7-Azetidinylquinolones as Antibacterial Agents. Synthesis and Structure-Activity Relationships[1]

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A series of novel antibacterial quinolones and naphthyridones has been prepared which contain 7-azetidinyl substituents in place of the usual piperazine or aminopyrrolidine groups. These azetidinyl derivatives were evaluated for in vitro activity by determining minimum inhibitory concentrations against a variety of bacteria. In vivo efficacy in the mouse infection model and blood levels in the mouse were determined for several compounds. The influence on the structure-activity relationships of varying substituents in the azetidine ring and at position 8 (CH, CF, CCl, N) and N-1 (ethyl, fluoroethyl, cyclopropyl, *tert*-butyl, 4-fluorophenyl, and 2,4-difluorophenyl) was also studied. Compounds with outstandingly broad-spectrum activity, particularly against Gram-positive organisms, improved in vivo efficacy, and high blood levels were identified in this work. 7-Azetidinyl-8-chloroquinolones were considered as warranting further development.

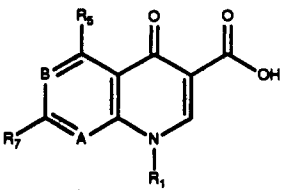
Since the discovery of nalidixic acid (1) 30 years ago,[2] the quinolone, naphthyridine and pyridobenzoxazine antibacterials—collectively known as "quinolones"—have become a significant class of chemotherapeutic agents.[3] The emergence of norfloxacin[4] (5) as a broad-spectrum, orally active quinolone antibacterial was a fortunate structural combination of previously known compounds[3]—the quinolone nucleus of oxolinic acid (2), the piperazine of pipemidic acid (3), and the fluorine of flumequine (4). This represented a new generation of drugs with increased potency. During recent years, attention has increasingly been given to the synthesis of quinolone antibacterials as a source of new agents.[5] A number of new compounds with successful chemical modifications, such as ciprofloxacin (6) and several other significant quinolone antibacterials (7-16), shown in Table I, were prepared and tested. Many of them were found to be useful antibacterial agents, now at an advanced stage of development or already marketed.[6]

Most of these examples contain a 7-piperazinyl or 7-pyrrolidinyl moiety. The greatly increased in vitro Gram-negative activity is characteristic of compounds having a piperazine moiety at C-7. C-7 substitution by diamines which mimic the piperazine group, such as 1-(3-amino or 3-aminomethyl)pyrrolidinyl ring also generally enhances the overall spectrum of activity.[6d,7]

As a continuation of our research project for potent broad-spectrum antibacterial agents that follow the quinolones substituted at the 7-position with azoles such as pyrrole, irloxacin (8),[8] or 4-methylimidazole, E-4345 (9),[9] and a series of (imidazolyl)phenylmethyl substituents attached to the 7-position via a carbon-carbon bond,[10] we have extended these modifications by introducing the rarely used azetidine as a cyclic amine substituent.

Although a few examples of C-7 azetidinyl-substituted quinolones have been reported,[11,12a] neither structure-activity relationships of substituted azetidines nor clinically useful agents (or even promising candidates) appended with an azetidinyl substituent at C-7 have been developed thus far. According to recent structure-activity studies,[12] a preference for five- and six-membered rings has clearly been identified. However, we carried out a theoretical structural analysis of 3-aminoazetidine by semiempirical calculations (mainly AM1) and molecular modeling (Chem-X from Chemical Design).[13] In light of these studies, there appeared to us to be an obvious analogy between aminoazetidine, piperazine, and aminopyrrolidine with regard to molecular geometry, volume, and relative interatomic distance between nitrogen atoms (Figure 1). Moreover, we felt that the introduction of additional substituents would allow modification of several physicochemical aspects and provide further insight into their SARs.

Table I. Previously Described Significant Quinolone Type Antibacterial Agents



compd	name	A	R_1	R_5	B	R_7
1	nalidixic acid	N	C_2H_5	H	CH	CH_3
2	oxolinic acid	CH	C_2H_5	H	$COCH_2O$	
3	pipemidic acid	N	C_2H_5	H	N	*a*
4	flumequine	$C(CH_2)_2CH(CH_3)$		H	CF	H
5	norfloxacin	CH	C_2H_5	H	CF	*a*
6	ciprofloxacin	CH	c-C_3H_5	H	CF	*a*
7	ofloxacin	$COCH_2CH(CH_3)$		H	CF	*b*
8	irloxacin	CH	C_2H_5	H	CF	*c*
9	E-4345	CF	c-C_3H_5	H	CF	*d*
10	lomefloxacin	CF	C_2H_5	H	CF	*e*
11	temafloxacin	CH	*f*	H	CF	*e*
12	tosufloxacin	N	*f*	H	CF	*g*
13	clinafloxacin	CCl	c-C_3H_5	H	CF	*g*
14	fleroxacin	CF	CH_2CH_2F	H	CF	*b*
15	sparfloxacin	CF	c-C_3H_5	NH_2	CF	*h*
16	difloxacin	CH	*i*	H	CF	*b*

[a] 1-Piperazinyl. [b] 4-Methyl-1-piperazinyl. [c] 1-Pyrrolyl. [d] 4-Methyl-1-imidazolyl. [e] 3-Methyl-1-piperazinyl. [f] 2,4-Difluorophenyl. [g] 3-Amino-1-pyrrolidinyl. [h] *cis*-3,5-Dimethyl-1-piperazinyl. [i] 4-Fluorophenyl.

Chemistry

The syntheses of the azetidines **21**, **23**, **26**, and **29** required to prepare the new quinolones are summarized

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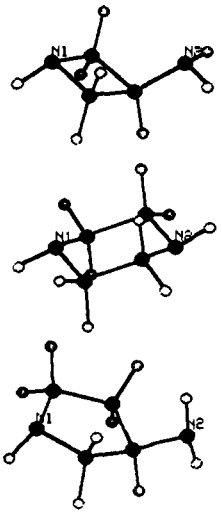
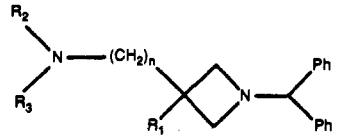


N_1-N_2[a] (Å)	Vol[b] (Å^3)	Surf[c] (Å^2)
3.25	63.8	73.4
2.90	75.9	83.8
3.65	76.3	85.3

Figure 1. AM1 calculated structures and some relevant parameters of 3-aminoazetidine, piperazine, and 3-aminopyrrolidine. [a]Interatomic distance between nitrogens. [b]Van der Waals volume. [c]Van der Waals surface.

in Scheme I. Some of the 3-monosubstituted azetidines had previously been described and were therefore prepared according to the literature.[14] In a similar fashion, the new 3,3-disubstituted azetidines were synthesized via slight modifications of the procedures already published for the monosubstituted type. Thus, stirring epichlorhydrin **17c** and benzhydrylamine in methanol (25 °C, 72 h; reflux, 72 h), via the procedure described by Gaertner,[15] gave the azetidinol **18c**[16] in 85% yield. This served as a quinolone C-7 substituent after hydrogenolysis. Mesylation of the resulting 3-hydroxyazetidine gave **19c** in 96% yield. The reaction of **19c** with sodium cyanide afforded 83% of the nitrile **24c**, which was reduced with lithium aluminum hydride to give **25p** in 75% yield. On the other hand,

Table II. Azetidine Nucleus

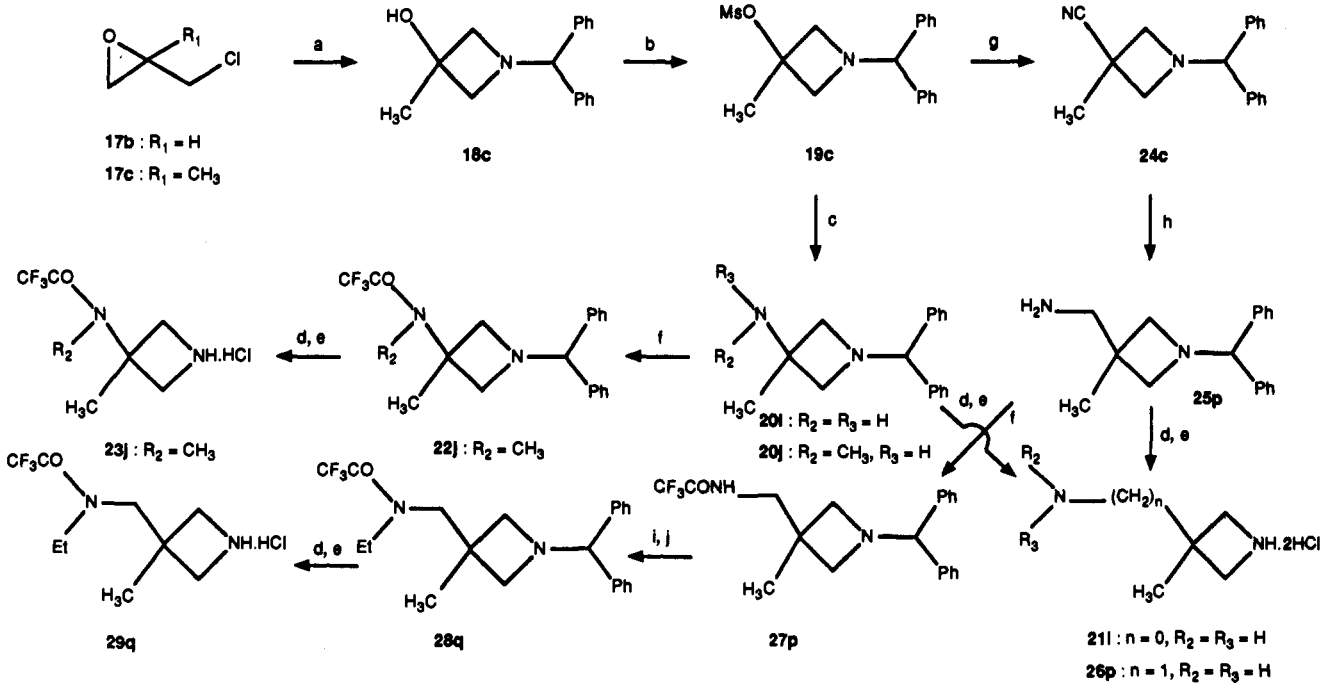


compd	n	R_1	R_2	R_3
20e	0	H	H	H
20f	0	H	Me	H
20g	0	H	Et	H
20h	0	H	Me	Me
20i	0	Me	H	H
20j	0	Me	Me	H
20k	0	Me	Me	Me
20l	0	H	$-(CH_2)_4-$	
20m	0	Me	$-(CH)_4-$	
25n	1	H	H	H
25o	1	H	Et	H
25p	1	Me	H	H
25q	1	Me	Et	H

displacement of the mesylate group of **19c** with ammonium hydroxide or alkylamines allowed compounds **20i–k** to be obtained in good yields. Some of the 3-aminoazetidines summarized in Table II needed to be protected before displacement of the 7-fluoro group of the quinolone in order to avoid reaction of the exocyclic amino group. Thus, the reaction of **20j** with trifluoroacetic anhydride provided compound **22j** in 80% yield. Removal of the benzhydryl group was achieved in all cases by protonation of the heterocyclic nitrogen atom, followed by hydrogenolysis over palladium hydroxide in ethanol. By this procedure,[17] the corresponding salts **21**, **23**, **26**, and **29** were obtained and could be condensed with the quinolone nuclei.

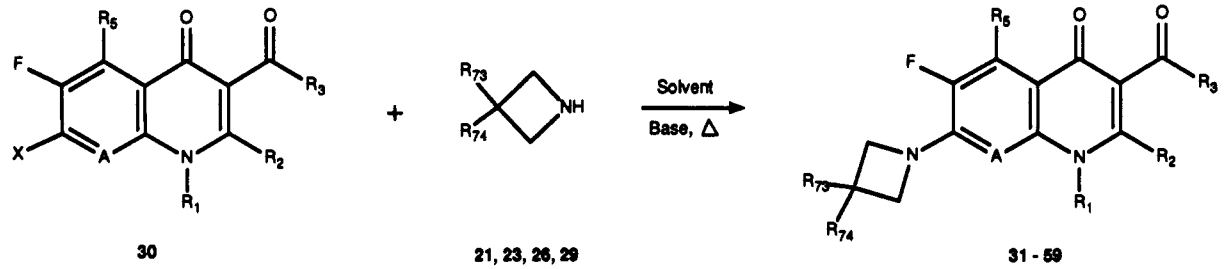
The title compounds **31–59** were synthesized as summarized in Scheme II. All the nuclei **30** reported in this study were prepared in a straightforward fashion according to previously published chemistry,[18] or by slight modifications of the same. The regiospecific nucleophilic aromatic substitution at C-7 of 6,7-difluoroquinolones, 6,7-

Scheme I[a]



[a] (a) Ph_2CHNH_2, CH_3OH; (b) MsCl, Et_3N, CH_2Cl_2; (c) R_2R_3NH; (d) HCl, Et_2O, 0 °C; (e) H_2, $Pd(OH)_2/C$, EtOH; (f) $(CF_3CO)_2O$, $CHCl_3$; (g) NaCN, DMF; (h) $LiAlH_4$, THF; (j) NaH, DMF; (j) EtI.

Scheme II



difluoroisothiazoloquinolones, and 7-chloro-6-fluoronaphthyridines **30** with the appropriate azetidine **21**, **23**, **26**, or **29** (Scheme II) proceeded smoothly at temperatures between 80 °C and reflux conditions, according to the general procedures A–F, to give compounds **31–59**. When a trifluoroacetylated intermediate was used, this protecting group was removed in the final step. The physical properties of compounds **a–h** and **j–w** and the structures of their substituents are summarized in Table III, and the physical properties of 7-(3-amino-3-methyl-1-azetidinyl)-quinolones **i** in Table IV.

Results and Discussion

The in vitro antibacterial activity of compounds **31–59** was evaluated against a variety of Gram-positive and Gram-negative bacteria. These activities were determined by conventional agar dilution procedures, and the results of these assays are summarized in Tables V and VI. Data for five Gram-positive and six Gram-negative bacteria are reported in the tables as representative examples. The data for ciprofloxacin (**6**) are included for comparison.

Among a series of quinolones featuring 7-azetidinyl substitution without a basic side chain (**31a–d**, **32a–d**, **32r–v**, and **33b**), only the 3-hydroxyazetidinyl derivatives, particularly the 8-fluoro **32b** and **33b**, showed comparable activity to that of **6** against Gram-negative bacteria. Addition of an alkyl group to **32b** to give the 3-hydroxy-3-methyl **32c** and the 3-hydroxy-3-ethyl **32d** derivatives resulted in a significant overall decrease in activity. However, against Gram-positive bacteria, 3-hydroxyazetidines **31a–d**, **32b**, and **33b** and their derivatives **32u** and **32v** compared very favorably with **6**, except against *Streptococcus faecalis*.

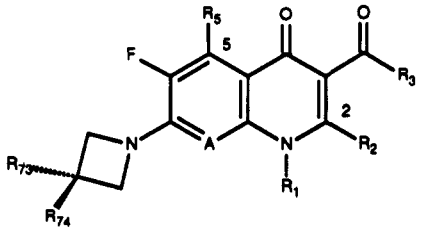
The generally excellent activity conferred by a basic side chain to pyrrolidine group, in addition to the well-established piperazine, as well as our own computational calculations,[13] prompted us to synthesize and test 7-(3-aminoazetidinyl)quinolones (**e–m**) and 7-(3-(aminomethyl)azetidinyl)quinolones (**n–q**) (Table III). The in vitro antibacterial activities of various analogues having either 3-aminoazetidine (**31e–36e**) or 3-amino-3-methylazetidine (**31i–36i**) appended at the 7-position of quinolones are shown in Tables V and VI. In both series of compounds the activity fluctuates within a narrow range, showing a similar relationship in that they were about equipotent. Nevertheless, the (3-methylazetidinyl)isothiazoloquinolone **36i** was slightly more active than its analogue **36e**. Noteworthy, however, is the fact that both compounds, **36e** and **36i**, showed a 2–8-fold enhancement in in vitro activity on Gram-positive and Gram-negative strains in comparison with **6**, with the exception of *Pseudomonas aeruginosa*. On the other hand, 3-(dimethylamino)-azetidine **31h** and **32h**, 3-(aminomethyl)azetidine **31n** and **32n**, and 3-((ethylamino)methyl)azetidine **31o** and **32o** series were equipotent in comparison with their 3-methyl counterparts **31k** and **32k**, **31p** and **32p**, and **31q** and **32q**, respectively. Conversely, a different effect was observed in the 3-methylamino series; the 3-methyl analogues were 2–4 times less active: **31j** < **31f**, **32j** < **32f**, and **35j** < **35f**. Similarly, the presence of a 1-(2,4-difluorophenyl) group on the quinolone ring and 3-aminoazetidine in the 7-position also increases the activity 2–4-fold in comparison with their 3-amino-3-methylazetidine counterparts: **45i** < **45e** and **46i** < **46e**.

In order to further define the effect of varying the C-3 substitution of the azetidine ring on activity, a series of quinolones **31** and **32** were tested, different amines being inserted into the C-3 position of the C-7 azetidine ring. From the data of the series **e** and **i** (amino), **f** and **j** (methylamino), **g** (ethylamino), **h** and **k** (dimethylamino), **n** and **p** (aminomethyl), and **o** and **q** (ethylaminomethyl), it follows that the contribution of the substituent to activity of the 3-monosubstituted azetidinyl derivatives **31–32** increases in the order $H_2NCH_2 \simeq EtNHCH_2 < EtNH \leq Me_2N < MeNH = NH_2$. The in vitro activity in the 3,3-disubstituted azetidinyl series appended with a 3-methyl group increases in the order $H_2NCH_2 \simeq EtNHCH_2 \simeq Me_2N < MeNH < NH_2$. The most interesting compounds in these series (**31e**, **31f**, **31i**, **32e**, **32f**, and **32i**) are essentially equipotent to **6** against enterobacteriaceae, but 2–4-fold less active against *P. aeruginosa*. However, the 3-amino compounds (**31e**, **31i**, **32e**, and **32i**) resulted in a general doubling of Gram-positive potency in comparison with **6**.

The structure–activity relationships (SARs) of the N-1 substitution in a series of analogues not substituted at C-8 (**31i**, **38i**, **43i**, **48i**, **52i**, and **55i**), with a fluoro appended at C-8 (**32i**, **39i**, **44i**, **49i**, **53i**, and **56i**), or with a chloro at C-8 (**34i**, **41i**, **46i**, **50i**, and **57i**) show the following increasing trend: 2-fluoroethyl ≤ ethyl < *tert*-butyl ≤ 4-fluorophenyl ≤ 2,4-difluorophenyl < cyclopropyl. This observation indicates that cyclopropyl is the most effective substituent here, as has been shown in numerous other studies[12b,19,20] for C-7 substituted quinolones other than azetidines.

Summarizing, the in vitro activity of the **e** (3-amino), **f** (3-methylamino), and **i** (3-amino-3-methyl) series possessing cyclopropyl or 2,4-difluorophenyl N-1 groups resulted on the whole in a broad spectrum of activity, and they compare very favorably with **6**. Against Gram-negative bacteria, compounds **36e** and **36i** (isothiazolone derivatives), **33e**, **33i**, and **45e** (5-amino-8-fluoro derivatives), and **46e**, **34f**, and **46f** (8-chloro derivatives) are essentially as active as **6**, but most notably show a 2–8-fold enhancement of in vitro activity against Gram-positive species.

Table III. Synthetic and Physical Data of the Quinolone Antibacterials Prepared for This Study[a]

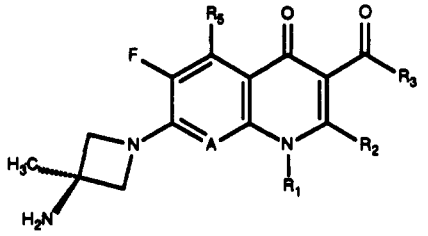


compd	A	R_1	R_2	R_3	R_5	R_{73}	R_{74}	mp, °C	analyses[b]	method (% yield)[c]	NMR, δ (DMSO-d_6, TFA) C_2H[d]	C_5H[e]
31a	CH	c-C_3H_5	H	OH	H	H	H	291–294	$C_{16}H_{15}FN_2O_3 \cdot 0.3H_2O$	A (41)	8.57	7.78
31b	CH	c-C_3H_5	H	OH	H	OH	H	296–298	$C_{16}H_{15}FN_2O_4$	A (27),	8.53	7.70
31c	CH	c-C_3H_5	H	OH	H	OH	Me	303–308	$C_{17}H_{17}FN_2O_4 \cdot 1.2H_2O$	A (98)	8.52	7.68
31d	CH	c-C_3H_5	H	OH	H	OH	Et	284–287	$C_{18}H_{19}FN_2O_4$	A (95)	8.55	7.73
31e	CH	c-C_3H_5	H	OH	H	NH_2	H	246–247	$C_{16}H_{16}FN_3O_3$	A (58)	8.56	7.77
31f	CH	c-C_3H_5	H	OH	H	NHMe	H	245–249	$C_{17}H_{16}FN_3O_3 \cdot 1.0H_2O$	B (39)	8.56	7.76
31g	CH	c-C_3H_5	H	OH	H	NHEt	H	220–224	$C_{18}H_{20}FN_3O_3 \cdot 0.7H_2O$	B (67)	8.60	7.85
31h	CH	c-C_3H_5	H	OH	H	NMe_2	H	255–261	$C_{18}H_{20}FN_3O_3$	A (88)	8.56	7.76
31j	CH	c-C_3H_5	H	OH	H	NHMe	Me	>300	$C_{18}H_{20}FN_3O_3 \cdot 0.4H_2O$	B (71)	8.60	7.75
31k	CH	c-C_3H_5	H	OH	H	NMe_2	Me	298–301	$C_{19}H_{22}FN_3O_3 \cdot 0.5H_2O$	A (100)	8.60	7.85
31n	CH	c-C_3H_5	H	OH	H	CH_2NH_2	H	234–239	$C_{17}H_{16}FN_3O_3 \cdot 1.1H_2O$	B (59)	8.55	7.75
31o	CH	c-C_3H_5	H	OH	H	CH_2NHEt	H	200–203	$C_{19}H_{22}FN_3O_3 \cdot 0.6H_2O$	B (65)	8.52	7.69
31p	CH	c-C_3H_5	H	OH	H	CH_2NH_2	Me	274–279	$C_{18}H_{20}FN_3O_3 \cdot 0.9H_2O$	B (76)	8.55	7.75
31q	CH	c-C_3H_5	H	OH	H	CH_2NHEt	Me	221–226	$C_{20}H_{24}FN_3O_3 \cdot 0.6H_2O$	B (41)	8.55	7.75
31w	CH	c-C_3H_5	H	OH	H	N(Me)CH_2COMe	Me	210–214	$C_{21}H_{24}FN_3O_4 \cdot 0.3H_2O$	F (45)	8.64	7.94
32a	CF	c-C_3H_5	H	OH	H	H	H	289–293	$C_{16}H_{14}F_2N_2O_3 \cdot 1.2H_2O$	A (88)	8.58	7.70
32b	CF	c-C_3H_5	H	OH	H	OH	H	286–288	$C_{16}H_{14}F_2N_2O_4 \cdot 0.3H_2O$	A (97)	8.55	7.75
32c	CF	c-C_3H_5	H	OH	H	OH	Me	290–294	$C_{17}H_{16}F_2N_2O_4 \cdot 0.5H_2O$	A (97)	8.56	7.66
32d	CF	c-C_3H_5	H	OH	H	OH	Et	257–259	$C_{18}H_{18}F_2N_2O_4 \cdot 0.5H_2O$	A (94)	8.52	7.58
32e	CF	c-C_3H_5	H	OH	H	NH_2	H	214–216	$C_{18}H_{15}F_2N_3O_3 \cdot 0.1H_2O$	B (21)	8.50	7.50
32f	CF	c-C_3H_5	H	OH	H	NHMe	H	270–272	$C_{17}H_{17}F_2N_3O_3 \cdot 0.3H_2O$	B (63)	8.58	7.66
32g	CF	c-C_3H_5	H	OH	H	NHEt	H	222–227	$C_{18}H_{19}F_2N_3O_3 \cdot 0.5H_2O$	B (64)	8.58	7.71
32h	CF	c-C_3H_5	H	OH	H	NMe_2	H	256–260	$C_{18}H_{19}F_2N_3O_3 \cdot 0.2H_2O$	A (88)	8.57	7.68
32j	CF	c-C_3H_5	H	OH	H	NHMe	Me	>300	$C_{18}H_{19}F_2N_3O_3 \cdot 0.1H_2O$	B (90)	8.60	7.75
32k	CF	c-C_3H_5	H	OH	H	NMe_2	Me	280–284	$C_{19}H_{21}F_2N_3O_3$	A (92)	8.62	7.76
32l	CF	c-C_3H_5	H	OH	H	$N(CH_2)_4$	H	224–227	$C_{20}H_{21}F_2N_3O_3$	A (90)	8.57	7.78
32m	CF	c-C_3H_5	H	OH	H	$N(CH)_4$	Me	249–252	$C_{21}H_{19}F_2N_3O_3$	E (92)	8.66	7.7
32n	CF	c-C_3H_5	H	OH	H	CH_2NH_2	H	190–195	$C_{17}H_{17}F_2N_3O_3 \cdot 0.4H_2O$	B (58)	8.55	7.71/
32o	CF	c-C_3H_5	H	OH	H	CH_2NHEt	H	237–242	$C_{19}H_{21}F_2N_3O_3$	B (51)	8.50	7.60
32p	CF	c-C_3H_5	H	OH	H	CH_2NH_2	Me	268–270	$C_{18}H_{19}F_2N_3O_3 \cdot 1.5H_2O$	B (74)	8.55	7.65
32q	CF	c-C_3H_5	H	OH	H	CH_2NHEt	Me	250–255	$C_{20}H_{23}F_2N_3O_3 \cdot 0.8H_2O$	B (56)	8.55	7.63
32r	CF	c-C_3H_5	H	OH	H	CO_2H	H	251–255	$C_{17}H_{14}F_2N_2O_5 \cdot 1.3H_2O$	A (28)	8.55	7.65
32s	CF	c-C_3H_5	H	OH	H	$CONH_2$	H	295–298	$C_{17}H_{15}F_2N_3O_4 \cdot 1.4H_2O$	A (66)	8.60	7.55/
32t	CF	c-C_3H_5	H	OH	H	CN	H	>325	$C_{17}H_{13}F_2N_3O_3 \cdot 0.2H_2O$	C (27)	8.60	7.75
32u	CF	c-C_3H_5	H	OH	H	OAc	H	259–262	$C_{18}H_{16}F_2N_2O_5 \cdot 0.3H_2O$	D (68)	8.60	7.70
32v	CF	c-C_3H_5	H	OH	H	OMs	H	240–244	$C_{17}H_{16}F_2N_2O_6S$	D (96)	8.57	7.68
33b	CF	c-C_3H_5	H	OH	NH_2	OH	H	271–275	$C_{16}H_{15}F_2N_3O_4 \cdot 0.7H_2O$	A (85)	8.43	
33e	CF	c-C_3H_5	H	OH	NH_2	NH_2	H	243–245	$C_{16}H_{16}F_2N_4O_3$	A (80)	8.40	
34e	CCl	c-C_3H_5	H	OH	H	NH_2	H	205–208	$C_{16}H_{15}FClN_3O_3 \cdot 0.4H_2O$	A (94)	8.73	7.74
34f	CCl	c-C_3H_5	H	OH	H	NHMe	H	249–251	$C_{17}H_{17}FClN_3O_3 \cdot 0.6H_2O$	B (58)	8.73	7.73
35f	N	c-C_3H_5	H	OH	H	NHMe	H	250–253	$C_{16}H_{17}FN_4O_3 \cdot 0.4H_2O$	B (66)	8.56	7.97
35h	N	c-C_3H_5	H	OH	H	NMe_2	H	249–251	$C_{17}H_{19}FN_4O_3 \cdot 0.7H_2O$	A (93)	8.59	8.04
35j	N	c-C_3H_5	H	OH	H	NHMe	Me	283–286	$C_{17}H_{19}FN_4O_3 \cdot 1.2H_2O$	B (61)	8.54	8.00
36e	CH	c-C_3H_5	-SNH-		H	NH_2	H	270 dec	$C_{16}H_{15}FN_4O_2S \cdot 0.9H_2O$	A (93)		7.60
36f	CH	c-C_3H_5	-SNH-		H	NHMe	H	270 dec	$C_{17}H_{17}FN_4O_2S$	B (89)		7.71
36g	CH	c-C_3H_5	-SNH-		H	NHEt	H	231–236	$C_{18}H_{19}FN_4O_2S \cdot 0.5H_2O$	B (71)		7.69
36h	CH	c-C_3H_5	-SNH-		H	NMe_2	H	287 dec	$C_{18}H_{19}FN_4O_2S$	A (97)		7.70
36j	CH	c-C_3H_5	-SNH-		H	NHMe	Me	>300	$C_{18}H_{19}FN_4O_2S \cdot 0.7H_2O$	B (93)		7.80
40e	CF	C_2H_5	H	OH	NH_2	NH_2	H	236–238	$C_{15}H_{16}F_2N_4O_3 \cdot 1.2H_2O$	A (85)	8.59	
45e	CF	2,4-F_2Ph	H	OH	NH_2	NH_2	H	224–227	$C_{19}H_{14}F_4N_4O_3 \cdot 0.3H_2O$	A (83)	8.30	
46e	CCl	2,4-F_2Ph	H	OH	H	NH_2	H	213–217	$C_{19}H_{13}F_3ClN_3O_3 \cdot 0.6H_2O$	A (78)	8.56	7.91
46f	CCl	2,4-F_2Ph	H	OH	H	NHMe	H	210–220	$C_{20}H_{15}F_3ClN_3O_3 \cdot 0.1H_2O$	B (70)	8.55	7.90
47e	N	2,4-F_2Ph	H	OH	H	NH_2	H	236–241	$C_{18}H_{13}F_3N_4O_3 \cdot 0.4H_2O$	A (71)	8.80	8.07
52j	CH	t-C_4H_9	H	OH	H	NHMe	Me	251–253	$C_{19}H_{24}FN_3O_3$	B (57)	8.81	7.90
54j	N	t-C_4H_9	H	OH	H	NHMe	Me	>300	$C_{18}H_{23}FN_4O_3 \cdot 0.7H_2O$	B (51)	8.82	8.00

[a] Abbreviations: c-C_3H_5 = cyclopropyl, 2,4-F_2Ph = 2,4-difluorophenyl, Me = methyl, Et = ethyl, t-C_4H_9 = *tert*-butyl, Ac = acetyl, Ms = methylsulfonyl, $N(CH_2)_4$ = 1-pyrrolidinyl, $N(CH)_4$ = 1-pyrrolyl. [b] C, H, and N analyses where within ±0.4% of the theoretical values, except as otherwise noted. [c] Yields are those obtained from the coupling step to final product, including deprotections when appropriate. [d] Singlet. [e] Doublet. / Multiplet.

In order to determine in vivo efficacy, several of these compounds were evaluated in mouse protection tests. **6** was used as a reference compound. Data on oral administration are given for *Staphylococcus aureus*, *P. aeruginosa*, and *Escherichia coli* (Table VII). Orally, most of the compounds shown in Table VII exhibit better activity against *E. coli* than **6**, and half of them also show better activity than this compound against *P. aeruginosa*. How-

Table IV. 7-(3-Amino-3-methyl-1-azetidinyl)quinolones[a]



compd	A	R_1	R_2	R_3	R_5	mp, °C	analyses[b]	method (% yield)[c]	NMR, δ (DMSO-d_6, TFA) C_2H[d]	NMR, δ (DMSO-d_6, TFA) C_5H[e]
31i	CH	c-C_3H_5	H	OH	H	293–295	$C_{17}H_{16}FN_3O_3 \cdot 0.8H_2O$	B (35)	8.55	7.75
32i	CF	c-C_3H_5	H	OH	H	298–300	$C_{17}H_{17}F_2N_3O_3 \cdot 1.2H_2O$	A (87)	8.61	7.74
33i	CF	c-C_3H_5	H	OH	NH_2	243–247	$C_{17}H_{18}F_2N_4O_3$	A (92)	8.42	
34i	CCl	c-C_3H_5	H	OH	H	284–285	$C_{17}H_{17}ClFN_3O_3 \cdot 0.2H_2O$	A (85)	8.70	7.70
35i	N	c-C_3H_5	H	OH	H	285–287	$C_{16}H_{17}FN_4O_3 \cdot 0.9H_2O$	A (75)	8.59	8.00
36i	CH	c-C_3H_5	-SNH-		H	297–302	$C_{17}H_{17}FN_4O_2S$	A (98)		7.72
37i	CF	c-C_3H_5	-SNH-		H	294–300	$C_{17}H_{16}F_2N_4O_2S \cdot 0.8H_2O$	A (92)		7.62
38i	CH	C_2H_5	H	OH	H	280–283	$C_{16}H_{16}FN_3O_3 \cdot 0.6H_2O$	B (36)	8.87	7.82
39i	CF	C_2H_5	H	OH	H	293–296	$C_{16}H_{17}F_2N_3O_3 \cdot 0.9H_2O$	B (35)	8.77	7.76
40i	CF	C_2H_5	H	OH	NH_2	274–279	$C_{16}H_{18}F_2N_4O_3 \cdot 0.5H_2O$	A (83)	8.60	
41i	CCl	C_2H_5	H	OH	H	280–282	$C_{16}H_{17}ClFN_3O_3 \cdot 1.4H_2O$	A (85)	8.75	7.75
42i	N	C_2H_5	H	OH	H	269–272	$C_{15}H_{17}FN_4O_3 \cdot 1.4H_2O$	A (76)	8.85	7.89
43i	CH	2,4-F_2Ph	H	OH	H	210–216	$C_{20}H_{16}F_3N_3O_3$	B (28)	8.70	7.70[f]
44i	CF	2,4-F_2Ph	H	OH	H	185–186	$C_{20}H_{15}F_4N_3O_3 \cdot 1.4H_2O$	B (13)	8.62	7.70[f]
45i	CF	2,4-F_2Ph	H	OH	NH_2	256–259	$C_{20}H_{16}F_4N_4O_3 \cdot 0.6H_2O$	A (81)	8.31	
46i	CCl	2,4-F_2Ph	H	OH	H	254–258	$C_{20}H_{15}ClF_3N_3O_3 \cdot 0.4H_2O$	A (87)	8.59	7.89
47i	N	2,4-F_2Ph	H	OH	H	244–248	$C_{19}H_{15}F_3N_4O_3 \cdot 1H_2O$	A (79)	8.82	8.10
48i	CH	CH_2CH_2F	H	OH	H	265–270	$C_{16}H_{17}F_2N_3O_3$	B (34)	8.78	7.81
49i	CF	CH_2CH_2F	H	OH	H	281–284	$C_{16}H_{16}F_3N_3O_3 \cdot 0.3H_2O$	B (45)	8.73	7.66
50i	CCl	CH_2CH_2F	H	OH	H	275–277	$C_{16}H_{16}ClF_2N_3O_3 \cdot 1.2H_2O$	A (85)	8.80	7.80
51i	N	CH_2CH_2F	H	OH	H	279–286	$C_{15}H_{16}F_2N_4O_3 \cdot 1.0H_2O$	A (73)	8.80	8.09
52i	CH	*t*-C_4H_9	H	OH	H	243–248	$C_{18}H_{22}FN_3O_3 \cdot 0.7H_2O$	A (81)	8.88	7.93
53i	CF	*t*-C_4H_9	H	OH	H	>280	$C_{18}H_{21}F_2N_3O_3 \cdot 0.1H_2O$	A (77)	8.62	7.80
54i	N	*t*-C_4H_9	H	OH	H	230–234	$C_{17}H_{21}FN_4O_3 \cdot 0.7H_2O$	A (73)	8.86	8.09
55i	CH	4-FPh	H	OH	H	270–276	$C_{20}H_{17}F_2N_3O_3$	B (51)	8.48	7.55[f]
56i	CF	4-FPh	H	OH	H	272–277	$C_{20}H_{16}F_3N_3O_3 \cdot 0.1H_2O$	B (60)	8.36	7.7[f]
57i	CCl	4-FPh	H	OH	H	256–259	$C_{20}H_{16}ClF_2N_3O_3 \cdot 0.1H_2O$	A (86)	8.46	7.88
58i	N	4-FPh	H	OH	H	258–260	$C_{19}H_{16}F_2N_4O_3$	A (78)	8.64	8.10
59i	$COCH_2CH(CH_3)$		H	OH	H	>300	$C_{17}H_{16}FN_3O_4 \cdot 1.1H_2O$	A (70)	8.66	7.47

[a] Abbreviations: c-C_3H_5 = cyclopropyl, 2,4-F_2Ph = 2,4-difluorophenyl, *t*-C_4H_9 = *tert*-butyl, 4-FPh = 4-fluorophenyl. [b–f] See Table III.

ever, the most noteworthy feature of the selected compounds shown in Table VII is the enhancement of the efficacy in systemic infections due to *S. aureus* in mice when compared with the standard quinolone **6**. Of particular interest are 16 compounds exhibiting activities 4–40 times greater than that of **6**.

It has been previously noted that the halogen at 8-position improves in vivo efficacy for piperazinyl and aminopyrrolidinyl derivatives,[12c,21] owing to improved oral absorption. The results in Table VII confirm this reported trend with regard to quinolones with an azetidine moiety. In this connection, series **34** and **57** (8-chloro) and series **32** and **56** (8-fluoro) displayed an overwhelming efficacy when compared with series **31** and **55** (8-unsubstituted), respectively. The 8-chloro-substituted compounds showed superior overall in vitro and in vivo activities in comparison with their 8-fluoro counterparts. This behavior differs from that previously observed in the 7-(3-aminopyrrolidinyl) quinolones,[7] which showed better in vitro activity of the 8-chloro derivatives with regard to 8-fluoro derivatives, while in vivo oral efficacy was higher in 8-fluoro-substituted compounds. A number of naphthyridines (**35i**, **35j**, **47e**, **47i**, and **58i**) in which C-8 is replaced by a nitrogen atom had outstanding in vivo efficacy, most notably in infections due to *S. aureus*. Finally, the 3-aminoazetidinyl (series **e** and **i**) and 3-(methylamino)azetidinyl (series **f** and **j**) quinolones, two of the most potent members of this series in vitro, demonstrated the best in vivo activity.

In conclusion, the in vivo efficacy of the 1-cyclopropyl derivative **34f** was less promising against *S. aureus* than one would expect from its in vitro spectrum, although it was somewhat more potent than **6** in systemic infections by Gram-negative microorganisms, *E. coli* and *P. aeruginosa*. Conversely, the 1-cyclopropyl derivative **34e** displayed better in vivo efficacy than would be expected from its in vitro activity. In the 1-(2,4-difluorophenyl) series the increase in in vitro potency correlated well with the in vivo efficacy, especially for the monosubstituted azetidines **46e** and **46f** (**46f** was twice as potent as **6** against *E. coli* and *P. aeruginosa*, and 35 times as potent against *S. aureus*). The chloro group appended at C-8 also increased the overall in vivo efficacy when the C-7 group is 3-amino-3-methyl-1-azetidinyl in compounds such as **34i**, **46i**, and **57i**, which exhibit excellent potency.

Results of preliminary pharmacokinetic studies in mice of selected compounds are given in Table VIII. Analogous data for **6** are provided for comparison. Most of the selected compounds of the present series have larger areas under the plasma level curves than the reference compound. The maximum AUCs corresponded to naphthyridines and C-8 fluoro-substituted quinolones. On the basis of the data from 1-cyclopropylquinolones and naphthyridines of the series **f** (3-methylamino), **i** (3-amino-3-methyl), and **j** (3-methyl-3-methylamino), it follows that the contribution of the 8-position substituent to oral absorption increases in the order 8-CCl < 8-CH < 8-CF

Table V. In Vitro Antibacterial Activity of 7-Azetidinyl-Substituted Quinolones (MIC, μg/mL)[a,b]

compd	Bs	Bc	Sf	Sa	Se	Pa	Mm	Pv	Kp	Ec	Ecl
31a	0.015	0.06	2	0.06	0.06	2	0.25	0.06	0.015	0.12	0.12
31b	0.015	0.12	1	0.12	0.12	2	0.25	0.12	0.12	0.12	0.12
31c	0.06	0.12	1	0.12	0.12	2	0.25	0.12	0.06	0.25	0.12
31d	0.015	1	1	0.12	0.12	2	0.5	0.25	0.12	0.12	0.25
31e	0.03	0.12	0.5	0.25	0.12	0.25	0.03	0.12	0.03	0.03	0.03
31f	0.03	0.12	1	0.25	0.12	0.5	0.03	0.25	0.03	0.03	0.03
31g	0.06	0.25	2	0.25	0.25	2	0.5	0.25	0.06	0.06	0.06
31h	0.015	0.12	1	0.12	0.12	2	0.12	0.12	0.015	0.06	0.06
31j	0.06	0.25	1	0.25	0.25	2	0.06	0.25	0.06	0.06	0.12
31k	0.06	0.25	2	0.25	0.25	4	0.25	0.5	0.25	0.25	0.25
31n	0.12	0.25	0.5	0.5	0.25	1	0.12	1	0.12	0.12	0.25
31o	0.06	0.5	4	0.5	1	4	0.5	1	0.06	0.25	0.12
31p	0.06	0.12	0.5	0.25	0.25	1	0.12	0.12	0.25	0.12	0.25
31q	0.12	0.12	1	0.25	0.5	4	0.5	0.25	0.5	0.12	0.25
31w	0.06	0.25	2	0.25	0.25	4	0.5	0.5	0.015	0.25	0.25
32a	0.015	0.25	1	0.25	0.12	2	0.25	0.25	0.25	0.25	0.25
32b	0.007	0.03	0.5	0.06	0.12	2	0.06	0.06	0.007	0.06	0.06
32c	0.015	0.25	1	0.25	0.25	4	0.5	0.5	0.5	0.5	0.5
32d	0.06	0.5	1	0.5	0.25	2	0.5	0.25	0.12	0.25	0.5
32e	0.03	0.12	0.25	0.12	0.12	0.5	0.03	0.12	0.03	0.03	0.06
32f	0.06	0.25	1	0.25	0.12	0.5	0.06	0.5	0.03	0.03	0.03
32g	0.06	0.25	1	0.25	0.25	2	0.06	0.25	0.06	0.06	0.06
32h	0.015	0.25	1	0.25	0.25	2	0.12	0.25	0.06	0.06	0.06
32j	0.12	0.5	1	0.5	0.5	2	0.12	1	0.12	0.12	0.12
32k	0.06	0.25	1	0.25	0.25	2	0.25	0.5	0.25	0.12	0.12
32l	0.06	0.12	0.5	0.12	0.12	2	0.12	0.25	0.12	0.06	0.06
32m	0.015	0.25	2	0.25	0.25	8	1	1	0.25	1	2
32n	0.06	0.12	0.12	0.12	0.12	2	0.25	1	0.25	0.25	0.25
32o	0.06	0.5	0.5	0.5	0.25	4	0.25	1	0.06	0.25	0.25
32p	0.25	0.5	2	1	0.5	4	3	1	0.25	0.5	0.5
32q	0.12	0.25	1	0.25	0.25	2	0.25	0.25	0.25	0.25	0.25
32r	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
32s	0.06	0.25	0.5	0.25	0.5	4	0.25	0.25	0.06	0.25	0.25
32t	0.06	0.5	4	1	0.5	8	1	1	0.5	1	1
32u	0.015	0.12	2	0.12	0.12	2	0.25	0.12	0.015	0.12	0.12
32v	0.015	0.12	0.5	0.06	0.06	8	0.5	0.25	0.015	0.25	0.5
33b	0.015	0.015	2	0.06	0.06	2	0.12	0.12	0.015	0.06	0.12
33e	0.015	0.015	0.25	0.06	0.12	0.25	0.015	0.06	0.015	0.015	0.015
34e	0.06	0.12	0.12	0.12	0.12	0.25	0.015	0.015	0.06	0.015	0.015
34f	0.015	0.12	0.25	0.06	0.06	0.25	0.015	0.015	0.12	0.015	0.015
35f	0.06	0.12	0.5	0.25	0.12	0.5	0.06	0.25	0.03	0.03	0.03
35h	0.015	0.12	2	0.25	0.12	2	0.12	0.12	0.12	0.06	0.12
35j	0.03	0.12	1	0.25	0.25	1	0.06	0.25	0.03	0.03	0.06
36e	0.03	0.06	0.12	0.06	0.06	0.25	0.015	0.12	0.03	0.007	0.03
36f	0.03	0.12	0.25	0.12	0.12	0.5	0.06	0.12	0.12	0.03	0.12
36g	0.03	0.25	0.5	0.06	0.06	0.5	0.06	0.12	0.03	0.03	0.03
36h	0.03	0.12	0.5	0.06	0.06	1	0.06	0.06	0.06	0.03	0.06
36j	0.03	0.06	0.06	0.06	0.06	0.5	0.06	0.12	0.03	0.03	0.06
40e	2	0.25	0.25	0.5	0.5	1	0.12	0.5	0.25	0.12	0.12
45e	0.015	0.06	0.06	0.03	0.06	0.12	0.03	0.12	0.06	0.015	0.015
46e	0.015	0.015	0.06	0.015	0.015	0.12	0.015	0.015	0.015	0.015	0.015
46f	0.015	0.06	0.12	0.015	0.06	0.25	0.12	0.12	0.12	0.015	0.12
47e	0.12	0.25	2	0.25	0.25	2	0.25	0.5	0.015	0.12	0.12
52j	0.06	0.25	0.5	0.25	0.25	4	0.5	0.5	0.06	0.25	0.25
54j	0.015	0.06	1	0.12	0.12	2	0.25	0.25	0.015	0.06	0.12
6	0.06	0.25	0.5	0.25	0.5	0.12	0.06	0.06	0.03	0.03	0.03

[a] Structures are shown in Table III. [b] Organisms selected for the table are as follows: Bs, *Bacillus subtilis* ATCC 6633; Bc, *Bacillus cereus* ATCC 11778; Sf, *Streptococcus faecalis* ATCC 10541; Sa, *Staphylococcus aureus* ATCC 25178; Se, *Staphylococcus epidermidis* ATCC 155-1; Pa, *Pseudomonas aeruginosa* ATCC 10145; Mm, *Morganella morganii* ATCC 8019; Pv, *Proteus vulgaris* ATCC 8427; Kp, *Klebsellia pneumoniae* ATCC 10031; Ec, *Escherichia coli* ATCC 23559; Ecl, *Enterobacter cloacae* ATCC 23355.

< 8-N (**34f** < **31f** < **32f**, **34i** < **31i** < **32i** < **35i**, and **31j** < **32j** < **35j**). This is in agreement with data found in literature,[7,22] as better blood levels are often associated with the naphthyridines, thus improving in vivo oral efficacy when compared with their 8-H quinolone counterparts. In the 7-(3-amino-3-methyl-1-azetidinyl)naphthyridine series the contribution of the 1-substituent to plasma levels increased in the order *tert*-butyl < cyclopropyl < 4-fluorophenyl < 2,4-difluorophenyl (**54i** < **35i** < **58i** < **47i**). The same trends seen with naphthyridines were also observed in the quinolone series (**52i** < **31i**, **52j** < **31j**, **34e** < **46e**, **34f** < **46f**, and **34i** < **46i**). It is noteworthy that the basic substituent appended at the azetidinyl ring was critical in the enhancement of blood levels. Thus, the AUC values for the 8-H quinolones **31** and 8-F quinolones **32** show the following increasing trend; aminomethyl < (ethylamino)methyl < amino < methylamino < dimethylamino < ethylamino (**31n** = **31o** < **31e** < **31f** < **31h** < **31g**, and **32n** < **32o** < **32e** < **32f** < **32h** = **32g**). The 8-chloro-1-cyclopropylquinolones **34e** (amino) and **34f** (methylamino) were shown to afford equal overall in vitro activity, but it can be seen that **34e** attains better blood levels than **34f**. This could explain the greater increase in in vivo efficacy of **34e** when compared with **34f**. On the other hand, the improved oral absorption properties exhibited by (2,4-difluorophenyl)quinolones **46e**, **46f**, and

Table VI. In Vitro Antibacterial Activity of 7-(3-Amino-3-methyl-1-azetidinyl) quinolones (MIC, μg/mL)[a,b]

compd	Bs	Bc	Sf	Sa	Se	Pa	Mm	Pv	Kp	Ec	Ecl
31i	0.06	0.12	0.5	0.12	0.12	0.5	0.06	0.06	0.12	0.06	0.12
32i	0.03	0.12	0.5	0.12	0.12	0.5	0.12	0.25	0.03	0.06	0.06
33i	0.015	0.06	0.25	0.06	0.06	0.5	0.015	0.12	0.015	0.015	0.015
34i	0.06	0.06	0.25	0.06	0.06	0.25	0.03	0.12	0.03	0.03	0.03
35i	0.03	0.12	0.25	0.25	0.12	0.5	0.06	0.12	0.03	0.03	0.03
36i	0.015	0.03	0.12	0.06	0.03	0.25	0.015	0.06	0.015	0.015	0.015
37i	0.03	0.12	0.5	0.12	0.06	0.5	0.06	0.12	0.06	0.06	0.06
38i	0.25	1	0.25	0.5	0.5	2	0.25	1	0.5	0.5	0.5
39i	0.12	0.5	2	0.5	0.5	2	0.12	1	0.015	0.12	0.12
40i	0.12	1	1	0.5	0.5	2	0.25	0.5	0.25	0.25	0.25
41i	0.06	0.25	1	0.25	0.25	1	0.06	0.5	0.03	0.03	0.06
42i	0.25	1	2	1	1	2	0.25	1	0.12	0.25	0.25
43i	0.12	0.25	0.12	0.25	0.25	2	0.25	0.25	0.12	0.12	0.25
44i	0.25	0.5	0.25	0.25	0.5	2	0.5	0.5	0.5	0.25	0.25
45i	0.06	0.06	0.03	0.06	0.06	0.5	0.12	0.25	0.25	0.12	0.06
46i	0.03	0.06	0.25	0.06	0.06	0.5	0.25	0.12	0.03	0.03	0.12
47i	0.06	0.12	0.5	0.12	0.12	1	0.25	0.5	0.06	0.12	0.12
48i	0.25	1	2	1	1	4	0.5	1	0.5	0.5	1
49i	0.25	1	4	1	1	4	1	1	1	1	1
50i	0.06	0.5	1	0.25	0.12	1	0.015	1	0.015	0.06	0.015
51i	0.12	0.5	2	0.5	0.5	2	0.12	1	0.06	0.06	0.12
52i	0.06	0.25	0.5	0.25	0.12	2	0.25	0.25	0.12	0.12	0.25
53i	0.12	0.5	2	0.5	0.5	2	0.5	1	0.06	0.25	0.25
54i	0.015	0.12	1	0.12	0.12	2	0.12	0.25	0.015	0.06	0.12
55i	0.06	0.12	2	0.12	0.12	2	0.25	0.25	0.12	0.12	0.12
56i	0.12	0.12	2	0.12	0.12	2	0.25	1	0.015	0.25	0.25
57i	0.015	0.06	0.25	0.06	0.06	0.5	0.12	0.12	0.03	0.03	0.06
58i	0.06	0.25	4	0.25	0.25	2	0.12	1	0.06	0.06	0.06
59i	0.12	0.5	0.5	0.5	0.25	2	0.25	1	0.015	0.12	0.12
6	0.06	0.25	0.5	0.25	0.5	0.12	0.06	0.06	0.03	0.03	0.03

[a] Structures are shown in Table IV. [b] See footnote b on Table V.

Table VII. Efficacy on Systemic Infections after Oral Administration in Mice of Selected Quinolones (ED_{50}, mg/kg)

compd	*S. aureus* HS-93	*E. coli* HM-42	*P. aeruginosa* HS-116
31e	44.0	3.6	82.2
31f	36.3	3.8	145.0
31h	35.6	1.3	44.5
31i	36.1	2.7	62.2
31j	16.5	1.9	69.8
31k	16.1	2.7	296.0
32b	29.7	11.3	61.3
32e	16.2	2.4	141.0
32f	10.6	1.5	28.5
32g	16.6	1.1	89.0
32h	19.8	1.7	90.8
32i	13.0	3.1	65.7
32j	15.0	1.4	27.2
32k	7.4	1.4	70.2
33i	7.2	3.3	71.0
34e	7.2	1.1	34.0
34f	15.2	2.0	39.0
34i	4.1	2.0	59.8
35i	10.7	2.8	52.0
35j	9.6	3.0	102.0
39i	8.2	4.1	57.3
46e	1.7	2.3	55.0
46f	1.3	1.3	30.0
46i	1.2	1.5	43.0
47e	5.3	1.5	75.2
47i	6.7	3.1	108.0
56i	10.9	3.2	159.0
57i	1.1	0.4	54.9
58i	7.5	1.3	82.7
6	45.1	3.0	70.3

Table VIII. Blood Level of Selected Quinolones after Oral Administration in Mice[a] (50 mg/kg)

compd	AUC[b]	compd	AUC
31e	3.0	32o	14.1
31f	4.2	34e	8.5
31g	18.1	34f	4.0
31h	10.6	34i	2.8
31i	7.0	35i	31.7
31j	8.4	35j	22.9
31n	0.0	46e	13.0
31o	0.0	46f	15.3
32e	23.0	46i	23.3
32f	32.7	47i	46.4
32g	38.2	52i	5.4
32h	38.2	52j	4.6
32i	20.0	54i	11.3
32j	15.8	58i	33.0
32n	1.7	6[c]	2.3

[a] These data were determined by a bioassay procedure and represent total activity present in the serum. [b] Area under the concentration–time curve recorded at 0.5, 1, 2, and 4 h after dosing (AUC, 0–4 h), μg/mL per hour. [c] Ciprofloxacin.

46i, associated with their very good in vitro activity against Gram-negative and especially Gram-positive organisms, greatly improved in vivo efficacy after oral administration in mice.

Summarizing, these investigations confirm that quinolone or naphthyridine derivatives bearing a substituted azetidine ring at C-7 exhibit very good in vitro and in vivo activity against Gram-negative and especially Gram-positive organisms. 8-Chloro-substituted quinolones exhibit the best overall microbiological profile, associated in some of them with promising pharmacokinetic properties.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All melting points were determined on a Bausch & Lomb apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr with a Nicolet FT-IR 5DXC spectrophotometer. Proton magnetic resonance spectra were recorded with either a Bruker AM-100 spectrometer operating at 100 MHz or a Varian Unity 300 spectrometer operating at 300.1 MHz. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Mass spectra were obtained with a Finnigan Mat TSQ-70 mass spectrometer. The IR, NMR, and mass spectral data of all compounds were consistent with the assigned structures. Elemental analyses were obtained for all new

quinolones reported. Carbon, hydrogen, and nitrogen analyses were within 0.4% of the theoretical values. All organic phases were dried over anhydrous $MgSO_4$ and removed in vacuo with a Büchi rotatory evaporator at aspiratory pressure. Chromatography was done using the medium-pressure flash method and Merck silica gel 60 (230–400-mesh ASTM).

Preparation of Azetidines (Scheme I). 1-(Diphenylmethyl)-3-methyl-3-azetidinol (18c). A mixture of 1-chloro-2,3-epoxy-2-methylpropane **17c** (12.5 g, 117.3 mmol) and diphenylmethylamine (21.5 g, 117.3 mmol) in methanol (50 mL) was stirred at room temperature for 3 days and then heated to reflux for an additional 3 days. After concentration of the reaction mixture under reduced pressure, the residue was washed with acetone and filtered to give the hydrochloride of **18c** (28.8 g, 85%): mp 187–197 °C; IR (KBr) 3322, 2587, 1455, 1242, 704 cm^{-1}.

1-(Diphenylmethyl)-3-ethyl-3-azetidinol (18d). To a stirred solution of 1-(diphenylmethyl)-3-azetidinone (3.05 g, 12.08 mmol) in diethyl ether (60 mL) at 0 °C under nitrogen atmosphere was added ethyllithium (64 mmol) in diethyl ether (140 mL). The reaction mixture was stirred at 0 °C for 2 h, and water (50 mL) was added cautiously. The organic layer was dried and concentrated under reduced pressure. A saturated solution of hydrogen chloride in methanol was added to a solution of the crude product in methanol to afford the hydrochloride of **18d** (3.12 g, 84%): mp 171–175 °C; IR (KBr) 3332, 2581, 1456, 699 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-(methylsulfonyl)oxiazetidine (19c). To a stirred solution of 1-(diphenylmethyl)-3-methyl-3-azetidinol (**18c**) (77.3 g, 0.328 mol) in CH_2Cl_2 (600 mL) was added triethylamine (50 g, 0.437 mol), and this mixture was cooled to 0 °C. At this temperature a solution of methanesulfonyl chloride (50 g, 0.437 mol) in CH_2Cl_2 (50 mL) was added dropwise. The reaction was allowed to reach room temperature and stirred overnight. The solution was washed with water, dried, and evaporated to give **19c** (104.6 g, 96%): mp 113–115 °C; IR (KBr) 1337, 1165, 941, 703 cm^{-1}.

3-Amino-1-(diphenylmethyl)-3-methylazetidine (20i). To a stirred solution of 1-(diphenylmethyl)-3-methyl-3-(methylsulfonyl)oxiazetidine (**19c**) (31 g, 0.094 mol) in 2-propanol (150 mL) was added ammonium hydroxide (100 mL). The mixture was heated at 70 °C for 3 h. After removal of the 2-propanol the solution was extracted with CH_2Cl_2, dried, and concentrated with a rotatory evaporator to give **20i** (16.3 g, 70%): mp 84–86 °C; IR (KBr) 3400, 1450, 1247, 626 cm^{-1}.

An analogous procedure was used to obtain the following compounds. Physical and spectral data are given below.

1-(Diphenylmethyl)-3-(methylamino)azetidine (20f): mp 71–74 °C; IR (KBr) 3290, 1430, 820 cm^{-1}.

3-(Dimethylamino)-1-(diphenylmethyl)azetidine (20h): IR (KBr) 2935, 2835, 1450, 706 cm^{-1}.

3-(Ethylamino)-1-(diphenylmethyl)azetidine dihydrochloride (20g): mp 42–46 °C; IR (KBr) 2860, 2821, 1451, 743, 703 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-(methylamino)azetidine (20j): mp 62–63 °C; IR (KBr) 3293, 2820, 1450, 705 cm^{-1}.

3-(Dimethylamino)-1-(diphenylmethyl)-3-methylazetidine (20k): mp 53–54 °C; IR (KBr) 2824, 1235, 706 cm^{-1}.

3-Cyano-1-(diphenylmethyl)-3-methylazetidine (24c). A mixture of 1-(diphenylmethyl)-3-methyl-3-(methylsulfonyl)oxiazetidine (**19c**) (33.1 g, 100 mmol) and sodium cyanide (11 g, 225 mmol) in DMF (90 mL) was heated at 65 °C with stirring for 6 h, cooled, and poured into an ice–water mixture. The precipitate was collected, washed with water, and dried to give **24c** (21.75, 83%): mp 86–88 °C; IR (KBr) 2843, 1492, 1452, 745, 706 cm^{-1}.

3-(Aminomethyl)-1-(diphenylmethyl)-3-methylazetidine (25p). A solution of 3-cyano-1-(diphenylmethyl)-3-methylazetidine (**24c**) (21.1 g, 80.5 mmol) in THF (150 mL) was slowly added to a suspension of lithium aluminum hydride (6.1 g, 161 mmol) in THF (250 mL), and the mixture was stirred overnight at room temperature. Excess hydride reagent was hydrolyzed by careful addition of ethanol. The mixture was filtered and evaporated, and the residue was dissolved with $CHCl_3$, washed with water, dried, and evaporated to give **25p** (16.1 g, 75%): mp 46–48 °C; IR (KBr) 1452, 744, 704 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-(((trifluoroacetyl)amino)methyl)azetidine (27p). To a stirred solution of 3-(aminomethyl)-1-(diphenylmethyl)-3-methylazetidine (**25p**) (14.72 g, 55.25 mmol) in $CHCl_3$ (100 mL) was added dropwise a solution of trifluoroacetic anhydride (14.8 g, 69.0 mmol) of $CHCl_3$ (50 mL). The reaction mixture was stirred at room temperature for 2 h, washed with water, 10% $NaHCO_3$ aqueous solution, and brine, dried, and concentrated with a rotatory evaporator to give **27p** (16.0 g, 80%): mp 127–128 °C; IR (KBr) 2297, 1727, 1125, 1148 cm^{-1}.

An analogous procedure was used to obtain the following compounds. Physical and spectral data are given below.

1-(Diphenylmethyl)-3-(((trifluoroacetyl)amino)methyl)azetidine (27n): mp 112–116 °C; IR, hydrochloride (KBr), 1718, 1185, 715 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-((trifluoroacetyl)amino)azetidine hydrochloride (22i): oil; IR (film) 3300, 1784, 1700, 1162, 702 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-(((trifluoroacetyl)amino)methyl)azetidine (27p): mp 127–128 °C; IR (KBr) 2297, 1727, 1175, 1148 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-[[*N*-ethyl-*N*-(trifluoroacetyl)amino]methyl]azetidine (28q). To a solution of **27p** (1.3 g, 3.6 mmol) in a mixture of dioxane (40 mL) and DMF (10 mL) was added sodium hydride (55%, 0.16 g, 3.6 mmol), and the reaction was stirred at 70 °C for 2 h. The mixture was cooled to room temperature and ethyl iodide (0.73 g, 4.6 mmol) added. The reaction mixture was then stirred at 70 °C for 4 h and evaporated, and the residue was partioned with $CHCl_3$ and water. The organic layer was dried and concentrated to afford **28q** (1.1 g, 79%): mp 191–194 °C; IR (KBr) 1686, 1214, 1149 cm^{-1}.

An analogous procedure was used to obtain the following compounds. Physical and spectral data are given below.

1-(Diphenylmethyl)-3-((trifluoroacetyl)amino)azetidine hydrochloride (22e): mp 105–108 °C; IR (KBr) 1719, 1456, 1182, 747, 703 cm^{-1}.

1-(Diphenylmethyl)-3-[*N*-methyl-*N*-(trifluoroacetyl)amino]azetidine (22f): mp 115–116 °C; IR (KBr) 1685, 1247, 1139, 1097 cm^{-1}.

1-(Diphenylmethyl)-3-[*N*-ethyl-*N*-(trifluoroacetyl)amino]azetidine (22g): mp, hydrochloride, 76–78 °C; IR (KBr) 1680, 1225, 1196, 1142, 704 cm^{-1}.

1-(Diphenylmethyl)-3-[[*N*-methyl-*N*-(trifluoroacetyl)amino]methyl]azetidine (22j): mp 152–155 °C; IR, hydrochloride (KBr), 1691, 1160, 702 cm^{-1}.

1-(Diphenylmethyl)-3-methyl-3-[[*N*-ethyl-*N*-(trifluoroacetyl)amino]methyl]azetidine hydrochloride (28q): mp 191–194 °C; IR (KBr) 1686, 1214, 1149 cm^{-1}.

3-Amino-3-methylazetidine (21i). A mixture of the dihydrochloride of 3-amino-1-(diphenylmethyl)-3-methylazetidine **20i** (22.0 g, 67.7 mmol) and 10% $Pd(OH)_2/C$ (2.2 g) in ethanol (400 mL) was treated with H_2 at room temperature and 60 psi for 2 h. The mixture was filtered, the solvent was evaporated, and the residue was washed with benzene to give **21i** (8.9 g, 83%): mp 196–199 °C; IR (KBr) 3300, 2300, 1575, 1515, 1235 cm^{-1}.

An analogous procedure was used to obtain the following compounds. Physical and spectral data are given below.

3-(Dimethylamino)azetidine dihydrochloride (21h): mp 178–180 °C; IR (KBr) 2880, 2600, 2460, 1460, 1240, 1020 cm^{-1}.

3-(Dimethylamino)-3-methylazetidine dihydrochloride (21k): mp 185–186 °C; IR (KBr) 3120, 2870, 1458, 1190 cm^{-1}.

3-[*N*-methyl-*N*-(trifluoroacetyl)amino]azetidine hydrochloride (23f): mp 162–164 °C; IR (KBr) 2990, 1696, 1159, 1102 cm^{-1}.

3-[*N*-ethyl-*N*-(trifluoroacetyl)amino]azetidine hydrochloride (23g): oil; IR (film) 1725, 1687, 1187 cm^{-1}.

3-Methyl-3-[*N*-methyl-*N*-(trifluoroacetyl)amino]azetidine hydrochloride (23j): mp 175–179 °C; IR (KBr) 3480, 2900, 1686, 1153 cm^{-1}.

3-(Aminomethyl)-3-methylazetidine dihydrochloride (26p): mp 223–226 °C; IR (KBr) 2980, 2940, 1580, 1500 cm^{-1}.

3-[[*N*-Ethyl-*N*-(trifluoroacetyl)amino]methyl]azetidine hydrochloride (29o): mp 90–96 °C; IR (KBr) 2940, 1673, 1150 cm^{-1}.

3-Methyl-3-[[*N*-ethyl-*N*-(trifluoroacetyl)amino]methyl]azetidine hydrochloride (29q): mp 120–123 °C; IR (KBr) 2960, 1688, 1270, 1190, 1130 cm^{-1}.

General Procedures for the Preparation of Quinolones and Naphthyridines (Scheme II). Method A. Preparation of 7-(3-Amino-3-methyl-1-azetidinyl)-8-chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic Acid (34i). A mixture containing 0.40 g (1.30 mmol) of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,[7] 0.27 g (1.70 mmol) of 3-amino-3-methylazetidine dihydrochloride **21i** and 0.70 g (6.90 mmol) of triethylamine in 7 mL of pyridine was heated to reflux for 3 h and then cooled to room temperature. After concentration of the reaction mixture under reduced pressure, the residue was diluted with water. The precipitated solid was collected by filtration and washed with water to give the crude product. This solid was dissolved in water, made basic with NH_3 (concentrated), filtered, and the pH adjusted to 7.2 by elimination of NH_3. The precipitated solid was collected and washed successively with water and ethanol to give **34i** (0.36 g, 57%): mp 284–285 °C; ^{1}H NMR (DMSO-d_6, TFA) δ 1.05 (m, 4 H), 1.57 (s, 3 H), 4.25 (m, 1 H), 4.51 (m, 4 H), 7.70 (d, J = 14.0 Hz, 1 H), 8.43 (bb, 2 H), 8.70 (s, 1 H); IR (KBr) 2945, 1639, 1611, 1444, 1356 cm^{-1}.

Method B. Preparation of 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-1,4-dihydro-7-(3-(methylamino)-1-azetidinyl)-4-oxo-3-quinolinecarboxylic Acid (32f). A mixture containing 0.85 g (3.00 mmol) of 1-cyclopropyl-1,4-dihydro-6,7,8-trifluoro-4-oxo-3-quinolinecarboxylic acid,[18] 1.20 g (5.00 mmol) of 3-(*N*-methyltrifluoroacetamido)azetidine hydrochloride **23f**, and 0.80 g (8.00 mmol) of triethylamine in 15 mL of pyridine was heated to reflux for 3 h and then cooled to room temperature. After concentration of the reaction mixture under reduced pressure, the residue was diluted with water and acidified with acetic acid. The precipitated solid was collected by filtration and washed with water to give 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-(*N*-methyltrifluoroacetamido)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic acid (1.10 g, 49%).

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-(*N*-methyltrifluoroacetamido)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic acid (1.10 g, 2.47 mmol) was treated with 25 mL of 1 N aqueous sodium hydroxide solution, heated to reflux for 2 h, and then cooled to room temperature. The reaction mixture was neutralized with acetic acid and the precipitate collected by filtration and washed with water to give **32f** (0.76 g, 88%): mp 270–272 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (d, J = 6.5 Hz, 4 H), 2.31 (s, 3 H), 3.66 (m, 1 H), 4.12 (m, 3 H), 4.52 (m, 2 H), 7.66 (dd, J = 12.3 Hz, J' = 1.7 Hz, 1 H), 8.58 (s, 1 H); IR (KBr) 3468, 3387, 2912, 1718, 1629, 1617, 1472 cm^{-1}.

Method C. Preparation of 7-(3-Cyano-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (32t). 7-(3-Carbamoyl-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**32s**) (0.57 g, 1.5 mmol) was treated with 12 mL of acetic anhydride, heated to reflux for 24 h, and then cooled to room temperature. The precipitated solid was collected by filtration and washed with water to give **32t** (0.15 g, 29%): mp >325 °C; ^{1}H NMR (DMSO-d_6, TFA) δ 1.20 (m, 4 H), 3.95 (m, 1 H), 4.60 (m, 5 H), 7.75 (d, J = 12.0 Hz, 1 H), 8.60 (s, 1 H); IR (KBr) 2250, 1735, 1635, 1650 cm^{-1}.

Method D. Preparation of 7-(3-acetoxy-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (32u). 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid (**32b**) (0.70 g, 2.08 mmol) in 20 mL of pyridine was added slowly to acetic anhydride (0.64 g, 6.2 mmol) at 0 °C and then stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was collected and washed with water to give **32u** (0.54 g, 68%): mp 259–262 °C; ^{1}H NMR (DMSO-d_6, TFA) δ 1.20 (d, J = 6.0 Hz, 4 H), 2.10 (s, 3 H), 4.05 (q, J = 6.0 Hz, 1 H), 4.40 (m, 2 H), 4.80 (m, 2 H), 5.3 (m, 1 H), 7.70 (dd, J = 13.0 Hz, J' = 2.0 Hz, 1 H), 8.60 (s, 1 H); IR (KBr) 1742, 1727, 1626, 1481 cm^{-1}.

Method E. Preparation of 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-methyl-3-(1-pyrrolyl)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic Acid (32m). A mixture containing 1.00 g (2.80 mmol) of 7-(3-amino-3-methyl-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**32i**) and 1.89 g (5.4 mmol) of 2,5-dimethoxytetrahydrofuran in 15 mL of acetic acid was heated to reflux for 15 min and then cooled to room temperature. The reaction mixture was diluted with water, and the precipitate was collected by filtration and washed with water to give **32m** (1.04 g, 48%): mp 249–252 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 4 H), 1.96 (s, 3 H), 3.90 (m, 1 H), 4.40–5.00 (complex signal, 4 H), 6.25 (t, J = 2.1 Hz, 2 H), 6.88 (t, J = 2.1 Hz, 2 H), 7.77 (dd, J = 13.0 Hz, J = 2.0 Hz, 1 H), 8.66 (s, 1 H); IR (KBr) 1727, 1628, 1527, 1446, 1412 cm^{-1}.

Method F. Preparation of 7-(3-(Acetonylmethylamino)-3-methyl-1-azetidinyl)-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic Acid (31w). To a suspension of chloroacetone (0.76 mL, 9.56 mmol) and anhydrous Na_2CO_3 (1.0 g, 9.56 mmol) in 350 mL of DMF was added 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-3-(methylamino)-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid, **31j** (3.0 g, 8.7 mmol), at room temperature, and the mixture was heated to 120–130 °C for 1.5 h. The reaction mixture was diluted with water, and the solid was collected by filtration and washed with water to give the crude product. This solid was purified over silica gel ($CHCl_3$) to give **31w** (1.41 g, 40%): mp 210–214 °C; ^{1}H NMR (DMSO-d_6, TFA) δ 1.18 (m, 4 H), 1.78 (s, 3 H), 2.29 (s, 3 H), 2.81 (s, 3 H), 4.15 and 4.55 (AB system, J = 14.0 Hz, 4 H), 4.40 (s, 2 H), 6.99 (d, J = 7.5 Hz, 1 H), 7.94 (d, J = 12.7 Hz, 1 H), 8.64 (s, 1 H); IR (KBr) 1719, 1631, 1529, 1474 cm^{-1}.

Microbiology. General Procedures for in Vitro Studies. The in vitro antibacterial activity was studied by side-by-side comparison with **6** and determined by a serial 2-fold agar dilution technique using Mueller Hinton medium. The inoculum size was adjusted to 10^5 cfu/mL, and concentrations of the compounds ranged from 0.007 to 16 μg/mL. Minimum inhibitory concentrations (MICs) were defined as the lowest concentration of the compound that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

In Vivo Studies (Mouse Protection Tests). The screening in vivo was carried out with 4 groups of 10 mice each. The mice were infected intraperitoneally with a suspension containing an amount of the indicated organism slightly greater than its lethal dose 100 (LD_{100}). Each group was treated orally with the test compound administered as a single dose immediately after infection. Four different doses, one per group, were selected depending on the in vitro activity of the test compound. ED_{50} values were calculated by interpolation among survival rates in each group after a week. They express the total dose of compound (mg/kg) required to protect 50% of the mice from an experimentally induced lethal systemic infection of the indicated organism.

Pharmacokinetic Studies. General Procedure. Mice were given a single 50 mg/kg oral dose. At the specified time intervals (0.5, 1, 2, and 4 h after dosing), blood was collected from groups of six mice. All samples were assayed by a disk agar diffusion bioassay procedure. *Bacillus subtilis* ATCC 6633 was used as the assay organism and Seed Agar as the growth medium. The plates were incubated at 37 °C for 18 h.

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