Synthesis of 7-(Alkenyl, Cycloalkenyl, and 1,2,3,6-Tetrahydro-4-pyridinyl)quinolones

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A series of 1-cyclopropyl-1,4-dihydro-4-oxoquinolines was prepared in which the C-7 position is substituted with a vinyl, a 1-cyclopentenyl, or a 1,2,3,6-tetrahydro-4-pyridinyl group. These quinolones were synthesized *via* a palladium-catalyzed cross coupling of a 7-quinolyltriflate with an appropriately functionalized vinylstannane.

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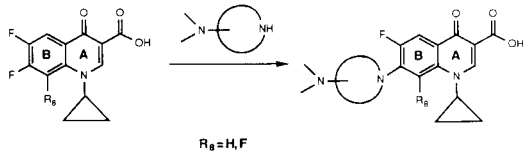
The reaction of 6,7-difluoroquinolone-3-carboxylic acid **1**, or its 6,7,8-trifluoroquinolone analog **2**, with nitrogen-heterocycles to afford the corresponding 7-substituted derivatives has become a standard operation in the preparation of quinolone antibacterials [1]. The high degree of regioselectivity, as well as the ease by which the nucleophilic aromatic substitution takes place, is mostly due to the resonance stabilization provided by the 4-carbonyl group of the 4-oxoquinoline ring system. Displacement of the C-7 fluorine can also be achieved by other nucleophiles, such as acyclic amines, alcohols and thiols [2]. Carbon-based nucleophiles, on the other hand, tend to add conjugatively to the C-2 position [3]. Thus, the incorporation of a carbon-bonded side chain at C-7 has required a nonconvergent approach involving elaboration of the side chain onto the aromatic ring **B** prior to or in conjunction with the construction of the heterocyclic ring **A** [4].

Figure 1

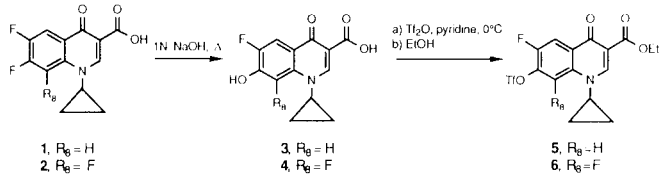


Recently, we reported the preparation of some novel 6-fluoro-1,8-naphthyridine antibacterials bearing a carbon-bonded, acyclic or cyclic vinyl substituent at C-7 [5]. The synthetic methodology for the acquisition of these compounds was based on a palladium-catalyzed cross coupling of a 7-chloro-1,8-naphthyridine with an appropriately substituted organotin reagent. We would like to present herein the extension of this methodology to the preparation of the corresponding 6-fluoro-4-oxoquinolyl derivatives.

Direct treatment of **1** (or its ethyl ester) with vinyltri-*n*-butyltin in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride resulted in the recovery of unchanged starting quinolone. As expected, aryl fluorides, unlike aryl iodides, bromides, and chlorides, do not undergo oxidative addition to palladium(0) complexes, even when activated by electron-withdrawing substituents on the ring [6]. Since the 7-fluoroquinolones are readily accessible from a variety of commercially available polyfluorinated benzenes, we made no attempts to prepare the more reactive 7-iodo or 7-bromo derivatives. Instead, the 7-fluoroquinolones were regiospecifically converted into the corresponding 7-quinolyltriflates, which coupled with a variety of organostannanes in the presence of lithium chloride and a palladium catalyst to form the new C-7 carbon-to-carbon bond.

Thus, treatment of **1** with a 1*N* aqueous solution of sodium hydroxide afforded the 7-hydroxy derivative **3** in essentially quantitative yield. Subsequent reaction of this compound with 2.5 equivalents of trifluoromethanesulfonic anhydride in pyridine, followed by ethanolysis of the resulting mixed anhydride intermediate, provided the 7-quinolyltriflate **5** in 72% yield (Scheme 1).

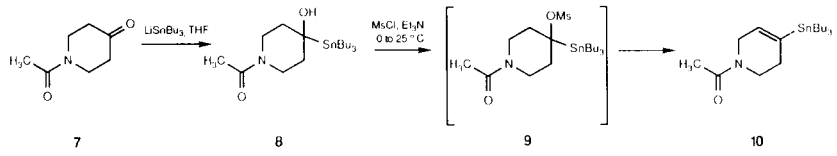
Scheme 1



1, R_8 = H
2, R_8 = F
3, R_8 = H
4, R_8 = F
5, R_8 = H
6, R_8 = F

The palladium-catalyzed cross coupling between 7-quinolyltriflate **5** and vinyltri-*n*-butyltin resulted, as expected, in the isolation of the 7-vinyl substituted quinolone **15** (Table 1, entry 1). The reaction was performed according to Stille's protocol [7], using 1.2 equivalents of the tin reagent, 3 equivalents of lithium chloride, and 2 mole % of either bis(triphenylphosphine)palladium(II) chloride or tetrakis(triphenylphosphine) palladium(0) as the catalyst. In some instances, additional amounts of the tin reagent and/or the catalyst were added to the reaction mixture to improve the yield of coupled product. Tetrahydrofuran or dioxane was used as the solvent, and the mixture was heated at gentle reflux overnight. The product was puri-

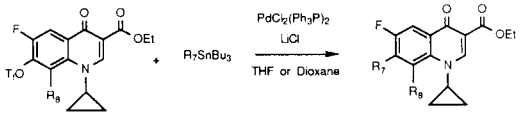
Scheme 2

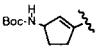


fied by trituration with cyclohexane, which removed most of the tin by-product, and finally by flash chromatography on silica gel.

A range of cyclic vinylstannanes bearing different functional groups also reacted with 7-quinolyltriflate **5** to afford the corresponding 7-substituted quinolones (Table 1, entries 2-3). The tin reagent **12** was prepared as reported previously [8], while **13** was synthesized from 1-acetyl-4-piperidone, **7**, by a sequence of reactions involving addition of lithium tri-*n*-butylstannate to the ketone, mesylation of the resulting alcohol, and subsequent elimination of the elements of methanesulfonic acid (Scheme 2) [9].

Table 1



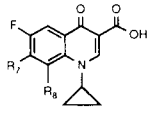
Entry	Substrate	R_8	Organotin	R_7	Product	% Yield
1	5	H	11	CH_2=CH-	15	(44)
2	5	H	12		16	(31)
3	5	H	13		17	(48)
4	6	F	11	CH_2=CH-	18	(74)
5	6	F	14		19	(22)

In all cases, the reaction proceeded with complete chemo and regioselectivity, and no C-6 substitution was detected. The yields of isolated product were usually moderate-to-good, with the exception shown in entry 2, Table 1. The low yield obtained in this particular case can be attributed to the unfavorable steric demands imposed by the presence of a bulky *tert*-butoxycarbonyl group at the 3-position of the cyclopentenylstannane [10]. Although we did not attempt to identify the by-products of this reaction, it is reasonable to assume that, in the absence of an effective transmetallation step, the product of the initial oxidative addition undergoes reductive elimination.

The extension of the above methodology to the synthesis of 7-substituted-6,8-difluoroquinolones, on the other hand, proved to be limited to very reactive, unhindered stannanes. Indeed, while the palladium-catalyzed coupling of 7-quinolyltriflate **6**, readily available from the 6,7,8-trifluoroquinolone **2** (Scheme 1), with vinyltri-*n*-butyltin afforded the 7-vinyl-6,8-difluoroquinolone **18** in 74% yield (entry 4, Table 1), the reaction of **6** with the cycloalkenylstannanes **13** and **14** [8,9] resulted in disappointingly low yields of the corresponding 7-substituted compounds. Prolonged reaction times and/or higher temperatures led, in most cases, to extensive decomposition of the starting 7-quinolyltrilfate, suggesting that the oxidative addition does take place, but the presence of the additional C-8 fluorine renders a palladium complex that is too sterically crowded for addition to cycloalkenylstannanes, and undergoes decomposition faster than transmetallation.

The quinolone esters **15**, **16**, **17**, and **18** were hydrolyzed with sodium hydroxide or hydrochloric acid (with concomitant removal of the *N*-*tert*-butoxycarbonyl or *N*-acetyl protecting groups) to afford the 7-(vinyl, 3-amino-1-cyclopenten-1-yl, or 1,2,3,6-tetrahydro-4-pyridinyl)-4-oxoquinoline-3-carboxylic acids **20**, **21**, **22**, and **23**, respectively (Table 2). These compounds were assayed against repre-

Table 2



Entry	Substrate	Product	R_7	R_8	% Yield
1	15	20	CH_2=CH-	H	(73)
2	16	21		F	(50)
3	17	22		H	(58)
4	18	23	CH_2=CH-	H	(69)

sentative Gram negative and Gram positive bacteria. Compared with their C-7 nitrogen-linked analogs, compound **21** was two to three dilutions less active *in vitro*, while **22** displayed essentially the same activity as the corresponding 4-piperazinyl substituted derivative. A detailed account of the microbiological data of these quinolones and their 1,8-naphthyridines counterparts is currently under preparation.

EXPERIMENTAL

Reactions were carried out in flame-dried glassware under an atmosphere of nitrogen or argon. Tetrahydrofuran was distilled from sodium benzophenone ketyl, dioxane from sodium, and dimethylformamide from calcium hydride. Organic solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a Büchi rotary evaporator. Thin-layer chromatography (tlc) was carried out on E. Merck silica gel 60 F_{254} pre-coated glass plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM, according to Still [11]. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded on a Nicolet MX-1 FTIR spectrometer. Proton (pmr) magnetic resonance spectra were obtained on either a Varian XL 200 or a Brüker AM 250 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Low (ms) and high resolution (hrms) mass spectra were recorded on either a Finnigan 4500 or a VG analytical 7070E/HF mass spectrometer. Elemental analysis were performed on a CEC 240XA elemental analyzer.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-hydroxy-4-oxo-3-quinolinecarboxylic Acid (**3**).

A solution of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, **1**, (12.07 g, 45.5 mmoles) in 1*N* sodium hydroxide (400 ml) was heated at reflux for 18 hours, and then allowed to cool to room temperature. The *p*H of the solution was adjusted to 4 with 5*N* hydrochloric acid, and the precipitated solid was filtered, washed successively with water and ether, and dried *in vacuo* to give **3** (11.90 g, 98%) as a tan powder; ir (potassium bromide): 1302, 1447, 1488, 1502, 1617, 1695, 1725 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.19-1.28 (m, 4H), 3.65-3.85 (m, 1H), 7.86 (d, 1H, J = 7.4 Hz), 7.95 (d, 1H, J = 11.0 Hz), 8.65 (s, 1H); ms: (ei) m/z 263 (M+), 243, 219 (base).

Anal. Calcd. for $C_{13}H_{10}FNO_4 \cdot 0.3HCl$: C, 56.95; H, 3.79; N, 5.11. Found: C, 56.89; H, 3.67; N, 5.12.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-hydroxy-4-oxo-3-quinolinecarboxylic Acid (**4**).

From 50.74 g (179 mmoles) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, **2**, the above procedure afforded **4** (46.08 g, 92%) as a yellow solid; ir (potassium bromide): 1326, 1472, 1617, 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.10-1.14 (m, 4H), 2.30-3.00 (br s, 1H), 3.98-4.09 (m, 1H), 7.96 (dd, 1H, J = 10.0, 2.0 Hz), 8.79 (s, 1H); ms: (ei) m/z 281 (M+), 237 (base), 222, 208.

Anal. Calcd. for $C_{13}H_9F_2NO_4 \cdot 0.2HCl$: C, 54.12; H, 3.21; N, 4.85. Found: C, 54.32; H, 3.07; N, 4.82.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[[(trifluoromethyl)sulfonyl]oxy]-3-quinolinecarboxylate (**5**).

To a solution of **3** (4.04 g, 15.3 mmoles) in dry pyridine (50 ml) at 0° (ice-water bath) was added dropwise triflic anhydride (10.80 g, 38.3 mmoles). The mixture was allowed to warm to room temperature and stirred for 2 hours overall. Absolute ethanol (30 ml) was added, and the solution stirred for an additional 45 minutes. It was then poured into water and the precipitated solid was filtered, washed with water, and dried *in vacuo* to give the title compound as a tan powder (4.34 g, 67%); ir (potassium bromide): 1242, 1497, 1618, 1727 cm^{-1}; pmr (deuteriochloroform): δ 1.17-1.18 (m, 2H), 1.30-1.44 (m, 2H), 1.41 (t, 3H, J = 7.0 Hz), 3.47-3.50 (m, 1H), 4.41 (q, 2H, J = 7.0 Hz), 7.96 (d, 1H, J = 6.0 Hz), 8.33 (d, 1H, J = 9.8 Hz), 8.63 (s, 1H); ms: (ei) m/z 423 (M+), 378, 351 (base), 290, 217.

Anal. Calcd. for $C_{16}H_{13}F_4NO_6S$: C, 45.41; H, 3.10; N, 3.31. Found: C, 45.63; H, 3.04; N, 3.21.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[[(trifluoromethyl)sulfonyl]oxy]-3-quinolinecarboxylate (**6**).

From 4.00 g (14.2 mmoles) of **4**, the above procedure provided **6** (3.90 g, 62%) as an off-white solid (3.90 g, 62%); ir (potassium bromide): 1244, 1483, 1621, 1733 cm^{-1}; pmr (deuteriochloroform): δ 1.10-1.12 (m, 2H), 1.22-1.26 (m, 2H), 1.34 (t, 3H, J = 7.1 Hz), 3.83-3.87 (m, 1H), 4.33 (q, 2H, J = 7.1 Hz), 8.12 (dd, 1H, J = 9.5, 2.1 Hz), 8.56 (s, 1H); ms: (ei) m/z 441 (M+), 396, 369 (base), 308, 235.

Anal. Calcd. for $C_{16}H_{12}F_5NO_6S$: C, 43.54; H, 2.74; N, 3.17. Found: C, 43.74; H, 2.56; N, 3.33.

General Procedure for the Coupling of Stannanes with 7-Quinolyltriflates. Ethyl 1-Cyclopropyl-7-ethenyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**15**).

A suspension of triflate **5** (1.02 g, 2.4 mmoles), bis(triphenylphosphinepalladium(II) chloride (0.034 g, 0.05 mmole), lithium chloride (0.31 g, 7.2 mmoles), vinyltri-*n*-butyltin (0.92 g, 2.9 mmoles), and 2,6-di-*tert*-butyl-4-methylphenol (5 crystals) in tetrahydrofuran (25 ml) was heated at 65° under nitrogen for 20 hours. The solvent was removed, the residue taken up in hexane and sonicated for *ca.* 20-30 minutes, and finally filtered to give 0.67 g of crude product. This material was chromatographed (dichloromethane-methanol 99:1) to afford the title compound (0.34 g, 44%) as a light yellow solid; ir (potassium bromide): 1167, 1241, 1472, 1620, 1727 cm^{-1}; pmr (deuteriochloroform): δ 1.16-1.22 (m, 2H), 1.32-1.35 (m, 2H), 1.41 (t, 3H, J = 7.1 Hz), 3.40-3.58 (m, 1H), 4.39 (q, 2H, J = 7.1 Hz), 5.61 (d, J = 11.0 Hz), 6.02 (d, 1H, J = 17.7 Hz), 6.96 (dd, 1H, J = 17.7, 11.0 Hz), 7.98 (d, 1H, J = 6.0 Hz), 8.08 (d, 1H, J = 10.7 Hz), 8.57 (s, 1H); ms: (ei) m/z 301 (M+), 256, 229 (base).

Anal. Calcd. for $C_{17}H_{16}FNO_3 \cdot 0.2H_2O$: C, 66.96; H, 5.42; N, 4.59. Found: C, 66.81; H, 5.34; N, 4.44.

Ethyl 1-Cyclopropyl-7-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1-cyclopenten-1-yl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**16**).

From 2.11 g (5.0 mmoles) of triflate **5**, 3.10 g (6.0 mmoles) of stannane **12**, 0.11 g (0.15 mmole) of bis(triphenylphosphine)palladium(II) chloride, 0.63 g (15.0 mmoles) of lithium chloride, and 2,6-di-*tert*-butyl-4-methylphenol (5 crystals) in dioxane (25 ml), the above procedure provided **16** (0.70 g, 31%) as a beige solid; ir (potassium bromide): 806, 1170, 1243, 1483, 1621, 1686, 1731

cm^{-1}; pmr (deuteriochloroform): δ 1.14-1.25 (m, 2H), 1.32-1.40 (m, 2H), 1.41 (t, 3H, J = 7.2 Hz), 1.48 (s, 9H), 1.70-1.80 (m, 1H), 2.47-2.66 (m, 1H), 2.70-3.07 (m, 2H), 3.43-3.56 (m, 1H), 4.40 (q, 2H, J = 7.1 Hz), 4.68-4.84 (m, 1H), 4.90-5.09 (m, 1H), 6.50 (br s, 1H), 7.83 (d, 1H, J = 6.1 Hz), 8.10 (d, 1H, J = 11.6 Hz), 8.59 (s, 1H); ms: (fab) m/z 457 (M + 1).

Anal. Calcd. for $C_{25}H_{29}FN_2O_5$: C, 65.77; H, 6.40; N, 6.14; F, 4.16. Found: C, 65.90; H, 6.36; N, 5.88; F, 4.42.

Ethyl 7-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**17**).

From 2.50 g (5.9 mmoles) of triflate **5**, 3.50 g (8.4 mmoles) of stannane **13**, 0.75 g (1.1 mmoles) of bis(triphenylphosphine)palladium(II) chloride, 0.90 g (20.0 mmoles) of lithium chloride, and 2,6-di-*tert*-butyl-4-methylphenol (5 crystals) in dioxane (60 ml), the above procedure provided **17** (1.13 g, 48%) as an off-white solid; ir (potassium bromide): 806, 1031, 1165, 1242, 1472, 1545, 1619, 1720 cm^{-1}; pmr (deuteriochloroform): δ 1.14-1.18 (m, 2H), 1.28-1.50 (m, 2H), 1.41 (t, 3H, J = 7.1 Hz), 2.17 and 2.19 (2 x s, 3H, CH_3CO), 2.50-2.70 (m, 2H), 3.42-3.54 (m, 1H), 3.68-3.75 (m, 1H), 3.83-3.89 (m, 1H), 4.18-4.22 (m, 1H), 4.25-4.50 (m, 1H), 4.43 (q, 2H, J = 7.1 Hz), 6.05-6.20 (2 x m, 1H), 7.77 (d, 1H, J = 6.0 Hz), 8.09 (dd, 1H, J = 11.0, 1.5 Hz), 8.59 (s, 1H); ms: (ei) m/z 398 (M+), 353, 326 (base), 284, 255, 82.

Anal. Calcd. for $C_{22}H_{23}FN_2O_4 \cdot 0.5CH_2Cl_2$: C, 61.29; H, 5.49; N, 6.35. Found: C, 61.66; H, 5.21; N, 6.11.

Ethyl 1-Cyclopropyl-7-ethenyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (**18**).

From 2.00 g (4.5 mmoles) of triflate **6**, 1.48 g (4.7 mmoles) of vinyltri-*n*-butyltin, 0.07 g (0.10 mmole) of bis(triphenylphosphine)palladium(II) chloride, 0.68 g (13.6 mmoles) of lithium chloride, and 2,6-di-*tert*-butyl-4-methylphenol (5 crystals) in tetrahydrofuran (24 ml), the above procedure provided **18** (1.07 g, 74%) as a light yellow solid; ir (potassium bromide): 1251, 1324, 1548, 1622, 1698, 1728 cm^{-1}; pmr (deuteriochloroform): δ 1.00-1.40 (m, 4H), 1.41 (t, 3H, J = 7.0 Hz), 3.89-3.98 (m, 1H), 4.39 (q, 2H, J = 7.0 Hz), 5.79 (d, 1H, J = 12.0 Hz), 6.21 (d, 1H, J = 18.0 Hz), 6.82 (dd, 1H, J = 18.0, 12.0 Hz), 7.97 (dd, 1H, J = 12.0, 2.0 Hz), 8.60 (s, 1H); ms: (ei) m/z 319 (M+), 274, 247 (base), 246.

Anal. Calcd. for $C_{17}H_{15}F_2NO_3 \cdot 0.3H_2O$: C, 62.88; H, 4.84; N, 4.31; F, 11.70. Found: C, 62.91; H, 5.04; N, 3.92; F, 11.49.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-oxo-1-cyclopenten-1-yl)-3-quinolinecarboxylate (**19**).

From 3.38 g (7.7 mmoles) of triflate **6**, 3.10 (g (8.4 mmoles) of stannane **14**, 0.11 g (0.15 mmole) of bis(triphenylphosphine)palladium(II) chloride, 0.97 g (23.0 mmoles) of lithium chloride, and 2,6-di-*tert*-butyl-4-methylphenol (3 crystals) in tetrahydrofuran (70 ml), the above procedure provided **19** (0.62 g, 22%) as a yellow solid after recrystallization from ethanol; pmr (deuteriochloroform): δ 1.10-1.20 (m, 2H), 1.22-1.35 (m, 2H), 1.41 (t, 3H, J = 7.0 Hz), 2.55-2.70 (m, 2H), 3.15-3.25 (m, 2H), 3.85-4.05 (m, 1H), 4.44 (q, 2H, J = 7.0 Hz), 6.60-6.70 (m, 1H), 8.10 (dd, 1H, J = 10.0, 2.0 Hz), 8.65 (s, 1H).

Anal. Calcd. for $C_{20}H_{17}F_2NO_4$: C, 64.34; H, 4.59; N, 3.75. Found: C, 64.16; H, 4.63; N, 3.88.

1-Cyclopropyl-7-ethenyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**20**).

A solution of **15** (0.26 g, 0.82 mmole) in a 1:1 mixture of tetrahydrofuran-ethanol (20 ml) was treated with 1*N* sodium hydroxide (5 ml), and the mixture heated at reflux for 18 hours. The volatiles were removed on a rotary evaporator and the remaining solution was titrated to *p*H 4 with concentrated hydrochloric acid. The precipitated solid was filtered, washed with ethanol and ether, and dried *in vacuo* to give the title compound (0.16 g, 73%) as a tan solid; ir (potassium bromide): 1506, 1542, 1608, 1730 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.00-1.22 (m, 2H), 1.24-1.40 (m, 2H), 3.80-4.00 (m, 1H), 5.79 (d, 1H, J = 11.2 Hz), 6.29 (d, 1H, J = 17.7 Hz), 7.05 (dd, 1H, J = 17.7, 11.2 Hz), 8.01 (d, 1H, J = 10.6 Hz), 8.45 (d, 1H, J = 6.0 Hz), 8.74 (s, 1H), 14.80 (br s, 1H); ms: (ci) m/z 274 (M + 1), 256, 229 (base).

Anal. Calcd. for $C_{15}H_{12}FNO_3 \cdot 0.3H_2O$: C, 64.65; H, 4.56; N, 5.03. Found: C, 64.76; H, 4.73; N, 4.92.

7-(3-Amino-1-cyclopenten-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**21**).

A solution of **16** (0.60 g, 1.3 mmoles) in tetrahydrofuran (25 ml) was treated with 5*N* hydrochloric acid (10 ml) and the resulting mixture stirred at 40-50° for 24 hours and at 25° for an additional 75 hours. The precipitated solids were filtered, washed with cold methanol and ether, and dried *in vacuo* to give **21** (215 mg, 50%) as an off-white solid; ir (potassium bromide): 746, 812, 867, 904, 1334, 1505, 1611, 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.08-1.50 (m, 4H), 1.90-2.10 (m, 1H), 2.33-2.59 (m, 2H), 2.82-3.01 (m, 1H), 3.02-3.22 (m, 1H), 3.82-4.06 (m, 1H), 4.35-4.58 (m, 1H), 6.49-6.72 (m, 1H), 8.07 (d, 1H, J = 10.9 Hz), 8.14-8.27 (m, 1H), 8.30-8.55 (m, 3H, NH_3+), 8.76 (s, 1H), 14.50-15.00 (br m, 1H); ms: (ei) m/z 328 (M), 284 (base), 267, 82.

Anal. Calcd. for $C_{18}H_{17}FN_2O_3 \cdot HCl \cdot H_2O$: C, 56.47; H, 5.27; N, 7.32. Found: C, 56.27; H, 5.19; N, 6.95.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3-quinolinecarboxylic Acid (**22**).

A solution of **17** (0.80 g, 2.0 mmoles) in 6*N* hydrochloric acid (50 ml) was heated on a steam bath for 2.75 hours, and then concentrated *in vacuo*. The residue was taken up in water (30 ml) and filtered to remove small amounts of solid material. The clear filtrate was titrated to *p*H 7 with dilute sodium hydroxide, cooled in an ice bath, and the precipitated solid was filtered and washed with water. This solid was then resuspended in water (20 ml) and redissolved by slow addition of 1*N* sodium hydroxide up to *p*H 11.5. The aqueous solution was extracted with dichloromethane, and then titrated to *p*H 7.4 with dilute hydrochloric acid; the precipitated solid was filtered, washed with water, and dried *in vacuo* to give the title compound (0.38 g, 58%) as an off-white solid, mp 233-234° dec; pmr (hexadeuteriodimethyl sulfoxide-trifluoroacetic acid): δ 1.20-1.25 (m, 2H), 1.30-1.34 (m, 2H), 2.77 (br s, 2H), 3.36-3.45 (m, 2H), 3.76-3.90 (m, 3H), 6.33 (s, 1H), 8.06 (d, 1H, J = 11.1 Hz), 8.19 (d, 1H, J = 6.3 Hz), 8.77 (s, 1H), 9.00-9.10 (m, 1H); ms: (ei) m/z 328 (M), 284 (base).

Anal. Calcd. for $C_{18}H_{17}FN_2O_3 \cdot 0.1H_2O$: C, 65.48; H, 5.25; N, 8.49. Found: C, 65.34; H, 5.15; N, 8.84.

1-Cyclopropyl-7-ethenyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**23**).

To a solution of **18** (0.30 g, 0.94 mmole) in a 1:1 mixture of tetrahydrofuran-methanol (20 ml) was added 0.5*N* sodium hydroxide (5 ml). The mixture was heated at reflux for 3 hours,

cooled to room temperature, and titrated to *p*H 4 with concentrated hydrochloric acid. The precipitated solid was filtered, washed with cold water, and dried *in vacuo* to give **23** (0.19 g, 69%) as a yellow solid, mp 200-204° dec; ir (potassium bromide): 1283, 1625, 1700, 1725, 3056 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.00-1.40 (m, 4H), 4.15-4.22 (m, 1H), 5.95 (d, 1H, J = 12.0 Hz), 6.20 (d, 1H, J = 18.0 Hz), 6.88 (dd, 1H, J = 18.0, 12.0 Hz), 7.91 (dd, 1H, J = 10.5, 2.0 Hz), 8.75 (s, 1H), 14.47 (br s, 1H); ms: (ei) m/z 291 (M+), 247 (base), 246.

Anal. Calcd. for $C_{15}H_{11}F_2NO_3$: C, 61.76; H, 3.81; N, 4.81. Found: C, 61.83; H, 3.76; N, 4.69.

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