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SYNTHESIS AND ANTITUMOR ACTIVITY OF 4-PHENYL-1-ARYLSULFONYL IMIDAZOLIDINONES

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Abstract - Novel 1-(1-benzoylindoline-5-sulfonyl)-4-phenyl-4,5-dihydroimidazolones **3** synthesized show highly potent and broad cytotoxicities. Among them compound **3b** (DW2143) exhibits much more potent cytotoxicities than doxorubicin and highly effective antitumor activities against murine (3LL, Colon 26) and human xenograft (NCI-H23, SW620) tumor models.

Highly potent cytotoxicities of novel 4-phenyl-1(N)-arylsulfonylimidazolidinones **1** containing sulfonylurea pharmacophore against the various cancer cell lines were previously demonstrated.[1,2] Especially compound **1c** exhibits 10 to 1000 times more cytotoxic[3] than prototype diarylsulfonylurea LY186641 (**2**, sulofenur),[1,2,4] which was noticed with its novel structure as a potential anticancer agent and peculiar mode of action. This impressive *in vitro* activity of **1c** led us to investigate its *in vivo* activity against the various cancer models.[1,5] However oral efficacy of **1c** was compatible with that of LY186641 (**2**). This moderate antitumor activity of **1c** was then proved to be attributed to its poor bioavailability (about 10% in mice). Thus structural modification of this series had been intensively attempted to improve their pharmacological profile. As a result, 4-phenyl-1-arylsulfonylimidazolidinone moiety of this analogues had been identified as an essential structural necessity for their activity.[2,6] Therefore the structural variation of **1** has been concentrated on aryl motif on sulfonyl group to enhance their efficacy. Accordingly, compounds **3** characterized with 1-substituted benzoylindoline as a aryl moiety of **1** have been prepared and their *in vitro* growth inhibitory activities against three human cancer cell lines (lung carcinoma A549, leukemia K562, and ovarian adenocarcinoma SK-OV-3) were initially measured. The most potent derivative (DW2143) was then further investigated to determine its spectrum and antitumor activities against murine (3LL, Colon 26) and human xenograft (NCI-H23, SW620) tumor models in mice.

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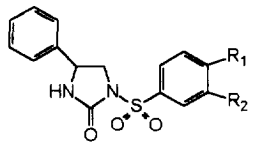
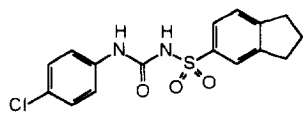
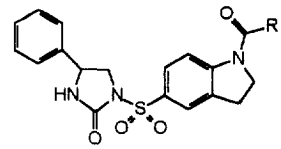


1a: R_1=Cl, R_2=H
1b: R_1=CH_3, R_2=H
1c: R_1,R_2=-$(CH_2)_3$-



2 (LY186641, sulofenur)



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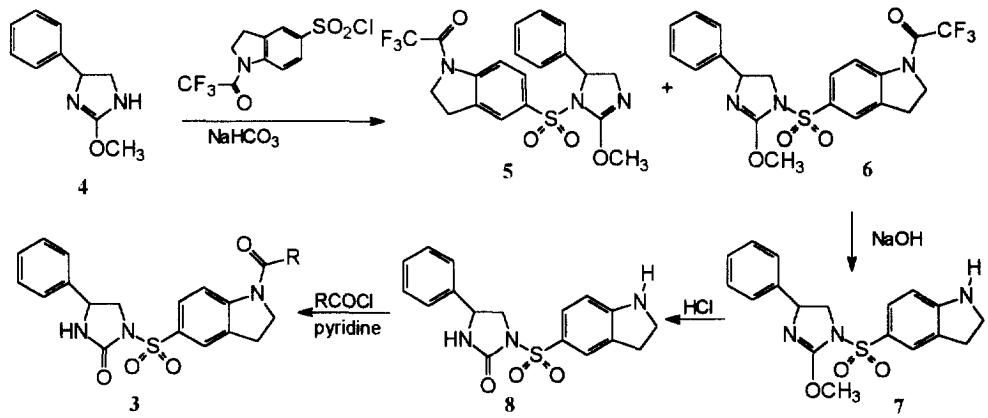
The procedure employed for the preparation of arylsulfonylimidazolidinones **3**[7] is illustrated in scheme 1. Treatment of imidazoline **4**[2] with 1-trifluoroacetylindoline-5-sulfonyl chloride in the presence of sodium bicarbonate in acetone-water(1:1) at room temperature produced regioisomers **5** and **6** with approximately 1 to 5 ratio.[8] Compound **6** was separated by flash column chromatography in 65% yield. After removal of trifluoroacetyl group of **6** by the reaction with sodium hydroxide in aqueous methanol at ambient temperature, treatment of resulting imidazoline **7** with hydrochloride produced imidazolone **8** quantitatively. Compound **8** was then converted to the final compounds **3** with reaction of the corresponding benzoyl chloride in the presence of pyridine in dichloromethane. Compound **3b** was obtained by catalytic hydrogenation of **3c** in the presence of Raney Ni..

Scheme 1. Synthesis of Arylsulfonylimidazolidinones **3**



Cytotoxicities of compounds **1c**, **2**, and **3** were measured against human lung carcinoma A549, human leukemia K562, and human ovarian cancer SK-OV-3 cell lines *in vitro* using MTT assay.[9] As shown in Table 1, cytotoxicities of compounds **3** containing substituted benzoyl group at 1-position of indoline moiety are enormously enhanced compared to those of lead compound **1c** and LY186641(**2**). This fact indicates that benzoyl group at 1-position of indoline moiety of **3** is believed to be an additional necessity for the potentiation of cytotoxicity of this series. Surprisingly cytotoxicities of compounds **3** are comparable with those of doxorubicin. Compound **3b** (DW2143) possesses the most potent cytotoxicities against all three different cell lines (cell line, IC_{50} values; A549, 0.20μM: K562, 0.44μM: SK-OV-3, 1.24μM).

Table 1. Arylsulfonylimidazolidinones **3** and their cytotoxicities

Compd No. **3**	Substituent R	Molecular Formula	mp[a] (°C)	$IC_{50}(\mu M)$[b] A549[c]	K562[c]	SK-OV-3[c]
a	C_6H_5	$C_{24}H_{21}N_3O_4S$	127	0.44	4.12	0.56
b	$C_6H_4(4\text{-}NH_2)$	$C_{24}H_{22}N_4O_6S$	216	0.20	0.44	1.24
c	$C_6H_4(4\text{-}NO_2)$	$C_{24}H_{20}N_4O_4S$	145	3.45	18.02	4.24
1c		$C_{18}H_{18}N_2O_3S$		4.74	42.66	12.13
2	LY186641	$C_{16}H_{15}ClN_2O_3S$		36.43	50.08	222.90
	doxorubicin	$C_{27}H_{29}NO_{11}$		1.99	1.77	4.15

[a]Melting points are uncorrected and located within 1.5°C from indicated values. [b]IC_{50} values were measured using the MTT assay and the incubation time was 2days are the mean value of three times measurements. [c]Cell Lines (medium); A549:human lung carcinoma (RPMI1640+10%FBS), K562: human chronic myelogenous leukemia (RPMI1640+10%FBS), SK-OV-3: human ovarian adenocarcinoma (RPMI1640+10%FBS).

Table 2. Antitumor activity of **3b** (DW2143)

tumor[a]	mice[b]	agent	dose[c] (mg/kg)	administered route	body weight change[d] (g)	TGI[e] (%)
		vechicle only		p.o.	3.0	
3LL	BDF1	**3b**	100	p.o.	-1.0	84.3
		doxorubicin	4	i.p.	-2.0	60.4
		vechicle only		p.o.	-3.0	
colon26	Balb/c	**3b**	65	p.o.	0.4	55.6
		doxorubicin	4	i.p.	-3.0	42.5
		vichicle only		p.o.	0.7	
NCI-H23	HTXM[f]	**3b**	65	p.o.	0.6	67.0
		doxorubicin	1, 2, 3	i.p.	-2.6	39.0
		vichicle only		p.o.	1.9	
SW620	HTXM[f]	**3b**	65	p.o.	1.0	87.0
		doxorubicin	1, 2, 3	i.p.	-2.6	49.0

[a]3LL: murine Lewis lung carcinoma, Colon26:murine colon carcinoma, NCI-H23:human lung carcinoma, SW620:human colon carcinoma. [b]Numbers of mice used were 6 per group for 3LL and Colon26 and 7 per group for NCI-H23 and SW620. [c] Dose schedules are described in References and Notes.[10] [d] Body weight change was calculated from day 0 to day 20. [e] Tumor growth inhibition (TGI%) was determined at day 20 for 3LL and Colon26 and day 19 for NCI-H23 and SW620 after transplantation. [f] Human tumor xenograft mice (HTXM: BALB/c-nu/nu mice) were purchased from Charles River Laboratories in Japan and used as 5 weeks old female.

The bioavailability of **3b** in mice was then proved to be about 40.0%, which is markedly improved compared to lead compound **1c** (about 10.0%). Such remarkable *in vitro* activity and good pharmacokinetic profile of **3b** led us to investigate its antitumor activities *in vivo* against murine Lewis lung carcinoma (3LL), murine colon carcinoma (Colon26), human lung carcinoma (NCI-H23) xenograft, and human colon carcinoma (SW620) xenograft tumor models in mice. The results are shown in Table 2. Without any significant change of body weight of mice, compound **3b** shows 84.3%, 55.6%, 67.0%, and 87.0% suppression of tumor growth of 3LL, Colon26, NCI-H23, and SW620, respectively. These antitumor activities are much superior to those of

doxorubicin, which was intraperitonially administered at its toxicity-limiting dose.[10] Therefore compound **3b** (DW2143) is considered to be a valuable candidate for the development of new anticancer agent containing sulfonylurea pharmacophore.

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References and Notes:

1. Jung, S.-H.; Song, J.-S.; Lee, H.-S.; Choi, S.-U.; Lee, C.-O. *Bioorg. Med. Chem. Letters*, **1996**, *6*, 2553-2558.
2. Jung, S.-H.; Song, J.-S.; Lee, H.-S.; Choi, S.-U.; Lee, C.-O. *Arch. Pharm. Res.*, **1996**, *19*, 570-580.
3. Level of cytotoxicities of **1c** is found in Table 1 as well as references 1 and 2.
4. a) Houghton, P. J.; Houghton, J. A. *Invest. New Drugs*, **1996**, *14*, 271-280. b) Howbert, J. J. *Drug of Future*, **1991**, *16*, 517-520. References therein.
5. tumor growth inhibition of **1c** ; about 80% tumor suppression against murine mammary adenocarcinoma MM48 in C3H/He mice at dose of 300mg/kg/day x 5 per orally.
6. Jung, S.-H.; Kwak, S.-J. *Arch. Pharm. Res.*, **1997**, *20*, 283-287 and unpublished results.
7. All compounds synthesized gave analytical and spectroscopical results consistent with the assigned structure.
8. The similar ratio of regioisomer formation was previously noticed in the reaction of **4** with the various benzenesulfonyl chlorides.[1,2]
9. Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monk, A.; Tierney, S.; Nofziger, T. M.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, 48, 4827-4833.
10. When the tumor volume of 3LL reached about 100mm^3, agents were administered on day 6, 7, 9, 11, 13, 15 after tumor transplantation. When tumor volume of Colon26 reached about 50mm^3, agents were administered on day 6, 8, 10, 12, and 14 after tumor transplantation. For NCI-H23 and SW620 human tumor xenograft models, agent **3b** was orally administered on day 2, 4, 6, 8, 10, 12 after tumor transplantation and doxorubicin was intraperitonially administered everyday at the dose of 1mg/kg on day 2 to 11, 2mg/kg on day12 to 14, and 3mg/kg on day 15 to 18. Compound **3b** (DW2143) was orally administered after dissolved in propylene glycol (Dose:100mg/kg/day x 2 and then 100mg/kg/2day x 4 for 3LL, 65mg/kg/2day x 5 for Colon26, 65mg/kg/2day x 6 for NCI-H23 and SW620). Doxorubicin was dissolved in sterilized saline prior to administration.