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# Synthesis and Cytotoxic Activity of 1-(1-Benzoylindoline-5-sulfonyl)-4-phenylimidazolidinones

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The novel 1-(1-benzoylindoline-5-sulfonyl)-4-phenyl-4,5-dihydroimidazolones **2** shows highly potent and broad cytotoxicities. Their cytotoxicities against human lung carcinoma A549, human chronic myelogenous leukemia K562, and human ovarian adenocarcinoma SK-OV-3 are compatible with doxorubicin. Compound **2p** (1-[(4-aminobenzoyl)indoline-5-sulfonyl])-4-phenyl-4,5-dihydroimidazolone) exhibits a cytotoxicity that is far more potent than doxorubicin and also exhibits highly effective antitumour activities against murine (3LL, Colon 26) and human xenograft (NCI-H23, SW620) tumor models.

**Key words:** 1-(1-Benzoylindoline-5-sulfonyl)-4-phenyl-4,5-dihydroimidazolones, Cytotoxicity, Substituent's effect

## INTRODUCTION

Highly potent cytotoxicities of novel 4-phenyl-1(*N*)-arylsulfonylimidazolidinones **1**, which contains sulfonylurea pharmacophore, against the various cancer cell lines were previously demonstrated (Jung, *et al.*, 1996; 1996; 1997; 1997). Previous studies on the relationship of the structure activity of this series revealed 4-phenyl-1-benzenesulfonylimidazolidinone as a basic pharmacophore (Jung, *et al.*, 2001; Lee, *et al.*, 2000; Kim *et al.*, 2001, 2003). The activity of this analog has been varied on the substituents around the phenyl group of sulfonyl. STERIMOL L parameters of the substituents at 4-position are well correlated with the activity of these analogs (Lee, *et al.*, 2000). Increment of STERIMOL L values of these substituents enhances the activity. Among them compound **1d**, which has the longest acetamido group, shows the most potent cytotoxicity. Fused bicyclic analog **1e** containing indanyl on sulfonyl shows very potent activity, which is comparable to doxorubicin. However, compound **1f** shows less potent activity than **1e**. This may imply that substituents of a small volume at the 3-position additionally increase the activity. These two factors are integrated into the design of the new structure **1g**, which contains indoline moiety. As a result, this compound shows very good cytotoxicity against tumor cell lines. In order to continue our search for potent analogs that have indoline, *N*-benzoylindoline analogs **2** were designed and prepared. Their *in vitro* inhibitory activities on growth against three human cancer cell lines (lung carcinoma A549, leukemia K562, and ovarian adenocarcinoma SK-OV-3) were measured.

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## MATERIALS AND METHODS

Melting points (mp) were determined using the Electrothermal 1A 9100 MK2 apparatus and were uncorrected. All commercial chemicals were used in the state they were obtained and all solvents were purified according to standard procedures prior to use (Perrin and Armarego, 1982). Thin-layer chromatography was performed on E Merck silica gel GF-254 pre-coated plates, and UV light was used for identification and spray 10% phosphomolybdic acid was used for colorization followed by heating. Flash column chromatography was performed with the E. Merck silica gel (230-400 mesh). IR spectra were recorded with the Jasco IR-Report-100 IR spectrometer in $cm^{-1}$ and were

corrected against the peak at 1601 $cm^{-1}$ of polystyrene. NMR spectra were measured against the peak of tetramethylsilane by using the JEOL JNM-EX90 NMR (89.45 MHz) spectrometer. Elemental analysis was performed with the EA1110 elemental analyzer (CE Instrument).

### Synthesis of 4-phenyl-1-(*N*-trifluoroacetylindoline-5-sulfonyl)-2-methoxy-4,5-dihydroimidazoline (6)

Sodium bicarbonate (2.14 g, 25.5 mmol) and water (30 mL) were added to the solution of 4-phenyl-2-methoxy-4,5-dihydroimidazoline **3** (3.0 g, 17.0 mmol) in acetone (200 mL). After 10 minutes of stirring at room temperature, *N*-trifluoroacetylindoline-5-sulfonyl chloride (6.5 g, 20.4 mmol) was added, and the resulting mixture was stirred for 7 h. The reaction mixture was concentrated under vacuum and the residue was extracted three times with dichloromethane (100 mL). The combined organic layers were dehydrated with anhydrous sodium sulfate and were concentrated under vacuum. Compound **6** was purified by flash column chromatography. Rf 0.19 (33% ethyl acetate-hexane); white solid; mp 164.5-166.0 °C; yield 41.5%; IR (KBr) 1690, 1650, 1360, 1140 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 89.45 MHz) δ 3.32 (t, *J* = 8.3 Hz, 2H), 3.73 (dd, *J* = 7.3, 9.3 Hz, 1H), 3.98 (s, 3H), 4.34-4.49 (m, 3H), 4.93 (dd, *J* = 7.3, 9.2 Hz, 1H), 7.14-7.26 (m, 5H), 7.83 (d, *J* = 9.8 Hz, 2H), 8.35 (d, *J* = 8.5 Hz, 1H); Anal. Calcd for $C_{20}H_{18}F_3N_3O_4S$: C 52.98, H 4.00, N 9.26. Found C 52.45, H 4.02, N 9.13.

### Synthesis of 4-phenyl-1-(*N*-trifluoroacetylindoline-5-sulfonyl)-4,5-dihydroimidazolone (7)

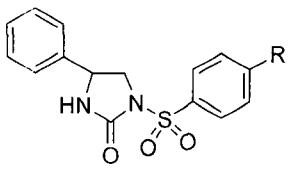
To the solution of compound **6** (3 g, 6.62 mmol) in 5 mL of methanol, 5 mL of 15% (w/w) hydrochloride in methanol was added. The resulting solution was stirred for 5 h at room temperature. White precipitate was collected and washed with diethyl ether to give pure compound **7**. Rf 0.26 (50% ethyl acetate-hexane); white solid; mp 182.3-183.7 °C; yield 94%; IR (KBr) 3350, 1740, 1690, 1360, 1160 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 89.45M Hz) δ 3.33 (t, *J* = 8.3 Hz, 2H), 3.68 (dd, *J* = 7.1, 9.0 Hz, 1H), 4.22-4.48 (m, 3H), 4.79 (dd, *J* = 7.1, 8.1Hz, 1H), 5.40 (s, 1H), 7.26-7.34 (m, 5H), 7.85-7.97 (m, 2H), 8.33 (d, *J* = 8.3 Hz, 1H); Anal. Calcd for $C_{19}H_{16}F_3N_3O_4S$: C 51.94, H 3.67; N 9.56, S 7.30. Found: C 52.11, H 3.67, N 9.50.

### Synthesis of 4-phenyl-1-[indoline-5-sulfonyl]-4,5-dihydroimidazolone (8)

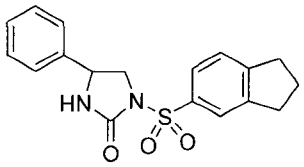
Compound **7** (2.7 g, 6.15 mmol) was suspended in 30 mL of methanol-water (1:1). Sodium hydroxide (1.1 equiv.) was added, and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated to a half the original volume and was extracted three times with 200 mL of dichloromethane each time. The combined organic layers were dehydrated with anhydrous magnesium sulfate and were concentrated under a vacuum. The residue was recrystallized from ethyl acetate to afford 1.51 g. White solid, yield 72.0%; IR (KBr) 3300, 1720, 1325, 1160; $^1$H-NMR (acetone-$d_6$, 89.45 MHz) δ 3.05 (t, *J* = 8.3 Hz, 2H), 3.37 (m, 1H), 3.60 (t, *J* = 8.3 Hz, 2H), 4.27(dd, *J* = 8.8, 9.4 Hz, 1H), 4.85 (dd, *J* = 6.2, 8.8 Hz, 1H), 5.82 (s, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 1H), 7.23-7.69 (m, 7H); Anal. Calcd for $C_{17}H_{17}N_3O_3S$: C59.46, H 4.99, N 12.24. Found: C 59.26, H 5.02, N 12.14.

### General procedure for the synthesis of 2

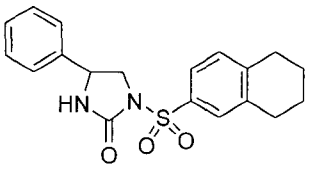
To the solution of compound **8** (0.1 g, 0.29 mmol) and 0.1 mL of pyridine in dichloromethane (6 mL), the corresponding benzoyl chloride (1.1 equivalent) was added at 5 °C. The resulting mixture was stirred at room temperature for 3 h and was washed with 3 mL of water three times. The organic layer was dehydrated with anhydrous magnesium sulfate and was concentrated under a vacuum.



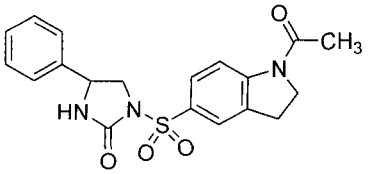

**1a** (R=H), **1b** (R=$CH_3$),
**1c** (R= $OCH_3$),**1d** (R=$NHCOCH_3$)



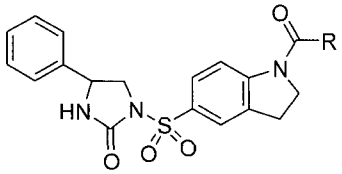

**1e**




**1f**




**1g**




**2** (target structure)

The residue was purified using flash column chromatography (hexane : ethyl acetate = 2 : 1).

**4-Phenyl-1-(*N*-benzoylindoline-5-sulfonyl)-4,5-dihydro-2-imidazolone (2a)**
Yield 76.0 %; mp 127.0-127.9 °C; IR (KBr) 3300, 1720, 1380, 1155 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.16 (t, J = 8.2 Hz, 2H), 3.49 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.08 (t, *J* = 8.2 Hz, 2H), 4.27 (t, *J* = 8.8, 9.0 Hz, 1H), 4.80 (dd, *J* = 8.9, 9.1 Hz, 1H), 7.23 (m, 2H), 7.35 (m, 4H), 7.52 (m, 3H), 7.62 (m, 2H), 7.79 (s, 2H), 8.22 (s, 1H); Anal. Calcd for $C_{24}H_{21}N_3O_4S$: C64.41, H 4.73, N 9.39. Found: C 64.20, H 4.84, N 9.27.

**4-Phenyl-1-[*N*-(4-methylbenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2b)**
Yield 68.0 %; mp 125.0-126.2 °C; IR (KBr) 3330, 1720, 1380, 1155 $cm^{-1}$; $^1$H-NMR (DMSO- $d_6$) δ 2.36 (s, 3H), 3.15 (t, *J* = 8.3 Hz, 2H), 3.47 (dd, *J* = 9.3, 9.5 Hz, 1H), 4.07 (t, *J* = 8.3 Hz, 2H), 4.27 (dd, *J* = 8.9, 9.0 Hz, 1H), 4.79 (dd, *J* = 6.3, 8.6 Hz, 1H), 7.20 (m, 2H), 7.25-7.75 (m, 9H), 7.77 (d, *J* = 9.2 Hz, 1H), 8.21 (s, 1H); Calcd for $C_{25}H_{23}N_3O_4S$: C 65.06, H 5.02, N 9.10. Found: C 64.90, H 5.12, N 8.94.

**4-Phenyl-1-[*N*-(2-hydroxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2c)**
Yield 76.0%; mp 221.0-222.1 °C; IR (KBr) 3400, 1720, 1360, 1180 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.12-3.16 (m, 2H), 3.49 (m, 1H), 4.26 (m, 3H), 4.78 (t, *J* = 7.5 Hz, 1H), 6.88-6.95 (m, 2H), 7.21-7.76 (m, 10H), 8.21 (s, 1H), 8.30 (s, 1H); Anal. Calcd for $C_{24}H_{21}N_3O_5S$: C 62.19, H 4.57, N 9.07. Found: C 61.93, H 4.63, N 8.95.

**4-Phenyl-1-[*N*-(4-hydroxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2d)**
Yield 70.0%; mp 256.1-257.8 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.18 (t, *J* = 8.6 Hz, 2H), 3.44 (dd, *J* = 6.8, 9.0 Hz, 1H), 3.96 (t, *J* = 8.6 Hz, 2H), 4.24 (dd, *J* = 7.0, 9.0 Hz, 1H), 4.76 (dd, *J* = 6.8, 9.0 Hz, 1H), 6.88-6.95 (m, 2H), 7.21-7.76 (m, 10H), 8.21 (s, 1H), 8.30 (s, 1H); Anal. Calcd. for $C_{24}H_{21}N_3O_5S$: C 62.19, H 4.57, N 9.07. Found: C 61.82, H 4.61, N 8.97.

**4-Phenyl-1-[*N*-(4-methoxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2e)**
Yield 69.0%; mp 220.3-222.0 °C; IR (KBr) 3250, 1725, 1365, 1155 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.43 (dd, *J* = 9.2, 9.3 Hz, 1H), 3.82 (s, 3H), 4.14 (t, *J* = 8.3 Hz, 2H), 4.27 (dd, *J* = 8.9, 9.1 Hz, 1H), 4.80 (dd, *J* = 6.7, 8.4 Hz, 1H), 7.03 (dd, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.31-7.40 (m, 3H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.74-7.84 (m, 3H), 8.21 (s, 1H); Anal. Calcd. for $C_{25}H_{23}N_3O_5S$: C 62.88, H 4.85, N 8.80. Found: C 62.53, H 4.97, N 8.71.

**4-Phenyl-1-[*N*-(3,4-dimethoxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2f)**
Yield 60.0%; mp 178.0-179.0 °C; IR (KBr) 1730, 1380, 1170 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.49 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 4.14 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 7.22-7.25 (m, 4H), 7.31-7.37 (m, 3H), 7.74-7.82 (m, 3H), 8.21 (s, 1H); Anal. Calcd. for $C_{26}H_{25}N_3O_6S$: C 61.53, H 4.96, N 8.28. Found: C 61.53, H 5.12, N 8.10.

**4-Phenyl-1-[*N*-(4-ethoxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2g)**
Yield 62.0%; mp 216.5-217.5 °C; IR (KBr) 3250, 1720, 1380, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 1.34 (t, *J* = 6.9 Hz, 3H), 3.15 (t, *J* = 8.3 Hz, 2H), 3.49 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.06-4.17 (m, 4H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.4 Hz, 1H), 7.00-7.37 (m, 7H), 7.58-7.84 (m, 5H), 8.20 (s, 1H); Anal. Calcd. for $C_{26}H_{25}N_3O_5S$: C 63.65, H 5.13, N 8.55. Found: C 63.34, H 5.32, N 8.36.

**4-Phenyl-1-[*N*-(3-chlorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2h)**
Yield 72.0%; mp 132.0-136.0 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.16 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 9.3, 9.4 Hz, 1H), 4.06 (t, *J* = 8.4 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.4 Hz, 1H), 7.22-7.41 (m, 5H), 7.53-7.80 (m, 6H), 8.01 (s, 1H), 8.21 (s, 1H); Anal. Calcd. for $C_{24}H_{20}ClN_3O_4S$: C 59.81, H 4.18, N 8.72. Found: C 59.63, H 4.25, N 8.52.

**4-Phenyl-1-[*N*-(4-chlorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2i)**
Yield 78.0%; mp 235.3 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.50 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.08 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.4 Hz, 1H), 7.22-7.45 (m, 2H), 7.31-7.37 (m, 3H), 7.56-7.68 (m, 4H), 7.77-7.80 (m, 2H), 8.05 (s, 1H), 8.21 (s, 1H); Anal. Calcd. for $C_{24}H_{20}ClN_3O_4S$: C 59.81, H 4.18, N 8.72. Found: C 59.72, H 4.26, N 8.57.

**4-Phenyl-1-[*N*-(3,5-dichlorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2j)**
Yield 79.0%; mp 235.8-236.0 °C; IR (KBr) 3250, 1720, 1380, 1150 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.19 (t, *J* = 8.3 Hz, 2H), 3.52 (m, 1H), 4.06 (t, *J* = 8.3 Hz, 2H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.81 (t, *J* = 8.3 Hz, 1H), 7.23 (m, 2H), 7.31-7.38 (m, 4H), 7.70 (m, 2H), 7.80 (m, 3H), 8.20 (s, 1H); Anal. Calcd. for $C_{24}H_{19}Cl_2N_3O_4S$: C 55.82, H 3.71, N 8.14. Found: C 55.63, H 3.90, N 8.02.

**4-Phenyl-1-[*N*-(3-fluorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2k)**

Yield 81.0%; mp 202.5 203.6 °C; IR (KBr) 3250, 1720, 1380, 1180 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.16 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 9.3, 9.4 Hz, 1H), 4.07 (t, *J* = 8.4 Hz, 2H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.3 Hz, 1H), 7.22-7.58 (m, 9H), 7.81 (m, 2H), 8.02 (s, 1H), 8.21(s, 1H); Anal. Calcd. for $C_{24}H_{20}FN_3O_4S$: C 61.92, H 4.33, N 9.03. Found: C 61.77, H 4.50, N 8.83.

**4-Phenyl-1-[*N*-(4-fluorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2l)**

Yield 67.0%; mp 134.0-135.1 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.50 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.08 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.6 Hz, 1H), 7.22-7.40 (m, 7H), 7.68-7.79 (m, 5H), 8.20 (s, 1H); Anal. Calcd. for $C_{24}H_{20}FN_3O_4S$: C 61.92, H 4.33, N 9.03. Found: C 61.80, H 4.46, N 8.78.

**4-Phenyl-1-[*N*-(2,4-difluorobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2m)**

Yield 71.0%; mp 128.0-129.2 °C; IR (KBr) 3250, 1720, 1380, 1180 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.18 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.06 (t, *J* = 8.3 Hz, 2H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.80 (t, *J* = 7.4 Hz, 1H), 7.22-7.50 (m, 8H), 7.65-7.81 (m, 3H), 8.22 (s, 1H); Anal. Calcd. for $C_{24}H_{19}F_2N_3O_4S$: C 59.62, H 3.96, N 8.69. Found: C 59.30, H 4.14, N 8.52.

**4-Phenyl-1-[*N*-(4-cyanobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2n)**

Yield 85.0%; mp 241.5-243.0 °C; IR (KBr) 3250, 2210, 1725, 1395, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.50 (m, 1H), 4.08 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 8.9 Hz, 1H), 4.79 (t, *J* = 7.1 Hz, 1H), 7.22-7.38 (m, 5H), 7.80-7.82 (m, 5H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.21 (s, 1H); Anal. Calcd. for $C_{25}H_{20}N_4O_4S$: C 63.55, H 4.27, N 11.86. Found: C 63.38, H 4.32, N 11.72.

**4-Phenyl-1-[*N*-(4-nitrobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2o)**

Yield 86.0%; mp 145.0-146.2 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.18 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 9.2, 9.3 Hz, 1H), 4.04 (t, *J*= 8.4 Hz, 2H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.80 (t, *J* = 7.4 Hz, 1H), 7.22-7.25 (m, 2H), 7.31-7.38 (m, 3H), 7.82-7.92 (m, 5H), 8.20 (s, 1H), 8.31 (d, *J* = 8.7 Hz, 2H); Anal. Calcd. for $C_{24}H_{20}N_4O_6S$: C 58.53, H 4.09, N 11.38. Found: C 58.40, H 4.21, N 11.21.

**4-Phenyl-1-[*N*-(4-aminobenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2p)**

Yield 86.0%; mp 216-217.0 °C; IR (KBr) 3300, 1710, 1380, 1150 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 9.2, 9.3 Hz, 1H), 4.10 (t, *J* = 8.4 Hz, 2H), 4.26 (m, 1H), 4.79 (t, *J* = 7.3 Hz, 1H), 6.97 (m, 2H), 7.20-7.40 (m, 5H), 7.52-7.54 (m, 2H), 7.73-7.83 (m, 3H), 8.20 (s, 1H); Anal. Calcd. for $C_{24}H_{22}N_4O_4S$: C 63.32, H 4.79, N 12.11. Found: C 63.24, H 4.87, N 11.96.

**4-Phenyl-1-[*N*-(3-trifluoromethylbenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2q)**

Yield 83.0%; mp 119.2-119.4 °C; IR (KBr) 3300, 1740, 1380, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.16 (t, *J* = 8.2 Hz, 2H), 3.49 (m, 1H), 4.07 (t, *J* = 8.3 Hz, 2H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.3 Hz, 1H), 7.22-7.38 (m, 5H), 7.80-7.82 (m, 5H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.21 (s, 1H); Anal. Calcd. for $C_{25}H_{20}F_3N_3O_4S$: C 58.25, H 3.91, N 11.06. Found: C 58.12, H 4.04, N 10.92.

**4-Phenyl-1-[*N*-(3-trifluoromethoxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2r)**

Yield 65.0%; mp 129.0-131.0 °C; IR (KBr) 3220, 1740, 1380, 1180, 1150 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.16 (t, *J* = 8.3 Hz, 2H), 3.50 (m, 1H), 4.07 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.5 Hz, 1H), 7.21-7.40 (m, 5H), 7.70-8.20 (m, 8H); Anal. Calcd. for $C_{25}H_{20}F_3N_3O_5S$: C 56.49, H 3.79, N 7.91. Found: C 56.20, H 3.97, N 7.60.

**4-Phenyl-1-[*N*-(4-trifluoromethoxybenzoyl)indoline-5-sulfonyl]-4,5-dihydro-2-imidazolone (2s)**

Yield 71.0%; mp 180-181.5 °C; IR (KBr) 3300, 1720, 1360, 1160 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 3.15 (t, *J* = 8.3 Hz, 2H), 3.50 (m, 1H), 4.07 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.79 (t, *J* = 7.4 Hz, 1H), 7.20-7.50 (m, 7H), 7.70-7.80 (m, 5H), 8.20 (s, 1H); Anal. Calcd. for $C_{25}H_{20}F_3N_3O_5S$: C 56.49, H 3.79, N 7.91. Found: C 56.31, H 3.93, N 7.71.

**Synthesis of 4-phenyl-1-(1-benzylindoline-5-sulfonyl)-4,5-dihydroimidazolone (9)**

Compound **7** (0.20 g, 0.58 mmol), benzyl bromide (0.10 g), and triethylamine (0.4 g) were dissolved in 5 mL of dimethylformamide. The reaction mixture was heated at 120 °C for 4 h. After the reaction mixture was cooled to room temperature, it was concentrated under a vacuum. The residue was recrystallized from ethyl acetate to afford 0.15 g. White solid, yield 60.0%; mp 188.0-189.1 °C; IR (KBr) 3300, 1720, 1325, 1160 $cm^{-1}$; $^1$H-NMR (acetone-*d6*, 89.45 MHz) δ 3.05 (t, *J* = 8.3 Hz, 2H), 3.37 (m, 1H), 3.60 (t, *J* = 8.3 Hz, 2H), 4.27 (dd, *J* = 8.8, 9.4 Hz, 1H), 4.61 (s, 2H), 4.85 (dd, *J* = 6.2, 8.8 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 1H), 7.23-7.69 (m, 12H); Anal. Calcd for $C_{24}H_{23}N_3O_3S$: C 66.49, H 5.35, N 9.69. Found: C 66.14, H 5.22, N 9.45.

### Biological assay

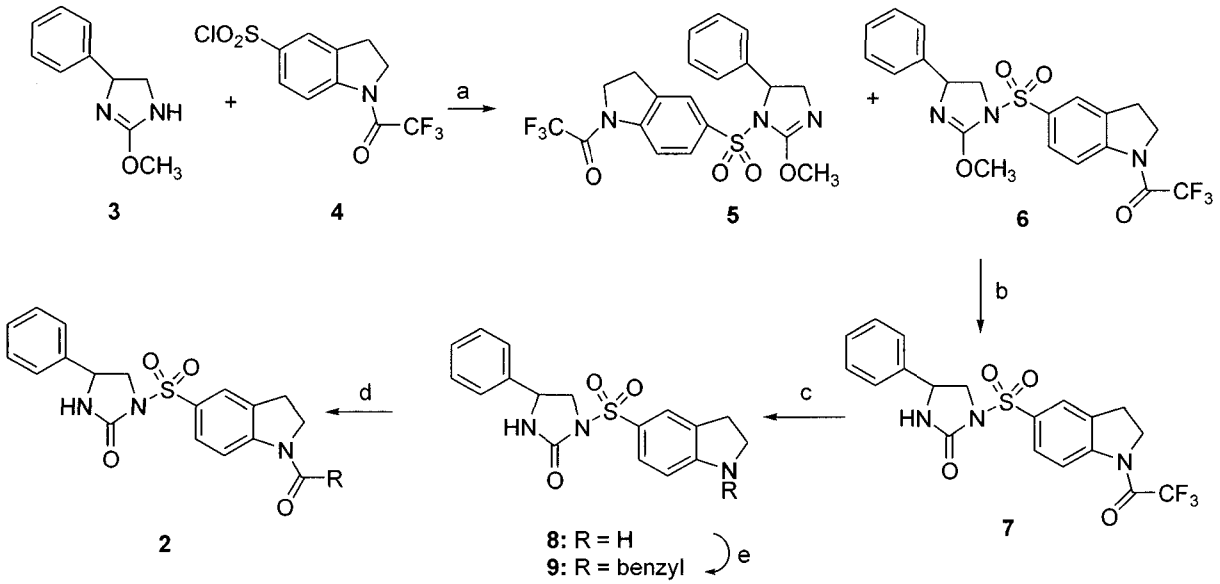
Cytotoxicities of analogs **2**, **8**, and **9** were measured against human lung carcinoma (A549), human leukemia cancer (K562), and human ovarian cancer (SK-OV-3) cell lines *in vitro* using the MTT assay (Scudiero, *et al.*, 1988). $IC_{50}$ values measured using the MTT assay are the mean values of a set of three measurements, and the incubation time was 2 days (medium:RPMI1640 + 10%FBS). The results from these tests are shown in Table I.

## RESULTS AND DISCUSSION

The procedure employed for the preparation of arylsulfonylimidazolidinones **2** is illustrated in Scheme 1, and compounds **2** obtained are listed in Table I. Treatment of imidazoline **3** 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 an approximate ratio of 1 to 5. Then, compound **6** was separated by flash column chromatography giving a 65% yield. After the removal of the trifluoroacetyl group of **6** through the use of the reaction with sodium hydroxide in aqueous methanol at room temperature, the resulting imidazoline **7** was treated with hydrochloride to produce imidazolone **8** in a quantitative yield. Compound **8** was then converted to the final compounds **2** using the reaction of the corresponding benzoyl chloride in the presence of pyridine in dichloromethane. Compound **2p** was obtained through catalytic hydrogenation of **2o** in the presence of Raney Ni. Compound **9** was prepared through the reaction of **8** with benzyl bromide in the presence of triethylamine.

Cytotoxicities of compounds **1e**, **2**, **8**, and **9** were measured against human lung carcinoma A549, human leukemia K562, and human ovarian cancer SK-OV-3 cell lines *in vitro* using the MTT assay. As shown in Table I, cytotoxicities of compounds **2** that contain the substituted benzoyl group at 1-position of indoline moiety are remarkable. Surprisingly, most of the synthesized compounds **2** exhibit comparable activities with those of doxorubicin, which is one of the most potent anticancer agents currently being used. In particular, compound **2p** (DW2143) possesses the most potent cytotoxicities against all three different cell lines ($IC_{50}$ values; A549: 0.20 μM, K562: 0.44 μM, SK-OV-3: 1.24 μM).

The structure activity relationship along the introduction of substituted benzoyl group at the 1-position of indoline moiety of **2** is noteworthy. Although any of the substituent constants on the benzoyl group are not linearly correlated with the cytotoxicities against the three cell lines, electronic properties may affect the activity against A549 and K562 cell lines. Compounds **2f**, **2p** possessing strong electron donating groups ($OCH_2CH_3$, $NH_2$) at the 4-position of benzoyl moiety of **2** show a more increased activity against these two lines in comparison to the activity of **2a**. However, the compounds **2h**, **2i**, **2l**, **2m**, **2n**, **2o**, and **2q** that were substituted with electron attracting groups (Cl, F, CN, $NO_2$, $CF_3$) on benzoyl moiety decrease the activity of this series. Against the SK-OV-3 cell line, none of compounds show a level of activity more potent than **2a**. However, compounds **2c** and **2p** show more potency in comparison to the compounds **2h**, **2l**, **3k**, **2l**, **2n**, and **2q**. These facts indicate that the electron donating property of substituents on the benzoyl group of **2** generally enhances the activity of this series. Interestingly,




**Scheme 1.** Synthesis of Arylsulfonylimidazolidinones (**2**). a) NaHCO3, b) HCl in methanol, c) NaOH in aqueous methanol, d) substituted benzoyl chloride, e) benzyl bromide.

**Table I.** Benzoylindolinesulfonylimidazolidinones **2** and their cytotoxicities

| Compd. No. **2** | 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-$CH_3$) | $C_{25}H_{23}N_3O_4S$ | 125 | 3.76 | 5.20 | 43.33 |
| **c** | $C_6H_4$(2-OH) | $C_{24}H_{21}N_3O_5S$ | 221 | 1.38 | 12.31 | 1.28 |
| **d** | $C_6H_4$(4-OH) | $C_{24}H_{21}N_3O_5S$ | 256 | 4.16 | 8.82 | 8.16 |
| **e** | $C_6H_4$(4-$OCH_3$) | $C_{25}H_{23}N_3O_5S$ | 220 | 3.28 | 4.58 | 2.87 |
| **f** | $C_6H_3$(3,4-di$OCH_3$) | $C_{26}H_{25}N_3O_6S$ | 178 | 3.26 | 0.43 | 23.86 |
| **g** | $C_6H_4$(4-$OCH_2CH_3$) | $C_{26}H_{25}N_3O_5S$ | 216 | 0.21 | 0.64 | 4.51 |
| **h** | $C_6H_4$(3-Cl) | $C_{24}H_{20}ClN_3O_4S$ | 132 | 3.36 | 14.60 | 5.39 |
| **i** | $C_6H_4$(4-Cl) | $C_{24}H_{20}ClN_3O_4S$ | 235 | 1.61 | 1.23 | 12.40 |
| **j** | $C_6H_3$(3,5-diCl) | $C_{24}H_{19}Cl_2N_3O_4S$ | 235 | 3.92 | 3.64 | 32.01 |
| **k** | $C_6H_4$(3-F) | $C_{24}H_{20}FN_3O_4S$ | 202 | 0.71 | 1.33 | 18.28 |
| **l** | $C_6H_4$(4-F) | $C_{24}H_{20}FN_3O_4S$ | 134 | 1.27 | 7.83 | 5.00 |
| **m** | $C_6H_3$(2,4-diF) | $C_{24}H_{19}F_2N_3O_4S$ | 128 | 4.01 | 11.72 | 3.14 |
| **n** | $C_6H_4$(4-CN) | $C_{25}H_{20}N_4O_4S$ | 241 | 3.37 | 10.51 | 2.05 |
| **o** | $C_6H_4$(4-$NO_2$) | $C_{24}H_{20}N_4O_6S$ | 145 | 3.45 | 18.02 | 4.24 |
| **p** | $C_6H_4$(4-$NH_2$) | $C_{24}H_{22}N_4O_4S$ | 216 | 0.20 | 0.44 | 1.24 |
| **q** | $C_6H_4$(3-$CF_3$) | $C_{25}H_{20}F_3N_3O_4S$ | 119 | 4.24 | 2.65 | 22.84 |
| **r** | $C_6H_4$(3-$OCF_3$) | $C_{25}H_{20}F_3N_3O_5S$ | 129 | 5.31 | 6.24 | 21.35 |
| **s** | $C_6H_4$(4-$OCF_3$) | $C_{25}H_{20}F_3N_3O_5S$ | 180 | 1.31 | 3.45 | 5.56 |
| **9** | | $C_{24}H_{23}N_3O_3S$ | 188 | 7.66 | 45.78 | 15.30 |
| **1e** | | $C_{18}H_{18}N_2O_3S$ | | 4.74 | 42.66 | 12.13 |
| | doxorubicin | $C_{27}H_{29}NO_{11}$ | | 1.99 | 1.77 | 4.15 |

[a]Melting points are uncorrected and are located within 1.5°C from indicated values. [b]$IC_{50}$ values, which were the mean value of three measurements, were measured using the MTT assay, and the incubation time was 2 days. [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 II.** Cytotoxicities of 2p on four day culture

| Human cancer cell lines[a] | $IC_{50}$ ($\mu$M)[b] | | Murine cancer cell cell lines[b] | $IC_{50}$ ($\mu$M)[b] | |
|---|---|---|---|---|---|
| | **2p** (DW2143) | Doxorubicin | | **2p** (DW2134) | Doxorubicin |
| BxPC-3 | 0.01 | 0.57 | WiDr | 0.22 | 0.10 |
| HepG2 | 1.71 | 0.13 | B16 | 0.36 | 0.04 |
| LoVo | 0.39 | 0.62 | Colon26 | 0.17 | 0.07 |
| MCF-7 | 3.72 | 1.17 | EL-4 | 0.52 | 0.02 |
| NCI-H69 | 0.10 | 0.79 | 3LL | 0.004 | 0.004 |
| SW480 | 8.28 | 1.79 | P388 | 0.19 | 0.03 |

[a]human cell lines (medium); BxPC-3: pancreatic adenocarcinoma (Eagle's MEM+10%FBS), HepG2: hepatocellular carcinoma (Dulbecos MEM+10%FBS+NEAA), LoVo: colon adenocarcinoma (HamF-12+10%FBS), MCF-7: breast adenocarcinoma (Eagle's MEM+10%FBS+Sodium pyruvate+NEAA), NCI-H69: lung small cell carcinoma (Eagle's MEM+10%FBS), SW480: colon adenocarcinoma (L-15+10%FBS), WiDr: colon adenocarcinoma(Eagles MEM+10%FBS+Sodium pyruvate+NEAA). [b]murine cancer cell lines; B16: malignant melanoma (Eagle's MEM+10%FBS), Colon26: colon carcinoma (RPMI1640+10%FBS), EL-4: lymphoma (RPMI1640+10%FBS), 3LL: Lewis lung carcinoma (RPMI1640+10%FBS), P388: lymphoid leukemia (RPMI1640+10%FBS). [b]$IC_{50}$ values are the mean values of three times measurements.

halogen substituted derivatives **2i**, **2l** at the 4-position of the benzoyl group show an activity that is more potent than the corresponding compounds **2h**, **2k** halogenated at the 3-position.

Compound **9** containing benzyl on indoline nitrogen shows less activity against all three cell lines when com-

pared to the benzoyl analog **2a**. This indicates that the carbonyl group on nitrogen is additionally required for the enhancement of cytotoxicity of this series.

Cytotoxicities of **2p** (DW2143) were further investigated *in vitro* against seven other human and five murine cancer cell lines. As shown in Table II, remarkably potent and broad cytotoxicities of **2p** were demonstrated. The bioavailability of **2p** in rats was proven to be about 40%. Such a remarkable *in vitro* activity and good pharmacokinetic profile of **2p** 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. Compound **2p** was orally administered after being dissolved in propylene glycol (Dose: 100 mg/kg/day × 2 and then 100 mg/kg/2 day × 4 for 3LL, 65 mg/kg/2 day × 5 for colon26, 65 mg/kg/2 day × 6 for NCI-H23 and SW620). Without any significant change in the body weight of mice, compound **2p** showed 84.3%, 55.6%, 67.0%, and 87% suppression of tumor growth of 3LL, Colon26, NCI-H23, and SW620, respectively (Moon *et al.*, 1999).

Therefore, 1-(1-benzoylindoline-5-sulfonyl)-4-phenyl-4,5-dihydroimidazolones **2** are considered to be a potential candidate for the development of new anticancer agents.

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