Quinolone Antibacterials: Synthesis and Biological Activity of Carbon Isosteres of the 1-Piperazinyl and 3-Amino-1-pyrrolidinyl Side Chains[1]

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A series of 6-fluoro-1,4-dihydro-4-oxo-3-quinoline- and 1,8-naphthyridinecarboxylic acids, substituted at the 7-position with carbon-linked side chains, was synthesized and evaluated for antibacterial activity and DNA-gyrase inhibition. Structural modifications focused on replacement of the heterocyclic nitrogen of the frequently found 1-piperazinyl and 3-amino-1-pyrrolidinyl side chains by an sp^2- or an sp^3-hybridized carbon. All new compounds displayed high *in vitro* and *in vivo* antibacterial activity. Potency relative to the standard nitrogenated agents was dependent on ring size and hybridization of the linking carbon atom of the side chain. Compounds with a 1,2,3,6-tetrahydro-4-pyridinyl substituent at C-7 were equipotent with their 1-piperazinyl analogs, whereas those having a 4-piperidinyl or a 3-amino-1-cyclopentenyl ring at C-7 were less active than the 1-piperazinyl or 3-amino-1-pyrrolidinyl substituted agents, respectively. This relative difference in antibacterial potency did not correlate with the observed activity against gyrase, where the majority of the new compounds were equally or more potent than their nitrogenated counterparts.

Introduction

Over the past decade, medicinal chemists have devoted a significant effort to develop structure–activity relationships for the quinolone class of antibacterial agents.[2-5] This effort has rendered several of the most potent, orally active anti-infective agents available today, filling the need for structurally novel therapeutic agents for use against increasingly resistant pathogens.[6-8]

The new fluoroquinolones are structurally characterized by the presence of an ethyl, cyclopropyl, or fluorinated phenyl ring at N-1 of the quinoline or 1,8-naphthyridine nucleus, by a fluorine atom at C-6, and by a five- or six-membered nitrogen-linked heterocycle at C-7. Particularly notable in this regard are the 1-piperazinyl and the 3-amino-1-pyrrolidinyl substituents, present in several of the clinically relevant quinolones (*e.g.*, ofloxacin,[9] enoxacin,[10] ciprofloxacin,[11] and tosulfoxacin[12]) (Figure 1).

While almost all of the nitrogen heterocycles evaluated at C-7 are linked to the quinoline ring through the heterocyclic nitrogen, the exact role of this nitrogen atom has not yet been unequivocally defined. Broad-spectrum antibacterial activity and, in particular, *in vivo* efficacy have been associated mainly with the presence of a second basic nitrogen properly positioned within the side chain (such as the 4-N of the piperazine or the 3-amino substituent of the pyrrolidine).[13] Rosoxacin is a well-known example of a first-generation quinolone possessing a pyridinyl ring at C-7 linked through a carbon, rather than through the nitrogen atom (Figure 1).[14a] More recently, Culbertson and Domagala have described the synthesis of 6-fluoroquinolones bearing different carbon-bonded aromatic heterocycles at C-7, some of which displayed a substantial level of antibacterial activity.[15,16] However, the evaluation of agents possessing nonaromatic, nitrogen-containing carbo- or heterocyclic rings directly attached to C-7 through a carbon–carbon bond has been elusive, mainly because of the absence of efficient methodologies for their preparation. We wish to report herein the synthesis and antibacterial activity of several of these agents, in particular those bearing carbon surrogates of the 1-piperazinyl and the 3-amino-1-pyrrolidinyl side chains.

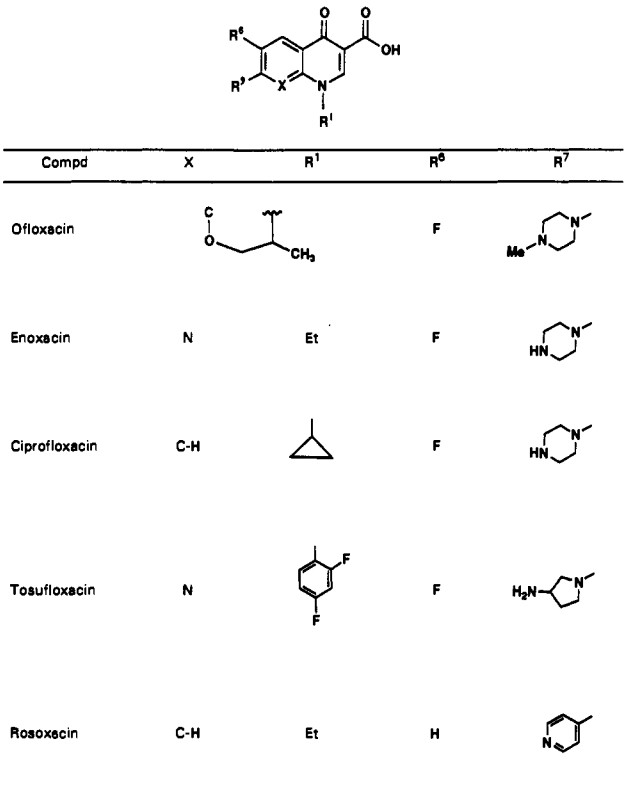

Figure 1. Structures of relevant quinolones.

From strictly chemical considerations, two distinct classes of compounds can be envisioned, depending on the hybridization of the carbon atom affecting the union between the side chain and the quinoline or naphthyridine ring. In one class, the nitrogen atom would be replaced by an sp^3-hybridized carbon; a hydrogen atom would then substitute the nitrogen electron lone pair creating a formal C–H isostere. Alternatively, substitution of the nitrogen atom by an sp^2-hybridized carbon would give rise to a C=C isostere in which the nitrogen electron lone pair

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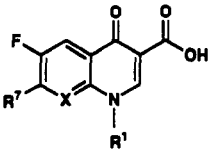
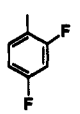
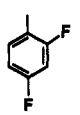
Table I. Physical Data of the Quinolone Antibacterials Prepared for This Study



compd	X	R^1	R^7	mp (°C)	formula (analysis)	ref
1	C-H			292–293	$C_{18}H_{19}FN_2O_3$ (CHN)	
2	C-H			233–234	$C_{18}H_{17}FN_2O_3 \cdot 0.1H_2O$ (CHN)	
3	C-H				$C_{18}H_{17}FN_2O_3 \cdot HCl \cdot H_2O$ (CHN)	20
4	N				$C_{17}H_{16}FN_3O_3 \cdot HCl \cdot 1.25H_2O$ (CHNCl)	19
5	N				$C_{17}H_{16}FN_3O_3 \cdot 1.5HCl$ (CHN)	
6	N				$C_{20}H_{14}F_3N_3O_3 \cdot 2HCl \cdot H_2O$ (CHN)	19
7	N				$C_{20}H_{14}F_3N_3O_3 \cdot HCl \cdot H_2O$ (CHN)	19

would be mimicked by a π-bond. We have prepared a series of side chains that incorporate both types of isosteric replacement as a single structural modification of their nitrogenated counterparts. Specifically, the 1-piperazinyl side chain has been substituted by either a 4-piperidine or a 4-(1,2,3,6-tetrahydropyridine), while the 3-amino-1-pyrrolidinyl side chain has been replaced by a 3-amino-1-cyclopentene (Figure 2). The new ring systems have been coupled to the C-7 position of several quinoline and naphthyridine nuclei already possessing other structural features associated with potent antibacterial activity (Table I). As discussed below, the single modification introduced in the side chains of the new quinolones allowed a direct evaluation of the two types of carbon substitution with each other and with respect to the corresponding nitrogen-linked analog.

Chemistry

The 7-(4-piperidinyl)- and 7-(1,2,3,6-tetrahydro-4-pyridinyl)quinolones 1 and 2 were both prepared from 1,4-dibromo-2,5-difluorobenzene as shown in Scheme I. Nucleophilic attack of 1-lithio-4-bromo-2,5-difluorobenzene onto ethyl 4-oxo-1-piperidinecarboxylate gave the 4,4-disubstituted piperidine **9**. Acid-catalyzed elimination of water, followed by displacement of the aromatic bromine by cyanide, provided the 4-aryl-1,2,3,6-tetrahydropyridine **10**. Treatment of this compound with 6 N HCl effected hydrolysis of the nitrile function and concomitant removal of the *N*-ethoxycarbonyl protecting group. The tetrahydropyridine nitrogen was subsequently reprotected to afford the common intermediate **11**.

Catalytic hydrogenation of the aliphatic double bond of **11** provided **12**, which was subsequently elaborated into the 4-oxoquinoline derivative **13** by well-established procedures.[17] Hydrolysis of the N-acetyl protecting group

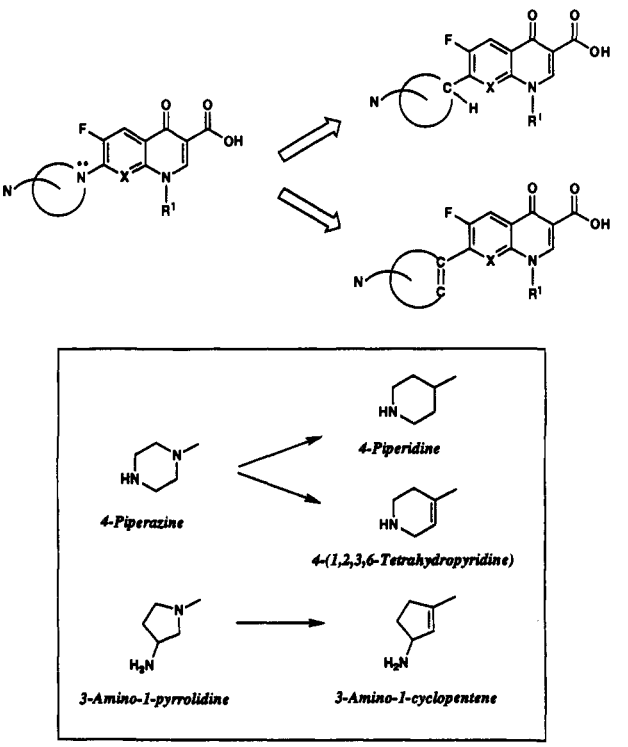
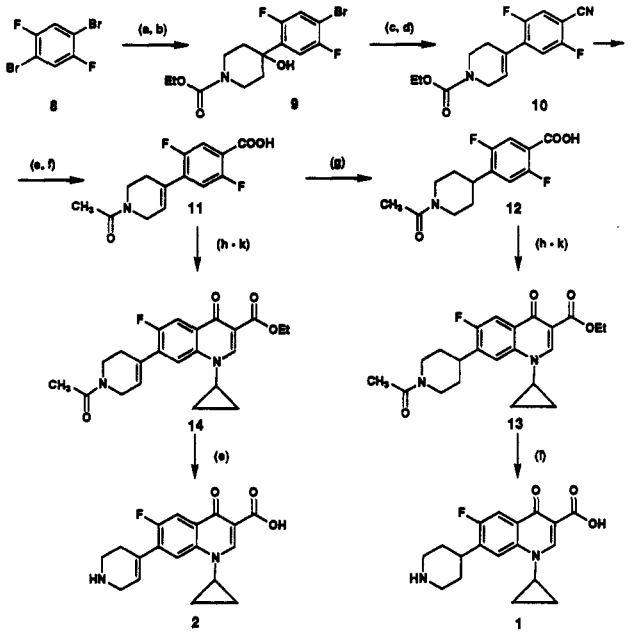


Figure 2. Carbon–isosteres of the most common nitrogenated side chains.

finally rendered **1**, the sp^3-carbon isostere of ciprofloxacin. Alternatively, direct elaboration of **11** into the 4-oxoquinoline **14** and subsequent removal of the tetrahydropyridine nitrogen protecting group afforded **2**, the sp^2-carbon isostere of ciprofloxacin.

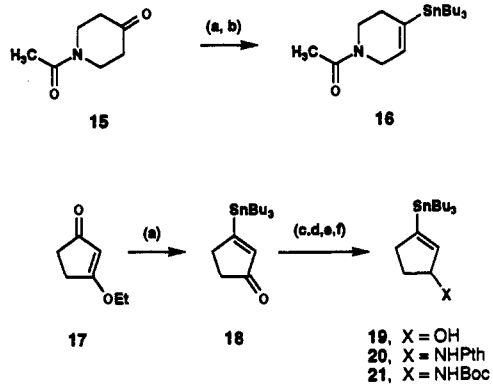
Compound **2**, as well as the other derivatives bearing a 1,2,3,6-tetrahydro-4-pyridinyl or a 3-amino-1-cyclopentenyl substituent at C-7, were also prepared by a more

Scheme I[a]



[a] **Reagents:** (a) *n*-BuLi, THF; (b) ethyl 4-oxo-1-piperidinecarboxylate; (c) *p*-TsOH; (d) CuCN, DMF; (e) 6 N HCl; (f) Ac_2O; (g) H_2, Pd/C; (h) CDI, $Mg(EtO_2CCH_2CO_2)_2$; (i) $(EtO)_3CH$, Ac_2O; (j) cyclopropylamine; (k) *t*-BuOK; (l) NaOH.

Scheme II[a]



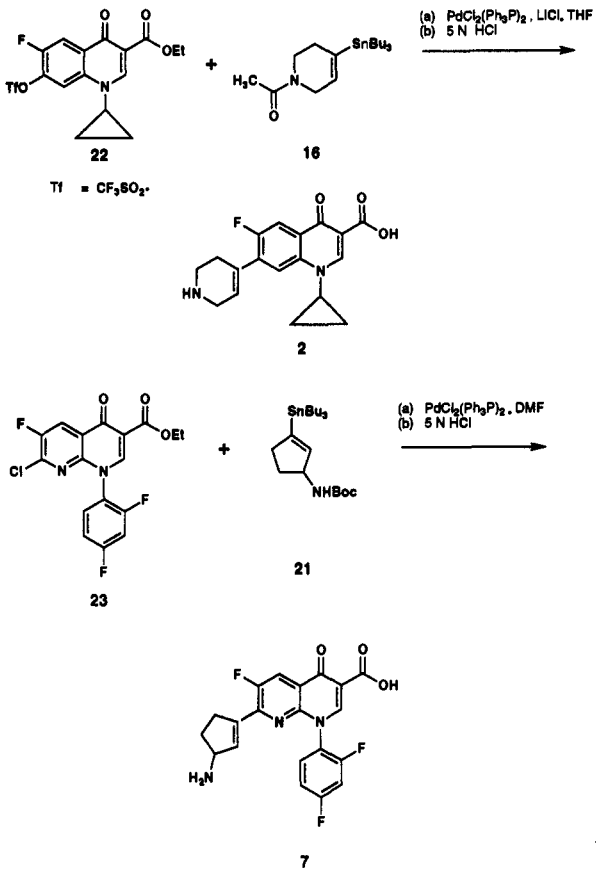
[a] **Reagents:** (a) Li(*n*-Bu_3Sn), THF, −78 °C; (b) CH_3SO_2Cl, pyridine, CH_2Cl_2; (c) $LiAlH_4$, Et_2O, −20 °C; (d) phthalimide, DEAD, Ph_3P, THF; (e) NH_2NH_2, EtOH; (f) Boc_2O, Et_3N, CH_2Cl_2.

convergent methodology involving a palladium-catalyzed cross-coupling of a 7-quinolyltriflate or a 7-chloro-1,8-naphthyridine with the cyclic vinylstannanes **16** and **21**. The syntheses of these novel tin reagents and their cross-coupled products have already been reported and are outlined in Schemes II and III.[18-20] It is noteworthy that, for the preparation of naphthyridines **4–7**, the 7-chloro substrate (e.g., **23**) proved to be sufficiently reactive that it made unnecessary the formation of the corresponding triflate derivative.

Biological Assays

The series of quinolones and naphthyridones prepared for this study was tested *in vitro* against an assortment or six Gram-negative and five Gram-positive organisms using standard microtitration techniques.[21] Their minimum inhibitory concentrations (MICs, μg/mL) are listed in Table II. The geometric means of the MICs for both Gram-negative (except *Pseudomonas aeruginosa*) and Gram-positive strains were calculated to facilitate comparison

Scheme III



in activity and are shown in Table III, along with those for the nitrogenated reference agents **A–F**.

The *in vivo* potency, expressed as the median protective dose (PD_{50}, mg/kg), was determined in acute, lethal systemic infections in female Charles River CD-1 mice, with a single dose of the compound administered at the time of challenge.[22] These results are presented in Table III.

The new compounds were also tested for their ability to inhibit bacterial DNA gyrase using a protocol previously reported.[23] The concentration of drug required to effect a 50% inhibition of the gyrase-mediated cleavage of supercoiled DNA (IC_{50}, μg/mL) is also listed in Table III.

Discussion of Results

A comparison of the biological activity of ciprofloxacin (**A**) and its 4-piperidinyl and 1,2,3,6-tetrahydro-4-pyridinyl analogs **1** and **2**, respectively, shows that the chemical nature of the isosteric replacement of the 1-piperazinyl nitrogen does translate into a substantial difference in antibacterial activity. Thus, whereas the sp^2-carbon-based derivative **2** is equipotent with ciprofloxacin, both *in vitro* and *in vivo*, the sp^3-carbon-linked analog **1** is 3–6 times less potent *in vitro* and 4–12 times less active *in vivo*.

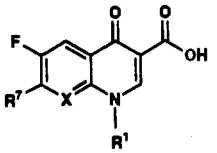
Although the chemistry employed in the synthesis of **1** did not lend itself to the preparation of the corresponding 7-(4-piperidinyl)naphthyridine, a comparison of the biological activity of the reference agent **B** with its 1,2,3,6-tetrahydro-4-pyridinyl analog **4** seems to follow the same trend observed for the quinolone series. Indeed, compound **4** is essentially equipotent with **B** both *in vitro* and *in vivo*. This equivalence between the 1-piperazinyl and the 1,2,3,6-tetrahydro-4-pyridinyl side chains apparently ex-

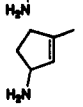
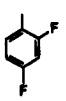
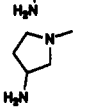
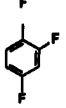
Table II. *In Vitro* Antibacterial Activity (MICs, μg/mL)[a]

	Gram-negative organisms						Gram-positive organisms				
	E. cl.	*E. co.*		*K. pn.*	*P. re.*	*P. ae.*	*S. au.*		*E. fa.*	*S. pn.*	*S. py.*
compd	MA-2646	Vogel	H560	MGH-2	M-1771	Ul-18	H-228	UC-76	MGH-2	SV-1	C-203
1	0.2	0.2	0.2	0.4	0.8	1.6	6.3	0.8	3.1	3.1	0.4
2	0.025	0.025	0.013	0.1	0.1	0.8	0.8	0.1	0.8	0.8	0.4
3	0.1	0.1	0.1	0.2	0.2	0.8	0.8	0.1	0.8	0.4	0.2
4	0.025	0.013	0.013	0.05	0.05	0.2	1.6	0.2	0.8	0.8	0.4
5	0.05	0.05	0.05	0.1	0.1	0.8	0.8	0.1	0.4	0.4	0.4
6	0.1	0.1	0.1	0.2	0.4	1.6	0.8	0.2	1.6	0.4	0.4
7	0.05	0.05	0.025	0.1	0.2	1.6	0.1	0.025	0.2	0.1	0.1

[a] *E. cl.* = (*Enterococcus cloacae*, *E. co.* = *E. coli*, *K. pn.* = *Klebsiella pneumoniae*, *P. re.* = *Providencia rettgeri*, *P. ae.* = *P. aeruginosa*, *S. au.* = *Staphylococcus aureus*, *E. fa.* = *Enterococcus faecalis*, *S. pn.* = *Streptococcus pneumoniae*, *S. py.* = *Streptococcus pyogenes*.

Table III. Comparative Biological Data for the Quinolones Prepared in This Study and Their Reference Agents[a]



				geometric mean MICs		protective dose (PD_{50}) po/sc (mg/kg)[b]		gyrase inhibition
compd	X	R^1	R^7	Gram-negative	Gram-positive	*E. co.* Vogel	*S. py.* C-203	IC_{50} (μg/mL)
A (ciprofloxacin)	CH			0.05	0.6	1.2/0.3	>260/28	5.3
1	CH			0.3	1.8	13.8/1.2	NT	3.8
2	CH			0.04	0.46	1.7/0.4	>100/NT	0.9
B	N			0.05	1.2	0.7/0.4	63/41	>25
4	N			0.03	0.6	0.5/0.1	42/18	3.8
C	N			0.4	0.2	NA	(2.4/0.6)[c]	NA
6	N			0.15	0.53	NT	NT	5.0
D	CH			0.04	0.09	3.4/0.5	97/11	2.6
3	CH			0.13	0.35	5.2/1.3	NT	2.8
E	N			0.02	0.1	2.0/0.6	32/14	3.0
5	N			0.07	0.35	1.2/0.4	50/17	3.8
F (tosufloxacin)	N			0.03	0.04	0.6/0.2	5.7/3.3	3.0
7	N			0.07	0.09	6.0/1.1	50/45	6.3

[a] NA = not available; NT = not tested. [b] *E. co.* = *E. coli*, *S. py.* = *S. pyogenes*. [c] *S. aureus* NCTC 10649 (ref 12).

tends to the 1-(2,4-difluorophenyl)-substituted naphthyridines (*cf.*, **6** and reference agent **C**), albeit the data available in this case is less complete.

In contrast to the above observations, the replacement of the 3-amino-1-pyrrolidinyl side chain by a 3-amino-1-cyclopentenyl ring resulted in a slight but systematic reduction of antibacterial activity (*cf.*, **3**, **5**, and **7** vs reference agents **D**, **E**, and **F**, respectively). This reduction was somewhat more apparent *in vitro* than *in vivo*, except for the 1-(2,4-difluorophenyl)-substituted naphthyridine

7, which showed a 10-fold decrease in activity in the mouse protection model. Compared with their 1,2,3,6-tetrahydro-4-pyridinyl analogs, however, the 3-amino-1-cyclopentenyl derivatives were more active against Gram-positive organisms, which agrees with the trend observed between pyrrolidinyl- and piperazinyl-substituted quinolones.

All of the compounds prepared in this study were potent inhibitors of *Escherichia coli* H560's gyrase. In particular, the 1,2,3,6-tetrahydro-4-pyridinyl analogs were substantially (*i.e.*, 6–7-fold) more active in this respect than their 1-piperazinyl counterparts (*cf.*, **2** vs **A**; **4** vs **B**). The 3-amino-1-cyclopentenyl derivatives, on the other hand, were only equipotent or slightly less active at inhibiting the bacterial enzyme than their 3-amino-1-pyrrolidinyl analogs.

In summary, the results obtained in this study support earlier observations, in that the attachment of the quinolone C-7 substituent need not be through a nitrogen atom to ensure significant microbiological activity. High *in vitro* as well as *in vivo* potency can still be achieved when said attachment is done *via* a carbon atom. However, the effectiveness of the nitrogen-by-carbon replacement upon antibacterial activity seems to be dependent on the ring size and the hybridization of the linking carbon atom of the side chain. Previous work in this area had demonstrated that the incorporation of a 4-pyridinyl ring at C-7 results in compounds with potent antibacterial activity, particularly against Gram-positive organisms.[14b] The present study shows that an aromatic substituent is not entirely necessary to achieve high potency, and that a 1,2,3,6-tetrahydro-4-pyridinyl group is a good mimic of the more standard 4-piperazinyl side chain. Indeed, all other substituents being equal, the six-membered sp^2-hybridized carbon isosteres were generally more active than the sp^3-hybridized ones and equipotent with their nitrogenated analogs, whereas the five-membered sp^2-hybridized carbon isosteres were less active than their pyrrolidinyl counterparts. Assuming that the efficacy of the 7-(3-amino-1-pyrrolidinyl)quinolones, as compared with the 1-piperazinyl-substituted ones, is due to the ability of the pyrrolidinyl side chain to adopt a piperazinyl conformation in space, then the difference in activity between the five- and the six-membered sp^2-carbon isosteres may be attributed to the more stringent conformational restriction of the 3-amino-1-cyclopentenyl ring system.[24] Since it would appear that such conformational restriction does not particularly affect the ability of these compounds to inhibit gyrase, one must conclude that the observed antibacterial activity is due to interactions at levels other than that of the enzyme. Additional research is obviously needed to establish the specific role of the side chain in the mechanism of action of quinolones.

Experimental Section

Air- or moisture-sensitive 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 rotary evaporator. Thin-layer chromatography was carried out on E. Merck silica gel 60 F_{254} precoated glass plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel 60, 230–400 mesh ASTM, according to the method of Still.[25] Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX-1 FTIR spectrometer. Proton and carbon-13 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. The purity of the final products was determined by high-pressure liquid chromatography on a system composed on a LKB 2150 pump, LKB 2152 controller, and an Applied Biosystems 783A programmable absorbance detector.

Ethyl 4-(4-Bromo-2,5-difluorophenyl)-4-hydroxy-1-piperidinecarboxylate (9). A solution of 1,4-dibromo-2,5-difluorobenzene (16.55 g, 60.85 mmol) in ethyl ether (400 mL) was cooled to −75 °C and treated dropwise with a solution of n-butyllithium in hexane (24.3 mL, 2.5 M). The mixture was allowed to warm to −50 °C and treated dropwise with a solution of 1-(ethoxycarbonyl)-4-piperidine (11.00 g, 64.33 mmol) in ethyl ether (100 mL). After stirring at −50 °C for an additional 30 min, the mixture was allowed to warm to room temperature and quenched by addition of ammonium chloride solution. The organic layer was decanted, dried, and concentrated, and the crude product was chromatographed (ethyl acetate–hexane 1:1) and recrystallized (toluene–hexane) to afford **9** (11.27 g, 51%): mp 133–136 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 1.71 (br d, 2H, J = 12.4 Hz), 2.12–2.27 (m, 2H), 3.26 (br t, 2H, J = 12.8 Hz), 4.07–4.21 (m + q, 4H, J_q = 7.1 Hz), 7.23–7.40 (m, 2H); MS (EI) m/z 365 (M + 1), 347, 318, 316, 238, 100, 56 (base).

Ethyl 4-(4-Cyano-2,5-difluorophenyl)-1,2,3,6-tetrahydro-1-pyridinecarboxylate (10). A solution of **9** (11.12 g, 30.5 mmol) and *p*-toluenesulfonic acid (0.70 g) in toluene (200 mL) was heated at reflux (Dean–Stark trap) for 16 h. The mixture was allowed to cool to room temperature, washed with sodium bicarbonate solution, dried, and concentrated, and the residue was chromatographed (chloroform) to afford 4-(4-bromo-2,5-difluorophenyl)-1-(ethoxycarbonyl)-1,2,3,6-tetrahydropyridine (8.40 g, 80%) as a syrup, which crystallized on standing: mp 40–44 °C; IR (LF) 1701, 1239, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 2.48 (br s, 2H), 3.67 (t, 2H, J = 5.6 Hz), 4.10–4.25 (m + q, 4H, J_q = 7.2 Hz), 6.01 (br s, 1H), 7.02 (dd, 1H, J = 9.0, 6.5 Hz), 7.23–7.31 (m, 1H); MS (EI) m/z 346 (M), 345, 316 (base), 272, 165, 91.

A suspension of the above compound (27.60 g, 79.8 mmol) and cuprous cyanide (9.00 g, 89.6 mmol) in *N,N*-dimethylformamide (300 mL) was heated at reflux for 20 h. The mixture was cooled to room temperature and shaken with concentrated ammonium hydroxide (800 mL), water (800 mL), and dichloromethane (1 L). The organic layer was decanted, washed with water, dried, and concentrated. The crude product was purified by chromatography (chloroform–ethyl acetate 30:1) and recrystallization (hexane) to give **10** (14.85 g, 63.5%): mp 85–87 °C; IR (KBr) 2247, 1712, 1231, 1179 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz), 2.49 (br s, 2H), 3.68 (t, 2H, J = 5.6 Hz), 4.17 (m + q, 4H, J_q = 7.1 Hz), 6.14 (br, s, 1H), 7.12 (dd, 1H, J = 9.4, 6.0 Hz), 7.31 (dd, 1H, J = 9.5, 5.1 Hz); MS (EI) m/z 292 (M), 263 (base), 219, 152.

4-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-2,5-difluorobenzoic Acid (11). A suspension of **10** (10.00 g, 34.25 mmol) in 6 N HCl (350 mL) was heated at reflux for 23 h. The resulting solution was concentrated to dryness and the residue was taken up in ethanol–ether (1:3, 200 mL), filtered, washed with ether, and dried *in vacuo* at 70 °C to give 4-(4-carboxy-2,5-difluorophenyl)-1,2,3,6-tetrahydropyridine as the hydrochloride salt (9.95 g). A portion of this material was recrystallized from water–1 N HCl: mp 286–290 °C dec; IR (KBr) 1712, 1700, 1408, 1174, 740 cm^{-1}; ^{1}H NMR (TFA) δ 3.00 (br s, 2H), 3.76–3.79 (m, 2H), 4.19 (br s, 2H), 6.25 (s, 1H), 7.22 (dd, 1H, J = 11.0, 5.8 Hz), 7.75–7.83 (m, 2H), 7.85 (dd, 1H, J = 10.7, 5.9 Hz); MS (EI) m/z 239 (M, base), 165, 82.

A suspension of the above compound (8.51 g, 29.1 mmol) in acetic anhydride (90 mL) was heated at reflux for 0.75 h. The suspension was filtered while still hot and the filtrate was concentrated to dryness. The residue was taken up in water (100 mL) and stirred on a steam bath for *ca.* 15 min; upon cooling to room temperature, the precipitated solids were filtered, washed with water, and recrystallized from acetic acid–water to afford **11** (6.27 g, 77%): mp 241–242 °C; IR (KBr) 1719, 1701, 1599,

1174, 748 cm^{-1}; ^{1}H NMR (TFA) δ 2.72 (s, 3H), 2.85–3.00 (m, 2H), 4.10–4.30 (m, 2H), 4.55–4.65 (m, 2H), 6.28 (s, 1H), 7.21 (dd, 1H, J = 11.1, 5.9 Hz), 7.85 (dd, 1H, J = 10.6, 5.9 Hz); MS (EI) m/z 281 (M), 239 (base), 165.

4-(1-Acetyl-4-piperidinyl)-2,5-difluorobenzoic Acid (12). A suspension of 11 (0.84 g, 3 mmol) and 10% Pd/C catalyst (0.5 g) in acetic acid (250 mL) was hydrogenated at 50 psi and 30 °C for ca. 6 min. The suspension was filtered and the filtrate was concentrated to give 12 (0.82 g, 97%). A portion of this material was recrystallized from acetic acid–water: mp 206–207 °C; ^{1}H NMR (TFA) δ 1.98–2.19 (m, 2H), 2.24–2.30 (m, 2H), 2.70 (s, 3H), 3.28–3.51 (m, 2H), 3.70 (br t, 1H, J = 12.8 Hz), 4.36 (br d, 1H, J = 12.4 Hz), 4.97 (br d, 1H, J = 12.9 Hz), 7.15 (dd, 1H, J = 11.2, 5.7 Hz), 7.83 (dd, 1H, J = 10.2, 6.0 Hz); MS (EI) m/z 283 (M), 268, 226, 57 (base).

Ethyl 7-(1-Acetyl-4-piperidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (13). A solution of 12 (2.25 g, 7.95 mmol) in dry tetrahydrofuran (120 mL) was cooled to 0 °C and treated with carbonyldiimidazole (2.00 g, 12.3 mmol). The mixture was allowed to warm to room temperature, stirred for an additional 1.5 h, and treated with magnesium ethyl malonate (3.10 g, 10.8 mmol). The resulting mixture was stirred at room temperature overnight and at reflux for an additional 1.5 h. The solvent was evaporated and the residue was shaken with a mixture of ethyl acetate (120 mL) and 3 N HCl (60 mL). The organic layer was decanted, washed with sodium bicarbonate solution, dried, and concentrated, and the residue was chromatographed (chloroform–methanol 40:1) to afford ethyl 4-(1-acetyl-4-piperidinyl)-2,5-difluoro-β-oxobenzenepropionate (2.86 g) as a colorless syrup.

A solution of the above product (2.68 g, 7.57 mmol) and triethyl orthoformate (1.9 mL) in acetic anhydride (16 mL) was heated at reflux for 1.25 h. The solution was concentrated at 80 °C under vacuum to give a syrup. This material was dissolved in ethyl ether (40 mL) and treated with cyclopropylamine (0.67 mL, 9.6 mmol). The resulting solution was stirred at room temperature for 6 h; the solvent was then evaporated, and the residue was redissolved in *tert*-butyl alcohol (35 mL) and treated with potassium *tert*-butoxide (0.93 g, 8.3 mmol). The mixture was heated in an oil bath at 65 °C for 1.5 h. The solvent was evaporated and the residue was taken up in chloroform and extracted with 0.5 N HCl. The organic, layer was decanted, dried, and concentrated, and the crude product was chromatographed (chloroform–methanol 30:1) to give 13 (1.42 g, 47%). A portion of this material was recrystallized from toluene: mp 195–201 °C; ^{1}H NMR ($CDCl_3$) δ 1.10–1.18 (m, 2H), 1.32–1.45 (m + t, 5H, J_t = 7.1 Hz), 1.59–1.84 (m, 2H), 1.95–2.10 (m, 2H), 2.17 (s, 3H), 2.72 (td, 1H, J_t = 13.0 Hz, J_d = 2.5 Hz), 3.19–3.35 (m, 2H), 3.42–3.51 (m, 1H), 3.96–4.05 (m, 1H), 4.40 (q, 2H, J = 7.1 Hz), 4.85–4.93 (m, 1H), 7.73 (d, 1H, J = 5.9 Hz), 8.08 (d, 1H, J = 10.5 Hz), 8.59 (s, 1H).

1-Cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-(4-piperidinyl)-3-quinolinecarboxylic Acid (1). A solution of 13 (0.51 g, 1.28 mmol) and 2 N NaOH (2 mL) in methanol (12 mL) was heated at reflux for 114 h. The solvent was evaporated, the residue was redissolved in water, and this solution was titrated to pH 4 with dilute HCl. The precipitated solid was filtered and dried to give 1 (0.37 g, 88%): mp 292–293 °C dec; ^{1}H NMR (DMSO-d_6 + 1 drop TFA) δ 1.19–1.30 (m, 2H), 1.33–1.45 (m, 2H), 1.92–2.18 (m, 4H), 3.08–3.22 (m, 2H), 3.27–3.60 (m, 3H), 3.91–3.97 (m, 1H), 8.03 (d, 1H, J = 10.3 Hz), 8.16 (d, 1H, J = 6.0 Hz), 8.60–8.80 (m, 1H), 8.77 (s, 1H); MS (EI) m/z 331 (M + 1, base), 286.

Ethyl 7-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (14). This compound was prepared from 11 by the same sequence of reactions described above for 13. For 14: mp 190–192 °C (toluene); ^{1}H NMR ($CDCl_3$) δ 1.11–1.20 (m, 2H), 1.32–1.45 (m + t, 5H, J_t = 7.1 Hz), 2.18 (d, 3H, J = 4.3 Hz), 2.60–2.65 (m, 2H), 3.42–3.53 (m, 1H), 3.71 (t, 1H, J = 5.6 Hz), 3.87 (t, 1H, J = 5.6 Hz), 4.18–4.23 (m, 1H), 4.29–4.45 (m + q, 3H, J_q = 7.1 Hz), 6.09–6.16 (m, 1H), 7.77 (d, 1H, J = 6.0 Hz), 8.08 (dd, 1H, J = 11.1, 1.4 Hz), 8.59 (s, 1H); MS (EI) m/z 398 (M), 326 (base), 280.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3-quinolinecarboxylic Acid (2). A solution 14 (0.80 g, 2.01 mmol) in 6 N HCl (50 mL) was heated on a steam bath for 2.75 h. The solvent was evaporated, the residue was redissolved in water, and the solution was titrated to pH 7 with dilute sodium hydroxide. The precipitated solid was filtered and dried to give 2 (0.38 g, 58%) as an off-white solid: mp 233–234 °C; ^{1}H NMR (DMSO-d_6 + TFA) δ 1.16–1.25 (m, 2H), 1.28–1.38 (m, 2H), 2.79 (br s, 2H), 3.38–3.41 (m, 2H), 3.87–3.95 (m, 3H), 6.33 (s, 1H), 8.05 (d, 1H, J = 11.1 Hz), 8.19 (d, 1H, J = 6.3 Hz), 8.77 (s, 1H), 9.08 (m, 1H); MS (EI) m/z 328 (M), 284 (base), 264.

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