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Studies on the Synthesis and *In Vitro* Antitumor Activity of the Isoquinolone Derivatives

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3-Arylisoquinolin-1(2*H*)-ones (**2**) are possible bioisosteres of the 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (**1**) which is in clinical evaluation for the treatment of cancer. Structure-activity relationship studies of 3-arylisoquinolin-1(2*H*)-ones (**2**) led to the synthesis of 3-arylquinolin-2(1*H*)-ones (**3**). A number of 3-phenyl substituted quinolin-2(1*H*)-ones were synthesized and tested for their *in vitro* antitumor activity against four different human tumor cell lines and 3-phenyl-*N*-benzyl-3,4-dihydroquinolin-2(1*H*)-one (**12**) showed the most potent activity.

Key words : 3-Arylisoquinolin-1-ones, 3-Arylquinolin-2-ones, Antitumor, Cytotoxicity

INTRODUCTION

5-[4'-(Piperidinomethyl)phenyl]-2,3-dihydroimidazo [2,1-*a*]isoquinoline (**1**) is an antitumor agent with diverse mechanism of action and is under clinical evaluation in Europe (Brunton *et al.*, 1993, Danhauser-Riedl *et al.*, 1991, Houlihan *et al.*, 1995a, Houlihan *et al.*, 1995b). It has been reported that structurally simpler compounds, such as 3-substituted isoquinolin-1-ones (**2**), had better antitumor activity than **1** in five different human tumor cell lines (Cheon *et al.*, 1997, Cheon *et al.*, 1998). Accordingly, these 3-substituted isoquinolin-1(2*H*)-ones (**2**) are considered to be bioisosteres of 5-substituted 2, 3-dihydroimidazo[2,1-*a*]isoquinolines because the imine bond of imidazo ring in **1** is mimicked by carbonyl of the lactam in isoquinolin-1(2*H*)-ones. Another possible explanation for the enhancement of biological activity of **2** is that isoquinolin-1-ones could be one of the hydrolyzed form of 2,3-dihydroimidazo[2,1-*a*]isoquinolines. The lactam portion of isoquinolin-1(2*H*)-ones may contribute to a tighter binding to a receptor through hydrogen bonding than the imidazo ring does. It will be interesting to transpose the carbonyl and nitrogen atom in the lactam portion of 3-substituted isoquinolin-1(2*H*)-ones. We report the results of the structure-activity relationship studies of 3-substituted isoquinolin-1(2*H*)-ones specially focused on the lactam portion of the lead compound.

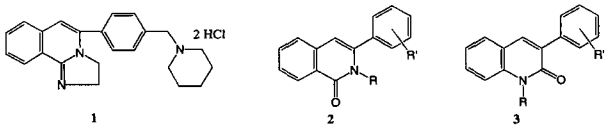

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Fig. 1.

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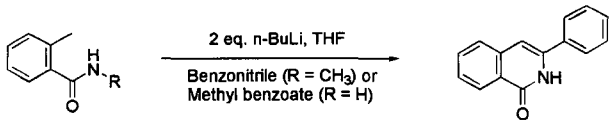
CHEMISTRY

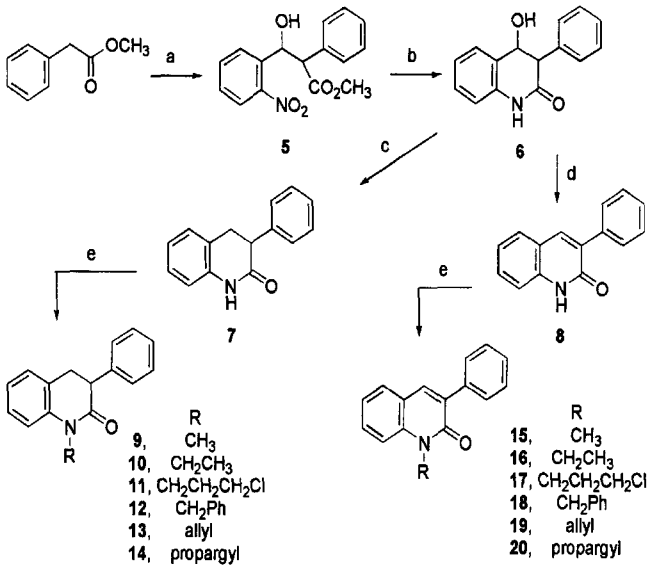
3-Phenylisoquinolin-1(2*H*)-one (**4**) and its derivatives were synthesized by the published method (Cheon *et al.*, 1998, Poindexter, 1982) as shown in Scheme 1.

3-Phenylquinolin-2(1*H*)-one analogs **15-20** were prepared from 2-nitrobenzaldehyde and methyl phenylacetate. An anion of methyl phenylacetate which was generated from lithium *N,N*-diisopropylamide (LDA) and methyl phenylacetate at -60°C reacted with 2-nitrobenzaldehyde and the resulting nitro hydroxy ester compound **5** was reduced under hydrogen in ethyl acetate to produce 4-hydroxy-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**6**). None of the 3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**7**) was formed during the reduction in ethyl acetate under *ca.* 1 atmospheric hydrogen balloon. Reduction of 4-hydroxy-3-phenyl-3,4-dihydroquinolin-



R = CH_3 or H 4

Scheme 1.



Scheme 2.

2(1*H*)-one (**6**) under H_2 (50 psi) in acetic acid afforded 3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**7**). While dehydration of 4-hydroxy-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one gave 3-phenylquinolin-2(1*H*)-ones (**8**). *N*-Alkylation of 3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**7**) or 3-phenylquinolin-2(1*H*)-one (**8**) was accomplished with suitable electrophiles in the presence of NaH. During the alkylation reactions a trace amount of *O*-alkylation products were formed and they were separated by flash chromatography (Scheme 2).

RESULTS AND DISCUSSION

The antitumor activities and structure-activity relationship studies of 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-a]isoquinoline (**1**), and 3-phenylisoquinolin-1-one (**4**) were reported (Houlihan *et al.*, 1995a, Cheon *et al.*, 1998). Extension of the structure-activity relationship studies of 3-phenylisoquinolin-1(2*H*)-one (**4**), we tested the effects of lactam moiety of the isoquinolinone to the *in vitro* antitumor activities against four different human tumor cell lines. If compound 4 binds to a receptor for its biological activities, the major binding forces are hydrogen bonding of the carbonyl and NH in lactam portion of the molecule. It will be interesting to transpose the carbonyl and nitrogen atom in the lactam portion of 3-substituted isoquinolin-1(2*H*)-ones. The transposed compound will be 3-substituted quinolin-2(1*H*)-ones. In this study the substituent at 3 position of quinolin-2(1*H*)-one was selected to be a phenyl because 3-phenyl isoquinolin-1(2*H*)-ones was the most potent compound. Among many different substituents tried (Scheme 2) at *N*-1 of **8**, ethyl (**16**) and allyl (**19**) substituted compounds showed some activity in 3-phenylquinolin-2(1*H*)-one series (Table).

Table *In vitro* antitumor activity (ED_{50} μg/ml)

	A549	SK-OV-3	SK-MEL-2	HCT-15
4	0.97	0.72	0.65	0.30
6	77	73	75	85
7	33	27	74	50
9	27	24	38	31
10	40	36	38	42
11	29	33	24	42
12	4.4	4.5	5.7	6.7
13	27	30	30	32
14	13	9.3	5.7	30
15	>100	>100	>100	80
16	14	12	22	15
17	8.4	36	26	19
18	31	94	50	7.3
19	20	19	26	11
20	>100	>100	>100	97

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

3-Phenyl-3,4-dihydroquinolin-2(1*H*)-ones (**7, 9-14**) were also synthesized and tested for their *in vitro* antitumor activity. They generally exhibited better activity than 3-phenylquinolines (**15-20**). Specially, *N*-benzyl (**12**) substituted compound displayed the best activity. Nonplanarity of the lactam ring in quinolinone structure of **7** may be an important feature for their activity.

CONCLUSION

Methyl, ethyl, allyl, propargyl, 3-chloropropyl, benzyl substituted 3-phenylquinolin-2-one and 3-phenyl-3,4-dihydroquinolin-2(1*H*)-one compounds, which are the analogs of 3-arylisoquinolin-1(2*H*)-ones (**1, 2, 4**), were synthesized and tested for their *in vitro* antitumor activity against four different human tumor cell lines. *N*-Benzyl-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**12**) exhibited the best activity.

EXPERIMENTAL SECTION

General Procedures

All nonaqueous reactions were performed under a positive pressure of argon, unless 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. Methylene chloride 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 were 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, Q=quintet, 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 Spectrophotometer or JASCO FT/IR-300E instrument and are reported in reciprocal centimeters.

Antitumor Assay (*in vitro*)

Antitumor assay was performed by Immunology Laboratory in College of Pharmacy, Chonnam National University 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) 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 concentration of DMSO 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 (4)

A stirred solution of *N*-methyl-*o*-toluamide (0.5 g, 3.35 mmol) in tetrahydrofuran (20 mL) under argon was treated dropwise with 1.6 M *n*-butyllithium in hexane (4.2 mL, 6.70 mmol) at ice-water bath temperature then allowed to stir for 2h 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 tetrahydrofuran (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 ethyl acetate and H_2O, the organic layer was separated, washed with H_2O, brine, dried over anhydrous $MgSO_4$, and filtered, and the filtrate was evaporated *in vacuo,* recrystalized from ethanol to give 259 mg of white solid (35%).; mp 198~200°C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 6.89 (s, 1H), 7.40-8.46 (m, 9H), 10.44 (bs, 1H).

Methyl 3-hydroxy-3-(2'-nitrophenyl)-2-phenylpropanoate (5)

To a solution of lithium *N,N*-diisopropylamide (prepared from *N,N*-diisopropylamine (2 mL, 14 mmol) and 1.6 M *n*-butyllithium in hexane (8.25 mL, 13.2 mmol) at ice-water bath temperature) in tetrahydrofuran (30 mL) at -60°C, was added dropwise a solution of methyl phenylacetate (0.95 mL, 6.62 mmol) in tetrahydrofuran (2 mL) and the mixture was slowly warmed to 0°C then recooled to -20°C. To this anion was added a solution of 2-nitrobenzaldehyde (1 g, 6.62 mmol) in tetrahydrofuran (3 mL) and the mixture was warmed to room temperature and stirring was continued for an additional 1h. The reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a mixture of two products. For analytical purposes two diastereoisomers were separated by column chromatography (hexanes:ethyl acetate=5:1). One isomer (yellow oil, 850 mg) ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.65 (s, 3H), 4.16 (d, 1H, *J*=4.2 Hz), 5.94 (d, 1H, *J*=4.2 Hz), 7.00~7.95 (m, 9H). Another isomer (yellow solid, 980 mg) ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.63 (s, 3H), 4.1 (d, 1H, *J*=7.3 Hz), 5.85 (d, 1H, *J*=7.3 Hz), 7.00~7.72 (m, 9H).

4-Hydroxy-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (6)

A solution of methyl 3-hydroxy-3-(2'-nitrophenyl)-2-phenylpropanoate (**5**, 2.37 g, 7.87 mmol) in ethyl acetate (60 mL) was added 1.1 g of 5% Pd/C and the mixture was stirred under H_2 (balloon) for 30 min at ambient temperature. The mixture was filtered and the filtrate was evaporated *in vacuo* to give 1.6 g of the product (83%) after column chromatograpy (silicagel, ethyl acetate-hexanes). ^{1}H-NMR (80 MHz, $CDCl_3$+DMSO-d_6) δ: 3.92 (d, 1H, *J*=5.7 Hz), 4.88 (d, 1H, *J*=5.7 Hz), 6.9~7.5 (m, 9H). MS (EI, m/z) 239 (M^+).

3-Phenyl-3,4-dihydroquinolin-2(1*H*)-one (7)

A solution of 4-hydroxy-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**6**, 50 mg, 0.209 mmol) in glacial acetic acid (10 mL) was added 130 mg of 5% Pd/C and the mixture was shaken using Parr shaker under H_2 (50

psi) overnight at ambient temperature. The mixture was filtered and the filtrate was diluted with ethyl acetate, and washed carefully with saturated $NaHCO_3$ solution followed by brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give 42 mg of the product (91%). ^{1}H-NMR (80 MHz, $CDCl_3$+DMSO-d_6) δ: 3.21 (d, 2H), 3.76 (m, 1H), 7.0-7.9 (m, 9H). MS (EI, m/z) 223 (M^+).

3-Phenylquinolin-2(1*H*)-one (8)

To a solution of 4-hydroxy-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**7**, 100 mg, 0.42 mmmol) in methylene chloride (20 mL) was added *p*-toluenesulfonic acid monohydrate (8 mg) and the mixture was refluxed for 2h. After cooling, the reaction mixture was diluted with methylene chloride and washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the filtrate gave 87 mg of the product (95%). ^{1}H-NMR (80 MHz, $CDCl_3$+ DMSO-d_6) δ: 7.1~7.9 (m, 10H). MS (EI, m/z) 221 (M^+).

***N*-Methyl-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (9)**

To a suspension of NaH (60% in oil dispersion, 27 mg, 0.67 mmol, used without washing off oil) in tetrahydrofuran (5 mL) and *N,N*-dimethylforamide (20 mL) was added 3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**7**) and the mixture was stirred at ambient temperature for 1 h. A solution of methyl iodide (0.04 mL, 0.67 mmol) in tetrahydrofuran (0.5 mL) was added to the reaction mixture and it was heated at 50~60°C for 25 min. After cooling to room temperature, it was diluted with ethyl acetate and the organic phase was washed with water, brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 40 mg (24%) of the product after column chromatograpy (silicagel, ethyl acetate-hexanes). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.21 (d, 2H, *J*=7.6 Hz), 3.44 (s, 3H), 3.85 (t, 3H, *J*=7.6 Hz), 6.94~7.46 (m, 9H). MS (EI, m/z) 237 (M^+).

The following compounds were prepared using the procedure described above for the compound **9**.

***N*-Ethyl-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (10)**

Yellow solid (36%), ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.28 (t, 3H, *J*=7.1 Hz), 3.19 (m, 2H), 3.83 (m, 1H), 4.04 (q, 2H, *J*=7.1 Hz), 6.96~7.37 (m, 9H). MS (EI, m/z) 251 (M^+).

***N*-(3-Chloropropyl)-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (11)**

Yellow solid (49%), ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.16 (Q, 2H, *J*=6.4 Hz), 3.20 (m, 2H), 3.61 (t, 2H, *J*= 6.4 Hz), 3.85 (m, 1H), 4.40 (t, 2H, *J*=6.4 Hz), 6.98-7.34 (m, 9H).

***N*-Benzyl-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (12)**

Yellow solid (42%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.27 (d, 2H, *J*=7.6 Hz), 3.98 (t, 1H, *J*=7.6 Hz), 5.27 (s, 2H), 6.91~7.56 (m, 14H). MS (EI, m/z) 313 (M^+).

***N*-Allyl-3-phenyl-3,4-dihydroquinolin-2(1*H*)-one (13)**

Yellow oil (29%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.23 (m, 2H), 3.90 (m, 1H), 4.55~5.23 (m, 4H), 5.74~6.14 (m, 1H), 6.90~7.55 (m, 9H).

3-Phenyl-*N*-propargyl-3,4-dihydroquinolin-2(1H)-one (14)

Yellow solid (37%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.29 (t, 1H, *J*=2.5 Hz), 3.20 (m, 2H), 3.87 (m, 1H), 4.74 (d, 2H, *J*=2.5 Hz), 7.00~7.54 (m, 9H). MS (EI, m/z) 261 (M^+).

***N*-Methyl-3-phenylquinolin-2(1*H*)-one (15)**

Yellow solid (73%) ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 3.72 (s, 3H), 7.07~7.85 (m, 10H). MS (EI, m/z) 235 (M^+).

***N*-Ethyl-3-phenylquinolin-2(1*H*)-one (16)**

Yellow oil (76.5%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.39 (t, 3H, *J*=7.2 Hz), 4.49 (q, 2H, *J*=7.2 Hz), 7.09~7.89 (m, 10H). MS (EI, m/z) 249 (M^+).

***N*-(3-Chloropropyl)-3-phenylquinolin-2(1*H*)-one (17)**

Yellow oil (38%), ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.36 (Q, 2H, *J*=6.4 Hz), 3.70 (t, 2H, *J*=6.4 Hz), 4.50 (t, 2H, *J*=6.4 Hz). MS (EI, m/z) 297 (M^+).

***N*-Benzyl-3-phenylquinolin-2(1*H*)-one (18)**

Yellow solid (63%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 5.61 (s, 2H), 7.06~7.85 (m, 15H).

N-Allyl-3-phenylquinolin-2(1H)-one (19)

Yellow oil (85%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 4.86~5.31 (m, 4H), 5.79~6.19 (m, 1H), 7.11~7.81 (m, 10H). MS (EI, m/z) 261 (M^+).

3-Phenyl-*N*-propargyl-3,4-dihydroquinolin-2(1*H*)-one (20)

Orange solid (67%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.24 (t, 1H, *J*=2.5 Hz), 5.16 (d, 2H, *J*=2.5 Hz), 7.24~7.79 (m, 10H). MS (EI, m/z) 259 (M^+).

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