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Synthesis and Evaluation of Cytotoxicity of Novel Arylsulfonylimidazolidinones Containing Sulfonylurea Pharmacophore

Sang-Hun Jung*, Jae-Shin Song*, Hui-Soon Lee*, Sang-Un Choi and Chong-Ock Lee****

**College of Pharmacy, Chung-Nam National University, Taejon 305-764, Korea and **Korea Research Institute of Chemical Technology, Taejon 305-343, Korea*

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Design and synthesis of novel 4-phenyl-1-arylsulfonylimidazolones **3** and 4-phenyl-3-arylsulfonylimidazolones **4** and evaluation of their cytotoxic activity against eleven human cancer cell lines and two murine leukemia cell lines *in vitro* were performed. As a result, a series of 4-phenyl-1(N)-arylsulfonylimidazolones (**3**) has been found to be the potential anticancer agent. Compounds **3b**, **3c**, and **3d** exhibit strong activity as indicated by their IC_{50} values 0.39, 3.19, 0.31 μg/mL against A549 and 0.80, 0.48, 0.0007 μg/mL against SK-Mel-2, respectively. These compounds also possess much more potent activity (10-1000 times) than LY186641 against eleven other cell lines.

Key word : Cytotoxicity, sulfonylurea, 4-phenyl-1(N)-arylsulfonylimidazolone

INTRODUCTION

Compounds containing sulfonylurea moiety have been investigated for the treatment of the nonhematogeneous cancers in the past decade (Grindey, 1988). Especially, the remarkable effectiveness of diarylsulfonylureas LY186641 (**1**) (Munshi *et al*, 1991, Taylor *et al*, 1989, Hainworth *et al*, 1989, Howbert, 1991, Grindey *et al*, 1987) and LY 295501 (**2**) (Shultz *et al*, 1993), has been demonstrated against the xenografts and the solid tumors such as lymphosarcoma (6C3HED), mammary adenocarcinoma (CA755, C3H), colon carcinoma (C-26), and ovarian carcinoma (M5). Although the mechanism of these diarylsulfonylureas has not been known, it is completely different from those of the other antineoplastic agents being used currently (Grindey *et al*, 1987, Grindey, 1990, Houghton *et al*, 1989, Houghton *et al*, 1990, Houghton *et al*, 1990). These are not cell cycle specific and do not show the cross resistance in multidrug resistant cell lines (Howbert, 1991). Furthermore these compounds do not have the side effects exhibited by the other anticancer agents being used (Grindey, 1988, Howbert, 1991). Such unique characteristics of diarylsulfonylureas as the anticancer agent led to the introduction of these compounds into the clinical trials (Munshi *et al*, 1991, Hainworth *et al*, 1989, Talbot *et al*, 1993, Taylor *et al*, 1992, Kamthan *et al*, 1992). However, the development of these diarylsulfonylureas has been seriously hampered due to the unexpected occurrence (Munshi *et al*, 1991, Hainworth *et al*, 1989, Talbot *et al*, 1993, Taylor *et al*, 1992, Kamthan *et al*, 1992) of anemia and methemoglobinemia and the poor effectiveness (Munshi *et al*, 1991, Hainworth *et al*, 1989) at the optimum dose without the serious side effects in the clinical trials.

Those advantages in mode of action and the drawbacks of diarylsulfonylureas led us to investigate the

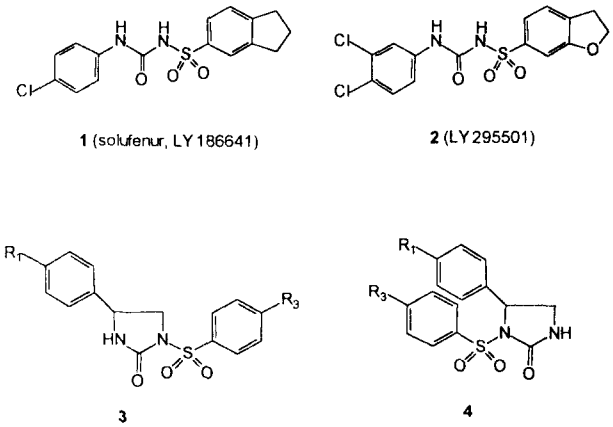
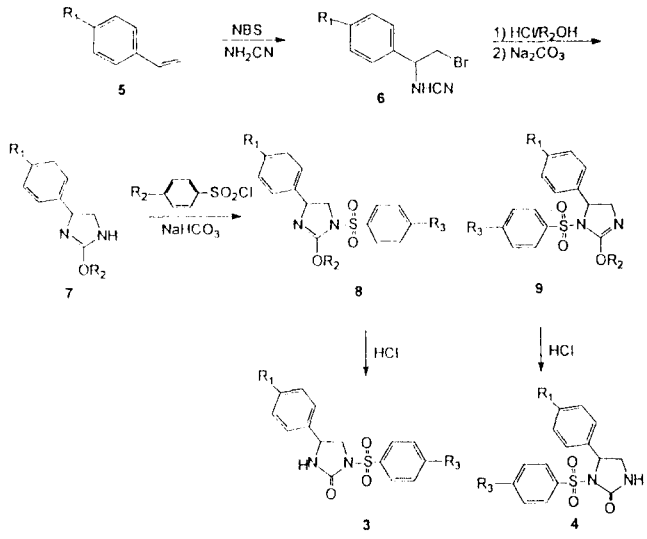


Fig. 1. Design of the novel arylsulfonylimidazolidinones **3** and **4**

Correspondence to: Sang-Hun Jung, Ph. D. College of Pharmacy, Chung-Nam National University, Taejon 305-764, Korea



Scheme 1. Synthesis of Novel Arylsulfonylimidazolidinones (Substituents R_1, R_2 and R_3 in this scheme are found in table 5)

new structural entity. Accordingly the novel arylsulfonylimidazolidinones **3** and **4** containing sulfonylurea pharmacophore of diarylsulfonylureas have been designed as shown in fig. 1, synthesized as shown in scheme 1, and tested against the various human solid tumors and murine leukemias *in vitro* (Jung, *et al*, 1996).

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 (200-430 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 in against the peak of tetramethylsilane by JEOL JNM-EX90 FT-NMR (89.45 MHz) and Varian Gemini 200 NMR spectrometers. Mass spectra (Ms) were obtained by GC-Mass PP-1000 mass spectrometer.

Synthesis

General procedure for the synthesis of 2-bromo-1-phenylethylcyanamides 6

The solution of styrene **5** (or substituted styrenes) in dichloromethane was added to the mixture of N-bromosuccinimide (1.3 equivalent) and cyanamide (2 equivalent) in dichloromethane over one hour 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 product was purified with flash column chromatography. The results for the preparation of compounds **6** are summarized in Table I. The spectra obtained for compounds **6** are listed in Table II.

Table I. Preparation of β-bromocyanamides **6**

entry No.	compd. No. **6**	substituents R_1	appearance	yield (%)	Rf value[a]
1	**a**	H	pale brownish oil	64	0.25
2	**b**	Br	pale brownish oil	69	0.21
3	**c**	Cl	pale brownish oil	70	0.15
4	**d**	Me	pale brownish oil	76	0.21

[a]The eluent for compounds **6** was 5% ethyl acetate-toluene.

Table II. Spectral data for bromocyanamides **6**

No.	compound No. **6**	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ), Ms (m/e, rel. int.)
1	**a**	IR (neat, NaCl) 3180, 2920, 2225; NMR δ 3.62 (d, J=7.2 Hz, 1H), 3.63 (d, J=6.0 Hz, 1H), 4.55 (dd, J=6.0, 7.2 Hz, 1H), 4.70 (s, 1H, exchangeable with D_2O), 7.39 (s, 5H); Ms 228 (8), 224 (9), 183 (34), 145 (11), 131 (100), 104(79) (EI).
2	**b**	IR (neat, NaCl) 3190, 2920, 2220; NMR δ 3.58 (d, J=7.1 Hz, 1H), 3.59 (d, J=6.0 Hz, 1H), 4.53 (dd, J=6.0, 7.1 Hz, 1H), 7.22 (d, J=8.4 Hz, 2H) 7.55 (d, J=8.4 Hz, 2H); Ms 306 (4), 304 (6) 302 (3), 265 (45), 263 (94), 261 (49), 223 (7), 211 (100), 209 (98), 182 (68) (EI).
3	**c**	IR (neat, NaCl) 3180, 2920, 2220; NMR δ 3.56 (d, J=6.7 Hz, 2H), 4.47 (t, J=6.7 Hz, 1H), 5.38 (s, 1H exchangeable with D_2O), 7.35 (s, 4H); Ms 258(1), 217 (13), 179 (4), 165 (100), 138 (42) (EI).
4	**d**	IR (neat, NaCl) 3200, 2210; NMR δ 2.35 (s, 3H), 3.59 (d, J=6.7 Hz, 2H), 4.45 (t, J=6.7 Hz, 1H), 4.70 (s, 1H, exchangeable with D_2O), 7.21 (S, 4H); Ms 240 (3), 238 (3), 199 (16), 197 (24), 159 (6), 145 (100), 118 (51) (EI).

General procedure for the synthesis of 2-alkoxy-4-aryl-4,5-dihydroimidazoles 7

The solution of bromocyanamide **6** in alcohol (methanol, ethanol, or isopropanol) 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 35-40°C for 6-8 hours and then sodium carbonate (2.5 equivalent) was added and stirred overnight at room

Table III. Preapration of imidazolines **7**

No.	precursor[a] No.	compd. No. **7**	substituents		appearance	m.p.(°C)	yield (%)
			R_1	R_2			
1	**6a**	**a**	H	Me	white solid	117.0-119.0	74
2	**6a**	**b**	H	Et	white solid	74.0- 76.0	67
3	**6a**	**c**	H	iPr	white solid	87.0- 88.0	72
4	**6b**	**d**	Br	Me	white solid	106.0-109.0	74
5	**6c**	**e**	Cl	Me	white solid	89.0- 91.0	60
6	**6d**	**f**	Me	Et	white solid	86.0- 87.0	70

[a]Precursor means the starting material for the preparatrion of the corresponding compounds **7**

Table IV. Spectral data for imidazolines **7**

No.	compd. No. **7**	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ), Ms (m/e, rel. int.)
1	**a**	IR (KBr) 3100, 2925, 1620; NMR δ 3.45 (dd, J=7.9, 10.8 Hz, 1H), 3.90 (s, 3H), 4.01 (dd, J=9.2, 10.8 Hz, 1H), 4.93 (dd, J=7.9, 9.2 Hz 1H), 7.31 (s, 5H); Ms 176 (100), 161 (46), 132 (50), 118 (56) (EI).
2	**b**	IR (KBr) 3120, 2980, 1620; NMR δ 1.34 (t, J=7.0 Hz, 3H), 3.43 (dd, J=7.9, 11.0 Hz, 1H), 4.00 (dd, J=9.2, 11.0 Hz, 1H), 4.30 (q, J=7.0 Hz, 2H), 4.90 (dd, J=7.9, 9.2 Hz, 1H), 5.10~5.30 (s, 1H, exchangeable with D_2O), 7.31 (s, 5H); Ms 190 (19), 162 (100), 161 (62), 132 (58), 118 (52) (EI).
3	**c**	IR (KBr) 3070, 2975, 1600; NMR δ 1.34 (d, J=6.1 Hz, 6H), 3.44 (dd, J=7.9, 10.6 Hz, 1H), 4.0 (dd, J=9.5, 10.6 Hz, 1H), 4.90~5.20 (s, 1H, exchangeable with D_2O), 4.94 (dd, J=7.9, 9.5 Hz, 1H), 5.13 (heptet, J=6.1 Hz, 1H), 7.30 (s, 5H); Ms 204 (30), 162 (100), 132 (51), 118 (43), 104 (44) (EI).
4	**d**	IR (KBr) 3100, 2950, 1620; NMR δ 3.38 (dd, J=7.9, 10.6 Hz, 1H), 3.90 (s, 3H), 4.00 (dd, J=9.5, 10.6 Hz, 1H), 4.92 (dd, J=7.9, 9.5 Hz, 1H), 7.26 (d, J=8.3 Hz, 2H), 7.47 (d, J=8.3 Hz, 2H); Ms 256 (56), 255 (100), 254 (51), 239 (31), 210 (93) (EI).
5	**e**	IR (KBr) 3100, 2950, 1620; NMR δ 3.38 (dd, J=7.9, 10.6 Hz, 1H), 3.90 (s, 3H), 4.00 (dd, J=10.6, 9.5 Hz, 1H), 4.93 (dd, J=7.9, 9.5 Hz, 1H), 7.29 (s, 4H); Ms 212 (32), 210 (100), 195 (46), 175 (92), 166 (100) (EI).
6	**f**	IR (KBr) 3100, 2975, 2860, 1610; NMR δ 1.33 (t, J=7.0 Hz, 3H), 2.33 (s, 3H), 3.42 (dd, J=7.9, 11.0 Hz, 1H), 3.97 (dd, J=9.2, 11 Hz, 1H), 4.0~4.4 (s, 1H, exchangeable with D_2O), 4.29 (q, J=7.0 Hz, 2H), 4.86 (dd, J=7.9, 9.2Hz), 7.19 (s, 4H); Ms 204 (16), 176 (82), 161 (26), 146 (100), 132 (83) (EI).

temperature. After the insoluble material was filtered off, the filtrate was concentrated to give the crude product. The crude product was recrystallized from ethyl acetate. In case of ethanol or isopropanol being used as the reaction solvent for the reaction of bromocyanamide **6** with alcoholic hydrochloride, the solvent was removed under vacuum after the completion of reaction and dichlomethane was added to the residue. The solution was extracted with water several times and the aqueous layer was treated with sodium carbonate at room temperature for 3 hours. The resulting mixture was extracted with dichloromethane. The organic layer was then dehydrated with anhydrous sodium sulfate and evaporated under vacuum. The crude product was recrystallized from ethyl acetate to give pure product **7**. The results for the preparation of compounds **7** are summarized in Table III. The spectra obtained for compounds **6** are listed in Table IV.

General procedure of the synthesis of N-arylsulfonylimidazoline 8 and 9

The arylsulfonyl chloride (1 equivalent) was added to the mixture of compounds **7** 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. The residue was then separated by flash column chromatography to give compounds **8** and **9** in approximate ratio of 4:1. The results for the preparation of compounds **8** and **9** are summarized in Table V. The spectra obtained for compounds **8** and **9** are listed in Table VI.

General procedure of the synthesis of imidazolidinones 3

Compounds **8** 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 hours 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. The results obtained are listed in Table

Table V. Preparation of N-arylsulfonylimidazolines **8** and **9**

entry No.	Precursor[a]	compd. No.	substituents			appearance	m.p. (°C)	yield (%)[b]	ratio (%)	Rf value
			R_1	R_2	R_3					
1	**7a**	**8a**	H	Me	H	white solid	98.5~99.5	79	78	0.22[e]
		9a				white solid	99.0~100.2		22	0.19[e]
2	**7a**	**8b**	H	Me	Me	white solid	119.8~120.7	79	85	0.22[f]
		9b				white solid	89.0~91.0		15	0.18[f]
3	**7a**	**8c**	H	Me	Cl	white solid	99.1~100.5	73	85	0.22[f]
		9c				white solid	105.5~108.0		15	0.19[f]
4	**7a**	**8d**	H	Me	indane[c]	white solid	106.0~108.5	77	88	0.24[f]
		9d				colorless oil	-		12	0.21[f]
5	**7b**	**8e**	H	Et	Me	white solid	116.0~117.0	78	83	0.19[g]
		9e				white solid	117.6~119.0		17	0.16[g]
6	**7c**	**8f**	H	iPr	Me	white solid	103.0~104.5	71	5:1[d]	0.30[f]
7	**7c**	**8g**	H	iPr	Cl	white solid	79~80	74	5:1[d]	0.31[f]
8	**7d**	**8h**	Br	Me	Me	white solid	128.5~130.5	67	74	0.26[f]
		9h				white solid	133.5~136.5		16	0.22[f]
9	**7d**	**8i**	Br	Me	Cl	white solid	113.5~115.5	57	86	0.24[g]
		9i				white solid	128.5~131.0		14	0.20[g]
10	**7d**	**8j**	Br	Me	indane[c]	white solid	123.5~126.0	78	72	0.25[g]
		9j				white solid	116.0~118.0		28	0.21[g]
11	**7e**	**8k**	Cl	Me	indane[c]	white solid	95.0~97.0	69	80	0.25[g]
		9k				semicrystaline	-		20	0.21[g]
12	**7f**	**8l**	Me	Et	H	white solid	88.5~90.5	60	82	0.21[g]
		9l				colorless oil	-		18	0.17[g]
13	**7f**	**8m**	Me	Et	Me	colorless oil	-	60	81	0.23[g]
		9m				colorless oil	-		19	0.19[g]
14	**7f**	**8n**	Me	Et	Cl	white solid	79.5~81.0	66	82	0.28[g]
		9n				colorless oil	-		18	0.24[g]
15	**7f**	**8o**	Me	Et	indane[c]	colorless oil	-	75	84	0.19[g]
		9o				white solid	106.0~107.5		16	0.16[g]

[a]Precursor means the starting material for the preparatrion of the corresponding compounds **8** and **9**. [b]Yields are the combined yield of two regioisomers **8** and **9** after isolation by chromatography. [c]Indane is represented for 5-indanyl connected to sulfonyl group as a substituted phenyl. [d]Ratio of two regioisomers formed were determined from NMR spectra of the crude products. [e]The eluent used is hexane-acetone (3:1). [f]The eluent used is hexane-acetone (4:1), [g]The eluent used is hexane-acetone (5:1).

VII and the spectra of compounds **3** are found in Table VIII.

General synthesis of imidazolidinones 4

Synthesis of imidazolidinones **4** from compounds **9** was performed with the procedure used for the preparation of **3**. The results obtained are listed in Table IX and the spectra of compounds **4** are found in Table X.

Biological assay

Cytotoxicity of compounds **3** and **4** was measured against human lung carcinoma A549 and human melanoma SK-MEL-2 cell lines *in vitro* using sulforhodamine B (SRB) assay (Everitt *et al*, 1987, Skehon *et al*, 1990). The cytotoxicity of these compounds is shown as IC_{50} value in Table XI and Table XIII. Compounds **3b**, **3c**, and **3d** were further tested against human ovarian (SK-OV-3), brain (XF 498), colon (HCT-15) and murine leukemia (L1210, P388) cell lines using SRB assay. Using MTT assay (Scudiero *et al*, 1988) these three compounds were also tested against human colon (colo 205), stomach (KATO III), melanoma (Malme-3M), colon (SNU C4), lung (HFL/B), and lymphoma (K562). The results from these tests are shown as IC_{50} values in Table XII.

RESULTS AND DISCUSSION

Synthesis

Intermediates **7** were prepared from the styrenes **5** according to Jung and Kohn's procedure (Jung *et al*, 1984). The treatment of styrenes **5** with N-bromosuccinimide and cyanamide in dichloromethane

Table VI. Spectral data for imidazolines **8** and **9**

entry No.	compd. No.	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ)
1	**8a**	IR (KBr) 3060, 3020, 2950, 1660; NMR δ 3.72 (dd, J=7.3, 9.5 Hz, 1H), 3.96 (s, 3H), 4.33 (dd, J=9.2, 9.5 Hz, 1H), 4.91 (dd, J=7.3, 9.2 Hz, 1H), 7.00-8.00 (s, 10H).
	9a	IR (KBr) 3030, 2950, 1665; NMR δ 3.57 (dd, J=5.3, 13.4 Hz, 1H), 3.94 (s, 3H), 4.11 (dd, J=9.9, 13.4 Hz, 1H), 5.37 (dd, J=5.3, 9.9 Hz, 1H), 7.20-7.70 (m, 10H).
2	**8b**	IR (KBr) 3020, 2960, 1650; NMR δ 2.46 (s, 3H), 3.71 (dd J=7.3, 9.5 Hz, 1H), 3.96 (s, 3H), 4.32 (dd, J=9.2, 9.5 Hz, 1H), 4.90 (dd, J=7.3, 9.2 Hz, 1H), 7.00-7.50 (m, 7H), 7.82 (d, J=8.6 Hz, 2H).
	9b	IR (KBr) 3025, 2950, 1665; NMR δ 2.40 (s, 3H), 3.56 (dd, J=5.3, 13.4 Hz, 1H), 3.94 (s, 3H), 4.10 (dd, J=9.7, 13.4 Hz, 1H), 5.34 (dd, J=5.3, 9.7 Hz, 1H), 7.10-7.40 (m, 7H) 7.49 (d, J=8.4 Hz, 2H).
3	**8c**	IR (KBr) 3025, 2960, 1650; NMR δ 3.71 (dd, J=7.3, 9.5 Hz, 1H), 3.97 (s, 3H), 4.34 (dd, J=9.2, 9.5 Hz, 1H), 4.93 (dd, J=7.3, 9.2 Hz, 1H), 7.00-7.30 (m, 5H), 7.51 (d, J=8.8 Hz, 2H), 7.85 (d, J=8.8 Hz, 2H).
	9c	IR (KBr) 3080, 2940, 1670; NMR δ 3.60 (dd, J=4.8, 13.4 Hz, 1H), 3.95 (s, 3H), 4.14 (dd, J=9.7, 13.4 Hz, 1H), 5.37 (dd J=4.8, 9.7 Hz, 1H), 7.20-7.60 (m, 9H).
4	**8d**	IR (KBr) 3020, 2950, 1650; NMR δ 2.14 (quintet, J=7.1 Hz, 2H), 2.75-3.10 (m, 4H), 3.72 (dd, J=7.3, 9.5 Hz, 1H), 3.97 (s, 3H), 4.32 (dd, J=9.2, 9.5 Hz, 1H), 4.90 (dd, J=7.3, 9.2 Hz, 1H), 7.00-7.80 (m, 8H).
	9d	IR (neat) 2950, 1665; NMR δ 2.08 (quintet, J=7.1 Hz, 2H), 2.88 (q, J=6.8 Hz, 4H), 3.55 (dd, J=5.3, 13.4 Hz, 1H), 3.94 (s, 3H), 4.09 (dd, J=9.9, 13.4 Hz, 1H), 5.33 (dd, J=5.3, 9.9 Hz, 1H), 7.00-7.70 (m, 8H).
5	**8e**	IR (KBr) 3050, 2975, 1650; NMR δ 1.37 (t, J=7.0Hz, 3H), 2.47 (s, 3H), 3.71 (dd, J=7.3, 9.5 Hz, 1H), 4.32 (dd, J= 9.2, 9.5 Hz, 1H), 4.34 (q, J=7.0 Hz, 2H), 4.90 (dd, J=7.3, 9.2 Hz, 1H), 6.90-7.40 (m, 7H), 7.82 (d, J=8.6 Hz, 2H).
	9e	IR (KBr) 3025, 2980, 1665; NMR δ 1.36 (t, J=7.0 Hz, 3H), 2.40 (s, 3H), 3.56 (dd, J=5.3, 13.4 Hz, 1H), 4.12 (dd, J= 9.9, 13.4 Hz, 1H), 4.32 (q, J=7.0 Hz, 2H), 5.35 (dd, J=5.3, 9.9 Hz, 1H), 7.10-7.30 (m, 7H), 7.52 (d, J=8.4 Hz, 2H).
6	**8f**	IR (KBr) 2980, 1645; NMR δ 1.34 (d, J=6.2 Hz, 6H), 2.47 (s, 3H), 3.69 (dd, J=7.3, 9.5Hz, 1H), 4.31 (dd, J=9.2, 9.5 Hz, 1H), 4.92 (dd, J=7.3, 9.2 Hz, 1H), 5.00 (heptet, J=6.2 Hz, 1H), 7.00-7.40 (m, 7H), 7.82 (d, J=8.6 Hz,
7	**8g**	IR (KBr) 3250, 2980, 1640; NMR δ 1.34 (d, J=6.2 Hz, 6H), 3.68 (dd, J=7.3, 9.5 Hz, 1H) 4.32 (dd, J=9.2, 9.5 Hz, 1H), 4.94 (dd, J=7.3, 9.2 Hz, 1H), 5.02 (heptet, J=6.2 Hz, 1H), 7.05-7.38 (m, 5H), 7.50 (d, J=8.8 Hz, 2H), 7.87 (d, J=8.8 Hz, 2H).
8	**8h**	IR (KBr) 3040, 2925, 2870, 1665; NMR δ 2.46 (s, 3H), 3.65 (dd, J=7.3, 9.7 Hz, 1H), 3.96 (s, 3H), 4.31 (dd, J= 9.2, 9.7 Hz, 1H), 4.86 (dd, J=9.2, 9.7 Hz, 1H), 6.96 (d, J=8.4 Hz, 2H), 7.10-7.40 (m, 4H), 7.89 (d, J=8.4 Hz, 2H).
	9h	IR (KBr) 3040, 2925, 2870, 1660; NMR δ 2.41 (s, 3H), 3.53 (dd, J=5.3, 13.4 Hz, 1H), 3.96 (s, 3H), 4.09 (dd, J=9.9, 13.4 Hz, 1H), 5.29 (dd, J=5.3, 9.9 Hz, 1H), 7.00-7.70 (m, 8H).
9	**8i**	IR (KBr) 3080, 2950, 1660; NMR δ 3.66 (dd, J=7.3, 9.7 Hz, 1H), 3.96 (s, 3H), 4.32 (dd, J=9.2, 9.7 Hz, 1H), 4.89 (dd, J=7.3, 9.2 Hz, 1H), 6.96 (d, J=8.4 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.52 (d, J=8.4Hz, 2H), 7.84 (d, J= 8.4 Hz, 2H).
	9i	IR (KBr) 3080, 2950, 1665; NMR δ 3.53 (dd, J=5.3, 13.6 Hz, 1H), 3.94 (s, 3H), 4.12 (dd, J=9.9, 13.6 Hz, 1H), 5.31 (dd, J=5.3, 9.9 Hz, 1H), 7.13 (d, J=8.4 Hz, 2H), 7.30-7.50 (m, 6H).
10	**8j**	IR (KBr) 3020, 2950, 1650; NMR δ 2.16 (quintet, J=7.1 Hz, 2H), 2.75-3.10 (m, 4H), 3.66 (dd, J=7.0, 9.7 Hz, 1H), 3.96 (s, 3H), 4.30 (dd, J=9.2, 9.7 Hz, 1H), 4.85 (dd, J=7.0, 9.2 Hz, 1H), 6.95 (d, J=8.4 Hz, 2H), 7.20-7.80 (m, 5H).
	9j	IR(KBr) 3050, 2950, 2875, 1660; NMR δ 2.11 (quintet, J=7.1 Hz, 2H), 2.91 (q, J=6.8 Hz, 4H), 3.50 (dd, J=13.4, 5.3 Hz, 1H), 3.94 (s, 3H), 4.08 (dd, J=9.9, 13.4 Hz, 1H), 5.27 (dd, J=5.3, 9.9 Hz, 1H), 7.11 (d, J=8.4 Hz, 2H), 7.20-7.60 (m, 5H).
11	**8k**	IR(KBr) 3050, 2950, 1650; NMR δ 2.16(quintet, J=7.1 Hz, 2H), 2.75-3.10(m, 4H), 3.66(dd, J=7.0, 9.7 Hz, 1H), 3.96(s, 3H), 4.30(dd, J=9.5, 9.7 Hz, 1H), 4.86(dd, J=7.0, 9.5 Hz, 1H), 6.90-7.90(m, 7H).
	9k	IR(KBr) 3050, 2950, 1665; NMR 2.11(quintet, J=7.1 Hz, 2H), 2.90(q, J=6.8 Hz, 4H), 3.50(dd, J=5.3, 13.6 Hz, 1H), 3.94(s, 3H), 4.08(dd, J=9.9, 13.6 Hz, 1H), 5.29(dd, J=5.3, 9.9 Hz, 1H), 7.00-7.60(m, 7H).
12	**8l**	IR(KBr) 3000, 2980, 2890, 1640; NMR δ 1.35(t, J=7.0 Hz, 3H), 2.31(s, 3H), 3.70(dd, J=7.3, 9.5 Hz, 1H), 4.31(dd, J=9.2, 9.5 Hz, 1H), 4.33(q, J=7.0 Hz, 2H), 4.88(dd, J=7.3, 9.2 Hz, 1H), 6.90-8.00(m, 9H).
	9l	IR(neat) 2980, 1660; NMR δ 1.34(t, J=7.0 Hz, 3H), 2.35(s, 3H), 3.55(dd, J=5.3, 13.4 Hz, 1H), 4.09(dd, J=9.9, 13.4 Hz, 1H), 4.29(q, J=7.0 Hz, 2H), 5.33(dd, J=5.3, 9.9 Hz, 1H), 7.00-7.70(m, 9H).
13	**8m**	IR(neat) 2980, 1650; NMR δ 1.35(t, J=7.0 Hz, 3H), 2.31(s, 3H), 2.46(s, 3H), 3.68(dd, J=7.5, 9.5 Hz, 1H), 4.29(dd, J=9.2, 9.5 Hz,1H), 4.33(q, J=7.0 Hz, 2H), 4.86(dd, J=7.5, 9.2 Hz, 1H), 6.90-7.20(m, 2H), 7.32(d, J=8.4 Hz, 2H), 7.79(d, J=8.4 Hz, 2H).
	9m	IR(neat) 2980, 1660; NMR δ 1.35(t, J=7.0 Hz, 3H), 2.35(s, 3H), 2.40(s, 3H), 3.53(dd, J=5.3, 13.4 Hz, 1H), 4.07(dd, J=9.9, 13.4 Hz, 1H), 4.29(q, J=7.0 Hz, 2H), 5.31(dd, J=5.3, 9.9 Hz, 1H), 7.00-7.30(m, 6H), 7.51(d, J= 8.4 Hz, 2H).

Table VI. Continued

entry No.	compd. No.	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ)
14	**8n**	IR (KBr) 3090, 2980, 1650; NMR δ 1.36 (t, J=7.0 Hz, 3H), 2.32 (s, 3H), 3.69 (dd, J=7.3, 9.2 Hz, 1H), 4.30 (t, J= 9.3 Hz, 1H), 4.35 (q, J=7.0 Hz, 2H), 4.90 (dd, J=7.3, 9.2 Hz, 1H), 6.90-7.20 (m, 4H), 7.50 (d, J=8.8 Hz, 2H), 7. 87 (d, J=8.8 Hz, 2H).
	9n	IR (neat) 3090, 2980, 1660; NMR δ 1.36 (t, J=7.0 Hz, 3H), 2.32 (s, 3H), 3.57 (dd, J=4.8, 13.4 Hz, 1H), 4.12 (dd, J=9.9, 13.4 Hz, 1H), 4.32 (q, J=7.0 Hz, 2H), 5.33 (dd, J=9.9, 4.8 Hz, 1H), 6.80-7.60 (m, 8H).
15	**8o**	IR (neat) 2950, 1650; NMR δ 1.36 (t, J=7.0 Hz, 3H), 2.15 (quintet, J=7.1 Hz, 2H), 2.31 (s, 3H), 2.70-3.10 (m, 4H), 3.70 (dd, J=7.3, 9.5 Hz, 1H), 4.29 (dd, J=9.2, 9.5 Hz, 1H), 4.33 (q, J=7.0 Hz, 2H), 4.86 (dd, J=7.3, 9.2 Hz, 1H), 7.00-7.90 (m, 7H).
	9o	IR (KBr) 2950, 2870, 1660; NMR δ 1.36 (t, J=7.0 Hz, 3H), 2.10 (quintet, J=7.1 Hz, 2H), 2.36 (s, 3H), 2.89 (q, J= 6.8 Hz, 4H), 3.55 (dd, J=5.3, 13.4 Hz, 1H), 4.09 (dd, J=9.9, 13.4 Hz, 1H), 4.31 (q, J=7.0 Hz, 2H), 5.31 (dd, J= 5.3, 9.9 Hz, 1H), 7.00-7.60 (m, 7H).

Table VII. Preparation of novel arylsulfonylimidazolidinones **3**

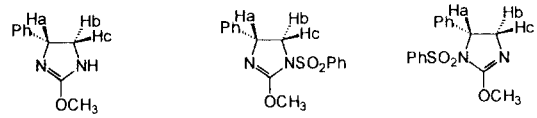
entry No.	Precursor[a]	compd. No.**3**	substituents		apperance	m.p. (°C)	yield (%)
			R_1	R_3			
1	**8a**	**a**	H	H	white solid	222.0-223.0	100
2	**8b**	**b**	H	Me	white solid	172.0-173.0	100
3	**8c**	**c**	H	Cl	white solid	151.5-152.5	100
4	**8d**	**d**	H	indane[b]	white solid	160.0-162.5	100
5	**8h**	**e**	Br	Me	white solid	234.0-235.5	100
6	**8i**	**f**	Br	Cl	white solid	237.0-239.5	100
7	**8j**	**g**	Br	indane[b]	white solid	191.6-193.1	100
8	**8k**	**h**	Cl	indane[b]	white solid	189.0-191.5	100
9	**8l**	**i**	Me	H	white solid	213.0-214.0	100
10	**8m**	**j**	Me	Me	white solid	233.0-234.0	100
11	**8n**	**k**	Me	Cl	white solid	191.0-193.0	100
12	**8o**	**l**	Me	indane[b]	white solid	186.0-187.5	100

[a]Precursor means the starting material for the preparatrion of the corresponding compounds **3**.
[b]indane is represented for 5-indanyl as a substituted phenyl.

gave the 2-bromo-1-phenylethylcyanamides **6** in 64-76% isolated yield after flash column chromatography. The results are shown in Table I. Compounds **6** can be stored at -10°C without major decomposition for at least one week. It is noteworthy that the parent peak in mass spectra of each compound **6** is the peak for the loss of CH_2Br unit from molecular ion. This indicates that the product **6** of the bromocyanamide addition reaction to styrene is the typical Markovnikoff product.

Compounds **6** were treated with alcohol containing 5% HCl at 35-40°C for 6-8 hours to form a isourea intermediate **10** and the resulting reaction mixture was then stirred with two equivalent of sodium carbonate at room temperature overnight to give compounds **7**. The results are summarized in Table III. The spectral data for **7** are listed in Table IV and consistent with the assigned structures.

Reaction of **7** with the corresponding arylsulfonyl chloride in the presence of sodium bicarbonate in acetone-water (1:1) produced compound **8** and **9** in an approximate ratio of 4:1. After workup, these regioisomers were separated by flash column chromatography. The results are shown in Table V and the spectral data of compound **8** and **9** are listed in Table VI. Structures of regioisomers **8** and **9** were as-



7a **8a** **9a**

	7a	**8a**	**9a**
Ha	4.93 (dd, J=7.9, 9.2 Hz)	4.91 (dd, J=7.3, 9.2 Hz)	5.37 (dd, J=5.3, 9.9 Hz)
Hb	4.01 (dd, J=9.2, 10.8 Hz)	4.33 (dd, J=9.2, 9.5 Hz)	4.11 (dd, J=9.9, 13.4 Hz)
Hc	3.45 (dd, J=7.9, 10.8 Hz)	3.72 (dd, J=7.3, 9.5 Hz)	3.57 (dd, J=5.3, 13.4 Hz)

Fig. 2. Typical NMR data of the protons on imidazoline ring of **7a**, **8a**, and **9a**

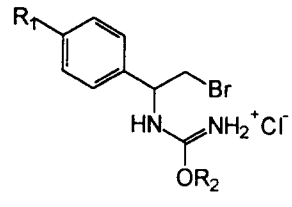


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Table VIII. Spectral data for imidazolidinones **3**

entry No.	compd. No. 3	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ)
1	**a**	IR (KBr) 3250, 2890, 1755, 1710; NMR δ 3.69 (dd, J=6.8, 9.2 Hz, 1H), 4.32 (dd, J=8.8, 9.2 Hz, 1H), 4.78 (dd, J=6.8, 8.8 Hz, 1H), 5.30 (s, 1H, exchangeable with D_2O), 7.20-8.10 (m, 5H).
2	**b**	IR (KBr) 3250, 3050, 1740, 1700; NMR δ 2.46 (s, 3H) 3.46 (dd, J=6.8, 9.2 Hz, 1H), 4.27 (dd, J=8.8, 9.2 Hz, 1H), 4.76 (dd, J=6.8, 8.8 Hz, 1H), 5.82 (s, 1H, exchangeable with D_2O), 7.00-7.50 (m, 7H), 7.87 (d, J=8.4 Hz, 2H),
3	**c**	IR (KBr) 3360, 1750, 1725; NMR δ 3.64 (dd, J=6.8, 9.2 Hz, 1H), 4.28 (dd, J=9.0, 9.2 Hz, 1H), 4.78 (dd, J=6.8, 9.0 Hz, 1H), 5.96 (s, 1H, exchangeable with D_2O), 7.10-7.70 (m, 7H), 7.92 (d, J=8.6 Hz, 2H).
4	**d**	IR (KBr) 3225, 3120, 1740; NMR δ 2.14 (quintet, J=7.4 Hz, 2H), 2.97 (m, 4H), 3.67 (dd, J=6.8, 9.2 Hz, 1H), 4.29 (dd, J=8.8, 9.2 Hz, 1H), 4.76 (dd, J=6.8, 8.8 Hz, 1H), 5.57 (s, 1H, exchangeable with D_2O), 7.10-7.80 (m, 8H).
5	**e**	IR (KBr) 3275, 1750, 1710; NMR δ 2.46 (s, 3H), 3.61 (dd, J=6.8, 9.2 Hz, 1H), 4.27 (dd, J=8.8, 9.2 Hz, 1H), 4.73 (dd, J=6.8, 8.8 Hz, 1H), 5.60 (s, 1H, exchangeable with D_2O), 7.09 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.4,Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H).
6	**f**	IR (KBr) 3225, 3090, 1760, 1710; NMR δ 3.63 (dd, J=6.8, 9.2 Hz, 1H), 4.29 (dd, J=8.8, 9.2 Hz, 1H), 4.76 (dd, J=6.8, 8.8 Hz, 1H), 5.44(s, 1H, exchangeable with D_2O), 7.11 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.6 Hz, 4H), 7.96 (d, J=8.6 Hz, 2H).
7	**g**	IR (KBr) 3300, 2950, 1750, 1713; NMR δ 2.16 (quintet, J=7.1 Hz, 2H), 2.95 (m, 4H), 3.63 (dd, J=6.8, 9.2 Hz, 1H), 4.27 (dd, J=8.8, 9.2 Hz, 1H) 4.74 (dd, ,J=6.8, 8.8 Hz, 1H), 5.50 (s, 1H, exchangable with D_2O), 7.00-8.00 (m, 7H).
8	**h**	IR (KBr) 3200, 3125, 2900, 1750; NMR δ 2.16 (quintet, J=7.1 Hz, 2H), 2.95 (m, 4H), 3.63 (dd, J=6.8, 9.2 Hz, 1H), 4.28 (dd, J=8.8, 9.2 Hz, 1H), 4.75 (dd, J=6.8, 8.8 Hz, 1H), 5.60 (s, 1H, exchangeable with D_2O), 7.00-8.00 (m, 7H).
9	**i**	IR (KBr) 3350, 3250, 1745, 1710; NMR δ 2.36 (s, 3H), 3.65 (dd, J=6.8, 9.5 Hz, 1H), 4.29 (dd, J=8.8, 9.5 Hz, 1H), 4.74 (dd, J=6.8, 8.8 Hz, 1H), 5.35 (s, 1H, exchangeable with D_2O), 7.00-8.20 (m, 9H).
10	**j**	IR (KBr) 3250, 3025, 1750, 1710; NMR δ 2.36 (s, 3H), 2.47 (s, 3H), 3.64 (dd, J=6.8, 8.8 Hz, 1H), 5.26 (1H, exchangeable with D_2O), 7.00-7.60 (m, 6H), 7.92 (d, J=8.1 Hz, 2H).
11	**k**	IR (KBr) 3250, 1745, 1710; NMR δ 2.36 (s, 3H), 3.64 (dd, J=6.9, 9.2 Hz, 1H), 4.28 (dd, J=8.8, 9.2 Hz, 1H), 4.75 (dd, J=6.9, 8.8 Hz, 1H), 5.40 (s, 1H, exchangeable with D_2O), 7.10-7.30 (m, 4H), 7.50 (d, J=8.4 Hz, 2H), 7.97 (d, J=8.4 Hz, 2H).
12	**l**	IR (KBr) 3250, 1740, 1705; NMR δ 2.15 (quintet, J=7.1 Hz, 2H), 2.95 (m, 4H), 3.62 (dd, J=6.8, 9.2 Hz, 1H), 4.26 (dd, J=8.8, 9.2 Hz, 1H), 4.73 (dd, J=6.8, 8.8 Hz, 1H), 5.49 (s, 1H, exchangeable with D_2O), 7.00-8.00 (m, 7H).

Table IX. Synthesis of imidazolidinones **4**

entry No.	precursor[a]	compd No. **4**	substituents		appearance	m.p.(°C)	yield (%)
			R_1	R_3			
1	**9b**	**b**	H	Me	white solid	217.0-219.0	100
2	**9d**	**d**	H	indane[b]	white solid	205.5-207.5	100
3	**9h**	**e**	Br	Me	white solid	212.8-214.8	100
4	**9i**	**f**	Br	Me	white solid	204.0-206.0	100
5	**9j**	**g**	Br	indane[b]	white solid	239.0-241.0	100
6	**9k**	**h**	Cl	Me	white solid	229.0-232.0	100
7	**9l**	**i**	Me	H	white solid	180.5-182.0	100
8	**9m**	**j**	Me	Me	white solid	199.0-200.4	100
9	**9n**	**k**	Me	Cl	white solid	183.0-185.0	100
10	**9o**	**l**	Me	indane[b]	white solid	208.0-209.0	100

[a]Precursor means the starting material for the preparatrion of the corresponding compounds **4**.
[b]indane is represented for 5-indanyl connected to sulfonyl group as a substituted phenyl.

signed based on the variation of chemical shifts of imidazoline ring protons compared to those of compounds **7** (Fig. 2). Sulfonylation on nitrogen of imidazoline **7** causes the larger down field shift on the protons at near site. In case of **8**, chemical shifts for Hb and Hc at 5-position moves to down field by about 0.3 ppm, but the chemical shift of Ha proton at 4-position of imidazoline ring has almost not been

Table X. Spectral data for imidazolidinones **4**

entry No.	compd. No. **4**	IR (ν_{max} cm^{-1}), NMR ($CDCl_3$, δ)
1	**b**	IR (KBr) 3250, 1720; NMR (200 MHz) δ 2.37 (s, 3H), 3.37 (dd, J=3.4, 9.0 Hz, 1H), 3.95 (dd, J=9.0, 9.3 Hz, 1H), 5.27 (1H, exchangeable with D_2O), 5.39 (dd, J=3.4, 9.3 Hz, 1H), 7.11 (d, J=8.0 Hz, 2H), 7.26-7.44 (m, 5H), 7.47 (d, J=8.4 Hz, 2H).
2	**d**	IR (KBr) 3250, 3130, 1720; NMR δ 2.07 (quintet, J=7.4 Hz, 2H) 2.90 (m, 4H), 3.35 (dd, J=3.2, 9.2 Hz, 1H), 3.52 (s, 1H, exchangeable with D_2O), 3.94 (dd, J=9.0, 9.2 Hz, 1H), 7.00-7.50 (m, 8H).
3	**e**	IR (KBr) 3250, 1730; NNR (200 MHz) δ 2.40 (s, 3H), 3.31 (dd, J=3.2, 9.2 Hz, 1H), 3.94 (dd, J=8.9, 9.2 Hz, 1H), 5.33 (dd, J=3.2, 8.9 Hz, 1H), 5.55 (s, 1H, exchangeable with D_2O), 7.16 (d, J=8.4 Hz, 4H), 7.41 (d, J= 8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H).
4	**f**	IR (KBr) 3280, 2900, 1750, 1730; NMR (200 MHz) δ 3.35 (dd, J=2.9, 9.1 5.50 (s, 1H, exchangeable with D $_2$O), 7.44 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H).
5	**g**	IR (KBr) 3360, 1740, 1710; NMR δ 2.08 (quintet, J=7.4 Hz, 2H), 3.31 (dd, J=3.0, 9.2 Hz, 1H), 3.94 (dd, J= 8.8, 9.2 Hz, 1H), 5.33 (dd, J=3.0, 8.8 Hz, 1H), 5.42 (s, 1H, exchangeable with D_2O), 7.00-7.70 (m, 7H).
6	**h**	IR (KBr) 3360, 1740, 1720; NMR (200 MHz) δ 2.01 (quintet, J=7.4 Hz, 2H), 2.78-2.95 (m, 4H), 3.33 (dd, J= 3.2, 9.2 Hz, 1H), 3.95 (dd, J= 9.2, 9.3 Hz, 1H), 5.34 (dd, J=3.2, 9.3 Hz, 1H), 5.68 (s, 1H, exchangeable with D_2O), 7.17-7.47 (m, 6H), 7.49 (dd, J=1.2, 7.9 Hz, 1H).
7	**i**	IR (KBr) 3280, 1735, 1710; NMR (200 MHz) δ 2.35 (s, 3H), 3.36 (dd, J=3.3, 9.1Hz, 1H), 3.94 (dd, J=9.1, 9.2 Hz, 1H), 5.36 (dd, J=3.3, 9.2 Hz, 1H), 5.75 (s, 1H, exchangeable with D_2O), 7.06 (d, J=8.3 Hz, 2H), 7.15 (d, J=8.3 Hz, 2H), 7.32 (d, J=7.9 Hz, 2H), 7.45-7.60 (m, 3H).
8	**j**	IR (KBr) 3250, 2920, 1720; NMR δ 2.37 (s, 3H), 2.39 (s, 3H), 3.34 (dd, J=3.2, 9.2 Hz, 1H), 3.91 (dd, J=8.9, 9.2 Hz, 1H), 5.05 (1H, exchageable with D_2O), 5.35 (dd, J=3.2, 8.9 Hz, 1H), 7.00-7.40 (m, 6H), 7.49 (d, J=8. 4 Hz, 2H).
9	**k**	IR (KBr) 3375, 2920, 1750, 1710; NMR (200 MHz) δ 2.37 (s, 3H), 3.38 (dd, J=3.0, 9.1 Hz, 1H), 3.97 (dd, J= 8.9, 9.1 Hz, 1H), 5.34 (dd, J=3.0, 9.0 Hz, 1H), 5.59 (1H, exchangeable with D_2O), 7.00-7.40 (m, 6H), 7.47 (d, J=8.8 Hz, 2H).
10	**l**	IR (KBr) 3250, 2950, 1720; NMR (200 MHz) δ 2.07 (quintet, J=7.4 Hz, 2H), 2.36 (s, 3H), 2.90 (m, 4H), 3.35 (dd, J=3.2, 9.2 Hz, 1H), 3.93 (dd, J=9.1, 9.2 Hz, 1H), 5.32 (s, 1H, exchangeable with D_2O), 5.35 (dd, J=3.2, 9.1 Hz, 1H), 7.10-7.30 (m, 6H), 7.46 (dd, J=1.8, 7.8 Hz, 1H).

changed compared to those of the protons of imidazoline ring of compounds **7**. In case of **9**, the larger down field shift (about 0.3 ppm) on the chemical shift for proton Ha at 4-position has been experienced on the sulfonylation compared to those chemical shifts of Hb and Hc at 5-position. Therefore major product was assigned as 4-phenyl-1-arylsulfonyl-2-alkoxyimidazolines **8**, while the minor products as 3-arylsulfonylated regioisomer **9**. The ratio of the formation of regioisomers **8** and **9** were not altered upon the variation on size of alkoxy group at 2-position of **7** as shown in Table V. These facts imply that the regioselectivity of sulfonylation of imidazoline **7** is mainly governed by phenyl substituent at 4-position.

Removal of O-alkyl group **8** to produce **3** was quantitatively accomplished by the treatment with anhydrous hydrochloride in ether. The results and the spectral data of **3** are shown in Table VII and 8, respectively. This reaction was very slow in the basic condition using aqueous sodium hydroxide even at reflux condition (Jung *et al*, 1985). Conversion of **9** to **4** was quantitatively performed according to procedure used for the removal of alkyl group of **8**. The results and the spectral data of **4** are listed in Table IX and X, respectively.

Biological activity

As shown in Table XI, some of the imidazolidinones **3** show very potent cytotoxicity against both A549 and SK-MEL-2 cell lines. Especially compounds **3b**, **3c**, and **3d** possess the remarkable cytotoxicity against human lung carcinoma A549 (IC_{50}: 3.94, 3.19, 0.31 μg/mL) and human melanoma SK-MEL-2 (IC_{50}: 0.80, 0.48, 0.0007 μg/mL). These IC_{50} values indicate that these compounds are 10-1000 times more potent than LY 186641(**1**). These three compounds were further tested against eleven other different cell lines using SRB or MTT assay. The results are shown in Table XII. Compared to LY 186641(**1**) these exhibit more active against these various cell lines. These compounds even show the potent activity against murine leukemia cell lines(L1210 and P388) unlike LY186641(**1**) (Howbert *et al*, 1990). These IC_{50} values certainly indicate that the activity of compounds **3** is very broad. Therefore these arylsulfonylimidazolidinones **3** could be the potential lead compounds for the development of novel anticancer agent.

Comparison of the cytotoxicity of compounds **3a**,

Table XI. Cytotoxicity of 1-arylsulfonylimidazolidinones **3**

entry No.	compd. No. **3**	substituents		IC_{50}[a]			
				A549		SK-MEL-2	
		R_1	R_3	μg/ml	μM	μg/ml	μM
1	**a**	H	H	43.70	144.54	35.19	116.39
2	**b**	H	Me	3.94	12.45	0.80	2.53
3	**c**	H	Cl	3.19	9.47	0.48	1.43
4	**d**	H	indane[b]	0.31	0.91	0.0007	0.002
5	**e**	Br	Me	>100	-	>100	-
6	**f**	Br	Cl	66.73	160.53	46.27	111.31
7	**g**	Br	indane[b]	14.29	33.92	13.74	32.61
8	**h**	Cl	indane[b]	32.54	86.34	24.24	64.32
9	**i**	Me	H	>100	-	>100	-
10	**j**	Me	Me	>100	-	>100	-
11	**k**	Me	Cl	55.52	158.26	43.32	123.48
12	**l**	Me	indane[b]	35.37	99.23	25.84	72.50
LY186641 (1)				3.97	11.34	4.53	12.91

[a]IC_{50} values are the mean value of three times measurement. [b]Indane is represented for 5-indanyl connected to sulfonyl group as a substituted phenyl.

Table XII. Cytotoxicity of compounds **3b**, **3c**, and **3d**

entry No[a].	compound cell[b]	IC_{50} (μg/mL)[c]			
		3b	**3c**	**3d**	LY186641(**1**)
1	ovary SK-OV-3	0.91	1.99	0.03	7.49
2	brain XF-498	1.95	2.55	0.37	3.46
3	colon HCT-15	0.15	0.65	0.04	2.95
4	murine leukemia L1210	2.07	1.68	0.001	23.52
5	murine leukemia P388	1.29	2.09	0.001	21.69
6	colon colo 205	2.82	5.69	4.16	57.30
7	stomach KATO III	4.34	16.60	10.30	41.50
8	melanoma Malme-3M	10.64	97.3	10.05	>100
9	colon SNU-C4	8.41	54.80	13.55	22.28
10	lung HFL/B	4.10	65.80	13.90	>100
11	lymphoma K562	6.70	39.80	4.10	19.20

[a]SRB assay method was used for the measurement of cytotoxicity of entry number 1-5 and MTT assay method was used for the measurement of cytotoxicity of entry number 6-11. [b]Cell lines used for the test are human cancer cell lines unless specified. [c]IC_{50} values are the mean value of three times measurement.

Table XIII. Cytotoxicity of 3-arylsulfonylimidazolidinones **4**

entry No.	compd. No. **4**	substituents		IC_{50}[a]			
				A549		SK-MEL-2	
		R_1	R_3	μg/ml	μM	μg/ml	μM
1	b	H	Me	>100	-	>100	-
2	d	H	indane[b]	20.03	58.50	13.35	38.99
3	e	Br	Me	26.50	67.04	31.61	79.97
4	f	Br	Cl	34.90	83.96	44.17	106.26
5	g	Br	indane[b]	>100	-	50.21	119.17
6	h	Cl	indane[b]	>100	-	60.72	161.12
7	i	Me	H	49.60	156.78	45.51	143.85
8	j	Me	Me	>100	-	77.46	234.44
9	k	Me	Cl	93.19	265.64	89.60	255.40
10	l	Me	indane[b]	32.20	90.34	31.59	88.63
LY186641(**1**)				3.97	11.34	4.53	12.91

[a]IC_{50} values are the mean value of three times measurement. [b]Indane is represented for 5-indanyl as a substituted phenyl.

3b, **3c**, and **3d** with those of the corresponding analogues **3e** and **3j**, **3f** and **3k**, **3g** and **3l** indicates that the phenyl group at 4 position of imidazolidinone ring is much better for the activity than the para sub-

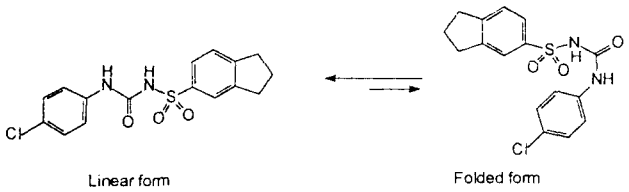

Fig. 3. The effective conformation of diarylsulfonylurea (**1**)

stituted phenyl group. This might reflect that the bulky substituent on the phenyl ring may reduce activity. Compounds (**3d**, **3g**, **3h**, **3l**) bearing indanyl group as aryl on sulfonyl function of **3** show more potent activity than the corresponding compounds containing other aryl substituents.

As shown in Table XIII, some of 3-arylsulfonylimidazolidinones **4** show the relatively strong cytotoxicity. IC_{50} values of compounds **4** are located about 20-34 μg/mL against SK-MEL-2. However, their activity are much weaker than their corresponding regioisomer **3**. Trend in the cytotoxicity of **4** depending on the substituents at R_1 and R_3 are the same as those shown in imidazolidinone series **3**. Compound **4d** is the most active one in this series.

As shown in Table XI and XIII, imidazolones **3** are more active than their corresponding regioisomer **4**. Such difference in cytotoxicity of compounds **3** and **4** might be a good experimental evidence for effective conformation of diarylsulfonylurea LY186641 (1), which can have many different conformation. The differenence in activity of **3** and **4** may be originated from the difference in their molecular shape. Two aryl groups in the series of **3** are obviously farther apart than those in the regioisomer **4** due to the fixation of urea moiety in five member ring. Therefore structure **3** should be very similar to the linear conformer of diarylsulfonylurea (**1**) and the structure **4** certainly resembles the folded conformer of diarylsulfonylurea as shown in fig. 3. The biological acitivity of compounds **3** and **4** certainly implies that the linear conformation of diarylsulfonylureas **1** and **2** could be the active conformation. Interestingly the linear conformation of sufonylurea herbicides structurally similar to diarylsulfonylurea **1** was theoretically predicted as the most stable and active one in water (Kang *et al*, 1990).

This discovery of novel 4-phenyl-1(N)-arylsulfonylimidazolidinones as the potential lead compound certainly expedites the further exploration of the compounds containing sulfonylurea pharmacophore for the new anticancer agent.

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