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Synthesis and Structure-Activity Relationship Studies of Substituted Isoquinoline Analogs as Antitumor Agent

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A number of substituted isoquinolin-1-ones, possible bioisosteres of the 5-aryl substituted 2,3-dihydroimidazo[2,1-*a*]isoquinolines, were synthesized and tested for their antitumor activity against five different human tumor cell lines. *O*-(3-hydroxypropyl) substituted compound (**15**) exhibited the best antitumor activity which is 3-5 times better than 5-[4'-(piperidinomethyl) phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (**1**).

Key words : Isoquinolin-1-ones, Antitumor, Bioisostere

INTRODUCTION

2,3-Dihydroimidazo[2,1-*a*]isoquinolines have been reported to have antitumor activity (Houlihan *et al.*, 1995a) or platelet activating factor (PAF, Berdel *et al.*, 1987) receptor antagonistic activity (Houlihan *et al.*, 1993, Berdel *et al.*, 1991) depending on their substituents at C-5 position. The mechanism of antitumor activity of this class of compounds was suggested to be macrophage activation and possible effect on signal transduction (Brunton *et al.*, 1993, Danhauser-Riedl *et al.*, 1991, Houlihan *et al.*, 1995b). Currently 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (**1**) is in clinical evaluation as a potential antitumor agent in Europe.

Structure-activity relationship studies of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines revealed that simple 3-substituted isoquinolin-1-ones had good antitumor activity in five different human tumor cell lines (Cheon *et al.*, 1997). In addition, substituted isoquinolin-1-one has been reported to have strong antitumor activity (Cho *et al.*, 1996). This compound was a key intermediate in the synthesis of benzo[*c*]phenanthridine class of antitumor agent. These facts suggested that 3-substituted isoquinolin-1-ones are considered to be bioisosteres of 5-substituted 2,3-dihydroimidazo[2,1-*a*]isoquinolines. In this paper we report the results of the studies to search for substituents on N-2 of 3-substituted isoquinolin-1-ones which can mimic the dihydroimidazo ring portion of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines.

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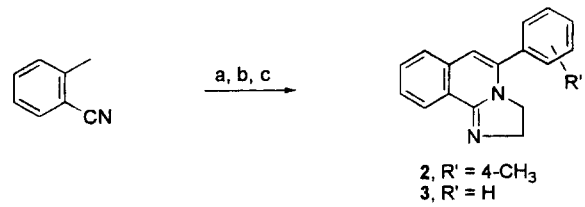
CHEMISTRY

5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinoline derivatives were synthesized by the published method (Cheon *et al.*, 1997) as shown in Scheme 1.

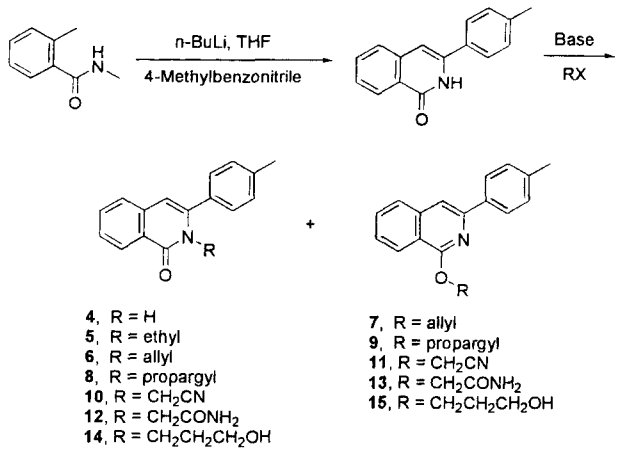
N-Substituted 3-arylisoquinolin-1-ones (**5, 6, 8, 10, 12, 14**) were prepared from either *N*-alkyl-*o*-toluamides and aryl esters (Cheon *et al.*, 1997) or *N*-methyl-*o*-toluamide and substituted benzonitriles. The dianion of *N*-methyl-*o*-toluamide reacted with substituted benzonitrile to afford 3-arylisoquinolin-1-ones (Poindexter, 1982). The nucleophilic substitution reaction of 3-arylisoquinolin-1-ones with suitable electrophiles gave mixture of *N*- and *O*-alkylated products that were separated by flash chromatography (Scheme 2).



2, R' = 4-CH_3
3, R' = H

a) $H_2NCH_2CH_2NH_2$ p-TsOH, b) n-BuLi, THF, aryl ester, c) p-TsOH

Scheme 1.



Scheme 2.

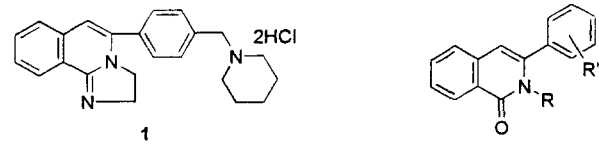


Fig. 1.

RESULTS AND DISCUSSION

The *in vitro* antitumor activities of 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (**1**), 5-(4'-methylphenyl)-2,3-dihydroimidazo[2,1-*a*]isoquinoline (**2**) and 5-phenyl-2,3-dihydroimidazo[2,1-*a*] isoquinoline (**3**) are equally very good (1~5 μg/ml against Abelson 8.1 tumor cell lines, Houlihan *et al.*, 1995a). We have chosen compound **2** as a lead to study the effects of N-2 substituent in *in vitro* antitumor activities against five different human tumor cell lines because compound **2** is equipotent to 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*] isoquinoline (**1**) that is in clinical trials. N-Ethyl-3-(4'-methylphenyl)isoquinolin-1-one (**5**) is one type of bioisosteres of compound 2 since compound **5** has an ethyl group at N-2 and it also has a carbonyl group which could be an equivalent to the imine in the dihydroimidazo ring portion of the compound **2**. The *in vitro* antitumor activity of compound **5** is the same as compound **1** (Table I). Compounds **6** (*N*-allyl), **8** (*N*-propargyl), and **12** (*N*-carbamoylmethyl)) showed slightly better activity than compound **5** but *N*-cyanomethyl substituted compound (**10**) showed no activity. *O*-Alkylated compounds **7, 9, 11, 13** and **15** are another type of bioisosteres which represent compounds with bond cleavage between C-3 and N-4 of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines. Both *N*-, *O*-allyl and *N*-, *O*-cyanomethyl substituted compounds (**6, 7, 10, 11**) displayed similar activity. *N*-Propargyl and *N*-carbamoylmethyl substituted compounds (**8, 12**) showed better activity than their *O*-substituted counterparts (**9, 13**). Interestingly *O*-(3-hydroxypropyl) substituted compound (**15**) exhibited the best activity which is about 3-5 times better than compound **1**.

Table I. *In vitro* antitumor activity against human tumor cell lines[a] (ED_{50} μg/ml)

	A549	SK-OV-3	SK-MEL-2	HCT-15	XF-498
1	18.0	14.9	12.3	11.1	11.9
4	8.5	6.3	5.4	3.9	14.2
5	18.4	28.2	18.4	20.0	14.5
6	11.3	14.5	11.6	12.2	8.3
7	14.4	20.8	15.3	10.7	17.8
8	17.1	19.9	19.1	7.8	14.8
9	21.1	>30	>30	12.9	26.5
10	>30	>30	>30	>30	>30
11	>30	>30	>30	>30	>30
12	13.3	7.3	11.8	15.6	11.0
13	>30	>30	>30	>30	>30
15	3.9	4.1	4.2	2.1	4.0
Doxorubicin	0.09	0.08	0.13	0.65	0.16

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

CONCLUSION

Ethyl, allyl, propargyl, cyanomethyl, carbamoylmethyl, 3-hydroxypropyl substituted 3-arylisoquinolinone compounds, which are bioisosteres of the 5-aryl substituted 2,3-dihydroimidazo[2,1-*a*]isoquinolines, were synthesized and tested for their *in vitro* antitumor activity. *O*-(3-Hydroxypropyl) substituted compound (**15**) exhibited the best activity which is 3-5 times better than compound **1**.

EXPERIMENTAL SECTION

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

N-Methyl-*o*-toluamide, *p*-tolunitrile, ethyl iodide, allyl bromide, borane-tetrahydrofuran complex (1 M), propargyl bromide, bromoacetonitrile were purchased from Aldrich Chemical Company. 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. All other reagents and solvents were of extra pure grade and were obtained from local suppliers.

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 δ (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, bm=broad multiplet. 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.

Antitumor test (*in vitro*)

Antitumor 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 hrs. 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 hrs. The protein stain assay was performed according to SRB method (Skehan *et al.*, 1990, Rubinstein *et al.*, 1990)

5-(4'-Methylphenyl)-2,3-dihydroimidazo[2,1-*a*]isoquinoline HCl (2)

To a stirred solution of 2-(*o*-methylphenyl)imidazoline (1.00 g, 6 mmol) in THF (60 ml) under Ar was added dropwise a 1.6 M solution of *n*-BuLi in hexane (8.1 ml, 13 mmol) at ice-water bath temperature. The mixture was allowed to stir at 0°C for 2 h and cooled to -78°C, and then treated dropwise with a solution of methyl 4-methylbenzoate (1.2 g, 8 mmol) in THF (8 ml). After an additional 0.5 h at -78°C, the reaction mixture was allowed to warm to -10°C, treated with saturated NH_4Cl solution. The mixture was evaporated and treated with ethyl acetate, washed with H_2O, brine, dried (anhydrous $MgSO_4$), and filtered, and the filtrate was evaporated *in vacuo* to give 2.2 g of a dark orange oil. A solution of this crude product (2.2 g) and p-toluenesulfonic acid (120 mg, 0.63 mmol) in toluene (60 ml) was refluxed for 8 h with continuous removal of H_2O (Dean-Stark trap). The toluene was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2, washed successively with H_2O, saturated $NaHCO_3$ solution, and brine. The organic solution was dried (anhydrous $MgSO_4$), filtered, and evaporated *in vacuo* to give the free base. The HCl salt was prepared by dissolving the free base in a mixture of methanol (5 ml) and acetyl chloride (0.47 g, 12 mmol) at ice-water bath temperature and evaporated *in vacuo,* then crystallized from dichloromethane-ethanol to give 1.78 g of white powder (40%): mp >250°C; ^{1}H-NMR (DMSO-d_6) 2.41 (s, 3H), 4.10 (t, 2H), 4.55 (t, 2H), 7.50~8.21 (m, 9H).

5-Phenyl-2,3-dihydroimidazo[2,1-a]isoquinoline HCl (3)

Obtained as a yellow powder (25%) by following the same procedure as described above for compound **2** and replacing methyl 4-methylbenzoate with methyl benzoate: mp >250°C; ^{1}H-NMR (DMSO-d_6) 4.08 (t, 2H), 4.53 (t, 2H), 7.6-8.02 (m, 9H), 8.01 (d, 2H).

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).

N-Ethyl-3-(4'-methylphenyl)isoquinolin-1-one (5)

In a 500 ml round-bottomed flask were placed *o*-tolunitrile (20 g, 170.8 mmol), 30~35% H_2O_2 (68.2 ml, 592.7 mmol), ethanol (200 ml), and 6 N NaOH (6.8 ml), allowed to stand for 12 h. The mixture was heated to 50°C and kept at that temperature for 3 h. The mixture, while still warm, was neutralized with 5% H_2SO_4, cooled to room temperature, extracted with CH_2-

Cl_2, dried (anhydrous $MgSO_4$), filtered, evaporated *in vacuo* to give 20 g of *o*-toluamide as white solid (100%): ^{1}H-NMR ($CDCl_3$) 2.50 (s, 3H), 5.72 (bs, 2H), 7.19~7.49 (m, 4H).

To a stirred solution of *o*-toluamide (30 g, 0.22 mol) in THF (300 ml) was added NaH (60% oil dispersion, 8.81 g, 0.22 mol) at ice-water bath temperature under Ar. After stirring for 1 h, a solution of ethyl iodide (41.18 g, 0.26 mol) in THF (200 ml) was added slowly for 12 h at room temperature. The precipitate was filtered, washed with CH_2Cl_2, brine, dried (anhydrous $MgSO_4$), 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, and allowed to stir for 2 h at the same temperature. To this mixture, after cooling to -78°C, was added a solution of methyl 4-methylbenzoate (1.1 g, 7.12 mmol) in THF (2 ml) and the reaction mixture was stirred for 1 h at -78°C, warmed to -10°C, quenched with saturated NH_4Cl, extracted with EtOAc, brine, dried (anhydrous $MgSO_4$), filtered, evaporated *in vacuo* to give 1.95 g of crude product. A solution of this crude product (1.95 g) and *p*-TsOH (0.112 g, 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 (anhydrous $MgSO_4$), 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 (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-Allyl-3-(4'-methylphenyl)isoquinolin-1-one (6)

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 (**6**) and 48 mg of 1-*O*-allyl-3-(4'-methylphenyl)isoquinoline-1-ol (**7**).

***N*-Allyl-3-(4'-methylphenyl)isoquinolin-1-one (6):** 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 (7): 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).

The following compounds were prepared using the procedures described above for compounds **6** and **7**.

***N*-Propargyl-3-(4'-methylphenyl)isoquinolin-1-one (8):** white powder (35%), mp 105~107°C; ^{1}H-NMR ($CDCl_3$) 2.22 (t, 1H), 2.51 (s, 3H), 4.61 (d, 2H), 6.41 (s, 1H), 7.31~8.51 (m, 8H).

1-*O*-Propargyl-3-(4'-methylphenyl)isoquinoline-1-ol (9): white power (60%), mp 91~94°C; ^{1}H-NMR ($CDCl_3$) 2.41 (s, 3H), 2.49 (t, 1H), 5.30 (d, 2H), 7.22~8.33 (m, 9H).

***N*-Cyanometyl-3-(4'-methylphenyl)isoquinolin-1-one (10):** white powder (24%), mp 159~162°C; ^{1}H-NMR ($CDCl_3$) 2.44 (s, 3H), 4.71 (s, 2H), 6.48 (s, 1H), 7.35~8.49 (m, 8H).

1-*O*-Cyanometyl-3-(4'-methylphenyl)isoquinoline-1-ol (11): white power (40%), mp 100~101°C; ^{1}H-NMR ($CDCl_3$) 2.42 (s, 3H), 5.30 (s, 2H), 7.35 (s, 1H), 7.42~8.25 (m, 8H).

***N*-Carbamoylmethyl-3-(4'-methylphenyl)isoquinolin-1-one (12):** To a solution of *N*-cyanoacetyl-3-(4'-methylphenyl)isoquinolin-1-one (**10**) (1.0 g, 2.25 mmol) in ethanol (15 ml) were added 30~35% H_2O_2 (4.2 ml) and 6 N NaOH (1.2 ml) and the mixture was allowed to stand overnight then warmed to 50°C and kept for 3 h at the same temperature. The reaction mixture was neutralized with 5% H_2SO_4 and cooled to room temperature, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and evaporated. Flash chromatography of the residue afforded 0.7 g (66%) of white solid.: mp 124~128°C; ^{1}H-NMR ($CDCl_3$) 2.43 (s, 3H), 3.42 (s, 2H), 6.43 (s, 1H), 7.20~8.51 (m, 8H); IR (KBr, cm^{-1}) 3395, 3205, 1710.

1-*O*-Carbamoylmethyl-3-(4'-methylphenyl)isoquinoline-1-ol (13): was prepared from 1-*O*-cyanoacetyl-3-(4'-methylphenyl)isoquinoline-1-ol (**11**) using the same procedure as above to give a white solid (61%): mp 220~223°C; ^{1}H-NMR ($CDCl_3$) 2.41 (s, 3H), 5.20 (s, 2H), 7.22~8.29 (m, 9H); IR (KBr, cm^{-1}) 3400, 3195, 1710.

***N*-(3-Hydroxypropyl)-3-(4'-methylphenyl)isoquinolin-1-one (14):** To a solution of *N*-allyl-3-(4'-methylphenyl)isoquinolin-1-one (**6**) (0.2 g, 0.72 mmol) in THF (20 ml) was added 1M borane-THF (1.8 ml, 1.8 mmol)

at ice-water bath temperature for 15 min. After stirring for 2 h at 0°C, water (2 ml), 3 N NaOH (0.4 ml, 1.1 mmol) and 30~35% H_2O_2 (0.4 ml) were added and the mixture was stirred for 10 min. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. Flash chromatography of the residue afforded 0.12 g (60%) of white powder.: mp 88~90°C; ^{1}H-NMR ($CDCl^3$) 1.61 (t, 2H), 2.43 (s, 3H), 3.43 (m, 2H), 3.91 (bs, 1H), 4.18 (t, 2H), 6.45 (s, 1H), 7.37-8.51 (m, 8H).

1-*O*-(3-Hydroxypropyl)-3-(4'-methylphenyl) isoquinoline-1-ol (15): was prepared from 1-O-allyl-3-(4'-methylphenyl)isoquinoline-1-ol (**7**) using the same procedure as above to give a yellow oil (75%): ^{1}H-NMR ($CDCl_3$) 2.21 (s, 3H), 2.40 (s, 2H), 3.76 (m, 2H), 4.86 (t, 2H), 7.22~8.27 (m, 9H).

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