Fluoronaphthyridines and Quinolones as Antibacterial Agents. 2. Synthesis and Structure-Activity Relationships of New 1-*tert*-Butyl 7-Substituted Derivatives

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Received August 10, 1989

A number of 7-substituted-1-*tert*-butyl-6-fluoroquinolone-3-carboxylic acids and 7-substituted-1-*tert*-butyl-6-fluoro-1,8-naphthyridine-3-carboxylic acids have been prepared and tested for antibacterial activities. Among those the 7-aminopyrrolidinyl **20b** and the 7-diazabicyclo naphthyridine **18b** are the most potent compounds in vitro and in vivo. Physicochemical data and acute toxicity are also discussed. Compound **18b**, BMY 40062, exhibits the most favorable overall properties, considering in vitro and in vivo microbiological activity, its low toxicity, and pharmacokinetic profile, and was selected for clinical evaluation.

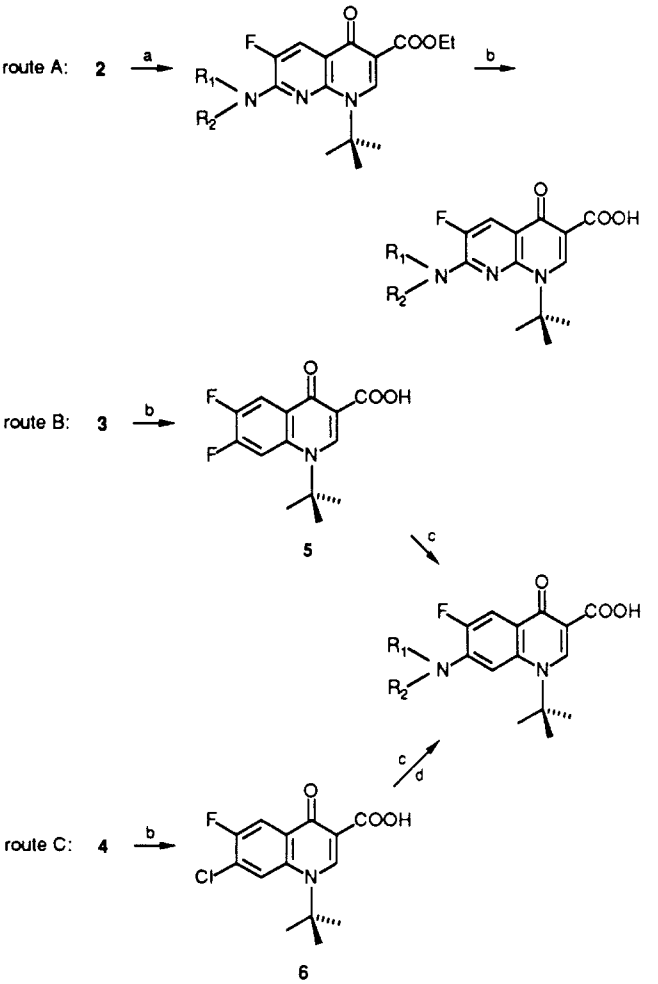
Since the introduction of nalidixic acid[1] as an antibacterial agent, a large number of 6-fluoroquinolones have been synthesized, and among those, several analogues containing a piperazinyl group substituent in 7-position were found to be useful antibacterial agents such as norfloxacin,[2] enoxacin,[3] ciprofloxacin,[4] ofloxacin,[5] and difloxacin.[6] These quinolones or naphthyridines were substituted differently in position 1. Recently[7] we have reported that, among the possible substituents at the 1-position of 1,4-dihydro-6-fluoro-4-oxo-7-(1-piperazinyl)-quinoline or 1,8-naphthyridine-3-carboxylic acids, a *tert*-butyl group (compounds **7a** and **7b**) improves antibacterial activity, especially against Gram-positive species. In this paper, we report the synthesis and antibacterial activity of 7-(substituted amino)-6-fluoro-1-*tert*-butyl-1,4-dihydroquinoline and 1,8-naphthyridine-3-carboxylic acid derivatives. It is known that aminopyrrolidine derivatives have better in vitro activity than the corresponding piperazine analogues,[28] which are generally less toxic, more soluble, and more hydrophilic. It was very attractive to keep the enhancement of activity brought by the pyrrolidine group without the associated toxicity. To try to meet this goal, diazabicyclo rings, which could be regarded as pyrrolidine or piperazine derivatives respectively 2,4 or 2,5 disubstituted, were introduced at C-7 of compounds **1a** and **1b** (Figure 1).

Chemistry

The ethyl esters **2-4** (Figure 2) were prepared as described previously[7] and served as starting materials for the synthesis of 7-amino-substituted quinolones and naphthyridines **7-34**.

Substitution of the 7-chlorine atom of carboxylate **2** (Scheme I, route A) with an appropriate amine in acetonitrile with a nonnucleophilic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene or an excess of amine yielded the expected 7-amino derivative ethyl esters (step 1). Hydrolysis with sodium hydroxide followed by neutralization afforded the expected compound (Table I). When a trifluoroacetylated intermediate was used, this protecting group was removed in the final step (compounds **20b** and **14b**). In the case of a monobenzylated diamino intermediate, catalytic hydrogenolysis was performed before alkaline hydrolysis (compound **15b**). Compounds **3** and **4** were first hydrolyzed to the acids **5** and **6**, and reaction with the appropriate amine in pyridine or in excess of amine yielded the corresponding quinolone acid (Scheme I, routes B and C). In the case of the trifluoroacetylated amino group an alkaline hydrolysis was necessary to obtain **20a**.

Scheme I[a]



[a] (a) HNR_1R_2, DBU/CH_3CN; (b) 2 N NaOH; (c) HNR_1R_2/pyridine; (d) HNR_1R_2 in excess.

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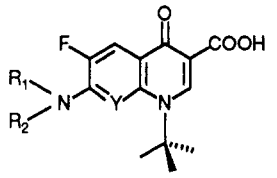
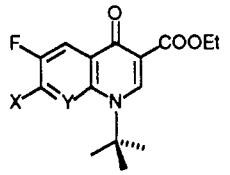


1a: Y = CH
b: Y = N

Figure 1. Structure of 7-(substituted amino)-1-*tert*-butyl-1,4-dihydro-6-fluoro-4-oxoquinoline-3-carboxylic acids (**1a**) and 7-(substituted amino)-1-*tert*-butyl-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**1b**).



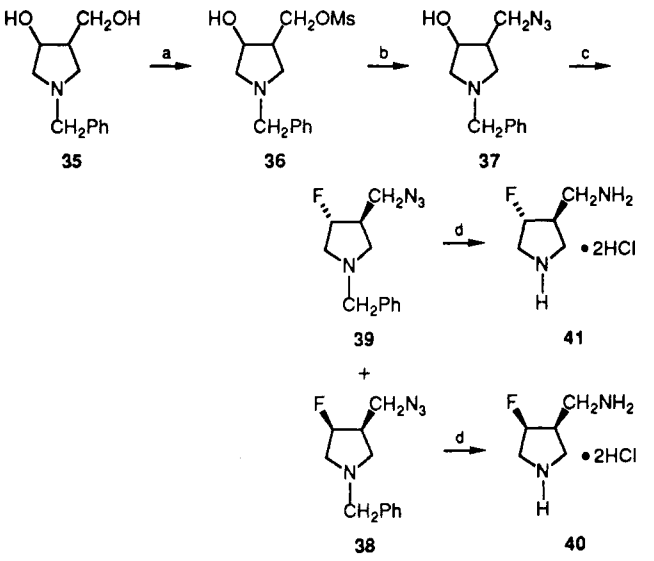
	X	Y
2	Cl	N
3	F	CH
4	Cl	CH

Figure 2. Structures of ethyl esters **2–4**.

Route B was preferred to route C to avoid a substitution at C-6.[8] The 3-amino or 3-(aminoalkyl) group of the pyrrolidines did not require protection as displacement occurred exclusively at the ring nitrogen as previously reported.[16] Thus, **20b** can be prepared in excellent yield by using 3-aminopyrrolidine instead of 3-[(trifluoroacetyl)amino]pyrrolidine. Structures and physical properties are displayed in Table I.

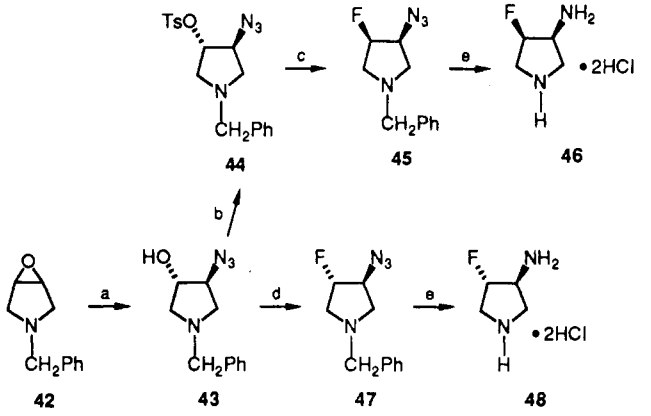
Piperazines and pyrrolidines that were not commercially available were synthesized by using reported methods,[10-17] except for amines **40**, **41**, **46**, and **56**. *cis*- and *trans*-3-fluoro-4-(aminomethyl)pyrrolidines (**40** and **41**) were prepared from 1-benzyl-3-hydroxy-4-(hydroxymethyl)-pyrrolidine (**35**)[16] with slight modification of a published method[15] (Scheme II). Cis and trans diastereoisomers **38** and **39** were separated at the fluorinating step. Treatment of each isomer with hydrogen in the presence of a palladium catalyst resulted in simultaneous debenzylation and reduction of the azide function.

Scheme II[a]



[a] (a) MsCl, Et_3N/CH_2Cl_2; (b) NaN_3/DMF, 75 °C; (c) DAST/CH_2Cl_2; (d) H_2–Pd/C, EtOH/1 N HCl.

Scheme III[a]



[a] (a) NaN_3, NH_4Cl/DMF, H_2O, 75 °C; (b) TsCl/pyridine; (c) nBu_4NF/THF; (d) DAST/CH_2Cl_2, −60 °C; (e) H_2–Pd/C, EtOH, 1 N HCl.

Synthesis of *cis* and *trans*-3-amino-4-fluoropyrrolidines (**46** and **48**) is summarized in Scheme III. Opening of the epoxide **42**[18] and tosylation of the resulting hydroxy derivative **43** were performed as described for the *N*-benzoyl analogue.[19,20] Exchange of the tosyl group by tetrabutylammonium fluoride gave the cis compound **45**. The only product isolated upon treatment of the hydroxy compound **43** with (diethylamino)sulfur trifluoride was the trans isomer **47**. Exposure of **45** and **47** to hydrogen in the presence of palladium catalyst resulted in reduction of the azide function, debenzylation, and formation of *cis*- and *trans*-3-amino-4-fluoropyrrolidines (**46** and **48**). NMR studies on intermediates from both sequences (**43** to **45**, **43** to **47**) demonstrate the cis and trans configurations based on assignments using NOE. The bicyclic amine **56**,

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Table I. Synthetic and Physical Data of the 1-*tert*-Butylquinolones (**1a**) and -naphthyridines (**1b**)[a]

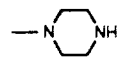
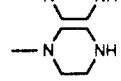
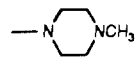
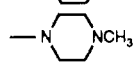
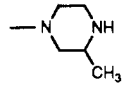
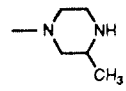
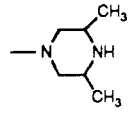
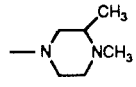
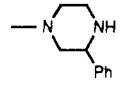
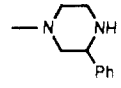
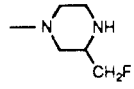
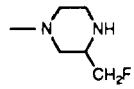
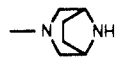
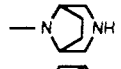
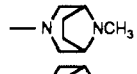
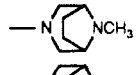
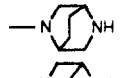
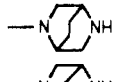
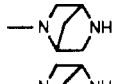
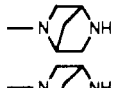
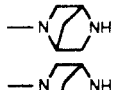
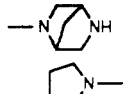
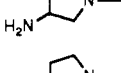
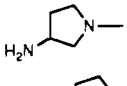
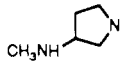
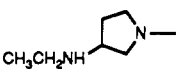
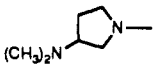
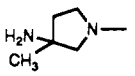
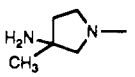
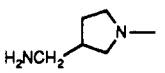
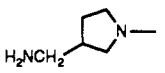
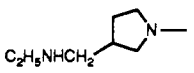
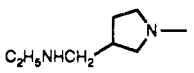
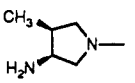
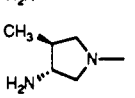
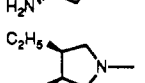
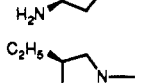
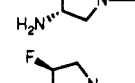
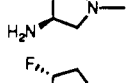
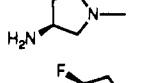
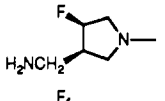
compd	method	Y	$-NR_1R_2$	ref	yield, %[b]	mp, °C	formula[c]
7a		CH			*e*	*e*	*e*
7b		N			*e*	*e*	*e*
8a	C	CH			37	>260	$C_{19}H_{24}FN_3O_3 \cdot HCl$
8b	A	N			38	223–224	$C_{18}H_{23}FN_4O_3$
9a	B	CH			25	194	$C_{19}H_{24}FN_3O_3$
9b	A	N			70	204–206	$C_{18}H_{23}FN_4O_3 \cdot H_2O$
10a	B	CH			59	197	$C_{20}H_{26}FN_3O_3 \cdot H_2O$
11b	A	N		9	53	204	$C_{19}H_{25}FN_4O_3 \cdot H_2O$
12a	B	CH			78	>260	$C_{24}H_{26}FN_3O_3 \cdot CH_3SO_3H \cdot H_2O$
12b	A	N		10	56	>260	$C_{23}H_{25}FN_4O_3CH_3SO_3H \cdot H_2O$
13a	B	CH		11	38	190	$C_{19}H_{23}F_2N_3O_3$
13b	A	N			37	247	$C_{18}H_{22}F_2N_4O_3 \cdot CH_3SO_3H \cdot H_2O$
14b	A	N		12	22	>260	$C_{19}H_{23}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
15b	A	N		12	24	>260	$C_{19}H_{23}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
16a	B	CH		12	18	>260	$C_{21}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$
16b	A	N			12	129	$C_{20}H_{25}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
17a	C	CH		12	17	164	$C_{20}H_{24}FN_3O_3 \cdot H_2O$
17b	A	N			60	268	$C_{19}H_{23}FN_4O_3 \cdot H_2O$
18a	B	CH	 (1*R*, 4*R*)		47	245	$C_{19}H_{22}FN_3O_3 \cdot H_2O$
18b	A	N	 (1*R*, 4*R*)		91	>260	$C_{18}H_{21}FN_4O_3 \cdot CH_3SO_3H$
19a	B	CH	 (1*S*, 4*S*)	12	64	243	$C_{19}H_{22}FN_3O_3 \cdot H_2O$
19b	A	N	 (1*S*, 4*S*)		63	250	$C_{18}H_{21}FN_4O_3 \cdot H_2O$
20a	B	CH		13	35	>260	$C_{18}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$
20b	A	N			90	256	$C_{17}H_{21}FN_4O_3 \cdot CH_3SO_3H$
21b	A	N		13	47	247–248	$C_{18}H_{23}FN_4O_3 \cdot H_2O$

Table I (Continued)

compd	method	Y	$-NR_1R_2$	ref	yield, %[b]	mp, °C	formula[c]
22b	A	N		13	46	230–240	$C_{19}H_{25}FN_4O_3 \cdot H_2O$
23b[d]	A	N			46	>260	$C_{19}H_{25}FN_4O_3 \cdot H_2O$
24a	C	CH		13	30	>260	$C_{19}H_{24}FN_3O_3 \cdot H_2O$
24b	A	N			71	>260	$C_{18}H_{23}FN_4O_3 \cdot H_2O$
25a	B	CH		14, 17	40	229–231	$C_{19}H_{24}FN_3O_3 \cdot H_2O$
25b	A	N			34	254	$C_{18}H_{23}FN_4O_3$
26a	B	CH		14, 17	10		$C_{21}H_{28}FN_3O_3 \cdot H_2O$
26b	A	N			60	244–246	$C_{20}H_{27}FN_4O_3$
27b	A	N		13	74	>260	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
28b	A	N		13	78	>260	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
29b	A	N		13	50	>260	$C_{19}H_{25}FN_4O_3 \cdot HCl$
30b	A	N		13	38	219	$C_{19}H_{25}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$
31b	A	N			62	>260	$C_{17}H_{20}F_2N_4O_3 \cdot CH_3SO_3H$
32b	A	N			51	>260	$C_{17}H_{20}F_2N_4O_3 \cdot CH_3SO_3H \cdot H_2O$
33b	A	N		15	32	230	$C_{18}H_{22}F_2N_4O_3 \cdot H_2O$
34b	A	N		15	44	208	$C_{18}H_{22}F_2N_4O_3 \cdot CH_3SO_3H \cdot H_2O$

[a] See Figure 1 for structures. [b] For route A, yields are given for the halogen exchange reaction and saponification, for route B, yields are given for the amine condensation. [c] C, H, and N analyses were within ±0.4% of the theoretical values, except as otherwise noted. [d] This compound was obtained by reductive N-methylation of **21b** as described in ref 23. [e] See ref 7.

enantiomer of the known amine **57**,[12] was obtained from **49**[21] by a seven-step sequence of reactions (Scheme IV). Tosylation of **49** yielded the intermediate **50**, which was converted to the acetate **51** with tetraethylammonium acetate as described for an analogous conversion.[21,22] Treatment of **51** with an excess of $LiBH_4$ gave the diol **52**. After tosylation, intramolecular cyclization of the resulting tritosyl derivative was performed by treatment with benzylamine. Deprotection of **54** by successive treatment with HBr/HOAc and H_2-Pd/C afforded **56** as a hydrobromide derivative.

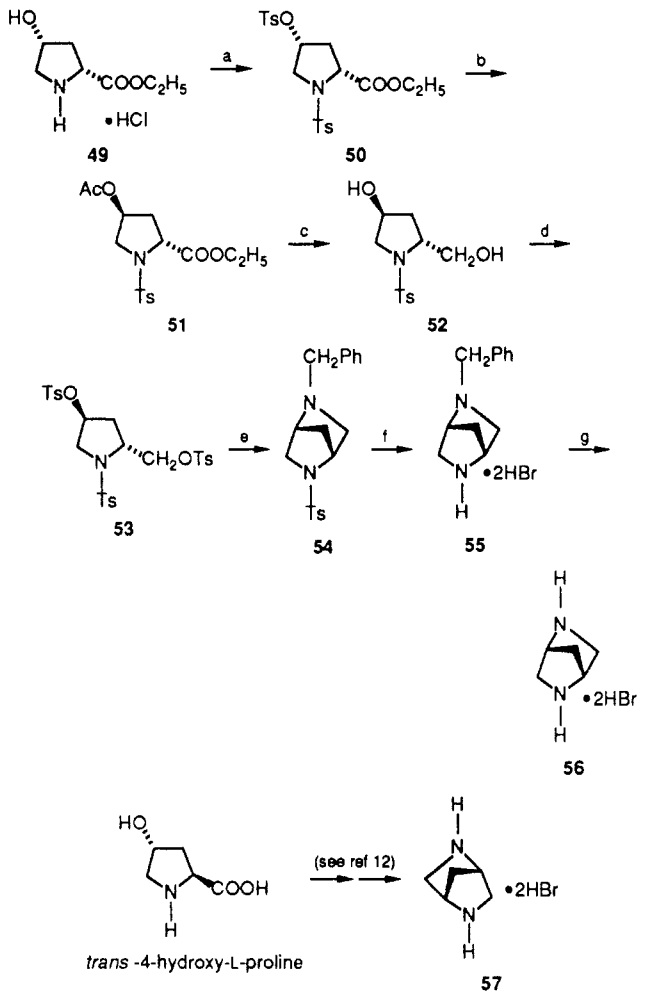
(21) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.
(22) Kende, A. S.; Demuth, T. P. *Tetrahedron Lett.* **1980**, *21*, 715.

Biological Evaluation of Compounds

Compounds **7–34** were evaluated for in vitro antibacterial activity against a variety of organisms. The minimum inhibitory concentrations (MICs) of these compounds against several Gram-positive and Gram-negative bacteria compared to norfloxacin and ciprofloxacin are displayed in Table II.

In the piperazine or bridged piperazine series the N-alkylated or C-alkylated derivatives were usually less active than the unsubstituted compounds. However, compound **9a** was at least as active as **7a**, and generally C-alkylation provided more potent derivatives than N-alkylation. The potency was not related to the size of the substituent, and 3-phenyl derivatives **12a** and **12b** had similar activity compared to the 3-methyl analogues **9a** and **9b**. In con-

Scheme IV[a]



[a] (a) TsCl, Et_3N/pyridine; (b) $(Et_4N^+)(OAc^-)$/AcOEt; (c) $LiBH_4$/THF, 25 °C; (d) TsCl, pyridine; (e) $PhCH_2NH_2$/toluene; (f) HBr/HOAc; (g) H_2–Pd/C, H_2O.

trast, the fluoromethyl compounds **13a** and **13b** were approximately 2–4 log 2 dilutions less active than the corresponding methyl derivatives **9a–b**.

As previously reported[23] for other derivatives substituted at N-1, aminopyrrolidine derivatives **20a–b** were more active in vitro than the corresponding piperazines **7a–b** and the (aminomethyl)pyrrolidine derivatives **25a–b** were less potent than **20a–b**.

N-Alkylation in the piperazine series always decreased in vitro activity while 3-amino-4-methylpyrrolidine derivatives **27b–28b** were more potent than **20b**. The trans isomer **28b** was about 2–4 log 2 dilutions more potent than the cis isomer **27b**, as active as ciprofloxacin against Gram-negative organisms and 4–8 times more active against Gram-positive bacteria. The ethyl analogues **29b–30b** were somewhat less active than the corresponding methyl compounds **27b–28b**.

Interestingly, the 3-fluoro-4-(aminomethyl) derivatives **33b–34b** were more potent than the corresponding unfluorinated derivative **25b**, even though the corresponding 3-fluoro-4-amino derivative pairs **31b–32b** were less active than **20b**.

The bridged piperazine series **14–19** showed no large difference in in vitro activity except for *Pseudomonas aeruginosa*, the best derivative being the naphthyridine chiral *R,R* isomer **18b**. The *S,S* antipode **19b** was about 4 times less active. The antimicrobial activity of N-1 fluorophenyl derivatives of the *S,S* antipode was recently reported,[24] but the *R,R* isomer has not been studied previously.

In order to determine in vivo efficacy, several of these compounds were selected for evaluation in the mouse protection tests. Ciprofloxacin and norfloxacin were used as comparative active principles.

Results of oral data are shown for *Staphylococcus aureus*, *P. aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* (Table III). Compounds **18b** and **20b**, two of the most potent members of this series in vitro, demonstrated the best activity in vivo. They were 3 times more active than ciprofloxacin against *S. aureus*, as active against *P. aeruginosa* and *E. coli*, and 2–3 times less active against *K. pneumoniae*. Most of the selected compounds were more active in vivo against *S. aureus* than ciprofloxacin. The fluoro aminomethyl derivatives **33b** and **34b**, which were very active in vitro, showed moderate in vivo activity when administered per os.

Solubility and Pharmacokinetic Properties

The water solubility of selected members of the present series is shown in Table IV. Substitution on the piperazine or pyrrolidine rings with a methyl group or a fluorine atom improves solubility in comparison to the unsubstituted derivative. The 3,4-trans-disubstituted pyrrolidine isomers are more soluble than the corresponding cis isomers (**27b–28b**, **33b–34b**).

Compound **20b**, one of the most active compounds in vitro and in vivo, exhibits poor water solubility as reported for derivatives with the 3-aminopyrrolidine group.[25] Water solubility is apparently an important property with potential influence on toxicity.

Acute toxicity data in mice are displayed in Table III for some selected compounds. Pyrrolidine derivatives appear to be more toxic than piperazine or bridged piperazine compounds; **20b** was the compound with lowest LD_{50} values of the series, a fact that might be related to the low water solubility. The compounds with highest LD_{50} values were **18b** and ciprofloxacin.

As solubility is a property that might be associated with the extent and rate of oral absorption of a compound as well as tissue distribution properties, pharmacokinetic data of several compounds after oral administration (25 mg/kg) to dogs are displayed in Table V in comparison with ciprofloxacin. All compounds of the present series tested have higher C_{max} values and larger areas under the plasma level curves. Urinary recoveries for pyrrolidine derivatives are, however, low, suggesting that hepatic clearance was more important than renal clearance. The candidate with most favorable properties, **18b**, was studied more extensively in dogs in comparison to ciprofloxacin after administration of an oral dose of 50 mg/kg (Figure 3).

The peak plasma concentration of **18b** appears at least 2 times higher than for ciprofloxacin with an increase of a factor of 3 in the area under the plasma level–time curve. Plasma concentrations of 0.6 μg/mL **18b** measured 24 h after administration compared favorably with values of 0.1 μg/mL determined for ciprofloxacin.

Summary of Results

These investigations confirm that quinolone or naphthyridine derivatives substituted by a *tert*-butyl group on

(23) Egawa, H.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Okada, H.; Uno, H.; Matsumoto, J. *J. Med. Chem.* **1984**, *27*, 1543.

(24) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1980**, *31*, 1598.

(25) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Shen, L.; Borodkin, S.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1586.

Table II. In Vitro Antibacterial Activity (MIC, μg/mL)

compound	*S. aureus* Smith A 9537	*E. faecalis* A 9808	*E. faecium* A 24885	*E. coli* A 15119	*K. pneumoniae* A 9664	*Enterobacter cloacae* A 9656	*Morganella morganii* A 15153	*S. marcescens* A 20019	*P. aeruginosa* A 9843
7a	0.06	1	4	0.06	0.13	0.13	0.25	0.5	0.5
7b	0.06	0.5	8	0.015	0.13	0.06	0.25	0.25	1
8a	0.03	4	16	0.03	0.25	0.25	0.25	1	0.5
8b	0.06	2	0.5	0.06	0.06	0.06	0.5	0.25	1
9a	0.06	1	4	0.008	0.015	0.03	0.5	0.5	1
9b	0.13	0.5	2	0.5	2	1	4	4	8
10a	0.25	2	8	0.13	0.5	0.13	1	2	4
11b	0.13	1	4	0.03	0.13	0.06	1	1	4
12a	0.06	0.5	4	0.06	0.25	0.13	0.5	2	1
12b	0.03	1	8	0.06	0.06	0.06	1	2	4
13a	0.13	2	8	0.25	0.13	0.13	0.5	1	4
13b	0.13	4	16	0.13	0.13	0.06	1	1	4
14b	0.06	1	4	0.13	0.13	0.25	0.5	1	4
15b	0.06	0.5	4	0.06	0.13	0.25	0.5	0.5	2
16a	0.13	2	8	0.5	0.13	0.13	1	0.5	4
16b	0.25	2	16	0.5	0.1	0.25	2	2	4
17a	0.13	1	4	0.5	0.25	0.25	1	2	2
17b	0.03	0.5	2	0.13	0.13	0.06	1	1	1
18a	0.5	2	4	0.5	0.13	0.25	2	0.25	0.5
18b	0.06	0.13	1	0.06	0.06	0.06	0.25	0.06	0.25
19a	0.25	4	16	2	0.5	0.5	1	2	1
19b	0.13	1	4	0.13	0.13	0.25	0.13	2	0.5
20a	0.03	0.25	2	0.06	0.25	0.13	0.5	1	1
20b	0.015	0.25	1	0.13	0.25	0.13	1	0.25	2
21b	0.06	0.5	8	0.06	0.13	0.06	0.5	1	2
22b	0.06	0.13	4	0.06	0.06	0.25	1	1	4
23b	0.03	0.5	8	0.25	0.13	1	0.5	1	1
24a	0.06	0.5	4	0.5	0.25	0.5	1	2	2
24b	0.015	0.5	4	0.06	0.06	0.13	0.5	0.5	2
25a	0.03	0.25	0.5	0.25	0.25	0.25	2	2	0.5
25b	0.03	0.25	2	0.5	0.25	0.5	1	2	1
26a	0.06	0.5	4	0.25	1	0.5	2	8	8
26b	0.13	2	8	0.13	0.25	0.25	1	1	2
27b	0.015	0.13	1	0.25	0.03	0.13	0.5	0.25	0.5
28b	0.008	0.06	0.5	0.015	0.06	0.015	0.13	0.13	0.25
29b	0.015	0.25	2	0.13	0.13	0.06	0.5	0.5	1
30b	0.015	0.13	2	0.03	0.06	0.03	0.25	0.25	1
31b	0.015	0.5	4	0.25	0.06	0.25	0.5	0.5	2
32b	0.003	0.25	2	0.5	0.5	0.5	0.5	0.5	2
33b	0.015	0.13	1	0.06	0.25	0.25	0.5	0.5	0.5
34b	0.004	0.03	0.25	0.06	0.13	0.06	0.5	1	0.5
norfloxacin	0.25	4	8	0.13	0.03	0.06	0.015	0.13	0.5
ciprofloxacin	0.13	0.5	4	0.03	0.03	0.008	0.015	0.3	0.13

Table III. Efficacy on Systematic Infections and Acute Toxicity with Oral Administration in Mice

	PD_{50}[a] mg/kg po				LD_{50}[b]	
compound	*S. aureus* A 9537	*P. aeruginosa* A 9843	*E. coli* A 15119	*K. pneumoniae* A 9664	iv	po
norfloxacin	1.9 (0.25)[c]	12.6 (0.5)	13 (0.13)	8 (0.03)		
ciprofloxacin	3.4 (0.13)	2.6 (0.13)	1 (0.03)	1.5 (0.03)	273	5000
7a	2.4 (0.06)	29 (0.5)	21.7 (0.06)	10.3 (0,13)	250	2500
7b	1.1 (0.06)	10.9 (1)	4.7 (0.015)	4.8 (0.13)	250	2500
9a	5.4 (0.06)	25 (1)	NT[d]	5.4 (0.015)		
18b	1.6 (0.06)	4.7 (0.25)	1.8 (0.06)	4.9 (0.06)	303	5000
19a	10 (0.25)	23 (1)	NT	NT		
19b	0.5 (0.13)	14 (0.5)	4 (0.13)	10.8 (0.13)		
20a	8.2 (0.03)	19.9 (1)	5.4 (0.06)	23 (0.25)		
20b	1.4 (0.015)	3.5 (2)	1.4 (0.13)	2.1 (0.25)	190	800
27b	1.6 (0.015)	9.0 (0.5)	2.4 (0.25)	4.1 (0.03)	113	1250
28b	1.6 (0.008)	6.3 (0.25)	2.4 (0.015)	6.3 (0.06)	131	2100
33b	4.5 (0.015)	18 (0.5)	18 (0.06)	18 (0.25)		
34b	0.8 (0.004)	18 (0.5)	NT	NT		

[a] Dose to protect 50% of mice from lethal infection po. [b] See Experimental Section. [c] Value in parentheses is the MIC in μg/mL. [d] Not tested.

N-1 exhibit very good in vitro and in vivo activity against Gram-negative and especially Gram-positive organisms. Compound **18b** demonstrates the best overall microbiological profile associated with a low toxicity and promising pharmacokinetic properties. Therefore, BMY 40062 (**18b**), which is substituted at C-7 by a diazabicyclo heptane ring, shares the very good in vitro activity usually brought by the aminopyrrolidine group and the low toxicity and good pharmacokinetic profile of C-7 piperazine derivatives. BMY 40062 was selected for clinical evaluation.[26]

Table IV. Aqueous Solubility of Selected Compounds

compound	solubility,[a] mg/mL	compound	solubility,[a] mg/mL
ciprofloxacin	0.07	**20a**	0.07
7a	0.13	**20b**	0.05
7b	0.82	**27b**	0.02
9a	1.56	**28b**	0.22
18a	0.23	**33b**	0.48
18b	0.08	**34b**	1.36

[a] Solubility determined at pH iso in water.

Table V. Pharmacokinetic Properties of Selected Compounds after Oral Administration in Dog[a] (25 mg/kg)

compound	C_{max}, μg/mL	$t_{1/2}$, h	AUC,[b] μg/(mL·h)	UR,[c] %
7b	5.8	4.8	50	12
18b	5.6	4.5	55	20
20b	4.5	4.5	40–50	8–10
27b	6.5	4	42	3
28b	4.2	4.5	43	2
ciprofloxacin	3	3.5	20	17

[a] See Experimental Section. [b] Area under the concentration/time, μg/(mL·h). [c] Urinary recovery, percent of administrated dose.

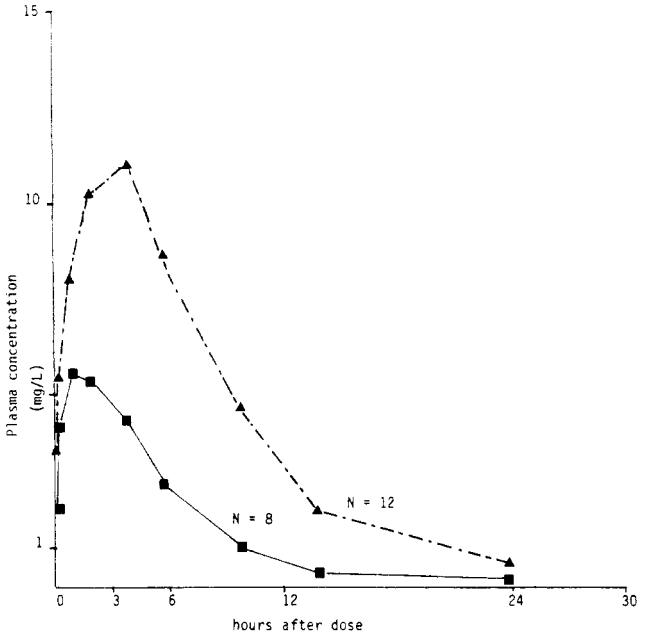


Figure 3. Mean plasma concentrations of **18b** (▲) and ciprofloxacin (■) after oral administration of 50 mg/kg to dogs in solution (mean values of pooled studies; n = 8 and 12).

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis was performed by the Microanalytical Laboratory, operated by the Bristol-Myers Analytical Department. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 783 infrared spectrometer. ^{1}H NMR spectra were determined on a Brucker AC 200 spectrometer. Chemical shifts are expressed in δ (ppm) relative to internal tetramethylsilane. Flash column chromatography was done with Merck silica gel 60, 70–230 mesh ASTM. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F_{254} TLC plates, and compound visualization was effected with iodine or a UV lamp. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter.

Microbiology. General Procedures. In Vitro Studies. The in vitro antibacterial activity was studied by a side-by-side comparison with norfloxacin and ciprofloxacin 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 concentration (MIC) was defined as the lowest concentration of the compound that prevents visible growth of bacteria after incubation at 37 °C for 18 h.

Acute Toxicity on Oral Administration to Mice. A solution of each test compound in sterile water was administered orally to OF1 strain female Swiss mice (18–25 g body weight, five per group). Seven days later, LD_{50} values were determined by using the Karber and Behrens method.[27]

Pharmacokinetic Studies—General Procedure. Plasma and urine levels in dogs were determined by microbiological assay. 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, and 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 standard used was the test compound itself.

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

Preparation of Amines. *trans*-4-Fluoro-3-(aminomethyl)pyrrolidine Dihydrochloride (41). To a solution of 0.193 g (0.82 mmol) of **39**[15] and 0.85 mL of aqueous 1 N hydrochloric acid in 10 mL of ethanol was added 0.2 g of 10% palladium on carbon. The mixture was placed under hydrogen. After 1.5 h there was added 0.2 g more of the catalyst and 0.85 mL of aqueous 1 N hydrochloric acid, and the mixture was hydrogenized again for 1.5 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to afford 0.130 g (83% yield) of **41** as a hygroscopic solid, which was used without further purification. An analytical sample was prepared by recrystallization from ethanol: ^{1}H NMR (DMSO-d_6) δ 8.87 (broad, 5 H, exchangeable), 5.46 (m, $^2J_{HF}$ = 53 Hz, C_4H), 3.6–2.7 (m, 7 H).

***cis*-4-Fluoro-3-(aminomethyl)pyrrolidine Dihydrochloride (40).** An analogous procedure described as above was used to convert **38** to **40** (70% yield). An analytical sample was prepared by recrystallization from ethanol: ^{1}H NMR (DMSO-d_6) δ 10.08, 8.48 (broad, 5 H, exchangeable), 5.46 (m, 1 H, $^2J_{HF}$ = 53 Hz, C_4H), 3.7–2.8 (m, 7 H).

***trans*-3-Azido-4-hydroxy-1-benzylpyrrolidine (43).** A mixture of 5.21 g (29.7 mmol) of **42**,[18] 2.12 g (39.6 mmol) of NH_4Cl, 11.62 g (178.7 mmol) of NaN_3, 80 mL of DMF, and 9.5 mL of H_2O was warmed on a steam bath for 5 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo leaving 5.9 g of **43** as an oil. The crude product was purified by flash chromatography with 70:30 ethyl acetate–hexane as the eluant to obtain 4.75 g (73% yield) of pure **43** as an oil: ^{1}H NMR (DMSO-d_6) δ 7.30 (m, 5 H, C_6H_5), 5.39 (d, 1 H, J = 2.8 Hz, OH), 4.06 (m, 1 H, C_4H), 3.65 (m, 1 H, C_3H), 3.57 (m, 2 H, CH_2Ph), 3–2.2 (broad m, 4 H, 2 CH_2N); IR (neat) 3360, 2940, 2810, 2110, 1260 cm^{-1}.

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***trans*-3-Azido-4-[(4-tolylsulfonyl)oxy]-1-benzylpyrrolidine (44).** To a solution of 3.74 g (17.1 mmol) of **43** in 38 mL of pyridine cooled at +5 °C was added 4.90 g (25.7 mmol) of 4-toluenesulfonyl chloride. The reaction mixture was stirred for 18 h at +5 °C. The pyridine was removed under reduced pressure. The mixture was partitioned between CH_2Cl_2 and a 10% aqueous sodium bicarbonate solution. The organic layer was washed with water, dried (Na_2SO_4), and concentrated with a rotary evaporator to obtain 6.33 g of **44** as an oil. The crude product was purified by flash chromatography with 20:80 ethyl acetate–hexane as the eluant to obtain 4.72 g (74% yield) of pure **44** as an oil: ^{1}H NMR (DMSO-d_6) δ 7.90–7.10 (m, 9 H, Ar), 4.70 (m, 1 H, C_4H), 4.16 (m, 1 H, C_3H), 3.57 (m, 2 H, CH_2Ph), 2.35 (s, 3 H, CH_3), 3–2.2 (m, 4 H, C_3N).

***trans*-3-Azido-4-fluoro-1-benzylpyrrolidine (47).** Under a nitrogen atmosphere, to a solution of 1 g (4.58 mmol) of **43** in 4 mL of CH_2Cl_2 cooled at −78 °C was added a solution of 1.53 g (9.47 mmol) of DAST in 4 mL of CH_2Cl_2 dropwise through an addition funnel. After being stirred for 15 min at −60 °C, the mixture was warmed to 0 °C, poured into a 10% aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried, and concentrated. The crude product was purified by flash chromatography with 99:1 CH_2Cl_2–MeOH as the eluant to obtain 0.305 g (30% yield) of pure **47**: ^{1}H NMR (DMSO-d_6) δ 7.3 (m, 5 H, C_6H_5), 5.06 (m, 1 H, $^2J_{HF}$ = 53 Hz, C_4H), 4.18 (m, 1 H, $^3J_{HF}$ = 21 Hz, C_3H), 3.62 (m, 2 H, CH_2Ph), 3.1–2.4 (m, 4 H, 2 CH_2N).

***trans*-3-Amino-4-fluoropyrrolidine Dihydrochloride (48).** To a solution of 0.300 g (1.36 mmol) of **47** and 1.36 mL (1.36 mmol) of aqueous 1 N hydrochloric acid in 10 mL of ethanol was added 0.150 g of 10% palladium on carbon. The mixture was placed under hydrogen. After 2 h, 1.36 mL (1.36 mmol) of 1 N hydrochloric acid was added, the catalyst was removed by filtration through Celite, and the filtrate was concentrated with a rotary evaporator to afford 0.192 g (80% yield) of **48** as a hygroscopic solid: ^{1}H NMR (DMSO-d_6) δ 9.43 (broad, 5 H, exchangeable), 5.5 (m, 1 H, $^2J_{HF}$ = 50 Hz, C_4H), 4.15–3.25 (m, 5 H, C_3H, C_2H_2, C_5H_2).

***cis*-3-Azido-4-fluoro-1-benzylpyrrolidine (45).** A solution of 4.72 g (12.67 mmol) of **44** in 78 mL of 1 M tetra-*n*-butylammonium fluoride in THF was heated under reflux under nitrogen overnight. The reaction mixture was concentrated and the residue was extracted with CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography with 25:75 ethyl acetate–hexane as the eluant to obtain 1.4 g (50% yield) of pure **45** as an oil: ^{1}H NMR (DMSO-d_6) δ 7.30 (m, 5 H, Ar), 5.25 (m, 1 H, $^2J_{HF}$ = 55 Hz, C_4H), 3.94 (m, 2 H, CH_2Ph), 3.1–2.65 (m, 4 H, 2 CH_2N).

***cis*-3-Amino-4-fluoropyrrolidine Dihydrochloride (49).** The procedure described for the preparation of compound **48** was used to convert **45** to **49**, which was isolated as a dihydrochloride–hygroscopic solid crystallized from ethanol (85% yield): ^{1}H NMR (DMSO-d_6) δ 9.5 (broad m, 5 H, exchangeable), 5.44 (m, 1 H, $^2J_{HF}$ = 53 Hz, C_4H), 3.93 (m, 1 H, C_3H), 3.75–3.1 (m, 4 H, 2 CH_2N).

***allo*-1-(4-Tolylsulfonyl)-4-[[(4-methylphenyl)sulfonyl]oxy]-D-proline Ethyl Ester (50).** To a cold solution of 7.4 g (37.7 mmol) of *allo*-4-hydroxy-D-proline ethyl ester hydrochloride (**49**)[21] and 3.81 g of triethylamine (37.7 mmol) in pyridine (74 mL) at −5 °C was added portionwise 15.82 g (83 mmol) of 4-toluenesulfonyl chloride. The cold solution was stirred 1 h at 0 °C and stored overnight in the refrigerator. Then the mixture was stirred at room temperature for 5 h and poured into ice water (55 mL). The precipitate was filtered, washed with water, and dried to give 13.1 g (74.2%) of the titled compound: mp 125 °C; $[\alpha]^{25}_D$ +26.48° (c = 2, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.8–7.3 (m, 8 H, 2 Ar), 5.0 (m, 1 H, C_4H), 4.47 (m, 1 H, C_2H), 4.03 (m, 2 H, CH_2CH_3), 3.33 (broad s, 2 H, C_5H_2), 2.39 (m, 6 H, 2 CH_3Ar), 2.3–2 (m, 2 H, C_3H_2), 1.11 (m, 3 H, CH_3CH_2).

4-(Acetyloxy)-1-[(4-methylphenyl)sulfonyl]-D-proline Ethyl Ester (51). To 35 mL of toluene were added 2 g (15 mmol) of anhydrous tetramethylammonium acetate and 5.48 g (11.7 mmol) of ethyl ester **50** under nitrogen. The mixture was refluxed overnight and then cooled. The organic layer was washed with water (2 × 10 mL), dried over magnesium sulfate, filtered, and evaporated to dryness. The residue (4 g) was taken up with 8 mL of 2-propanol. The mixture was stirred for 30 min at 0 °C, and the resulting crystalline product was collected and dried under reduced pressure to give 3.3 g (74%) of the titled compound: mp 81 °C; $[\alpha]^{25}_D$ +82° (c = 2, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.8–7.4 (m, 4 H, Ar), 5.03 (m, 1 H, C_4H), 4.15 (m, 2 H, C_2H), 3.75–3.30 (m, 2 H, CH_2N), 2.39 (s, 3 H, CH_3Ar), 2.4–2.0 (m, 2 H, C_3H_2), 1.53 (s, 3 H, CH_3CO), 1.21 (t, 3 H, J = 7 Hz, CH_3CH_2).

4-Hydroxy-1-(4-tolylsulfonyl)-D-prolinol (52). To an ice-cold solution of 31.5 g (88.7 mmol) of 4-(acetyloxy)-1-(4-tolylsulfonyl)-D-proline ethyl ester (**51**) in 315 mL of THF was added 3.37 g (177 mmol) of lithium borohydride. The mixture was stirred at 0 °C for 0.5 h and then kept at a temperature below 25 °C overnight. The mixture was cooled to 0 °C and the pH adjusted to 3 with 30 mL of 6 N hydrochloric acid. The solution was concentrated, and the residue was tritured with 250 mL of water to give a crystalline solid. The white precipitate was filtered, washed with cold water, and dried under reduced pressure to give 22 g (91% yield) of the titled compound: mp 127 °C; $[\alpha]^{25}_D$ +36.6° (c = 1.0, acetone); ^{1}H NMR (DMSO-d_6) δ 7.8–7.3 (m, 4 H, Ar), 6.55 (broad m, 1 H, exchangeable), 4.76 (m, 1 H, exchangeable), 4.19 (m, 1 H, C_4H), 3.7–2.8 (m, 5 H), 2.39 (s, 3 H, CH_3Ar), 1.93 (m, 1 H, C_3H_a), 1.44 (m, 1 H, C_3H_b).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-2-[[(4-tolylsulfonyl)oxy]methyl]-4-[(4-tolylsulfonyl)oxy]pyrrolidine (53). To an ice-cold solution of 21.92 g (80.8 mmol) of (2*R*,4*S*)-1-(4-tolylsulfonyl)-2-(hydroxymethyl)-4-hydroxypyrrolidine (**52**) in 100 mL of pyridine were added 53.92 g (282 mmol) of 4-toluylsulfonyl chloride in one portion. The temperature rose to 50 °C. The mixture was cooled at 10 °C and kept for 2 h at this temperature and then at room temperature overnight. The mixture was poured into 0.5 L of 2 N hydrochloric acid. After cooling, a precipitate was collected, washed with cold water, and dried under reduced pressure. This precipitate was taken up with 100 mL of ethanol, filtered, washed with cold ethanol, and dried under reduced pressure to give 40.6 g (86%) of the titled compound: mp 134 °C; $[\alpha]^{25}_D$ +57.13° (c = 1.9, acetone); ^{1}H NMR (DMSO-d_6) δ 7.9–7.3 (m, 12 H, Ar), 4.89 (m, 1 H, C_4H), 4.20 (m, 2 H, CH_2N), 3.59 (m, 1 H, C_2H), 3.53–3.35 (m, 2 H, CH_2N), 2.43 (s, 3 H, CH_3Ar), 2.35 (s, 3 H, CH_3Ar), 1.97–1.93 (m, 1 H, CHN).

(1*R*,4*R*)-2-(4-Tolylsulfonyl)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane (54). A mixture of 26.97 g (46.53 mmol) of (2*R*,4*S*)-1-(4-tolylsulfonyl)-2-[[(4-tolylsulfonyl)oxy]methyl]-4-[(4-tolylsulfonyl)oxy]pyrrolidine (**53**) and 16.40 g (153 mmol) of benzylamine in 150 mL of toluene was heated under reflux. After 6 h 1 g of benzylamine was added and the reflux continued for 3 h. The mixture was cooled and filtered and the residue was washed with 50 mL of toluene. The combined organic layers were evaporated to dryness, and the resulting solid was taken up with 20 mL of 2-propanol. After cooling, the product was filtered, washed with cold 2-propanol, and dried under reduced pressure to give 14.34 g of the titled compound (90%): mp 124 °C; $[\alpha]^{25}_D$ −15.72° (c = 1.6, acetone); ^{1}H NMR (DMSO-d_6) δ 7.9–7.4 (m, 4 H, Ts), 7.5–7.15 (m, 5 H, Ar), 1.60 (d, 1 H, J = 9.4 Hz, C_7H_a), 0.88 (d, 1 H, J = 9.4 Hz, C_7H_b).

(1*R*,4*R*)-5-(Phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane Dihydrobromide (55). To a hot solution of 28.5 mL of hydrobromic acid 33% in acetic acid and 140 mL of acetic acid at 70 °C was added 14.28 g (41.7 mmol) of (1*R*,4*R*)-2-(4-toluylsulfonyl)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane (**54**). The solution was stirred for 12 h. The resulting suspension was cooled (18–20 °C). The precipitate was filtered, washed with diisopropyl ether, and dried at 40 °C under reduced pressure to give 12.94 g (89%) of the titled compound: mp 276 °C; $[\alpha]^{25}_D$ −0.38° (c = 1, H_2O); ^{1}H NMR (DMSO-d_6, D_2O) δ 7.61–7.46 (m, 5 H, Ar), 4.48–4.26 (m, 4 H, CH_2Ph, 2 $CHCH_2$), 3.69–3.36 (m, 4 H, 2 CH_2N), 2.11–2.04 (m, 1 H, C_1H).

(1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptane Dihydrobromide (56). A suspension of 7.6 g (21.7 mmol) of (1*R*,4*R*)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane dihydrobromide (**55**) and 3.7 g of 10% Pd on C in 120 mL of water was hydrogenated at atmospheric pressure at 40 °C. The reaction was completed within 8 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was taken up with ethanol, and the resulting precipitate was filtered to give 5.14 g (91%) of the titled compound: mp 285 °C; $[\alpha]^{25}_D$ −19.83° (c = 1.2, 0.1 N HCl); ^{1}H NMR (DMSO-d_6) δ 9.30 (broad m, 4 H, exchangeable),

4.48 (broad m, 2 H, C_5H, C_2H), 3.40 (m, 4 H, 2 CH_2N), 2.04 (broad s, 2 H, C_7H_2).

General Procedure for the Preparation of Naphthyridines and Quinolones (Scheme I). Method A. 7-[(1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (18b). To a stirred mixture of 8.63 g (26.4 mmol) of **2** and 8.92 g (34.3 mmol) of (1*R*,4*R*)-2,5-diazabicyclo-[2.2.1]heptane dihydrobromide in 150 mL of acetonitrile was added 16 g (105 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. After complete addition, the reaction mixture was heated at 70–75 °C for 2 h. After cooling, the precipitate was filtered to give 9.46 g (92%) of ethyl ester, mp 248 °C. A suspension of 4.58 g (11.8 mmol) of the crude ethyl ester in 47.2 mL (47.2 mmol) of 1 N NaOH was heated under reflux for 30 min. The solution was cooled to 10 °C, and the pH was adjusted to 7.5 with 7.6 mL of 6 N HCl. The precipitate was filtered and dried to give 7.7 g (99%) of the expected compound purified as a methanesulfonate: mp 260 °C; IR 1730, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.86 (s, 1 H, C_2H), 8.12 (d, 1 H, J = 12.5 Hz, C_5H), 5.12 (m, 1 H, C_1H), 4.55 (m, 1 H, C_4H), 3.96 (broad m, 2 H, C_3H_2), 3.44 (broad m, 2 H, C_7H_2), 2.33 (s, 3 H, CH_3SO_3H), 2.10 (broad m, 2 H, C_7H_2), 1.8 (s, 9 H, tBu); $[\alpha]^{25}_D$ +158.5° (c = 0.25, 0.1 N HCl).

7-(3-Amino-1-pyrrolidinyl)-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (20b). To a stirred mixture of 34.41 g (105 mmol) of **2** and 21.75 g (137 mmol) of 3-aminopyrrolidine[14] in 500 mL of acetonitrile was added 63.41 g (417 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The solution was heated at 65 °C for 1 h. The suspension was cooled and the precipitate was filtered and washed with acetonitrile to give 35.33 g (89%) of the titled compound, mp 256 °C, which was used without further purification. Hydrolysis of 12 g (32 mmol) of the above product was carried out in 128 mL of 1 N NaOH at reflux for 15 min. The solution was cooled and adjusted to pH 6.5 with 2 N HCl. The precipitate was filtered and washed with water, dried, and purified as a methanesulfonate, to give 11.4 g (78%) of the titled compound: mp 258 °C; IR 1728, 1640, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.86 (s, 1 H, C_2H), 8.08 (d, J = 12.8 Hz, 1 H, C_5H), 3.75–4.2 (broad m, 5 H, pyrrolidine), 2.31 (s, 3 H, CH_3SO_3H), 2.21–2.4 (broad m, 2 H, pyrrolidine), 1.88 (s, 9 H, tBu).

Method B. 7-(3-Amino-1-pyrrolidinyl)-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (20a). To a stirred mixture of 0.6 g (2.13 mmol) of **3** and 0.7 g (3.2 mmol) of 3-[(trifluoroacetyl)amino]pyrrolidine in 3 mL of pyridine was added 1.3 mL (8.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The solution was stirred for 30 min at room temperature, evaporated to dryness, and poured into water. The pH was adjusted to 7.5 with 1 N hydrochloric acid. The precipitate was filtered to give 0.430 g (45%) of trifluoracetyl intermediate, mp 200 °C. A suspension of 0.409 g (0.92 mmol) of the above compound into 2 mL of 1 N NaOH was refluxed 2 h. The solution was cooled and the pH was adjusted to 7.5 with 10% aqueous acetic acid. The precipitate was filtered, washed with water, dried, and purified as a hydrochloride in ethanol to give 0.200 g (56%) of the titled compound: mp 260 °C; IR 1690, 1635, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.67 (s, 1 H, C_2H), 7.90 (d, 1 H, J = 14.2 Hz, C_5H), 7.06 (d, 1 H, J = 7.2 Hz, C_8H), 3.60–4.04 (broad m, 5 H, pyrrolidine), 2.05–2.5 (broad m, 2 H, pyrrolidine), 1.87 (s, 9 H, t-Bu).

7-[3-(Fluoromethyl)-4-piperazinyl]-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic Acid (13a). To a mixture of 0.610 g (2.17 mmol) of **3** and 0.500 g (2.17 mmol) of 3-(fluoromethyl)piperazine dihydrochloride in 10 mL of acetonitrile was added 1.2 g (7.85 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene. The solution was heated under reflux for 2 h, cooled, and evaporated to dryness. The residue was taken up in ethyl acetate and the filtrate was evaporated to dryness. The crude product was crystallized in 2-propanol to give 0.31 g of the titled compound (38%): mp 190 °C; IR 3340, 1720, 1630, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.91 (s, 1 H, C_2H), 7.94 (d, 1 H, J = 13.2 Hz, C_5H), 7.45 (d, 1 H, J = 7.5 Hz, C_8H), 4.43 (dd, J_{H-H} = 5 Hz, J_{HF} = 49 Hz, CH_2F), 2.6–3.7 (broad m, 7 H, piperazine), 1.87 (s, 9 H, tBu).

Method C. 7-(4-Methyl-1-piperazinyl)-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (8a). A mixture of 1.4 g (4.7 mmol) of **4** and 2.08 mL (18.8 mmol) of *N*-methylpiperazine was heated at 100 °C under nitrogen for 18 h. The mixture was evaporated to dryness under reduced pressure. The residue was dissolved in water, and the solution was adjusted to pH 7.0 with 5 N hydrochloric acid. The precipitate was filtered and washed with water to give 0.63 g of a crude material, which was purified as a hydrochloride in ethanol to give 0.54 g (29%) of the titled compound: mp 260 °C; IR 3600, 3460, 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.96 (s, 1 H, C_2H), 8.55 (d, 1 H, J = 12.8 Hz, C_5H), 7.48 (d, 1 H, J = 7.5 Hz, C_8H), 3.90–3.20 (broad m, 8 H, 4 CH_2N), 2.86 (s, 3 H, CH_3N), 1.83 (s, 9 H, tBu).

Acknowledgment. We thank the Analytical Department for spectral determinations and microanalyses. We especially thank Dr. J. Saint-Germain for the recording and interpretation of the NMR spectra.

Registry No. **2**, 116163-18-9; **3**, 116163-43-0; **4**, 116163-44-1; **7a**, 116162-74-4; **7b**, 116162-91-5; **8a**, 125197-06-0; **8a** (free base), 116162-81-3; **8b**, 125197-41-3; **8b** ethyl ester, 125197-52-6; **9a**, 125197-07-1; **9b**, 125197-42-4; **9b** ethyl ester, 125197-53-7; **10a**, 116162-85-7; **11b**, 116162-96-0; **12a**, 125197-09-3; **12a** (free base), 125197-08-2; **12b**, 125197-44-6; **12b** (free base), 125197-43-5; **13a**, 125197-10-6; **13b**, 125197-46-8; **13b** ethyl ester, 125197-54-8; **13b** (free base), 125197-45-7; **14b**, 125197-11-7; **14b** (free base), 116162-97-1; **15b**, 125197-12-8; **15b** (free base), 118329-79-6; **16a**, 125197-13-9; **16a** (free base), 125197-58-2; **16b**, 125197-47-9; **16b** ethyl ester, 125197-55-9; **16b** (free base), 116163-04-3; **17a**, 125197-14-0; **17b**, 125197-48-0; **17b** ethyl ester, 125197-56-0; **18a**, 116258-14-1; **18b**, 125277-78-3; **18b** ethyl ester, 116163-20-3; **18b** (free base), 116143-32-9; **19a**, 116162-83-5; **19b**, 116258-15-2; **19b** ethyl ester, 125277-79-4; **20a**, 125227-54-5; **20a** (*N*-trifluoroacetylamide ethyl ester, 125197-60-6; **20a** (free base), 125197-59-3; **20b**, 125353-42-6; **20b** (free base), 125277-80-7; **20b** ethyl ester, 125277-81-8; **21b**, 125197-15-1; **22b**, 125197-16-2; **23b**, 125197-17-3; **23b** ethyl ester, 125197-68-4; **24a**, 125197-18-4; **24b**, 125197-49-1; **24b** ethyl ester, 125197-69-5; **25a**, 125197-19-5; **25b**, 125197-50-4; **25b** ethyl ester, 125197-64-0; **26a**, 125197-20-8; **26b**, 125197-51-5; **26b** ethyl ester, 125197-65-1; **27b**, 125197-22-0; **27b** (free base), 125197-21-9; **28b**, 125197-24-2; **28b** (free base), 125197-23-1; **29b**, 125197-25-3; **29b** (free base), 125197-61-7; **30b**, 125227-55-6; **30b** (free base), 125197-62-8; **31b**, 125197-27-5; **31b** ethyl ester, 125197-66-2; **21b** (free base), 125197-26-4; **32b**, 125303-63-1; **32b** ethyl ester, 125197-67-3; **32b** (free base), 125197-63-9; **33b**, 125197-28-6; **34b**, 125197-30-0; **34b** (free base), 125197-29-7; **38**, 125197-31-1; **39**, 125197-32-2; **40**, 125197-33-3; **41**, 125197-34-4; **42**, 75390-09-9; **43**, 125197-35-5; **44**, 125197-36-6; **45**, 125197-37-7; **46**, 125197-38-8; **47**, 125197-39-9; **48**, 125197-40-2; **49**, 77449-99-1; **50**, 116143-05-6; **51**, 116143-06-7; **52**, 116143-08-9; **53**, 116143-09-0; **54**, 118354-72-6; **55**, 116258-17-4; **56**, 116258-16-3; benzylamine, 100-46-9; 3-aminopyrrolidine, 79286-79-6; 2-(fluoromethyl)-piperazine dihydrochloride, 116163-30-5; *N*-methylpiperazine, 109-01-3.