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SYNTHESIS AND EVALUATION OF CYTOTOXIC ACTIVITY OF NOVEL ARYLSULFONYLIMIDAZOLIDINONES

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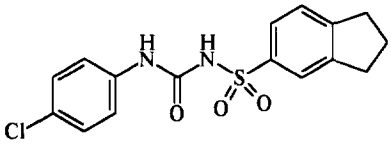
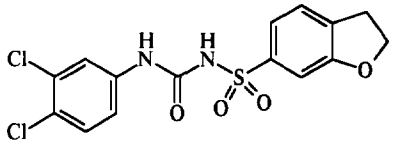
Abstract-Synthesis of novel arylsulfonylimidazolidinones **3** and **4** containing sulfonylurea pharmacophore and evaluation of their *in vitro* cytotoxicity against human cell lines were investigated. As a result, a series of 4-phenyl-1(N)-arylsulfonylimidazolidinones have been found to be the potential anticancer agent.

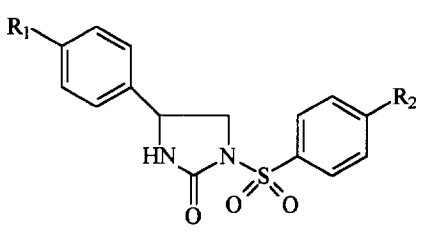
The diarylsulfonylureas are well known for their herbicidal activities[1)] and hypoglycemic properties[2)]. A series of these compounds have been recently proved to have antineoplastic activity[3,4)]. Especially, remarkable effectiveness of LY186641 (**1**, sulofenur) and LY295501 (**2**) has been demonstrated against various solid tumors[3)] and xenografts[3,5-9)]. Although the mechanism of action of these compounds has not been identified, they do not exhibit the inhibition of DNA, RNA, or protein synthesis[3,5-10)]. These agents are not the cell cycle specific and do not show cross resistance in multidrug resistance cell lines[3,5)]. Such unique characteristics of these diarylsulfonylureas led to the introduction of diarylsulfonylureas into the clinical trials[11-15)]. However, the development of these agents has been seriously hampered due to the unexpected occurrence of anemia, methemoglobinemia, and the poor effectiveness at the optimum dose without the serious side effects in the clinical trials[11-15)]. The peculiar mode of action and the drawbacks of the diarylsulfonylureas led us to investigate the new structural entity. The novel arylsulfonylimidazolidinones **3** and **4** (Figure 1) containing sulfonylurea pharmacophore of diarylsulfonylurea have been designed, synthesized, and tested against various human soild tumor, murine leukemia cell lines *in vitro*, and murine mammary ardrenocarcinoma (MM48) *in vivo*.



1 (solufenur, LY 186641)



2 (LY 295501)



3

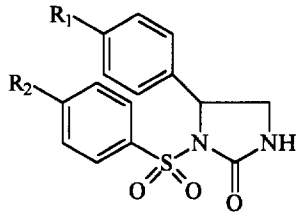


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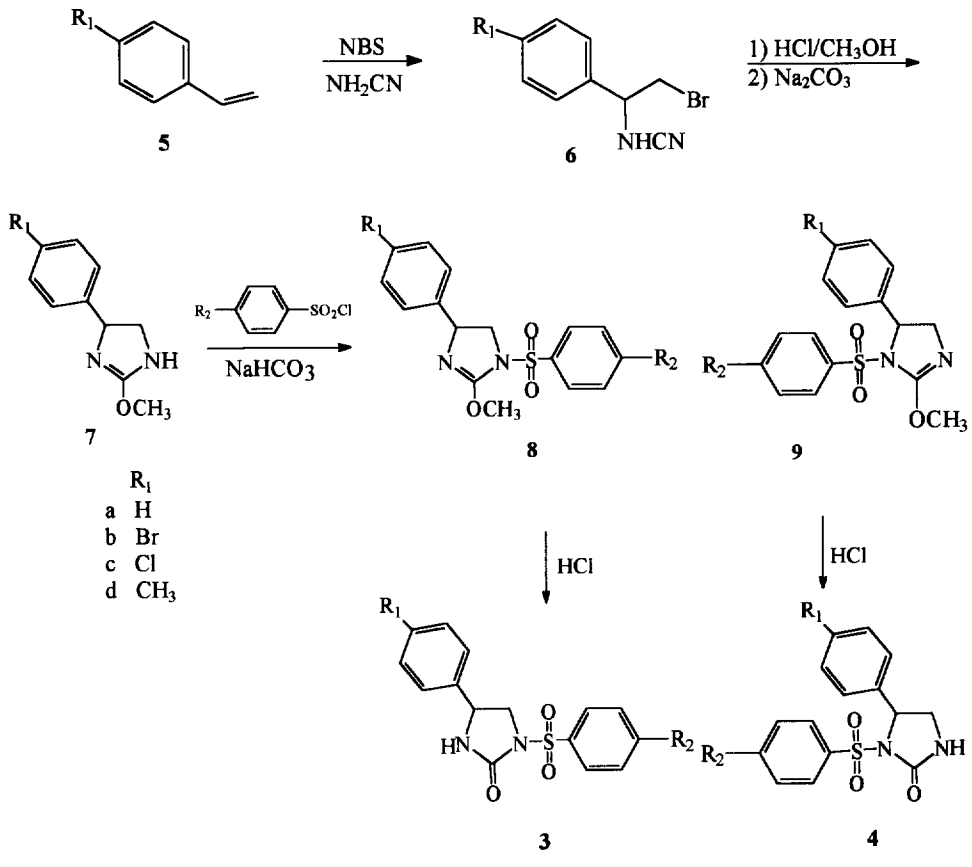
Figure 1. Design of novel arylsulfonylimidazolidinones

Synthesis-The arylsulfonylimidazolidinones **3** and **4** were synthesized as shown in Scheme 1. Intermediates **7** were prepared from styrenes **5** according to Jung and Kohn's procedure[16]. Reaction of **7** with corresponding arylsulfonyl chlorides in the presence of sodium bicarbonate in acetone-water (1:1) produced **8** and **9** in an approximate ratio of 5:1[17]. These regioisomers were separated by flash column chromatography. Structures of these regioisomers **8** and **9** were assigned based on the variation of chemical shifts of the imidazoline ring protons compared to those of **7**[18]. Sulfonylation on the nitrogen of imidazolines **7** causes larger down field shift on the imidazoline ring protons at near site of sulfonylated nitrogen. In case of **8**, the chemical shift for the protons at 5-position of the imidazoline ring moves to down field by about 0.3 ppm, but the chemical shift of the proton at 4-position has almost not been changed compared to the signals for the corresponding protons of the imidazoline ring of compound **7**. In case of the regioisomer **9**, larger down field shift of the chemical shift (about 0.3ppm) for the proton at 4-position has been experienced on the sulfonylation. Therefore the major products were assigned as 4-phenyl-1-arylsulfonyl-2-methoxyimidazolines **8**, while the minor products as 3-arylsulfonylated regioisomers **9**. Removal of *O*-methyl group of **8** and **9** in the final step was quantitatively accomplished by treatment with anhydrous hydrochloride in ether.

Structure Activity Relationship - Cytotoxicity of **3** and **4** were measured against human lung carcinoma A549 and human melanoma SK-MEL-2 cell lines in vitro using sulforhodamine B (SRB) assay[19]. The cytotoxicity of these compounds are shown as IC_{50} value in Table 1 and 2. As shown in Table 1, most of compounds **3** exhibit the potent cytotoxicity against both A549 and SK-Mel-2 cell lines. Especially compounds **3b**, **3c**, and **3d** possess the remarkable activity against both cell lines. These IC_{50} values indicate that these compounds are 10 to 1000 times more potent than LY186641 (**1**). Compound **3d** exhibits very strong activity against human ovarian (SK-OV-3, IC_{50} = 0.08 μM/mL), brain (XF498, IC_{50} = 1.08 μM/mL), and colon (HCT-15, IC_{50} = 0.13 μM/mL) cancer cell lines. This compound even shows very powerful activity against murine leukemia (L1210, IC_{50} = 0.0058 μM/mL; P388, IC_{50} = 0.0029 μM/mL) cell lines unlike LY 186641 (**1**)[3]. Such IC_{50} values certainly indicate that spectrum of these imidazolones **3** is very broad. The most potent compound **3d** was evaluated for antitumor activity in mice (C3H/He) bearing murine mammary adrenocarcinoma (MM48)[20]. Compound **3d** showed 80-90% suppression of tumor growth at the dose of 300mg/kg/day.



Scheme 1. Synthesis of Novel Arylsulfonylimidazolidinones
(Substituents R_1 and R_2 for compounds **8**, **9**, **3**, and **4** are found in Table 1).

Comparison of the cytotoxicity of **3b**, **3e**, and **3j** indicate that a phenyl group at 4-position of the imidazolone ring is much better for the activity than the para substituted phenyl group. This trend can be also found in the series of **3c**, **3f** and **3k** or **3d**, **3g**, **3h**, and **3l**. This fact might reflect that the bulky substituents on the phenyl ring at the 4-position of **3** reduce the activity. Compounds **3d**, **3g**, **3h**, and **3l**, which bore 5-indanesulfonyl group at the 1-position, show more potent activity than the corresponding compounds containing other benzenesulfonyl groups. A series of 3-arylsulfonyl analogues **4** show dramatically reduced activity compared to the corresponding **3** as shown in Table 2. Therefore, the more effective regioisomer is the 1-arylsulfonyl-4-phenylimidazolidinones **3**.

Fixation of urea moiety into the five member ring in **3** led to two aryl groups farther away each other unlike in **4**. Conformation of **3** certainly resembles the linear conformer of the diarylsulfonylurea. This might indicate that the more effective conformer of diarylsulfonylureas **1** and **2** for their activity is linear one[21].

Table 1. Cytotoxicity of 1-Arylsulfonylimidazolidinones **3**[22)]

Compd. No.**3**	Substituent		molecular formular	IC_{50}[a] A549	SK-MEL-2
	R_1	R_2		μM	μM
a	H	H	$C_{15}H_{14}N_2O_3S$	144.54	116.39
b	H	Me	$C_{16}H_{16}N_2O_3S$	12.45	2.53
c	H	Cl	$C_{15}H_{13}N_2ClO_3S$	9.47	1.43
d	H	indane[b]	$C_{18}H_{18}N_2O_3S$	0.91	0.002
e	Br	Me	$C_{16}H_{15}N_2BrO_3S$	>253.00	>253.00
f	Br	Cl	$C_{15}H_{12}N_2BrClO_3S$	160.53	111.31
g	Br	indane[b]	$C_{18}H_{17}N_2BrO_3S$	33.92	32.61
h	Cl	indane[b]	$C_{18}H_{17}N_2ClO_3S$	86.34	64.32
i	Me	H	$C_{16}H_{16}N_2O_3S$	>316.08	>316.08
j	Me	Me	$C_{17}H_{18}N_2O_3S$	>302.66	>302.66
k	Me	Cl	$C_{16}H_{15}N_2ClO_3S$	158.26	123.48
l	Me	indane[b]	$C_{19}H_{20}N_2O_3S$	99.23	72.50
LY186641 (**1**)			$C_{16}H_{15}N_2ClO_3S$	11.34	12.91

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

Table 2. Cytotoxicity of 3-Arylsulfonylimidazolidinones **4**[22)]

Compd. No. **4**	Substituent		molecular formular	IC_{50}[a] A549	SK-MEL-2
	R_1	R_2		μM	μM
b	H	Me	$C_{16}H_{16}N_2O_3S$	>316.09	>316.09
d	H	indane[b]	$C_{18}H_{18}N_2O_3S$	58.50	38.99
e	Br	Me	$C_{16}H_{15}N_2BrO_3S$	67.04	79.97
f	Br	Cl	$C_{15}H_{12}N_2BrClO_3S$	83.96	106.23
g	Br	indane[b]	$C_{18}H_{17}N_2BrO_3S$	>237.35	119.17
h	Cl	indane[b]	$C_{18}H_{17}N_2ClO_3S$	>265.35	161.12
i	Me	H	$C_{16}H_{16}N_2O_3S$	156.78	143.85
j	Me	Me	$C_{17}H_{18}N_2O_3S$	>302.66	234.44
k	Me	Cl	$C_{16}H_{15}N_2ClO_3S$	265.64	255.40
l	Me	indane[b]	$C_{19}H_{20}N_2O_3S$	90.34	88.63
LY186641 (**1**)			$C_{16}H_{15}N_2ClO_3S$	11.34	12.91

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

These novel 1-arylsulfonyl-4-phenylimidazolidinones could be the potential lead compounds for the development of anticancer agent containing sulfonylurea pharmacophore.

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The treatment of styrene or styrenes substituted at para position with one equivalent of N-bromosuccinimide and two equivalent of cyanamide in dichloromethane at room temperature gave the corresponding 2-bromo-1-phenylethyl cyanamides **6** (**6a** 64%; **6b** 69%; **6c** 70%; **6d** 76% isolated yield after flash column

chromatography). The cyanamides **6** were then reacted with methanol containing 5% hydrochloride at 35-40 °C for 6-8 hours and the resulting reaction mixture was stirred with three equivalent of sodium carbonate at room temperature overnight. After the insoluble material was filtered off, the solvent was evaporated under vacuum. The residue was stirred in dichloromethane and the insoluble material was removed by the filtration. The filtrate was concentrated under vacuum and the residue was recrystallized from ethyl acetate to give white solid **7** (**7a** 74%; **7b** 73%, **7c** 60%; **7d** 71%).

17. Yield and ratio for the formation of compounds **8** and **9** were calculated after flash column chromatographic separation: compounds number, % yield combined for **8** and **9** (ratio of **8** and **9**) - **8a+9a** 79 (78:22); **8b+9b** 78 (85:15); **8c+9c** 73 (85:15); **8d+9d** 77 (88:12); **8e+9e** 67 (74: 26); **8f+9f** 57 (86:14); **8g+9g** 78 (72:28); **8h+9h** 69 (80:20); **8i+9i** 60 (82:18); **8j+9j** 55 (83:17); **8k+9k** 66 (82:18); **8l+9l** 71 (85:15).
18. The variation of the chemical shifts for the protons at 4,5-position of imidazoline ring of **7a** on the sulfonylation provides the basis for the structural assignment of the series of regioisomers **8** and **9**. The following chemical shifts for the illustration are only listed for **7a** and the products **8a** and **9a** from the sulfonylation of **7a** with benzenesulfonyl chloride measured by the JEOL JNM-EX 90 FT-NMR spectrometer(89.45MHz) from the resonance of tetramethylsilane. NMR for **7a** ($CDCl_3$) δ 3.45 (dd, J = 7.9, 10.8Hz, 1H), 3.90(s, 3H), 4.01 (dd, J = 9.2, 10.8Hz, 1H), 4.93 (dd, J = 7.9, 9.2Hz, 1H), 7.31(m, 5H); NMR for **8a** ($CDCl_3$) δ 3.72 (dd, J = 7.3, 9.5Hz, 1H), 3.96 (s, 3H), 4.33 (dd, J = 9.2, 9.5Hz, 1H), 4.91 (dd, J = 7.3, 9.2Hz, 1H), 7.20-7.70 (m, 10H); NMR for **9a** ($CDCl_3$) δ 3.57 (dd, J = 5.3, 13.4Hz, 1H), 3.94 (s, 3H), 4.11 (dd, J = 9.9, 13.4Hz, 1H), 5.37 (dd, J = 5.3, 9.9Hz, 1H), 7.20-7.70 (m, 10H).
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20. Mammary adrenocarcinoma (MM48) cells were implanted intradermally (i. d.) into the right inguinal flank of mice. The compounds **3d** and **1** suspended in 0.5% carboxymethylcellulose (CMC) were administered perorally (p. o.) to the mice on 1, 2, 3, 4, and 5 days after implantation. Tumor size [(length x width)$^{1/2}$ mm] was measured day 4, 7, 11, 14, and 18. LY 186641 (**1**) was administered at the dose 300mg/kg/day that was most effective dose in the previous report[3] and showed 80-90% suppression at this dose.
21. The linear conformation of sulfonylurea herbicides has been predicted as the most stable and effective one in water[23].
22. All new copmpounds gave analytical and spectroscopical results consistent with the assigned strucutre.
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