Fluoronaphthyridines as Antibacterial Agents. 4. Synthesis and Structure–Activity Relationships of 5-Substituted-6-fluoro-7-(cycloalkylamino)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids

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A series of 5-substituted-6-fluoro-7-(cycloalkylamino)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids have been prepared and tested for their in vitro and in vivo antibacterial activities. The 5-methyl group gave better in vitro activity with the 1-cyclopropyl appendage, but poorer activity with the 1-*tert*-butyl moiety. With the 1-(2,4-difluorophenyl) substitution, the influence of the 7-cycloalkylamino group was determinant: a (3*S*)-3-aminopyrrolidine was shown to enhance greatly the in vitro and in vivo activity of the 5-methyl derivative. Compound **33** (BMY 43748) was selected as a promising candidate for an improved therapeutic agent.

While positions 1, 7, and 8 of 4-quinolones have been intensively explored, the 5-position has been scarcely studied in the quinolone series.[1-7] As an example, sparfloxacin,[3] a 5-amino-substituted quinolone, was reported as a potent in vitro and in vivo antibacterial derivative. More recently, introduction of a methyl group at the 5-position of the quinolone[1] was shown to increase the in vitro antibacterial activity especially with a 1-cyclopropyl appendage.

In the continuation of our work on 1-*tert*-butylnaphthyridines,[10-12] we were interested in the influence of the 5-alkyl substitution. To obtain good structure–activity relationships (SAR) we have also performed 5-alkyl substitution with 1-cyclopropyl and 1-aryl moieties.

Chemistry

The general method used for the preparation of 4-oxo-5-substituted-naphthyridines is illustrated in Scheme I. Deprotonation of the 2,6-dichloro-5-fluoronicotinic acid with 2 equiv of lithium diisopropylamine (LDA) or methyllithium at low temperature, followed by alkylation with methyl iodide or ethyl iodide, afforded **1a** and **1b**, respectively.[8] The 4-phenylnicotinic acid **1c** was obtained in a one-pot procedure via a 4-(chlorozincio)nicotinic acid derivative by reaction of the carbanion of nicotinic acid with zinc chloride, which was then cross-coupled with phenyl iodide with $Pd(PPh_3)_4$ as a catalyst.[9]

The synthetic pathway from **1** to **5** was performed according to known procedures.[10,11] All the naphthyridines synthesized are listed in Table I. The 5-hydrogen analogues are included for comparison.

Results and Discussion

The in vitro antibacterial activities are disclosed in Table II. In the comparison of 5-methyl vs 5-hydrogen analogues, the 1-substituent proved to be crucial to maintain good in vitro activity as reported recently.[1] With the 1-*tert*-butyl or the 1-fluoro-*tert*-butyl group, addition of a methyl group at the 5-position was detrimental to the in vitro activity regardless of the 7-cycloalkylamine (**8** > **9**, **10** > **11**, **12** > **13** (except against some Gram-negative strains) and **14** > **15**).

However with a 1-cyclopropyl appendage, the 5-methyl derivative showed better in vitro activity than the 5-hydrogen analogue (**17** > **16**, **20** > **19**, and **23** > **22**). Keeping (3*S*)-3-aminopyrrolidine as a 7-substituent and a cyclo-

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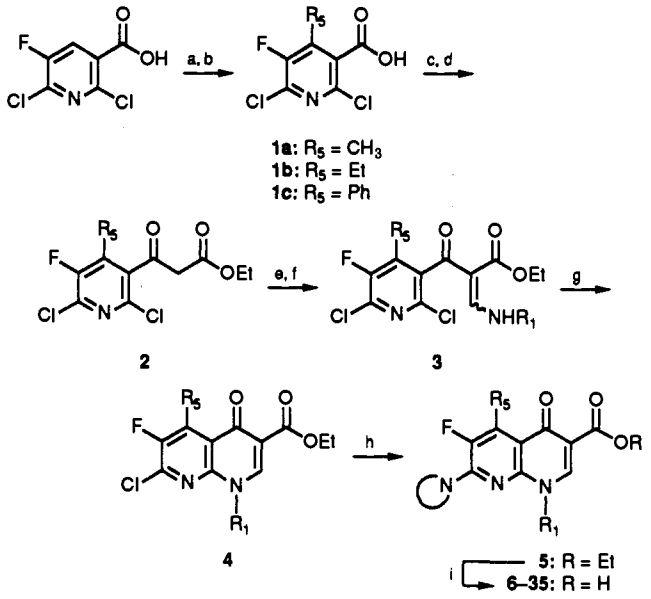
Scheme I[a]



[a] (a) LDA, THF; (b) R_5I, −75 °C, THF (R_5 = CH_3 or Et) or $ZnCl_2$, PhI, $Pd(PPh_3)_4$ for R_5 = Ph; (c) ClCOCOCl or PCl_5; (d) $HO_2CCH_2CO_2Et$, 2BuLi; (e) $HC(OEt)_3$, Ac_2O; (f) R_1NH_2, EtOH; (g) K_2CO_3, CH_3CN, or NaH, dioxane; (h) cyclic amine, DBU, CH_3CN; (i) NaOH or HCl.

propyl group at N-1, the influence of the size of the 5-substituent was studied. The in vitro data clearly demonstrated that addition of a methyl group at C-5 gave at least 2-fold better activity against Gram-positive organisms and similar or even better activity against Gram-negative organisms. On the other hand a dramatic decrease in the in vitro spectrum was observed with an ethyl group (**24** vs **22**) at C-5. The influence of bulkiness was confirmed by replacing the 5-hydrogen with a phenyl group (**25** vs **22**), which gave very poor antibacterial activity over all the in vitro spectrum. In this C-5-substituted series, with a cyclopropyl at N-1, the order of antimicrobial potency was Me > H ≫ Et > Ph.

With the 2,4-difluorophenyl substitution at the position N-1, the results were more varied: the piperazine group at C-7 with a methyl group at C-5 (**26** vs **27**) gave equal or better in vitro activity against Gram-positive strains but was equal or less active against Gram-negative organisms. Concerning the 2,5-diazabicyclo[2.2.1] bridged piperazine analogues, **29** was superior in activity to **28** (Me > H) with Gram-positive organisms, but **28** > **29** (H > Me) with Gram-negative strains. The 2,5-diazabicyclo[2.2.2] bridged piperazine analogue **30** was as active or less active than analogue **29**. The (3*S*)-3-aminopyrrolidine derivative **33** showed better overall in vitro activity with a methyl at C-5 compared to a hydrogen in this position (**31**).

A dozen derivatives were tested for in vivo antibacterial activities by oral administration to mice (Table III). In general, the trends observed in in vitro assays are confirmed in vivo for the 1-*tert*-butyl derivatives. Addition at C-5 of a methyl group to 1-*tert*-butyl naphthyridines resulted in a decrease of the in vivo potency when compared to the 5-hydrogen analogues (**11** < **10** and **13** < **12**).

The in vivo efficacy in the cyclopropyl series was less promising than one would expect when related to the in vitro spectrum. When they were substituted by a 7-piperazine moiety, the 5-methyl derivatives showed equal or lesser in vivo activity compared to their 5-hydrogen counterparts (**17** < **16**). With a bridged piperazine or a (3*S*)-3-aminopyrrolidine at position 7, there was only a small improvement in the in vivo potency, specifically for *Streptococcus* infection, compared to the piperazine (**20** ~ **23** > **17**).

In the 1-(2,4-difluorophenyl) series, the increase in in vitro potency correlated well with the in vivo efficacy, especially for the bridged piperazines **29** and **28** (**29** exhibiting the best anti-*Staphylococcus* property of all the compounds tested). C-5 Methylation of the 7-(3-aminopyrrolidinyl) derivative **33** conferred the same in vivo efficacy as the 5-hydrogen analogue **32** (tosufloxacin), but was slightly better against streptococcal infection. Methylation of the amino group of the pyrrolidine of the derivative **33** (**34**) led to the best anti-*Streptococcus* in vivo activity of all the compounds studied.

Physicochemical properties (aqueous solubility, log *D*) are shown in Table IV. With the 1-*tert*-butyl group series, introduction of a methyl at C-5 (**13** vs **12**), resulted in improved aqueous solubility and a dramatic increase in lipophilicity.

In the cyclopropyl series, addition of a methyl at C-5 led to a decrease in aqueous solubility when a bridged piperazine was appended at C-7 (**20** < **19**). The increase in aqueous solubility and lipophilicity was also observed when N-1 had a 2,4-difluorophenyl group and C-7 had a 3-aminopyrrolidine residue: **33** was twice as soluble as **32** (tosufloxacin). Introduction of the methyl group at C-5 showed a considerable increase in log *D* (difference of 1.12 between **33** and **32**). The highly lipophilic property of **33** may contribute to its excellent in vivo efficacy.

Acute toxicity was measured as the LD_{50} and was within the range of C-5 or non C-5-substituted quinolone analogues (except **30** with a very low LD_{50} after intravenous administration). Structure–activity relationships confirmed the previous results[11,13] that 3-aminopyrrolidine derivatives usually brought higher toxicity than piperazine derivatives.

Preliminary pharmacokinetic studies in mice were carried out on compounds **10**–**13**, **17**, **20**, **23**, **28**, **29**, **32**, **33**, **34**, and **35** (Table V). It was clearly demonstrated that addition of a methyl group at C-5 with 1-*tert*-butyl, 1-cyclopropyl, or 1-(2,4-difluorophenyl) groups gave a boost to the pharmacokinetic parameters, the C_{max}'s and AUC's being at least doubled: **11** vs **10**, **13** vs **12**, **29** vs **28**, and **33** vs **32** (tosufloxacin). On the other hand, urinary recovery decreased with methylation at C-5 (**10** vs **11**, **12** vs **13**, and **32** vs **33**). The highest levels were obtained with derivatives substituted at C-7 with bridged piperazines in the 1-*tert*-butyl and 1-cyclopropyl series (**10** and **20**). In the 5-methyl-1-cyclopropyl series the order of urinary recovery levels was **20** > **23** > **17**. With a 1-(2,4-difluorophenyl) group the best urinary recovery percentage was found with tosufloxacin (**32**). The maximum AUC's were reached with **11**, **29**, and **33**, with equal AUC's after oral

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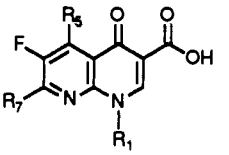
Table I. 1,5,7-Trisubstituted Naphthyridines



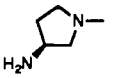
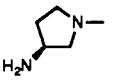
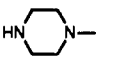
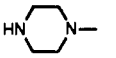
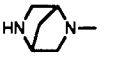
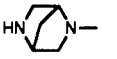
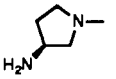
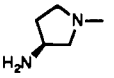
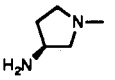
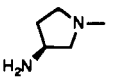
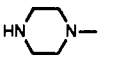
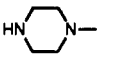
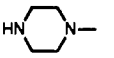
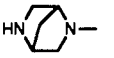
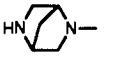
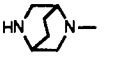
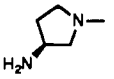
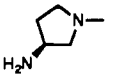
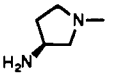
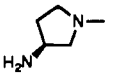
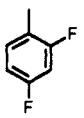
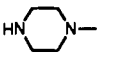
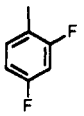
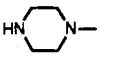
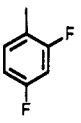
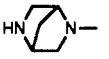
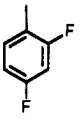
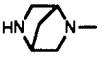
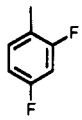
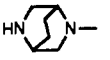
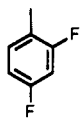
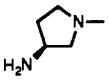
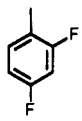
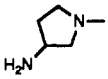
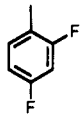
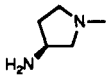
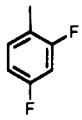
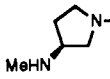
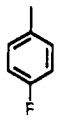
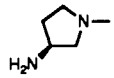
no.	R_1	R_5	R_7[d]	% yield[a]	mp, °C	formula[b]	ref
6	Et	CH_3		30	>260	$C_{16}H_{19}FN_4O_3 \cdot HCl \cdot H_2O$	
7	2-F-Et	CH_3		26	>260	$C_{16}H_{18}F_2N_4O_3 \cdot C_7H_7SO_3H \cdot H_2O$	
8	*t*-Bu	H					10
9	*t*-Bu	CH_3		56	>270	$C_{18}H_{23}FN_4O_3 \cdot HCl \cdot 1.5H_2O$	
10	*t*-Bu	H					11
11	*t*-Bu	CH_3		54	>270	$C_{19}H_{23}FN_4O_3 \cdot HCl \cdot 2H_2O$	
12	*t*-Bu	H					12
13	*t*-Bu	CH_3		37	>260	$C_{18}H_{23}FN_4O_3 \cdot HCl \cdot 1.3H_2O$	
14	F-*t*-Bu	H					13
15	F-*t*-Bu	CH_3		18	>260	$C_{18}H_{22}F_2N_4O_3 \cdot HCl \cdot 2H_2O$	
16	c-Pr	H					14
17	c-Pr	CH_3		41	>270	$C_{17}H_{19}FN_4O_3 \cdot HCl$	
18	c-Pr	Et		91	>250	$C_{18}H_{21}FN_4O_3 \cdot HCl \cdot H_2O$[c]	
19	c-Pr	H					15
20	c-Pr	CH_3		71	>260	$C_{18}H_{19}FN_4O_3CH_3SO_3H \cdot 1.5H_2O$[c]	
21	c-Pr	CH_3		79	>260	$C_{19}H_{21}FN_4O_3 \cdot HCl$[c]	
22	c-Pr	H		41	>260	$C_{16}H_{17}FN_4O_3 \cdot HCl \cdot H_2O$	
23	c-Pr	CH_3		40	>270	$C_{17}H_{19}FN_4O_3 \cdot HCl \cdot H_2O$	
24	c-Pr	Et		66	>250	$C_{18}H_{21}FN_4O_3 \cdot HCl$	
25	c-Pr	Ph		67	262–265	$C_{22}H_{21}FN_4O_3 \cdot CH_3SO_3H$	
26		H					16
27		CH_3		52	>270	$C_{20}H_{17}F_3N_4O_3 \cdot HCl \cdot H_2O$	

Table I (Continued)

no.	R_1	R_5	R_7[d]	% yield[a]	mp, °C	formula[b]	ref
28		H		61	>260	$C_{20}H_{15}F_3N_4O_3 \cdot HCl \cdot H_2O$	
29		CH_3		75	>260	$C_{22}H_{19}F_3N_4O_3 \cdot HCl \cdot H_2O$	
30		CH_3		70	>260	$C_{22}H_{19}F_3N_4O_3 \cdot HCl$	
31		H					17
32		H					16
33		CH_3		71	>265	$C_{20}H_{17}F_3N_4O_3 \cdot HCl \cdot 2H_2O$	
34		CH_3		36	>260	$C_{21}H_{19}F_3N_4O_3 \cdot HCl$	
35		CH_3		54	230	$C_{20}H_{18}F_2N_4O_3 \cdot HCl \cdot H_2O$	

[a] Yields are those obtained from the final step (hydrolysis), including the salt formation. [b] The analyses are within ±0.4% of theoretical values except for 18, 20, and 21. [c] See the Experimental Section. [d] (3*S*)-3-Aminopyrrolidinyl and (1*R*,4*R*)-3,6-diazabicyclo[2.2.1]heptyl.

or intravenous administration for the last two compounds. Longer half-lives were noted with the 5-methyl derivatives as compared to the 5-hydrogen analogues (**11** vs **10**, **13** vs **12**, **29** vs **28**, and **33** vs **32**).

The same trends seen with mice were also observed after administration to dogs (Table VI). Compound **33** displayed the best C_{max}'s and AUC's of all the derivatives tested.

In summary we have demonstrated that the C-5 methyl addition to naphthyridines seemed to be the highest permissible bulkiness (ethyl or phenyl at C-5 decreased the activity) and could lead to an increase in the overall antibacterial potency when the N-1 substitution is cyclopropyl, but to a decrease in the activity when N-1 is a *tert*-butyl group. The 2,4-difluorophenyl substitution at N-1 was shown to afford equal or reduced activity with piperazines or bridged piperazines at C-7 but with enhanced antimicrobial activity when C-7 was a (3*S*)-3-aminopyrrolidine, with improved water solubility and lipophilicity giving good intracellular penetration and very high tissue concentration. Derivative **33** (BMY 43748), which possessed excellent broad-spectrum activity against Gram-positive and Gram-negative pathogens as well as good pharmacokinetic properties, is under preclinical evaluation.

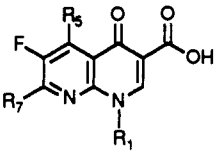
Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR SXC spectrophotometer. ^1H and ^{19}F NMR spectra were recorded 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 60F, 70–230 mesh ASTM. Elemental analyses were performed by the Bristol-Myers Squibb Analytical Department, and the results were analyzed for C, H, and N were within ±0.4% of theoretical values (except for compounds **18**, **20**, and **21**). **18**: Anal. ($C_{18}H_{21}FN_4O_3 \cdot HCl \cdot H_2O$) C, H; N: calcd, 13.50; found, 12.88. **20**: Anal. ($C_{18}H_{19}FN_4O_3 \cdot CH_3SO_3H \cdot 1.5H_2O$) C, H; N: calcd, 11.63; found, 11.15. **21**: Anal. ($C_{19}H_{21}FN_4O_3 \cdot HCl$) H, N; C: calcd, 55.68; found, 55.17.

Microbiology. General Procedures of in Vitro Studies. The in vitro antibacterial activity was studied by a side-by-side comparison with ciprofloxacin (CIP) and determined by a 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 (MIC's) 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.[18]

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



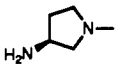
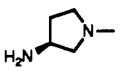
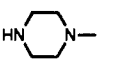
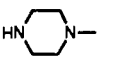
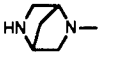
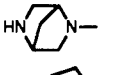
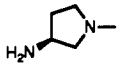
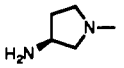
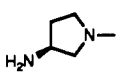
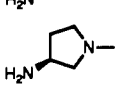
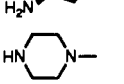
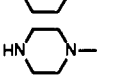
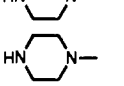
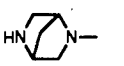
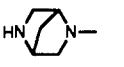
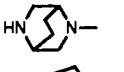
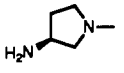
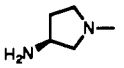
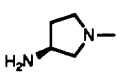
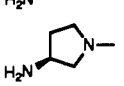
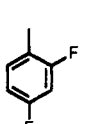
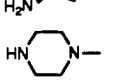
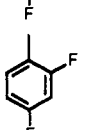
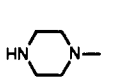
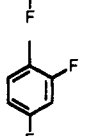
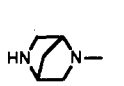
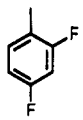
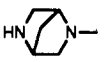
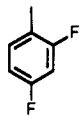
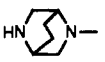
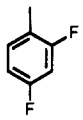
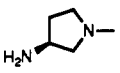
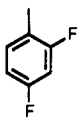
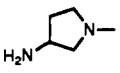
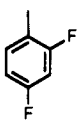
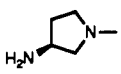
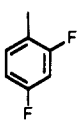
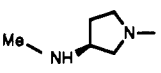
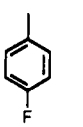
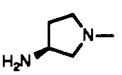
no.	R_1	R_5	R_7	S. pn.	E. fa.	S. au.	E. co.	K. pn.	E. cl.	P. mi.	M. mo.	S. ma.	P. ae.	B. fr.
CIP				0.25	0.5	0.13	0.008	0.06	0.03	0.008	0.008	0.03	0.25	4
6	Et	CH_3		0.5	2	0.016	0.002	0.016	0.008	0.13	0.03	0.13	1	
7	2-F-Et	CH_3		0.5	0.5	0.002	0.001	0.002	0.002	0.03	0.016	0.016	0.25	2
8	*t*-Bu	H		1	1	0.06	0.02	0.03	0.06	0.13	0.06	0.06	0.5	8
9	*t*-Bu	CH_3		1	2	0.03	0.06	0.06	0.25	0.5	0.25	0.25	4	>32
10	*t*-Bu	H		0.13	0.5	0.003	0.008	0.02	0.02	0.06	0.06	0.06	0.25	4
11	*t*-Bu	CH_3		0.25	0.5	0.02	0.03	0.06	0.13	0.25	0.13	0.13	2	32
12	*t*-Bu	H		0.008	0.06	0.004	0.02	0.03	0.03	0.13	0.13	0.25	0.25	1
13	*t*-Bu	CH_3		0.25	0.13	0.004	0.004	0.03	0.03	0.06	0.06	0.13	1	4
14	F-*t*-Bu	H		0.03	4	0.03	0.03	0.03	0.13	0.5	0.06	0.25	1	16
15	F-*t*-Bu	CH_3		2	2	0.25	0.016	0.03	0.25	0.5	0.5	0.5	2	2
16	c-Pr	H			8	0.25	0.03	0.06	0.06	0.25	0.06	0.25	0.5	
17	c-Pr	CH_3		1	1	0.03	0.008	0.02	0.03	0.13	0.06	0.13	0.5	32
18	c-Pr	Et		0.25	16	0.5	0.5	1	1	8	4	1	16	1
19	c-Pr	H			1	0.13	0.06	0.06	0.03	0.06	0.06	0.25	0.25	
20	c-Pr	CH_3		0.13	0.13	0.002	0.002	0.002	0.002	0.016	0.016	0.03	0.25	1
21	c-Pr	CH_3		0.13	0.13	0.03	0.008	0.016	0.06	0.13	0.06	0.13	0.5	16
22	c-Pr	H		0.25	0.25	0.016	0.002	0.004	0.016	0.03	0.004	0.016	0.25	2
23	c-Pr	CH_3		0.13	0.13	0.004	0.002	0.004	0.002	0.008	0.016	0.004	0.25	0.25
24	c-Pr	Et		1	16	1	0.25	0.25	0.25	2	0.5	0.5	4	1
25	c-Pr	Ph		8	64	2	1	2	2	16	8	16	32	125
26		H		0.5	1	0.03	0.016	0.03	0.03	0.06	0.13	0.13	0.5	2
27		CH_3		0.25	1	0.016	0.016	0.03	0.03	0.25	0.13	0.25	1	4
28		H		0.25	0.5	0.016	0.004	0.008	0.016	0.03	0.06	0.06	0.25	1

Table II (Continued)

no.	R_1	R_5	R_7	S. pn.	E. fa.	S. au.	E. co.	K. pn.	E. cl.	P. mi.	M. mo.	S. ma.	P. ae.	B. fr.
29		CH_3		0.06	0.13	0.008	0.008	0.06	0.03	0.06	0.13	0.13	0.5	4
30		CH_3		0.06	0.25	0.008	0.008	0.008	0.008	0.13	0.13	0.5	0.5	4
31		H		0.06	0.13	0.008	0.008	0.008	0.016	0.03	0.06	0.06	0.25	0.5
32 (TOSU)[b]		H		0.06	0.25	0.016	0.004	0.016	0.03	0.03	0.06	0.13	0.25	1
33		CH_3		0.03	0.06	0.002	0.002	0.002	0.002	0.008	0.03	0.03	0.25	0.25
34		CH_3		0.06	0.25	0.008	0.016	0.016	0.03	0.13	0.06	0.25	1	2
35		CH_3		0.03	0.06	0.004	0.002	0.002	0.002	0.008	0.008	0.03	0.25	

[a] Organisms selected for the table are as follows: S. pn., *Streptococcus pneumoniae* A 9585; E. fa., *Enterococcus faecalis* A 9809; S. au., *Staphylococcus aureus* A 9537; E. co., *Escherichia coli* A 15119; K. pn., *Klebsellia pneumoniae* A 9664; E. cl., *Enterobacter cloacae* A 9656; P. mi., *Proteus mirabilis* A 9900; M. mo., *Morganella morganii* A 15153; S. ma., *Serratia marcescens* A 20019; P. ae., *Pseudomonas aeruginosa* A 9843; B. fr., *Bacillus fragilis* A 22862. [b] TOSU = tosufloxacin.

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

	PD_{50},[a] mg/kg				LD_{50},[b] mg/kg	
no.	*S. aureus* A 15090	*S. pneumoniae* A 9585	*E. coli* A 15119	*P. aeruginosa* A 9843	iv	po
CIP	8.0 (5.5–12.2)	>50	1.2 (0.9–1.6)	2.6 (1.8–3.8)	273	5000
10	1.6 (1.1–2.3)	29.7 (12.7–50.3)	1.8 (1.2–2.6)	4.7 (3.2–7.6)	303	5000
11	12.5 (7.9–18.5)			4.1 (2.5–6.5)		
12	1.0 (0.5–1.9)	>25		4.6 (2.5–7.7)	100	350
13	4.1 (2.5–6.3)	>25		25 (14.5–37.2)		
16	7.0 (3.5–11)		0.4 (0.3–0.6)	3.6 (2.1–6.3)		
17	9.6 (6.2–13.5)	>50	1.2 (0.7–2.1)	5.6 (3.8–8.4)		
20	5.4 (3.2–7.9)	43 (38.2–55.6)	0.9 (0.6–1.4)	2.7 (2.0–3.7)	131	1750
23	5.5 (3.3–9.9)	19 (12.8–30.1)	1.8 (1.3–2.5)	2.8 (1.8–4.2)	56	2500
28	9.5 (4.7–16.5)			2.7 (1.3–4.5)		
29	0.7 (0.45–0.9)			1.6 (0.8–2.3)		
30	5.4 (3.5–8.0)	9.5 (5.7–16.2)		1.4 (0.8–2.1)	24	2500
32 (TOSU)	2.1 (1.3–3.0)	11.4 (7.3–18.5)	1.8 (0.6–3.5)	2.9 (1.8–5.3)	81	2500
33	1.7 (1.0–2.7)	7.9 (4.1–12.2)	1.8 (0.5–3.1)	2.2 (1.4–3.6)	84	2500
34	1.8 (1.0–2.8)	4.1 (2.2–7.2)	2.7 (1.9–3.2)	1.8 (1.2–2.5)	94	2500
35	4.2 (2.3–8.6)	14.4 (9.9–20.5)	4.9 (2.9–8.1)	2.9 (1.4–4.7)	94	2500

[a] Dose to protect 50% of mice from lethal infection po (95% confidence limits). [b] See the Experimental Section.

Pharmacokinetics in Mice. Levels of selected compounds in blood and urine samples from mice were determined as previously described.[19]

Pharmacokinetics in Dogs. Plasma and urine levels in dogs

(14) Sanchez, J. P.; Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Nichols, J. B.; Trehan, A. K. Quinolone Antibacterial Agents. Synthesis and Structure–Activity Relationships of 8-Substituted Quinoline-3-carboxylic Acids and 1,8-Naphthyridine-3-carboxylic Acids. *J. Med. Chem.* **1988**, *31*, 983–991.

(15) Kiely, J. S.; Hutt, M. P.; Culbertson, T. P.; Bucsh, R. A.; Worth, D. F.; Lesheski, L. E.; Gogliotti, R. D.; Sesnie, J. A.; Solomon, M.; Mich, T. F. Quinolone Antibacterials: Preparation and Activity of Bridged Bicyclic Analogues of the C_7-Piperazine. *J. Med. Chem.* **1991**, *34*, 656–663.

Table IV. Solubility[a] and log D[a] of Selected Compounds

no.	solubility (mg/mL)	log D
CIP	0.07	−0.70
6	0.03	
8	0.82	−0.33
10	0.08	−0.41
12	0.01	0.04
13	0.57	1.14
14	0.06	−0.56
19	0.09	
20	0.02	0.48
23	0.07	0.78
24	0.07	1.37
29	0.05	0.59
30	0.01	0.40
32 (TOSU)	0.02	0.10
33	0.05	1.22
34	0.01	1.38
35	0.08	0.91

[a] See the Experimental Section.

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

no.	route admin	C_{max}, μg/mL	$t_{1/2}$, min	AUC,[b] μg/mL per h	% UR[c]
CIP	po	6	56	7	3
	iv	22	70	19	25
10	po	10	96	14	34
	iv	13	95	25	39
11	iv	22	186	74	12
12	po	4	66	6	10
13	po	7	170	15	7
	iv	7	170	16	8
17	po	3	164	15	12
	iv	14	74	16	11
20	po	9	77	26	34
	iv	19	90	40	41
23	po	4	160	20	17
	iv	13	160	35	18
28	po	2	103	3	7
	iv	11	89	20	12
29	po	20	143	56	11
	iv	31	125	52	13
32 (TOSU)[d]	po	10	144	36	33
	iv	29	83	33	30
33	po	10	176	60	8
	iv	21	160	64	6
34	po	6			13
35	po	6	197	19	10

[a] See the Experimental Section. All values are accurate to ±50% and have been obtained from duplicate or triplicate experiments. [b] Area under the time–concentration curve. [c] Urinary recovery. [d] TOSU = tosufloxacin.

were determined by microbiological assay. The test organism was *Bacillus subtilis* ATCC 6633, and the standard used was the test substance itself.[13]

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

	C_{max}, μg/mL	$t_{1/2}$, h	AUC[b] μg/mL per h	% UR[c]
CIP	3	3.5	20	17
20	2.6	7	27	7
23	3	3	20	2.5
32	1.3		18	4.5
33	3.3	11	37	3
34	2	20	32	2.5
35	2.1	8	22	1.5

[a] See the Experimental Section. All values are accurate to ±50% and have been obtained from duplicate or triplicate experiments. [b] Area under the time–concentration curve. [c] Urinary recovery.

Solubility Studies. General Studies. A known excess of weight of the compound was shaken overnight at 22 °C with a known volume of pH 7.2 buffer for injection. The contents were filtered, and the clear filtrate was analyzed after appropriate dilution by HPLC (UV absorbance detection).

Distribution Coefficient Studies. A 10-mL solution of 10 μg/mL of the tested compound in pH 7.2 buffer saturated with 1-octanol was injected in 10 mL of 1-octanol saturated with pH 7.2 buffer in a shaking cell at 25 °C. The mixture was stirred for 12 h at 25 °C and centrifuged, and the two phases were separated. The concentration of each phase was determined by HPLC (UV absorbance detection). The logarithm of the coefficient of distribution (log D) was measured as the logarithm of the ratio of the concentration of the organic phase to the concentration of the aqueous phase.

Chemistry. Preparation of 4-Substituted Nicotinic Acids. 2,6-Dichloro-4-methyl-5-fluoronicotinic Acid (1a). A solution of 10 g of 2,6-dichloro-5-fluoronicotinic acid (47.6 mmol) in 220 mL of dry THF was cooled at −70 °C. A solution of MeLi (60 mL, 1.6 M in ether, 96 mmol) was added during 15 min. The reaction mixture was warmed to −30 °C and stirred for 2 h at this temperature. After cooling at −60 °C, 8.6 mL (114 mmol) of methyl iodide was added. Then the reaction mixture was allowed to reach 0 °C for 2 h and treated with water (10 mL). After concentration in vacuo, 500 mL of water were added, and the basic aqueous layer was washed with ether (2 × 150 mL). After acidification (pH = 1) with 1 N HCl, the aqueous layer was extracted with ether (2 × 300 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by crystallization from CH_2Cl_2 to provide 5.69 g (yield 53%) of **1a**: mp 124 °C; ^{1}H NMR (DMSO-d_6) δ 2.31 (d, J_{H-F} = 2 Hz, 3 H). Anal. Calcd for $C_7H_4Cl_2FNO_2$: C, 37.53; H, 1.80; N, 6.25. Found: C, 37.24; H, 1.91; N, 6.21.

2,6-Dichloro-4-ethyl-5-fluoronicotinic Acid (1b). The preparation of this nicotinic acid was accomplished according to the same procedure described above, except that deprotonation of the starting acid was carried out with LDA and that ethyl iodide was used as alkylating agent (yield 34%): ^{1}H NMR (DMSO-d_6) δ 1.16 (t, 3 H, 5-CH_2CH_3), 2.66 (dq, 2 H, 5-CH_2CH_3).

2,6-Dichloro-4-phenyl-5-fluoronicotinic Acid (1c). A solution of 9 mL (22 mmol) of 2.5 M *n*-BuLi in hexanes was added to 25 mL of dry THF, cooled to −25 °C, and treated dropwise with 3.6 mL (20 mmol) of diisopropylamine in 6 mL of THF. The temperature of the solution was then allowed to rise to 5 °C in 1 h. At that time the solution was cooled to −75 °C, and a solution of 2.11 g (10 mmol) of 2,6-dichloro-5-fluoronicotinic acid in 25 mL of dry THF was added dropwise during 1 h. The mixture was kept at −75 °C for 3.5 h. The temperature was then allowed to rise to −60 °C for 20 min and cooled again to −75 °C. A solution of 23 mL (23 mmol) of 1 M zinc chloride in ether was then added during 6 min. The solution was allowed to warm to room temperature for 1 h and kept 15 min at 25 °C. This solution was transferred into a dropping funnel having a rubber septum inlet and was added dropwise to a mixture of 2.45 g (12 mmol) of phenyl iodide and 1.01 g (0.88 mmol) of $Pd(PPh_3)_4$ in 12 mL of dry THF. The dark red solution was stirred overnight, poured into a saturated solution of NH_4Cl, and acidified with 35 mL of 2 N HCl. The aqueous layer was separated and extracted twice with 100 mL of ether. The organic layers were combined and extracted

(16) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. Synthesis and Structure–Activity Relationships of New Arylfluoronaphthyridine Antibacterial Agents. *J. Med. Chem.* **1986**, *29*, 2363–2369.

(17) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Shen, L.; Borodkin, S.; Pernet, A. G. Asymmetric Synthesis and Properties of the Enantiomers of the Antibacterial Agent 7-(3-Aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride. *J. Med. Chem.* **1988**, *31*, 1586.

(18) Behrens, B.; Karber, G. Wie sind Reihenversuche für biologische Auswertungen am zweckmässigsten anzuordnen? *Arch. Exp. Pathol. Pharmakol.* **1935**, *177*, 379–388.

(19) Kessler, R. E.; Bies, M.; Buck, R. E.; Chisholm, D. R.; Pursiano, T. A.; Tsai, Y. H.; Misiek, M.; Price, K. E.; Leitner, F. Comparison of a New Cephalosporin, BMY 28142, with Other Broad-Spectrum β-Lactam Antibiotics. *Antimicrob. Agents Chemother.* **1985**, *27*, 207–216.

twice with 25 mL of a 10% $NaHCO_3$ aqueous solution. The aqueous layers were combined and washed with ether. The combined aqueous layers were cooled, acidified with 4.8 mL of concentrated HCl, and extracted with 60 mL of ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 2.22 g of crude product. It was stirred in 4 mL of toluene and filtered (0.71 g of insoluble starting material), and the filtrate was evaporated and chromatographed over silica gel using CH_2Cl_2–MeOH (97:3) as an eluant. There was obtained 0.33 g (yield 11%) of 1c: mp 159–60 °C; ^1H NMR (DMSO-d_6) δ 7.51 (s, aromatic H); ^{19}F NMR (DMSO-d_6) δ −116.8 (s); IR 2929, 1718, 1365, 1289 cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_2FNO_2$: C, 50.38; H, 2.11; N, 4.90. Found: C, 49.98; H, 2.28; N, 4.45.

As a typical example the preparation of **13** is described.

3-(2,6-Dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionic Acid Ethyl Ester (2a). A mixture of 3 g of 2,6-dichloro-4-methyl-5-fluoronicotinic acid (**1a**) (13.3 mmol) and 2.77 g of PCl_5 (13.3 mmol) was heated at 100 °C for 8 min. Then 10 mL of toluene was added, and the mixture was concentrated in vacuo. Coevaporation with toluene was repeated three times to obtain the crude oily acid chloride. An amount of 2.13 g of diethyl malonate (13.3 mmol) and 1.36 mL of ethanol were dissolved in 9 mL of dry ether. The resulting solution was added to a suspension of 0.32 g (13.3 mmol) of magnesium in 0.68 mL of ethanol containing a few drops of CCl_4. The mixture was refluxed for 2 h to obtain diethyl ethoxymagnesium malonate. After cooling in an ice bath, the solution of the above acid chloride in 15 mL of dry ether was added slowly at 5 °C. After the addition, the ice bath was removed and the reaction was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with 20 mL of water, acidified with 0.75 mL of 1 M H_2SO_4, extracted with ether, dried ($MgSO_4$), and evaporated to dryness. The residue was suspended in 15 mL of water containing 95 mg of 4-toluenesulfonic acid monohydrate. The mixture was refluxed for 2.5 h. After cooling at room temperature, 45 mL of water was added, and the mixture was extracted with ether, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness to give 3.05 g (yield 78%) of **2a** as an oil.

2-[[(1,1-Dimethylethyl)amino]methylene]-3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionic Acid Ethyl Ester (3a) (R_1 = *tert*-Butyl). A solution of 2.81 g (9.55 mmol) of 3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionic acid ethyl ester (**2a**) in 2.4 mL (14.33 mmol) of triethyl orthoformate and 2.25 mL (23.87 mmol) of acetic anhydride was heated at 130 °C for 3 h. Additional triethyl orthoformate (0.8 mL, 4.78 mmol) was added, and the mixture was heated for a further 12 h. The solution was evaporated under reduced pressure to yield 2-(ethoxymethylene)-3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionic acid ethyl ester as an oil (yield 94%).

To a cold solution of 1.85 g (5.3 mmol) of 2-(ethoxymethylene)-3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionic acid ethyl ester in 6.7 mL of ethanol was added 0.84 mL (7.9 mmol) of *tert*-butylamine. After 1 h at room temperature, the solvent was evaporated, and the residue was washed with hexane and chromatographed over silica gel with hexane–AcOEt (80:20) as an eluant to yield 1.22 g (yield 61%) of **3a** (R_1 = *tert*-butyl) as an oil.

7-Chloro-6-fluoro-5-methyl-1-(1,1-dimethylethyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (4a) (R_1 = *tert*-Butyl). To a solution of 1.17 g (3.1 mmol) of 3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxo-2-[[(1,1-dimethylethyl)amino]methylene]propanoic acid ethyl ester in 12 mL of dioxane was added 143 mg (3.1 mmol) of 50% NaH in oil. The reaction mixture was stirred 1 h at room temperature. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and water, dried ($MgSO_4$), and evaporated to provide 1.05 g of crude product, which was crystallized from ether to give 0.6 g (yield 57%) of **4a** (R_1 = *tert*-butyl): mp 178 °C; ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, ester CH_3), 1.87 (s, 9 H, *tert*-butyl), 2.93 (d, 3 H, 5-CH_3), 4.40 (q, 2 H, ester CH_2), 8.87 (s, 1 H, H-2).

7-Chloro-6-fluoro-5-ethyl-1-cyclopropyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (4b) (R_1 = Cyclopropyl). Compound **4b** (R_1 = cyclopropyl) was obtained by the same procedure used for **4a** except that the cyclization of **3b** (R_1 = cyclopropyl, R_5 = CH_3) was run in CH_3CN with K_2CO_3 (yield 60%): mp 156 °C; ^1H NMR (DMSO-d_6) δ 1.03–1.13 (dm, 4 H, cyclopropyl CH_2), 1.19 (t, 3 H, 5-CH_2CH_3), 1.25 (t, 3 H, ester CH_3), 3.37 (dq, 2 H, 5-CH_2CH_3), 3.60 (m, 1 H, cyclopropyl CH), 4.23 (q, 2 H, ester CH_2), 8.48 (s, 1 H, H-2). Anal. Calcd for $C_{16}H_{16}ClFN_2O_3$: C, 56.73; H, 4.76; N, 8.27. Found: C, 56.46; H, 4.85; N, 7.93.

7-Chloro-6-fluoro-5-phenyl-1-cyclopropyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (4c) (R_1 = Cyclopropyl). Compound **4c** (R_1 = cyclopropyl, R_5 = phenyl) was obtained by the same procedure used for the synthesis of **4b** (R_1 = cyclopropyl, R_5 = Me) (yield 59%): mp 253 °C; ^1H NMR (DMSO-d_6) δ 1.02–1.07 (m, 4 H, cyclopropyl CH_2), 1.20 (t, 3 H, ester CH_3), 3.66 (m, 1 H, cyclopropyl CH), 4.15 (q, 2 H, ester CH_2), 7.24 and 7.42 (2 m, 5 H, 5-phenyl), 8.51 (s, 1 H, H-2).

7-Chloro-6-fluoro-5-methyl-1-(2,4-difluorophenyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (4a) (R_1 = 2,4-Difluorophenyl, R_5 = CH_3). Compound **4a** (R_1 = 2,4-difluorophenyl, R_5 = Me) was obtained by the same procedure used for the synthesis of **4b** (R_1 = cyclopropyl, R_5 = Me) (yield 91%): mp 188–189 °C; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3 H, ester CH_3), 2.96 (d, J_{H-F} = 2.6 Hz, 3 H, 5-CH_3), 4.40 (q, 2 H, ester CH_2), 7.08 and 7.39 (2 m, 3 H, H of 1-(2,4-difluorophenyl), 8.43 (s, 1 H, H-2).

7-[(3*S*)-3-Aminopyrrolidinyl]-1-(1,1-dimethylethyl)-6-fluoro-5-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (5a) (R_1 = *tert*-Butyl, R_5 = CH_3, R_7 = (3*S*)-3-Aminopyrrolidinyl). To a suspension of 0.28 g (1.74 mmol) of (3*S*)-(3-aminopyrrolidine) dihydrochloride in 5 mL of CH_3CN was added 0.82 mL (5.53 mmol) of DBU and 0.54 g (1.58 mmol) of 7-chloro-6-fluoro-5-methyl-1-(1,1-dimethylethyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid ethyl ester (**4a**) (R_1 = *tert*-butyl, R_5 = CH_3). The mixture was heated at 70 °C for 1 h. The solution was cooled at room temperature and filtered. The solid was washed with cold CH_3CN and recrystallized from CH_3CN to give a first crop of 0.18 g of **5a**. The filtrate was evaporated under reduced pressure, and the residue was chromatographed over silica gel with CH_2Cl_2–MeOH (elution gradient) to provide a second crop of 0.19 g. Finally, there was obtained 0.37 g (yield 59%) of **5a** (R_1 = *tert*-butyl, R_5 = Me, R_7 = (3*S*)-3-aminopyrrolidinyl): mp 202 °C; ^1H NMR ($CDCl_3$) δ 1.39 (t, 3 H, ester CH_3), 1.85 (s, 9 H, *tert*-butyl), 1.84 and 2.16 (2 m, 2 H, pyrrolidine CH_2), 2.80 (d, 3 H, 5-CH_3), 3.54 (m, 1 H, pyrrolidine CH_2), 3.95 (m, 4 H, pyrrolidine CH_2 and CH), 4.40 (q, 2 H, ester CH_2), 8.71 (s, 1 H, H-2).

7-[(3*S*)-3-Aminopyrrolidinyl]-1-(1,1-dimethylethyl)-6-fluoro-5-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (13) (R_1 = *tert*-Butyl, R_5 = CH_3, R_7 = (3*S*)-3-Aminopyrrolidinyl). A suspension of 0.37 g (0.94 mmol) of 7-[(3*S*)-3-aminopyrrolidinyl]-1-(1,1-dimethylethyl)-6-fluoro-5-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid ethyl ester (**5a**) (R_1 = *tert*-butyl, R_5 = CH_3, R_7 = (3*S*)-3-aminopyrrolidinyl) in 0.94 mL (1.88 mmol) of 2 N NaOH was refluxed for 1 h. The mixture was cooled, filtered, and diluted with water. The pH was brought to 7.8 with 1 N HCl, and the precipitate was collected to afford 0.21 g (yield 63%) of the corresponding amino acid: mp 232 °C. To a suspension of 0.15 g (0.41 mmol) of the above amino acid in 1.5 mL of EtOH was added 0.21 mL (0.42 mmol) of 2 N HCl, and the mixture was heated, filtered, and evaporated to dryness and recrystallized from 2-propanol to give 0.098 g (yield 59%) of **13**: mp >260 °C; ^1H NMR (DMSO-d_6) δ 1.87 (s, 9 H, *tert*-butyl), 2.19–2.30 (m, 2 H, pyrrolidine CH_2), 2.71 (d, 3 H, 5-CH_3), 3.97 (m, 5 H, pyrrolidine CH_2 and CH), 8.40 (br s, 2 H, NH_2), 8.86 (s, 1 H, H-2); IR 3434, 2930, 1701, 1620, 1444 cm^{-1}. Anal. Calcd for $C_{18}H_{23}FN_4O_3 \cdot HCl \cdot 3H_2O$: C, 51.20; H, 6.35; N, 13.26. Found: C, 51.27; H, 6.04; N, 12.91.