Articles

Synthesis and Antibacterial Activity of Some Novel 1-Substituted 1,4-Dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic Acids. Potent Antistaphylococcal Agents

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The palladium-catalyzed coupling of 3- and 4-(trialkylstannyl)pyridines with 7-bromo or 7-chloro 1-substituted 1,4-dihydro-4-oxo-3-quinolinecarboxylates has provided access to the corresponding 1-substituted 1,4-dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic acids. The antibacterial activity of these derivatives was studied with the finding that the optimal 1- and 7-position substituents for Gram positive activity are cyclopropyl and 4-(2,6-dimethylpyridinyl), respectively. We find that for the fluorine-substituted derivatives studied, the position of the fluorine on the quinolone nucleus or the number of fluorine atoms does not seem to be important for good Gram positive activity. For 1-cyclopropyl 7-(2,6-dimethyl-4-pyridinyl) derivatives, the 6-fluoro **4a**, 8-fluoro **10d**, 6,8-difluoro **10b**, and 5,6,8-trifluoro **8**, all provided equal antibacterial activity activity against *Staphylococcus aureus* ATCC 29213. There is also a correlation between the substitution on the 7-(4-pyridinyl) group and the Gram positive activity, particularly for *S. aureus*, clearly indicating that the 2,6-dimethylpyridinyl group is optimal. The MIC_{50} value for the most potent agents in this study against *S. aureus* ATCC 29213 is 0.008 μg/mL. By comparison, ciprofloxacin and aminopyrrolidine **28** gave values of 0.25 and 0.015 μg/mL, respectively, against this organism.

Introduction

The first quinolone antibacterial agent, nalidixic acid, was discovered in our laboratory over 30 years ago.[1] This agent is still in use today against urinary tract infections caused by *Escherichia coli*. Most of the quinolones introduced after nalidixic acid were primarily Gram negative antibacterial agents.[2–6] Key modifications that are common to many of these later quinolones include the introduction of a fluorine in the 6-position as well as a heterocycle in the 7-position. These variations continue to be among the most studied quinolone modifications to date.[7–14] One example of this modification that provided a quinolone with improved Gram positive activity is illustrated with rosoxacin. Rosoxacin is a quinolone containing a 4-pyridinyl group at the 7-position of the quinolone nucleus and has a broad spectrum of activity that included limited activity against *Staphylococcus aureus*.[7,8] Modification of rosoxacin by the introduction of a 6-fluorine or by changing the 7-(4-pyridinyl) group to a 7-(2,6-dimethylpyridinyl) group results in small improvements in the Gram positive profile (Table 3). Incorporation of both the 6-fluorine and the dimethylpyridine resulted in a more substantial improvement in Gram positive activity without materially compromising the Gram negative potency of this series.[15]

Other representatives of this type of structural modification include norfloxacin,[16] ciprofloxacin,[17] 1-ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolindinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, **27** (CI-934),[18,19] 1-cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolindinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, **28** (PD-117,558),[20] and 7-[3(*R*)-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, **29** (PD-138,312),[21] as well as 1,8-naphthyridines tosufloxacin[22,23] and temafloxacin.[24] Among the compounds in this group, **27**–**29**, which contain an aminopyrrolidine group in the 7-position (Chart 1), exhibit improved activity against Gram positive organisms. Other modifications reported to improve the Gram positive potency include tetracyclic thiazolo[3,2-*a*]quinoline-4-carboxylic acids.[25]

In this study, we sought to further improve the Gram positive activity of the rosoxacin-type agents and report the antibacterial activity and structure–activity relationships (SAR) of a series of 7-(4-pyridinyl)- and 7-(3-pyridinyl)quinolones.[26] This work includes three facets of the SAR in pyridinylquinolones: effect of substitution at the 1-position, fluorine substitution, and variation of the 7-pyridinyl group.

Chemistry

The quinolones used in this study were all prepared through the intermediate β-keto esters **1d**,**e**[27] and **5**. We illustrate two convenient routes (Scheme 1) for the preparation of the required β-keto esters below. In one approach (method A), Friedel–Crafts acylation of 2,5-

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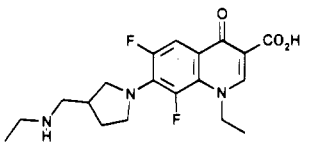
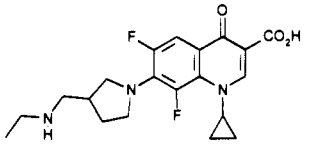
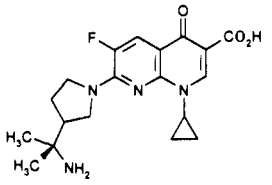
Chart 1



27



28



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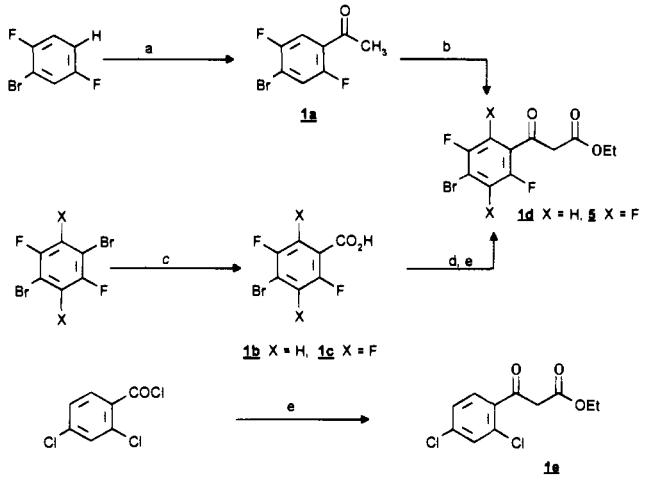
Scheme 1[a]



[a] (a) CH_3COCl, $AlCl_3$; (b) diethyl carbonate–NaH; (c) BuLi, CO_2; (d) $SOCl_2$ or PCl_5; (e) ethyl hydrogen malonate, BuLi.

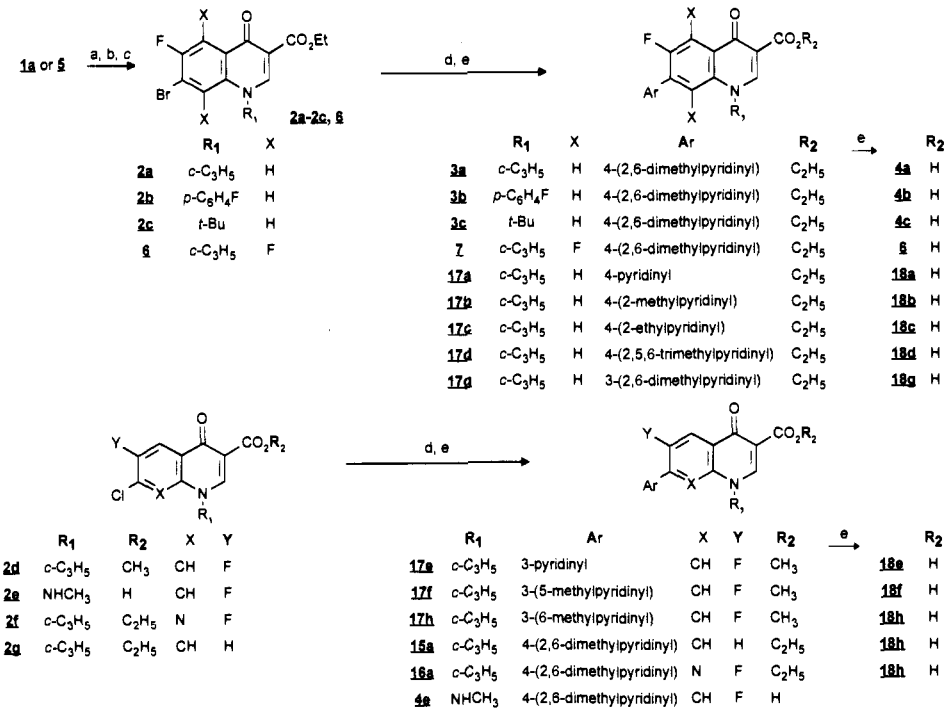
difluorobromobenzene with acetyl chloride gave the acetophenone and subsequent treatment of this material with NaH in diethyl carbonate gave **1d**.[28] Alternatively, treatment of 1,4-dibromo-2,5-difluorobenzene with BuLi and CO_2 gave the benzoic acid.[29] This acid was converted into **1d** by treatment of the acid chloride with ethyl hydrogen malonate–BuLi (method B).[30] β-Keto esters **1e** and **5** were prepared as described for **1d** using method B. Each β-keto ester was, in turn, converted into the appropriate 7-haloquinoline intermediate. Treatment of β-keto esters **1d** and **5** with *N,N*-dimethylformamide dimethyl acetal[31] followed by the appropriate primary amine gave the corresponding aminomethylene derivatives. These were converted into bromoquinolones **2a–c** and **6** with K_2CO_3 in DMF. Similarly, **1e** was converted into the 7-chloroquinolone **2g** except that triethyl orthoformate and acetic anhydride followed by cyclopropylamine was used in place of the sequence described above. Pyridinylquinolones **3a–c**, **4e**, **7**, **15a**, **16a**, and **17a–h** were readily obtained using the palladium-catalyzed Stille-type coupling[32–35] of pyridinylstannanes with the corresponding 7-bromo- or 7-chloroquinolones **6** and **2a–g**. This reaction was effected by heating the pyridinylstannane and haloquinolone at 150 °C in ethanol using a sealed vessel or in DMF or dioxane–HMPA at reflux. The resultant esters were hydrolyzed in dilute acid at reflux or with hydroxide to give the desired quinolones (Scheme 2). Target **4d** was obtained as described previously.[25] Trifluoroquinolone ester **7** served as a valuable intermediate (Scheme 3) for the preparation of the corresponding 6,8-difluoro and 8-monofluoro analogs. Treatment of ester **7** with benzyl mercaptan or thiophenol and NaH furnished sulfides **9a,b**, which were readily desulfurized with Ra Ni in ethanol (reflux) to give **10a**. In a similar fashion, monofluoride **10c** was obtained when **7** was treated with 1,2-benzenedithiol–NaH followed by Ra Ni desulfurization. Hydrolysis of **10a,c** in dilute HCl gave **10b**,[36]**d**, respectively. Access to the 2-(hydroxymethyl)- and 2-(aminomethyl)pyridinyl derivatives **21a,b** and **24a,b–26a,b** was effected by rearrangement of the corresponding *N*-oxide **19** (Ac_2O, reflux). This rearrangement gave the acetate **20**, and hydrolysis under standard conditions (aqueous HCl, reflux) afforded quinolone **21b**. Selective hydrolysis of **20** (EtOH–HCl) gave the intermediate alcohol **21a**. This alcohol was readily converted into the corresponding ether **23** and the amino derivatives **24b**, **25b**, and **26b** *via* chloride **22** (Scheme 4).

Biological Results and Discussion

When the 1-position substituent was changed from ethyl (**4d**) to cyclopropyl (**4a**), the antibacterial activity against Gram negative bacteria improved only marginally; however, activity against Gram positive strains improved at least 4-fold. This can be contrasted with the results found in 7-piperazinylquinolones where this modification significantly improves the antibacterial activity against *E. coli*. Other 1-position substituents that we examined included methylamino[37] (**4e**), *p*-fluorophenyl[38] (**4b**), and *tert*-butyl[39] (**4c**). When compared to its ethyl isostere **4d**, the methylamino group (**4e**) was detrimental to the antibacterial activity in all six strains tested. The *tert*-butyl substitution (**4c**) had no advantage over **4d** as its activity was essentially equivalent against all the organisms tested with the exception of *E. coli*, where it was 4-fold less active. The *p*-fluorophenyl substitution on N-1, which gave improved activity in 7-amino-6-fluoroquinolones, proved to be approximately comparable to **4d** against Gram negative strains but was 4-fold less active against all Gram positive organisms tested.

We studied the effect of fluorine substitution on 1-cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)quinolones (Table 1). Each fluorinated derivative (**4a**, **10d,b**, and **8**) was nearly 8 times more active than the corresponding nonfluorinated derivative (**15b**) against *S. aureus*. In particular, when the 6-position of 1-cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)quinolones is substituted with a fluorine, significant improvements in the Gram positive antibacterial activity (≥8-fold) are observed (Table 1). This parallels the result for the 1-ethyl counterparts which show comparable improvement in activity (Table 3). Activity against *E. coli* and *Bacteroides fragilis* is improved 4–8-fold with the addition of the 6-fluorine; however *Pseudomonas aeruginosa* proved to be insensitive to this change. The effect of fluorine substitution on rosoxacin was also reported by Nishimura and coworkers.[40] When the fluorine was switched from the

Scheme 2[a]



	R_1	X
2a	c-C_3H_5	H
2b	p-C_6H_4F	H
2c	t-Bu	H
6	c-C_3H_5	F

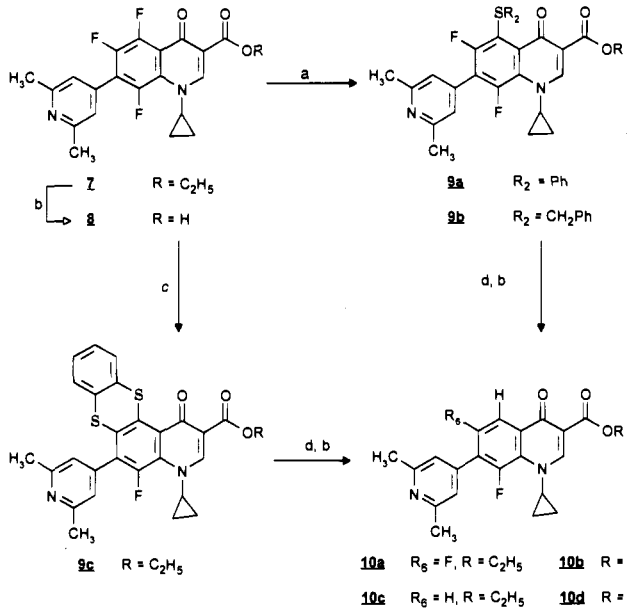
	R_1	X	Ar	R_2		R_2
3a	c-C_3H_5	H	4-(2,6-dimethylpyridinyl)	C_2H_5		4a H
3b	p-C_6H_4F	H	4-(2,6-dimethylpyridinyl)	C_2H_5		4b H
3c	t-Bu	H	4-(2,6-dimethylpyridinyl)	C_2H_5		4c H
7	c-C_3H_5	F	4-(2,6-dimethylpyridinyl)	C_2H_5		8 H
17a	c-C_3H_5	H	4-pyridinyl	C_2H_5		18a H
17b	c-C_3H_5	H	4-(2-methylpyridinyl)	C_2H_5		18b H
17c	c-C_3H_5	H	4-(2-ethylpyridinyl)	C_2H_5		18c H
17d	c-C_3H_5	H	4-(2,5,6-trimethylpyridinyl)	C_2H_5		18d H
17g	c-C_3H_5	H	3-(2,6-dimethylpyridinyl)	C_2H_5		18g H

	R_1	R_2	X	Y
2d	c-C_3H_5	CH_3	CH	F
2e	$NHCH_3$	H	CH	F
2f	c-C_3H_5	C_2H_5	N	F
2g	c-C_3H_5	C_2H_5	CH	H

	R_1	Ar	X	Y	R_2		R_2
17e	c-C_3H_5	3-pyridinyl	CH	F	CH_3		18e H
17f	c-C_3H_5	3-(5-methylpyridinyl)	CH	F	CH_3		18f H
17h	c-C_3H_5	3-(6-methylpyridinyl)	CH	F	CH_3		18h H
15a	c-C_3H_5	4-(2,6-dimethylpyridinyl)	CH	H	C_2H_5		18h H
16a	c-C_3H_5	4-(2,6-dimethylpyridinyl)	N	F	C_2H_5		18h H
4e	$NHCH_3$	4-(2,6-dimethylpyridinyl)	CH	F	H		

[a] (a) *N,N*-Dimethylformamide dimethyl acetal; (b) primary amine (cyclopropylamine, *p*-fluoroaniline, or *tert*-butylamine); (c) K_2CO_3; (d) $ArSn(CH_3)_3$ or $ArSn(Bu)_3$, $PdCl_2(PPh_3)_2$; (e) ester hydrolysis (aq HCl reflux) except for **15b** (NaOH in EtOH–H_2O) and **4c** (1 M KOH).

Scheme 3[a]

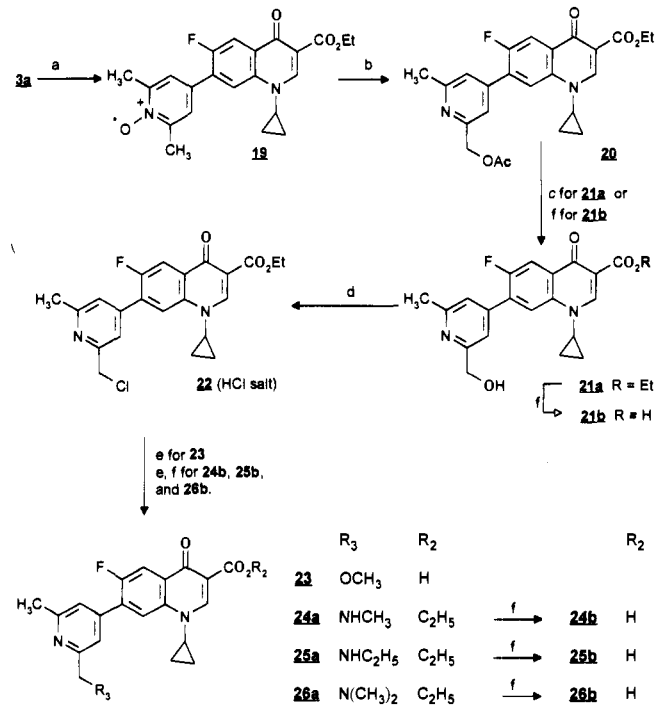


7 R = C_2H_5; 8 R = H; 9a R_2 = Ph; 9b R_2 = CH_2Ph; 9c R = C_2H_5

10a R_6 = F, R = C_2H_5; 10b R = H; 10c R_6 = H, R = C_2H_5; 10d R = H

[a] (a) NaSPh or $NaSCH_2Ph$; (b) 1 M HCl, reflux (**10b**), K_2CO_3 in H_2O–EtOH (**10d**); (c) 1,2-$C_6H_4S_2Na_2$; (d) Ra Ni in EtOH (**10a**), in toluene (**10c**).

Scheme 4[a]



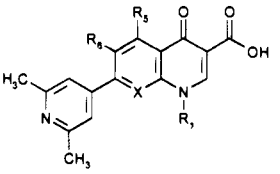
	R_3	R_2			R_2
23	OCH_3	H			
24a	$NHCH_3$	C_2H_5	f	24b	H
25a	NHC_2H_5	C_2H_5	f	25b	H
26a	$N(CH_3)_2$	C_2H_5	f	26b	H

[a] (a) *m*-CPBA; (b) Ac_2O, reflux; (c) ethanol–HCl; (d) $SOCl_2$; (e) methylamine, ethylamine, dimethylamine, or $NaOCH_3$; (f) hydrolysis (6 N HCl).

6-position, **4a**, to the 8-position, **10d**, identical activity against *E. coli* and *S. aureus* was obtained. Similar results were reported for the same modification in the 7-(aminopyrrolidinyl) 1-cyclopropyl derivatives.[41] The antibacterial activity of the corresponding 6-fluoro naphthyridine **16b** was comparable to that of **4d**.

The effect of substitution on the 7-(4-pyridine) ring seems to indicate a clear trend for the Gram positive activity, particularly against *S. aureus*. The optimal pyridine substituent is the 2,6-dimethylpyridine (**4a**). Gram positive activity drops when fewer methyl groups are attached to the ring, as with **18a,b**. When the size of the pyridine ring is increased by the addition of a methyl group as in **18d** or when the methyl in **18b** is changed to ethyl (**18c**), the Gram positive activity is also reduced. These changes in the pyridine substitution seem to have little effect on Gram negative activity. With a 3-pyridinyl group attached to the 7-position, Gram positive activity is reduced when compared to the

Table 1. Antibacterial Activity of Substituted 7-(2,6-Dimethyl-4-pyridinyl)quinolones[a]



no.	R_1	R_5	R_6	X	SA	SF	SP	EC	PA	BF
4d	C_2H_5	H	F	CH	0.03	0.25	0.25	0.06	4.0	2.0
4c	*t*-Bu	H	F	CH	0.03	0.25	0.125	0.25	>4.0	1.0
4b	*p*-C_6H_4F	H	F	CH	0.125	1.0	1.0	0.125	4.0	1.0
4e	$NHCH_3$	H	F	CH	0.06	0.5	1.0	0.25	>4.0	>4.0
4a	c-C_3H_5	H	F	CH	0.008	0.06	0.03	0.03	2.0	0.5
16b	c-C_3H_5	H	F	N	0.03	0.125	0.25	0.125	8.0	2.0
15b	c-C_3H_5	H	H	CH	0.06	0.5	0.5	0.25	>4.0	>4.0
10b	c-C_3H_5	H	F	CF	0.008	0.06	0.016	0.06	4.0	0.125
8	c-C_3H_5	F	F	CF	0.008	0.06	0.03	0.13	8.0	0.5
10d	c-C_3H_5	H	H	CF	0.008	nt	nt	0.06	nt	nt

[a] Antibacterial data in Tables 1–3 are the MIC_{50} values in μg/mL; nt indicates that the compound was not tested against that particular strain. The organisms used in this study were *E. coli* ATCC 1-25922 (EC), *P. aeruginosa* ATCC 27853 (PA), *B. fragilis* ATCC 25285 (BF), *S. aureus* ATCC 29213 (SA), *S. faecalis* ATCC 29212 (SF), and *S. pyogenes* ATCC 6301 (SP).

4-pyridinyl. However, **18e** had better activity against *E. coli* than any of the pyridinylquinolones reported in this study.

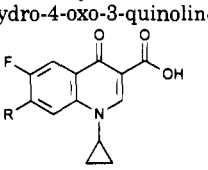
We next sought to study analogs containing an aminoalkyl appendage on the pyridine ring as these derivatives are somewhat structurally related to aminopyrrolidine derivatives **27** and **28**. The (aminoalkyl)-pyridines prepared for this analysis were **24b**, **25b**, and **26b**. All of these derivatives showed lower overall *in vitro* antibacterial activity when compared to **4a**. The alcohol **21b** and methyl ether **23** show slightly improved Gram positive activity when compared to the corresponding amino analogs **24b**, **25b**, and **26b**. When the comparison is made to **4a**, all the compounds in this subset show lowered Gram positive activity and comparable Gram negative activity.

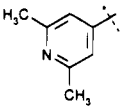
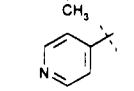
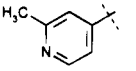
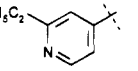
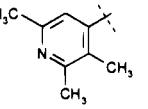
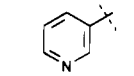
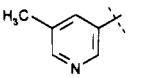
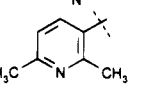
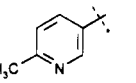
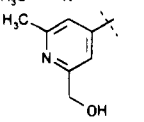
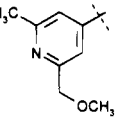
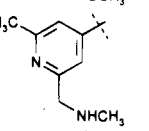
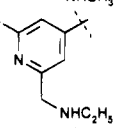
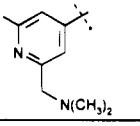
When compared with fluoroquinolones such as ciprofloxacin, aminopyrrolidine **28**, and tosufloxacin, the pyridinylquinolones discussed in this report offer excellent overall antibacterial activity. In particular, **4a** is active against *B. fragilis* and Gram positive organisms with exceptional activity against *S. aureus*. Additional studies indicate that **4a** shows excellent activity against a wide range of organisms[42,43] including anaerobic bacteria[44,45] and Gram positive pathogens,[46,47] particularly *Staphylococcal* strains which include ciprofloxacin resistant and methicillin resistant *S. aureus*.[48,49]

Conclusion

We have found that for a number of 1-substituted 1,4-dihydro-4-oxo-7-(2,6-dimethyl-4-pyridinyl)-3-quinolinecarboxylic acids, the optimal 1-position substituent for Gram positive antibacterial activity, particularly against *S. aureus*, is the cyclopropyl group. This group gave comparatively little improvement in the Gram negative activity of these compounds. This result differs from that of other quinolone families such as piperazinylquinolones. Among the 1-cyclopropylpyridinylquinolones, the 6-fluoro derivative **4a** provides the best overall antibacterial activity of all the compounds in this study while maintaining excellent antistaphylococcal activity. Modifications to the pyridinyl group of **4a** gave only compounds with reduced Gram positive activity.

Table 2. Antibacterial Activity of 7-Substituted 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

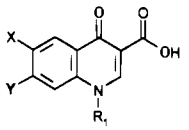


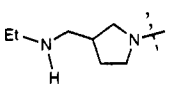
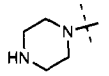
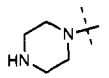
No	R	SA	SF	SP	EC	PA	BF
4a		0.008	0.06	0.03	0.03	2.0	0.5
18a		0.06	0.5	0.25	0.03	2.0	1.0
18b		0.016	0.06	0.06	0.03	2.0	0.5
18c		0.03	0.25	0.25	0.125	4.0	1.0
18d		0.06	0.5	0.25	0.125	8.0	4.0
18e		0.016	0.25	0.125	0.008	1.0	0.5
18f		0.016	0.125	0.06	0.06	2.0	0.25
18g		1.0	4.0	8.0	0.5	>16	4.0
18h		0.03	0.25	0.25	0.03	2.0	0.25
21b		0.03	0.125	0.06	0.06	4.0	1.0
23		0.03	0.125	0.125	0.25	8.0	1.0
24b		0.125	0.2	0.25	0.016	1.0	2.0
25b		0.5	2.0	0.5	0.06	8.0	8.0
26b		0.06	0.5	0.5	0.06	8.0	2.0

Experimental Section

Microbial Cultures. All cultures were obtained originally from the American Type Culture Collection (Rockville, MD) and consisted of the following screening organisms: *E. coli* ATCC 1-25922 (EC), *P. aeruginosa* ATCC 27853 (PA), *S. aureus* ATCC 29213 (SA), *Streptococcus faecalis* ATCC 29212

Table 3. Antibacterial Activity of Selected Reference Compounds



compd	R_1	X	Y	SA	SF	SP	EC	PA	BF
4a		F	DMP[a]	0.008	0.06	0.03	0.03	2.0	0.5
rosoxacin	C_2H_5	H	PYR[b]	0.5	16	16	0.125	16	8
dimethylrosoxacin	C_2H_5	H	DMP	0.25	1	32	0.25	2	16
6-fluororosoxacin	C_2H_5	F	PYR	0.25	1	2	0.125	2	16
4d	C_2H_5	F	DMP	0.03	0.25	0.25	0.06	4	2
28		F		0.015	0.03	0.015	0.004	2.0	0.125
ciprofloxacin		F		0.25	0.5	0.25	0.004	.125	2.0
norfloxacin	C_2H_5	F		2.0	4.0	4.0	0.125	2.0	8.0

[a] DMP = 2,6-dimethyl-4-pyridinyl. [b] PYR = 4-pyridinyl.

(SF), *Streptococcus pneumoniae* ATCC 6301 (SP), and *B. fragilis* ATCC 25285 (BF). All cultures were stored as frozen stock.

MIC Determinations. A broth microdilution method[50,51] was used to quantitate antibacterial activity for these compounds. The SA, SF, EC, and PA cultures were inoculated into Mueller Hinton II medium (BBL, Inc., Baltimore, MD). The SP culture was inoculated into brain heart infusion (BHI) broth (DIFCO Laboratories, Detroit, MI), supplemented with 10% heat-inactivated horse serum. The BF culture was inoculated into BHI broth supplemented with 5 μg/mL hemin and 0.5 μg/mL vitamin K. All but the BF cultures were grown for 18–24 h at 37 °C; the BF culture was grown for 48 h at 37 °C under anaerobic conditions (5% CO_2, 10% H_2, and 85% N_2). The resulting suspensions were adjusted to an absorbance of 0.1 unit (λ = 650 nm) using a Bausch and Lomb colorimeter and further diluted 1:10 in the respective medium to form the inoculum for each test. The inoculum was transferred to 96-well microdilution plates using an MIC 2000 automated inoculator (Dynatech Laboratories, Inc., Alexandria, VA). The final culture density was 10^5 cells/mL, and the plates were incubated at 37 °C for 24 h, except the BF culture which was incubated anaerobically for 48 h. The MIC was defined as the lowest concentration of compound which completely inhibited visible growth or turbidity present in the well.

General. Melting points are uncorrected. Spectral data were recorded as follows: proton NMR spectra (IBM AM-200 or JOEL GSX-270 spectrometer), chemical ionization mass spectra (Hewlett-Packard 5980A mass spectrometer), and infrared spectra (Nicolet 10DX FTIR spectrometer). ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants are in hertz (Hz). Carbon, hydrogen, and nitrogen elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and are within 0.4% of theoretical values unless otherwise noted.

Preparation of (Trialkylstannyl)pyridine Derivatives. (Trialkylstannyl)pyridine derivatives were obtained from the corresponding pyridinyl bromides by the general method illustrated below. In most cases these materials were used directly without any purification. Due to the possible toxicity of tin reagents, these compounds should be handled only in a fume hood.[52]

2,6-Dimethyl-3-(trimethylstannyl)pyridine. 3-Bromo-2,6-dimethylpyridine[53] (9.3 g, 0.05 mol) was taken up in 200 mL of ether under nitrogen and chilled to −78 °C, and then 20.5 mL of 2.6 M BuLi was added. After 15 min, 10.6 g (0.053 mol) of chlorotrimethylstannane in 30 mL of ether was added; the mixture was allowed to warm to room temperature over 2 h and the reaction quenched with 200 mL of water. The ether layer was dried ($MgSO_4$), filtered, and concentrated to give 12.4 g (92%) of the stannane.

2,6-Dimethyl-4-(tributylstannyl)pyridine: prepared in the same manner as 2,6-dimethyl-3-(trimethylstannyl)pyridine using 4-bromo-2,6-dimethylpyridine[54] and chlorotributylstannane (99%).

2-Ethyl-4-(trimethylstannyl)pyridine: prepared in the same manner as 2,6-dimethyl-3-(trimethylstannyl)pyridine using 2-ethyl-4-bromopyridine[55] to give the stannane as an orange oil (83%).

2,3,6-Trimethyl-4-(trimethylstannyl)pyridine: prepared in the same manner as 2,6-dimethyl-3-(trimethylstannyl)-pyridine above. Thus 4.76 g (0.023 mol) of 4-bromo-2,3,6-trimethylpyridine, obtained from 2,3,6-trimethyl-4-nitropyridine and 4 equiv of PBr_3, gave 7.19 g (100%) of the crude stannane as a brown oil.

3-Methyl-5-(tributylstannyl)pyridine: prepared by the general procedure illustrated for 2,6-dimethyl-3-(trimethylstannyl)pyridine with the modification that the resultant oil was diluted with hexane and filtered through Super-Cell. The filtrate was concentrated under vacuum at 90 °C. Thus 17.2 g of 3-bromo-5-methylpyridine[56] gave 35 g (92%) of the stannane as a yellow oil.

2-Methyl-5-(tributylstannyl)pyridine: prepared as above using 5-bromo-2-methylpyridine[56] to give the stannane as a brown oil (81%).

Preparation of 7-Haloquinolinecarboxylates. 4-Bromo-2,5-difluoroacetophenone, 1a. Method A. To a stirred mixture of 20 g (0.1 mol) of 2,5-difluorobromobenzene and 35.2 g (0.26 mol) of $AlCl_3$ at 60 °C under nitrogen was added 12 g (0.15 mol) of acetyl chloride in a dropwise manner. The mixture was stirred at 95 °C for 1.5 h and then poured into 250 g of ice. To this mixture was added 17 mL of concentrated HCl followed by extraction into ether. The ether extracts were washed with brine and then concentrated and distilled to give 18.4 g (76%): bp 65 °C/0.1 mmHg; ^1H NMR ($CDCl_3$) δ 7.65 (dd, 1H), 7.42 (dd, 1H), 2.5 (d, 3H); CIMS-CH_4 *m/z* 235 (M + H). Anal. ($C_8H_5F_2BrO$) C, H.

Ethyl (4-Bromo-2,5-difluorobenzoyl)acetate, 1d. To an ice-chilled solution of 18.6 g (79 mmol) of 4-bromo-2,5-difluoroacetophenone in 200 mL of diethyl carbonate was added 6.8 g (17 mmol) of 60% NaH oil dispersion. The mixture was allowed to stir at room temperature for 3 h and then poured into 700 mL of ice containing 25 mL of acetic acid. The mixture was extracted with ether; the ether extract was brine washed, dried ($MgSO_4$), concentrated, and distilled (bp 115–

120 °C/0.1–0.05 mmHg) to give an oil which crystallized on standing (13.9 g, 58%): mp 55–58 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 12.25 (s, 1H), 7.69 (dd, 1H), 7.35 (dd, 1H), 5.85 (s, 1H), 4.25 (q, 2H), 1.32 (t, 3H); CIMS-CH_4 *m/z* 307 (M + H). Anal. ($C_{11}H_9F_2BrO_3$) C, H.

Ethyl (4-Bromo-2,5-difluorobenzoyl)acetate, 1d. Method B. A mixture of 22.3 g (94 mmol) of 4-bromo-2,5-difluorobenzoic acid[29] and 112 mL of thionyl chloride was heated at reflux for 3 h and then concentrated under vacuum to give the acid chloride. The acid chloride was converted into **1d** using the method of Wierenga and Skulnick.[30] Thus the acid chloride above gave, after recrystallization from hexane, 21 g (73%): mp 51–53 °C. This material was spectroscopically identical with the material obtained by method A.

Ethyl 1-Cyclopropyl-7-bromo-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate, 2a. A solution of 18.7 g (61 mmol) of **1d** and 8 mL (61 mmol) of *N,N*-dimethylformamide dimethyl acetal in 44 mL of THF was stirred overnight at room temperature. The mixture was concentrated under vacuum to give the dimethylenamine as a dark oil. The oil was taken up in 90 mL of THF, cyclopropylamine (4.2 mL, 61 mmol) was added, and then the mixture was stirred in an ice bath for 1 h. The mixture was concentrated under vacuum to give a dark oil. This oil was combined with 11.5 g of K_2CO_3 (83 mmol) in 90 mL of DMF and heated for 1 h (steam bath). After this time the mixture was added to ice water and the precipitate filtered and recrystallized from ethanol (ca. 2 L) to give **2a**, 16.6 g (77%): mp 252–254 °C; ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.15 (m, 2H), 4.37 (q, 2H), 3.46 (m, 1H), 1.42 (t, 3H), 1.19–1.42 (t, 3H); CIMS-CH_4 *m/z* 354 (M + H). Anal. ($C_{15}H_{13}FBrNO_3$) C, H, N.

Ethyl 7-Bromo-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate, 2b. Using the procedure described for **2a**, 3 g of **1d** was converted into the dimethylenamine. This intermediate was treated with 1.08 g (9.8 mmol) of 4-fluoroaniline in 15 mL of dioxane at reflux for 60 h. The resultant white solid was filtered and washed with ether to give 2.1 g of **2b** (52%): mp 312–314 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 8.22 (d, 1H), 7.58–7.32 (m, 4H), 7.16 (d, 1H), 4.49 (q, 2H), 1.40 (t, 3H); CIMS-CH_4 *m/z* 408 (M + H). Anal. ($C_{18}H_{12}F_2BrNO_3$) C, H.

Ethyl 2,4-Dichloro-β-oxobenzenepropanoate, 1e. This was prepared using method B as described for **1d** from 2,4-dichlorobenzoyl chloride (Aldrich) (78%): bp 128–132 °C/0.40 mmHg (lit.[27] bp 155–165 °C/0.30 mmHg); IR (film) 1741 cm^{-1}; CIMS-CH_4 *m/z* 261 (M + H); ^{1}H NMR ($CDCl_3$) δ 12.50 (s, 0.6H), 7.26–7.63 (m, 3H), 5.57 (s, 0.8H), 4.16–4.38 (m, 2.2H), 1.28 and 1.36 (pair of t, *J* = 7.3, 3H).

Ethyl 7-Chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate, 2g. The β-keto ester **1e** was treated with triethyl orthoformate in acetic anhydride followed by cyclopropylamine to give ethyl 2,4-dichloro-α-[(cyclopropylamino)-methylene]-β-oxobenzenepropanoate (85%): mp 146–147 °C; IR (KBr) 1685, 1670 cm^{-1}; CIMS-CH_4 *m/z* 328 (M + H); ^{1}H NMR ($CDCl_3$) δ 11.02 (br s, 1H), 8.30 and 8.25 (pair of d, *J* = 14.1, 1H), 7.35–7.09 (m, 3H), 3.98 and 3.91 (pair of q, *J* = 6.8, 2H), 3.01 (m, 1H), 0.79–1.01 (m, 7H). Anal. ($C_{15}H_{15}Cl_2NO_3$) C, H, N. Cyclization of the this enamine in dioxane–K_2CO_3 at reflux gave 7-chloroquinoline **2g** (94%): mp 179–181 °C; IR (KBr) 1718, 1685 cm^{-1}; CIMS-CH_4 *m/z* 292 (M + H); ^{1}H NMR (CF_3COOD) δ 9.40 (s, 1H), 8.70 (d, *J* = 6.1, 1H), 8.68 (s, 1H), 8.01 (dd, *J* = 1.3, 9.8, 1H), 4.71 (q, *J* = 7.2, 2H), 4.18 (m, 1H), 1.68–1.79 (m, 2H), 1.56 (t, *J* = 7.2, 3H), 1.52–1.59 (m, 2H). Anal. ($C_{15}H_{14}ClNO_3$) C, H, N.

Ethyl 7-Bromo-1-cyclopropyl-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate, 6. To 4-Bromo-2,3,5,6-tetrafluorobenzoic acid[57] was added 10.9 g (52.3 mmol) of PCl_5. After stirring overnight the contents of the reaction mixture were distilled at aspirator pressure to give the acid chloride (bp 95–100 °C) to give 10.15 g. The acid chloride (33.4 g, 0.115 mol) was converted into β-keto ester **5** by the method described for **1d** to give 34.18 g (86%; bp 112–117 °C/0.8 mmHg). Using the procedure described for **2a**, 68.77 g (0.20 mol) of **5** in 200 mL of THF was converted into the dimethylenamine. To the THF solution of the enamine was added 14 mL of cyclopropylamine; the mixture was then concentrated and recrystallized (EtOH) to give the corresponding cyclopropylenamine (64.45 g, 79%): mp 168–169.5 °C. This material was dissolved in 300 mL of DMF and combined with 60 g of K_2CO_3, and the resulting mixture was heated at 150 °C for 1.5 h. The mixture was cooled, poured into water, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated. The residue was recrystallized form acetonitrile to give 37.82 g (62%): mp 187–190 °C. Anal. ($C_{15}H_{11}F_3BrNO_3$) C, H, N.

7-(2,6-Dimethyl-4-pyridinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylates. 1-Cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 4a. To a solution of **2a** (1.3 g, 3.7 mmol) in 25 mL of dioxane and 1 mL of HMPA were added 1.1 g (4.0 mmol) of 2,6-dimethyl-4-(trimethylstannyl)pyridine[35] and 166 mg (0.24 mmol) of $PdCl_2(PPh_3)_2$. The stirred mixture was heated at reflux for 24 h. The mixture was filtered, and the filtrate was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a solid. This material was washed with ether to give 1.05 g of ester **3a** (75%): mp 215–216 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.21 (d, 1H), 8.00 (d, 1H), 7.29 (s, 2H), 4.42 (q, 2H), 3.57 (m, 1H), 2.66 (s, 6H), 1.43 (m, 5H), 1.21 (m, 2H). Anal. ($C_{22}H_{21}FN_2O_3$) C, H, N. The ester from above (**3a**) was saponified in 25 mL of 0.27 M NaOH at reflux for 2.5 h. The cooled mixture was treated with Darco and filtered, and the pH of the filtrate was adjusted to 5–5.5 with acetic acid giving a precipitate. The solid was collected, washed with EtOH and ether, and then recrystallized (EtOH) to give **4a**, 0.69 g (76%): mp 301 °C; ^{1}H NMR (CF_3COOD) δ 9.56 (s, 1H), 8.95 (d, 1H), 8.57 (d, 1H), 8.02 (s, 2H), 4.39 (m, 1H), 2.98 (s, 6H), 1.75 (m, 2H), 1.58 (m, 2H). Anal. ($C_{20}H_{17}FN_2O_3$) C, H, N.

7-(2,6-Dimethyl-4-pyridinyl)-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 4b. This was prepared in the same manner as **4a**. Thus 2.3 g (5.7 mmol) of **2b** gave 1.62 g of ester **3b** (66%): mp 261–264 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 8.25 (d, 1H), 7.88 (m, 2H), 7.56 (m, 2H), 7.21 (d, 1H), 7.12 (s, 2H), 2.45 (s, 6H). Anal. ($C_{23}H_{16}F_2N_2O_3$) C, H, N. The above ester **3b** (1.5 g, 3.5 mmol) was saponified in NaOH as described for **4a** to give **4b** (86%): mp 257–259 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 8.25 (d, 1H), 7.88 (m, 2H), 7.56 (m, 2H), 7.21 (d, 2H), 7.12 (s, 2H), 2.45 (s, 6H). Anal. ($C_{23}H_{16}F_2N_2O_3$) C, H, N.

1-*tert*-Butyl-6-fluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-3-quinolinecarboxylic Acid, 4c. Using the procedure described for **2a**, 5.00 g (16.3 mmol) of **1d** in 50 mL of THF was converted into the dimethylenamine. This enamine solution was chilled in ice, and then 2.1 mL (20 mmol) of *tert*-butylamine was added. After stirring for 1.5 h the mixture was concentrated and then filtered through silica gel (ether) to give 5.76 g of the intermediate enamine. This material (4.94 g, 12.66 mmol) was combined with 5.25 g (38 mmol) of K_2CO_3 in 50 mL of DMF and heated at 60–65 °C for 4 h. The mixture was then poured into water and extracted with $CHCl_3$. The extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The resulting solid was rinsed with hexane and dried to give 3.54 g of **2c** (75%): mp 199–203 °C. Ester **2c** (1.47 g, 3.97 mmol) and 1.98 g (4.76 mmol) of 4-(tributylstannyl)-2,6-dimethylpyridine were combined in 10 mL of ethanol with 140 mg (0.2 mmol) of $PdCl_2(PPh_3)_2$. The mixture was heated in a sealed tube at 150 °C for 3 h. Extractive workup as in **4a** using $CHCl_3$ gave 1.34 g of **3c** (85%): mp 307–310 °C. Hydrolysis (1 M KOH, 1 h) followed by neutralization and recrystallization gave **4c** (62%): mp 285–286 °C; ^{1}H NMR ($CDCl_3$) δ 14.65 (s, 1H), 9.16 (s, 1H), 8.37 (d, 1H), 8.16 (d, 1H), 7.20 (s, 2H), 2.67 (s, 6H), 1.99 (s, 9H); IR (KBr) 1730, 1605 cm^{-1}. Anal. ($C_{21}H_{21}FN_2O_3$) C, H, N.

Ethyl 1-Cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-3-quinolinecarboxylate, 7. This was prepared by the coupling as described for **4a** except that the reaction was attempted using THF in place of dioxane; this modification gave no appreciable reaction after 24 h at reflux. The THF was then distilled out and replaced by dioxane. Thus 17.8 g (45.6 mmol) of **6** gave an amber oil which was crystallized from ethanol to give 6.67 g of **7**, and the

liquors from the crystallization were combined and chromatographed on silica gel (EtOAc followed by 5% MeOH–EtOAc) giving an additional 1.54 g (43%): mp 221.5–222.5 °C (ethanol, Darco). Anal. ($C_{22}H_{19}F_3N_2O_3$) C, H, N.

1-Cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-3-quinolinecarboxylic Acid, 8. This was prepared in the same manner as indicated for **4a**. Thus 2.8 g (7 mmol) of **6** gave the crude ester **7**. This material was immediately hydrolyzed by heating at reflux in 100 mL of 1 M HCl for 2 h. The mixture was then filtered, concentrated, dissolved in 50 mL of aqueous K_2CO_3, treated with Darco, and filtered. The filtrate was acidified with concentrated HCl and then neutralized with aqueous NaOAc to give a precipitate. This was recrystallized from ethanol to give 1.6 g of **8** (59%): mp 264–266 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.30 (s, 2H), 4.08 (s, 1H), 2.55 (s, 6), 1.15 (m, 4). Anal. ($C_{20}H_{15}F_3N_2O_3$) C, H, N.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-6-fluoro-4-oxo-5-(phenylthio)-3-quinolinecarboxylate, 9a. Ester **7** (5.00 g, 12.0 mmol) was suspended in THF, the mixture was chilled in ice, and 1.25 mL of thiophenol (12.2 mmol) was added. To this cold mixture was added 0.58 g of NaH as a 60% oil dispersion in small portions. The reaction mixture became a clear yellow solution and was diluted with ether and ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated to give 5.70 g of a light yellow solid. This preparation was repeated on 7.50 g of **7** to give an additional 10.1 g of material. These preparations were combined and recrystallized from acetonitrile to give 11.96 g of **9a** (76%): mp 230–231 °C; ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 7.38–7.10 (m, 5H), 6.92 (s, 2H), 4.40 (q, 2H), 3.93, (m, 1H), 2.55 (s, 6H), 1.41 (t, 3H), 1.26–1.10 (m, 4H). Anal. ($C_{28}H_{24}F_2N_2O_3S$) C, H, N.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-6-fluoro-4-oxo-5-[(phenylmethyl)-thio]-3-quinolinecarboxylate, 9b. Ester **7** was converted into **9b** in the same manner as described for **9a**. Thus 4.16 g (10.0 mmol) of **7** and 1.24 g (10 mmol) of benzyl mercaptan gave 4.9 g of **9b** (94%): mp 197–199 °C. Anal. ($C_{29}H_{26}F_2N_2O_3S$) C, H, N.

Ethyl 4-Cyclopropyl-1,4-dihydro-6-(2,6-dimethyl-4-pyridinyl)-5-fluoro-1-oxo-1,4-benzodithiino[2,3-*f*]quinoline-2-carboxylate, 9c. Ester **7** (1.00 g, 2.6 mmol) was added to 0.50 g (3.5 mmol) of 1,2-benzenedithiol and 0.18 g (4.5 mmol) of NaH (60% oil dispersion) in 40 mL of dioxane. The mixture was heated to reflux overnight, cooled, diluted with water, chilled in ice, and filtered. The resulting solid was dried and chromatographed on silica gel (EtOAc) to give 1.06 g of **9c** (80%): mp 276–278 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H), 7.53 (m, 1H), 7.20 (m, 3H), 6.92 (s, 2H), 4.41 (q, 2H), 3.85 (m, 1H), 2.64 (s, 6H), 1.41 (t, 3H), 1.17 (m, 2H), 1.06 (m, 2H). Anal. ($C_{28}H_{23}FN_2O_3S_2$) C, H, N.

1-Cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)-8-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 10d. Treatment of 0.56 g (1.1 mmol) of **9c** in 5 mL of toluene with Ra Ni in 10 mL of absolute ethanol at reflux for 1 h followed by hot filtration through Celite and concentration of the filtrate gave 0.43 g of a yellow residue. This material was taken up in 10 mL of ethanol, combined with 0.41 g of K_2CO_3 in 5 mL of water, and heated overnight at 50 °C. The resultant mixture was concentrated to dryness, dissolved in water, treated with 0.5 mL of glacial acetic acid, and then chilled in ice, filtered, and dried to give 0.28 g of **10d** (74%): mp 232–235 °C (EtOAc–$CHCl_3$); ^{1}H NMR (CF_3COOD) δ 9.66 (s, 1H), 8.84 (d, 1H), 8.22 (dd, 1H), 8.08 (s, 2H), 4.73 (m, 1H), 3.04 (s, 6H), 1.71 (m, 2H), 1.62 (m, 2H). Anal. ($C_{20}H_{17}FN_2O_3$) C, H, N.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-3-quinolinecarboxylic Acid, 10b. Ester **9a** (2.12 g, 4.07 mmol) was suspended in 100 mL of ethanol and heated to reflux. Ra Ni (Aldrich), prewashed in ethanol, was added to **9a**, and after 15 min the mixture was filtered and concentrated to give a yellow residue. Column chromatography on silica gel using EtOAc gave 1.0 g of **10a** as a white solid (62%): mp 186.5–187 °C. Alternatively, when **9b** was treated in the same manner, a 48% yield of **10a** was obtained. The ester (1 g) was suspended in 20 mL of 1 M HCl and heated to reflux for 2 h, cooled, neutralized with saturated NaOAc, extracted with EtOAc, dried (Na_2SO_4), filtered, concentrated, and recrystallized (EtOH) to give 0.70 g of **10b** as white needles (75%): mp 246–248.5 °C; ^{1}H NMR ($CDCl_3$) δ 14.3 (s, 1H), 8.91 (s, 1H), 8.12 (dd, 1H), 7.10 (s, 2H), 4.06 (m, 1H), 2.65 (s, 6H), 1.4–1.2 (m, 4H); IR (KBr) 1720, 1610 cm^{-1}; CIMS-CH_4 *m/z* 371 (M + H). Anal. ($C_{20}H_{16}F_2N_2O_3$) C, H, N.

1-Cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid, 16b. Ester **2f**[58] was converted into **16b** in the same manner as described for **8**. Thus 6.2 g (16 mmol) of **2f** and 5.6 g (20 mmol) of 4-(trimethylstannyl)-2,6-dimethylpyridine gave, after recrystallization from DMF-ethanol, 3.5 g of **16b** as cream-colored flakes (62%): mp 264–266 °C; ^{1}H NMR (CF_3COOD) δ 9.58 (s, 1H), 8.95 (d, 1H), 8.58 (s, 2H), 4.42 (m, 1H), 3.08 (s, 6H), 1.8–1.5 (m, 4H). Anal. ($C_{19}H_{16}FN_3O_3$) C, H, N.

6-Fluoro-1-(methylamino)-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid, 4e. A mixture of 27 g (0.1 mol) of 7-chloro-6-fluoro-1,4-dihydro-1-(methylamino)-4-oxo-3-quinolinecarboxylic acid[36] (**2e**), 47.2 g (0.12 mol) of 4-(tributylstannyl)-2,6-dimethylpyridine, and 2.1 g (3 mmol) $PdCl_2(PPh_3)_2$ was combined in 25 mL of DMF and heated in an oil bath under N_2 at 150–60 °C for 3 h. After this time the solvent was removed under vacuum, and the residue was stirred with ether, filtered, and dried. This material was filtered through a silica gel plug using $CHCl_3$ followed by 5% MeOH–$CHCl_3$ and recrystallized from DMF to give 14 g of **4e** (41%): mp 285 °C; CIMS-CH_4 *m/z* 342 (M + H); IR (KBr) 1728, 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6–$CDCl_3$) δ 14.9 (s, 1H), 9.15 (s, 1H), 8.3 (d, J = 5, 1H), 8.15 (d, J = 8, 1H), 7.3 (s, 2H), 6.8 (q, 1H), 3.0 (d, 3H), 2.65 (s, 6H). Anal. ($C_{18}H_{16}FN_3O_3$) C, H, N.

1-Cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid, 15b. Ester **2g** was converted into **15a** as described for **3c**, except that the coupling was done at 170 °C to give 43% of **15a**: mp 185–195 °C; CIMS-CH_4 *m/z* 363 (M + H); IR (KBr) 1728, 1688 cm^{-1}; ^{1}H NMR (CF_3COOD) δ 9.52 (s, 1H), 9.02 (s, 1H), 8.98 (d, J = 8.8, 1H), 8.36 (d, J = 8.5, 1H), 8.10 (s, 2H), 4.74 (q, J = 7.1, 2H), 4.35 (m, 1H), 2.98 (s, 6H), 1.70–1.81 (m, 2H), 1.57 (t, J = 7.1, 3H), 1.48–1.58 (m, 2H). Anal. $C_{22}H_{22}N_2O_3$) C, H, N. Ester **15a** was saponified in ethanolic NaOH followed by neutralization with acetic acid to give **15b** (35%): mp 282–285 °C; CIMS-CH_4 *m/z* 335 (M + H); ^{1}H NMR (CF_3COOD) δ 11.72 (s, 1H), 9.60 (s, 1H), 9.04 (s, 1H), 8.99 (d, J = 8.6, 1H), 8.37 (dd, J = 1.2, 8.6, 1H), 8.10 (s, 2H), 4.36 (m, 1H), 2.98 (s, 6H), 1.72–1.84 (m, 2H), 1.49–1.58 (m, 2H). Anal. ($C_{20}H_{18}N_2O_3$) C, H, N.

1-Cyclopropyl-7-(4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18a. Ester **2a** was converted into **18a** exactly as described for **4a** to give the intermediate ester **17a** (67%): CIMS-CH_4 *m/z* 353 (M + H); ^{1}H NMR ($CDCl_3$) δ 8.75 (d, 2H), 8.60 (s, 1H), 8.20 (d, 1H), 8.02 (d, 1H) 7.55 (d, 2H), 4.49 (q, 2H), 3.59 (m, 1H), 1.40 (m, 5H), 1.25 (m, 2H). Ester **17a** was saponified as described for **4a** to give **18a**: mp >315 °C (DMF); ^{1}H NMR (CF_3COOD) δ 9.57 (s, 1H), 9.13 (d, 2H), 9.08 (d, 1H), 8.65 (d, 1H), 8.56 (2, 2H), 4.49 (m, 1H), 1.80 (m, 2H), 1.60 (m, 2H). Anal. ($C_{18}H_{13}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(2-ethyl-4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18c. Ester **2a** was converted into **18c** as described for **4c**. Thus 10.0 g (29.4 mmol) of **2a**, 9.5 g (35.2 mmol) of 2-ethyl-4-(trimethylstannyl)-pyridine, and 1 g of $PdCl_2(PPh_3)_2$ were heated at 150 °C in 100 mL of ethanol for 5 h. Extractive workup and hydrolysis in 3 M HCl (reflux) followed by recrystallization (acetonitrile) gave 3.08 g of **18c** (30%): mp 286–288 °C; ^{1}H NMR (CF_3COOD) δ 9.58 (s, 1H), 9.04 (d, 1H), 8.96 (d, 1H), 8.65 (d, 1H), 8.35 (d and s superimposed, 2H), 4.37 (m, 1H), 3.38 (q, 2H), 1.68 and 1.61 (m, and t superimposed, 7H); CIMS-CH_4 *m/z* 353 (M + H). Anal. ($C_{20}H_{17}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(2-methyl-4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18b. Ester **2a** (6.1 g, 18 mmol), 5.1 g (20 mmol) of 2-methyl-4-(trimethylstannyl)pyridine,[35] and 2 mmol of $PdCl_2(PPh_3)_2$ were heated in 100 mL of ethanol (5 h, 150 °C). Filtration, hydrolysis (2

M HCl), neutralization ($NaHCO_3$), and recrystallization (DMF) gave **18b**, 1.21 g (20%): mp 287–288 °C; ^1H NMR (DMSO-d_6) δ 14.7 (br s, 1H), 8.81 (s, 1H), 8.67 (s, 1H), 8.42 (d, 1H), 8.14 (d, 1H), 7.62 (s, 1H), 7.53 (br d, 1H), 3.96 (m, 1H), 2.60 (s, 3H), 1.3 (m, 4H). Anal. ($C_{19}H_{15}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(2,3,6-trimethyl-4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18d. Ester **2a** (7.8 g, 22 mmol), 6.76 g (24 mmol) of 2,3,6-trimethyl-4-(trimethylstannyl)pyridine, and 1.5 g (2.4 mmol) of $PdCl_2(PPh_3)_2$ were heated as above for 8 h. The product mixture was taken up in additional hot ethanol, filtered, concentrated, and chromatographed (silica gel) using 5% 2-propanol–ethyl acetate to give the ester **17d** (11%). The ester was hydrolyzed (2 M HCl) and, after extractive workup, recrystallized (acetonitrile) to give **18d** (31%): mp 297–298 °C; ^1H NMR (DMSO-d_6) δ 14.6 (br s, 1H), 8.79 (s, 1H), 8.22 (d, 1H), 8.15 (d, 1H), 7.10 (s, 1H), 3.89 (m, 1H), 2.52 (s, 3H), 2.47 (s, 3H), 2.08 (s, 3H), 1.37 (m, 4H). Anal. ($C_{21}H_{19}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(3-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18e. Ester **2d** was converted into **18e** as described for **4a** with the exceptions indicated below. Thus 6 g (0.2 mol) of **2d**, 6 g (0.025 mol) of 3-(trimethylstannyl)pyridine,[59] and 700 mg of $PdCl_2(PPh_3)_2$ were refluxed for 18 h in 100 mL of dioxane containing 3.6 mL of HMPA. The reaction was worked up by precipitation of the product with ether. The precipitate was collected and taken up in dilute HCl, treated with charcoal, and reprecipitated by neutralizing the mixture using NH_4OH. The acidic extraction was repeated except that the mixture was made basic (NH_4OH). The product was precipitated by neutralization with acetic acid, filtered hot, rinsed with water, and dried to give 2.8 g (59%): mp 273–275 °C. Anal. ($C_{18}H_{13}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(5-methyl-3-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18f. Ester **2d** was converted into **18f** exactly as described for **4e**. Thus 7.4 g (25 mmol) of **2d**, 15 g (40 mmol) of 3-methyl-5-(tributylstannyl)pyridine, and 1 g of $PdCl_2(PPh_3)_2$ gave 3 g of **18f** (35%): mp 260–264 °C; ^1H NMR (CF_3COOD) δ 9.60 (s, 1H), 9.23 (br s, 1H), 9.02 (d, 1H), 8.94 (br s, 1H), 8.91 (br s, 1H), 8.63 (d, 1H), 4.38 (m, 1H), 3.82 (s, 3H), 1.75 (m, 2H), 1.55 (m, 2H). Anal. ($C_{19}H_{15}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(6-methyl-3-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18h. Ester **2d** was converted into **18h** in the manner described for **4e**. Thus 5 g (17 mmol) of **2d**, 6.5 g (25 mmol) of 2-methyl-5-(tributylstannyl)pyridine, and 700 mg of $PdCl_2(PPh_3)_2$ were heated in 15 mL of DMF for 6 h. After cooling, the mixture was diluted with hexane, filtered, and hydrolyzed in 3 M HCl. The hydrolysis mixture was treated with Darco, filtered, concentrated, rinsed with water, and dried to give 2.7 g of **18h** (47%): mp 243–245 °C; ^1H NMR (CF_3COOD) δ 9.58 (s, 1H), 9.20 (br s, 1H), 9.02 (d, 1H), 8.92 (d, 1H), 8.61 (d, 1H), 8.22 (d, 1H), 4.36 (m, 1H), 3.08 (s, 3H), 1.78 (m, 2H), 1.58 (m, 2H). Anal. ($C_{19}H_{15}FN_2O_3$) C, H, N.

1-Cyclopropyl-7-(2,6-methyl-3-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, 18g. Ester **2a** was converted into **18g** as described for **4c**. Thus 10.2 g (30 mmol) of **2a**, 12.3 g (45.6 mmol) of 2,6-dimethyl-3-(trimethylstannyl)pyridine, and 0.5 g of $PdCl_2(PPh_3)_2$ were combined in ethanol and heated for 5 h. Filtration, solvent removal, hydrolysis (3 M HCl), extractive workup, and recrystallization (acetonitrile) gave 430 mg of **18g** (4%): mp 223–224 °C; CIMS-CH_4 m/z 353 (M + H); ^1H NMR (DMSO-d_6) δ 14.8 (br s, 1H), 8.80 (s, 1H), 8.28 (d, 1H), 8.15 (d, 1H), 7.68 (d, 1H), 7.28 (d, 1H), 3.88 (m, 1H), 2.54 (s, 3H), 2.37 (s, 3H), 1.29 (m, 4H). Anal. ($C_{22}H_{17}FN_2O_3$) H, N; C: calcd, 68.17; found, 67.59.

Modified 7-(2,6-Dimethyl-4-pyridinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylates. Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-(acetoxymethyl)-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylate, 20. To ester **3a** (2.5 g, 6.6 mmol) in 85 mL of CH_2Cl_2 was added 1.55 g (72 mmol) of *m*-chloroperbenzoic acid. After stirring at room temperature for 16 h, the solvent was removed under vacuum and the residue treated with $NaHCO_3$ (aqueous), filtered, washed (H_2O), dried, and triturated with ether to give 2.4 g of **19** (92%): mp 250–252 °C; ^1H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.42 (s, 2H), 4.42 (q, 2H), 3.58 (m, 1H), 2.62 (s, 6H), 1.43 (m, 5H), 1.23 (m, 2H). *N*-Oxide **19** was heated in 10 mL of acetic anhydride at reflux (1 h), cooled, treated with ethanol, and diluted with ether (ca. 250 mL). The resulting solid was filtered to give 1.6 g of material which was combined with a second crop to give 2.4 g of **20** (90%): mp 165–167 °C (EtOAc); CIMS-CH_4 m/z 439 (M + H); ^1H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.21 (d, 1H), 7.97 (d, 1H), 7.49 (s, 1H), 7.42 (s, 1H), 5.25 (s, 2H), 4.42 (q, 2H), 3.55 (m, 1H), 2.66 (s, 3H), 2.19 (s, 3H), 1.41 (m, 5H), 1.20 (m, 2H). Anal. ($C_{24}H_{23}FN_2O_3$) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-(hydroxymethyl)-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylic Acid, 21b. Ester **20** was hydrolyzed in 30 mL of 6 M HCl (reflux, 2 h). The mixture was neutralized (concentrated NH_4OH) and the pH adjusted to 4–5 with acetic acid. The resultant precipitate was washed with water to give 0.92 g of **21b** (73%): mp 270–272 °C (ethanol); ^1H NMR (CF_3COOD) δ 9.59 (s, 1H), 9.00 (d, 1H), 8.60 (d, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 5.45 (s, 2H), 4.35 (m, 1H), 3.10 (s, 3H), 1.75 (m, 2H), 1.55 (m, 2H). Anal. ($C_{20}H_{17}FN_2O_4$) C, H, N.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-(hydroxymethyl)-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylate, 21a. Ester **20** (1.5 g, 30 mmol) was heated at reflux in 38 mL of saturated ethanol–HCl for 1 h. The solvent was removed under vacuum and the residue treated with $NaHCO_3$ (aqueous), filtered, rinsed with water, and dried to give 1.3 g of **21a** (93%): mp 225–228 °C (ethanol); CIMS-CH_4 m/z 397 (M + H); ^1H NMR ($CDCl_3$–DMSO-d_6) δ 8.60 (s, 1H), 8.15 (d, 2H), 8.01 (d, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 4.83 (d, 2H), 4.60 (t, 1H), 4.38 (q, 2H), 3.58 (m, 1H), 2.68 (s, 3H), 1.42 (m, 5H), 1.20 (m, 2H). Anal. ($C_{22}H_{21}FN_2O_4$) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-(methoxymethyl)-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylate, 23. Ester **21a** (2 g, 5 mmol) was refluxed with 10 mL of $SOCl_2$ for 2 h and then concentrated under vacuum while maintaining the temperature below 50 °C to give the chloromethyl derivative **22** as the HCl salt. The chloride **22** (1.52 g, 3.6 mmol) was treated with 1.5 g (27 mmol) of NaOMe in methanol (wet) at reflux for 24 h. The resulting mixture was poured into ice containing added acetic acid, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated to give 1.11 g of **23** (81%): mp 192–193 °C (EtOAc); ^1H NMR (CF_3COOD) δ 9.60 (s, 1H), 9.00 (d, 1H), 8.60 (d, 1H), 8.20 (s, 2H), 5.11 (s, 2H), 3.75 (s, 3H), 3.05 (s, 3H), 1.75 (m, 2H), 1.55 (m, 2H). Anal. ($C_{21}H_{19}FN_2O_4$) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-[(dimethylamino)methyl]-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylic Acid Hydrochloride, 26b. The chloride **22** (2 g, 4 mmol) in 20 mL of CH_2Cl_2 (chilled in ice) was treated with 20 mL of 40% dimethylamine, the mixture was stirred overnight at room temperature, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under vacuum, and the residue was subjected to preparative layer chromatography (Analtech silica gel GF, 3% isopropylamine–ethyl acetate) to give 1.25 g of **26a** (74%): CIMS-CH_4 m/z 424 (M + H); ^1H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.20 (d, 1H), 8.03 (d, 1H), 7.50 (s, 1H), 7.28 (s, 1H), 4.40 (q, 2H), 3.70 (s, 2H), 3.58 (m, 1H), 2.67 (s, 3H), 2.39 (s, 6H), 1.42 (m, 5H), 1.20 (m, 2H). The above ester was hydrolyzed in 25 mL of 6 M HCl (2 h), the solvent removed under vacuum, and the residue recrystallized (EtOH–Et_2O) to give 0.46 g (36% from **22**): mp 262–264 °C dec; ^1H NMR (CF_3COOD) δ 9.60 (s, 1H), 9.10 (brs, 1H), 8.75 (brs, 1H), 8.62 (d, 1H), 8.40 (s, 1H), 5.15 (s, 2H), 4.40 (m, 1H), 3.27 (s, 6H), 3.10 (s, 3H), 1.75 (m, 2H), 1.55 (m, 2H). Anal. ($C_{22}H_{22}FN_3O_3$·HCl) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-[(methylamino)methyl]-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylic acid hydrochloride, 24b: prepared by the same method as described for **26b** except that 40% methylamine was used giving **24b** after hydrolysis (36% from **22**): mp 262–265 °C (EtOH); ^1H NMR (CF_3COOD) δ 9.58 (s, 1H), 9.05 (brs, 1H), 8.64 (brs, 1H), 8.60 (d, 1H), 8.34 (s, 1H), 5.07 (s, 2H), 4.39 (m, 1H), 3.22 (s, 3H), 3.08 (s, 3H), 1.77 (m, 2H), 1.55 (m, 2H). Anal. ($C_{21}H_{20}FN_3O_3$ HCl) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[2-[(ethylamino)-methyl]-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylic acid hydrochloride, 25b: prepared by the same method as described for **26b** except that 70% ethylamine was used giving **25b** after hydrolysis (37% from **22**): mp 277 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 1H), 8.50 (d, 1H), 8.17 (d, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 4.35 (s, 2H), 3.98 (m, 1H), 3.07 (q, 2H), 2.65 (s, 3H), 1.55–1.15 (m, 4H). Anal. ($C_{22}H_{22}FN_3O_3$·HCl) C, H, N.

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