A General Method for the Preparation of 2-Substituted-4-oxo-3-quinolinecarboxylic Acids

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A general method for preparing 2-substituted-4-oxo-3-quinolinecarboxylic acids and 2-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids as new analogs in the quinolone class of antiinfectives has been developed. The reaction of a Grignard reagent in the presence of copper(I) iodide with the 4-oxo-3-quinolinecarboxylic acid esters and 4-oxo-1,8-naphthyridine-3-carboxylic acid esters yields the desired 2-substituent. Reintroduction of the 2,3-double bond is effected by phenylselenation of the 3-position, oxidation to the selenoxide, and *in situ* syn-elimisation. Depending on the degree of steric crowding between the 2-substituent and the 3-carboxylic acid group, hydrolysis of the ester to the carboxylic acid could be carried out under acidic or basic conditions.

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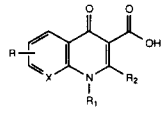
We would like to report a new and general method for preparing 2-substituted-4-oxo-3-quinolinecarboxylic acids and 4-oxo-1,8-naphthyridine-3-carboxylic acids of general structure **1**. Compounds such as **1** belong to the "quinolone" class of antibacterial agents. These types of antimicrobials have received much attention and interest both chemically and clinically. The chemical literature contains a number of publications describing C-2 substituted quinolones. These reports primarily describe various C-2 to N-1 bridged analogs [1-7,15,16] of structure **2**. Only the C-2 methyl, hydroxyl, or alkylthio analogs have been reported in which no bridge between N-1 and C-2 exists [8-14] (**3**).

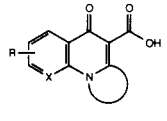
The reported methods for preparing C-2 alkylated 4-oxo-3-quinolinecarboxylic acids are somewhat limited (Figure 2). One method involves the condensation of an

Figure 1



R_1, R_2 = alkyl, alkenyl, aryl
X = N, C-halogen, C-H

1



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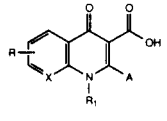
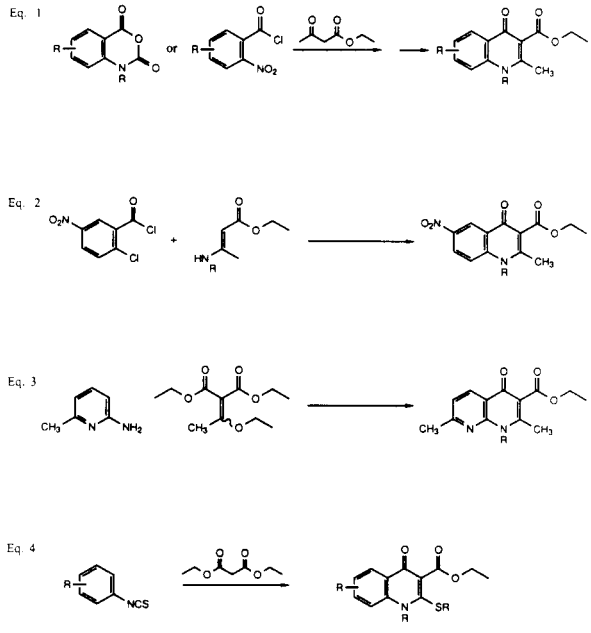


3

A = CH_3, SCH_3, OH

isatoic anhydride or an activated 2-nitrobenzoic acid derivative with ethyl acetoacetate to give 2-methyloxolinic acid derivatives [9,11] (Eq 1). An alternative is the condensation of a 2-chlorobenzoyl chloride with a 3-alkylamino methacrylate to produce 2-methyl-*N*-alkyl-4-oxo-3-quinolinecarboxylic acids [8] (Eq 2). A third alternative employs the condensation of a 2-aminopyridine with diethyl ethoxyethylidinemalonate at high temperatures to give a 2-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid [10] (Eq 3). The 2-thioalkyl analogs are prepared by condensation of an arylisothiocyanate with a malonic acid derivative followed by cyclization [14] (Eq 4).

Figure 2



These approaches are restricted by the poor availability of both the aryl precursors and the pyridone ring synthons carrying substituents other than methyl. The necessity of

the complete synthesis of the 4-oxoquinoline or 4-oxo-1,8-naphthyridine ring system for each new C-2 substituent desired is an additional drawback to these methods.

We have developed a general method for preparing a wide variety of C-2 substituted 4-oxo-3-quinolinecarboxylic acids and 4-oxo-1,8-naphthyridine-3-carboxylic acids. This method has the advantage of being capable of providing multiple analogs from a common intermediate *via* its reaction with a Grignard reagent.

This approach is based upon the known ability of Grignard reagents catalyzed by copper(I) ions or lithium diorganocopper reagents to add to 2,3-unsaturated esters in a 1,4 manner [17]. We viewed the 4-oxo-3-quinolinecarboxylates as a doubly activated system by virture of the fact that both the 4-carbonyl and 3-carbethoxy groups both activate the C-2 position. We reasoned that carbon nucleophiles would add to the C-2 position in a Michael fashion to afford the C-2 substituted adduct with good selectivity. This has proven to be the case for 4-oxo-3-quinoline- and 4-oxo-1,8-naphthyridine-3-carboxylic acid esters.

Treatment of ethyl 6,7,8-trifluoro-4-oxo-quinoline-3-carboxylate (**4**) with methylmagnesium halide in the presence of cuprous iodide readily gave ethyl 2,3-dihydro-2-methyl-6,7,8-trifluoro-4-oxo-quinoline-3-carboxylate (**5a**). This addition reaction is also applicable to phenyl and vinyl Grignards which give **5b** and **5c**, respectively, Figure 3. We briefly examined the use of a diorganolithio copper reagent in place of a Grignard species and found that this too would successfully add to C-2 (Table I, Entry 5). It was observed that excess organometallic reagent and excess cuprous iodide do not substantially improve the overall yield of the addition product (Table I, Entries 3 and 4). Moreover, for the 4-oxo-1,8-naphthyridine nucleus, **6**, this procedure, employing methylmagnesium bromide, gave the adduct **7** (Table I, Entry 6).

Figure 3

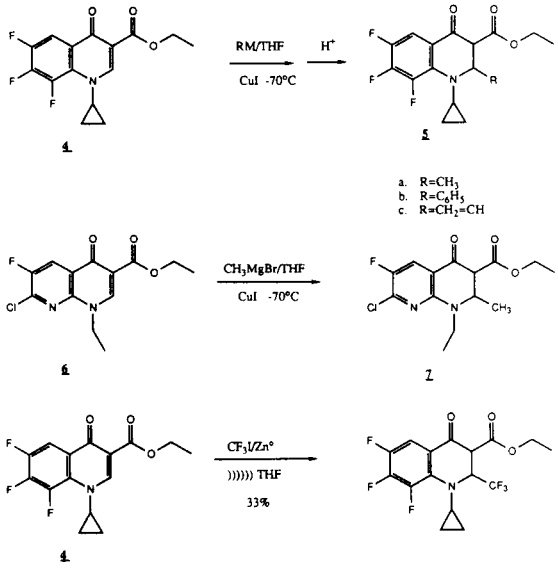


Table I

Entry	Substrate [a]	RM (mole %)	CuI (mole %)	Product [b] (yield, %)
1	**4**	CH_3MgBr (100)	30	**5a** (66)
2	**4**	C_6H_5MgCl (200)	10	**5b** (44)
3	**4**	$CH_2CHMgBr$ (100)	10	**5c** (80)
4	**4**	$CH_2CHMgBr$ (200)	30	**5c** (88)
5	**4**	CH_3Li (400)	200	**5a** (62)
6	**6**	CH_3MgBr (100)	30	**7** (66)

[a] All reactions run in THF at –70° except entry 2 which was run in diethyl ether. [b] Isolated yield.

For purposes of extending the scope of this reaction, we studied the introduction of a trifluoromethyl group at the 2-position. The known organometallic trifluoromethyl species capable of acting as a nucleophile are limited to the cuprous [18] and zinc [19] derivatives. Using the procedure employing zinc and ultrasonic irradiation [19], it is possible to add the trifluoromethyl anion to the C-2 position of **4** to give **8** in a low but still usable yield.

With the availability of several potentially interesting new 4-oxoquinoline structures, we turned our attention to the reintroduction of the 2,3 double bond into the Michael addition products, **5a-c**, **7**, and **8**. Our initial attempts involving quinone-based oxidation, as is successful with

FIGURE 4

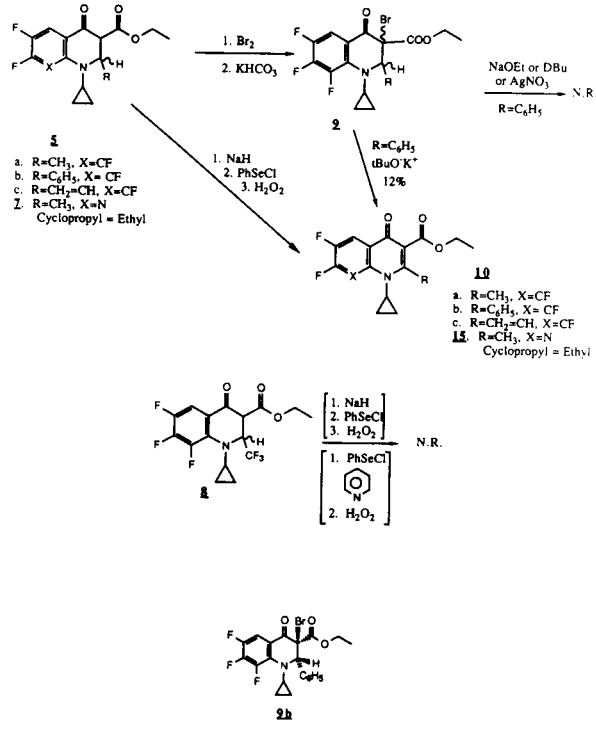
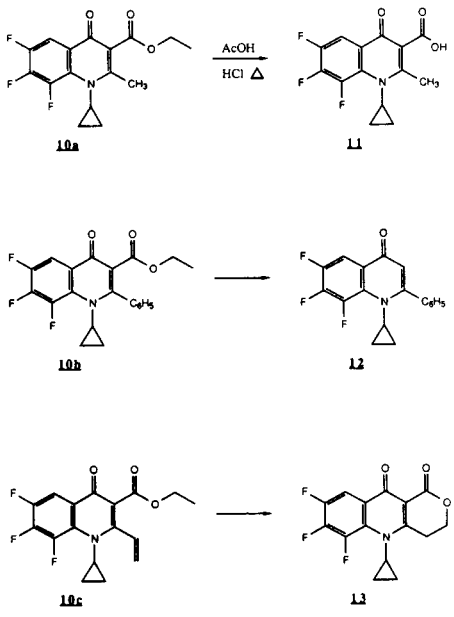


FIGURE 5



2-unsubstituted-2,3-dihydro-4-oxoquinolines [20], and similar systems [21] proved completely unsuccessful in our case. Addition of molecular bromine to **5b** followed by basic workup produced the 2-phenyl-3-bromo-product **9b** in good yield. The analogous reaction on the 2-methyl analog **5a** gave the desired 3-bromo-2-methyl compound **9a**, but attempted purification of **9a** resulted in extensive decomposition. Dehydrobromination of **9b** was attempted using sodium ethoxide, potassium *t*-butoxide, DBU, or silver nitrate. These methods gave low yields of the desired products. From the reaction of potassium *t*-butoxide with **9b** approximately 15% yield of **10b** was obtained along with recovered **9b**. These results can be rationalized on the basis of the probable existence of an anti orientation of the 3-bromo and 2-phenyl substituents which would preclude a normal antiperiplanar dehydrobromination.

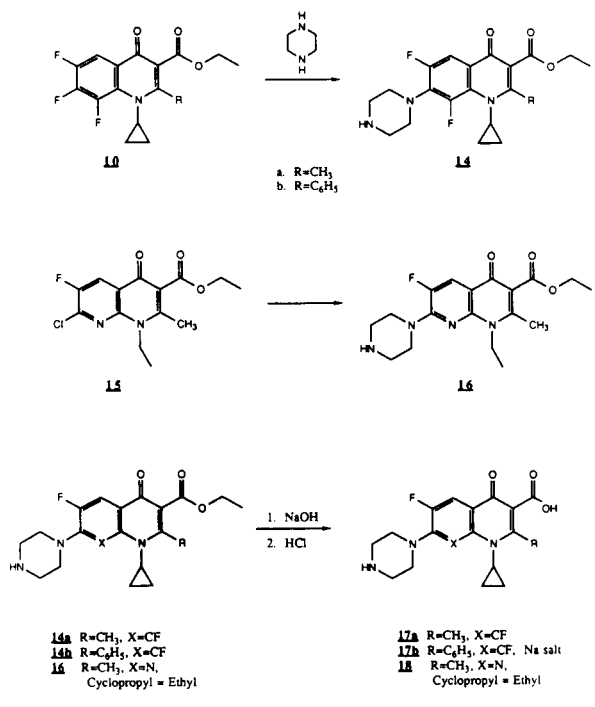
The proposed existence of a syn orientation of the C-3 bromine and the C-2 hydrogen suggested that selenium based syn-elimination chemistry [22] might be successful in introducing the desired 2,3-unsaturation. Indeed, addition of phenylselenyl chloride to the anion of **5a-c** and **7** followed by oxidation and *in situ* elimination readily produced the desired esters, **10a**, **10b**, **10c**, and **10d**.

However, this elimination failed with the 2-trifluoromethyl derivative, **8**, to give any oxidized product. We attribute this failure to a change in the site of selenation from predominantly at C-3 in the previous cases to exclusively *O*-selenation in the case of **8** (2-CF_3). Thus oxidation and subsequent hydrolysis regenerates **8**. The alternative procedure of Liotta [23] was also unsuccessful.

In order to produce the corresponding 4-oxo-3-quinoline-3-carboxylic acids, the hydrolysis of the esters was examined. Previous workers have successfully employed acetic acid/hydrochloric acid mixtures at reflux. For acid **10a**, this type of hydrolysis gave the acid **11a**, albeit in a surprisingly low yield. Acetic acid/hydrochloric acid hydrolysis of the phenyl derivative **10b** led to decarboxylation giving **12**. These results are likely due to initial hydrolysis followed by decarboxylation as a means of relieving steric crowding. Compound **10c** was hydrolyzed to **11c** successfully but the product exists exclusively as the cyclized structure **13**, and as **13**, decarboxylation is precluded.

The alternative base-catalyzed hydrolysis seemed as risky as acid hydrolysis had proven to be. This conclusion was based on the fact that the quinolones are susceptible to displacement of the 7-fluorine atom by hydroxide ion [24]. Since our ultimate goal was to produce 7-heterocyclic-amine substituted quinolones, it was decided to couple an amine to the esters **10a**, **10b**, and **8** and to perform the necessary hydrolysis on the coupled products. Thus, reaction of piperazine with **10a**, **10b**, and **8** provided the 7-piperazinylquinolone esters **14a**, **14b**, and **16**. For **10c** addition of piperazine was unsuccessful; the only isolable product appeared to be the one arising from 1,6 addition of the amine to the vinyl group.

FIGURE 6



For **14a**, **14b**, and **16** hydrolysis of the esters under basic conditions was straightforward and gave the targeted structures **17a**, **17b**, and **18**, respectively.

All these compounds possessed minimum inhibitory concentrations greater than 25 micrograms/milliliter, which is in contrast to the known activity of the C-2 to N-1

bridged analogs, but is in agreement with the reported inactivity of the known C-2 methylated analogs.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Nicolet FT IR SX-20 with 2 cm^{-1} resolution. Proton magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts are reported in delta units relative to tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with a 11/250 data system. Column chromatography was performed with W. R. Grace silica gel 60, 230-400. Solutions were dried over magnesium sulfate. All concentrations of solutions were performed under reduced pressure on a Buchi rotary evaporator. The CHN elemental analyses were performed on either a Control Equipment Corporation Model 240XA or a Carlo-Erba Model 1106 Elemental Analyzer and halogen determinations were performed by the closed flask combustion method, employing a titrimetric determination. All new products and intermediates had analytical results within +/−0.4% of theoretical values. The hplc purity of the final products was performed on reverse phase C18 columns using 20% tetrahydrofurna/80% 0.05*M* ammonium phosphate buffer (*p*H 3.0) mobile phase at 1.0 m*ℓ*/minute with product detection by absorbance at 287 nm.

General Method for Addition of an Organometallic Reagent to a Quinolone Ester.

1-Cyclopropyl-6,7,8-trifluoro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (**5a**).

A slurry composed of 15 g (48.2 mmoles) of **4** [25] and 2.7 g (14.2 mmoles) of cuprous iodide in 1 *ℓ* of tetrahydrofuran, was treated with 26 m*ℓ* of 2.8 *M* methylmagnesium bromide (72.8 mmoles) at −70°. The greenish-yellow mix was stirred at −70° for 1.5 hours. Saturated ammonium chloride solution (500 m*ℓ*) was then added at −70° and the mixture allowed to warm to room temperature. The tetrahydrofuran was removed and the residue extracted with 1.2 *ℓ* of methylene chloride. The organic layer was washed with saturated sodium chloride solution, dried, and concentrated to give 16 g of crude product. The crude material was taken up in methylene chloride and eluted through a silica gel column. The appropriate fractions were pooled and evaporated to yield 11 g (70%), which was recrystallized from 95% ethanol to give 9.57 g (61%) of **5a**, mp 76-78°; ir (potassium bromide): 1662, 1509, 1278, 1239, 647 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 12.10 (br s, 1H), 7.27 (apparent dt, 1H, J = 10, 2.3 Hz), 4.40-4.10 (m, 3H), 3.24-2.97 (m, 1H), 1.30 (t, 3H), 1.16 (d, 3H, J = 6.3 Hz), 0.60-0.95 (m, 4H); ms: − M^+ = 327, 312, 266 (base).

Anal. Calcd. for $C_{16}H_{16}F_3NO_3$: C, 58.72; H, 4.93; N, 4.28; F, 17.41. Found: C, 58.76; H, 4.81; N, 4.14; F, 17.50.

1-Cyclopropyl-6,7,8-trifluoro-1,2,3,4-tetrahydro-2-phenyl-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester **5b**.

Ester **4** (5.45 g, 17.5 mmoles), cuprous iodide (0.33 g, 1.7 mmoles), and phenylmagnesium chloride (2.0 *M*, 8.75 m*ℓ*, 17.5 mmoles) in diethyl ether at −10° were employed in this experiment following the procedure described for **5a**. It was necessary to add a second 8.75 m*ℓ* of phenylmagnesium chloride to consume all starting material. The crude product was purified by crystallization from 95% ethanol to give **5b** as bright yellow crystals (3.02 g, 44%); ir (potassium bromide): 3600-3400, 3200-3000, 1659, 1510, 1242, 1041, 870, 814, 702 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 12.25 (br s, 1H), 7.40-7.22 (m, 6H), 5.37 (s, 1H), 4.21 (q, 2H, J = 7 Hz), 2.94-2.86 (m, 1H), 1.23 (t, 3H, J = 7 Hz), 0.88-0.79 (m, 4H); ms: − M^+ = 389, 324 (base), 266.

Anal. Calcd. for $C_{21}H_{18}F_3NO_3$: C, 64.77; H, 4.59; N, 3.60; F, 14.64. Found: C, 64.65; H, 4.66; N, 3.47; F, 14.43.

7-Chloro-1-ethyl-6-fluoro-1,2,3,4-tetrahydro-2-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**7**).

Ester **4** (3.06 g, 10.2 mmoles), cuprous iodide (0.75 g, 3.9 mmoles), and methylmagnesium bromide (3.0 *M*, 3.5 m*ℓ*, 10.5 mmoles) were employed in this experiment following the procedure described for **5a**. It was necessary to add a second 3.5 m*ℓ* of methylmagnesium bromide to consume all starting material. The crude product was purified by flash chromatography on silica gel with methylene chloride to give **7** as bright yellow crystals (2.14 g, 66%). This material was used without further purification in the next reaction; ir (potassium bromide): 3000-2800, 1659, 1376, 1257, 743 cm^{-1}; ^{1}H nmr (deuteriochloroorm): ppm 12.00 (s, 0.8 H) enol, 7.84 (d, 0.2, J = 7.5) keto, 7.57 (d, 0.8, J = 7.5) enol, 4.57 (q, 1H), 4.43-3.91 (m, 4H), 3.25-3.07 (m, 1H), 1.39-1.15 (m, 9H); ms: − M^+ = 314, 299, 253 (base).

1-Cyclopropyl-2-ethenyl-6,7,8-trifluoro-1,2,3,4-tetrahydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester **5c**.

Ester **4** (5.45 g, 17.5 mmoles), cuprous iodide (1.0 g, 5.3 mmoles), and vinylmagnesium bromide (1.0 *M*, 35 m*ℓ*, 35 mmoles) were employed as described for **5a**. The crude product was purified by flash chromatography on silica gel with methylene chloride to give **5c** as bright yellow crystals (5.22 g, 88%); ir (potassium bromide): 3100-2800, 1658, 1510, 1240, 1041, 645 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 12.03 (br s, 1H), 7.23-7.17 (m, 1H), 5.78-5.67 (m, 1H), 5.04 (d, 1H, J = 17 Hz), 4.95 (d, 1H, J = 10 Hz), 4.70 (d, 1H, J = 5.8 Hz), 4.23 (q, 2H, J = 7.5 Hz), 2.98 (m, 1H), 1.28 (t, 3H, J = 7.5 Hz), 0.81-0.56 (m, 4H); ms: − M^+ = 339, 321, 293, 266 (base).

Anal. Calcd. for $C_{17}H_{16}F_3NO_3$: C, 59.07; H, 4.34; N, 4.31. Found: C, 59.06; H, 4.35; N, 4.04.

General Procedure for Reintroduction of the 2,3 Double Bond [22].

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-2-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**15**).

Sodium hydride (0.40 g, 60% by wt of oil dispersion) was placed in the reaction vessel and rinsed once with tetrahydrofuran, then suspended in 40 m*ℓ* of dry tetrahydrofuran, cooled to 0°, and the crude enol ester **7** (2.0 g, 6.35 mmoles) in 8 m*ℓ* of dry tetrahydrofuran was added over a 20 minute period. Phenylselenyl chloride (1.34 g, 7.0 mmoles) in 5 m*ℓ* of dry tetrahydrofuran was then added rapidly and the solution poured slowly into a beaker with 50 m*ℓ* of 1/1 v/v ether-pentane, 25 m*ℓ* of saturated sodium bicarbonate solution, and ice with stirring. The aqueous layer was separated and washed with ether-pentane and the combined organic extracts washed with saturated sodium bicarbonate solution, and ice with stirring. The aqueous layer was separated and washed with ether-pentane and the combined organic extracts washed with saturated sodium chloride solution, dried, and evaporated to give 3.0 g of crude selenide. The crude selenide in 30 m*ℓ* of methylene chloride was oxidized by slow addition of 1.8 m*ℓ* of 30% hydrogen peroxide in 3 m*ℓ* of water (15.8 mmoles) keep-

ing the temperature between 25-30° by occasionally using an ice bath. Addition was complete in 20 minutes and reaction allowed to stir for 10 minutes. The reaction was then poured into 25 mℓ of methylene chloride and 10 mℓ of 10% sodium bicarbonate with stirring. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated sodium chloride, dried, and evaporated to give crude **15**. Recrystallization from tetrahydrofuran/hexane yielded 0.97 g (49%) of **15**; ^{1}H nmr (deuteriochloroform): ppm 8.40 (d, 1H, J = 7.3 Hz), 4.58-4.38 (m, 4H), 2.58 (s, 3H), 1.44-1.37 (m, 6H); ms: M$^+$ = 312, 267, 240 (base), 212.

Anal. Calcd. for $C_{14}H_{14}ClFN_2O_3$: C, 53.76; H, 4.51; N, 8.96. Found: C, 53.90; H, 4.66; N, 9.01.

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-2-methyl-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester **10a**.

The quinoline **5a** (3.8 g, 11.6 mmoles) was treated as described for the preparation of **15** with sodium hydride (0.7 g, 21 mmoles), phenylselenyl chloride (2.4 g, 12.7 mmoles), and 30% hydrogen peroxide (3.0 g, 26.5 mmoles) to give crude **10a**. Purification was accomplished *via* flash chromatography on silica gel using 5% methanol in methylene chloride to elute **10a**. After pooling the appropriate fractions and evaporation of the solvent, crystallization from 95% ethanol gave **10a** (3.02 g, 80%); ir: (potassium bromide); 3100-2900, 1725, 1611, 1485, 1211, 1126, 839, 792 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.84 (apparent dt, 1H, J = 8, 2.3 Hz), 4.32 (q, 2H, J = 6.9 Hz), 3.59-3.53 (m, 1H), 2.56 (s, 3H), 1.31 (t, 3H, J = 6.9 Hz), 1.27-1.20 (m, 2H), 0.80-0.78 (m, 2H); ms: M$^+$ = 325, 280, 264, 252 (base).

Anal. Calcd. for $C_{16}H_{14}F_3NO_3$: C, 59.07; H, 4.34; N, 4.31; F, 17.52. Found: C, 58.90; H, 4.35; N, 4.27; F, 17.42.

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-2-phenyl-3-quinolinecarboxylic Acid Ethyl Ester **10b**.

The quinoline **5b** (16.7 g, 43 mmoles) was treated as described for the synthesis of **15** with sodium hydride (1.68 g, 70 mmoles), phenylselenyl chloride (10.0 g, 52.2 mmoles), and 30% hydrogen peroxide (12.0 g, 106 mmoles) to give crude **10b**. Purification was accomplished *via* flash chromatography on silica gel using 5% methanol in methylene chloride to elute **10b**. After pooling the appropriate fractions and evaporation of the solvent, crystallization from 95% ethanol gave **10b** (8.8 g, 53%); ir (potassium bromide): weak 3100-2900, 1740, 1611, 1481, 1415, 1176, 1109, 1034, 704 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): ppm 7.94-7.87 (m, 1H), 7.65-7.62 (m, 2H), 7.55-7.52 (m, 3H), 3.87 (q, 2H, J = 6.8 Hz), 3.62-3.37 (m, 1H), 0.83 (t, 3H, J = 6.8 Hz), 0.75-0.64 (m, 4H); ms: M$^+$ = 388, 342, 322, 312 (base).

Anal. Calcd. for $C_{21}H_{16}F_3NO_3$: C, 65.13; H, 4.10; N, 3.62. Found: C, 64.96; H, 4.27; N, 3.62.

1-Cyclopropyl-2-ethenyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester **10c**.

The quinolone **5c** (1.00 g, 2.9 mmoles) was treated as described above with sodium hydride (0.11 g, 4.6 mmoles), phenylselenyl chloride (0.71 g, 3.7 mmoles), and 30% hydrogen peroxide (1.0 g, 8.8 mmoles) to give crude **10c**. Purification was accomplished *via* flash chromatography on silica gel using 5% methanol in methylene chloride to elute **10c**. Pooling the appropriate fractions and evaporation of the solvent gave **10c** (0.64 g, 64%); ir (potassium bromide): 3000-2800, 1736, 1612, 1485, 1120, 635 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.9 (m, 1H), 6.83 (dd, 1H, J = 17.7, 11.6), 5.19 (d, 1H, J = 17.7), 5.78 (d, 1H, J = 11.6), 4.32 (q, 2H, J = 6.91), 3.59-3.56 (m, 1H), 1.26 (t, 3H, J = 6.91), 1.17-1.14 (m, 2H), 0.76-0.74 (m, 2H); ms: M$^+$ = 337, 292, 264 (base).

Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.53; H, 4.18; N, 4.15. Found: C, 60.19; H, 4.05; N, 3.96.

1-Cyclopropyl-6,7,8-trifluoro-2-phenyl-4(1*H*)-quinolinone **12**.

The quinoline **10b** (3.00 g, 7.7 mmoles) was dissolved in acetic acid (60 mℓ), concentrated hydrochloric acid (3 mℓ), and water (4 mℓ) and heated on a steam bath for 8 hours then cooled to room temperature. The depositied solid was collected and dried to give **12** (1.00 g, 34%); ^{1}H nmr (deuteriochloroform): ppm 7.93-7.83 (m, 1H), 7.79-7.59 (m, 2H), 7.57-7.54 (m, 3H), 6.19 (s, 1H), 3.86-3.82 (m, 1H), 0.70-0.56 (m, 4H); ms: M$^+$ = 315 (base), 296.

Anal. Calcd. for $C_{18}H_{12}F_3NO{\cdot}0.8HCl$: C, 62.75; H, 3.74; N, 4.07. Found: C, 62.64; H, 3.67; N, 3.91.

Hydrolysis of 1-Cyclopropyl-2-ethenyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester, **10c**. 5-Cyclopropyl-6,7,8-trifluoro-3,4-dihydro-1*H*-pyrano[4,3-*b*]quinoline-1,10(5*H*)-dione **13**.

The vinyl-ester **10c** was dissolved in warm acetic acid (20 mℓ) and concentrated hydrochloric acid (1 mℓ) and water (1 mℓ) were added. The reaction was heated on a steam bath for 4 hours, at which time tlc indicated the reaction was complete. The solution was evaporated to a solid and crystallized from 95% ethanol to give **13** (0.25 g, 47%); ir (potassium bromide): 1729, 1611, 1478, 807, 782, cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.83-7.70 (m, 2H), 4.38 (t, 2H, J = 6 Hz), 3.69-3.61 (m, 1H), 3.36-3.33 (br m, 2H), 1.65-1.21 (m, 4H); ms: M$^+$ = 309 (base), 290, 264, 250.

Anal. Calcd. for $C_{15}H_{10}F_3NO_3{\cdot}0.125H_2O$: C, 57.83; H, 3.39; N, 4.50. Found: C, 57.84; H, 3.24; N, 4.46.

1-Cyclopropyl-2-methyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid **11**.

The quinoline **10a** (0.50 g, 1.5 mmoles) was dissolved in acetic acid (5 mℓ), concentrated hydrochloric acid (1 mℓ), and water (1 mℓ) and heated on a steam bath for 6 hours, then cooled to room temperature. The solid obtained after evaporation of the solvents was crystallized from 95% ethanol to give **11** (0.20 g, 45%); ir (potassium bromide): 1716, 1608, 1558, 1487, 810, cm^{-1}; ^{1}H nmr (deuteriochloroform): 15.00 (br s, 1H), 8.02-7.98 (m, 1H), 3.97-3.90 (m, 1H), 3.00 (s, 3H), 1.30-1.30 (m, 2H), 0.96-0.86 (m, 2H); ms: M$^+$ +1 = 298, 279, 264, 253 (base), 238.

Anal. Calcd. for $C_{14}H_{10}F_3NO_3$: C, 49.05; H, 3.31; N, 4.09. Found: C, 49.02; H, 3.25; N, 4.16.

General Procedure for Coupling of Piperazine to Quinoline Substrates.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-2-methyl-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic Acid Ethyl Ester (**14a**).

The ester **10a** (1.0 g, 3.1 mmoles), piperazine (0.7 g, 8.1 mmoles), and triethylamine (0.3 g, 3.1 mmoles) were combined in acetonitrile (20 ml) and the mixture refluxed overnight. The reaction was cooled, evaporated, and the residue taken up in methylene chloride, washed with water, and dried. After concentrating to dryness, the crude product was recrystallized from ethyl acetate to give **14a** (0.45 g, 37%). The mother liquor yielded another 0.24 g (20%) of **14a**; ir (potassium bromide): 3000-2800, 1728, 1611, 1474, 1207, 785 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.73 (dd, 1H, J = 11.8 and 1.8), 4.39 (q, 2H, J = 7.1 Hz), 3.64-3.55 (m, 1H), 3.31-3.25 (m, 4H), 3.10-3.00 (m, 1H), 2.61 (s,

1H), 1.38 (t, 3H, J = 7.1), 1.26-1.18 (m, 2H), 0.80-0.77 (m, 2H); ms: M^+ = 391, 349 (base).

Anal. Calcd. for $C_{20}H_{22}F_2N_3O_3 \cdot 0.5H_2O$: C, 61.37; H, 5.91; N, 10.74; F, 9.71. Found: C, 61.36; H, 6.11; N, 10.55; F, 9.54.

1-Ethyl-6-fluoro-1,4-dihydro-2-methyl-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**16**).

The ester **15** (0.97 g) was reacted as in the reaction described for the preparation of **14a**. After evaporating *in vacuo* the residue was taken up in methylene chloride and any solids that did not dissolve were removed by filtration. The solution was dried over magnesium sulfate and evaporated to give 0.70 g of crude material **16** which was carried on and hydrolyzed without further purification; ^{1}H nmr (deuteriochloroform): ppm 8.1 (2, 1H), 4.5 (q, 4H), 3.8 (m, 4H), 3.0 (m, 2H), 2.7 (m, 2H).

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-2-phenyl-7-(1-piperazinyl)-3-quinolinecarboxylic Acid Ethyl Ester (**14b**).

The ester **10b** (1.0 g, 2.6 mmoles) was reacted as in the reaction described for **14a**. A second equivalent of piperazine being added after the first 24 hours at reflux, and the solution refluxed an additional 24 hours. The reaction was cooled and let stand for three days. The reaction was evaporated, taken up in methylene chloride, and washed with sodium bicarbonate solution. The methylene chloride layer was dried and evaporated to give a yellow oil, which was used without further purification. A small sample was recrystallized from methanol to give **14b** as a white solid; ir: (potassium bromide): 3100-2800, 1731, 1610, 1471, 1179, 1032, 764, 702 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): ppm 7.62-7.52 (m, 6H), 3.86 (q, 2H, J = 7.2 Hz), 3.60-3.34 (m broad, 1H), 3.33-3.22 (m, 4H), 2.86-2.75 (m, 4H), 0.82 (t, 3H, J = 7.2 Hz), 0.78-0.60 (m, 4H); ms: M^+ = 453, 411 (base), 380.

Anal. Calcd. for $C_{25}H_{24}F_2N_3O_3$: C, 66.21; H, 5.56; N, 9.27. Found: C, 65.93; H, 5.32; N, 9.46.

General Procedure for Hydrolysis of Esters.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-2-methyl-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic Acid (**17a**).

The piperazine ester **14a** (0.45 g, 1.1 mmoles) was combined with 2.87 mℓ of 1*N* sodium hydroxlide, 6 mℓ of tetrahydrofuran and 6 mℓ of ethanol. The reaction was refluxed for 4 hours, concentrated, and the residue dissolved in methylene chloride/water. The methylene chloride layer was separated and the aqueous layer acidified to *p*H 3 with concentrated hydrochloric acid. The solution was concentrated to dryness and treated with 4 mℓ of concentrated hydrochloric acid and filtered to remove insoluble material. The bright yellow filtrate was concentrated to dryness and suspended in ethanol which was evaporated to dryness. This procedure was repeated four times; the yellow solid was dried under vacuum. The solid obtained was dissolved in 1*N* sodium hydroxide and the solution acidified with concentrated hydrochloric acid to *p*H 6-7. The solution was stirred overnight and the cream-colored solid formed was collected and dried to give **17a** (0.15 g, 33%); ir (potassium bromide): 5500-3300, 2900-2600, 1709, 1508, 1479, 1287, 813 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.48 (d, 1H, J = 11.7 Hz), 3.90-3.84 (m, 1H), 3.67-3.55 (m, 4H), 3.55-3.40 (m, 4H), 2.93 (s, 1H), 1.36-1.333 (m, 2H), 0.84-0.80 (s broad, 2H); ms: M^+ = 363, 319, 277 (base).

Anal. Calcd. for $C_{18}H_{16}F_2N_3O_3 \cdot 0.5H_2O$: C, 58.06; H, 5.41; N, 11.28; F, 10.21. Found: C, 58.07; H, 5.12; N, 11.20; F, 9.48.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-2-phenyl-7-(1-piperazinyl)-3-quinolinecarboxylic Acid (**17b**).

The oily piperazine ester **14b** was combined with 50 mℓ of tetrahydrofuran, 10 mℓ of ethanol and 2 mℓ of water, and to this solution was added 0.75 mℓ of 50% sodium hydroxide. The reaction was heated on a steam bath for 90 minutes. The reaction was cooled and neutralized to *p*H 7 with hydrochloric acid and evaporated until only 5 mℓ remained. This was diluted with 100 mℓ water and stirred for 1 hour. The pinkish precipitate was collected and washed with water and absolute ethanol which retained the color leaving a white solid which was washed with diethyl ether to give 0.48 g (41% from **5b**) of **17b**, the sodium salt of the carboxylic acid; ir (potassium bromide): 3600-3200, 3100-2600, 1594, 1472, 1410, 1188, 1044, 715, 581 cm^{-1}; ^{1}H nmr (deuteriotrifluoroacetic acid): ppm 8.23 (dd, 1H, J = 11, 1.5 Hz), 7.81-7.67 (m, 5H), 4.15-4.03 (m, 5H), 3.85-3.70 (m, 4H), 1.20-1.03 (m, 2H), 0.90-0.8 (m, 2H); ms: M^+ = 425, 381, 339, 91 (base).

Anal. Calcd. for $C_{23}H_{19}F_2N_3O_3Na \cdot H_2O$: C, 59.35; H, 4.76; N, 9.03. Found: C, 59.16; H, 4.58; N, 8.79.

1-Ethyl-6-fluoro-1,4-dihydro-2-methyl-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic Acid (**18**).

A properly equipped flask was charged with 0.70 g of crude ester 16 along with 10 mℓ of tetrahydrofuran, 20 mℓ of ethanol, 10 mℓ of 1*N* sodium hydroxide, and 10 mℓ of water. The solution was refluxed 4 hours and cooled to room temperature. The solution was evaporated and the residue triturated in methanol and 2-propanol. The alcohol mother liquor yielded 50 mg of pure product on standing. The remaining residue was taken up in dilute ammonium chloride solution and evaporated until a small amount of solid came out of solution. This yielded 40 mg of pure product **18**. A significant amount of product still remained in the crude fractions. Total yield of isolated product was 90 mg (18%) of **18**; ^{1}H nmr (deuteriotrifluoroacetic acid): ppm 8.35 (d, 1H, J = 12.5 Hz), 5.09-5.03 (m, 2H), 4.60-4.45 (m, 4H), 3.85-3.75 (m, 4H), 3.35 (m, 3H), 1.66 (t, 3H, J = 7 Hz); ms: M^+ = 334, 317, 290 (base).

Anal. Calcd. for $C_{16}H_{16}FN_4O_3$: C, 57.48; H, 5.73; N, 16.76. Found: C, 57.11; H, 5.77; N, 16.61.

(*trans*)-1-Cyclopropyl-3-bromo-6,7,8-trifluoro-1,2,3,4-tetrahydro-2-phenyl-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester **9b**.

The 2-phenylquinoline **5b** (2.50 g, 6.4 mmoles) was dissolved in ether (50 mℓ) and bromine (0.33 mℓ, 6.4 mmoles) was added dropwise to give a cloudy yellow-brown solution. After stirring five minutes, saturated potassium bicarbonate solution (50 mℓ) was added to the reaction mixture and the resulting orange ether layer was separated. The ether layer was washed with saturated potassium bicarbonate solution, dried, and evaporated to give a yellow solid. This solid was crystallized from diisopropyl ether to give **9b** (1.71 g, 57%); ^{1}H nmr (deuteriochloroform): ppm 7.67-7.60 (m, 1H), 7.28-7.03 (m, 5H), 4.84 (s, 1H), 4.00-3.93 (m, 1H), 3.92-3.75 (m, 1H), 2.94-2.88 (m, 1H), 1.15-0.80 (m, 7H); ir (potassium bromide): 1744, 1686, 1497, 1405, 1360, 1289, 1253 cm^{-1}; ms: M^+ = 469, 467, 388, 342 (base).

Anal. Calcd. for $C_{21}H_{17}BrF_3NO_3$: C, 53.86; H, 3.66; N, 2.99. Found: C, 53.93; H, 3.68; N, 2.91.

Dehydrohalogenation of **9b**.

A sample of **9b** (1.00 g, 2.1 mmoles) was dissolved in ether and potassium *t*-butoxide (0.26 g, 2.3 mmoles) was added causing the reaction mixture to take on a cloudy appearance. After monitoring the reaction by tlc, for 20 minutes no further changes were apparent. The reaction was quenched with ammonium chloride

solution and the crude reaction mixture purified by flash chromatography to give after recrystallization from 95% ethanol **10b** (0.1 g, 12%). The remainder of the mass recovered was impure starting bromide **9b**.

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