative structure activity relationship of the 4-substituted series shows that only STERIMOL L values are well correlated. The increment of substituent's volume enhances the activity against both cell lines. The small substituent at 3-position additionally increases the activity. However naphthyl group in place of phenyl reduces the activity. Therefore the phenyl motif with sterically large substituent at 4-position and small substituent at 3-position may be important for their activity. Integration of these substituents' effects into the structural design led to discover the more potent analog, 4-phenyl-1-(*N*-acetylindoline-5-sulfonyl) imidazolidinone (**1n**).

Key words: 4-Phenyl-1-Arylsulfonylimidazolidinone, Cytotoxicity, Substituent's effect, QSAR

INTRODUCTION

Arylsulfonylimidazolidinones were reported (Jung *et al.*, 1996; 1996; 1997; 1997) as analogs possessing the structural characteristics of novel antineoplastic diarylsulfonylurea (Houghton and Houghton, 1996; Howbert, 1991) and broad spectrum of potent activity against the various 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). All substituents at the various position on phenyl at 4-position reduce their activity (Jung *et al.*, 1996). Therefore phenyl moiety without substituent should be optimum at this site for binding to its putative receptor. However their activity were varied on the kind of substitutent on phenyl group on sulfonyl function of **1** (Jung *et al.*, 1996). For the more explicit investigation of this substituents' effect, some analogs of **1** were synthesized and their cytotoxicity were measured against human lung (A549) and colon (HCT-15) cancer cell lines. Furthermore, analysis of the structural geometry of the series versus their cytotoxicity were performed to search for the best parameter of QSAR. These substituents' effects were then integrated into structural design of **1** to explore the more potent analog.



Ar: indicated in table 1

Fig. 1. 1-Arylsulfonyl-4-phenylimidazolidinones (**1**)

MATERIALS AND METHODS

Melting points (m.p.) 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, 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 (200-430mesh). IR spectra were recorded

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with Jasco IR-Report-100 IR spectrometer in cm^{-1} and corrected against peak at 1601 cm^{-1} of polystyrene. NMR spectra were measured in δ against the peak of tetramethylsilane by JEOL JNM-EX90 NMR (89.45) spectrometers. Elemental analysis was performed with EA1110 elemental analyzer (CE Instrument).

General procedure of the synthesis of *N*-arylsulfonylimidazoline 3a and 3b:

The corresponding arylsulfonyl chloride (1 equivalent) was added to the mixture of compounds **2** and sodium bicarbonate (1.5 equivalent) in acetone-water (1:1). The resulting mixture was stirred for two hours at room temperature and then extracted with dichloromethane three times. The organic layer was dehydrated with anhydrous sodium sulfate and evaporated under vacuum. Compounds **3a** and **3b** were then separated from the residue by flash column chromatography.

1-(4-Methoxybenzenesulfonyl)-4-phenyl-2-methoxy-4, 5-dihydroimidazole (3a-1) Rf 0.31 (33% Acetone-Hexanes); white solid; Yield 60%; IR (KBr) 1650, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.72 (dd, J=7.3, 9.4 Hz, 1H), 3.97 (s, 3H), 4.02 (s, 3H), 4.32 (dd, J=9.2, 9.5 Hz, 1H), 4.91 (dd, J=7.3, 9.4 Hz, 1H), 7.10-7.49 (m, 9H).

3-(4-Methoxybenzenesulfonyl)-4-phenyl-2-methoxy-4, 5-dihydroimidazole (3b-1) Rf 0.20 (33% Acetone-Hexanes); white solid; Yield 26%; IR (KBr) 1660, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.54 (dd, J=5.2, 13.5 Hz, 1H), 3.98 (s, 3H), 4.05 (s, 3H), 4.10 (dd, J=9.7, 13.5 Hz, 1H), 5.37 (dd, J=5.2, 9.7 Hz, 1H), 7.20-7.70 (m, 9H).

1-(4-Acetamidobenzenesulfonyl)-4-phenyl-2-ethoxy-4, 5-dihydroimidazole (3a-2) Rf 0.46 (50% Acetone-Hexanes); white solid; Yield 56%; IR (KBr) 3400, 1660, 1365, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J=7.0 Hz, 3H), 2.15 (s, 3H), 3.68 (dd, J=7.2, 9.2Hz, 1H), 4.31 (dd, J=9.0, 9.2 Hz, 1H), 4.34 (q, J=7.0 Hz, 2H), 4.89 (dd, J=7.2, 9.0 Hz, 1H), 7.00-7.40 (m, 5H), 7.60-7.95 (m, 4H), 8.50 (s, 1H).

3-(4-Acetamidobenzenesulfonyl)-4-phenyl-2-ethoxy-4, 5-dihydroimidazole (3b-2) Rf 0.27 (50% Acetone-Hexanes); white solid; Yield 14%; IR (KBr) 3300, 1660, 1340, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J=7.0 Hz, 3H), 2.12 (s, 3H), 3.55 (dd, J=5.3, 13.5 Hz, 1H), 4.00 (dd, J=9.8, 13.5Hz, 1H), 4.29(q, J=7.0 Hz, 2H), 5.33 (dd, J=5.3, 9.8 Hz, 1H), 7.29 (m, 5H), 7.30-7.65 (m, 4H), 8.49 (s, 1H).

1-(4-Fluorobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole(3a-3) Rf 0.36 (33% Acetone-Hexanes); white solid; Yield 62%; IR (KBr) 1680, 1380, 1175 cm^{-1} ; NMR ($CDCl_3$) δ 3.71 (dd, J=7.4, 9.4 Hz, 1H), 3.97 (s, 3H), 4.34 (dd, J=9.4, 9.4 Hz, 1H), 4.93 (dd, J=7.4, 9.4 Hz, 1H), 7.20 (m, 7H), 7.90 (m, 2H).

3-(4-Fluorobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-di-hydroimidazole (3b-3) Rf 0.28 (33% Acetone-Hexanes); white solid; Yield 27%; IR (KBr) 1675, 1360, 1180 cm^{-1} ; NMR ($CDCl_3$) δ 3.50 (dd, J=4.8, 13.6 Hz, 1H), 3.97 (s, 3H), 4.20 (dd, J=9.9, 13.6 Hz, 1H), 5.30 (dd, J=4.8, 9.9 Hz, 1H), 6.90-7.70 (m, 9H).

1-(4-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3a-4) Rf 0.36 (33% Ethyl acetate-Hexanes); white solid; Yield 56%; IR (KBr) 1660, 1350, 1170cm^{-1}; NMR ($CDCl_3$) δ 3.77 (dd, J=7.2, 9.4 Hz, 1H), 3.99 (s, 3H), 4.39 (dd, J=9.2, 9.4 Hz, 1H), 4.98 (dd, J=7.2, 9.2 Hz, 1H), 7.06-7.33 (m, 5H), 8.09 (d, J=7.0 Hz, 2H), 8.38 (d, J=7.0 Hz, 2H).

3-(4-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-4) Rf 0.24 (33% Ethyl acetate-Hexanes); white solid; Yield 26%; IR (KBr) 1670, 1360, 1180cm^{-1}; NMR ($CDCl_3$) δ 3.68 (dd, J=4.6, 13.7 Hz, 1H), 4.01 (s, 3H), 4.23 (dd, J=9.7, 13.7 Hz, 1H), 5.46 (dd, J=4.6, 9.7 Hz, 1H), 7.19-7.43 (m, 5H), 7.62 (d, J=7.3 Hz, 2H), 8.17 (d, J=7.3 Hz, 2H).

1-(3-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3a-5) Rf 0.27 (33% Ethyl acetate-Hexanes); white solid; Yield 6%; IR (KBr) 1675, 1375, 1180 cm^{-1}; NMR ($CDCl_3$) δ 3.78 (dd, J=7.0, 9.5 Hz, 1H), 4.00 (s, 3H), 4.39 (dd, J=9.2, 9.5 Hz, 1H), 4.98 (dd, J=7.0, 9.5 Hz, 1H), 7.05-7.30 (m, 5H), 7.57 (t, J=8.2 Hz, 1H), 8.23 (d, J=8.2 Hz, 1H), 8.50 (d, J=8.2 Hz, 1H), 8.75 (m, 1H).

3-(3-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-5) Rf 0.20 (33% Ethyl acetate-Hexanes); white solid; Yield 26%; IR (KBr) 1680, 1365, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (dd, J=4.4, 13.6 Hz, 1H), 4.00 (s, 3H), 4.19 (dd, J=9.7, 13.6 Hz, 1H), 5.55 (dd, J=4.4, 9.7 Hz, 1H), 7.20-7.70 (m, 7H). 8.21-8.38 (m, 2H).

1-(2-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3a-6) Rf 0.20 (33% Ethyl acetate-Hexanes); white solid; Yield 65%; IR (KBr) 1650, 1350, 1170 cm^{-1}; NMR ($CDCl_3$) δ 3.95 (s, 3H), 4.05 (dd, J=7.7, 9.7 Hz, 1H), 4.54 (dd, J=9.4, 9.7 Hz, 1H), 5.08 (dd, J=7.7, 9.4 Hz, 1H), 7.31 (s, 5H), 7.68-7.76 (m, 3H), 8.17-8.28 (m, 1H).

3-(2-Nitrobenzenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-6) Rf 0.13 (33% Ethyl acetate-Hexanes); white solid; Yield 22%; IR (KBr) 1650, 1350, 1170 cm^{-1};

NMR ($CDCl_3$) δ 3.65 (dd, J=4.3, 13.9 Hz, 1H), 3.88 (s, 3H), 4.24 (dd, J=9.9, 13.9 Hz, 1H), 5.48 (dd, J=4.3, 9.9 Hz, 1H), 7.20-8.10 (m, 9H).

1-(5,6,7,8-Tetrahydronaphthalene-2-sulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3a-7) Rf 0.35 (50% Acetone-Hexanes); white solid; Yield 61%; IR (KBr) 1650, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.73 (m, 4H), 3.68 (dd, J=7.1, 9.5 Hz, 1H), 3.93 (s, 3H), 4.26 (dd, J=9.2, 9.5 Hz, 1H), 4.86 (dd, J=7.1, 9.2 Hz, 1H), 6.97-7.26 (m, 7H), 7.54 (m, 1H).

3-(5,6,7,8-Tetrahydronaphthalene-2-sulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-7) Rf 0.27 (50% Acetone-Hexanes); white solid; Yield 15%; IR (KBr) 1660, 1380, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.75 (m, 4H), 3.51 (dd, J=5.2, 13.3 Hz, 1H), 3.98 (s, 3H), 4.05 (dd, J=9.9, 13.3 Hz, 1H), 5.30 (dd, J=5.2, 9.9 Hz, 1H), 7.00-7.65 (m, 8H)

1-(1-Naphthalenesulfonyl)-4-phenyl-2-ethoxy-4,5-dihydroimidazole (3a-8) Rf 0.35 (50% Acetone-Hexanes); white solid; Yield 70%; IR (KBr) 1680, 1360, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (t, J=7,0 Hz, 3H), 3.94 (dd, J=7.1, 9.5 Hz, 1H), 4.19(q, J=7,0 Hz, 2H), 4.48 (dd, J=9.2, 9.5 Hz, 1H), 4.93 (dd, J=7.1, 9.2 Hz, 1H), 7.07-8.74 (m, 12H).

3-(1-Naphthalenesulfonyl)-4-phenyl-2-ethoxy-4,5-dihydroimidazole (3b-8) Rf 0.27 (50% Acetone-Hexanes); white solid; Yield 18%; IR (KBr) 1670, 1380, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (t, J=7,1 Hz, 3H), 3.58 (dd, J=5.3, 13.4 Hz, 1H), 4.10 (q, J=7,1 Hz, 2H), 4.19 (dd, J=9.9, 13.4 Hz, 1H), 5.58 (dd, J=5.3, 9.9 Hz, 1H), 7.22-8.25 (m, 12H).

1-(2-Naphthalenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3a-9) Rf 0.23 (33% Acetone-Hexanes); white solid; Yield 60%; IR (KBr) 1660, 1370, 1180 cm^{-1}; NMR ($CDCl_3$) δ 3.78 (dd, J=7.2, 9.5 Hz, 1H), 3.96 (s, 3H), 4.38 (dd, J=9.4, 9.5 Hz, 1H), 4.90 (dd, J=7.2, 9.4 Hz, 1H), 7.00-7.25 (m, 5H), 7.59-7.71 (m, 4H), 7.90-8.00 (m, 2H), 8.45 (s, 1H).

3-(2-Naphthalenesulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-9) Rf 0.12 (33% Acetone-Hexanes); white solid; Yield 11%; IR (KBr) 1660, 1360, 1180 cm^{-1}; NMR ($CDCl_3$) δ 3.58 (dd, J=5.0, 14.0 Hz, 1H), 3.94 (s, 3H), 4.19 (dd, J=9.8, 14.0 Hz, 1H), 5.42 (dd, J=5.0, 9.8 Hz, 1H), 7.23-8.01 (m, 12H).

1-(1-Acetylindoline-5-sulfonyl)-4-phenyl-2-methoxy-4, 5-dihydroimidazole (3a-10) Rf 0.28 (33% Ethyl acetate-Hexanes); white solid; Yield 49%; IR (KBr) 1670, 1380, 1180 cm^{-1}; NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.21 (t, J=8.4 Hz, 2H), 3.70 (dd, J=7.2, 9.4 Hz, 1H), 3.95 (s, 3H), 4.10 (t, J= 8.4 Hz, 2H), 4.31 (dd, J=9.2, 9.5 Hz, 1H), 4.88 (dd, J=7.4, 9.2 Hz, 1H), 7.00-7.40 (m, 6H), 7.70 (m, 2H).

3-(1-Acetylindoline-5-sulfonyl)-4-phenyl-2-methoxy-4,5-dihydroimidazole (3b-10) Rf 0.18 (33% Ethyl acetate-Hexanes); white solid; Yield 21%; IR (KBr) 1660, 1395, 1180 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.10 (t, J=8.5 Hz, 2H), 3.55 (dd, J=5.0, 13.4 Hz, 1H), 3.93 (s, 3H), 4.13 (m, 3H), 5.35 (dd, J=5.0, 9.8 Hz, 1H), 7.10-7.60 (m, 8H).

General procedure of the synthesis of imidazolidinones 1: The corresponding compounds **3a** were dispersed in ether and then hydrochloride (1.5 equivalent) in ether (more than 5% w/w concentration) was added. The resulting mixture was stirred for 3 h at room temperature. During the reaction, the reaction mixture became clear solution and then reprecipitated. The white solid was collected, washed with ether, and dried in vacuum oven below 60°C. These reactions can be done in methanolic hydrochloride instead of ethereal hydrochloride.

1-(4-Methoxybenzenesulfonyl)-4-phenylimidazolidinone (1c) obtained from **3a-1**, white solid; Yield 93%; m.p. 181.4-182.2°C; IR (KBr) 3280, 1740, 1720, 1350, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (dd, J=6.8, 9.2 Hz, 1H), 3.97 (s, 3H), 4.28 (dd, J=8.8, 9.2 Hz, 1H), 4.78(dd, J=6.8, 8.8 Hz, 1H), 6.10(s, exchangeable, 1H), 7.10-7.80 (m, 7H), 7.90-8.10 (m, 2H); Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C 57.82, H 4.85 N 8.43; Found C 57.65, H 4.95, N 8.38.

1-(4-Acetamidobenzenesulfonyl)-4-phenylimidazolidinone (1d) obtained from **3a-2**, white solid; Yield 65%; m.p. 216.4-217.2°C; IR (KBr) 3300, 3260, 1725, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.53 (dd, J=6.2, 8,8 Hz, 1H), 4.31 (dd, J=8.8, 8.9 Hz, 1H), 4.83 (dd, J= 6.2, 8.9 Hz, 1H), 6.20 (s, exchangeable, 1H), 7.20-8.30 (m, 9H), 10.54 (s, exchageable, 1H); Anal. Calcd for $C_{17}H_{17}N_3O_4S$: C 56.81, H 4.77, N 11.69; Found C 56.57, H 4.81, N 11.72.

1-(4-Fluorobenzenesulfonyl)-4-phenylimidazolidinone (1f) obtained from **3a-3**, white solid; Yield 71%; m.p. 146.0-147.8°C; IR (KBr) 3225, 1725, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (dd, J=6.8, 9.2 Hz, 1H), 4.28 (dd, J=8.8, 9.2 Hz, 1H), 4.78 (dd, J=6.8, 8.8 Hz, 1H), 6.10 (s, exchangeable, 1H), 7.10-7.80 (m, 7H), 7.90-8.10 (m, 2H); Anal. Calcd for $C_{15}H_{13}N_2O_3S$: C 56.24, H 4.09, N 8.74; Found C 56.34, H 4.11, N 8.62.

1-(4-Nitrobenzenesulfonyl)-4-phenylimidazolidinone (1g) obtained from **3a-4**, white solid; Yield 50%; m.p. 212.0-213.8°C; IR (KBr) 3220, 1730, 1360, 1180 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (dd, J=6.4, 9,0 Hz, 1H), 4.38 (dd,

J=9.0, 9.2 Hz, 1H), 4.85 (dd, J=6.4, 9.2 Hz, 1H), 6.15 (s, exchangeable, 1H), 7.26-7.50 (m, 5H), 8.20 (d, J=9.0 Hz, 2H), 8.46 (d, J=9.0 Hz, 2H); Anal. Calcd for $C_{15}H_{13}N_3O_5S$: C 51.87, H 3.77, N 12.10; Found C 51.64, H 3.87, N 12.02.

1-(3-Nitrobenzenesulfonyl)-4-phenylimidazolidinone (1h) obtained from **3a-5**, white solid; Yield 62 %; m.p. 157.5-158.6°C; IR (KBr) 3275, 1760, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (dd, J=6.2, 8.8 Hz, 1H), 4.41 (dd, J=8.8, 9.0 Hz, 1H), 4.88 (dd, J=6.2, 9.0 Hz, 1H), 6.10(s, exchangeable, 1H), 7.43 (m, 6H), 8.00 (t, J=8.3 Hz, 1H), 8.43 (d, J=8.3 Hz, 1H), 8.63 (d, J=8.3 Hz, 1H). Anal. Calcd for $C_{15}H_{13}N_3O_5S$: C 51.87, H 3.77, N 12.10; Found C 51.68, H 3.83, N 12.17.

1-(2-Nitrobenzenesulfonyl)-4-phenylimidazolidinone (1j) obtained from **3a-6**, white solid; Yield 30 %; m.p. 142.5-143.4°C; IR (KBr) 3280, 1740, 1720, 1350, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.67 (dd, J=6.2, 9,0 Hz, 1H), 4.41 (dd, J=9.0, 9.4 Hz, 1H), 4.95 (dd, J=6.2, 9.4 Hz, 1H), 6.15 (s, exchangeable, 1H), 7.38 (m, 5H), 7.89-8.46 (m, 4H); Anal. Calcd for $C_{15}H_{13}N_3O_5S$: C 51.87, H 3.77, N 12.10; Found C 51.74, H 3.81, N 12.15.

1-(5,6,7,8-Tetrahydronaphthalene-2-sulfonyl)-4-phenylimidazolidinone (1k) obtained from **3a-7**, white solid; Yield 30%; m.p. 196.7-198.0°C; IR (KBr) 3280, 1720, 1350, 1160 cm^{-1}; NMR(DMSO-d_6) δ 1.78 (m, 4H), 2.82 (m, 4H), 3.54 (dd, J=6.2, 8,9 Hz, 1H), 4.31 (dd, J=8.9, 9.2 Hz, 1H), 4.83 (dd. J=6.2, 9.2 Hz, 1H), 7.30-7.88 (m, 7H), 8.23 (m, 1H); Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C 64.02, H 5.66, N 7.86; Found C 63.89, H 5.70, N 7.90.

1-(1-Naphthalenesulfonyl)-4-phenylimidazolidinone (1l) obtained from **3a-8**, white solid; Yield 62%; m.p. 157.5-159.0°C; IR (KBr) 3275, 1760, 1360, 1160 cm^{-1}; NMR (DMSO-d_6) δ 3.71 (dd, J=5.4, 9.2 Hz, 1H), 4.49 (dd, J= 8.8, 9.2 Hz, 1H), 4.85 (dd, J=5.4, 8.8 Hz, 1H), 7.27 (m, 5H), 7.63-7.79 (m, 3H), 8.09-8.61 (m, 4H); Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C 64.76, H 4.58, N 7.95; Found C 64.58, H 4.70, N 8.15.

1-(2-Naphthalenesulfonyl)-4-phenylimidazolidinone (1m) obtained from **3a-9**, white solid; Yield 71.3%; m.p. 153.7-155.0°C; IR (KBr) 3275, 1760, 1360, 1160 cm^{-1}; NMR (DMSO-d_6) δ 3.64 (dd, J=6.2, 9,4 Hz, 1H), 4.43 (dd, J=8.8, 9.4 Hz, 1H), 4.88 (dd, J=6.2, 8.8 Hz, 1H), 7.33 (m, 5H), 7.74-8.29 (m, 6H), 8.68(s, 1H); Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C 64.76, H 4.58, N 7.95; Found C 64.62, H 4.68, N 8.17.

1-(1-Acetylindoline-5-sulfonyl)-4-phenylimidazolidinone (1n) obtained from **3a-10**, white solid; Yield 75%; m.p. 253.0-254.3°C; IR (KBr) 3400, 3220, 1720, 1650, 1360, 1180, 1160 cm^{-1}; NMR (DMSO-d_6) δ 3.27 (t, J=8.5 Hz, 2H), 3.64 (dd, J=6.2, 9,4 Hz, 1H), 4.20 (t, J= 8.5 Hz, 2H), 4.43 (dd, J=8.8, 9.4 Hz, 1H), 4.88 (dd, J=6.2, 8.8 Hz, 1H), 7.33(m, 6H), 7.74-8.29 (m, 2H), 8.68 (s, 1H); Anal. Calcd for $C_{19}H_{19}N_3O_4S$: C 59.21, H 4.97, N 10.90; Found C 59.12, H 5.10, N 10.87.

Biological assay

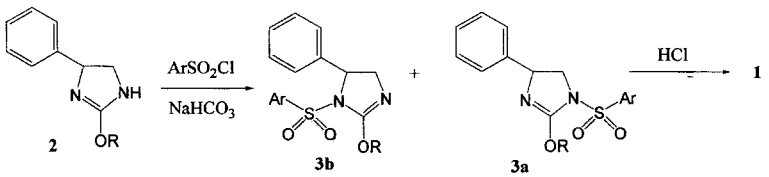
Cytotoxicities of compounds **1** (Jung *et al.*, 1996) were measured against human lung carcinoma (A549), human ovarian (SK-OV-3), human melanoma (SK-MEL-2), brain (XF 498), and colon (HCT-15) cell lines *in vitro* using sulforhodamine B(SRB) assay (Everitt *et al.*, 1987, Skehon *et al.*, 1990). The results from these tests are shown as IC_{50} values in Table I.

QSAR analysis

Compound **1a** with benzenesulfonyl group was selected as a basic unit and seven derivatives with a substituent at 4-position of benzenesulfonyl group were included for QSAR analysis. The logarithmic values of inversed IC_{50} of these compounds against A549 and HCT-15 were correlated with STERIMOL L parameters (Skagerberg *et al.*, 1989). The L parameter was 2.06, 2.87, 3.98, 5.09, 3.52, 2.65, and 3.44 for 4-hydrogen (**1a**), 4-methyl (**1b**), 4-methoxy (**1c**), 4-acetamido (**1d**), 4-chloro (**1e**), and 4-fluoro (**1f**) group, respectively. The fitting was done using least square method.

RESULTS AND DISCUSSION

For finding the substituents' effect on phenyl at sulfonyl function of **1** for their activity, compounds **1** with the various substituents at this phenyl were prepared as shown in scheme 1. Their cytotoxicity were measured against human lung (A549) and colon (HCT-15) cancer cell lines (Everitt *et al.*, 1987, Skehon *et al.*, 1990). The



Scheme 1. Synthesis of 1-arylsulfonyl-4-phenylimidazolidinones (**1**)

Table I. Cytotoxicity of compounds 1

entry No	comp'd. No.	Ar	molecular formular	IC_{50}(M)[a]		L[b]
				A549	HCT-15	
1	1a[c]	Ph	$C_{15}H_{14}N_2O_3S$	144.54	15.21	2.06
2	1b[c]	4CH_3Ph	$C_{16}H_{16}N_2O_3S$	12.45	2.05	2.87
3	1c	4CH_3OPh	$C_{16}H_{16}N_2O_4S$	4.06	1.53	3.98
4	1d	4CH_3CONHPh	$C_{17}H_{17}N_3O_4S$	2.28	0.86	5.09
5	1e[c]	4ClPh	$C_{15}H_{13}ClN_2O_3S$	9.47	0.44	3.52
6	1f	4FPh	$C_{15}H_{13}FN_2O_3S$	20.57	4.05	2.65
7	1g	4O_2NPh	$C_{15}H_{13}N_3O_5S$	18.65	2.16	3.44
8	1h	3O_2NPh	$C_{15}H_{13}N_3O_5S$	26.86	2.96	
9	1i	2O_2NPh	$C_{15}H_{13}N_3O_5S$	29.73	15.46	
10	1j[c]		$C_{18}H_{18}N_2O_3S$	0.91	0.13	
11	1k		$C_{19}H_{20}N_2O_3S$	5.36	2.55	
12	1l		$C_{19}H_{20}N_2O_3S$	103.0	51.64	
13	1m		$C_{19}H_{20}N_2O_3S$	29.02	17.16	
14	1n		$C_{19}H_{19}N_3O_4S$	0.54	0.21	
		sulofenur	$C_{16}H_{15}ClN_2O_3S$	25.26	14.22	

[a]IC_{50} values are the mean value of three times measurement. Cell lines used for test are human lung (A549) and colon (HCT-15) cancer cell lines. [b] Parameter L values are for the substituents on phenyl group of entry number 1 to 7. [c]Compounds 1a, 1b, 1e, and 1j are prevously reported (Jung *et al.*, 1996).

results are listed in Table I.

Introduction of the substituents at 4-position (entry No. 1-7 in Table I) of phenyl on sulfonyl group of **1** enhance the activity against both cell lines regardless of their electronic or hydrophobic properties compared to the activity of **1a**,. Analysis of quantitative structure acticity relationship with these seven compounds possessing a substituent at 4-position shows the best correlation of cytotoxicity with STERIMOL L parameter (Skagerberg *et al.*, 1989) as shown in equation [1] for activity against A549 and equation [2] for activity against HCT-15.

Log 1/C=0.540(0.107)L-2.931(0.374) [1]
n=7r=0.914 s=0.257

Log 1/C=0.377(0.148)L-1.586(0.518) [2]
n=7r=0.751 s=0.356

STERIMOL L value is the parameter for length of substituents and reflects their volume. Increment of L value certainly enhances the activity of analogs **1** against both cell lines. Therefore the volume of substituents at 4-position is major factor to increase the activity of **1**. Compound **1d** with acetamido group, the largest substituents of seven, exhibits the most potent activity among these seven compounds. Nitro substitued compounds **1g**, **1h**, and **1i** show the potentiated activity compared to **1a**. Especially the enhancement of activity of 4-substituted one is most pronounced. This might result from the most volume increase due to substitution at 4-position. This fact also implies the importance of the volume increase at this site for activity of **1**. However the effects of substitution at 3-position may be additive. Compounds **1j** and **1k** are considered to be 3,4-disubstituted analogs of **1** and exhibit remarkable activity against both cell lines. Compound **1k** with tetrahydronaphthylsulfonyl group has more volume increase at 3-position compared to **1j** with indanesulfonyl group and shows less activity. Therefore the larger volume increment at 3-position seems to be less favorable. Naphthyl groups in place of phenyl reduces the activity of **1** as shown in the activity of **1l** and **1m.** This might indicate that the extension of aromatic ring on phenyl motif at sulfonyl do not increase the volume at these sites as much as sp^3 hybridized substituents. Therefore only phenyl motif on sulfonyl function of **1** is required at this position for their potent activity.

Based on these effects of substituents' at 3 and 4-position of phenyl, compound **1n** with *N*-acetylindoline moiety was designed and shows much enhanced activity against both cell lines as shown in Table I. These reflect that the steric factor of the substituents at 3, 4-position of phenyl moiety on sulfonyl of **1** is an important parameter for the

enhancement of activity of this series. Considering these results and the structure activity relationship of **1** observed previously, 4-phenyl-1-(benzenesulfonyl)imidazolidinone moiety is considered as a pharmacophore of this series.

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