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Evaluation of Anticancer Activity of 4-Vinyl-1-Arylsulfonylimidazolidinones

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To continue exploration of structure activity relationship of novel 1-(indoline-5-sulfonyl)-4-phenylimidazolidinones (**1**) reported as anticancer agent with broad spectrum, three 1-(arylsulfonyl)-4-vinylimidazolidinones (**2**) were synthesized from methyl serinate (**3**) in 8 steps. Reaction of intermediate 2-phenoxycarbonylaminobut-3-enyl p-toluenesulfonate (**10**) with arylsulfonamide in the presence of potassium carbonate produced corresponding **2** and N-(4-vinyloxazolidin-2-yl)arylsulfonamide **11** in approximately equal ratio. This reaction is believed to undergo through urea intermediate **16** as shown in scheme 3. 1-Arylsufonyl-4-vinylimidazolidinones **2** show much reduced activity against human colon carcinoma (Colo205), human chronic myelogenous leukemia (K562), and human ovarian adenocarcinoma (SK-OV-3) and compatible activity against human lung carcinoma (A549) compared to **1**. Therefore phenyl at 4-position should be the optimum planar motif for the activity of **1**.

Key words: Synthesis and cytotoxicity of 1-arylsulfonyl-4-vinylimidazolidinones

INTRODUCTION

The series of novel 4-phenyl-1(N)-arylsulfonylimidazolidinones **1** were reported as analogs possessing broad spectrum of cytotoxicity against the various cancer cell lines (Jung *et al.*, 1996, 1996, 1997, 1998, 2004, Moon *et al.*, 1999). Among them, very potent (S)-(+)-4-phenyl-1-[N-(4-aminobenzoyl)indoline-5-sulfonyl]-2-imidazolidinone (DW2282) was extensively tested against *in vivo* tumor models (Lee *et al.*, 2002) and characterized its mechanism action as an apoptotic inducer (Hwang *et al.*, 1999). Recently, mechanisms of the derivatives of DW2282 have been further elaborated as promising antimitotic agent causing G2/M phase cell cycle arrest (Kim *et al.*, 2004). These agents are even more remarkable due to inhibition of tublin polymerization with efficacy against multidrug-resistant cell lines. Previous studies on the structure activity relationship of this series revealed 4-phenyl-1-benzenesulfonylimidazolidinone as a basic pharmacophore (Lee *et al.*, 2000; Jung *et al.*, 2001; Kim *et al*, 2002; Choo *et al.*, 2003). The activity of this analog has been varied on the substituents around the phenyl group of sulfonyl. STERIMOLL parameters of the substituents at 4-position are well correlated with the activity of these analogs (Lee *et al.*, 2000). Replacement of phenyl with cyclohexyl at 4-position abolished the activity (Jung and Kwak, 1977). Naphthyl analogs remarkably reduce the activity (Jung *et al.*, 2000). These indicate that increment of size and volume at this position exerts the adverse effect for the enhancement of activity of these analogs. In this regard, it was necessary to investigate the effect of the smaller size of planar motif at this position on the activity. Thus, compound **2** as shown in Fig. 1 was designed, synthesized, and tested *in vitro* against human cancer cell lines.

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MATERIALS AND METHODS

Melting points (m.p.) 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

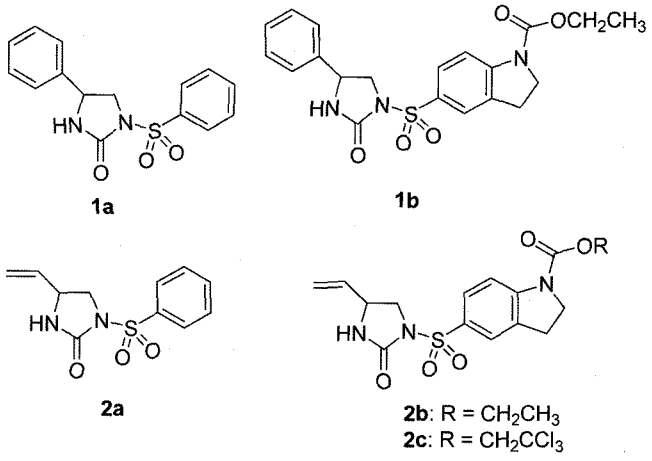

Fig. 1. Arylsulfonylimidazolidinones

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 Varian Unity 400 (400 MHz) spectrometer. Mass spectra and high resolution mass spectra (HRMS) were measured by JEOL JMS-HX110A/HX110A.

Synthesis of Methyl-3-hydroxy-2-phenoxycarbonylpropionate (4)

Suspension of DL-serine methyl ester hydrochloride (5 g, 32 mmole) in tetrahydrofuran (100 mL) was mixed with aqueous solution (100 mL) of potassium carbonate (8.9 g, 64 mmole) at room temperature. To this mixture, solution of phenyl chloroformate (5.49 g, 35.2 mmole) in tetrahydrofuran (100 mL) was slowly dropped with stirring. After two hour stirring at room temperature, reaction mixture was extracted with ethyl acetate three times. Organic layers combined was washed with water and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography to give pure **4** (6.97 g).

Yield 91.0%: Rf 0.24 (50% Ethyl acetate-Hexane); colorless liquid; IR (film) 3350, 3025, 2940, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.59 (m, 1H, OH), 3.81 (s, 3H), 3.96 (ddd, J = 11.6, 6.0, 3.6 Hz, 1H), 4.04 (ddd, J = 11.6, 6.0, 3.6 Hz, 1H), 4.50 (dt, J = 8.0, 3.6 Hz, 1H), 6.11 (d, J = 7.6 Hz, NH), 7.14 (d, J = 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1 H), 7.36 (m, 2H).

Synthesis of Methyl phenyl-2,2-dimethylloxazolidine-3,4-dicarboxylate (5)

Boron trifluoride etherate (1.154 g, 1.6 mmole) was added to the mixture of acetone (100 mL) and 2,2-dimethoxypropane (30 mL) and then the solution of **4** (6.50 g, 27.2 mmole) in acetone (10 mL) was added slowly. The resulting mixture was stirred at room temperature for two hours and concentrated under vacuum. Dichloromethane (50 mL) was added to the residue and washed with 10% aqueous sodium bicarbonate (50 mL) twice. The organic layer was dehyrated with anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography to give **5** (5.0 g).

Yield 66.0%; Rf 0.63 (50% Ethyl acetate-Hexane); yellow liquid; IR (film) 3020, 2950, 1750, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.74 (s, 3H), 3.81 (s, 3H), 4.21 (dd, J = 9.2, 2.4 Hz, 1H), 4.27 (dd, J = 9.2, 6.8 Hz, 1H), 4.69 (dd, j = 6.8, 2.4 Hz, 1H), 7.08 (m, 2H), 7.18 (m, 1H) 7.36 (m, 2H).

Synthesis of Phenyl-4-hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylate (6)

Solution of **5** (4.1 g, 14.7 mmole) in tetrahydrofuran (70 mL) was cooled to 0°C and lithium chloride (1.25 g, 29.4 mmole), sodium borohydride (1.11g, 29.4 mmole), and absolute ethanol (200 mL) were sequentially added. The resulting mixture was stirred at room temperature for 10 h and then 10% aqueous citric acid was added until pH reached 4. The reaction mixture was concentrated under vacuum. The residue was dispersed in water (200 mL) and extracted with dichloromethane three times. The combined organic layers were dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography to give **6** (2.94 g).

Yield 80%; Rf 0.48 (50% Ethyl acetate-Hexane); yellow liquid; IR (film) 3450, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (broad s, 3H), 1.69 (broad s, 3H), 3.25-3.30 (m, 1H, OH), 3.65-3.72 (m, 1H), 3.82-3.91 (m, 2H), 4.07 - 4.20 (m, 3H), 7.12 (m, 2H), 7.18 (m, 1H) 7.36 (m, 2H).

Synthesis of Phenyl-2,2-dimethyl-4-formyloxazolidine-3-carboxylate (7)

The solution of oxalyl chloride (2.12 g, 16.8 mmole) in dichloromethane (24 mL) was cooled to -80°C and then the solution of dimethylsufoxide (1.77 g, 22.7 mmole) in dichloromethane (24 mL) was carefully added for 25 minutes under -65°C. The solution of **6** (2.83 g, 11.3 mmole) in dichloromethane (24 mL) was added to the reaction mixture for 25 minutes under -65 °C. After stirring for one hour, the solution of triethylamine (4.6 g) in dichloromethane (24 mL) was added. The resulting mixture was stirred for one hour and then the reaction temperature was increased to room temperature. Hexane 300 mL) was added and washed with saturated aqueous potassium bisulfite (160 mL). Aqueous layer extracted with ether three times. The combined organic layers extracted with saturated aqueous

sodium bicarbonate and brine. The organic layer was dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The residue was dried under vacuum overnight to give **7** (2.7 g).

Yield 85%; Rf 0.59 (50% Ethyl acetate-Hexane); white solid; m.p. 84-87°C; IR (KBr) 1730, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (broad s, 3H), 1.74 (broad s, 3H), 4.21-4.27 (m, 2H), 4.49-4.59 (m, 1H), 7.09-7.39 (m, 5H), 9.74 (s, 1H).

Synthesis of Phenyl-2,2-dimethyl-4-ehtenyloxazolidine-3-carboxylate (8)

Potassium bis(trimethylsilyl)amide (22 mL of 0.5M in toluene, 11 mmole) was added to the suspension of methyltriphenylphosphonium bromide (4.10 g, 11.5 mmole) in tetrahydrofuran at room temperature under nitrogen gas and the mixture was stirred for one hour. The resulting mixture was then cooled to -78°C and the solution of **7** (1.63 g, 6.55 mmole) in tetrahydrofuran (20 mL) was added dropwise. After removing cold bath, the reaction was stirred at room temperature for 24 h and methanol (100 mL) was added. The reaction mixture was poured to the saturated aqueous potassium sodium tartrate solution (200 mL) and extracted with ether twice. The organic layers were dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by the flash column chromatography to give **8** (1.5 g).

Yield 88.0%; Rf 0.75 (50% Ethyl acetate-Hexane); yellow liquid; IR (film) 3050, 2970, 1720, 1370 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.72 (s, 3H), 3.87(dd, J = 8.8, 1.6 Hz, 1H), 4.15 (m, 1H), 4.55 (m, 1H), 5.25 (d, J = 10.0 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.85-5.97 (m, 1H), 7.09-7.20 (m, 3H), 7.35 (m, 2H).

Synthesis of Phenyl-1-hydroxy-3-buten-2-yl-carbamate (9)

p-Toluenesulfonic acid H_2O (0.21 g, 1.1 mmole) was added to the solution of **8** (1.5 g, 2.2 mmole) in methanol (10 mL) and the reaction mixture was stirred for 8 h at room temperature. After concentration under vacuum, the residue was dispersed in 50 mL of water and extracted with dichloromethane three times. The combined organic layers were dehydrated with anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography to give **9** (0.89 g).

Yield 70.6%; Rf 0.40 (50% Ethyl acetate-Hexane); white solid; m.p. 54-56°C; IR (film) 3350, 3300, 3050, 2930, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.70-3.73 (m, 1H), 3.77-3.82 (m, 1H), 4.38 (broad m, 1H, OH), 5.31 (d, J = 10.8 Hz, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.50 (broad d, 1H, NH), 5.87 (ddd, J = 5.2, 10.8, 17.2 Hz, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.21 (t, J = 6.4 Hz, 1H), 7.36 (m, 2H).

Synthesis of 2-Phenoxycarbonylaminobut-3-enyl *p*-toluenesulfonate (10)

p-Toluenesulfonyl chloride (0.96 g, 5.07 mmole) was added to the solution of **9** (0.8 g, 3.9 mmole) in pyridine (10 mL) at 0 °C and the mixture was stirred for 12 h. After addition of cold water (100 mL), the mixture was extracted with ether three times. The combined organic layers were extracted with cold 5% hydrochloric acid and water. After dehydration with anhydrous sodium sulfate and concentration under vacuum, the residue was purified by the flash column chromatography to give **10** (0.7 g).

Yield 50%; Rf 0.69 (50% Ethyl acetate-Hexane); white solid; m.p. 82-84°C; IR (KBr) 3350, 3050, 2930, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.44 (s, 3H), 4.1 (dd, J = 4.6, 10.4 Hz, 1H), 4.2 (dd, J = 3.8, 10.4 Hz, 1H). 4.5 (m, 1H), 5.28 (d, J = 10.4 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.39 (broad s, 1H, NH), 5.78 (ddd, J = 5.6, 10.5, 17.2 Hz, 1H), 7.09 (d, J = 8.0, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.35 (m, 4H), 7.80 (d, J = 6.8 Hz, 2H).

General procedure for the preparation of 2 and 11

After the mixture of **10** (0.1 g, 0.28 mmole), potassium carbonate (0.077 g, 0.56 mmole) and water (0.2 mL) in butanone (5 mL) was refluxed for 30 minutes, corresponding benzenesulfomamide (0.28 mmole) was added and refluxed for three hours. The reaction mixture was cooled to room temperature and chloroform (50 mL) was added. The resulting mixture was washed with water two times. The organic layer was dehydrated with anhyrous sodium sulfate and concentrated in vacuum and the crude product was separated by flash column chromatography.

Synthesis of 2a and 11a

Benzenesulfonamide was used for Synthesis of **2a** and **11a**.

1-Benzensulfonyl-4-vinylimidazolidinone (2a)

Yield 26.8%; Rf 0.33 (50% Ethyl acetate-Hexane); white solid; m.p. 117-119°C; IR (KBr) 3300, 1735, 1700 cm^{-1}; NMR (acetone-d_6) δ 3.58 (dd, J = 6.4, 9.2Hz, 1H), 4.12 (dd, J = 8.4, 9.2 Hz, 1H), 4.27-4.31 (m, 1H), 5.18 (d, J = 10.4 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.85 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 6.95 (broad, s, 1H), 7.62-7.66 (m, 2H), 7.72-7.76 (m, 1H), 8.02-8.04 (m, 1H); Mass m/e (rel. intensity) 252 (M+, 0.4 %), 225(1.8), 188 (100), 161 (14), 141(42), 111(23), 106 (38), 77(83); HRMS calcd. for $C_{11}H_{12}N_2O_3S$ 252.0569, observed 252.0551.

N-(4-Vinyloxazolidin-2-yl)benzenesulfonamide (11a)

Yield 30.3%; Rf 0.24 (50% Ethyl acetate-Hexane); pale yellow liquid; IR (KBr) 3330, 1740, 1610 cm^{-1}; NMR (acetone-d_6) δ 4.24 (dd, J = 5.4, 8.0 Hz, 1H), 4.68-4.76

(m, 2H), 5.21-5.35 (m, 2H), 5.91-6.00 (m, 1H), 7.52-7.59 (m, 3H), 7.97-7.90 (m, 2H), 8.25 (broad s, 1H); Mass m/e (rel. intensity) 252 (M+, 72), 225 (5), 188 (100), 175 (6), 159 (38), 141 (28), 119 (47), 111 (4), 96 (9), 77 (85); HRMS calcd for $C_{11}H_{12}N_2O_3S$ 252.0569, observed 252.0561.

Synthesis of 2b and 11b

1-Ethoxycarbonylindolin-5-sulfonamide was used for synthesis of **2b** and **11b**.

1-(1-Ethoxycarbonylidolin-5-sulfonyl)-4-vinylimidazolidinone (2b)

Yield 24.2%; Rf 0.18 (50% Ethyl acetate-Hexane); white solid; m.p. 142-144°C; IR (KBr) 3300, 2970, 1720 cm^{-1}; NMR (acetone-d_6) δ 1.31 (t, J = 7.0 Hz, 3H), 3.23 (t, J = 8.8 Hz, 2H), 3.54 (dd, J = 6.4, 9.0 Hz, 1H), 4.08 (dd, J = 8.0, 9.0 Hz, 1H), 4.12 (t, J = 8.8 Hz, 2H), 4.23-4.28 (m, 3H), 5.18 (d, J = 10.4 Hz, 1H) 5.29 (d, J = 17.2 Hz, 1H), 5.85 (ddd, J = ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 6.83 (broad s, 1H), 7.79-7.83 (m, 3H); Mass m/e (rel. intensity) 365 (M+, 45), 320(3), 301 (100), 273 (28), 246 (8), 228 (13), 206 (9), 190 (21), 162 (5), 144 (6), 117 (15); HRMS calcd for $C_{16}H_{19}N_3O_5S$ 365.1045, observed 365.1046.

N-(4-Vinyloxazolidin-2-yl)-1-ethoxycarbonylindolin-5-sulfonamide (11b)

Yield 11.4%; Rf 0.12 (50% Ethyl acetate-Hexane); white solid; m.p. 136-138°C; IR (film) 3350, 2970, 1700 cm^{-1}; NMR (acetone-d_6) δ 1.33 (t, J = 7.0 Hz, 3H), 3.20 (t, J = 8.8 Hz, 2H), 4.09 (t, J = 8.8 Hz, 2H), 4.22 (dd, J = 5.0, 8.0 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 4.66-4.75 (m, 2H), 5.26 (d, J = 10.2 Hz, 1H), 5.33 (d, J = 17.2 Hz, 1H) 5.96 (ddd, J = 6.4, 10.2, 17.2 Hz, 1H), 7.64-7.85 (m, 3H), 8.20 (broad s, 1H); Mass m/e (rel. intensity) 365 (M+, 100), 337 (6), 301 (19), 273 (12), 254 (10), 228 (24), 190 (13), 175 (3), 159 (9), 134 (9), 117 (17); HRMS calcd. for $C_{16}H_{19}N_3O_5S$ 365.1045, observed 365.1043.

Synthesis of 2c and 11c

1-(2,2,2-Trichloroethoxycarbonyl)indolin-5-sulfonamide was used for synthesis of **2c** and **11c**.

1-[1-(2,2,2-Trichloroethoxy)carbonylindolin-5-sulfonyl]-4-vinylimidazolidinone (2c)

Yield 32.2%; Rf 0.21 (50% Ethyl acetate-Hexane); white solid; m.p. 149-152°C; IR (KBr) 3270, 3050, 2970, 1720, 1590 cm^{-1}; NMR (acetone-d_6) δ 3.32 (t, J = 8.2 Hz, 2H), 3.56 (dd, J = 6.2, 9.4 Hz, 1H), 4.01 (dd, J = 8.8, 9.0 Hz, 1H), 4.26-4.31 (m, 3H), 5.01 (s, 2H), 5.18 (d, J = 10.0 Hz, 1H) 5.30 (d, J = 17.2 Hz, 1H), 5.85 (ddd, J = 6.4, 10.0, 17.2 Hz, 1H), 6.90 (broad s, 1H), 7.84-7.95 m, 3H); Mass m/e (rel. intensity) 471 (M+4, 5), 469 (M+2, 15), 467 (M+, 15), 409 (3), 407(31), 405 (97), 403 (100), 369 (10), 350 (8), 320 (14), 228 (13), 144 (11), 117 (18); HRMS calcd. for $C_{16}H_{16}Cl_3N_3O_5S$ 468.9849, observed 468.9850.

N-(4-Vinyloxazolidin-2-yl)-1-(2,2,2trichloroethoxycarbony)lindolin-5-sulfonamide (11c)

Yield 26.3%; Rf 0.12(50% Ethyl acetate-Hexane); white solid; m.p. 149-151°C; IR (KBr) 3330, 3050, 2970, 1710 cm^{-1}; NMR (acetone-d_6) δ 3.29 (t, J = 8.0 Hz, 2H), 4.21-4.25 (m, 3H), 4.67-4.77 (m, 2H), 5.00 (s, 2H), 5.27 (d, J = 10.4 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.96 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 7.69-8.21 (m, 3H), 8.21 (broad s, 1H); Mass m/e (rel. intensity) 473 (M+6, 5), 471 (M+4, 36), 469 (M+2, 100), 467 (M+, 98), 433 (10), 403 (21), 320 (12), 228 (21), 175 (6), 159 (11), 117 (17); HRMS calcd. for $C_{16}H_{16}Cl_3N_3O_5S$ 468.9849, observed 468.9661.

Reaction of 12a or 12b with sulfonamide 13 (Scheme 2)

After the mixture of **13** (0.24 g, 0.88 mmole), potassium carbonate (0.24 g, 1.76 mmole) and water (0.2 mL) in butanone (5 mL) was refluxed for 30 minutes, **12a** (or **12b**) (0.3 g, 0.88 mmole) was added and refluxed for three hours. The reaction mixture was cooled to room temperature and chloroform (50 mL) was added. The resulting mixture was washed with water two times. The organic layer was dehydrated with anhyrous sodium sulfate and concentrated in vacuum and the crude product was separated by flash column chromatography.

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Recovery yield 84.5%, Rf 0.38 (50% Ethyl acetate-Hexane); brown solid; m.p. 155-157°C; IR (KBr) 3300, 3220, 1680 cm^{-1}; NMR (acetone-d_6) δ 1.36 (t, J = 7.1 Hz, 3H), 3.2 (t, J = 8.8 Hz, 2H), 4.1 (t, J = 8.8 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 7.68-7.84 (m, 3H).

4-Vinyloxazolidin-2-one (14)

Yield 83%; Rf 0.26 (50% Ethyl acetate-Hexane); pale yellow liquid; IR (film) 3250, 1740 cm^{-1}; NMR(acetone-d_6) δ 3.98 (dd, J = 6.0, 8.0 Hz, 1H), 4.42 (m, 1H), 4.51 (t, J = 8.0 Hz, 1H), 5.20 (d, J = 10.2 Hz, 1H), 5.32 (d, J = 16.9 Hz, 1H), 5.91 (ddd, J = 6.4, 10.2, 16.9 Hz, 1H), 6.80 (broad s, 1H); Mass m/e (rel. intensity) 113 (M+, 100), 86 (54), 83 (86), 68 (99), 58 (13), 55 (97), 54 (99); HRMS calcd. for $C_5H_7NO_2$ 113.0477, observed 113.0479.

Biological assay

Cytotoxicities of analogs **2**, and **11** were measured against human lung carcinoma (A549), human colon carcinoma (Colo205), human chronic myelogenous leukemia (K562), and human ovarian adenocarcinoma (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

Table I. Cytotoxicity of **2** and **11**

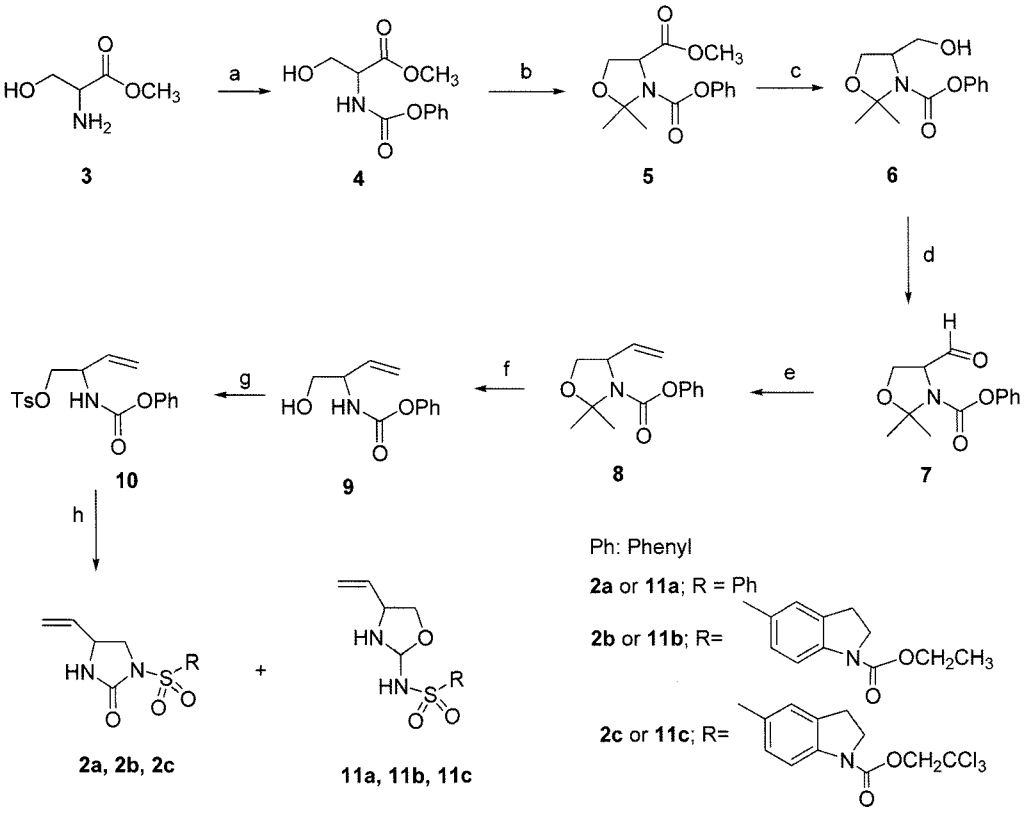
Compounds	Mol. Formula	IC_{50} (mM)[a]			
		A549[b]	Colo205[b]	K562[b]	SK-OV-3[b]
2a	$C_{11}H_{12}N_2O_3S$	>70	>70	>70	>70
2b	$C_{16}H_{19}N_3O_5S$	12.44	>70	21.55	>70
2c	$C_{16}H_{16}Cl_3N_3O_5S$	1.00	>70	7.80	>70
11a	$C_{11}H_{12}N_2O_3S$	>70	>70	>70	>70
11b	$C_{16}H_{19}N_3O_5S$	47.97	>70	>70	>70
11c	$C_{16}H_{16}Cl_3N_3O_5S$	14.29	>70	24.29	>70
1b[c]	$C_{20}H_{21}N_3O_5S$	14.22	2.42	0.61	1.39
doxorubicin	$C_{27}H_{29}NO_{11}$	1.77	0.95	0.92	0.63

[a]IC_{50} values, which were the mean value of three measurements, were measured using the MTT assay and the incubation time was 2 days. [b]Cell lines; A549: human lung carcinoma, Colo205: human colon carcinoma, K562: human chronic myelogenous leukemia, and SK-OV-3: human ovarian adenocarcinoma, [c]**1b**: 1-(1-ethoxycarbonylindoline-5-sulfonyl)-4-phenylimidazolidinone (Yoon et al, 1998).

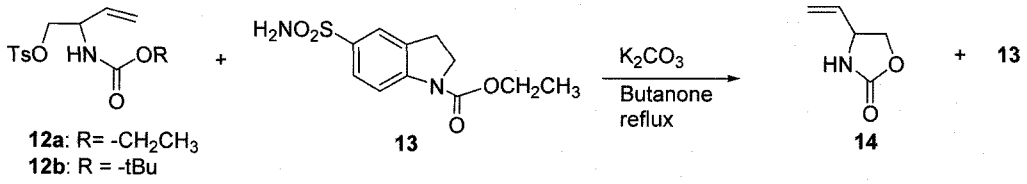
mean values of a set of three measurements, and the incubation time was 2 days (medium: RPMI1640 + 10%FBS). The results from these tests are shown in Table I.

RESULT AND DISCUSSION

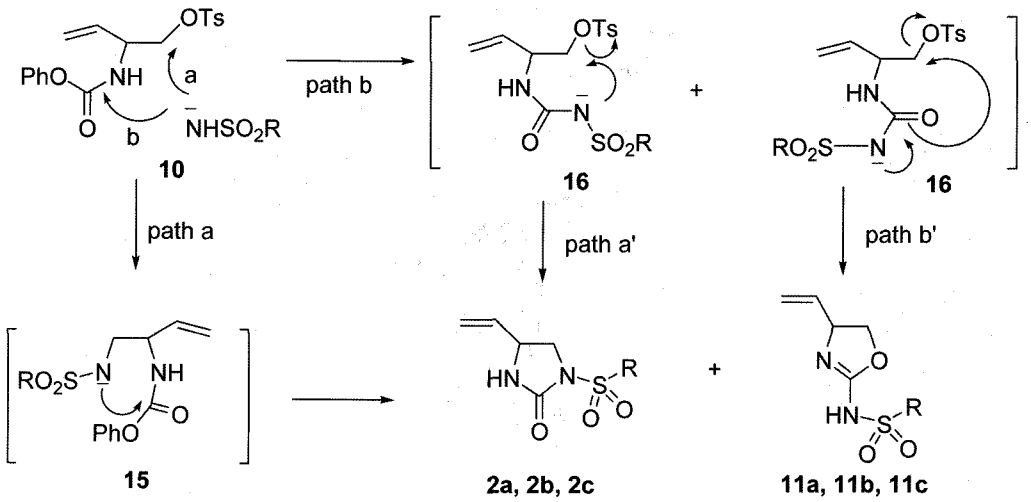
Scheme 1 illustrates the synthetic pathway of compounds **2**. (DL)-Methyl serinate was converted to **9** according to the combination of reported procedures for the preparation of *tert*-butyl 1-hydroxy-3-buten-2-yl-carbamate in six steps (Moriwake, *et al*, 1987; Williams, *et al*, 1996; Garner and Park, 1987). Compound **9** was transformed to tosylate **10**, which was then reacted with the appropreate benzenesulfonamides in the presence of potassium carbonate to give corresponding **2** and **11** in approximately equal ratio. This reaction could proceed two different ways as shown in Scheme 3. One is the initial formation of **15** by SN2 replacement of toluenesulfonate group of **10** and urea **16** by the replacement of phenoxy group of **10** at the same time. These intermediates then undergo cyclization to produce **2** and **11**. The other one is the formation of urea **16** only, which then undergoes two modes of cyclization to give **2** and **11**. The reaction of toluenesulfonate **12a** (or **12b**) with **13** under the same condition gave only product **14** (yield 83.0 %) and recovered **13** in 83.5%. This indicates that replacement of toluenesulfonate group of **12** with sulfonamide in the presence of base dose not occur unlike **10**. This result



Scheme 1. Synthetic pathway of **2**. (a) Phenyl chloroformate, K_2CO_3; (b) $BF_3.OEt_2$, 2,2-dimethoxypropane, acetone, room temperature; (c) LiCl, $NaBH_4$; (d) oxalyl chloride, dimethylsulfoxide, triethylamine; (e) methyltriphenylphosphonium bromide, potassium bis(trimethylsilyl)amide; (f) *p*-toluenesulfonic acid, methanol; (g) *p*-toluenesulfonyl chloride, pyridine; (h) RSO_2NH_2, K_2CO_3, H_2O in 2-butanpne, reflux.



Scheme 2. Reaction of tosylate **12a** (or **12b**) with **13**



Scheme 3. Reaction mechanism for the reaction of **10** with sulfonamide in the presence of K_2CO_3

implies that the reaction of **10** with sulfonamide in the presence of potassium carbonate obviously went through path b. Usually, β-ureido bromide undergoes cyclization through path b' to form 2-aminooxazoline (Jung, *et al*, 2001). Partial formation of imidazolidinone from **16** in the presence of base might be attributed from the stabilized nitrogen anion by sulfonyl function of **16**. Thus, reaction of **10** with sulfonamide should proceed through path b mechanism due to the superior leaving group ability of phenoxy group of **10** compared to alkoxy group of **12** and stabilization of intermediate nitrogen anion of **16** by sulfonyl group.

Cytotoxicities of compounds **2**, **11**, and **1b** were measured against human lung carcinoma (A549), human colon carcinoma (Colo205), human chronic myelogenous leukemia (K562), and human ovarian adenocarcinoma (SK-OV-3) cell lines *in vitro* using MTT assay. In order to investigate the variation of cytotoxicity along with structural change, phenyl substituent at 4-position of **1b** was altered to vinyl group as shown in **2b**. Although **2b** shows the compatible activity against A549, this exhibits the reduced activity against K562 (IC_{50} 7.80 mM), Colo205, and SK-OV-3 compared to **1b**. The same trend appears for **2c**. Therefore replacement of phenyl with vinyl causes the reduction in activity except A549 cell line. Naphthyl substituted analogs at this position show much less activity (Jung *et al*, 2000). Although mid size planar π-system such as five member hetero-aromatics at this position should be further tested for the enhancement of activity of this series, theses all indicate that phenyl group at 4-position of 4-phenyl-1-arylsulfonylimidazolidinones as cytotoxic compounds might be the optimum size. Oxazolines **11** are much less potent or inactive as showed in their 4-phenyl analogs (Jung, *et al*, 2001).

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