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Stereochemical Requirement at 4-Position of 4-Phenyl-1-arylsulfonylimidazolidinones for their Cytotoxicities

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In order to investigate the stereochemical requirements of planar structure at 4-position of 4-phenyl-1-arylsulfonylimidazolidinones (**1**) for their cytoxicities against human cancer cell lines, the size, the distance from imidazolidinone ring, and the conformation of this moiety were variegated. Replacement of phenyl moiety with naphthyl in compouds **2** and **3** or benzyl moiety in compound **4** sharply reduced activity of **1**. Conformational restriction on phenyl ring in compound **5** also resulted in the loss of activity of **1**. Therefore, phenyl moiety without any substituents directly attached to imidazolidinone ring of **1** should be considered as an essential pharmacophore for this analog.

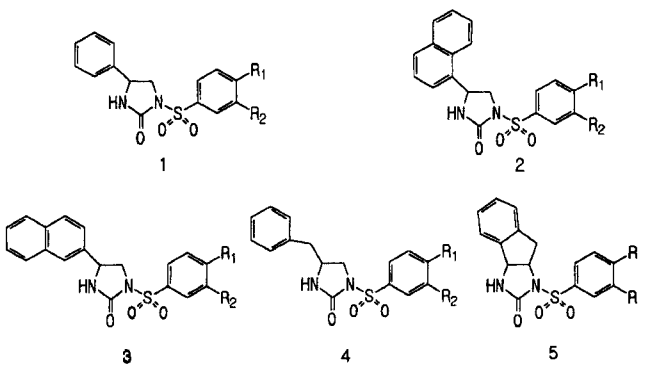
Key words: Stereochemical requirement, 4-Phenyl-1-arylsulfonylimidazolidinones, Cytotoxicity

INTRODUCTION

Unique structure and mode of action of diarylsulfonylureas as a novel antineoplastic agent (Howbert, 1991, Houghton and Houghton, 1996) led us to investigate the various compounds containing sulfonylurea pharmacophore. As a result, highly potent cytotoxicities of novel 4-phenyl-1-arylsulfonyl imidazolidinones **1** having this structural characteristics against various cancer cell lines were previously demonstrated (Jung, *et al.*, 1996, 1996, Jung, *et al.*, 1997). To find out the structure activity relationship of this analog, the role of phenyl function for their activity was initially defined (Jung and Kwak, 1997). Replacement of phenyl moiety with cyclohexyl at 4-position of imidazole ring of **1** completely removed the activity of this analog. This fact clearly proved the importance of aromatic structural motif at 4-position of imidazole ring of **1** for their activities. Therefore, the further exploration of various stereochemical factors influencing their activity around 4-position such as size of aromatic ring, distance between two aromatic rings, and conformational relationship between aromatic ring and imidazole ring of **1** have been attempted for the more effective design in these series. Now we have synthesized compounds **2, 3, 4,** and **5** as shown in Scheme 1 and 2 and measured their cytotoxicities.

MATERIALS AND METHODS

Melting points (m.p.) were determined on Electrothermal 1A 9100 MK2 apparatus and were 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



a' : R_1=Cl, R_2=H; b' : R_1=CH_3, R_2=H; c' : R_1,R_2= $-(CH_2)_3-$

Fig. 1. Arylsulfonylimidazolidinones

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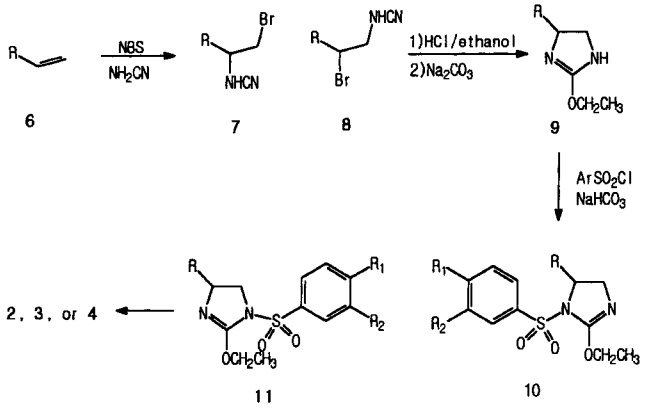
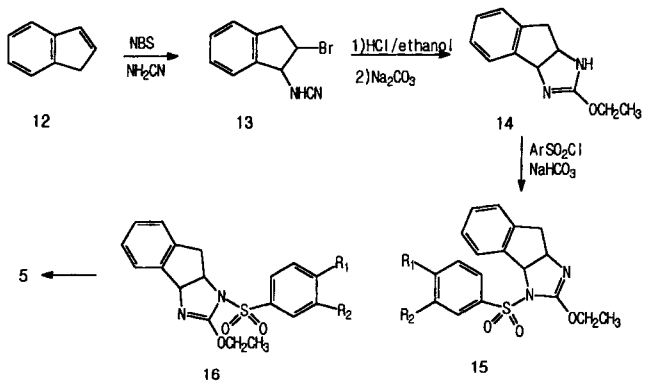


R= a:1-naphthyl, b:2-naphthyl, or c:benzyl
R_1 and R_2 are shown in figure 1.

Scheme 1. Synthesis of compounds **2, 3,** or **4**



R_1 and R_2 are shown in figure 1.

Scheme 2. Synthesis of compounds **5**

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 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 Varian Gemini 200NMR (200MHz) or JEOL JNM-EX90 NMR (89.45 MHz) spectrometers. Mass spectra (Ms) were obtained by GC-Mass PP-1000 mass spectrometer. Elemental analysis was performed with EA1110 elemental analyzer (CE Instrument).

General procedure for the synthesis of bromocyanamide 7, 8 and 13:

The solution of **6a, 6b, 6c,** or **12** in dichloromethane was added to the mixture of *N*-bromosuccinimide (1.3 equivalent) and cyanamide (2 equivalent) in dichloromethane over 1 h at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight and washed with 5% aqueous sodium thiosulfate and brine. After dehydration with anhydrous sodium sulfate, the solvent was evaporated under vacuum. The crude products were purified by flash column chromatography.

2-Bromo-1-(1-naphthyl)ethylcyanamide (7a)- Rf 0.29 (hexane : ethyl acetate=2 : 1); yield 45%; brown oil; IR (KBr) 3440, 2950, 2205cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 3.72 (m, 2H), 4.90 (1H, exchangeable proton), 5.32 (dd, J=5.0, 8.1 Hz, 1H), 7.45~7.88 (m, 7H); MS(rel %) 277 (8.5), 276(57), 275(8.0), 274(60), 235(50), 233(59), 221 (8.0), 219(8.5), 181(100), 154(100).

2-Bromo-1-(2-naphthyl)ethylcyanamide (7b)- Rf 0.14 (hexane : ethyl acetate=4 : 1); yield 63%; brown oil; IR (KBr); 3190 2920 2220 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 3.69 (d, J=7.0 Hz, 2H), 4.68 (t, J=7.0 Hz, 1H), 4.66 (1H, exchangeable proton), 7.35~7.90 (m, 7H) ; Ms(rel %); 277(3.1) 276(15.2), 275(2.3) 274(18.2), 235(12.2), 233(11.0), 195(10), 181(100), 154(48.9).

2-Bromo-3-phenylpropylcyanamide (7c)- Rf 0.09 (hexane: ethyl acetate=4 : 1); yield 25%; yellow oil; IR (KBr) 3200, 2925, 2220 cm^{-1}; NMR (200MHz,$CDCl_3$) δ 3.23 (d, J=7.5 Hz, 2H), 3.34 (dd, J=7.0, 14.2 Hz, 1H), 3.46 (dd, J=3.9, 14.2 Hz, 1H), 4.32 (m, 1H), 4.79 (1H, exchangeable proton), 7.28 (m, 5H); Ms(rel %) 241 (45.3), 239 (47.0), 199 (6.8), 197(6.6), 185 (8.9), 183 (6.8), 117(100): **1-bromo-2-cyanamino-3-phenylpropane (8c)**- Rf 0.15 (hexane : ethyl acetate=4 : 1); yield 19%; yellow solid; m.p. 27.9~30.2; yield 19%; IR (KBr) 3190, 2925, 2220 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 2.98 (m, 2H), 3.40 (dd, J=6.8,11.8 Hz, 1H), 3.53 (m, 2H), 4.09 (1H, ex-changeable proton), 7.28 (m, 5H); Ms(rel %) 241(2.3), 240(7.1), 239(3.8), 238(7.3), 172(4.2), 170(3.7), 149 (13.2), 147 (11.0), 91(100).

2-Bromo-1-cyanaminoindane (13)- Rf 0.19 (benzene : acetone=9 : 1); yield 49%; white solide; m.p. 103.9~105.6°C; NMR (200MHz, $CDCl_3$) 3.27 (dd, J=7.8, 16.1 Hz, 1H), 3.61 (dd, J=7.3, 16.1 Hz, 1H), 4.38 (m, 1H), 4.49 (1H, exchangeable proton), 4.76 (d, J=7.8 Hz, 1H), 7.34 (m, 4H).

General procedure for the synthesis of 2-alkoxy-4,5-dihydroimidazoles 9 and 14:

The solution of bromocyanamide **7, 8,** or **13** in alcohol (methanol or ethanol) was added to the alcoholic hydrochloride (1.5 equivalent) at room temperature. The concentration of hydrochloride was controlled to be

more than 5% hydrochloride in the resulting solution. The reaction mixture was stirred at room temperature for 6-8 h and then sodium carbonate (2.5 equivalent) was added and stirred overnight at room temperature. After the insoluble material was filtered off, the filtrate was concentrated to give the crude product. The crude product **14** was recrystallized from ethyl acetate. However, crude products **9a, 9b,** and **9c** were used in the next reaction without purification due to the difficulty in chromatographic separation.

4-(2-Naphthyl)-2-ethoxy-4,5-dihydroimidazole (9b)-IR (KBr) 3400, 2960, 1620 cm^{-1}; NMR (89.45 MHz, $CDCl_3$) δ 1.37 (t, J=7.1 Hz, 3H), 3.52 (dd, J=7.9, 10.6 Hz, 1H), 3.90 (1H, exchangeable proton), 4.07 (dd, J=9.5, 10.6 Hz, 1H), 4.35 (q, J=7.1 Hz, 2H), 5.10 (dd, J=7.9, 9.5 Hz, 1H), 7.39~7.87 (m, 7H).

2-Ethoxy-cis-3a,8b-dihydroindano[1,2-d]imidazole (14) - white solid; yield 49%; IR (KBr) 3200, 2970, 2920, 1610, 1295 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.24 (t, J= 7.1 Hz, 3H), 3.10 (dd, J=2.5, 17.2 Hz, 1H), 3.35 (dd, J=7.3, 17.2 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 4.35 (1H, exchangeable proton), 4.71 (m, 1H) 5.24 (d, J=8.1 Hz,1H), 7.25 (m, 4H).

General procedure for the synthesis of *N*-arylsulfonylimidazoline 11 and 16:

The corresponding arylsulfonyl chloride (1 equivalent) was added to the mixture of compounds **9** or **14** and sodium bicarbonate (1.5 equivalent) in acetone-water (1:1). The resulting mixture was stirred for 2 h at room temperature and then extracted with dichloromethane three times. The organic layer was dehydrated with anhydrous sodium sulfate and evaporated under vacuum. The residue was then separated by flash column chromatography to give compounds **10** and **11** (**15** and **16** from **14**) in approximate ratio of 1:4.

3-(4-Chlorobenzenesulfonyl)-4-(1-naphthyl)-2-ethoxy-4,5-dihydroimidazole (10a-a')- Rf 0.16 (hexane : ethyl acetate=2 : 1); yield 12%; white solid; m.p. 135.4~136.5°C; IR (KBr) 3420, 1660, 1365, 1165 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.42 (t, J=7.1 Hz, 3H), 3.58 (dd, J=5.3, 13.6 Hz, 1H), 4.34 (m, 3H), 6.13 (dd, J=5.3, 10.1 Hz,1H), 7.29~7.95 (m, 11H):**1-(4-Chlorobenzenesulfonyl)-4-(1-naphthyl)-2-ethoxy-4,5-dihydroimidazole(11a-a')**- Rf 0.26 (hexane : ethyl acetate=2 : 1); yield 44%; white solid; m.p. 123.1 126.9°C; IR (KBr) 3400, 3050, 2970, 1655cm^{-1}; NMR (89.45MHz, $CDCl_3$) 1.43 (t, J=7.1 Hz, 3H), 3.70 (dd, J=7.1, 9.7 Hz, 1H), 4.50 (m, 3H), 5.65 (dd, J=7.1, 9.5 Hz, 1H), 7.30~7.94 (m, 11H).

1-(4-Methylbenzenesulfonyl)-4-(1-naphthyl)-2-ethoxy-4,5-dihydroimidazole (11b-b')- Rf 0.43 (hexane : ethyl acetate=2 : 1); yield 45%; white solid; m.p. 123.5-124.7 °C; IR (KBr) 3420, 3040, 2960, 1650 cm^{-1}; NMR (89.45 MHz, $CDCl_3$) δ 1.40 (t, J=7.1 Hz, 3H), 2.44 (s, 3H), 3.72 (dd, J=7.2, 9.5 Hz,1H), 4.45 (m, 3H), 5.63 (dd, J=7.1, 9.5 Hz,1H), 7.23 7.93 (m, 11H).

3-(Indane-5-sulfonyl)-4-(1-naphthyl)-2-ethoxy-4,5-dihydroimidazole (10a-c')- Rf 0.40 (hexane : ethyl acetate =2 : 1); yield 13%; white solid; m.p. 130.4~132.0°C; IR (KBr) 3400, 2940, 2900, 1660 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H), 2.06 (m, 2H), 2.86 (m, 4H), 3.51 (dd, J=5.3, 13.2 Hz, 1H), 4.30 (m, 3H), 6.09 (dd, J=5.3, 9.9 Hz, 1H), 7.24 7.80 (m, 10H).**1-(Indane-5-sulfonyl)-4-(1-naphthyl)-2-ethoxy-4,5-dihydroimidazole (11a-c')**- Rf 0.5(hexane : ethyl acetate =2 : 1); yield 47%; white solid; m.p. 123.7~125.9°C; IR (KBr) 3400, 2940, 1650 cm^{-1}; NMR (89.45MHz, $CDCl_3$) 1.47 (t, J=7.1 Hz, 3H), 2.13 (m, 2H), 2.95 (m, 4H), 3.72 (dd, J=7.0, 9.4 Hz, 1H), 4.50 (m, 3H), 5.62 (dd, J=7.0, 9.7 Hz, 1H), 7.25 7.93 (m, 10H).

3-(4-Chlorobenzenesulfonyl)-4-(2-naphthyl)-2-ethoxy-4, 5-dihydroimidazole (10b-a')- Rf 0.22 (hexane : ethyl acetate=2 : 1); white wax; IR (KBr) 3350, 3050, 2975, 1660 cm^{-1}; NMR (200MHz, $CDCl_3$) 1.41 (t, J=7.0 Hz, 3H), 3.67 (dd, J=4.8, 13.6 Hz, 1H), 4.21 (dd, J=9.9, 13.6 Hz, 1H), 4.37 (q, J=7.0 Hz, 2H), 5.55(dd, J=4.8, 9.9 Hz, 1H), 7.16~7.32 (m, 2H), 7.40~7.50 (m, 4H), 7.80~7.90 (m, 5H): **1-(4-Chlorobenzenesulfonyl)-4-(2-naphthyl)-2-ethoxy-4,5-dihydroimidazole(11b-a')**- Rf 0.37 (hexane : ethyl acetate=2 : 1); white wax; IR (KBr) 3400, 3050, 2975, 1655 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.41 (t, J=7.0 Hz, 3H), 3.80 (dd, J=7.2, 9.6 Hz, 1H), 4.41 (m, 3H), 5.11 (dd, J=7.2, 9.2 Hz, 1H), 7.20 (dd, J=1.7, 8.5 Hz, 1H), 7.43 7.57 (m, 5H), 7.73 7.90 (m, 5H).

1-(4-Methylbenzenesulfonyl)-4-(2-naphthyl)-2-methoxy-4,5-dihydroimidazole (11b-b')- Rf 0.28 (hexane : ethyl acetate=2 : 1); yield 45%; white solid; m.p. 125.8~127.4 °C; IR (KBr) 3400, 3050, 2950, 1660 cm^{-1}; NMR (89.45 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.80 (dd, J=7.1, 9.6 Hz, 1H), 4.02 (s, 3H), 4.40 (dd, J=9.4, 9.6 Hz, 1H), 5.06 (dd, J=7.1, 9.4 Hz,1H), 7.23~7.85 (m, 11H).

3-(Indane-5-sulfonyl)-4-(2-naphthyl)-2-methoxy-4,5-dihydroimidazole (10b-c')- Rf 0.17 (hexane : ethyl acetate =2 : 1); yield 16%; white solid; m.p. 135.6 137.5°C; IR (KBr) 3400, 3050, 2950, 1660 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.97 (m, 2H), 2.50~2.93 (m, 4H), 3.63 (dd, J=5.1, 13.6 Hz, 1H), 3.99 (s, 3H), 4.16 (dd, J=9.9, 13.6 Hz, 1H), 5.50 (dd, J=5.1, 9.9 Hz, 1H), 7.17~7.79 (m,10H):**1-(Indane-5-sulfonyl)-4-(2-naphthyl)-2-methoxy-4,5-dihydroimidazole (11b-c')**- Rf 0.33 (hexane : ethyl

acetate=2 : 1); yield 49%; white solid; m.p. 103.8~105.6 °C; IR (KBr) 3400, 2950, 1660 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 2.09 (m, 2H), 2.91 (m, 4H), 3.80 (dd, J=7.1, 9.6 Hz, 1H), 4.01 (s, 3H), 4.39 (dd, J=9.4, 9.6 Hz, 1H), 5.06 (dd, J=7.1, 9.4 Hz, 1H), 7.11~7.79 (m, 10H).

3-(4-Chlorobenzensulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (10c-a')- Rf 0.46 (hexane : ethyl acetate=2 : 1); yield 22%; white solid; IR (KBr) 3325, 2980, 1610 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.18 (t, J= 6.8 Hz 3H), 3.13 (d, J=7.7 Hz, 2H), 3.61 (m, 2H), 4.22 (m, 3H), 7.11 7.47 (m, 7H), 7.89 (d, J=8.8 Hz, 2H):**1-(4-Chlorobenzensulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (11c-a')**- Rf 0.32 (hexane : ethyl acetate =2 : 1); yield 40%; colorless oil; IR (KBr) 3400, 2980, 2925, 1660 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.31 (t, J= 7.1 Hz, 3H), 2.62 (dd, J=8.5, 13.8 Hz, 1H), 2.96 (dd, J=4.8, 13.8 Hz, 1H), 3.60 (dd, J=6.3, 9.4 Hz, 1H), 3.83 (dd, J=8.8, 9.4 Hz, 1H), 4.11 (m, 1H), 4.26 (q, J=7.1 Hz, 2H), 7.11~7.32 (m, 5H), 7.46 (m, 2H), 7.74 (m, 2H).

3-(4-Methylbenzenesulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (10c-b')- Rf 0.32 (hexane : ethyl acetate=2 : 1); yield 20%; yellow oil; IR (KBr) 3300, 2960, 2905, 1600 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.17 (t, J=7.0 Hz, 3H), 2.39 (s, 3H), 3.12 (d, J=7.5 Hz, 2H), 3.57 (m, 2H), 4.22 (m, 3H), 7.18~7.88 (m, 7H), 7.84 (d, J=8.3 Hz,2H): **1-(4-Methylbenzenesulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (11c-b')**- Rf 0.20 (HX : EA=2 : 1); yield 50%; yellow oil; IR (KBr) 2960, 2910, 1650cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.30 (t, J= 7.1 Hz, 3H), 2.42 (s, 3H), 2.51 (dd, J=8.7, 13.6 Hz, 1H), 2.96 (dd, J=5.0, 13.6 Hz, 1H), 3.58 (dd, J=6.2, 9.5 Hz, 1H), 3.77 (dd, J=8.7, 9.5 Hz, 1H), 4.03 (m, 1H), 4.22 (q, J=7.1 Hz, 2H), 7.09 7.30 (m, 7H), 7.70 (d, J=8.4 Hz, 2H).

3-(Indane-5-sulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (10c-c')- Rf 0.44 (hexane : ethyl acetate =2 : 1); yield 7%; yellow oil; IR(KBr) 3305, 2940, 1605 cm^{-1}; NMR (89.45MHz, $CDCl_3$) 1.17 (t, J=7.2 Hz, 3H), 2.09 (m, 2H), 2.94 (m, 4H), 3.11 (d, J=7.2 Hz, 2H), 3.57 (m, 2H), 4.20 (m, 3H), 7.13~7.32 (m, 6H), 7.74 (m, 2H): **1-(Indane-5-sulfonyl)-4-phenylmethyl-2-ethoxy-4,5-dihydroimidazole (11c-c')**- Rf 0.31 (hexane : ethyl acetate =2 : 1); yield 45%; yellow oil; IR (KBr) 2950, 1650cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.32 (t, J=7.0 Hz, 3H), 2.13 (m, 2H), 2.50 (dd, J=8.8, 13.8 Hz, 1H), 2.95 (m, 5H), 3.59 (dd, J=6.0, 9.4 Hz, 1H), 3.78 (dd, J=6.4, 9.4 Hz, 1H), 4.03 (m, 1H), 4.25 (q, J=7.0 Hz, 2H), 7.11 7.33 (m, 6H), 7.59~7.73 (m, 2H).

2-Ethoxy-*cis*-3a,8b-dihydro-1-(4-chlorobenzenesulfonyl) indano[1,2-d]imidazole (15-a')- Rf 0.48 (hexane : ethyl acetate=2 : 1); yield 28%; white solid; m.p. 164.4~166.6 °C; IR (KBr) 3060, 2960, 2925, 1650 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.22 (t, J=7.0 Hz, 3H), 3.06 (dd, J=2.7, 16.9 Hz, 1H), 3.41 (dd, J=7.9, 16.9 Hz, 1H), 4.16 (qd, J=1.8, 7.0 Hz, 2H), 4.72 (dt, J=2.7, 7.9 Hz,1H), 5.81 (d, J=7.9 Hz, 1H), 7.26~7.52 (m, 5H), 7.87 (m, 3H): **2-Ethoxy-*cis*-3a,8b-dihydro-3-(4-chlorobenzene-sulfonyl)indano[1,2-d]imidazole (16-a')**- Rf 0.61 (hexane : ethyl acetate=2 : 1); yield 43%; white solid; m.p. 152.7 ~154.0°C; IR (KBr) 3075, 2960, 2910, 1650 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 1.23 (t, J=7.1 Hz,3H), 3.50 (d, J=4.7 Hz, 2H), 4.19 (q, J=7.1 Hz, 2H), 5.03 (m, 1H), 5.33 (d, J=8.3 Hz, 1H), 7.33 (m, 4H), 7.49 (d, J=8.6 Hz, 2H), 7.90 (d, J=8.6 Hz, 2H).

2-Ethoxy-*cis*-3a,8b-dihydro-1-(4-methylbenzenesulfonyl) indano[1,2-d]imidazole (15-b')- Rf 0.18 (hexane : ethyl acetate=2 : 1); yield 21%; white solid; m.p. 167.7 ~171.2°C; IR (KBr) 3050, 2960, 2910, 1650 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.22 (t, J=7.1 Hz, 3H), 2.43 (s, 3H), 3.07 (dd, J=2.4, 17.1 Hz, 1H), 3.37 (dd, J=8.2, 17.1 Hz, 1H), 4.13 (m, 2H), 4.66(dt, J=2.4, 8.2 Hz, 1H), 5.78 (d, J=8.2 Hz, 1H), 7.28 (m, 5H), 7.82 (m, 3H): **2-Ethoxy-*cis*-3a,8b-dihydro-3-(4-methylbenzenesulfonyl)indano [1, 2-d] imidazole (16-b')**- Rf 0.25 (hexane : ethyl acetate= 2 : 1) ; white solid; m.p. decomposed at 200°C; IR (KBr) 2900, 2830, 1640 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.24 (t, J= 7.1 Hz, 3H), 2.44 (s, 3H), 3.52 (d, J=4.5 Hz, 2H), 4.18 (m, 2H), 5.03 (m, 1H), 5.29 (d, J=8.4 Hz, 1H), 7.20 ~7.42 (m, 6H), 7.83 (dd, J=1.9, 8.4 Hz, 2H).

2-Ethoxy-*cis*-3a,8b-dihydro-1-(indane-5-sulfonyl)indano [1,2-d]imidazole (15-c')- Rf 0.29 (hexane : ethyl acetate =2 : 1); yield 28%; white solid; m.p. 158.4~160.7°C; IR (KBr) 3050, 2950, 2920, 1640 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 1.23 (t, J=7.1 Hz, 3H), 2.14 (m, 2H), 2.97 (m, 4H), 3.07 (dd, J=2.4, 17.1 Hz, 1H), 3.37 (dd, J=8.1, 17.1 Hz, 1H), 4.15 (m, 2H), 4.66 (dt, J=2.4, 8.1 Hz, 2H), 5.77 (d, J=8.1 Hz, 1H), 7.22~7.37 (m, 4H), 7.69~ 7.87(m, 3H): **2-Ethoxy-cis-3a,8b-dihydro-3-(indane-5-sulfonyl)indano[1,2-d]imidazole (16-c')**- Rf 0.38 (hexane : ethyl acetate=2 : 1); yield 35%; white solid; m.p. 154.1~ 156.2°C; IR (KBr) 2910, 1640 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 2.15 (m, 2H), 2.98 (m, 4H), 3.53 (d, J=4.5 Hz, 2H), 4.20 (m, 2H), 5.03 (m, 1H), 5.30 (d, J=8.4 Hz, 1H), 7.22~7.44(m, 5H), 7.71~7.81 (m, 2H).

General procedure for the synthesis of imidazolidinones 2, 3, 4, and 5

Compounds **11** or **16** 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-Chlorobenzenelfonyl)-4-(1-naphthyl)imidazolidinone (2-a')- Rf 0.43 (hexane : ethyl acetate=1:1); yield 100%; white solid; m.p. decomposed at 196.0°C; IR (KBr) 3400, 1720, 1360, 1160 cm^{-1}; NMR (89.45 , DMSO-d_6) δ 3.50 (dd, J=5.5, 9.1 Hz, 1H), 4.60 (dd, J=8.9, 9.1 Hz, 1H), 5.61 (dd, J=5.5, 8.9 Hz, 1H), 7.39~8.05 (m, 11H), 8.44 (1H, exchangeable proton); Anal. Calcd for $C_{19}H_{15}ClN_2O_3S$: C 58.99, H 3.91, N 7.24, S 8.29; Found C 58.58, H 3.73, N 7.30, S 8.31.

1-(4-Methylbenzenesulfonyl)-4-(1-naphthyl)imidazolidinone(2-b')- Rf 0.31 (hexane : ethyl acetate=1 : 1) ; yield 100%; white solid; m.p. decomposed at 193.0° C; IR (KBr) 3240, 1735, 1700, 1345, 1160 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.67 (dd, J=6.2, 9.3 Hz, 1H), 4.48 (dd, J=9.0, 9.3 Hz, 1H), 5.47 (dd, J=6.2, 9.0 Hz, 1H), 6.47 (1H, exchangeable proton), 7.19~ 7.92 (m, 11H); Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C 65.56, H 4.95, N 7.64, S 8.75; Found C 65.26, H 4.70, N 7.36, S 8.39.

1-(Indane-5-sulfonyl)-4-(1-naphthyl)imidazolidinone (2-c')- Rf 0.33 (hexane : ethyl acetate=1 : 1); yield 100 %; white solid; m.p. 180.3-181.5°C; IR (KBr) 3400, 2940, 1720, 1350, 1145 cm^{-1}; NMR (89.45MHz, $CDCl_3$) δ 2.12 (m, 2H), 2.94 (m, 4H), 3.76 (dd, J=6.4, 9.4 Hz, 1H), 4.56 (dd, J=9.0, 9.4 Hz, 1H), 5.52 (dd, J=6.4, 9.0 Hz, 1H), 5.52 (1H, exchangeable proton), 7.38~ 7.81 (m, 10H); Anal. Calcd for $C_{22}H_{20}N_2O_3S$: C 67.33, H 5.14, N 7.14, S 8.17; Found C 66.96, H 4.77, N 6.79, S 7.92.

1-(4-Chlorobenzenelsulfonyl)-4-(2-naphthyl)imidazolidinone (3-a')- Rf 0.21 (hexane : ethyl acetate=2 : 1); yield 100%; white solid; m.p. 190.3 192.3°C; IR (KBr) 3350, 1730, 1360, 1170 cm^{-1}; NMR (200MHz, DMSO-d_6) δ 3.72 (dd, J=5.9, 9.3 Hz, 1H), 4.48 (dd, J=9.0, 9.3 Hz, 1H), 5.09 (dd, J=5.9, 9.0 Hz, 1H), 7.43~7.85 (m, 11H), 8.52 (1H, exchangeable proton); Anal. Calcd for $C_{19}H_{15}ClN_2O_3S$: C 58.99, H 3.91, N 7.24, S 8.29; Found C 58.55, H 3.76, N 6.92, S 8.13.

1-(4-Methylbenzenesulfonyl)-4-(2-naphthyl)imidazolidinone (3-b')- Rf 0.36 (hexane : ethyl acetate=1 : 1); yield 100%; white solid; m.p. 227.2 229.9°C; IR (KBr) 3420, 1740, 1720, 1340, 1160 cm^{-1}; NMR (89.45MHz, DMSO -d_6) δ 2.41 (s, 3H), 3.59 (dd, J=5.9, 9.2 Hz, 1H), 4.36 (dd, J=8.7, 9.2 Hz, 1H), 4.98 (dd, J=5.9, 8.7 Hz, 1H), 7.28~ 7.98 (m, 11H), 8.32 (1H, exchangeable proton); Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C 65.56, H 4.95, N 7.64, S 8.75; Found C 65.42, H 4.58, N 7.45, S 8.83.

1-(Indane-5-sulfonyl)-4-(2-naphthyl)imidazolidinone (3-c')- Rf 0.39 (hexane : ethyl acetate=1 : 1); yield 100 %; white solid; m.p. 209.4 211.7°C; IR (KBr) 3350, 2940, 1725, 1360 cm^{-1}; NMR (200MHz, DMSO-d_6) δ 2.14 (m, 2H), 3.03 (m, 4H), 3.70 (dd, J=5.9, 9.3 Hz, 1H), 4.45 (dd, J=8.9, 9.3 Hz, 1H), 5.05 (dd, J=5.9, 8.9 Hz, 1H), 7.43 (dd, J=1.8, 8.5 Hz, 1H), 7.53~8.03 (m, 9H), 8.41 (1H, exchangeable); Anal. Calcd for $C_{22}H_{20}N_2O_3S$: C 67.33, H 5.14, N 7.14, S 8.17; Found C 67.35, H 4.87, N 7.01, S 8.24.

1-(4-Chlorobenzensulfonyl)-4-phenylmethylimidazolidinone (4-a')- Rf 0.32 (hexane : ethyl acetate=1 : 1); yield 100%; white solid; m.p. 138.3~140.8°C; yield 100 %; IR (KBr) 3275, 3075, 2950, 2900, 1730, 1350, 1160 cm^{-1}; NMR (200MHz, DMSO-d_6) 2.83 (m, 2H), 3.59 (dd, J=5.5, 9.0 Hz, 1H), 3.92 (dd, J=8.7, 9.0 Hz, 1H), 4.04 (m, 1H), 7.35 (m, 5H), 7.76 (d, J=8.7 Hz, 1H), 7.90 (d, J=8.7 Hz, 1H), 8.02 (1H, exchangeable proton); Anal. Calcd for $C_{16}H_{15}ClN_2O_3S$: C 54.78, H 4.31, N 7.99, S 9.14; Found C 54.76, H 3.98, N 7.61, S 9.18.

1-(4-Methylbenzenesulfonyl)-4-phenylmethylimidazolidinone (4-b')- Rf 0.25 (hexane : ethyl acetate=1 : 1); yield 100%; white solid; m.p. 138.0 140.0°C; yield 100%; IR (KBr) 3260, 3040, 2950, 1730, 1695, 1350, 1160cm^{-1}; NMR (200MHz, DMSO-d_6) δ 2.49 (s, 3H), 2.75 (dd, J=7.0, 13.6 Hz, 1H), 2.87 (dd, J=5.2, 13.6 Hz, 1H), 3.57 (dd, J=5.2, 9.1 Hz, 1H), 3.87 (dd, J=8.4, 9.1 Hz, 1H), 4.01 (m, 1H), 7.33 (m, 5H), 7.48 (d, J=8.4 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 7.91 (1H, exchangeable proton); Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C 61.80, H 5.49, N 8.48, S 9.70; Found C 61.66, H 5.15, N 8.32, S 9.59.

1-(Indane-5-sulfonyl)-4-phenylmethylimidazolidinone (4-c')- Rf 0.28 (hexane : ethyl acetate=1 : 1); yield 100 %; white solid; m.p. 142.3~143.8°C; yield 100%; IR (KBr) 3270, 2930, 1745, 1700, 1350, 1155, 1140 cm^{-1}; NMR (200MHz, DMSO-d_6) δ 2.15 (m, 2H), 2.81 (m, 2H), 3.02 (m, 4H), 3.56 (dd, J=5.3, 9.0 Hz, 1H), 3.87 (dd, J=8.6, 9.0 Hz, 1H), 4.01 (m, 1H), 7.35 (m, 5H), 7.50 (d, J=7.9 Hz, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.74 (s, 1H), 7.89 (1H, exchangeable proton); Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C 64.02, H 5.66, N 7.86, S 8.99; Found C 64.11, H 5.38, N 7.67, S 9.06.

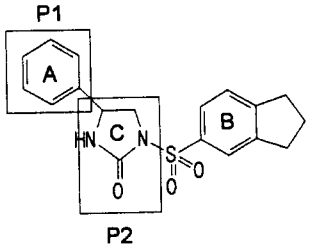
***cis*-3a,8b-Dihydro-3-(*p*-chlorobenzenesulfonyl) indano [1,2-d]imidazol-2-one (5-a')**- Rf 0.35 (hexane : ethyl acetate=1 : 1); yield 100%; white solid; m.p. decomposed

Tablel I. Cytotoxicity of compounds **1, 2, 3, 4,** and **5**

entry No.	Compound[a]	IC_{50} (μg/mL)[b]				
		A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	1-a'	3.19	0.91	0.48	1.95	0.15
2	1-b'	3.94	1.99	0.80	2.55	0.65
3	1-c'	0.31	0.03	0.0007	0.37	0.04
4	2-a'	>100	92.28	14.43	>100	77.63
5	2-b'	20.12	26.10	25.90	47.90	27.60
6	2-c'	18.57	12.70	12.03	54.30	14.30
7	3-a'	>100	>100	>100	>100	>100
8	3-b'	>100	>100	>100	>100	>100
9	3-c'	>100	>100	>100	>100	>100
10	4-a'	30.00	30.57	33.29	27.65	36.45
11	4-b'	40.78	43.21	32.54	26.90	41.08
12	4-c'	50.40	63.74	62.38	50.81	83.15
13	5-a'	>100	>100	>100	>100	>100
14	5-b'	>100	>100	>100	>100	>100
15	5-c'	>100	>100	>100	>100	>100

[a] Structures of compounds 1, 2, 3, 4, and 5 are found in Fig. 1. [b]IC50 values are the mean value of three times measurement. Cell lines used for the test are human lung (A549), ovary (SK-OV-3), melanoma (SK-MEL-2), brain (XF-498), and colon (HCT-15) cancer cell lines.

Table II. Select molecular parameters of compounds 1-c', 2-c', 3-c', 4-c', and 5-c'



Compounds	P1-P2 Plane Angle[a]	A-B Distance[b](Å)	Torsion[c] (∠O=C-N-S)	Planarity[d] (∠NCNS)
1-c'	89.69	8.692	-5.4	176.3
2-c'	90.69	8.799	-18.3	162.8
3-c'	89.34	8.700	-4.3	177.3
4-c'	102.76	9.315	-21.2	160.1
5-c'	64.76	8.448	8.8	-169.4

[a] Plane angle: torsion angle between phenyl moiety and imidazolidinone ring. [b] Distance: distance between two centers of two aromatic ring and distance for compounds 2-c' and 3-c' from the center of benzene ring of naphthyl group connected to imidazolidinone. [c] Tosion: torsion angle between C=O and N-S. [d] Planarity: torsion angle between N-C and N-S.

at 218.0°C; IR (KBr) 3300, 3250, 1730, 1695, 1340, 1160 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 3.54 (m, 2H), 5.07 (m, 2H), 6.02 (1H, exchangeable proton), 7.26 (m, 4H), 7.50 (d, J=8.7 Hz, 2H), 8.02 (d, J=8.7 Hz, 2H); Anal. Calcd for $C_{16}H_{13}ClN_2O_3S$: C 55.10, H 3.76, N 8.03, S 9.19; Found C 55.34, H 3.52, N 7.74, S 9.09.

***cis*-3a,8b-Dihydro-3-(4-methylbenzenesulfonyl)indano [1,2-d]imidazol-2-one(5-b')**- Rf 0.23 (hexane : ethyl acetate =2 : 1); yield 100%; white solid; m.p. decomposed at 248.0°C; IR (KBr) 3320, 2900, 1720, 1700, 1340, 1155 cm^{-1}; NMR (200MHz, $CDCl_3$) 2.44 (s, 3H), 3.56 (m, 2H), 5.06 (m, 3H), 5.76 (1H, exchangeable proton), 7.29 (m, 6H), 7.97 (d, J=8.1 Hz, 2H); Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C 62.18, H 4.91, N 8.53, S 9.76; Found C 62.88, H 4.56, N 8.38, S 9.91.

***cis*-3a,8b-Dihydro-3-(indane-5-sulfonyl)indano[1,2-d]imidazol-2-one (5-c')**- Rf 0.25 (hexane : ethyl acetate =2 : 1); yield 100%; white solid; m.p. decomposed at 237.5 °C; IR (KBr) 3330, 2925, 1740, 1700, 1340, 1160, 1140 cm^{-1}; NMR (200MHz, $CDCl_3$) δ 2.16 (m, 2H), 3.03 (m, 4H), 3.54 (m, 2H), 5.11 (m, 2H), 7.40 (m, 4H), 7.55 (d, J=8.1 Hz, 1H), 7.85 (m, 2H), 8.46 (1H, exchangeable proton); Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C 64.39, H 5.12, N 7.90, S 9.05; Found C 64.06, H 4.63, N 7.55, S 9.02.

Biological assay

Cytotoxicities of compounds **1** (Jung, *et al.*, 1996), **2, 3, 4**, and **5** 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.

RESULTS AND DISCUSSION

Compounds **2, 3, 4,** and **5** were prepared as shown in scheme 1 and 2 using the procedure previously reported (Jung, *et al.*, 1996) from the corresponding olefin. Their cytotoxicities were measured against five human cancer cell lines (Everitt *et al*, 1987, Skehon *et al*, 1990). The results are listed in Table I. The molecular parameters such as plane angle (angle between aromatic ring at 4-position and imidazolidinone ring), distance between two aromatic ring (from two centers of two aromatic rings), torsion angle ∠O=C-N-S, and planarity ∠NCNS were obtained by molecular computation using MOPAC 6.0 (PM3 MO) (Stewart, I. J. P., 1990) about compounds 1-c', 2-c', 3-c', 4-c', and 5-c' as shown in Table II. Compounds 1-c', 2-c', 3-c', and 4-c' shows essentially same type of optimized structure as shown in Table II. These compounds have nearly same plane angles (about 90°). Two aromatic rings located in trans and parallel each other. This conformation of **1** was also demonstrated by X-ray crystallography (Park *et al.*, 1999).

For finding the size effect of planar structure at 4-position of **1**, phenyl group was replaced with naphthyl moiety as shown in compounds **2** and **3**. This replacement resulted in the enlargement of planar structural unit at this position, which has been recognized as an essential pharmacophore for the potent activity of **1** (Jung and Kwak, 1997). This structural modification markedly reduced the cytotoxicity of **1** against all five cancer cell lines as shown in Table I. This decrement of activity of **2** and **3** compared to **1** should mainly originate from unfitting to the binding site of their putative receptor due to the increment of size of planar structure by naphthyl moiety. The different pattern of substitution of naphthyl at 4-position of **2** and **3** variated the size effect. Substituent 1-naphthyl in compound **2** and 2-naphthyl in compound **3** could be considered as a ortho: meta substitution and a meta:para substitution on phenyl group of **1**, respectively. Therefore the adverse size effect is more evident in compounds **3**. These facts might rationalize that compounds **3** are less active than compounds **2**. These results indicate that the optimum size of planar structure at 4-position of imidazolidinone ring of **1** for their potent activity may equal to the size of phenyl or the smaller one.

To confirm the optimum distance between two aromatic moieties at 4-position and on sulfonyl group at 1-position of **1**, phenyl group was replaced with benzyl as shown in compounds **4**. The model study indicated that methylene insertion between phenyl and imida-zolidinone ring of **1** increases the distance between two aromatic ring by about 0.6Å as shown in Table II. This replacement sharply decreased the activity of **1** against all five human cancer cell lines as shown in Table I. Therefore phenyl group must be directly connected to imidazolidinone ring for the potent activity of this analog and the distance between two aromatic rings should remain in about 8.7Å.

The plane angle between phenyl ring and imida-zolidinone ring has been estimated as near 90° by the molecular model study and NMR study (Jung, *et al.*, 1996). To find out the importance of this plane angle and conformational freedom of phenyl group of **1** for the activity, compounds **5** were prepared. In these compounds, plane angle is restricted by connecting between ortho position of phenyl and 5-position of imidazolidinone with methylene bridge. From this restriction, the distance between two aromatic rings is slightly variated about 0.2Å. However plane angle is seriously altered to about 65° as shown in Table II. Such conformational change in compounds **5** completely abolished the activity of **1** as shown in Table I. This results might imply that the right plane angle between phenyl and imidazolidinone rings should be an important factor for their activity, although ortho substitutent effect by the methylene unit could be considered as another factor for the loss of activity in **5**.

In conclusion, phenyl moiety without any substituents directly attached to imidazolidinone ring of **1** should be considered as an essential pharmacophore for this analog.

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