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Synthesis of 3-Fluoro-2-substituted amino-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic Acids Employing the Tandem Double Ring Closure Reaction of *N*-Acetyl-*N*-(2-hydroxyphenyl)anthranilic Acid as the Key Step

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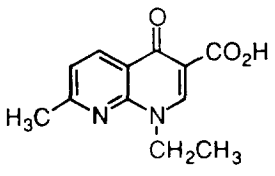
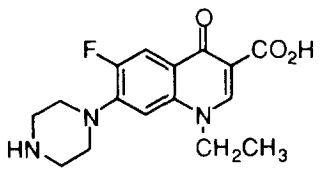
Abstract: A general synthetic method for the preparation of 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acids has been developed making use of the tandem double ring closure reaction of *N*-(2-hydroxyphenyl)anthranilic acid as the key step. 2-(4-Methylpiperazin-1-yl)-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid, an oxygen isostere of a potent antibacterial, A-57,207 was thus synthesized.

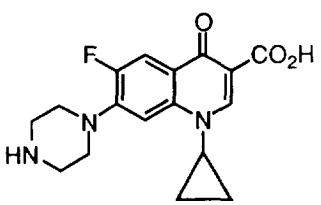
1,4-Dihydro-4-oxoquinoline-3-carboxylic acids having substituents at the 1– and 7–positions, as exemplified by norfloxacin and ciprofloxacin, constitute the basic structural frame for numerous therapeutically important antimicrobials collectively known as quinolones.[1] These antibacterials have become available as a result of systematic and imaginative structural modifications made on nalidixic acid, a prototype antibacterial discovered by Lesher et al.[2] These efforts of structural modifications stretching over several decades are, however, not likely to cease but to continue. The antitumor activity[3] observed recently with quinolone derivatives will undoubtedly foster these research activities. Such efforts of medicinal chemical purpose, consequently, have resulted in the quinolone and related ring systems to emerge as most extensively studied nitrogen heterocycles. In this report, we wish to describe a general synthetic method which we have developed for the preparation of 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acids as well as the synthesis of 2-(4-methylpiperazin-1-yl)-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid, an isostere of a potent antibacterial, A-57,207.



nalidixic acid

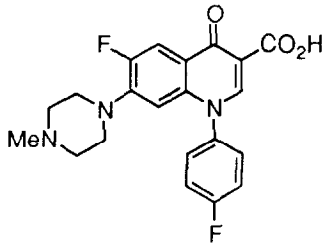


norfloxacin

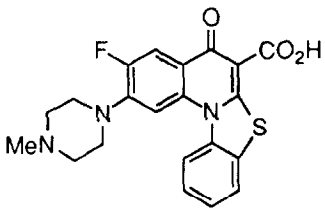


ciprofloxacin

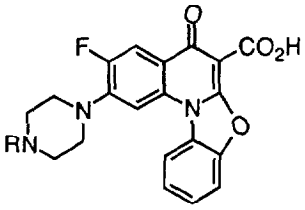
Recently, Chu *et al.*[4] found during a structural modification study that quinolones having an aryl group at the 1-position such as difloxacin are also active with potencies comparable to those having a small alkyl group at the position. It was a discovery of considerable significance in view of the fact that it had been generally believed that a small alkyl group at the 1-position is essential for the antimicrobial activity of quinolones. Subsequently, they observed that conformationally restricted analogs of the 1-aryl quinolones such as A-57,207 (**2**) obtained by bridging the aryl ring to the 2-position of the quinolone by a sulfur atom also possess potent, broad spectrum of antibacterial activities.[5]



difloxacin (**1**)



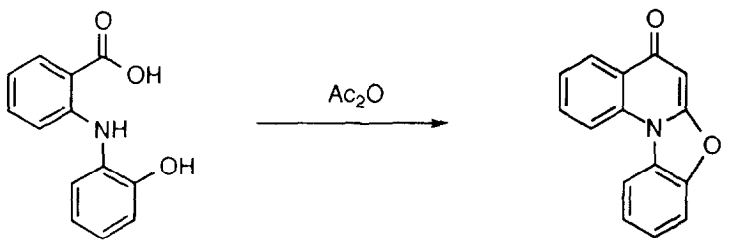
A-57,207 (**2**)



3

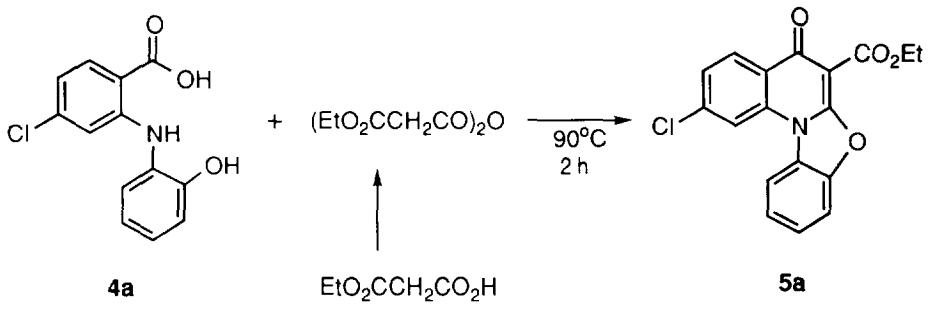
The oxygen analogs of **2** and related compounds, *i.e.*, compounds in which the sulfur in **2** is isosterically replaced with an oxygen atom were thought to be of interest to us. Since they are isosteres of the potent antibacterial, these compounds are expected to have biological activities similar or even superior to that of A-57,207. However, in spite of this expected antibacterial activity these oxygen analogs have not yet been synthesized and tested for their biological activity. We discovered that the synthetic approach[5] that was used for the preparation of **2**, which involves the condensation of ethyl 2,4-dichloro-5-fluorobenzoylacetate with 2-chlorobenzothiazole in the presence of a base to afford the key intermediate for the synthesis is ineffective when chlorobenzoxazole is used in place of 2-chlorobenzothiazole,[6] although the synthetic details are described in the patent literature.[7] We have succeeded in the preparation of these compounds for the first time by a novel approach, making use of the tandem double ring closure reaction of *N*-(2-hydroxyphenyl)anthranilic acid.

In 1974, Kim *et al.* reported that the treatment of *N*-(2-hydroxyphenyl)anthranilic acid with refluxing acetic anhydride affords 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline in good yield (Scheme 1).[8] We

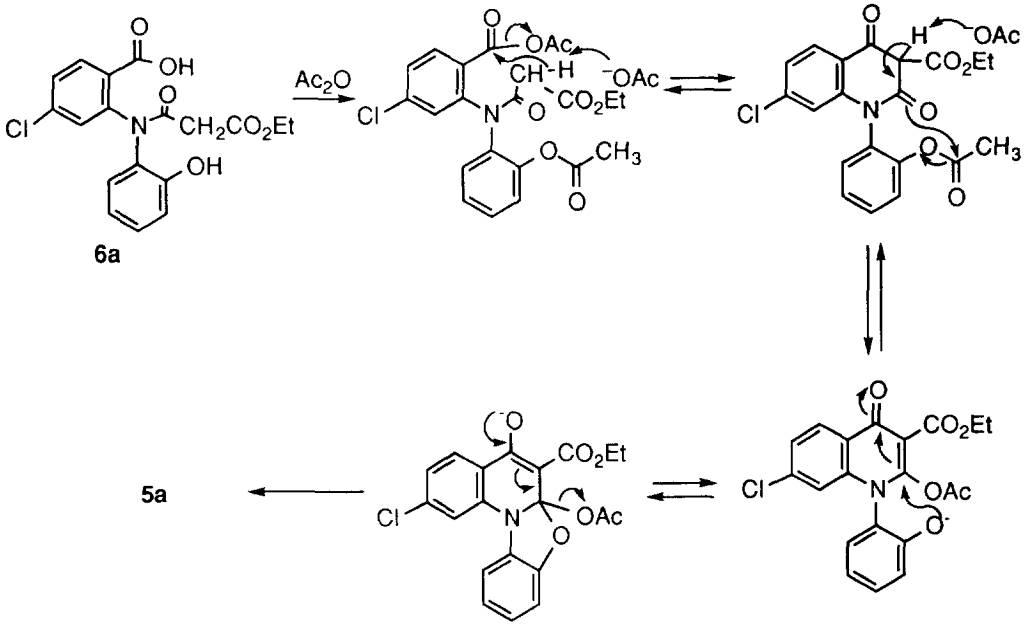


Scheme 1

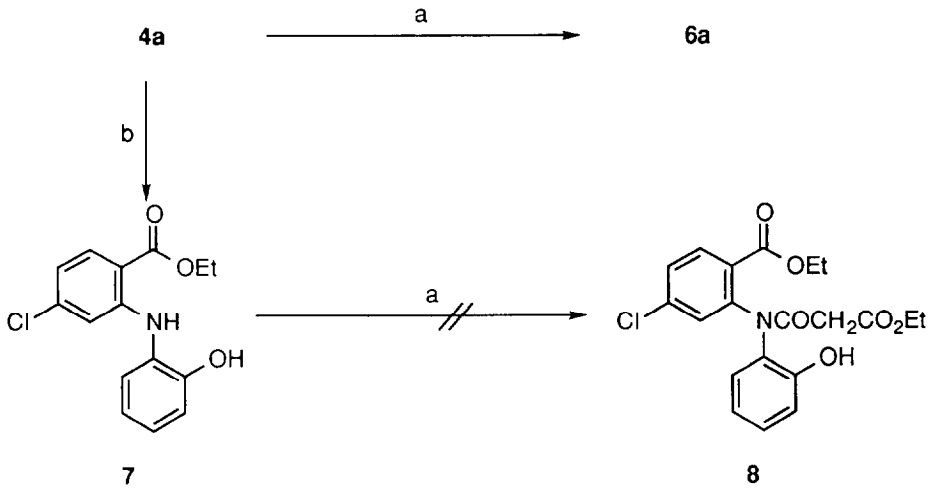
envisioned that the use of ethyl malonic acid anhydride in place of acetic anhydride in the ring formation reaction would provide 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline having an ethoxycarbonyl group at the desired position (**5a**) (Scheme 2). However, when we put the idea in practice by heating **4a** with ethyl malonic acid anhydride, **5a** was indeed obtained but in an extremely poor yield (3%). The reaction mixture gave a complex mixture from which **5a** was isolated by silica gel column chromatography. The yield of the reaction appears to be due to the unstable nature of the anhydride at the high reaction temperature. Accordingly, improvement of the yield was imperative in order for the reaction to be useful for the preparation of the target compounds.



Scheme 2

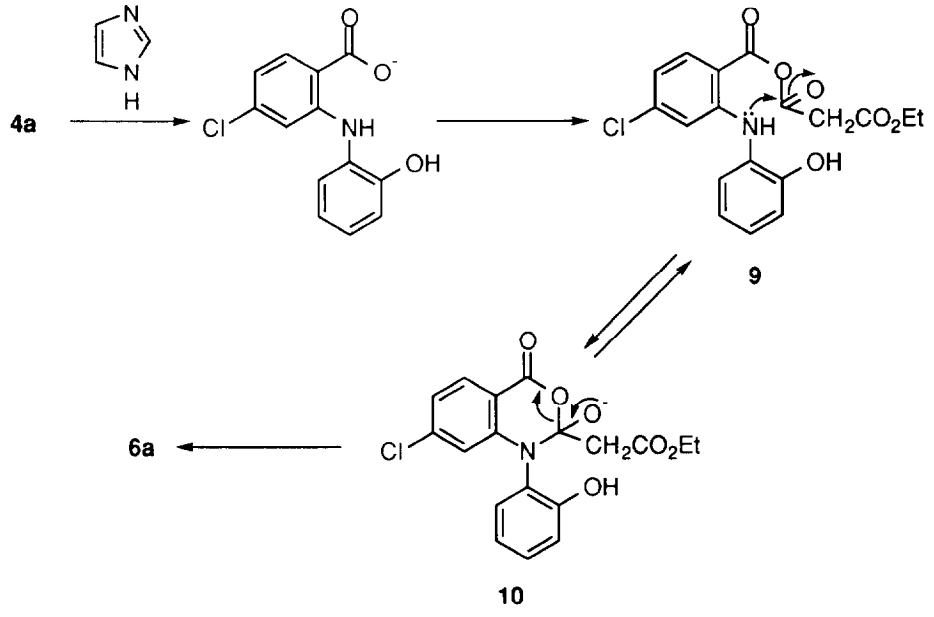


Scheme 3



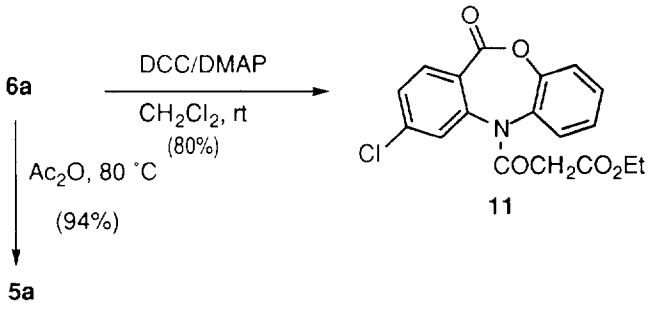
Reagents and conditions: a) $ClCOCH_2CO_2Et$, imidazole (3 eq.), 4 h, 72% b) H^+, EtOH, 18 h

Scheme 4



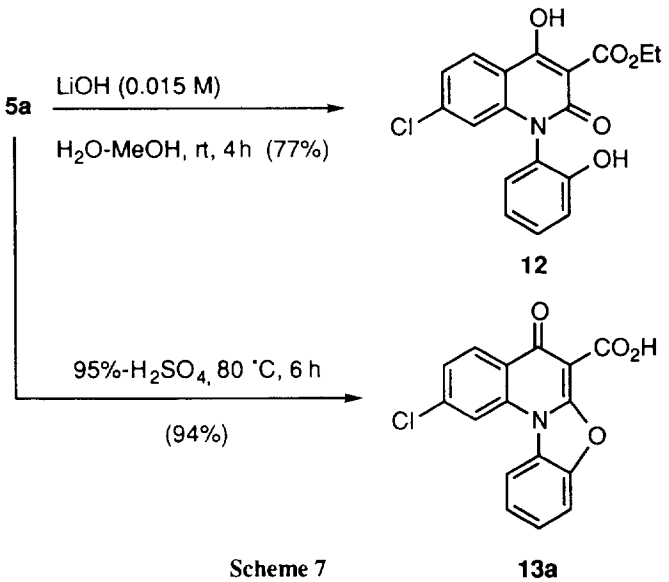
Scheme 5

The proposed reaction mechanism for the tandem double ring closure reaction starts with the initial acetylation of all three functional groups to form an intermediate which undergoes tandem cyclizations to form the quinolone.[8] It was expected from the reaction mechanism that a *N*-acylated compound such as **6a** would serve as a viable intermediate to produce **5a** upon the treatment with acetic anhydride by following the reaction path shown in Scheme 3. In order to test this possibility, the *N*-acylated compound **6a** was prepared. The chemoselective *N*-acylation of **4a** was eventually achieved, after experiencing considerable difficulties initially, by reaction it with ethylmalonyl chloride in the presence of 3 molar equivalents of imidazole (Scheme 4). It appears that under these reaction conditions the acid chloride initially reacts with the carboxylate rather than with the amino group to form an anhydride intermediate which then undergoes the O → N acyl migration, giving **6a** (Scheme 5). In support of this proposal, we observed that the ethyl ester of **4a** fails to undergo *N*-acylation upon treatment with the acid chloride. Only the unreacted starting material was recovered. The treatment of **6a** thus obtained with DCC in methylene chloride afforded oxazepinone **11** in 80% yield, which supports the assigned structure for **6a** (Scheme 6). As anticipated, the treatment of **6a** with an excess of acetic anhydride at 80° C yielded **5a** in 92% yield. The structure of the product was established on the basis of the spectral data and elemental analysis (see experimental section). Attempted hydrolysis of the ester moiety in **5a** under alkaline conditions failed but caused instead the cleavage of the oxazole ring to form **12**, which is not unexpected in the light of literature precedents.[8] On the other hand, under acidic conditions of concentrated sulfuric acid at 80 °C the hydrolysis of the ester took place cleanly, giving **13a** in 94% yield (Scheme 7).

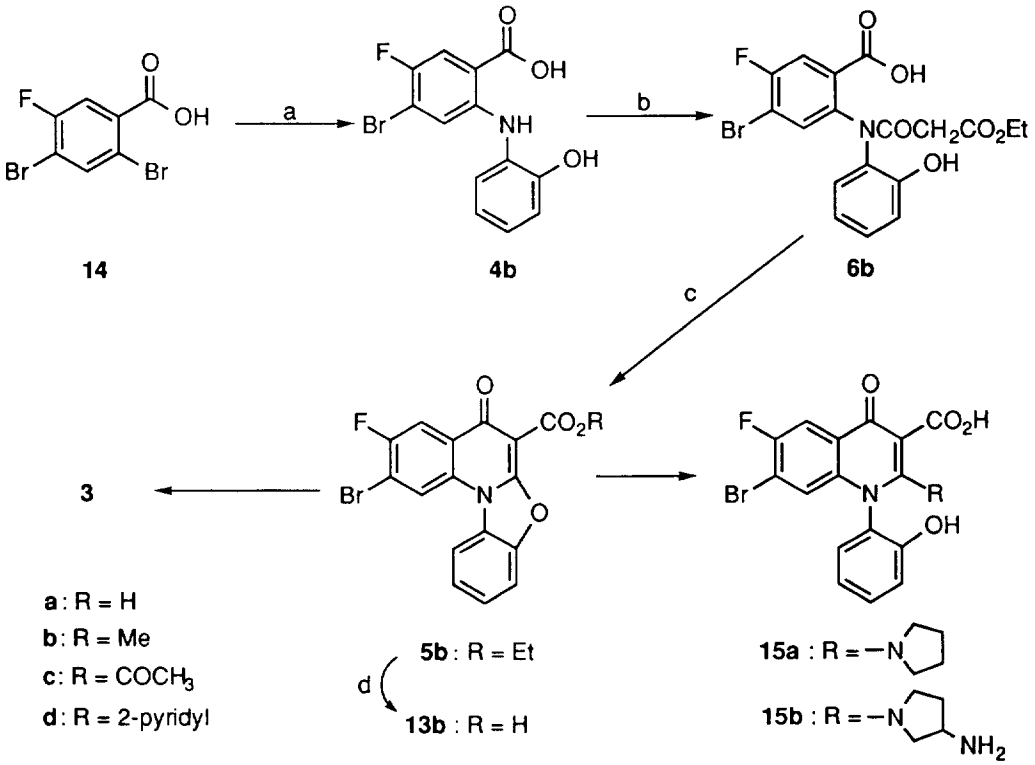


Scheme 6

After establishing the general synthetic scheme for the preparation of potential quinolone antibacterials having benzoxazolo[3,2-*a*]quinoline ring frame, we now turned our attention to the synthesis of the oxygen analogs of A-57,207. The treatment of 2,4-dibromo-5-fluorobenzoic acid potassium salt with 2-aminophenol in the presence of cupric chloride in refluxing *n*-butanol afforded **4b**. The latter compound was then allowed to react with ethyl malonyl chloride in the presence of imidazole in methylene chloride to give **6b**. The tandem double cyclization of **6b** to **5b** was carried out simply by heating unpurified **6b** from the above reaction in acetic anhydride at 80 °C for 3 h, giving **5b** in 60% yield from **4b**. The latter **5b** was then treated with concentrated sulfuric acid at 70 °C for 6 h to give **13b** in 91.4% yield (Scheme 8). The starting material for the synthesis, *i.e.*, 2,4-dibromo-5-fluorobenzoic acid (**14**) was prepared from



Scheme 7

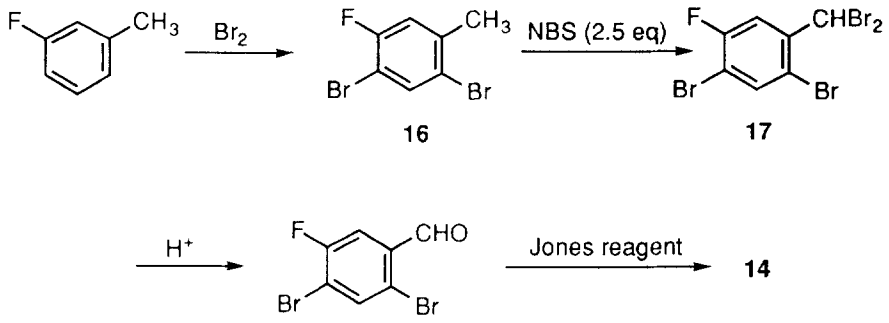


Reagents and conditions: a) 2-aminophenol (2.5 eq.), $CuCl_2$/ *n*-BuOH, 1 h, Δ, 20%; b) i. $ClCOCH_2CO_2Et$, imidazole (3 eq.)/ CH_2Cl_2, 4 h. ii. HCO_2H, 12 h; c) Ac_2O, 80 °C, 1 h, 60% (two steps of b and c); d) 95% H_2SO_4, 80 °C, 6 h, 91.4%.

Scheme 8

3-fluorotoluene in an overall yield of 38% following the reaction path shown in scheme 9. The bromination of 3-fluorotoluene with bromine by a literature method[9] gave 2,4-dibromo-5-fluorotoluene (**16**) in 59% yield. The product (**16**) was treated with 2.5 equivalents of *N*-bromosuccinimide, giving **17** whose dibromomethyl moiety was converted into the corresponding aldehyde under acidic conditions, then the product thus obtained was oxidized without purification with the Jones reagent, giving **14**.

The debromo-amination reaction at the 2-position of **13b** proceeded smoothly when the latter compound was allowed to react with piperazine in 1-methyl-2-pyrrolidinone at 110° C for 3 h, giving **3a** in 59.4% yield (Scheme 8). Similarly, **3b~3d** were prepared (Scheme 8). Interestingly, an attempted debromo-amination with refluxing pyrrolidine resulted in the nucleophilic ring cleavage of the oxazole at the 6*a* position, giving 1-(2-hydroxyphenyl)-2-(1-pyrrolidino)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**15a**) in good yield. A similar result was obtained when **13b** was treated with 3-aminopyrrolidine in refluxing acetonitrile.



Scheme 9

Disappointingly, none of the compounds described in this report showed significant antibacterial activity in an *in vitro* assay. This lack of antibacterial activity shown by the compounds deserves a comment. Recentely, Ohta and Koga constructed a receptor model for the 1-substituents of quinolone antibacterials.[10] From the study they arrived at the conclusion that in the case of N_1-phenyl quinolones, conformers whose two aromatic rings are oriented having dihedral angle of 110° would interact with the receptor. The lack of antibacterial activity shown by **3a-d** may then be understood on the basis of the planarity of its molecular shape. The PM3 calculations showed that while the phenyl ring of benzothiazolo[3,2-*a*]quinolone orients out of the plan of quinolone nucleus having a dihedral angle of 23°, the two rings in benzoxazolo[3,2-*a*]quinolone are oriented having a near coplanar conformation. The increased electrophilicity of the oxazole ring compared with the thiazole in A-57,207 may also contribute the failure of the present compounds to exhibit antibacterial activity.

In conclusion, we have developed a facile method for the preparation of 2-substituted amino-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acids. The key step of the synthesis involves

the tandem double ring closure reaction of *N*-carbethoxyacetyl-*N*-(2-hydroxyphenyl)anthranilic acid with acetic anhydride. In comparison to 5,12-dihydro-5-oxobenzthiazolo[3,2-*a*]quinolines, chemical and biological properties of 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolines appear to be significantly different: The higher electronegativity of the oxygen in the latter compounds together with increased ring strain originated with the oxazole ring make the benzoxazolo[3,2-*a*]quinolones highly susceptible to nucleophilic attack at the 6*a*-position as demonstrated by **5a,b** whose oxazole ring underwent a ready ring cleavage upon treatment with a base. Such nucleophilic ring cleavage, if it occurs with biological bases such as DNA nucleotides, may possibly result in cytotoxic activity. Thus, although the representative derivatives of benzoxazolo[3,2-*a*]quinolone ring system, **3a-d** failed to show the expected antibacterial activity, the present ring system and its derivatives are thought to be of considerable interest to medicinal chemists.

EXPERIMENTAL

General Remarks

Infrared (IR) spectra were recorded on a Perkin Elmer 843 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with Bruker AM 300 (300 MHz) instrument and chemical shifts are reported in ppm relative to tetramethylsilane (TMS) or DMSO as internal reference. Mass spectra were obtained with KRATOS MS 25 RFA spectrometer. Flash column chromatography was performed on silica gel 60 (230~400 mesh). Thin layer chromatography (TLC) was carry out on silica coated glass sheets (Merck silica gel 60 F-254). Melting points were uncorrected. Microanalyses were performed by the Korea Basic Science Center on a Carlo Erba elemental analyzer type CE1108.

4-Chloro-*N*-(2-hydroxyphenyl)anthranilic acid (**4a**)

To a hot mixture of 2,4-dichlorobenzoic acid potassium salt (22 g) and 2-aminophenol (2.5 eq.) in *n*-butanol (60 ml) was added cupric chloride (0.2 g). The resulting mixture was heated under reflux for 2 h., cooled to room temperature and treated with sodium bicarbonate (20 g) and water (100 ml). The organic solvent was removed by steam distillation. The dark distillation residue was filtered and the filtrate was acidified to pH 1 with concentrated hydrochloric acid, causing the separation of a precipitate. The precipitate was collected on a filter, dissolved in hot ethanol, treated with charcoal, filtered, and the filtrate was poured into cold water to give a precipitate. The collected precipitate was redissolved in ether (200 ml) and the ether solution was washed with 1% aqueous sodium bicarbonate solution to remove 4-chlorobenzoic acid, a by-product from the reaction. The organic layer was washed with water, and with brine, then dried over $MgSO_4$, and evaporated under reduced pressure to give a yellowish solid which was recrystallized from benzene to give analytically pure **4a**. Yield: 10 g (33.4%). Mp 203~205 °C. IR (KBr) cm^{-1}: 3450, 3430, 1680; ^{1}H-NMR (DMSO-D_6): 6.63 (1H, d), 6.80 (1H, s), 6.88 (1H, t), 6.99 (1H, d), 7.08 (1H, t), 7.22 (1H, d), 7.35 (1H, s), 7.91 (1H, d), 9.35 (1H, s); MS (EI) *m/z*: 263 (M^+), 245 (M^+-H_2O). Anal. calcd. for $C_{13}H_{10}ClNO_3$: C 59.21, H 3.82, N 5.31. found: C 59.46, H 3.98, N 5.12.

4-Bromo-5-fluoro-*N*-(2-hydroxyphenyl)anthranilic acid (**4b**) was prepared similarly starting with 2,4-dibromo-5-fluorobenzoic acid potassium salt (39.6 g, 0.11 mole) and 2-aminophenol (26.6 g, 0.24 mole). Yield: 7.62 g (20%). Mp (benzene) 228~230 °C. IR (KBr) cm^{-1}: 3440, 3390, 3380-2600, 1680; ^{1}H-NMR (DMSO-D_6): 6.82 (1H, t), 7.00 (2H, m), 7.15 (1H, d), 7.26 (1H, d), 7.70 (1H, d), 9.28 (1H, s), 9.75 (1H, s); MS (EI) *m/z*: 328 (M^++2), 326 (M^+). Anal. calcd. for $C_{13}H_9BrFNO_3$: C 47.88, H 2.78, N 4.30. found: C 47.93, H 2.84, N 4.28.

4-Chloro-*N*-(2-hydroxyphenyl)anthranilic acid, ethyl ester (**7**)

To a solution of **4a** (2 g, 7.6 mmole) in absolute ethanol (200 ml) was added concentrated sulfuric acid (0.5 ml), and then refluxed for 18 h. The organic solvent was evaporated under reduced pressure, and the residue was dissolved in ether (100 ml). The solution was washed with saturated aqueous solution of sodium bicarbonate, with water, and with brine, then was dried over $MgSO_4$. After evaporation of the solvent the residue was subjected to flash column chromatography (silica gel, hexane/ethyl acetate: 20:1, 15:1, 10:1). Yield: 1.88 g (85%). Mp (hexane) 114.5~117 °C. IR (KBr) cm^{-1}: 3449, 3380, 1675; ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t), 4.35 (2H, q), 5.65 (1H, s), 6.58 (1H, d), 6.71 (1H, dd), 6.95 (1H, t), 7.06 (1H, d), 7.20 (2H, m), 7.90 (1H, d), 9.05 (1H, s); MS (EI) *m/z*: 291 (M^+), 245 (M^+ - EtOH), 217. Anal. calcd. for $C_{15}H_{14}ClNO_3$: C 61.76, H 4.84, N 4.80. found: C 61.84, H 4.89, N 4.67.

N-Carbethoxyacetyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic acid (**6a**)

To a solution of the **4a** (8 g, 30 mmole) and imidazole (6.13 g, 90 mmole) in methylene chloride (200 ml) was added carbethoxyacetyl chloride (4.26 ml, 5.03 g, 33 mmole). The resulting solution was stirred for 4 h at ambient temperature and washed with 2% hydrochloric acid, with brine, and was dried over $MgSO_4$, then filtered. The solvent was evaporated and the residue was dissolved in ether (200 ml). The ether solution was washed with water and extracted with 1% aqueous solution of sodium bicarbonate. The combined extract was acidified with 5% hydrochloric acid to pH ~3 and was saturated with table salt. The acidic solution was then extracted with ether (100 ml x 3). The combined ether solution was dried ($MgSO_4$), filtered and concentrated to about 50 ml. The concentrated solution was cooled in ice bath to give a crystalline solid which was filtered and recrystallized from ether to give **6a** (8.15 g, 72%) as a white crystalline solid. Mp 159.5~162.5 °C. IR (KBr) cm^{-1}: 3500, 3600-2500, 1740, 1695, 1650; ^{1}H-NMR (DMSO-D_6): 1.22 (3H, t), 3.39 (2H, d), 4.12 (2H, q), 6.98 (2H, dd), 7.22 (1H, d), 7.31 (2H, t), 7.47 (1H, dd), 7.65 (1H, d), 11.31, ; MS (EI) *m/z*: 377 (M^+), 360 (M^+- OH). Anal. calcd. for $C_{18}H_{16}ClNO_6$: C 57.22, H 4.27, N 3.71. found: C 57.29, H 4.27, N 3.70.

N-Carbethoxyacetyl-10-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-one (**11**)

To a solution of **6a** (188.5 mg, 0.5 mmole) in methylene chloride (100 ml) was added slowly a solution of DCC (103.2 mg, 0.5 mmole) and 4-dimethylaminopyridine (6 mg) in methylene chloride (20 ml). After standing for 6 h at room temperature, the dicyclohexylurea formed was filtered off, and the filtrate was concentrated under reduced pressure and chilled in ice. The precipitate was recrystallized from ethanol to give **11** (120 mg, 67%) as a white solid. Mp 115~117 °C. IR (KBr) cm^{-1}: 1747, 1727, 1687; ^{1}H-NMR ($CDCl_3$): 1.22 (3H, t), 3.42 (2H, dd), 4.13 (2H, q), 7.20~7.81 (6H, m), 7.83 (1H, d); MS (FAB)

m/z: 382 (M^+ + Na), 360 (MH^+). Anal. calcd. for $C_{18}H_{14}ClNO_5$: C 60.09, H 3.92, N 3.89. found: C 60.12, H 3.91, N 3.92.

2-Chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid, ethyl ester (**5a**)

A solution of **6a** (1 g, 2.6 mmole) in acetic anhydride (10 ml) was stirred for 4 h at 80 °C. The reaction mixture was cooled in an ice bath, filtered, and the solid filter residue was washed with ethanol, then recrystallized from ethanol to give **5a** (0.83 g, 91.7%) as a white crystalline solid. Mp 220.2~221.5 °C. IR (KBr) cm^{-1}: 1700, 1640; ^{1}H-NMR (TFA-D): 1.97 (3H, t), 5.13 (2H, q), 8.24 (2H, t), 8.36 (2H, t), 8.91 (1H, t), 9.11 (1H, d), 9.19 (1H, s); MS (EI) *m/z*: 341 (M^+), 296 (M^+- OEt). Anal. calcd. for $C_{18}H_{12}ClNO_4$: C 63.26, H 3.54, N 4.10. found: C 63.27, H 3.24, N 3.72.

2-Bromo-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid, ethyl ester (**5b**)

To a solution of the **4b** (3.26 g, 10 mmole) and imidazole (2.25 g, 33 mmole) in dry methylene chloride (200 ml) was added carbethoxyacetyl chloride (1.4 ml, 1.66 g, 11 mmole). The resulting solution was stirred for 4 h at ambient temperature and washed with 2% hydrochloric acid, with brine, and dried over $MgSO_4$, then filtered. The solvent was evaporated and the residue was dissolved in ether (100 ml). The ether solution was washed with water and extracted with 1% aqueous solution of sodium bicarbonate. The combined extract was acidified with 5% hydrochloric acid to pH ~3 and saturated with table salt. The acidic solution was then extracted with ether (100 ml x 3). The combined ether solution was dried ($MgSO_4$), filtered, and concentrated to give an oily residue which was dissolved in acetic anhydride (5 ml) and stirred for 4 h at 80 °C. The resulting red solution was cooled in an ice bath, filtered, and the solid filter residue was washed with water and ethanol. The yellowish solid thus obtained was recrystallized from ethanol to give **5b** (2.4 g) as a white crystalline solid in 60% yield from **4b**. Mp 239~243 °C. IR (KBr) cm^{-1}: 1722, 1699; ^{1}H-NMR (TFA-D): 1.68 (3H, t), 4.36 (2H, q), 7.98 (2H, q), 8.10 (1H, t), 8.50 (1H, d), 8.60 (1H, dd), 9.17 (1H, d); ^{13}C-NMR (TFA-D): 2.65, 55.77, 83.36, 102.60, 102.94 (d, J=235 Hz), 105.67, 109.70 (d, J=33.3 Hz), 113.05, 113.31, 116.42, 118.90, 120.66, 121.20, 138.56, 146.12, 147.74, 157.44, 163.09; MS (FAB) *m/z*: 427 (M^+ + 2 + Na), 425 (M^+ + Na), 405 (MH^+ + 2), 403 (MH^+), 357 (M^+ + 2 - EtO), 357 (M^+ - EtO). Anal. calcd. for $C_{18}H_{11}BrFNO_4$: C 53.48, H 2.74, N 3.46. found: C 53.42 H 2.66, N 3.52.

Hydrolysis of **5a** under basic conditions to give 7-chloro-4-hydroxy-1-(2-hydroxyphenyl)-1,2-dihydro-2-oxoquinoline-3-carboxylic acid, ethyl ester (**12**)

To a milky solution of **5a** (100 mg, 0.29 mmole) in 15 ml of methanol/water (7/3) was added 1 M LiOH (1.3 ml) and stirred for 4 h at room temperature to give a clear solution. The reaction mixture was concentrated to about 5 ml and acidified to pH~3. The solid formed was collected on a filter and recrystallized from ethanol to give **12** as a white crystalline solid. Yield: 80 mg (76.8%); Mp > 280 °C. IR (KBr) cm^{-1}: 3203, 1644, 1618; ^{1}H-NMR (DMSO-D_6): 1.30 (3H, t), 4.33 (2H, q), 6.44 (1H, s), 6.99 (1H, t), 7.06 (1H, d), 7.15 (1H, dd), 7.30~7.40 (2H, m), 8.06 (1H, d), 9.79 (1H, s), 13.3 (1H, s); MS (EI) *m/z*: 359 (M^+), 313 (M^+ - EtOH), 256. Anal. calcd. for $C_{18}H_{14}ClNO_5$: C 60.09, H 3.92, N 3.89. found: C 60.01, H 3.94, N 3.85.

General procedure for the preparation of 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acids (**13**)

A solution of **5** (1 g) in 95% sulfuric acid (5 ml) was stirred for 6 h at 80 °C, cooled and poured into crushed ice to give a white solid which was collected on a filter, washed with water, and ethanol. The crude product was recrystallized from trifluoroacetic acid-water to give pure **13** as a white solid.

2-Chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**13a**)

Yield: 0.86 g (93.7%). Mp (1-methyl-2-pyrrolidinone) >280 °C. IR (KBr) cm^{-1}: 3500~2000, 1730, 1600; ^{1}H-NMR (TFA-D): 7.99 (2H, m), 8.10 (1H, t), 8.14 (1H, m), 8.60 (1H, dd), 8.82 (1H, d), 8.87 (1H, s); MS (EI) *m/z*: 313 (M^+). Anal. calcd. for $C_{16}H_8ClNO_4$: C 61.26, H 2.57, N 4.46. found: C 61.29, H 2.55, N 4.63.

2-Bromo-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**13b**)

Yield: 0.85 g (91.4%). Mp (1-methyl-2-pyrrolidinone) 275~276 °C. IR (KBr) cm^{-1}: 3500~2000, 1710, 1706; ^{1}H-NMR (TFA-D): 7.65 (2H, m), 7.80 (1H, d), 8.18 (1H, d), 8.28 (1H, t), 8.86 (1H, d); MS (EI) *m/z*: 375 (M^+), 333 ($M^+ + 2 - CO_2$), 331 ($M^+ - CO_2$). Anal. calcd. for $C_{16}H_7BrFNO_4$: C 51.09, H 1.88, N 3.72. found: C 50.91 H 1.89, N 3.78.

General procedure for synthesis of **3a~d**

A mixture of **13b** (200 mg, 0.53 mmole) and appropriate piperazine (2.4 mmole) in 1-methyl-2-pyrrolidinone (7 ml) was stirred at 110 °C. The reaction was monitored by TLC until **13b** had been consumed, at which point the mixture was cooled to give a precipitate. The precipitate was collected on a filter, washed with ethanol, and with water to give **3a~d** as a solid.

3-Fluoro-2-(piperazin-1-yl)-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**3a**)

Reaction time: 3 h. Yield: 120 mg (59.4%). Mp >280 °C. IR (KBr) cm^{-1}: 3500 ~ 2500, 3219 (NH), 1725, 1630; ^{1}H-NMR (TFA-D): 3.85 (4H, s), 4.10 (4H, s), 7.95 (2H, m), 8.11 (1H, d), 8.15 (1H, d), 8.48 (2H, m); MS (FAB) *m/z*: 382 (MH^+). Anal. calcd. for $C_{20}H_{16}FN_3O_4 \cdot 1/2\ H_2O$: C 61.53, H 4.39, N 10.77. found: C 61.85, H 4.06, N 10.52.

3-Fluoro-2-(4-methylpiperazin-1-yl)-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**3b**)

Reaction time: 1.5 h. Yield: 110 mg (52.2%). Mp >280 °C. IR (KBr) cm^{-1}: 3452, 1731.8, 1631; ^{1}H-NMR (TFA-D): 3.24 (3H, s), 3.60 (2H, t), 3.65 (2H, t), 3.99 (2H, d), 4.34 (2H, d), 7.93~8.00 (2H, m), 8.10 (1H, d), 8.19 (1H, d), 8.42~8.50 (2H, m); MS (EI) *m/z*: 395 (M^+), 351 ($M^+ - CO_2$). Anal. calcd. for $C_{21}H_{18}FN_3O_4$: C 63.79, H 4.59, N 10.63. found: C 63.59 H 4.43, N 10.42.

2-(4-Acetylpiperazin-1-yl)-3-fluoro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**3c**)

Reaction time: 5 h. Yield: 133 mg (59%). Mp >280 °C. IR (KBr) cm^{-1}: 3500 ~ 2500, 1717, 1630; ^{1}H-NMR (TFA-D): 2.48 (3H, s), 3.87~3.95 (4H, d), 4.00~4.20 (4H, d), 7.80~7.91 (3H, m), 8.06 (1H, d),

8.30~8.40 (2H, t); MS (FAB) *m/z*: 446 (M^+ + Na), 406 (MH^+ - H_2O). Anal. calcd. for $C_{22}H_{18}FN_3O_5 \cdot 1/3\ H_2O$: C 61.54, H 4.38, N 9.79. found: C 61.82, H 4.27, N 9.68.

3-Fluoro-2-(4-(2-pyridyl)piperazinyl)-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinoline-6-carboxylic acid (**3d**).

Reaction time: 3.5 h. Yield: 171 mg (70%). mp >280 °C. IR (KBr) cm^{-1}: 3400~2000, 1721, 1614; ^{1}H-NMR (TFA-D): 4.15 (8H, s), 7.08 (1H, d), 7.30 (1H, d), 7.80~8.10 (6H, m), 8.36 (2H, t); MS (FAB) *m/z*: 459 (MH^+), 414 (MH^+ - CO_2). Anal. calcd. for $C_{25}H_{19}FN_4O_4 \cdot H_2O$: C 63.02, H 4.44, N 11.76. found: C 63.14, H 4.49, N 11.73.

6-Fluoro-1-(2-Hydroxyphenyl)-2-(pyrrolidin-1-yl)-7-bromo-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**15a**)

A mixture of **13b** (200 mg, 0.53 mmole) and pyrrolidine (5 ml) was refluxed for 3 h and the excess pyrrolidine was evaporated under reduced pressure to give an oily residue. To the residue was added acetonitrile (5 ml) to give a solid which was collected on a filter. The solid was suspended in 5% HCl (5 ml), and was boiled for 5 min, cooled, filtered to give **15a** (120 mg, 62%) as a yellow solid. Mp 213~215 °C. IR (KBr) cm^{-1}: 3368, 1708, 1632; ^{1}H-NMR (TFA-D): 1.96 (4H, m), 3.26 (2H, s), 3.43 (2H, s), 7.33 (4H, m), 7.64 (1H, t), 7.95 (1H, d); MS (FAB) *m/z*: 405 (MH^+ + 2 - CO_2), 403 (MH^+ - CO_2). Anal. calcd. for $C_{20}H_{16}BrFN_2O_4 \cdot 1/2H_2O$: C 52.64, H 3.73, N 6.14. found: C 52.41, H 4.01, N 6.31.

2-(3-Aminopyrrolidin-1-yl)-7-bromo-6-fluoro-1-(2-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**15b**)

A mixture of **13b** (220 mg, 0.59 mmole) and 3-aminopyrrolidine (202 mg) in acetonitrile (30 ml) was refluxed for 3.5 h, cooled, filtered, and the filter residue was washed with a small amount of acetonitrile and cold water to give **15b** (180 mg, 65%) as a white powder. Mp 220 °C (dec). IR (KBr) cm^{-1}: 3500~3200 (OH, NH_2), 3500~2000, 1636, 1600; ^{1}H-NMR (TFA-D): 2.0~2.4 (2H, m), 3.10~3.70 (4H, m), 4.00~4.50 (1H, m), 7.10~7.50 (4H, m), 7.73 (1H, s), 8.0~8.15 (1H, m); MS (FAB) *m/z*: 486 (M^+ + 2 + Na), 484 (M^+ + Na), 464 (MH^+ + 2), 462 (MH^+), 446 (M^+ + 2 -OH), 444 (M^+ -OH). Anal. calcd. for $C_{20}H_{17}BrFN_3O_4 \cdot 1/2H_2O$: C 50.97, H 3.85, N 8.92. found: C 51.29, H 4.05, N 8.94.

2,4-Dibromo-5-fluorobenzoic acid (**14**)

To a mixture of 3-fluorotoluene (57 g, 0.52 mmole) and iron powder (10 g) was added bromine (66.8 ml, 1.3 mole) dropwise under stirring with a mechanical stirrer for 2.5 h at 50 °C. After the addition, the reaction mixture was heated on a steam bath for 1 h, then was cooled. Aqueous NaOH solution (10%) was added to pH~9, then acidified with 5% HCl to pH~2. The mixture was filtered and the filtrate was extracted with petroleum ether (300 ml x 3). The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give an oily residue which was distillated under reduced pressure to give **16**[10] (82 g, 59%, $bp_{0.3}$ 52 °C) as a colorless liquid.

To a warm mixture of **16** (81 g, 0.3 mole) and *N*-bromosuccinimide (134. 5 g, 0.76 mole) in carbon tetrachloride (300 ml) was added 1, 1'-azobis(isobutyronitrile) (1 g), and then refluxed for 12 h. The reaction mixture was cooled to room temperature and the succinimide was removed by filtration. The filtrate was

concentrated to give a yellow oil which was dissolved in 95% H_2SO_4 (300 ml) and stirred for 8 h at 60 °C. The reaction mixture was cooled to room temperature and extracted with methylene chloride (200 ml x 3). The combined extract was washed with a saturated aqueous solution of sodium thiosulfate (100 ml x 3), water (100 ml x 3), and brine (100 ml x 2), then was concentrated to give a pale yellow solid. The solid was dissolved in acetone (300 ml) and to the resulting solution was added the Jones reagent (8 N, 35 ml, 0.3 mole) for 1h at room temperature. The resulting red solution was stirred for 2 h, filtered *via* filter agent (Celite®), and the filtrate was concentrated to give a yellowish solid. The solid was suspended in water (200 ml) and the aqueous medium was made alkaline with 10% aqueous solution of NaOH. The alkaline solution was washed with methylene chloride (30 ml x 3) and was acidified with concentrated hydrochloric acid to pH~1 to give a white precipitate which was collected on a filter, washed with cold water several times, and dried under vacuum to give **14** (58.86 g, total yield: 38.1%) as a white solid. Mp 147~149 °C. IR (KBr) cm^{-1}: 3500~2000, 1707; ^{1}H-NMR ($CDCl_3$): 7.77 (1H, d, J = 8.73 Hz), 7.93 (1H, d, J=6.21 Hz); MS (EI) *m/z*: 300 (M^+ + 4), 298 (M^++2), 296 (M^+), 283, 281. Anal. calcd. for $C_7H_3Br_2FO_2$: C 28.22, H 1.01. found: C 28.22, H 0.95.

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6. The patent literature[7] reports that ethyl 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolin-6-carboxylic acid was obtained by reacting ethyl 2,4-dichloro-5-fluorobenzoylacetate with 2-chlorobenzoxazole in the presence of 2 molar equivalents of sodium hydride, but we were unable to reproduce the results. Furthermore, no spectral or physical data for the compounds are recorded.
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