Arch Pharm Res Vol 24, No 4, 276-280, 2001

Archives of Pharmacal Research
http://apr.psk.or.kr

Structure-Activity Relationship Studies of Isoquinolinone Type Anticancer Agent

Seung Hoon Cheon, Joon Suck Park, Joon Yeol Lee, You Na Lee, Hyo Yi, Byung-Ho Chung, Bo-Gil Choi, Won-Jea Cho, Sang-Un Choi[1], and Chong-Ock Lee[1]

College of Pharmacy, Chonnam National University, and Research Institute of Drug Development, Chonnam National University, 300 Yongbong-Dong, Buk-Ku, Kwangju 500-757, Korea, [1]Screening & Toxicology Research Center, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung, Taejeon 305-606, Korea

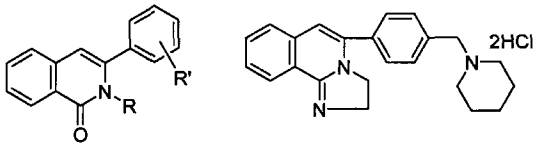
(Received April 20, 2001)

Substituted isoquinolin-1-ones (**1**) were synthesized to test their *in vitro* anticancer activity. 3-Biphenyl-*N*-methylisoquinolin-1-one (**7**) showed the most potent anticancer activity against five different human cancer cell lines.

Key words: Isoquinolin-1-ones, 3-biphenylisoquinolin-1-ones, Anticancer, Cytotoxicity

INTRODUCTION

Substituted isoquinolin-1-ones (**1**) displayed diverse biological activities including glycoprotein IIb/IIIa antagonistic activity (Hutchinson, *et al.*, 1996), poly(ADP-ribose) polymerase (PARP) inhibitory activity (Watson, *et al.*, 1998), and anticancer activity (Berry, *et al.*, 1996, Cheon, *et al.*, 1997, Cheon, *et al.*, 1998, Cheon, *et al.*, 1999, Cho, *et al.*, 1996). Structurally related 5-[4'-(piperidinomethyl) phenyl]-2,3-dihydroimidazo[2,1-a]isoquinoline (**2**) was reported to be an anticancer agent with undefined mechanism of action (Brunton *et al.*, 1993, Danhauser-Riedl *et al.*, 1991, Houlihan *et al.*, 1995a, Houlihan *et al.*, 1995b). Substituted isoquinolin-1-ones (**1**) could be considered as bioisosteres of 5-substituted 2,3-dihydroimidazo[2,1-a] isoquinolines because the imine bond of the imdazo ring in **2** is mimicked by carbonyl of the lactam in isoquinolin-1-ones (Fig. 1). Some derivatives of **1** showed stronger *in vitro* anticancer activity than **2**. Compound **3** was found to have 5 to 30 times better *in vitro* anticancer activity depending on the cancer cell lines (Cheon, *et al.*, 1997). Substituents at the N of the isoquinolin-1-ones generally lowered the *in vitro* anticancer activity (Cheon, *et al.*, 1998). 4-(Piperidinomethyl)phenyl or 4-methylphenyl substituted at 3 position of the isoquinolin-1-ones did not increase the *in vitro* anticancer activity (Cheon, *et al.*, 1998). As continuation of the structure-activity relationship studies of this series, the changes on the N and C-3 of isoquinolin-1-ones (**1**) led to the discovery of a very potent compound. *N*-Methyl-3-biphenylisoquinolin-1-one (**7**) exhibited the most potent *in vitro* anticancer activity against five different human cancer cell lines.



1 2

Fig. 1. Structures of isoquinolines

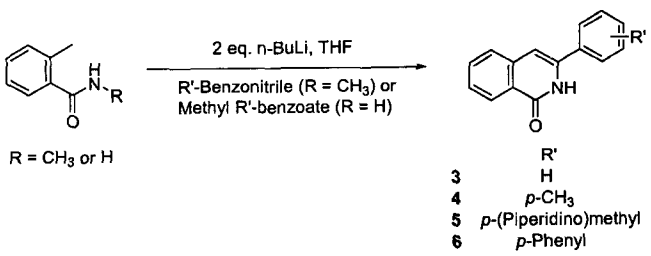
Correspondence to: Seung Hoon Cheon, College of Pharmacy, Chonnam National University, 300 Yongbong-Dong, Buk-Ku, Kwangju 500-757, Korea
E-mail: shcheon@chonnam.ac.kr

Chemistry

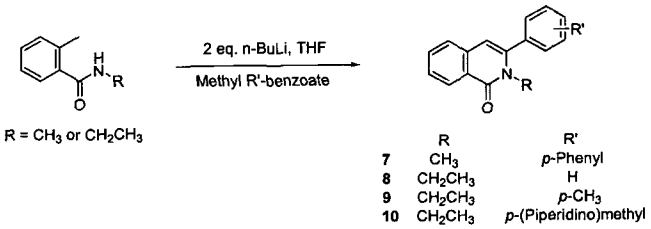
3-(Substituted-phenyl)isoquinolin-1(2*H*)-one (**3**) and its derivatives (**4-6**) were synthesized by the published method (Cheon *et al.*, 1998, Poindexter, 1982) as shown in Scheme 1.

N-Alkyl 3-(substituted-aryl)isoquinolin-1-ones (**7-10**) were prepared from *N*-alkyl-*o*-toluamides and aryl esters (Cheon *et al.*, 1997) as shown in Scheme 2.

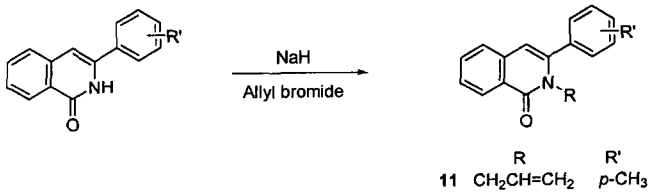
N-Allylation of 3-(*p*-toluyl)isoquinolin-2(1*H*)-one (**4**) with allyl bromide in the presence of NaH afforded *N*-allyl-3-(*p*-toluyl)isoquinolin-1-one (**11**) and 1-*O*-allyl-3-(p-toluyl) isoquinolin-1-ol as a 9:1 mixture which were separated by flash chromatography (Scheme 3).



Scheme 1. Synthesis of isoquinolines I



Scheme 2. Synthesis of isoquinolines II



Scheme 3. *N*-alkylation of isoquinolines

MATERIALS AND METHODS

General Procedures

All nonaqueous reactions were performed under a positive pressure of argon, unless otherwise noted. Flash column chromatography was performed as described by Still, *et al.* (Still, 1978) employing Merck 60 (230-400 mesh) silica gel.

Materials

Chemical reagents were purchased from Aldrich Chemical Company. Solvents were of extra pure grade and obtained from local suppliers. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was distilled under argon from calcium hydride. Thin layer chromatography (TLC) was carried out using E. Merck Silica Gel 60 precoated plates.

Analytical instruments

Melting points were determined by the capillary method on Electrothermal IA9200 digital melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on Bruker AC80 or Varian 300 spectrometers and are reported in ppm downfield from tetramethylsilane (TMS). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, bs=broad singlet. Mass spectra (MS) were obtained on Shimazu GCMS QP2000A instrument applying an electron-impact ionization (EI) method. Infrared spectra (IR) were determined neat or in pressed KBr disks on either PERKIN-ELMER 783 Spectophotometer or JASCO FT/IR-300E instrument and are reported in reciprocal centimeters.

Anticancer activity test (*in vitro*)

Anticancer assay was performed by Pharmaceutical Screening Laboratory in Korea Research Institute of Chemical Technology using five different human tumor cell lines, A-549 (human lung), SK-OV-3 (human ovarian), SK-MEL-2 (human melanoma), HCT-15 (human colon), XF-498 (human CNS) which were purchased from the National Cancer Institute (NCI) in U.S.A.

The cells were grown at 37°C in RPMI 1640 medium supplemented with 10% FBS and separated using PBS containing 0.25% trypsin and 3 mM EDTA. 5×10^3- 2×10^4 cells were added to each well of 96 well plate and incubated at 37°C for 24 h. Each compound was dissolved in DMSO and diluted with the above medium at five different concentrations with the range of 0.1-30 μg/mL. The DMSO concentration was set to be below 0.5% and filtrated using 0.22 mg filter. After removing the well medium by aspiration, a 200 mL portion of the solution was added to above well plates which were placed in 5% CO_2 incubator for 48 h. The protein stain assay was performed according to SRB method (Skehan *et al.*, 1990, Rubinstein *et al.*, 1990).

3-Phenylisoquinolin-1(2*H*)-one (3). A stirred solution of *N*-methyl-*o*-toluamide (0.5 g, 3.35 mmol) in THF (20 mL) under Ar was treated dropwise with 1.6 M *n*-BuLi in hexane (4.2 mL, 6.70 mmol) at ice-water bath temperature then allowed to stir for 2 h at the same temperature. The mixture was then cooled to -65°C, and treated dropwise with a solution of benzonitrile (431.5 mg, 4.19 mmol) in THF (1.5 mL). After an additional 0.5 h at -65°C, the reaction mixture was allowed to warm to room temperature, treated with saturated NH_4Cl solution. The mixture was then evaporated *in vacuo* and diluted with EtOAc and H_2O, the organic layer was separated, washed with H_2O, brine, dried ($MgSO_4$), and filtered, and the filtrate was evaporated *in vacuo*, recrystalized from EtOH to give 259 mg of white solid (35%).; mp 198-200°C; ^{1}H-NMR ($CDCl_3$) 6.89 (s, 1H), 7.40-8.46 (m, 9H), 10.44 (bs, 1H).

3-(4'-Methylphenyl)isoquinolin-1-one (4). A stirred solution of *N*-methyl-*o*-toluamide (3 g, 0.02 mol) in THF (200

mL) was treated dropwise under Ar with 1.6 M *n*-BuLi in hexane (25 mL, 0.04 mol) at ice-water bath temperature and allowed to stir for 2 h at the same temperature. The mixture was then cooled to -65°C, and treated dropwise with a solution of *p*-tolunitrile (2.93 g, 0.025 mol) in THF (9 mL). After an additional 0.5 h at -65°C, the reaction mixture was allowed to warm to room temperature, quenched with saturated NH_4Cl solution. The mixture was evaporated *in vacuo* and the residue was diluted with ethyl acetate, washed with H_2O, brine, dried (anhydrous $MgSO_4$), and filtered, and the filtrate was evaporated *in vacuo*, recrystallized from ethanol-methanol to give 1.8 g of white solid (38%): mp 223-227°C; ^{1}H-NMR ($CDCl_3$) 2.42 (s, 3H), 6.72 (s, 1H), 7.35-8.45 (m, 8H), 10.35 (bs, 1H).

3-[4'-(Piperidinomethyl)phenyl]isoquinolin-1-one HCl (5). Obtained following the same procedure for the synthesis of **4** as a yellow solid after crystalization from ethanol (48%).; mp 175-177°C; ^{1}H-NMR ($CDCl_3$) 1.52(b, 6H), 2.42(b, 4H), 3.67(s, 2H), 6.77(s, 1H), 7.35-8.45(m, 8H), 10.98(bs, 1H).

3-(Biphenyl)isoquinolin-1-one (6). Obtained following the same procedure for the synthesis of **4** as a yellow solid after crystalization from EtOAc-Hexanes (27%).; mp >300°C (decompose); ^{1}H-NMR ($CDCl_3$) 3.18(s, 1H), 6.82 (s, 1H), 7.36-7.88(m, 12H), 8.37-8.47(d, 1H); IR (KBr) 1660 cm^{-1}; MS (EI) m/z 298.

3-Biphenyl-*N*-methylisoquinolin-1-one (7). To a stirred solution of *N*-methyl o-toluamide (1 g, 6.7 mmol) in THF (50 mL) was added dropwise, at -65°C under Ar atmosphere, 1.6 M n-BuLi until the reaction mixture displayed persistent red (required about 4 mL, 6.4 mmol). An additional 4.2 mL (6.7 mmol) of 1.6 M n-BuLi was added dropwise to the reaction mixture at -65°C under Ar atmosphere and the mixture was allowed to warm to 0°C then cooled to -65°C. A solution of methyl 4-phenylbenzoate (1.25 g, 5.9 mmol) in THF (5 mL) was added to the reaction mixture at -65°C under Ar atmosphere and the mixture was slowly warmed to 0°C, quenched with saturated NH_4Cl, extracted with EtOAc, brine, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 1.5 g of crude product. A solution of this crude product (1.5 g) and *p*-TsOH (0.5 g, 2.62 mmol) in toluene (100 mL) was refluxed for 24h with continuous removal of H_2O (Dean-Stark trap). The toluene was removed *in vacuo*, and the residue was dissolved in EtOAc, washed with H_2O, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 1 g of solid. It was purified by flash chromatography, recrystallized from ethyl acetate to afford yellow solid (20%); mp 85-86°C; ^{1}H-NMR ($CDCl_3$) 3.48(s, 3H), 6.49(s, 1H), 7.25-7.76(m, 12H), 8.45 (d, 1H); IR (KBr) 2240 cm^{-1}; MS (EI) m/z 179.

***N*-Ethyl-3-phenylisoquinolin-1-one (8)**. In a 500 mL round-bottomed flask were placed of o-tolunitrile (20 g, 170.8 mmol), 30-35% H_2O_2 (68.2 mL, 592.7 mmol), EtOH (200 mL), and 6N NaOH (6.8 mL), allowed to stand for 12 h, maintained at 50°C for 3 h. The mixture, while still warm, was neutralized with 5% H_2SO_4, cooled to room temperature, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 20 g of white solid (100%); ^{1}H-NMR ($CDCl_3$) 2.50(s, 3H), 5.72(bs, 2H), 7.19-7.49(m, 4H).

A stirred solution of *o*-toluamide (30 g, 0.22 mol) in THF (300 mL) was treated with NaH (8.81 g, 0.22 mol) at ice-water bath temperature under Ar atmosphere, allowed to stir for 1 h, slowly added a solution of ethyl iodide (41.18 g, 0.26 mol) in THF (200 mL) for 12 h at room temperature, filtered, washed with CH_2Cl_2, brine, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 37.09 g of off-white solid. (100%, monoethyl amide contents >80% by ^{1}H-NMR); ^{1}H-NMR ($CDCl_3$) 1.27(t, 3H), 2.45(s, 3H), 3.49(q, 2H), 5.74(bs, 1H), 7.24-7.54(m, 4H).

A stirred solution of crude *N*-ethyl *o*-toluamide (1 g, 5.93 mmol, monoethyl amide contents >80%) in THF (20 mL) was treated dropwise with 1.6 M *n*-BuLi (7.41 mL, 11.86 mmol) at ice-water bath temperature under Ar atmosphere, allowed to stir for 2 h at the same temperature, added a solution of methyl benzoate (968.8 mg, 7.12 mmol) in THF (2 mL) at -78°C, stirred for 1 h at -78°C, warmed to -10°C, quenched with saturated NH_4Cl, extracted with EtOAc, brine, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 1.95 g of crude product. A solution of this crude product (1.95 g) and *p*-TsOH (112.7 mg, 0.593 mmol) in toluene (30 mL) was refluxed for *ca.* 8 h with continuous removal of H_2O (Dean-Stark trap). The toluene was removed *in vacuo*, and the residue was dissolved in EtOAc, washed with H_2O, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 1.7 g of solid. It was purified by flash chromatography, recrystallized from ethyl acetate to afford yellow solid (40%); mp 78-81°C; ^{1}H-NMR ($CDCl_3$) 1.15(t, 3H), 4.00(q, 2H), 6.38(s, 1H), 7.34-8.51(m, 9H).

***N*-Ethyl-3-[4'-(methyl)phenyl]isoquinolin-1-one (9)**. Obtained as a white solid (53%); mp 124-125°C; ^{1}H-NMR ($CDCl_3$) 1.14(t, 3H), 2.42(s, 3H), 4.00(q, 2H), 6.36 (s, 1H), 7.32-8.50(m, 8H).

***N*-Ethyl-3-[4'-(piperidinomethyl)phenyl]isoquinolin-1-one HCl (10)**. Obtained as a yellow powder (34%); mp 298.5-300.5°C; ^{1}H-NMR ($CDCl_3$) 1.15(t, 3H), 1.65(s, 2H), 1.92(s, 3H), 2.66(q, 3H), 3.50(d, 2H), 3.99(q, 2H), 4.18(d, 2H), 6.36(s, 1H), 7.37-8.66(m, 8H).

***N*-Allyl-3-(4'-methylphenyl)isoquinolin-1-one (11)**. To a stirred solution of 3-(4'-methylphenyl)isoquinolin-1-one (0.4 g, 1.7 mmol) in THF (10 mL) and DMF (20 mL) was

added NaH (60% in mineral oil, 68 mg, 1.7 mmol) at ice-water bath temperature and the mixture was stirred for 1 h at the same temperature. A solution of allyl bromide (250 mg, 2.04 mmol) in THF (10 mL) was added dropwise to the reaction mixture followed by NaI (200 mg) and it was refluxed for 3 h. After cooling to 0°C, excess NaH (20.4 mg, 0.51 mmol) was added and the reaction mixture was stirred for 0.5 h. To this mixture was added a solution of allyl bromide (61 mg, 0.51 mmol) in THF (6 mL) and it was refluxed for 2 h. After cooling to room temperature, solvents were evaporated under reduced pressure and the residue was diluted with ethyl acetate, washed with water, brine and dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated *in vacuo* and the product was purified by flash column chromatography to give 420 mg of *N*-allyl-3-(4'-methylphenyl)isoquinolin-1-one (**11**) and 48 mg of 1-*O*-allyl-3-(4'-methylphenyl)isoquinoline-1-ol.

N-Allyl-3-(4'-methylphenyl)isoquinolin-1-one (**11**): oil; ^{1}H-NMR ($CDCl_3$) 2.41 (s, 3H), 4.57 (m, 2H), 4.94 (q, 1H), 5.00 (m, 1H), 5.62-6.02 (m, 1H), 6.40 (s, 1H), 7.34-8.51 (m, 8H).

1-*O*-Allyl-3-(4'-methylphenyl)isoquinoline-1-ol: white power, mp 60-61°C; ^{1}H-NMR ($CDCl_3$) 2.40 (s, 3H), 5.12-5.22 (m, 2H), 5.39 (q, 1H), 5.62 (q, 1H), 6.04-6.53 (m, 1H), 7.21-8.32 (m, 9H).

RESULTS AND DISCUSSION

Isoquinolin-1-ones with the same 4'-(piperidinomethyl) phenyl substituent at C-3 as 5-[4'-(piperidinomethyl) phenyl]-2,3-dihydroimidazo[2,1-a]isoquinoline (**2**) did not show any appreciable *in vitro* anticancer activity (compounds **5** and **10**, Table I). 4-Methylphenyl or biphenyl substitution at C-3 of isoquinolin-1-ones (compounds **4** and **6**) did not improve the activity of **3**. Compound **6**, however, showed excellent *in vitro* anticancer activity against one cell line (XF-498, human CNS cancer cell line). Interestingly biphenyl substitution at C-3 of *N*-methylisoquinolin-1-one (compound **7**) displayed 5 to 300 times better activity than **3** except one cell line. In human melanoma cell line (SK-MEL-2) **3** had three times better activity than **7**. It is difficult to explain the activity differences between compounds **6** and **7**. 3-Substituted *N*-ethylisoquinolin-1-ones (compounds **8**, **9** and **10**) showed less potent activity than compounds **3**, **4** and **5**, respectively. Finally *N*-allyl substituted 3-(4'-methylphenyl)isoquinolin-1-one (**11**) showed better activity than **9** but less activity than **4**. It is worth mentioning that the *in vitro* anticancer activity of **7** is better than doxorubicin in human colon and CNS cancer cell lines.

Table I. *In vitro* anticancer activity (ED_{50} μg/ml)

	A549	SK-OV-3	SK-MEL-2	HCT-15	XF-498
3	0.97	0.72	0.65	0.30	2.65
4	9	6	5	3	14
5	>30	>30	>30	>30	>30
6	>30	>30	>30	>30	0.01
7	0.16	0.14	2.10	0.001	0.02
8	15	30	24	14	18
9	18	28	18	20	15
10	>30	>30	>30	>30	>30
11	11.3	14.5	11.6	12.2	8.3
Doxorubicin	0.09	0.08	0.13	0.65	0.16

A-549 (human lung), SK-OV-3 (human ovarian), SK-MEL-2 (human melanoma), HCT-15 (human colon), XF-498 (human CNS)

CONCLUSION

N and C-3 substituted isoquinolin-1-ones were designed and synthesized to test their *in vitro* anticancer activity against five different human cancer cell lines. 3-Phenylisoquinolin-1-one (**3**) and 3-biphenyl-*N*-methylisoquinolin-1-one (**7**) showed better activity than the other compounds synthesized. 3-Biphenyl-*N*-methylisoquinolin-1-one (**7**) exhibited the most potent activity comparable to that of doxorubicin.

ACKNOWLEDGEMENTS

This study was supported by RESEARCH FUND, Chonnam National University, 1996 and it was greatly appreciated.

This study was financially supported by Chonnam National University in the program, 1996 and it was greatly appreciated.

REFERENCES

Berdel, W. E. and Munder, P. G., Antitumor Analogs of PAF, In Snyder, F. (Ed). *Platelet-Activating Factor and Related Lipid Mediators*. Plenum Press, New York, pp. 449-467, 1987.

Berry, J. M. and Threadgill, M. D., Labeled compounds of interest as antitumor agents. V. Syntheses of [18O]-5-methylisoquinolinone and 1-(furan-2-yl-[18O]-methoxy) -5-methylisoquinoline. *J. Labelled Compd. Radiopharm.*, 38, 935-940 (1996).

Brunton, V. G. and Workman, P., *Br. J. Cancer*, 67, 989 (1993).

Cheon, S. H., Park, J. S., Jeong, S. H., Chung, B. H., Choi, B. G., Cho, W. J., Kang, B. H., and Lee, C. O., Synthesis and Structure-Activity Relationship Studies of 2,3-Dihydroimidazo[2,1-a]isoquinoline Analogs as Antitumor Agents. *Arch. Pharm. Res.*, 20, 138-143 (1997).

Cheon, S. H., Park, J. S., Chung, B. H., Choi, B. G., Cho, W. J., Choi, S. U., and Lee, C. O., Synthesis and structure-activity relationship studies of substituted

isoquinoline analogs as antitumor agent. *Arch. Pharm. Res.*, 21, 193-197 (1998).

Cheon, S. H., Lee, J. Y., Chung, B. H., Choi, B. G., Cho, W. J., and Kim, T. S., Studies on the synthesis and in vitro antitumor activity of the isoquinolone derivatives. ynthesis and structure-activity relationship studies of substituted isoquinoline analogs as antitumor agent. *Arch. Pharm. Res.*, 22, 179-183 (1999).

Cho, W. J., Yoo, S. J., Chung, B. H., Choi, B. G., Cheon, S. H., Whang, S. H., Kim, S. K., Kang, B. H., and Lee, C. O., Synthesis of Benzo[c]phenanthridine Derivatives and their in Vitro Antitumor Activities. *Arch. Pharm. Res.*, 19, 321-325 (1996).

Danhauser-Riedl, S., Felix, S. B., Houlihan, W. J., Zafferani, M., Steinhauser, G., Oberberg, D., Kalvelage, H., Busch, R., Rastetter, J., and Berdel, W. F., *Cancer Res.*, 51, 43 (1991)

Dive, C., Watson, J. V., and Workman, P., Multiparametric Flow Cytometry of the Modulation of Tumor Cell Membrane Permeability by Developmental Antitumor Ether Lipid SRI 62-834 in EMT6 Mouse Mammary Tumor and HL6O Human Promyelocytic Leukemia cells. *Cancer Res.*, 51, 799-806 (1990).

Houlihan, W. J. and Parrino, V. A., Directed Lithiation of 2-Phenyl- and 2-(*o*-methylphenyl)imidazoline. *J. Org. Chem.*, 47, 5177-5180 (1982).

Houlihan, W. J., Cheon, S. H., Parrino, V. A., Handley, D. A., and Larson, D. A., Structural Modification of 5-Aryl-2,3-dihydroimidazo[2,1-a]isoquinoline Platelet Activating Factor Receptor Antagonists. *J. Med. Chem.*, 36, 3098-3102 (1993).

Houlihan, W. J., Munder, P. G., Handley, D. A., Cheon, S. H., and Parrino, V. A., Antitumor Activity of 5-Aryl-2,3-dihydroimidazo[2,1-a]isoquinolines. *J. Med. Chem.*, 38, 234-240 (1995a).

Houlihan, W. J., Munder, P. G., Handley, D. A., and Nemecek, G. A., Priclinical Pharmacology and Possible Mechanism of Action of the Novel Antitumor Agent 5-(4'-Piperidinomethylphenyl)-2,3-dihydroimidazo[2,1-a]isoquinoline. *Arzneim.-Forsch./Drug Res.*, 45(II), 1133-1137 (1995b).

Hutchinson, J. H., Cook, J. J., Brashear, K. M., Breslin, M. J., Glass, J. D., Gould, R. J., Halczenko, W., Holahan, M. A., and Lynch, R. J., Non-peptide glycoprotein IIb/IIIa antagonists. 11. Design and in vivo evaluation of 3,4-dihydro-1(1H)-isoquinolinone-based antagonists and ethyl ester prodrugs. *J. Med. Chem.*, 39, 4583-4591 (1996).

Modest, E. J., Berens, M. E., Piantadosi, C., and Noseda, A., Pharmacological Effects and Anticancer Activity of New Ether Phospholipid Analogs, In Kabara J. J. (Ed). *The Pharm.acological Effect of lipids III, Role of Lipids in Cancer Research.* The American Oil Chemists' Society, Champaign, IL, pp. 330-337, 1989.

Munder, P. G. and Westphal, O., Antitumoral and Other Biomedical Activities of Synthetic Ether Lysophospholipids, In Waksman, B. H. (Ed). *1939-1989: Fifty Years Progress in Allergy.* Karger, New York, pp. 206-235, 1990.

Noseda, A., Godwin, P. L., and Modest, E. J., Effects of Antineoplastic Ether Lipids on Model and Biological Membranes, *Biochim. Biophys. Acta*, 945, 92-100 (1988).

Poindexter, G. S., Convenient preparation of 3'-substituted-1(2H)-isoquinolines. *J. Org. Chem.*, 47, 3787-3788 (1982).

Rubinstein, L. V., Shoemaker, R. H., Paul, K. D., Simon, R. M., Tosini, S., Skehan, P., Scudiero, D., Monks, A., and Boyd, M. R., *J. Natl. Cancer Inst.*, 82, 1113 (1990).

Seewald, M. J., Olsen, R. A., Sehgal, I., Melder, D. C., Modest, E. J., and Powis, G., Inhibition of Growth Factor-Dependent Inositol Phosphate Ca^{2+} Signaling by Antitumor Ether Lipid Analogues. *Cancer Res.*, 50, 4458-4463 (1990).

Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J. B., Vistica, D. T., Warren, J. T., Bokesch, H., Kenny, S., and Boyd, M. R., *J. Natl. Cancer Inst.*, 82, 1107 (1990).

Still, W. C., Kahn, M., and Mitra, A. J., *J. Org. Chem.*, 43, 2923 (1978)

Uberall, F., Oberhuber, H., Maly, K., Zaknun J., Demuth, L., and Grunicke, H. H., Hexadecylphosphocholine Inhibits Inositol Phosphate Formation and Protein Kinase C Activity. *Cancer Res.*, 51, 807-812 (1991).

Watson, C. Y., Whish, W. J. D., Treadgill, M. D., Synthesis of 3-substituted benzamides and 5-substituted isoquinolin-1(2H)-ones and preliminary evaluation as inhibitors of poly(ADP-ribose)polymerase (PARP). *Bioorg. Med. Chem.*, 6, 721-734 (1998).

Workman, P., Antitumor Ether Lipids: Endocytosis as a Determination of Cellular Sensitivity. *Cancer Cells*, 3, 315-317 (1991).