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The one-pot reaction of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (6) with *tert*-butyl acetoacetate gave 3-*tert*-butyl 7-ethyl 9-cyclopropyl-4-fluoro-6,9-dihydro-2-methyl-6-oxofuro[3,2-*h*]quinoline-3,7-dicarboxylate (5). This regioselective cyclization was rationalized by the Hard and Soft Acids and Bases principle. By use of a similar furan-forming reaction, we prepared 2-(amino-methyl)furo[3,2-*h*]quinoline-7-carboxylic acid 4. Compound 4 showed weak antibacterial activity.

Quinolone antibacterials are currently used for chemotherapy against bacterial infectious diseases. Throughout studies in this field over the past three decades, a series of 6-fluoro-7-(cyclic-amino)quinolone derivatives are widely known to show potent antibacterial activity; an example of this type is 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (AM-1155, **1**) possessing a 1-piperazinyl group as the 7-(cyclic amino) substituent [2]. Recently, several novel carbon substituents have been introduced to the C-7 position [3,4].

8-carbons, 9-nitrogen, and 9a- and 9b-carbons of compound **4**.

Before the actual synthesis, we speculated on a plausible synthetic route leading to the desired furo[3,2-*h*]quinolone **5**. *tert*-Butyl acetoacetate reacts with ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate in the presence of sodium hydride to afford ethyl 7-(1-*tert*-butoxycarbonyl-2-oxo-1-propyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate [6]. In addition, the oxygen in the C-7 side chain of 7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-
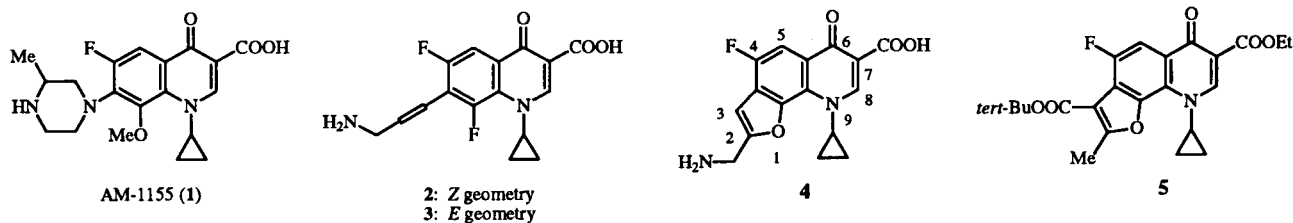

Figure 1

In our previous paper [5], we reported the synthesis of [(*Z*)- and (*E*)-3-amino-1-propenyl]quinolones **2** and **3** with potent antibacterial activity. Compound **3** may assume many conformations caused by rotation around the C(7)-C(1') and the C(2')-C(3') axes of the (*E*)-3-amino-1-propenyl group. As an extension of our studies with potential antibacterial agents as the objective, we designed compound **4** which was conformationally restricted by forming an oxygen-bridge, and had the carbon-nitrogen framework of the (*E*)-3-amino-1-propenyl moiety of **3** along with an 8-oxy moiety of **1**. Accordingly, compound **4** was anticipated to show the same level of activity or to possess more potent activity than **3**. This paper deals with furan ring formation and the synthesis and antibacterial activity of the target compound **4**.

2-Methylfuro[3,2-*h*]quinolone **5** was selected as an intermediate for the synthesis of target compound **4**, because **5** has the framework comprising 1-oxygen, 2- to

6,8-difluoroquinolone **12**, in the presence of sodium hydride, attacks selectively the C-8 carbon of the same molecule to give an oxazine ring as in **13** (Scheme 2) [7]. Considering the above facts, when 6,7,8-trifluoroquinolone **6** is allowed to react under similar conditions but with at least a twofold molar excess of the enolate anion of *tert*-butyl acetoacetate, enolate **8** could be produced *via* compound **7** (Scheme 1). The equilibrated enolate **8b** would subsequently be subjected to the intramolecular cyclization to its C-8 carbon atom and would result in forming the desired furo[3,2-*h*]quinolone **5**.

In fact, treatment of **6** with *tert*-butyl acetoacetate afforded exclusively cyclization product **5** in 66% yield in a one-pot reaction (Scheme 1). The structure of **5** was confirmed by its ^{1}H-nmr spectrum; the signal of the C-5 proton of **5** appeared at δ 7.74 ppm as a doublet due to *ortho*-coupling to the C-4 fluorine (J_{5H-4F} = 11.0 Hz). The possible isomeric furo[2,3-*g*]quinolone **9** which might be
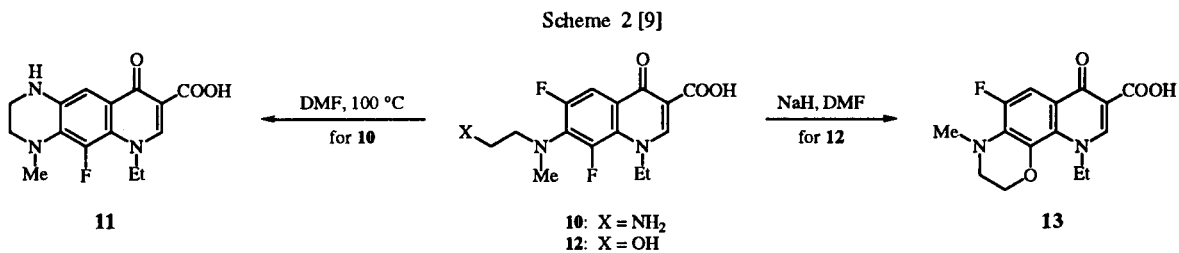
Scheme 1
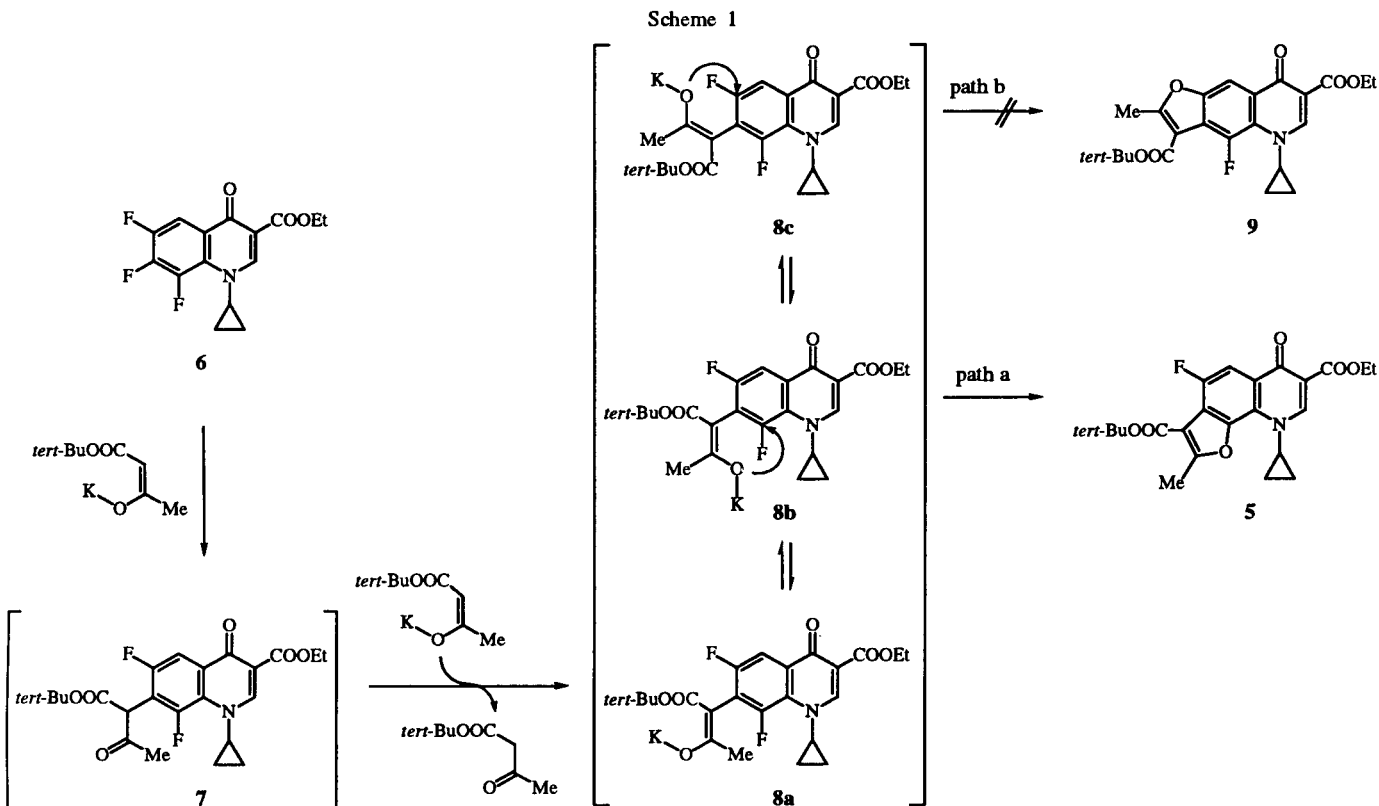
produced through path b was not detected on thin layer chromatography of the reaction mixture. Thus we have found a regioselective furan-forming reaction.

Yakobson *et al.* [8] reported that a similar condensation of hexafluorobenzene with ethyl acetoacetate gave ethyl 2-methyl-4,5,6,7-tetrafluorobenzofuran-3-carboxylate. They did not apply the reaction to halo compounds other than hexafluorobenzene, which was a symmetric molecule and was highly activated against nucleophilic attack due to the inductive effect of the fluorine atoms. In our case, it is observed that the furan-forming reaction with trifluoro compound 6 proceeded regioselectively.

The regioselectivity in the cyclization of 8 is rationalized by the Hard and Soft Acids and Bases Principle [9] as follows. We previously reported that the thermal cyclization of 7-[[N-(2-aminoethyl)-N-methyl]amino]-6,8-difluoroquinolone 10 selectively gave pyrazine derivative 11 (Scheme 2) [7]. This observation suggests that the C-6

position of 10 should be rather a soft acid, because the amino group of 10 is a soft base. The cyclization of hydroxy derivative 12 occurred selectively at C-8 and gave the oxazine derivative 13 (Scheme 2) [7]. The nucleophile in the latter reaction is a metalated alkoxide (a hard base), and hence the C-8 position of 12 should be a harder acid than the C-6 position. Despite some differences in the N-1, the C-3, and the C-7 substituents of 8 from those of 10 and 12, the C-8 position of the enolate 8 would be harder than the C-6 position. The oxygen anion of the enolate 8 is a hard base. Therefore the cyclization may be reasonably understood to proceed more favorably to 5 through path a than to 9 through path b.

The *tert*-butyl ester moiety of 5 was converted to the carboxyl group, compound 14 (Scheme 3). Decarboxylation of 14 by heating with copper powder in quinoline gave compound 15. Reaction of 15 with N-bromosuccinimide and benzoyl peroxide in refluxing carbon tetrachloride gave

Scheme 2 [9]

a mixture of the desired product **16** and unreacted **15**; isolation of **16**, however, failed.

Compound **4** showed less potent *in vitro* antibacterial activity than the lead compound **3**. Thus the minimum inhibitory

Scheme 3
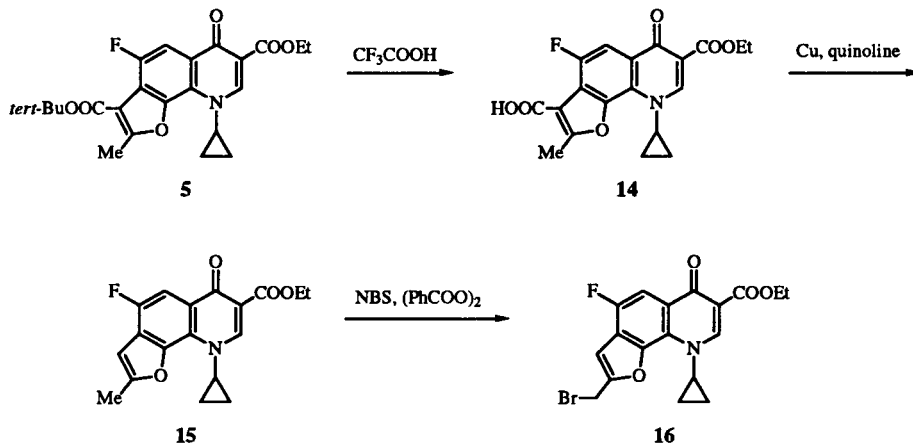
Our efforts then turned to an alternative synthetic route to **4** (Scheme 4). Condensation of **6** with methyl 4-methoxyacetoacetate instead of *tert*-butyl acetoacetate gave furo[3,2-h]quinolone **17** in moderate yield. The ^{1}H-nmr spectrum of **17** shows the presence of the C-4 fluorine coupled to the adjacent C-5 hydrogen with J = 11.0 Hz, establishing the structure of **17**.

concentrations [10] of **4** against *Staphylococcus aureus* 209P JC-1, *Escherichia coli* NIHJ JC-2, and *Pseudomonas aeruginosa* 12 were 3.13, 0.1, and 0.78 μg/ml, respectively, while those of **3** were 0.39, 0.025, and 0.39 μg/ml, respectively.

In conclusion, we developed a furan-forming reaction consisting of a condensation of 6,7,8-trifluoroquinolone **6** with *tert*-butyl acetoacetate. The reaction proceeded in a

Scheme 4
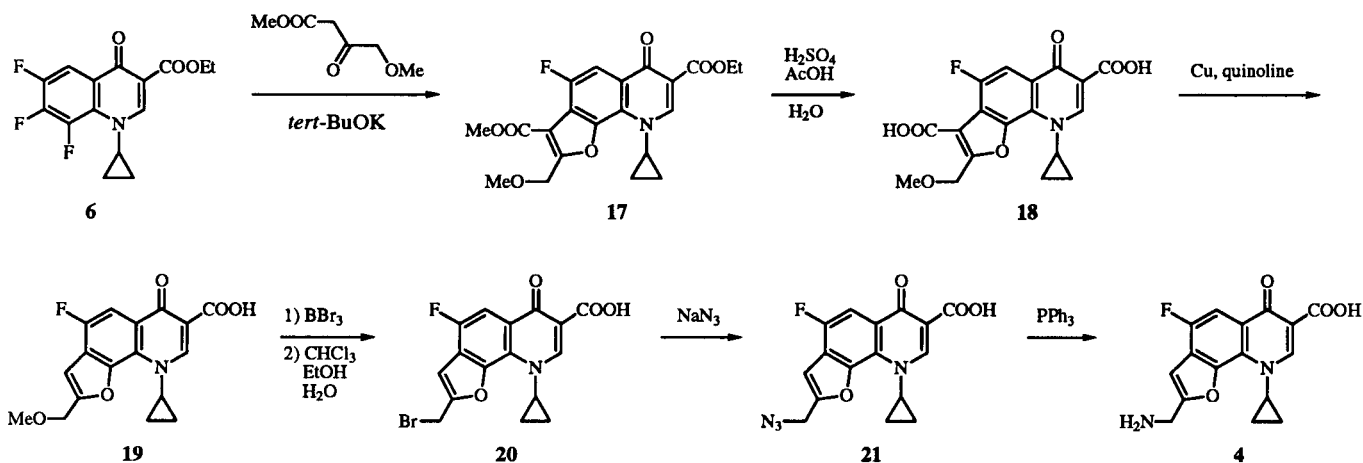
The ester moieties of **17** were hydrolyzed under acidic conditions to give 3,7-dicarboxylic acid **18**, which was then heated with copper powder in quinoline to give 7-carboxylic acid **19**. On treatment of **19** with boron tribromide, the methoxy group was converted to a bromine atom, giving a mixture of **20** and its boron chelate; the chelate liberated **20** on hydrolysis. The bromide **20** was treated with sodium azide to give azide **21**. Reduction of the azido group of **21** with triphenylphosphine gave 2-(aminomethyl)furo[3,2-h]-quinolone **4**.

regioselective fashion to give furo[3,2-h]quinolone **5**. Also prepared was 2-(aminomethyl)furo[3,2-h]quinolone **4** designed with the objective of obtaining a more highly active antibacterial agent. Unexpectedly, compound **4** was less active than the lead compound **3**.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (ir) spectra

were recorded on a Perkin Elmer 1600 Series FTIR spectrophotometer. The ^{1}H nmr spectra were taken at 200 MHz on a Varian Gemini-200 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standards. Electron-impact (EI), secondary ion (SI), and atmospheric pressure chemical ionization (APCI) mass spectra (ms) were obtained on a JEOL JMS D-300, Hitachi M-80B, and Hitachi M-1000 LC API mass spectrometers, respectively. The spectral data for all compounds were consistent with assigned structures. All compounds were analyzed for C, H, Br, F, and N.

3-tert-Butyl 7-Ethyl 9-Cyclopropyl-4-fluoro-6,9-dihydro-2-methyl-6-oxofuro[3,2-h]quinoline-3,7-dicarboxylate (5).

Potassium tert-butoxide (10.82 g, 96.4 mmoles) was added to a mixture of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate [11] (6, 10.00 g, 32.1 mmoles) and tert-butyl acetoacetate (15.26 g, 96.4 mmoles) in N,N-dimethylformamide (100 ml) and the whole mixture was heated at 100° for 3.5 hours. Ice-water and dilute acetic acid were added to the mixture. The resulting precipitate was collected by filtration, washed successively with water, ethanol, and diisopropyl ether, and then dried to give 9.17 g (66%) of 5, mp 218-219° (chloroform-ethanol); ir (potassium bromide): 1723, 1700, 1618 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15-1.5 (m, 4H, cyclopropyl CH$_2$CH$_2$), 1.44 (t, 3H, J = 7.0 Hz, CH$_2$CH$_3$), 1.64 (s, 9H, tert-Bu), 2.81 (s, 3H, 2-Me), 4.05-4.2 (m, 1H, cyclopropyl CH), 4.42 (q, 2H, J = 7.0 Hz, CH$_2$CH$_3$), 8.07 (d, 1H, J = 11.0 Hz, 5-H), 8.66 (s, 1H, 8-H); ms: (APCI) 430 (M$^+$+1).

Anal. Calcd. for C$_{23}$H$_{24}$FNO$_6$: C, 64.33; H, 5.63; F, 4.42; N, 3.26. Found: C, 64.32; H, 5.60; F, 4.47; N, 3.20.

7-Ethoxycarbonyl-9-cyclopropyl-4-fluoro-6,9-dihydro-2-methyl-6-oxofuro[3,2-h]quinoline-3-carboxylic Acid (14).

Trifluoroacetic acid (12 ml) was added to a mixture of 5 (5.70 g, 13.3 mmoles) in dichloromethane (12 ml) with ice-cooling. The resulting mixture was stirred at room temperature for 15 hours and concentrated *in vacuo*. The residue was triturated with ethanol. The resulting precipitate was collected by filtration, washed successively with ethanol and diisopropyl ether, and then dried to give 4.95 g (100%) of 14, mp 288-290° (chloroform-ethanol); ir (potassium bromide): 3395, 1732, 1700, 1616 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.2-1.4 (m, 4H, cyclopropyl CH$_2$CH$_2$), 1.28 (t, 3H, J = 7.0 Hz, CH$_2$CH$_3$), 2.80 (s, 3H, 2-Me), 4.05-4.25 (m, 1H, cyclopropyl CH), 4.24 (q, 2H, J = 7.0 Hz, CH$_2$CH$_3$), 7.77 (d, 1H, J = 11.0 Hz, 5-H), 8.50 (s, 1H, 8-H), 13.24 (broad s, 1H, COOH); ms: (EI) 373 (M$^+$), 329, 301.

Anal. Calcd. for C$_{19}$H$_{16}$FNO$_6$: C, 61.13; H, 4.32; F, 5.09; N, 3.75. Found: C, 60.85; H, 4.52; F, 4.92; N, 3.66.

Ethyl 9-Cyclopropyl-4-fluoro-6,9-dihydro-2-methyl-6-oxofuro[3,2-h]quinoline-7-carboxylate (15).

A mixture of 14 (4.95 g, 13.3 mmoles) and copper powder (500 mg, 7.87 mmoles) in quinoline (20 ml) was heated at 150° for 45 minutes. The mixture was filtered and the filter pad was washed with chloroform. The washing solution was combined with the filtrate and concentrated *in vacuo*. Ethyl acetate (50 ml) was added to the residue and the resulting precipitate was collected by filtration, washed successively with ethanol and diisopropyl ether, and then dried to give 2.60 g (60%) of 15, mp 245-246° (acetonitrile); ir (potassium bromide): 1723, 1621 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.15-1.4 (m, 4H, cyclopropyl CH$_2$CH$_2$), 1.28 (t,

3H, J = 7.0 Hz, CH$_2$CH$_3$), 2.59 (d, 3H, J = 0.5 Hz, 2-Me), 4.05-4.3 (m, 1H, cyclopropyl CH), 4.24 (q, 2H, J = 7.0 Hz, CH$_2$CH$_3$), 6.96 (d, 1H, J = 1.0 Hz, 3-H), 7.73 (d, 1H, J = 10.0 Hz, 5-H), 8.49 (s, 1H, 8-H); ms: (EI) 329 (M$^+$), 257.

Anal. Calcd. for C$_{18}$H$_{16}$FNO$_4$: C, 65.65; H, 4.90; F, 5.77; N, 4.25. Found: C, 65.55; H, 4.82; F, 5.55; N, 4.32.

Ethyl 2-Bromomethyl-9-cyclopropyl-4-fluoro-6,9-dihydro-6-oxofuro[3,2-h]quinoline-7-carboxylate (16).

A mixture of 15 (1.33 g, 4.04 mmoles), N-bromosuccinimide (1.44 g, 8.09 mmoles), and benzoyl peroxide (49 mg, 0.20 mmole) in carbon tetrachloride (50 ml) was heated to reflux for 3 hours. The mixture was concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel eluting with a mixture of chloroform and ethanol (20:1) to give 763 mg of a 22:3 mixture of 16 and 15; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.15-1.5 (m, 4H, cyclopropyl CH$_2$CH$_2$), 1.28 (t, 3H, J = 7.0 Hz, CH$_2$CH$_3$), 2.59 (d, 0.12 x 3H, J = 0.5 Hz, 2-Me), 4.05-4.3 (m, 1H, cyclopropyl CH), 4.24 (q, 2H, J = 7.0 Hz, CH$_2$CH$_3$), 5.02 (s, 0.88 x 2H, CH$_2$Br), 6.96 (d, 0.12 x 1H, J = 1.0 Hz, 3-H), 7.37 (s, 0.88 x 1H, 3-H), 7.73 (d, 0.12 x 1H, J = 10.0 Hz, 5-H), 7.77 (d, 0.88 x 1H, J = 10.0 Hz, 5-H), 8.49 (s, 0.12 x 1H, 8-H), 8.51 (s, 0.88 x 1H, 8-H).

7-Ethyl 3-Methyl 9-Cyclopropyl-4-fluoro-6,9-dihydro-2-methoxymethyl-6-oxofuro[3,2-h]quinoline-3,7-dicarboxylate (17).

By the procedure described for the preparation of 5, the reaction of 6 (37.0 g, 0.119 mole) with methyl 4-methoxyacetoacetate (52.1 g, 0.357 mole) gave 28.53 g (58%) of 17, mp 196-197° (chloroform-ethanol); ir (potassium bromide): 1712, 1692, 1620 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.2-1.4 (4H, m, cyclopropyl CH$_2$CH$_2$), 1.29 (t, 3H, J = 7.0 Hz, CH$_2$CH$_3$), 3.39 (s, 3H, CH$_2$OMe), 3.92 (s, 3H, COOMe), 4.05-4.3 (m, 1H, cyclopropyl CH), 4.24 (q, 2H, J = 7.0 Hz, CH$_2$CH$_3$), 4.93 (s, 2H, CH$_2$OMe), 7.82 (d, 1H, J = 11.0 Hz, 5-H), 8.52 (s, 1H, 8-H); ms: (SI) 418 (M$^+$+1), 372.

Anal. Calcd. for C$_{21}$H$_{20}$FNO$_7$: C, 60.43; H, 4.83; F, 4.55; N, 3.36. Found: C, 60.39; H, 4.80; F, 4.51; N, 3.32.

9-Cyclopropyl-4-fluoro-6,9-dihydro-2-methoxymethyl-6-oxofuro[3,2-h]quinoline-3,7-dicarboxylic Acid (18).

A mixture of 17 (16.8 g, 40.3 mmoles) in acetic acid-water-sulfuric acid (8:6:3 v/v, 170 ml) was heated to reflux for 4 hours and then ice-water was added. The resulting precipitate was collected by filtration, washed successively with water, ethanol, and diisopropyl ether, and then dried to give 14.7 g (97%) of 18, mp 300-303° dec (N,N-dimethylformamide-ethanol); ir (potassium bromide): 1732, 1690 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.3-1.45 (m, 4H, cyclopropyl CH$_2$CH$_2$), 3.40 (s, 3H, CH$_2$OMe), 4.25-4.4 (m, 1H, cyclopropyl CH), 4.96 (s, 2H, CH$_2$OMe), 7.95 (d, 1H, J = 11.0 Hz, 5-H), 8.79 (s, 1H, 8-H), 13.7 (broad s, 1H, COOH); ms: (EI) 375 (M$^+$), 331.

Anal. Calcd. for C$_{18}$H$_{14}$FNO$_7$: C, 57.61; H, 3.76; F, 5.06; N, 3.73. Found: C, 57.39; H, 3.86; F, 4.94; N, 3.76.

9-Cyclopropyl-4-fluoro-6,9-dihydro-2-methoxymethyl-6-oxofuro[3,2-h]quinoline-7-carboxylic Acid (19).

A mixture of 18 (28.02 g, 74.7 mmoles) and copper powder (280 mg, 4.41 mmoles) in quinoline (80 ml) was heated at 130° for 32 hours. The mixture was filtered and the filter pad was washed with chloroform. The washing solution was combined with the filtrate and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with a mixture of chloroform and ethanol (100:1

to 20:1) to give 17.06 g (69%) of **19**, mp 204-205° (chloroform-ethanol); ir (potassium bromide): 1737, 1730, 1614 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.3-1.45 (m, 4H, cyclopropyl CH$_2$CH$_2$), 3.38 (s, 3H, CH$_2$O*Me*), 4.25-4.4 (m, 1H, cyclopropyl CH), 4.72 (s, 2H, C*H$_2$*OMe), 7.39 (s, 1H, 3-H), 7.90 (d, 1H, J = 10.0 Hz, 5-H), 8.77 (s, 1H, 8-H), 15.1 (s, 1H, COOH); ms: (EI) 331 (M$^+$), 287.

Anal. Calcd. for C$_{17}$H$_{14}$FNO$_5$: C, 61.63; H, 4.26; F, 5.73; N, 4.23. Found: C, 61.52; H, 4.28; F, 5.72; N, 4.17.

2-Bromomethyl-9-cyclopropyl-4-fluoro-6,9-dihydro-6-oxo-furo[3,2-*h*]quinoline-7-carboxylic Acid (20).

Boron tribromide (1*N* solution in dichloromethane, 27.0 ml, 27.0 mmoles) was added to a stirred mixture of **19** (3.00 g, 9.06 mmoles) in dichloromethane (30 ml) with ice-cooling. The resulting mixture was stirred at room temperature for 3 hours and concentrated *in vacuo* to leave a residual solid consisting of **20** and its boron chelate. Chroloform (180 ml), ethanol (70 ml), and water (10 ml) were added to the residue and the resulting mixture was heated to reflux for 19 hours and concentrated *in vacuo*. The residue was triturated with ethanol. The resulting precipitate was collected by filtration, washed successively with ethanol and diisopropyl ether, and then dried to give 2.99 g (87%) of **20**, mp 255-258° (chloroform-ethanol); ir (potassium bromide): 1723, 1613 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.25-1.5 (4H, m, cyclopropyl CH$_2$CH$_2$), 4.2-4.4 (m, 1H, cyclopropyl CH), 5.05 (s, 2H, CH$_2$Br), 7.48 (s, 1H, 3-H), 7.93 (d, 1H, J = 9.5 Hz, 5-H), 8.78 (s, 1H, 8-H), 15.1 (broad s, 1H, COOH); ms: (SI) 380 (M$^+$+1), 362, 335.

Anal. Calcd. for C$_{16}$H$_{11}$BrFNO$_4$: C, 50.55; H, 2.92; Br, 21.02; F, 5.00; N, 3.68. Found: C, 50.68; H, 2.90; Br, 21.21; F, 4.93; N, 3.67.

2-Aminomethyl-9-cyclopropyl-4-fluoro-6,9-dihydro-6-oxo-furo[3,2-*h*]quinoline-7-carboxylic Acid (4).

A mixture of **20** (700 mg, 1.842 mmoles) and sodium azide (419 mg, 6.45 mmoles) in *N,N*-dimethylformamide (7.0 ml) was heated at 80° for 5 hours. The mixture was concentrated *in vacuo*. Dilute acetic acid was added to the residue. The resulting precipitate was collected by filtration, washed successively with water and ethanol, and then dried to give 610 mg (97%) of 2-azido-methyl-9-cyclopropyl-4-fluoro-6,9-dihydro-6-oxofuro[3,2-*h*]-quinoline-7-carboxylic acid (**21**).

A mixture of **21** (610 mg), triphenylphosphine (725 mg, 2.76 mmoles), water (0.5 ml), and *N,N*-dimethylformamide (6.0 ml) was stirred at room temperature for 6 hours. The mixture was

concentrated *in vacuo*. The residue was triturated with ethanol. The resulting precipitate was collected by filtration, washed with ethanol, and then dried to give 472 mg of crude crystals. Reprecipitation of the crystals, on treatment with aqueous acetic acid and subsequently with aqueous ammonia, gave 450 mg (79%) of **4**•1/4H$_2$O, mp 225-228°; ir (potassium bromide): 3380, 1734 cm^{-1}; ^{1}H nmr (deuterioacetic acid): δ 1.3-1.6 (m, 4H, cyclopropyl CH$_2$CH$_2$), 4.35-4.55 (m, 1H, cyclopropyl CH), 4.70 (s, 2H, C*H$_2$*NH$_2$), 7.38 (s, 1H, 3-H), 8.07 (d, 1H, J = 9.5 Hz, 5-H), 9.01 (s, 1H, 8-H); ms: (EI) 316 (M$^+$), 272.

Anal. Calcd. for C$_{16}$H$_{13}$FN$_2$O$_4$: C, 59.91; H, 4.24; F, 5.92; N, 8.73. Found: C, 59.96; H, 4.14; F, 5.84; N, 8.63.

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