Fluoronaphthyridines and -quinolones as Antibacterial Agents. 3. Synthesis and Structure–Activity Relationships of New 1-(1,1-Dimethyl-2-fluoroethyl), 1-[1-Methyl-1-(fluoromethyl)-2-fluoroethyl], and 1-[1,1-(Difluoromethyl)-2-fluoroethyl] Substituted Derivatives

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A series of novel *N*-1-(mono-, -(di- and -(trifluoro-*tert*-butyl)quinolones and -naphthyridines has been prepared. Structure–activity relationship (SAR) studies indicated that the in vitro antibacterial potency was the following order: 1-(1,1-dimethyl-2-fluoroethyl) > 1-[1-methyl-1-(fluoromethyl)-2-fluoroethyl] > 1-[1,1-(difluoromethyl)-2-fluoroethyl] substituents. In the quinolone series the monofluoro-*tert*-butyl derivatives were found to possess better in vitro antibacterial activity than the nonfluorinated-*tert*-butyl equivalents. In vivo PD_{50} values of the 1-fluoro-*tert*-butyl-substituted derivatives reflect pharmacokinetic behavior and incomplete oral absorption.

Introduction

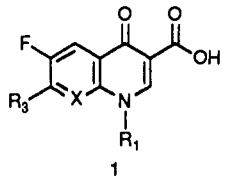
Besides the essential fluorine atom in position 6 of the quinolone nucleus, characterizing a "new" generation of quinolones, many important derivatives have been synthesized with additional fluorine atoms, located essentially at the N-1- or the C-8-positions of the quinolones (Table I).

For the C-8-position, examples are **1e** (lomefloxacin)[1] and **1f** (CI 934)[2] which are 8-fluoro analogues of **1a** (norfloxacin).[3] Fleroxacin[4] (**1g**), with fluoro substitutions at C-8 and at N-1 (2-fluoroethyl), is an analogue of pefloxacin[5] (**1b**) (Chart I).

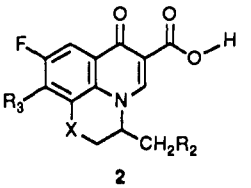
Addition of fluorine at C-8 was reported to enhance antibacterial activity,[6-8] especially in vivo, and to improve the pharmacokinetic characteristics, except for *N*-1-aryl-substituted quinolones.[9] Recently, the fluoro substitution at position C-5 and C-8 on the quinolone nucleus was reported.[10] Compared to the monofluoro substitution at C-8 (H at C-5), the difluoro substitution at C-5 and C-8 was shown to decrease the in vitro antibacterial activity and to bring a similar in vivo activity. Considering the *N*-1-fluoroalkyl substitution, 3-(fluoromethyl) analogue **2b** (R_2 = F, X = O)[11] of **2a** (ofloxacin[12]) as well as 1-thio analogue **2c** (MF-961)[13] are described. Additional incomplete data for the N-1 substitution are also known: 2-fluoro and 2,2-difluorocyclopropyl[14,15] analogues of ciprofloxacin[16,17] (**1d**), 2-fluoroethyl analogues[3,18,19] of norfloxacin (**1a**) and enoxacin[20] (**1c**), and 2-fluoroethyl and 2,2,2-trifluoroethyl analogues[8] of **1f** are described.

However, in spite of availability of all derivatives described above, no structure–activity relationships (SAR) have been published on the effect of mono- and polyfluoro substitutions of the *N*-1-alkyl groups of the quinolones and naphthyridines. To extend our recent investigations[21,22] on the *N*-1-*tert*-butylquinolones **3a** and -naphthyridines **4a** (Chart II) which showed unexpected enhanced antibacterial activity, especially against Gram-positive organisms, we prepared a series of 7-(cycloalkylamino-substituted)-6-fluoro-4-oxo-1,4-dihydro-1-(1,1-dimethyl-2-fluoroethyl)quinoline and -1,8-naphthyridine-3-carboxylic acids (**3b** and **4b**) as well as the 1-[1-methyl-1-(fluoromethyl)-2-fluoroethyl] (**3c** and **4c**) and the 1-[1,1-(difluoromethyl)-2-fluoroethyl] **4d** analogues (Chart II). The biological in vitro and in vivo activities [minimum inhibitory concentrations (MICs), PD_{50}], as well as pharma-

Chart I



1



2

	name	X	R_1	R_2	R_3
1a	norfloxacin	CH	Et		HN⌒N—
1b	pefloxacin	CH	Et		MeN⌒N—
1c	enoxacin	N	Et		HN⌒N—
1d	ciprofloxacin	CH	△		HN⌒N—
1e	lomefloxacin	CF	Et		HN⌒N— (Me)
1f	CI-934	CF	Et		EtNH⌒N—
1g	fleroxacin	CF	CH_2CH_2F		MeN⌒N—
2a	ofloxacin	O		H	MeN⌒N—
2b		O		F	MeN⌒N—
2c	MF-961	S		F	MeN⌒N—

(1) Hokuriku Pharmaceutical Co. Ltd.; NY-198; *Drugs Future* **1986**, *11*, 578.
(2) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. *J. Med. Chem.* **1986**, *29*, 445.
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‡ Bristol-Myers Squibb Co.

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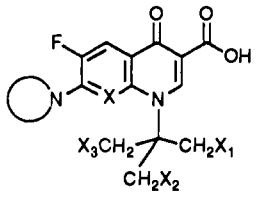
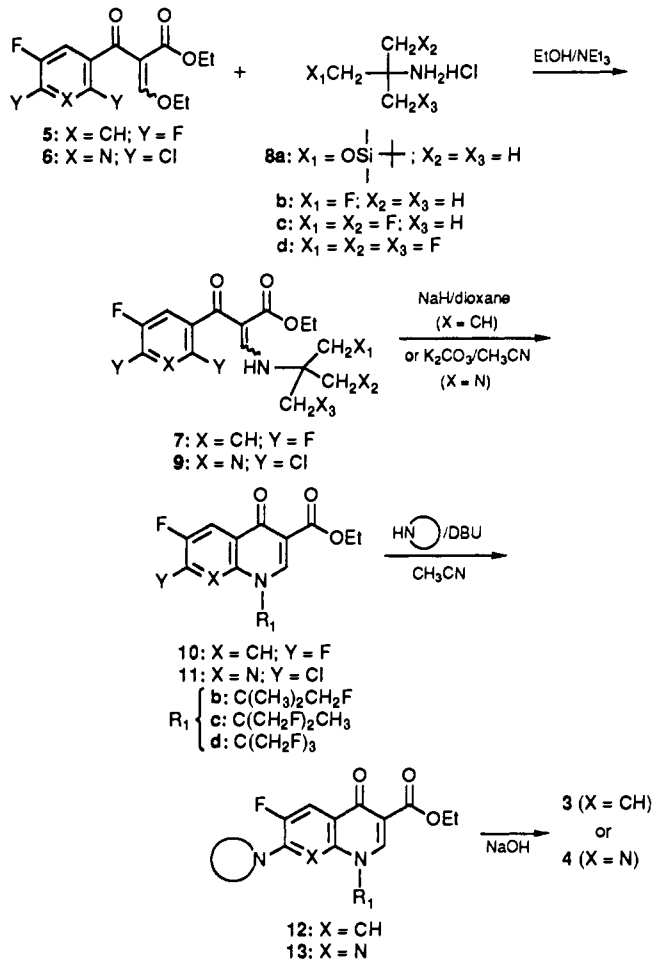
Chart II



3: X = CH
4: X = N

	X_1	X_2	X_3
3a	H	H	H
3b	F	H	H
3c	F	F	H
4a	H	H	H
4b	F	H	H
4c	F	F	H
4d	F	F	F

Scheme I



5: X = CH; Y = F
6: X = N; Y = Cl

8a: X_1 = OSi(t-Bu)Me$_2$; $X_2 = X_3$ = H
b: X_1 = F; $X_2 = X_3$ = H
c: $X_1 = X_2$ = F; X_3 = H
d: $X_1 = X_2 = X_3$ = F

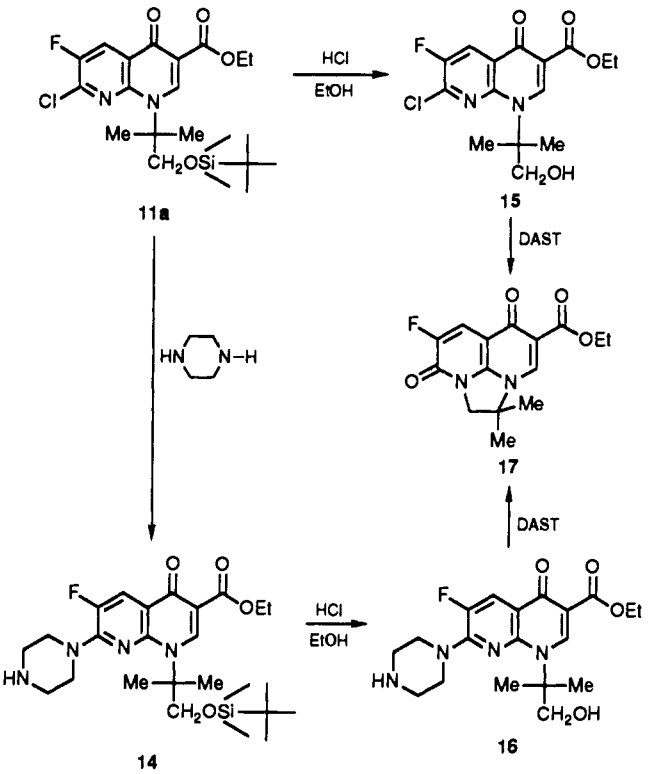
7: X = CH; Y = F
9: X = N; Y = Cl

10: X = CH; Y = F
11: X = N; Y = Cl
R_1: b: $C(CH_3)_2CH_2F$; c: $C(CH_2F)_2CH_3$; d: $C(CH_2F)_3$

12: X = CH
13: X = N

cokinetic parameters of these fluoro-*tert*-butylquinolones and naphthyridines, are reported in this paper and are compared to those of the nonfluorinated *tert*-butyl analogues.

Scheme II



11a

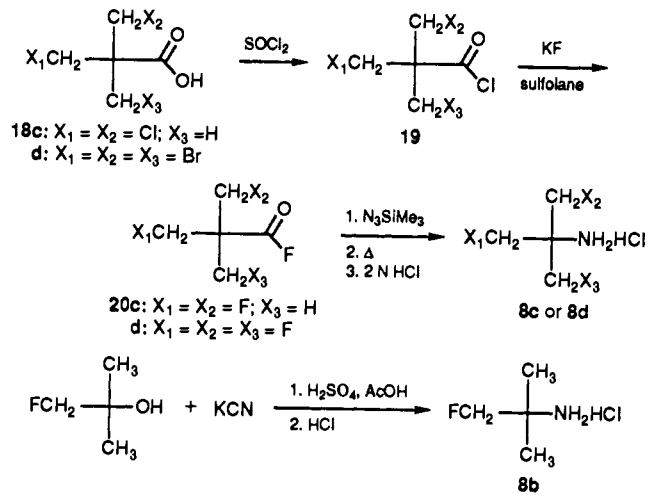
15

17

14

16

Scheme III



18c: $X_1 = X_2$ = Cl; X_3 = H
d: $X_1 = X_2 = X_3$ = Br

19

20c: $X_1 = X_2$ = F; X_3 = H
d: $X_1 = X_2 = X_3$ = F

8c or 8d

8b

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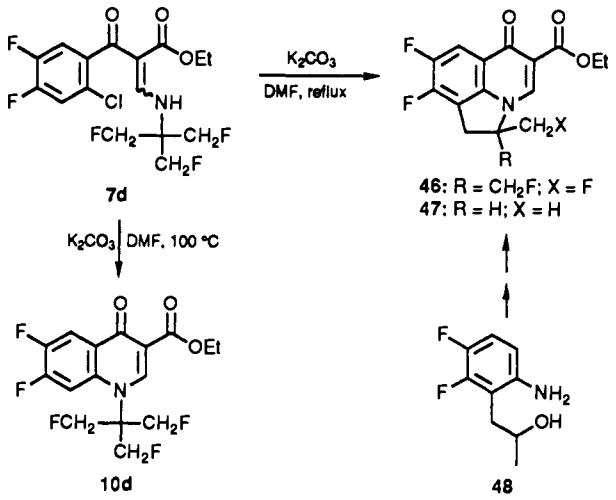
Scheme IV



Chemistry

The first approach to synthetize a naphthyridine with the *N*-1-(1,1-dimethyl-2-fluoroethyl) substituent was to fluorinate the corresponding alcohol **15** as described for the preparation of 3-(fluoromethyl)ofloxacin[11] (**2b**; Chart I). Silylated alcohol **11a** (11, R_1 = $C(CH_3)_2CH_2OSi(Me)_2$-*t*-Bu, Y = Cl) was prepared according to Scheme I via silyl enamine **9a**, which was obtained by condensation of **6**[7] with amine **8a**. The silyl ethers **11a** and **14** were deprotected with anhydrous HCl in EtOH to give alcohols **15** and **16** (Scheme II). Our attempts to fluorinate alcohol **15** with diethylamidosulfur trifluoride (DAST) led to the unexpected tricycle **17** (Scheme II). More surprisingly, alcohol **16** gave with DAST the same product (**17**) with loss of the piperazine ring. A similar elimination–cyclization was described on a *N*-1-(2-chloroethyl)-1,8-naphthyridine-3-carboxylic acid ethyl ester when the reaction was carried on with K_2CO_3 in DMF.[23]

The second approach was to synthetize the fluoro-*tert*-butylamines **8** followed by the reaction with the ethoxymethylenic compounds **5**[24] and **6**[7] in EtOH.

Di- and trifluoroamines **8c** and **8d** were obtained from di- and trihalogenopivalic acids **18c** and **18d**,[25] by a method described,[26a,26b] as shown in Scheme III. In our hands the procedure described in Bayer's patent,[26b] for 1,1-dimethyl-2-fluoroethylamine (**8b**), gave a mixture of **8b** and 2-chloro analogue **8** (X_1 = Cl, X_2 = X_3 = H) in a 15/85 ratio. Then we started a new synthesis with 2-fluoro-*tert*-butanol[27] which gave the *N*-formyl-1,1-dimethyl-2-fluoroethylamine by a modified Ritter reaction.[28] This derivative was hydrolyzed to amine **8b** with 2 N HCl. The chlorohydrates of amines **8** were added to products **5**[24] and **6**[7] in presence of triethylamine (TEA) to yield enamine derivatives **7** and **9**, which were cyclized with K_2CO_3 in CH_3CN for naphthyridines **11** or with NaH in dioxane for quinolones **10** with the exception of enamine **7d**. This last compound **7d** could not be cyclized under the above described classical conditions but with K_2CO_3 in DMF at 100–120 °C to give **10d** in low yield (Scheme IV). When the reaction took place in refluxing DMF, the unexpected tricycle **46** was obtained. Such a tricycle like **47** resulted also from a different synthetic route, starting with the 2-(2-hydroxypropyl)-3,4-difluoroaniline **48**.[29]

Some amines, selected from previous papers,[22,30–32] were condensed on the quinolones and naphthyridines nuclei **10** and **11** in the presence of DBU in refluxing CH_3CN to give the corresponding esters **12** and **13**.

A synthesis of (3*S*)-3-aminopyrrolidine, now commercially available,[34] was described earlier.[30] (2*S*,4*S*)-2-Methyl-4-aminopyrrolidine was prepared according to known procedures.[31] (1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptane[22] and 4-methyl-3-aminopyrrolidine[22] as well as 3-aminoazetidine[32,33] were obtained as described previously.

The condensation step of the amines was followed by mild basic hydrolysis of esters **12** and **13**. This careful hydrolysis was necessary to avoid the degradation of the molecule with loss of the fluorine atom on the *tert*-butyl group, a reaction which we observed after heating with an excess of NaOH. The final compounds **3** and **4** were isolated as hydrochloride or methanesulfonate salts.

Results and Discussion

Table II summarizes the in vitro antibacterial data of the (fluoro-*tert*-butyl)quinolones and -naphthyridines against four Gram-positive bacteria (*Streptococcus pneumoniae* A 9585, *Enterococcus faecalis* A 9809, *Staphylococcus aureus* A 9537, and *Staphylococcus aureus* A 24227), eight Gram-negative bacteria (*Escherichia coli* A 15119, *Klebsellia pneumoniae* A 9664, *Enterobacter cloacae* A 9656, *Proteus mirabilis* A 9900, *Morganella morganii* A 15153, *Serratia marcescens* A 20019, *Pseudomonas aeruginosa* A 9843, and *Haemophilus influenzae* A 21515), and against *Bacteroides fragilis* A 22862. The data for ciprofloxacin (**1d**) and fleroxacin (**1g**) are included for comparison. With a piperazine ring substitution in position 7, the potency rank order was **33** > **34** > **35** and **22** > **23**. With the bridged piperazine (2,5-diazabicyclo-[2.2.1]heptane), the same order was obtained all over the spectrum (**37** > **38** > **39**), as well as with the (3*S*)-amino-

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(26) (a) Hagemann, H.; Klauke, E. German Patent DE 3 326 875, 1985; *Chem. Abstr.* **1985**, *103*, 177972*q*. (b) Baasner, B.; Hagemann, H.; Schwanborn, M. German Patent DE 3 611 195, 1988; *Chem. Abstr.* **1988**, *108*, 55489*v*.
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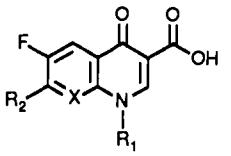
(34) (3*S*)-3-Aminopyrrolidine is now commercially available from American Tokyo Kasei, Inc.

Table I. 1-Substituted Quinolones and Naphthyridines



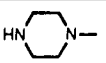
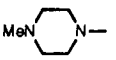
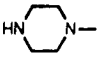
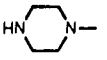
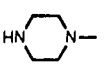
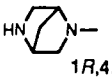
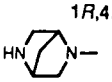
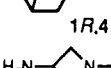
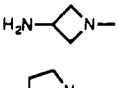
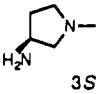
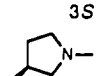
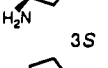
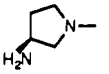
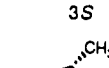
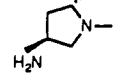
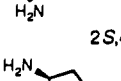
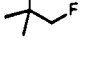
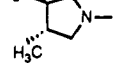
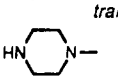
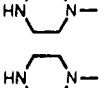
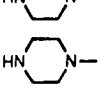
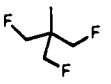
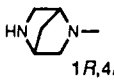
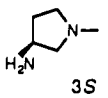
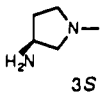
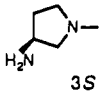
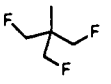
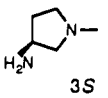
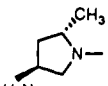
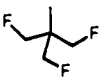
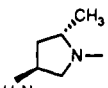
no.	X	R_1	R_2	% yield[a]	mp, °C	formula[b]	ref
1d	CH						16, 17
1g	CF	CH_2CH_2F					4
21	CH						21
22	CH			63	210	$C_{18}H_{21}F_2N_3O_3 \cdot HCl \cdot 2H_2O$	
23	CH			63	>260	$C_{18}H_{20}F_3N_3O_3 \cdot HCl \cdot 1.5H_2O$	
24	CH		 *1R,4R*	34	245	$C_{19}H_{22}FN_3O_3 \cdot H_2O$	
25	CH		 *1R,4R*	69	>260	$C_{19}H_{21}F_2N_3O_3 \cdot HCl \cdot 2H_2O$	
26	CH			77	>260	$C_{17}H_{19}F_2N_3O_3 \cdot HCl$	
27	CH		 *3S*	60	225	$C_{18}H_{22}FN_3O_3 \cdot CH_3SO_3H \cdot 2H_2O$	
28	CH		 *3S*	83	>260	$C_{18}H_{21}F_2N_3O_3 \cdot CH_3SO_3H$	
29	CH		 *3S*	51	>260	$C_{18}H_{20}F_3N_3O_3 \cdot CH_3SO_3H \cdot 0.5H_2O$	
30	CH		 *2S,4S*	41	240	$C_{19}H_{23}F_2N_3O_3 \cdot CH_3SO_3H \cdot 3H_2O$	
31	CH		 *trans*	80	>260	$C_{19}H_{23}F_2N_3O_3 \cdot CH_3SO_3H \cdot 3H_2O$	
32	N						21
33	N			70	>260	$C_{17}H_{20}F_2N_4O_3 \cdot HCl \cdot H_2O$	
34	N			30	250–60	$C_{17}H_{19}F_3N_4O_3 \cdot HCl \cdot H_2O$	
35	N			89	>260	$C_{17}H_{18}F_4N_4O_3 \cdot HCl \cdot 2.5H_2O$	
36	N		 *1R,4R*				22, 32
37	N		 *1R,4R*	60	>260	$C_{18}H_{20}F_2N_4O_3 \cdot HCl \cdot 2H_2O$	
38	N		 *1R,4R*	50	>260	$C_{18}H_{19}F_3N_4O_3 \cdot HCl$	

Table I (Continued)

no.	X	R_1	R_2	% yield[a]	mp, °C	formula[b]	ref
39	N		 1*R*,4*R*	84	>260	$C_{18}H_{18}F_4N_4O_3 \cdot HCl$	
40	N		 3*S*				36
41	N		 3*S*	46	>260	$C_{17}H_{20}F_2N_4O_3 \cdot HCl \cdot H_2O$	
42	N		 3*S*	76	>260	$C_{17}H_{19}F_3N_4O_3 \cdot CH_3SO_3H$	
43	N		 3*S*	79	252–55	$C_{17}H_{18}F_4N_4O_3 \cdot HCl \cdot H_2O$	
44	N		 2*S*,4*S*	65	>260	$C_{18}H_{22}F_2N_4O_3 \cdot HCl$	
45	N		 2*S*,4*S*	78	>260	$C_{18}H_{20}F_4N_4O_3 \cdot HCl$	

[a] Yields are those obtained from the final step (hydrolysis), including the salt formation. [b] The analyses are within ±0.4% of theoretical values.

pyrrolidine (**28** > **29** and **41** > **42** > **43**).

Increasing the number of fluorine atoms, on the *N*-1-*tert*-butyl group, from one to two and then to three led to a decrease in the in vitro activity, either for the naphthyridines or the quinolones series.

Compared to the *tert*-butyl analogues, the (monofluoro-*tert*-butyl)quinolone analogues were found more active: **22** > **21**, **25** > **24**, and **28** > **27** (except for one strain of *S. aureus* and *H. influenzae*). The opposite effect was observed in the naphthyridine series; the monofluoro-*tert*-butyl analogues were 2–4 times less active: **32** > **33**, **36** (BMY 40062[22,35]) > **37** and **40** (BMY 40868[36]) > **41**. (Fluoro-*tert*-butyl)quinolones **22**, **25**, and **28** demonstrated a better in vitro antibacterial activity than the corresponding (fluoro-*tert*-butyl)naphthyridines **33**, **41**, and **37**, respectively. In the 7-cycloalkylamine-*N*-1-(monofluoro-*tert*-butyl)quinolones series, the 3(*S*)-aminopyrrolidine was found to be the best amine. 3(*S*)-Aminopyrrolidine derivative **28** was superior to *trans*-4-methyl-3-aminopyrrolidine derivative **31** itself as active or a little inferior to 3-aminoazetidine derivative **26**, piperazine derivative **22**, and (2*S*,4*S*)-2-methyl-4-aminopyrrolidine derivative **30**. This last one was slightly more potent than bridged piperazine derivative **25**.

The order of in vitro potency of the substituents in position 7 of the (monofluoro-*tert*-butyl)quinolones [3-(*S*)-aminopyrrolidine > *trans*-4-methyl-3-aminopyrrolidine ≥ 3-aminoazetidine ≅ piperazine ≅ (2*S*,4*S*)-2-methyl-4-aminopyrrolidine > 2,5-diazabicyclo[2.2.1]heptane] was following the potency order of quinolone analogues of previous studies.[7,22,32] Particularly the 3(*S*)-aminopyrrolidine was now recognized as one of the most potent amine in position 7 of quinolones and naphthyridines. For the *N*-1-(monofluoro-*tert*-butyl)naphthyridines, the most potent compound was **44** [(2*S*,4*S*)-2-methyl-4-aminopyrrolidine), which was better than **41** 3(*S*)-aminopyrrolidine] itself better than **37** (bridged piperazine) and **33** (piperazine). Among all these derivatives, **28** showed excellent antibacterial activity and was more potent than ciprofloxacin (**1d**) against all the species. The piperazine, 3-aminoazetidine, and 3-amino-4-methylpyrrolidine 7-substituted *N*-1-(monofluoro-*tert*-butyl)quinolones **22**, **26**, and **31** exhibited the same rank order of activity as did **1d** (CIP).

It was well-known that substitution at C-7 with the 3-aminopyrrolidine allowed one to obtain extremely potent derivatives but with very low solubility in water.[37]

Table III summarizes the solubility of selected compounds in water. The introduction of a fluorine atom on the *tert*-butyl group increased the solubility in water compared to that of the "parent" *tert*-butyl derivative: **22** was 8 times more soluble than **21**, and **33** and **37** were 2 times more soluble than **32** and **36**, respectively. The derivative **28** was 5 times more soluble in water than **1d** (CIP).

The trifluoro-*tert*-butyl group gives a better or equal solubility compared to the monofluoro-*tert*-butyl groups: **39** = **37**, **43** > **41** and **45** > **44**.

In order to determine the in vivo efficacy, compounds **28**, **36**, **37**, and **40** were selected for evaluation in the mouse protection tests (Table IV). Ciprofloxacin **1d** was used as comparative active principle. The PD_{50} of **28**, **37**, and ciprofloxacin (**1d**) are quite similar on *S. aureus*, the most potent in vivo being naphthyridines **36** (BMY 40062) and

(35) Fung-Tomc, J.; Desiderio, J. V.; Tsai, Y. H.; Warr, G.; Kessler, R. E. *Antimicrob. Agents Chemother.* **1989**, *33*, 906.
(36) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Remuzon, P.; Weber, A. *Reviews Infect. Dis.* **1989**, *11*, suppl 5, S912.
(37) Chu, D. T. W.; Fernandes, P. B. *Antimicrob. Agents Chemother.* **1989**, *33*, 131.

Table II. In Vitro Antibacterial Activity of Substituted Quinolones and Naphthyridines (MIC, μg/mL)[a]

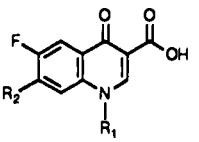
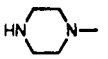
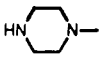
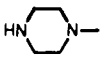
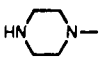
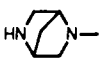
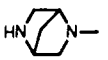
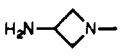
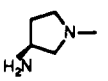
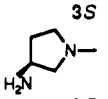
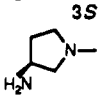
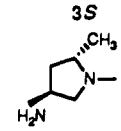
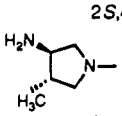
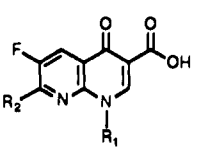
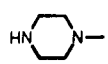
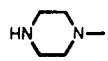
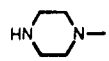
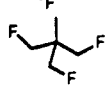
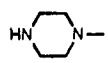
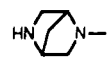
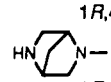
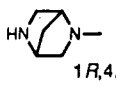
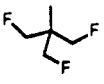
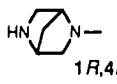
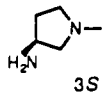
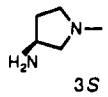
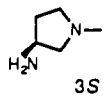
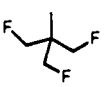
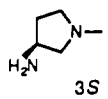
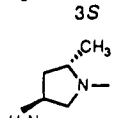
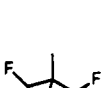
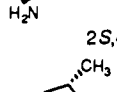
no.	R_1	R_2	S. pn.	E. fa.	S. au.	S. au.	E. co.	K. pn.	E. cl.	P. mi.	M. mo.	S. ma.	P. ae.	H. in.	B. fr.
															
		Quinolones													
1d	△		0.25	0.5	0.06	0.13	0.008	0.06	0.03	0.008	0.008	0.03	0.25	0.03	4
1g	CH_2CH_2F		2	8	0.06	0.25	0.03	0.13	0.13	0.06	0.03	0.13	2	0.13	1
21				2	0.25		0.06	0.06	0.13	0.25	0.25	0.5	0.5		
22			1	0.25	0.13	0.06	0.016	0.016	0.03	0.03	0.016	0.06	0.25	0.016	8
23			8	1	1	2	0.13	0.13	0.25	0.13	0.06	0.5	1	0.06	16
24		 1*R*,4*R*		2	0.5		0.5	0.13	0.25	4	2	4	0.5		
25		 1*R*,4*R*	1	0.5	0.5	0.25	0.016	0.06	0.06	0.06	0.13	0.13	0.25	0.008	8
26			1	0.5	0.016	0.016	0.004	0.016	0.06	0.06	0.016	0.13	0.5	0.06	2
27		 3*S*	0.06	0.13	0.008	0.03	0.016	0.5	0.06	0.06	0.13	0.13	0.25	0.008	8
28		 3*S*	0.06	0.13	0.03	0.016	0.002	0.004	0.004	0.004	0.002	0.016	0.13	0.016	2
29		 3*S*	0.5	0.5	0.06	0.13	0.008	0.13	0.06	0.03	0.016	0.13	0.25	0.001	4
30		 2*S*,4*S*	0.25	0.25	0.03	0.03	0.03	0.13	0.06	0.13	0.5	0.25	1	0.016	4
31		 *trans*	0.25	0.25	0.03	0.06	0.008	0.13	0.03	0.06	0.06	0.13	0.5	0.008	4
															
		Naphthyridines													
32			1	1	0.06	0.25	0.016	0.03	0.06	0.13	0.06	0.06	0.5	0.016	8
33			0.5	2	0.25	0.5	0.13	0.25	0.25	0.25	0.13	0.25	1	0.13	16
34			16	16	4	4	0.13	0.25	0.25	1	0.13	0.5	4	0.25	125
35			32	16	8	8	0.5	1	0.5	2	0.5	1	16	0.5	125
36		 1*R*,4*R*	0.13	0.5	0903	0.03	0.008	0.016	0.016	0.06	0.06	0.06	0.25	0.03	4
37		 1*R*,4*R*	0.5	2	0.25	2	0.06	0.25	0.13	0.5	0.25	0.25	0.5	0.13	8

Table II (Continued)

no.	R_1	R_2	S. pn.	E. fa.	S. au.	S. au.	E. co.	K. pn.	E. cl.	P. mi.	M. mo.	S. ma.	P. ae.	H. in.	B. fr.
38		 1*R*,4*R*	8	4	2	2	0.13	0.5	0.13	0.5	0.13	0.5	1	0.016	32
39		 1*R*,4*R*	32	32	4	4	0.25	0.5	0.25	1	0.25	1	4	0.06	125
40		 3*S*	0.008	0.06	0.004	0.002	0.016	0.03	0.03	0.13	0.13	0.25	0.25		1
41		 3*S*	0.03	4	0.03	0.13	0.03	0.03	0.13	0.5	0.06	0.25	1	0.5	16
42		 3*S*	16	16	8	4	0.5	2	0.5	4	0.5	2	8	0.25	125
43		 3*S*	32	32	4	8	0.5	2	2	2	2	2	32	0.25	125
44		 2*S*,4*S*	0.13	0.13	0.008	0.008	0.016	0.06	0.06	0.13	0.13	0.13	1	0.016	16
45		 2*S*,4*S*	8	4	0.5	1	0.5	2	1	4	2	2	32	0.5	125

[a] Organisms selected for the table are as follows: S. pn., *Streptococcus pneumoniae* A 9585; E. fa., *Enterococcus faecalis* A9809; S. au., *Staphylococcus aureus* A9537 and A24227; E. co., *Escherichia coli* A15119; K. pn.; *Klebsellia pneumoniae* A 9664; E. cl., *Enterobacter cloacae* A9656; P. mi.; *Proteus mirabilis* A9900; M. mo.; Morganella *morganii* A15153; S. ma., *Serratia marcescens* A20019; P. ae., *Pseudomonas aeruginosa* A9843; H. in., *Haemophilus influenzae* A 21515; B. fr., *Bacillus fragilis* A22862.

Table III. Solubility of Selected Compounds

no.	H_2O[a] solubility,[b] mg/mL	no.	H_2O[a] solubility,[b] mg/mL
1d (CIP)	0.07	**37**	0.2
21	0.13	**39**	0.24
22	1	**40**	0.01
27	0.25	**41**	0.06
28	0.37	**43**	0.2
32	0.82	**44**	0.23
33	1.6	**45**	0.5
36	0.08		

[a] Solubility determined at 20 °C and pH isoelectric in H_2O. [b] See the Experimental Section.

40 (BMY 40868). Against *P. aeruginosa* and *E. coli*, **1d** (CIP) was found to be the most effective antibacterial in vivo. Compound **36** presents a good efficacy against *S. pneumoniae* infections compared to the other derivatives.

Acute toxicity data in mice is displayed in Table IV for some selected compounds: **27**, **28**, **36**, **37**, **40**, and **1d** (CIP). Monofluorinated *tert*-butylquinolone **28** was not found more toxic than *tert*-butylquinolone analogue **27**. Compound **28** was less toxic than *tert*-butylnaphthyridine analogue **40**.

Some standard pharmacokinetic properties of selected compounds are displayed in Table V for mice and in Table VI for dogs. In mice, **1g** (FLE) and **36** showed the best pharmacokinetic profile after oral and intramuscular administration, as was already known. The pharmacokinetics profile of orally administered quinolone **28**, with a fluoro-*tert*-butyl group at N-1 and a pyrrolidine substituent at position 7, was unsatisfactory. Compound **28** was poorer than the *tert*-butyl "parent" compound **27**, the latter showing pharmacokinetic parameters that were half-reduced, compared to those of **1d** (CIP). In dogs, **36** (BMY 40062) presented the best pharmacokinetic profile after oral administration. The poor pharmacokinetic parameters of **28** were confirmed (low C_{max} and AUCs). The quinolone **27** was similar to **1d** (CIP) except for urinary recovery.

As a result of the present study, addition of a fluorine atom on the *N*-1-*tert*-butyl appendage of the quinolones

Table IV. Efficacy on Systemic Infections and Acute Toxicity of Selected Compounds after Oral Administration to Mice

	PD_{50},[a] mg/kg po				LD_{50}[b]	
no.	*S. aureus* A 9606	*P. aeruginosa* A 9843	*E. coli* A 15119	*S. pneumoniae* A9585	iv	po
1d (CIP)	31	2.6	0.4	>69	273	5000
27	14.4	10.2	9.5	>25	188	3500
28	26.4	23.7	NT[c]	>50	169	>2500
36	1.6	4.7	1.8	29.7	303	5000
37	25	4.9	2.4	57.4	NT	NT
40	1	4.6	1.2	>25	100	350

[a] Dose to protect 50% of mice from lethal infection po. [b] See the Experimental Section. [c] Not tested.

Table V. Pharmacokinetic Properties of Selected Compounds after Oral and Intramuscular Administration to Mice[a] (40 mg/kg)

no.		C_{max}, μg/mL	$t_{1/2}$, min	AUC,[b] μg/mL·h	% UR[c]
1d	po	6	56	7	30
(CIP)	im	15	54	21	46
1g	po	12	58	23	51
(FLE)	im	20	61	32	64
27	po	3	66	5	14
	im	6	54	15	24
28	po	1		0.6	4
	im	8	109	14	27
36	po	10	96	14	34
	im	13	95	25	39
37	po	4		7	
	im	8		20	
40	po	4	66	6	10

[a] See the Experimental Section. [b] Area under the time–concentration curve. [c] Urinary recovery.

Table VI. Pharmacokinetic Properties of Selected Compounds after Oral Administration to Dogs[a] (25 mg/kg)

no.	C_{max}, μg/mL	$t_{1/2}$, h	AUC,[b] μg/mL·h	%[c] UR
1d (CIP)	3	3.5	20	17
27	2.8	4	30	7.7
28	0.6	7	7.3	4.6
36	5.6	4.5	55	20
40	4.5	4.5	45	9

[a] See the Experimental Section. [b] Area under time–concentration curve. [c] Urinary recovery.

was shown to increase the in vitro potency on both Gram-positive and Gram-negative species, especially for compound **28**, which was found to possess broad and potent in vitro antibacterial activity, better than that of **1d** (CIP), but with in vivo mouse protection efficacy and pharmacokinetic properties considered to be inferior to available standards.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken with a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis were performed by the Microanalytical Laboratory, operated by the Bristol-Myers Analytical Department. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 783 infrared spectrophotometer. ^{1}H NMR spectra were determined on a Bruker AC 200 apparatus. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Flash column chromatography was performed with Merck silica gel 60, 70–230 mesh ASTM. Electron-impact mass spectra (MS) were obtained from the Laboratoire de Spectrométrie de masse, ENSCP, 11 rue P. et M. Curie, Paris, France.

Microbiology. General Procedures. In Vitro Studies. The in vitro antibacterial activity was studied by a side-by-side comparison with ciprofloxacin (**1d**) and determined by the serial 2-fold dilution technique using nutrient broth. The inoculum size was adjusted to 10^6 CFU–mL, and the concentration of the compounds ranged from 0.0005 to 250 μg/mL. Minimum inhibitory concentrations (MICs) were defined as the lowest concentration of the compound that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

In Vivo Studies (Mouse Protection Test). A solution of each test compound in sterile water was administered orally to OF1-strain female Swiss mice (18–25 g of body weight, five per group). Seven days later, LD_{50} values were determined by using the Karber and Behrens method.[38]

Pharmacokinetics in Mice. Levels of selected compounds in blood and urine samples from mice were determined as previously described.[39] Each compound was administered orally with a blunt needle and syringe set and intramuscularly to different groups of mice at a dose of 40 mg/kg. Blood samples were collected from the orbital sinus at 5, 15, 30, 60, 120, and 180 min after administration of drug. Urine samples were collected over 24 h.

Concentrations of antibiotics in blood and urine were measured by the agar disk diffusion microbioassay method with *Salmonella enteritidis* A9531 as the assay organism.

Pharmacokinetics in Dogs. Plasma and urine levels in dogs were determined by microbiological assay. The selected compounds were administered in solution by oral gavage. Blood samples were obtained at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after dosing. Plasma was separated by centrifugation and frozen until tested. Urine was collected 0–4, 4–8, 8–24 h after dosing and frozen until analysis. Plasma levels and urinary excretion of test compounds were determined by using the agar plates system. The test organism was *Bacillus subtilis* ATCC 6633 and the used standard was the test substance itself.

Solubility Studies. General Procedure. A known excess of weight of the compound was shaken overnight with a known volume of water at 25 °C for injection. The contents were filtered, and the clear filtrate was analyzed after appropriate dilution by HPLC (UV absorbance detection).

2-Fluoro-1,1-dimethylethylamine, Hydrochloride (8b). To an ice-cold solution of 8.2 g (0.126 mol) of potassium cyanide in 13.9 mL of acetic acid was added a solution of 14.8 mL of 98% sulfuric acid in 13.9 mL of acetic acid, followed by 10 g (0.108 mol) of 2-fluoro-1,1-dimethylethanol.[27] The mixture was heated at 50 °C for 1 h 30 min and allowed to stand for 2 h at room temperature. The suspension was poured into 130 mL of ice-cooled H_2O and carefully neutralized with solid K_2CO_3. The aqueous layer was extracted with three portions of 150 mL of ether, dried ($MgSO_4$), and evaporated to yield 6 g of the crude 2-fluoro-1,1-dimethylethylamine-*N*-carboxaldehyde. The above formamide (6 g) was heated in 15 mL of 2 N HCl at 92–95 °C for 30 min. The water was evaporated under vacuum and the residue was crystallized from acetone to give 3.24 g of **8b**: yield 23.5%; mp 252 °C (lit.[26b] mp 248 °C).

1-Methyl-1-(fluoromethyl)-2-fluoroethylamine, Hydrochloride (8c). A mixture of 51.15 g (0.27 mol) of 2-(chloromethyl)-2-methyl-3-chloropropanoic acid chloride **19c** and 73 g (1.25 mol) of spray-dried KF in 130 mL of dry sulfolane was heated at 200 °C for 5 h. The reaction mixture was cooled at 90 °C and 105 mL of dry toluene was added in three portions. The toluene was distilled off until the internal temperature reached 180 °C. The toluenic distillates were collected to give about 21 g of acid fluoride **20c** to which was added 24 g (0.21 mol) of trimethylsilyl azide. The solution was heated at 80 °C overnight. Excess trimethylsilyl azide was distilled off and the resulting toluenic solution of the isocyanate was carefully added to 41 mL of concentrated HCl. The mixture was heated at 60 °C for 1 h. The solvents were distilled off under reduced pressure, and the hydrochloride salt of the amine was crystallized from acetone to give 13.8 g of **8c**: yield 35.5% (from the acid chloride **19c**); mp 226 °C dec (lit.[26b] mp 214 °C dec).

1,1-(Difluoromethyl)-2-fluoroethylamine, Hydrochloride (8d). This amine was prepared according to the same procedure as for **8c** starting from the 2,2-(dibromomethyl)-2-bromopropanoic acid (**18d**):[25] yield 25% (from acid chloride **19d**); mp 222 °C dec (lit.[26b] mp 220 °C dec).

7-Chloro-6-fluoro-1-[1,1-dimethyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (11a). To a solution of 19.45 g (0.095 mol) of 1.1-dimethyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethylamine in 50 mL of absolute ethanol was added, dropwise in about 15 min, a solution of 31.93 g (0.095 mol) of 3-(2,6-dichloro-3-fluoro-5-pyridinyl)-3-oxo-2-(ethoxymethylene)propanoic acid ethyl ester (**6**)[7] in 125 mL of absolute ethanol at 35 °C. The solution was stirred for 2 h and

(38) Behrens, B.; Karber, G. *Arch. Exp. Pharm.* **1935**, *177*, 379.

(39) Kessler, R. E.; Bies, M.; Buck, R. E.; Chisholm, D. R.; Pursiano, T. A.; Tsai, Y. H.; Misiek, M.; Price, K. E.; Leitner, F. *Antimicrob. Agents Chemother.* **1985**, *27*, 207.

evaporated to dryness to provide 48.4 g of **9a** as an oil (**9**, X_1 = OSi(tBu)(Me_2), X_2 = X_3 = H) which was used without further purification.

A mixture of 44.4 g (0.09 mol) of the above enamine **9a** and 12.44 g (0.09 mol) of K_2CO_3 was heated in 210 mL of refluxing CH_3CN overnight. The solvent was evaporated to dryness and the residue was taken up with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and recrystallized from AcOEt to afford 16.24 g of **11a**; yield 39.5%; mp 120 °C.

7-Piperazinyl-6-fluoro-1-[1,1-dimethyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (14). A mixture of 1.37 g (3 mmol) of the above ester **11a**, 0.27 g (3.2 mmol) of piperazine, and 0.53 g (3.5 mmol) of DBU in 10 mL of CH_3CN was heated under reflux for 2 h. After cooling and filtration of the insoluble material, the solvent was evaporated. The residue was taken up with AcOEt, washed (H_2O), and dried ($MgSO_4$) to yield 1.1 g of **14**: yield 72.3%; mp 128–129 °C.

7-Piperazinyl-6-fluoro-1-(1,1-dimethyl-2-hydroxyethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (16). A solution of 1.1 g (2.17 mmol) of the ester **14** and 0.93 g of 5.1 N HCl in EtOH was heated under reflux for 8 h. The mixture was evaporated to dryness until no silanol was detected. The residue was recrystallized from 2-propanol to afford 0.68 g of the crude chlorhydrate. The salt was taken up with CH_2Cl_2 and 1 N NaOH; the organic layer was dried ($MgSO_4$) and evaporated. The ester crystallized from Et_2O to yield 0.14 g of **16**: yield 16.4%; mp 172 °C.

Compound **15** was obtained according to the same procedure with **11a** as starting material.

8-Fluoro-1,2-dihydro-2,2-dimethyl-6,9-dioxo-6*H*,9*H*-imidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylic Acid Ethyl Ester (17). To a suspension of 1.37 g (4 mmol) of alcohol **15** in 30 mL of CH_2Cl_2 was added a solution of 0.96 g (6 mmol) of DAST in 30 mL of CH_2Cl_2. After overnight stirring at room temperature, 10 mL of methanol was added to obtain a clear solution which was evaporated to dryness and chromatographed over silica gel (CH_2Cl_2/MeOH 98/2) to yield 0.72 g of **17**: yield 59%; mp 297 °C; MS *m/z* M + 1 = 307 (100); NMR ($CDCl_3$) δ 1.4 (3 H, t, CH_3, ester), 1.76 (6 H, s, 2,2-dimethyl), 4.33 (2 H, s, 1-CH_2), 4.38 (2 H, q, CH_2 ester), 7.82 (1 H, d, *J* = 9.8 Hz, H-7), 8.0 (1 H, s, H-4); IR (cm^{-1}) 1683, 1660, 1620, 1580.

As a typical example, the preparation of quinolone **22** is described.

3-(2-Chloro-4,5-difluorophenyl)-3-oxo-2-[[(1,1-dimethyl-2-fluoroethyl)amino]methylene]propanoic Acid Ethyl Ester (7b). To a solution of 0.33 g (2.6 mmol) of 2-fluoro-1,1-dimethylethylamine hydrochloride (**8b**) and 0.33 mL (2.6 mmol) of TEA in 12 mL of dry EtOH was added 0.83 g (2.6 mmol) of 3-(2-chloro-4,5-difluorophenyl)-3-oxo-2-(ethoxymethylene)-propanoic acid ethyl ester (**5**).[24] The reaction mixture was stirred for 3 h. The solvent was evaporated and the residue was extracted with AcOEt, washed with H_2O, dried ($MgSO_4$), and concentrated to give 0.9 g of **7b** (**7**, X_1 = F, X_2 = X_3 = H): yield 96%; mp 70 °C.

6,7-Difluoro-1-(1,1-dimethyl-2-fluoroethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (10b). To a solution of 1.73 g (4.7 mmol) of enamine **7b** (**7**, X_1 = F, X_2 = X_3 = H) in 8.5 mL of dry dioxane was added portionwise 0.28 g (5.8 mmol) of 50% NaH in oil at room temperature. The reaction mixture was heated under reflux for 4 h, a further addition of 0.05 g of 50% NaH was made to complete the reaction. The reaction mixture was cooled and diluted with CH_2Cl_2 and poured into cold brine. The organic layer was decanted, dried ($MgSO_4$), and concentrated to give 1.64 g of crude product which was purified over silica gel (CH_2Cl_2/MeOH 98/2) to yield 0.52 g of **10b** (**10**, R_1 = $C(CH_3)_2CH_2F$, Y = F): yield 33%; mp 202 °C.

7-Piperazinyl-6-fluoro-1-(1,1-dimethyl-2-fluoroethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (12b). A mixture of 0.4 g (1.22 mmol) of ester **10b**, 0.156 g (1.8 mmol) of piperazine, and 0.36 mL (2.4 mmol) of DBU in 3.2 mL of dry CH_3CN was heated at 70 °C for 4 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with H_2O and dried ($MgSO_4$) to provide 0.5 g of crude material which was purified by chromatography (CH_2Cl_2/MeOH 90/10) to give 0.3 g of **12b** (N◯ = 1-piperazinyl, R_1 = $C(CH_3)_2CH_2F$): yield 62.5%; mp 198 °C.

7-Piperazinyl-6-fluoro-1-(1,1-dimethyl-2-fluoroethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Hydrochloride (22). To a solution of 0.29 g (0.74 mmol) of the above ester **12b** in 3 mL of EtOH was added 0.74 mL (1.48 mmol) of 2 N aqueous NaOH, in two portions over 6 h. The solvent was evaporated and the residue was dissolved in H_2O. To this was added 0.74 mL (1.48 mmol) of cold 2 N HCl; the precipitate was filtered to give 0.22 g of the amino acid, which was transformed into its hydrochloride salt in boiling EtOH, yielding 0.17 g of **22**: yield 63.2%; mp 210 °C; ^1H NMR (DMSO-d_6) δ 1.88 (6 H, s, 2 CH_3, *gem*-dimethyl), 3.30–3.55 (8 H, 2 m, piperazine CH_2), 5.08 (2 H, d, J_{H-F} = 49 Hz, CH_2F); 7.38 (1 H, d, J_{H-F} = 8 Hz, H-8), 8.04 (1 H, d, J_{H-F} = 12 Hz, H-5), 8.9 (1 H, s, H-2).

6,7-Difluoro-1-[1,1-(difluoromethyl)-2-fluoroethyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (10d). A mixture of 1.8 g (4.5 mmol) of **7d** (**7**, X_1 = X_2 = X_3 = F) and 0.62 g (4.5 mmol) of K_2CO_3 in 12 mL of DMF was heated at 100 °C for 4 h. The solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and H_2O. Evaporation of the dried organic layer gave 2.01 g of an oil which was purified by chromatography (CH_2Cl_2/AcOEt 8/2) to yield 0.18 g of **10d** (yield 11%) and 1.3 g of unreacted material.

8,9-Difluoro-2,2-(difluoromethyl)-6-oxo-1,2-dihydro-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid Ethyl Ester (46). A mixture of 0.5 g (1.25 mmol) of **7d** and 0.5 g (3.6 mmol) of K_2CO_3 in 6 mL of dry DMF was heated under reflux for 2 h. The black mixture was poured into 50 mL of H_2O and extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid which was recrystallized from MeOH. It was obtained 0.13 g of **46**: yield 30.2%; mp 260–265 °C; MS *m/z* M + 1 = 344 (100); ^1H NMR (DMSO-d_6) δ 1.25 (3 H, t, CH_3 ethyl ester), 3.61 (2 H, s, H-1), 4.22 (2 H, q, CH_2 ethyl ester), 4.81–5.21 (4 H, AA'X pattern, CH_2F, J_{H-F} = 47 Hz), 7.73–7.82 (1 H, dd, J_{H-F} = 11 Hz, H-7), 8.77 (1 H, s, H-4).

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