Introduction of Heterocycles at the 2-Position of Indoline as Ester Bioisosteres

Sunkyung Lee, Kyu Yang Yi,* and Sung-eun Yoo

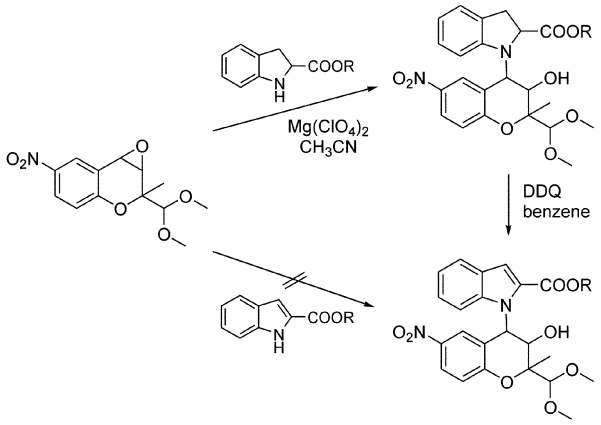
Medicinal Science Division, Korea Research Institute of Chemical Technology,
P.O. Box 107, Yoosung-gu, Daejeon 305-600, Korea
Received November 25, 2003

In this study, we attempted to prepare compounds with heterocyclic replacements for metabolically unstable esters of benzopyranyl indole-2-carboxylic esters, which showed good *in vitro* and *in vivo* cardioprotective efficacies possibly through the opening of mitochondrial ATP-sensitive potassium channel (K_{ATP}). Initially, we tried to construct indolin-2-yl-heterocycles using unprotected indoline-2-carboxylic acid, but the cyclization was proceeded with oxidation of the indoline ring to the indole, which didn't react with benzopyranyl epoxide. Thus we introduced *N*-Boc group to deplete the electron density of the indoline ring. We successfully prepared various indolin-2-yl-heterocycles by the cyclization of the building blocks including carboxamide, β-hydroxy amide, hydrazide, nitrile starting from *N*-Boc-indoline-2-carboxylic acid.

Key Words : *N*-Boc protection, Ester bioisostere, Indolin-2-yl-heterocycles

Introduction

In previous study, we found that benzopyranyl indole-2-carbocylic ester analogs showed good *in vitro* and *in vivo* cardioprotective efficacies possibly through the opening of mitochondrial ATP-sensitive potassium channel (K_{ATP}).[1] Regardless the good efficacies of the compounds, we were concerned on the susceptibility of the ester group to metabolic cleavage. Then, as a starting point in the design, the hydrolytically stable bioisosteres of the ester functionality in benzopyranyl indoles were considered. In this paper we describe the synthesis of various indolin-2-yl-heterocycles, bioisosterically replaced for ester group including oxazole, oxadiazole, and tetrazole.

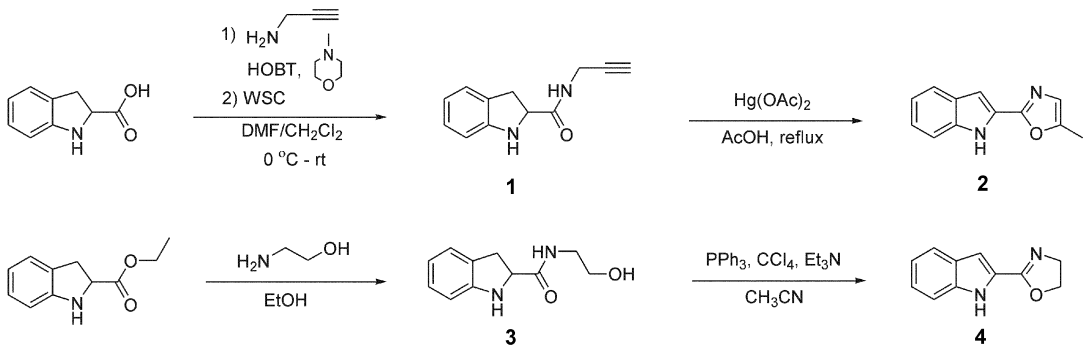


Scheme 1

Results and Discussion

As shown in Scheme 1, previously we prepared benzopyranyl indoline-2-carboxilic ester analogs from optically pure benzopyranyl epoxides with the indolines by epoxide opening in the presence of magnesium perchlorate in CH_3CN.[2] The same reaction with an indole didn't give any reasonable yield of products under various conditions, but the oxidation of benzopyranyl indolines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided desired benzopyranyl indoles in good yields.[1]

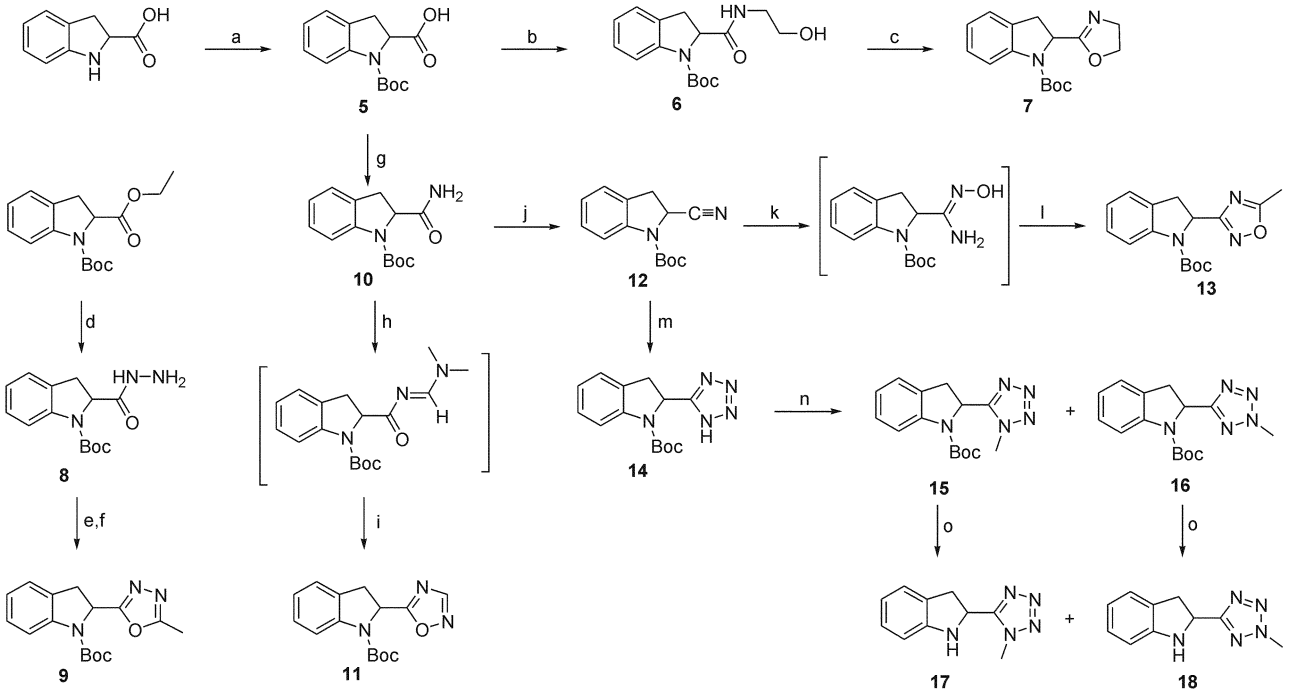
Primarily, we attempted to prepare indoline compounds with heterocyclic replacements for esters by construction of



1 **2** **3** **4**

Scheme 2

*To whom correspondence should be addressed: Tel: +82-42-860-7143; Fax: +82-42-861-1291; e-mail: kyyi@krict.re.kr



Scheme 3. *Reagents and conditions*: (a) Et_3N, $(Boc)_2O$, dioxane; (b) ethanolamine, DCC, HOBT, CH_2Cl_2; (c) DAST, K_2CO_3, CH_2Cl_2; (d) $NH_2NH_2{\cdot}H_2O$, CH_3OH; (e) $CH_3C(OEt)_3$, CH_3OH; (f) *t*-BuOK, *t*-BuOH; (g) $ClCO_2Et$, NH_3(g), THF; (h) DMFDMA; (i) NH_2OH, AcOH, dioxane; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (k) NH_2OH, EtOH; (l) Ac_2O; (m) NaN_3, $Et_3N{\cdot}HCl$, toluene; (n) CH_3I, K_2CO_3, DMF; (o) TFA, CH_2Cl_2.

the ring from indoline-2-carboxylic acid (Scheme 2). The acid was smoothly coupled with propargylamine using water soluble carbodiimide (WSC) to give the amide **1**, and following treatment of **1** with $Hg(OAc)_2$ in acetic acid gave the cyclized oxazole **2**[3] with an additional oxidation of the indoline ring to the indole. The 2-hydroxyethylamide **3** was cyclized to oxazoline through the amide-*O*-triphenylphosphonium salt in the presence of triphenylphosphine/CCl_4,[4] which oxidaized the indoline to the indole, too. The indoline seemed to readily oxidize to the indole, presumably due to the high electron density.[5] Thus we decided to deplete the electron density by *N*-Boc protection.

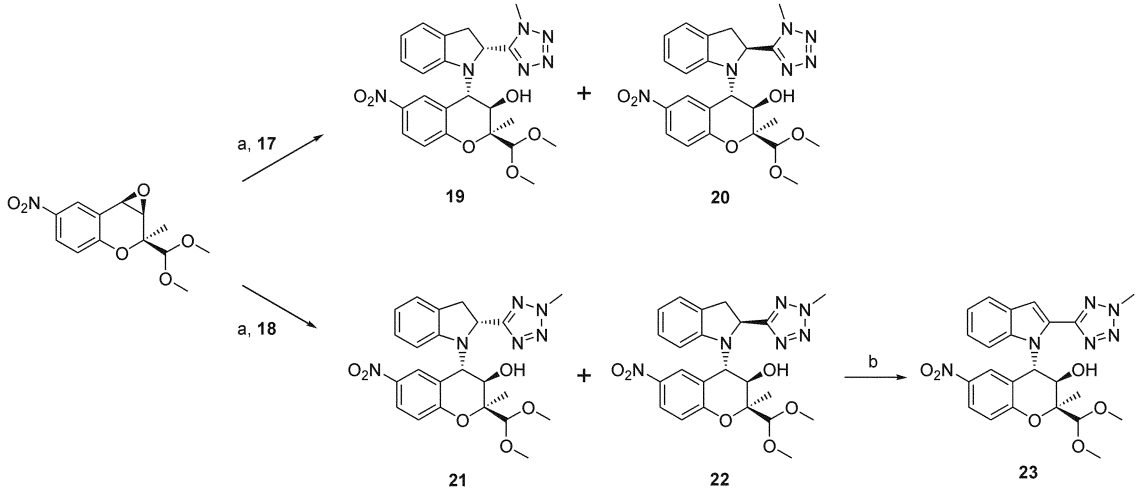
We prepared indolin-2-yl-heterocycles by the cyclization of the building blocks including *β*-hydroxy amide **6**, hydrazide **8**, carboxamide **10**, and nitrile **12**, starting from *N*-Boc-indoline-2-carboxylic acid **5** (Scheme 3).

N-Boc-protected compound **5** was readily obtained from indoline-2-carboxylic acid using di-*t*-butylcarbonate in the presence of triethylamine in 94% yield. The acid **5** was converted to *β*-hydroxy amide **6**, which was cyclized to oxazoline **7** with diethylaminosulfur trifluoride (DAST).[6] The dehydrative ring-closure using DAST gave the higher yield (91%) than Mitsunobu condition (62%).

Synthesis of 5-methyl-1,3,4-oxadiazole **9** was achieved by treatment of ester with hydrazine followed by cyclization with triethyl orthoacetate.[7] The reaction of carboxamide **10** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) and subsequent cyclization of the intermediate amidine with hydroxylamine afforded 1,2,4-oxadiazole **11**.[8] 5-Methyl-1,2,4-oxadiazole **13** was obtained in similar method through *N*-hydroxy amidine precursor from nitrile **12**.[9] The required nitrile **12** was prepared by dehydration of carboxamide **10**. We employed the Swern oxidation conditions[10] for this transformation using the "activated" dimethyl sulfoxide species, because of acid-sensitive *N*-Boc group.[11] It has been reported that both acid-sensitive (epoxide, acetonide, silyl, *N*-Boc, *N*-Cbz) and alkaline-sensitive groups (Ac, Bz, ester, silyl) were completely unaffected under this mild conditions.[12]

The tetrazole **14** was obtained from the nitrile **12** using the classical triethylamine hydrochloride/sodium azide procedure in excellent yield (91%).[13] The *N*-methylation of tetrazole gave the regioisomeric 1-methyl (**15**, 46%), and 2-methyltetrazole (**16**, 51%), which were assigned by ^{1}H nmr specta. The *N*-methyl peak of 1-methytetrazole **15** was very broad presumably due to the restriction of rotation by *N*-Boc group, while that of 2-methyltetrazole **16** was very sharp. *N*-Boc group of both tetrazoles (**15**, **16**) were deprotected under acidic condition (TFA : CH_2Cl_2 = 1 : 1). Resulting racemic terazole indoline compounds (**17**, **18**) were smoothly reacted with optically pure (2*S*, 3*R*, 4*R*) epoxide in the presence of magnesium perchlorate to yield the benzopyranyl indolines (**19**-**22**) as shown in Scheme 4.[14] The reactions provided two separable diastereoisomers at indoline-2-position, respectively, of which absolute stereochemistry was confirmed by the synthesis of authentic compound using commercially available (–)-(*S*)-indoline-2-carboxylic acid as a starting material. The indole compound **23** was prepared by oxidation of the corresponding indoline (**21**, **22**) with DDQ in good yield (91%).

With the benzopyranyl indol-2-yl-heterocycles in hand,



Scheme 4. *Reagents and conditions*: (a) $Mg(ClO_4)_2$, CH_3CN; (b) DDQ, benzene.

we will continuously study the anti-ischemic effects of these compounds to expect the increased metabolic stabilities as well as efficacies.

Conclusion

We prepared various indolin-2-yl-heterocycles, bioisosterically replaced for ester group by the construction of the heterocyclic ring starting from *N*-Boc-indoline-2-carboxylic acid to avoid oxidation of the indoline ring to the indole by the depletion of electron density of the indoline ring.

Experimental Section

Chemistry. Anhydrous solvents were dried by conventional methods. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. For purification of products by column chromatography, Merck silica gel 60 (230-400 mesh) was used. ^{1}H NMR spectra were recorded on a Varian Gemini 200 with TMS as an internal standard. Chemical shifts are reported in δ (ppm). Mass spectra were obtained with a JEOL JMS-DX 303 instrument by using electro impact techniques.

Indoline-2-(*N*-propargyl)carboxamide (1). To a solution of indoline-2-carboxylic acid (500 mg, 3.1 mmol), 1-hydroxybenzotriazole (430 mg, 3.1 mmol), *N*-methylmorpholine (0.6 mL, 5.1 mmol), and propargylamine (0.2 mL, 3.0 mmol) in CH_2Cl_2-DMF (1 : 1, 40 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (300 mg, 3.1 mmol) at 0 °C. The solution was stirred overnight at room temperature and washed with water, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in CH_2Cl_2) to yield the propargylamide **1** (220 mg, 36%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.22 (m, 1H), 3.09 (dd, 1H, J = 8.6, 16.5 Hz), 3.60 (dd, 1H, J = 10.8, 16.5 Hz), 4.09 (m, 2H), 4.45 (dd, 1H, J = 8.8, 10.7 Hz), 6.74-6.87 (m, 2H), 7.05-7.13 (m, 2H), 7.31 (brs, 1H).

2-(5-Methyl-1,3-oxazol-2-yl)-1*H*-indole (2). A solution of the compound **1** (140 mg, 0.7 mmol) and $Hg(OAc)_2$ (27 mg, 0.077 mmol) in acetic acid (8 mL) was heated at reflux for 3 h. All volatiles were removed under reduced pressure, and to the residue was added an aqueous solution of saturated K_2CO_3. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in CH_2Cl_2) to yield the oxazole **2** (75 mg, 54%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.77 (s, 3H), 6.22 (s, 1H), 7.28-7.41 (m, 2H), 7.53 (s, 1H), 7.85 (dd, 1H, J = 1.8, 7.8 Hz), 8.0 (d, 1H, J = 8.3 Hz), 9.9 (brs, 1H).

Indoline-2-(*N*-2-hydroxyethyl)carboxamide (3). To a solution of indoline-2-carboxylic acid ethyl ester (191 mg, 1.0 mmol) in ethanol (10 mL) was added 2-ethanolamine (0.3 mL, 6.0 mmol). The solution was heated at reflux for 4 h, and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol in CH_2Cl_2) to yield the compound **3** (189 mg, 92%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.02 (m, 1H), 3.29-3.64 (m, 5H), 4.32 (dd, 1H, J = 9.0, 10.6 Hz), 6.69 (m, 2H), 7.03 (m, 2H).

2-(1,3-Oxazolin-2-yl)-1*H*-indole (4). To a solution of the compound **3** (50 mg, 0.24 mmol), Et_3N (0.12 mL, 1.0 mmol) and CCl_4 (0.1 mL, 1.0 mmol) in CH_3CN (5 mL) was added a solution of triphenylphosphine in CH_3CN (3 mL) dropwise over 30 min, and the reaction mixture was stirred for 3 h at room temperature, filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in CH_2Cl_2) to yield the compound **4** (28 mg, 62%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.09 (t, 2H, J = 9.4 Hz), 4.50 (t, 1H, J = 9.4 Hz), 7.05-7.40 (m, 4H), 7.66 (d, 1H, J = 8.2 Hz), 9.94 (brs, 1H).

1-(*tert*-Butoxycarbonyl)-indoline-2-carboxylic acid (5). To a solution of indoline-2-carboxylic acid (5.0 g, 30.7 mmol) and Et_3N (12.8 mL, 92 mmol) in THF (50 mL) was added di-*tert*-butylcarbonate (13.4 g, 61.4 mmol), and the

reaction mixture was continuously stirred for 6 h at room temperature. The suspension was concentrated under reduced pressure, and the residue was dissolved in an aqueous solution of 1N NaOH, and washed with ether. The aqueous layer was acidified with conc. HCl until the solution became cloudy, and was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol in CH_2Cl_2) to yield the compound **5** as an off white solid (7.6 g, 94%); ^{1}H NMR (200 MHz, CD_3OD): δ 1.27(s, 9H), 3.1-3.6 (m, 2H), 4.91 (m, 1H), 6.90-7.22 (m, 3H), 7.80 (m, 1H).

1-(*tert*-Butoxycarbonyl)-indoline-2-(*N*-2-hydroxyethyl)-carboxamide (6). To a solution of the compound **5** (1.0 g, 3.8 mmol) in CH_2Cl_2 (20 mL) were added ethanolamine (0.46 mL, 7.6 mmol), dicyclohexylcarbodiimide (862 mg, 4.18 mmol), and 1-hydroxybenotriazole (564 mg, 4.19 mmol). The reaction mixture was stirred overnight at room temperature, and washed with an aqueous solution of 0.5 N NaOH. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol in CH_2Cl_2) to yield the compound **6** (1.12 g, 97%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (d, 1H, J = 6.0 Hz), 3.42 (s, 3H), 3.49 (s, 3H), 4.35-4.44 (m, 3H), 4.57 (m, 1H), 7.04 (d, 1H, J = 8.0 Hz), 8.10-8.24 (m, 2H); MS 306 [M^+].

1-(*tert*-Butoxycarbonyl)-2-(oxazolin-2-yl)-indoline (7). To a solution of the amide **6** (90 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) were added diethylaminosulfur trifluoride (42 μL, 0.32 mmol) and K_2CO_3 (80 mg, 0.58 mmol) at -78 °C. The reaction mixture was warmed to room temperature and stirred for 4 h, then washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in dichloromethane) to yield the compound **7** (77 mg, 91%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (s, 9H), 3.14 (dd, 1H, J = 4.2, 14.0 Hz), 3.48 (dd, 1H, J = 10.6, 14.1 Hz), 3.82 (m, 2H), 4.23 (m, 2H), 5.10 (m, 1H), 6.93 (1H, dd, J = 7.3, 7.5 Hz), 7.14 (m, 2H), 7.8 (br, 1H); MS 288 [M^+].

1-(*tert*-Butoxycarbonyl)-indoline-2-carboxyhydrazide (8). Ethyl 1-(*tert*-butyloxycarbonyl)indoline-2-carboxylate (1.0 g, 3.0 mmol) was dissolved in methanol (10 mL) and hydrazine hydrate (1.5 mL), and the solution was heated at reflux for 20 h. An acidic solution was washed with CH_2Cl_2 (10 mL), and basified with an aqueous solution of 2 N NaOH to pH 8-9, then extracted with ethyl acetate (15 mL × 2). Evaporation of the solvents yielded the hydrazide **8** (920 mg, 96%), which was used without further purification; ^{1}H NMR (200 MHz, $CDCl_3$/DMSO): δ 1.53 (s, 9H), 3.09 (dd, 1H, J = 4.9, 14.7 Hz), 3.44 (dd, 1H, J = 11.0, 15.5 Hz), 4.78 (dd, 1H, J = 5.1, 11.0 Hz), 6.92 (dd, 1H, J = 7.3, 7.5 Hz), 7.12 (d, 2H), 7.65 (br, 1H), 8.91 (br, 1H).

1-(*tert*-Butoxycarbonyl)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-indoline (9). A solution of the hydrazide **9** (300 mg, 1.08 mmol) and triethyl orthoacetate (1.4 mL, 10.8 mmol) in methanol (5 mL) was heated at reflux for 9 h and cooled, then concentrated under reduced pressure. The residue was dissolved in *tert*-butanol (5 mL), and potassium *tert*-butoxide (180 mg, 1.6 mmol) was added to it. The reaction mixture was heated at reflux for 11 h, and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and an aqueous solution of 2 M K_2CO_3. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 1 : 1) to afford the oxadiazole **9** (100 mg, 31%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.49 (s, 3H), 3.28 (dd, 1H, J = 3.9, 16.5 Hz), 3.65 (dd, 1H, J = 10.7, 16.5 Hz), 5.68 (dd, 1H, J = 4.0, 10.6 Hz), 6.99 (dd, 1H, J = 7.3, 7.4 Hz), 7.2 (m, 2H), 7.79 (br, 1H); MS 301 [M^+].

1-(*tert*-Butoxycarbonyl)-indoline-2-carboxamide (10). To a solution of the acid **5** (2.63 g, 10 mmol) and Et_3N (2.8 mL, 20 mmol) in THF (100 mL) was added ethyl chloroformate (1.3 mL, 12 mmol) dropwise at 0 °C, and it was stirred for 30 min. Gaseous NH_3 was bobbled into the solution for 30 min, and the reaction mixture was continuously stirred for 2 h at room temperature. Water was added to the mixture, which was extracted with ethyl acetate. The organic layer was washed with brine and water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 1 : 1) to yield the compound **10** (2.5 g, 95%) as an off white solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.53 (s, 9H), 3.08 (dd, 1H, J = 4.3, 16.3 Hz), 3.52 (dd, 1H, J = 11.4, 16.3 Hz), 4.82 (m, 1H), 6.88 (dd, 1H, J = 7.0, 7.3 Hz), 7.14 (m, 2H), 7.84 (br, 1H); MS 262 [M^+].

1-(*tert*-Butoxycarbonyl)-2-(1,2,4-oxadiazol-5-yl)-indoline (11). A solution of the amide **10** (1.0 g, 3.8 mmol) in dimethylformamide dimethyacetal (4 mL) was heated at reflux for 3 h, and was concentrated under reduced pressure. To the residue an 1 M solution of hydroxylamine hydrochloride in 1 N NaOH (742 mg, 10.5 mL), dioxane (10.5 mL), and acetic acid (14 mL) were added. The resulting mixture was heated at reflux for 4 h, and all volatiles were removed under reduced pressure. To the residue an aqueous solution of saturated $NaHCO_3$ was added, and it was extracted with CH_2Cl_2. The organic layer was washed with an aqueous solution of saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give an off white solid (510 mg, 47%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.21 (dd, 1H, J = 3.9, 16.5 Hz), 3.79 (dd, 1H, J = 11.0, 16.6 Hz), 5.72 (dd, 1H, J = 3.7, 10.8 Hz), 7.03 (dd, 1H, J = 7.3, 7.4 Hz), 7.13-7.28 (m, 2H), 7.91 (br, 1H), 8.37 (s, 1H).

1-(*tert*-Butoxycarbonyl)-indoline-2-carbonitrile (12). To a solution of the amide **10** (4.0 g, 15.2 mmol) and DMSO (2.16 mL, 25.9 mmol) in CH_2Cl_2 (40 mL) was added a solution of oxalyl chloride (1.73 mL, 19.8 mmol) in CH_2Cl_2 (10 mL) dropwise at -78 °C. After stirring for 15 min at -78 °C, Et_3N (1.73 mL, 19.8 mmol) was added dropwise to the mixture, and it was stirred for 1 h at -78 °C. The reaction

mixture was quenched with water (50 mL), warmed to room temperature, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 4 : 1) to give the nitrile **12** (2.38 g, 64%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61 (s, 9H), 3.27-3.68 (m, 2H), 5.08 (br, 1H), 7.06 (dd, 1H, *J* = 7.5, 8.0 Hz), 7.20 (m, 2H), 7.79 (br, 1H); MS 244 [M^+].

1-(*tert*-Butoxycarbonyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)-indoline (13). The nitrile **12** (1.0 g, 4.08 mmol), hydroxylamine hydrochloride (848 mg, 12.24 mmol), and K_2CO_3 (1.04 g, 8.16 mmol) were added to boiling ethanol (15 mL), and it was heated at reflux for 12 h. After evaporation of ethanol, the residue was dried over P_2O_5 in high vacuum, and was treated with acetic anhydride (15 mL) at 0 ^{o}C. The mixture was heated at reflux for 2 h, and excess acetic anhydride was removed under reduced pressure. The residue was treated with an aqueous solution of saturated K_2CO_3, then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the compound **13** (280 mg, 22%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (s, 9H), 2.42 (s, 3H), 3.2-3.6 (m, 2H), 5.02 (m, 1H), 7.04 (dd, 1H, *J* = 7.3, 7.3 Hz), 7.20 (m, 2H), 7.41 (br, 1H).

1-(*tert*-Butoxycarbonyl)-2-(terazol-5-yl)-indoline (14). To a solution of the nitrile compound **12** (600 mg, 2.46 mmol) in toluene (50 mL) were added NaN_3 (1.28 g, 19.7 mmol) and triethylamine hydrochloride (2.71 g, 19.7 mmol) and the reaction mixture was stirred at 80 ^{o}C for 3 h. To the mixture water was added and the layers were separated. The aqueous layer was extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol in CH_2Cl_2) to give an off white solid (640 mg, 91%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.09 (m, 1H), 3.76 (dd, 1H, *J* = 11.0, 16.9 Hz), 5.85 (dd, 1H, *J* = 4.5, 11.0 Hz), 7.00 (dd, 1H, *J* = 7.0, 7.9 Hz), 7.22 (m, 2H), 7.78 (br, 1H).

1-(*tert*-Butoxycarbonyl)-2-(1-methylterazol-5-yl)-indoline (15). To a solution of the compound **14** (450 mg, 1.57 mmol) in DMF were added K_2CO_3 (420 mg, 3 mmol) and CH_3I (180 mL, 3 mmol), and the reaction mixture was stirred at room temperature for 5 h. To the mixture water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give the regioisomers, 1-methyltetrazole compound (**15**, 220 mg, 46%, R_f = 0.24 in hexane : ethyl acetate = 2 : 1), and 2-methyltetrazole compound (**16**, 240 mg, 51%, R_f = 0.29 in hexane : ethyl acetate = 2 : 1): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.21 (m, 1H), 3.76 (dd, 1H, *J* = 11.6, 15.9 Hz), 4.0 (brs, 3H), 4.59 (m, 1H), 5.81 (m, 1H), 7.07 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.2 (m, 2H), 7.65 (brs, 1H).

1-(*tert*-Butoxycarbonyl)-2-(2-methylterazol-5-yl)-indoline (16). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.19 (dd, 1H, *J* = 3.3, 16.3 Hz), 3.68 (dd, 1H, J = 10.4, 16.1 Hz), 4.27 (s, 3H), 5.78 (dd, 1H, *J* = 3.2, 10.4 Hz), 6.98 (dd, 1H, *J* = 7.3, 7.5 Hz), 7.23 (m, 2H), 7.80 (brs, 1H).

2-(1-Methylterazol-5-yl)-indoline (17). A solution of the compound **15** (200 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) was stirred for 4 h at room temperature, and the solvent was evaporated under reduced pressure. To the residue an aqueous solution of saturated $NaHCO_3$ was added carefully, which was extracted with CH_2Cl_2. The organic layer was carefully washed with an aqueous solution of saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 1 : 1) to yield an off white solid **17** (82 mg, 61%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.17 (dd, 1H, *J* = 9.4, 15.8 Hz), 3.63 (dd, 1H, *J* = 10.2, 15.8 Hz), 4.11 (s, 3H), 5.52 (dd, 1H, *J* = 9.7, 10.3 Hz), 6.8 (m, 2H), 7.1 (m, 2H).

2-(2-Methylterazol-5-yl)-indoline (18). Using the compound **16** (200 mg, 0.66 mmol) the same reaction as the preparation of the compound **17** was proceeded to give an off white solid (83 mg, 62%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.5 (m, 2H), 3.63 (dd, 1H, *J* = 10.2, 15.8 Hz), 4.11 (s, 3H), 5.19 (dd, 1H, *J* = 7.3, 8.7 Hz), 6.75 (m, 2H), 7.08 (m, 2H).

1-[(2*S*,3*R*,4*S*)-3,4-Dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2*H*-1-benzopyran-4-yl]-2-(2*R*)-(1-methyltetrazol-5-yl)-indoline (19). The reaction mixture of tetrazole indoline **17** (150 mg, 0.75 mmol), optically pure (2*S*, 3*R*,4*R*) epoxide (210 mg, 0.75 mmol), and $Mg(ClO_4)_2$, (167 mg, 0.75 mmol) in CH_3CN (0.8 mL) was stirred at room temperature for 6 h, and it was concentrated under reduced pressure. Resulting two diastereomers were separated by silica gel column chromatography (hexane : ethyl acetate = 2 : 1), and the isomer (**19**) with 2*R* at indoline ring, faster moving one, was obtained as a pale yellow foam (62 mg, 17%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (s, 3H), 3.2-3.5 (m, 8H), 4.11 (s, 3H), 4.3-4.5 (m, 2H), 5.5-5.8 (m, 2H), 6.6-7.0 (m, 3H), 7.18 (m, 2H), 7.8-8.1 (m, 2H).

1-[(2*S*,3*R*,4*S*)-3,4-Dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2*H*-1-benzopyran-4-yl]-2-(2*S*)-(1-methyltetrazol-5-yl)-indoline (20). From the reaction to prepare the compound **19**, the isomer (**20**) with 2*S* at indoline ring, slower moving one, was obtained as a pale yellow foam (48 mg, 13%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (s, 3H), 3.2-3.8 (m, 7H), 3.9-4.1 (m, 2H), 4.28 (s, 3H), 4.3-4.5 (m, 2H), 5.63 (m, 1H), 6.21 (m, 1H), 6.7-7.0 (m, 3H), 7.16 (m, 1H), 7.8-8.2 (m, 2H).

1-[(2*S*,3*R*,4*S*)-3,4-Dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2*H*-1-benzopyran-4-yl]-2-(2*R*)-(2-methyltetrazol-5-yl)-indoline (21). The same reaction for the preparation of the compound **19** was proceeded except using the tetrazole indoline **18** (150 mg, 0.75 mmol) as a starting material. The isomer (**21**) with 2*R* at indoline ring, faster moving one, was obtained as a pale yellow foam (160 mg, 45%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (s, 3H), 3.41 (s, 3H), 3.48 (s, 3H), 3.61 (m, 2H), 3.99 (s, 3H), 4.19 (m,

1H), 4.32 (m, 1H), 5.13 (d, 1H), 5.38 (m, 1H), 6.5-6.9 (m, 3H), 7.18 (m, 2H), 7.8-8.0 (m, 2H).

1-[(2*S*,3*R*,4*S*)-3,4-Dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2*H*-1-benzopyran-4-yl]-2-(2*S*)-(2-methyltetrazol-5-yl)-indoline (22). From the reaction to prepare the compound **21**, the isomer (**22**) with 2*S* at indoline ring, slower moving one, was obtained as a pale yellow foam (170 mg, 47%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.5-3.7 (m, 2H), 4.21 (m, 1H), 4.42 (s, 3H), 4.5-4.7 (m, 2H), 5.30 (m, 1H), 5.82 (m, 1H), 6.7 (m, 2H), 6.90 (d, 1H, J = 9.0 Hz), 7.12 (m, 1H), 8.02 (dd, 1H, J = 2.8, 7.8 Hz), 8.41 (brs, 1H).

1-[(2*S*,3*R*,4*S*)-3,4-Dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2*H*-1-benzopyran-4-yl]-2-(2-methyltetrazol-5-yl)-1*H*-indole (23). To a solution of indoline compounds (**21**, **22**, 50 mg, 0.104 mmol) in benzene (4 mL) was added DDQ (47 mg, 0.21 mmol) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate (4 mL) and washed with 10% NaOH and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give the pale yellow foam (45.3 mg, 91%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65 (s, 3H), 3.52 (s, 3H), 3.54 (s, 3H), 3.68 (d, 1H, J = 10.2 Hz), 4.45 (s, 3H), 4.48 (d, 1H, J = 10.3 Hz), 4.67 (s, 1H), 6.50 (d, 1H, J = 8.1 Hz), 6.9-7.2 (m, 3H), 7.35 (s, 1H), 7.72 (m, 2H), 8.12 (dd, 1H, J = 1.8, 8.9 Hz).

References

1. Lee, S.; Yi, K.Y.; Kim, S.-K.; Suh, J.; Kim, N. J.; Yoo, S.-e.; Lee, B. H.; Seo, H. W.; Kim, S.-O.; Lim, H. *Europ. J. Med. Chem.* **2003**, *38*, 459.
2. Yoo, S.-e.; Yi, K. Y.; Lee, S.; Suh, J.; Kim, N.; Lee, B. H.; Seo, H. W.; Kim, S.-O.; Lee, D.-H.; Lim, H.; Shin, H. S. *J. Med. Chem.* **2001**, *44*, 4207.
3. Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreves, R. J. *J. Med. Chem.* **1993**, *36*, 1529.
4. Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.
5. Collot, V.; Schmitt, M.; Marwah, A. K.; Norberg, B.; Bourguignon, J.-J. *Tetrahedron Lett.* **1997**, *38*, 8033.
6. (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Wiliams, D. R. *Org. Lett.* **2000**, *2*, 1165. (b) Jones, G.; Butler, D. C.; Richards, C. J. *Tetrahedron Lett.* **2000**, *41*, 9351.
7. Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726.
8. Lin, Y.; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
9. Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLead, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128.
10. Omura, K.; Swern, D. *Tetrahedron Lett.* **1978**, *34*, 1651.
11. Ubukata, M.; Sonoda, T.; Isono, K. *Natural Product Letters* **1992**, *1*, 149.
12. Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* **1997**, *38*, 2099.
13. Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.
14. Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661.