7-Azetidinylquinolones as Antibacterial Agents. 2.[1] Synthesis and Biological Activity of 7-(2,3-Disubstituted-1-azetidinyl)-4-oxoquinoline- and -1,8-naphthyridine-3-carboxylic Acids. Properties and Structure–Activity Relationships of Quinolones with an Azetidine Moiety[2]

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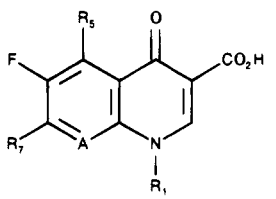
A series of 7-(2,3-disubstituted-1-azetidinyl)-1,4-dihydro-6-fluoro-4-oxoquinoline- and -1,8-naphthyridine-3-carboxylic acids, with varied substituents at the 1-, 5-, and 8-positions, was prepared to study the effects on potency and physicochemical properties of the substituent at position 2 of the azetidine moiety. The activity of the title compounds was determined *in vitro* against Gram-positive and Gram-negative bacteria, and the *in vivo* efficacy of selected derivatives was determined using a mouse infection model. The X-ray crystal structures of **6b**, **6c**, and **6d** were found to be in reasonable agreement with the corresponding AM1 calculated geometries. Correlations between antibacterial potency of all the synthesized 7-azetidinylquinolones and naphthyridines and their calculated electronic properties and experimental capacity factors were established. Antibacterial efficacy and pharmacokinetic and physicochemical properties of selected derivatives were compared to the relevant 7-(3-amino-1-azetidinyl) and 7-(3-amino-3-methyl-1-azetidinyl) analogues (for Part 1, see: *J. Med. Chem.* **1993**, *36*, 801–810). A combination of a cyclopropyl or a substituted phenyl group at N-1 and a *trans*-3-amino-2-methyl-1-azetidinyl group at C-7 conferred the best overall antibacterial, pharmacokinetic, and physicochemical properties to the azetidinylquinolones studied.

Quinolonecarboxylic acids constitute a class of extremely potent and orally active broad-spectrum antibacterial agents.[3] Most of these agents are substituted at the 7-position by cyclic aliphatic amines, especially diamines. Norfloxacin (**1a**),[4] characterized by having a piperazine moiety at C-7, is generally considered as the first fluoroquinolone noted for significant increases in activity relative to its predecessors. Ciprofloxacin[5] (**1b**), incorporating a cyclopropyl group, also contains a piperazine at C-7. More recently, this piperazine group has been successfully replaced with 3-(ethylamino)-methylpyrrolidine or 3-aminopyrrolidine[6] and with 3-(aminomethyl)-3-methylpyrrolidine.[7] Various combinations of functionalities at C-1 and C-8 led to a number of quinolones substituted at C-7 with a 3-aminopyrrolidine group, such as tosufloxacin[8] (**2a**) and clinafloxacin[9] (**2b**). Other diamines such as the 3-methyl- and 3,5-dimethylpiperazinyl 7-substituted quinolones, lomefloxacin[10] (**3**) and sparfloxacin[11] (**4**), with enhanced *in vivo* properties, were brought into the market. *N*-1-*tert*-Butylnaphthyridines substituted at C-7 with a 2-methylpiperazine have been claimed to have better *in vitro* antibacterial activity than when substituted with a 3-methylpiperazine.[12]

As part of an ongoing research project in the quest for novel quinolones to improve the spectrum of activity, we have been preparing several quinolone C-7 structural analogues. These investigations led to a series of compounds substituted at the 7-position with azoles such as pyrrole (irloxacin[13]), or 4-methylimidazole (E-4345[14]) and a series of (imidazolyl)phenylmethyl substituents attached to the 7-position via a carbon–carbon bond.[15] More recently, we have invested considerable effort into those C-7 groups bearing a 3-monosubstituted- and 3,3-disubstituted azetidine.[1] This latter series showed broad-spectrum activity, particularly against Gram-positive organisms, improved *in vivo* efficacy, and high blood levels in the mouse. 8-Chloro-1-cyclopropylquinolones **5a–b**, 1-(2,4-difluorophenyl)-naphthyridine **5c**, and 8-chloro-1-(2,4-difluorophenyl)-quinolones **5d** and **6a** exhibited the best overall microbiological profile.

Since our previous efforts had proven that 3-aminoazetidines or 3-amino-3-methylazetidines were excel-

Chart 1



	R_1	A	R_5	R_7
1a	ethyl	CH	H	1-piperazinyl
1b	cyclopropyl	CH	H	1-piperazinyl
2a	2,4-difluorophenyl	N	H	3-amino-1-pyrrolidinyl
2b	cyclopropyl	CCl	H	3-amino-1-pyrrolidinyl
3	ethyl	CF	H	3-amino-1-pyrrolidinyl
4	cyclopropyl	CF	NH_2	3,5-dimethyl-1-piperazinyl

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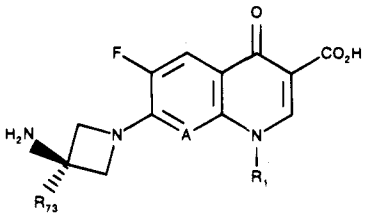
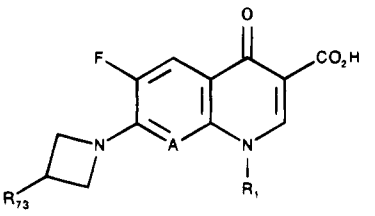
Chart 2

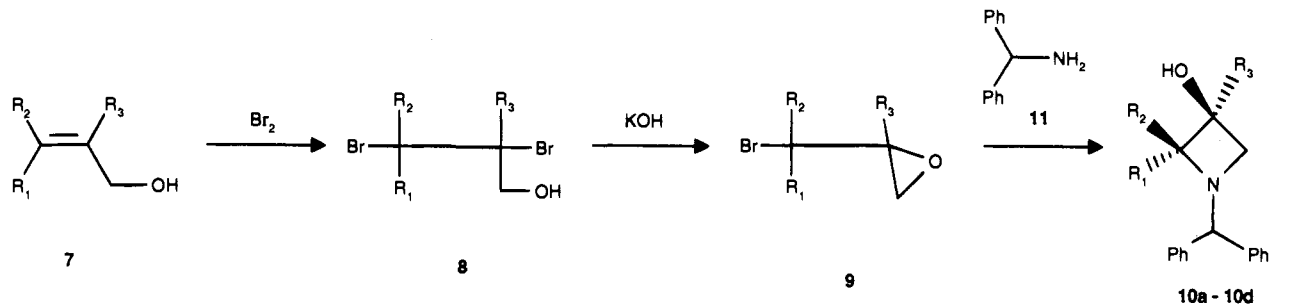


	R_1	A	R_{73}
5a	c-C_3H_5	CCl	H
5b	c-C_3H_5	CCl	Me
5c	2,4-F_2Ph	N	H
5d	2,4-F_2Ph	CCl	Me



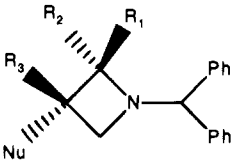
	R_1	A	R_{73}
6a	2,4-F_2Ph	CCl	NHMe
6b	c-C_3H_5	CH	H
6c	c-C_3H_5	CF	H
6d	c-C_3H_5	CH	NHEt

Scheme 1



lent replacements for the standard piperazine moiety or aminopyrrolidine moiety, our attention then shifted to 2-substituted azetidines, in order to investigate what effect alkyl groups on position 2 of the 3-aminoazetidine ring have on the overall antibacterial potency of the molecules. The effect of two methyl groups on the 3-aminoazetidine ring was also worthy of exploration because of the increase of steric bulk and the presumed lipophilicity increase. The role that positional isomers might play on the solubility of 7-azetidinylquinolones was of particular interest, as solubility was found to be isomer-dependent for methyl-substituted pyrrolidine ring quinolones.[7] In this study, we have focused on a series of 2,3-disubstituted azetidines and several 2,2,3- and 2,3,3-trisubstituted azetidines as 7-position substituents on the quinolone and naphthyridine nucleus. We report the synthesis, physicochemical properties, and antibacterial activity of this series of compounds as well as *in vivo* efficacy and pharmacokinetic properties in mice of several of these agents. We also have carried out the single-crystal X-ray analysis of compounds **6b–d** in order to know the solid-state conformation of azetidinyl quinolones. A comparison of AM1-derived geometrical parameters with the experimental X-ray parameters was acceptable thus providing validation for theoretical calculations. We also report here the results of an extensive quantitative structure–activity relationships[2] study for the azetidinyl quinolones, including those previously published[1] and the new quinolones reported in this article, and we try to rationalize these results discussing how these structure–activity relationships hold qualitatively as the substituents change at other positions of the quinolone nucleus.

Table 1. Azetidine Nucleus

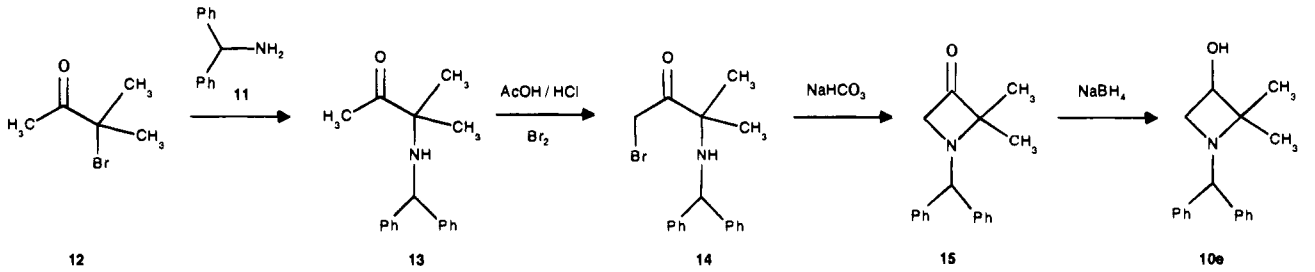


compd	isomerism	R_1	R_2	R_3	Nu
10a	*trans*	Me	H	H	OH
10b	*cis*	H	Me	H	OH
10c	*cis*	H	Et	H	OH
10d	*trans*	Me	H	Me	OH
10e		Me	Me	H	OH
18f	*trans*	Me	H	H	NH_2
18g	*cis*	H	Me	H	NH_2
18h	*cis*	H	Et	H	NH_2
18i		Me	Me	H	NH_2
18j	*trans*	Me	H	Me	NH_2
18k	*trans*	Me	H	H	NHMe
18l	*trans*	Me	H	H	NMe_2
18m	*trans*	Me	H	H	CH_2NH_2
18n	*trans*	Me	H	H	CH_2NHEt
18o	*trans*	Me	H	H	CN
18p	*trans*	Me	H	H	$CH_2NHCOCF_3$
18q	*trans*	Me	H	H	$CH_2N(Et)COCF_3$

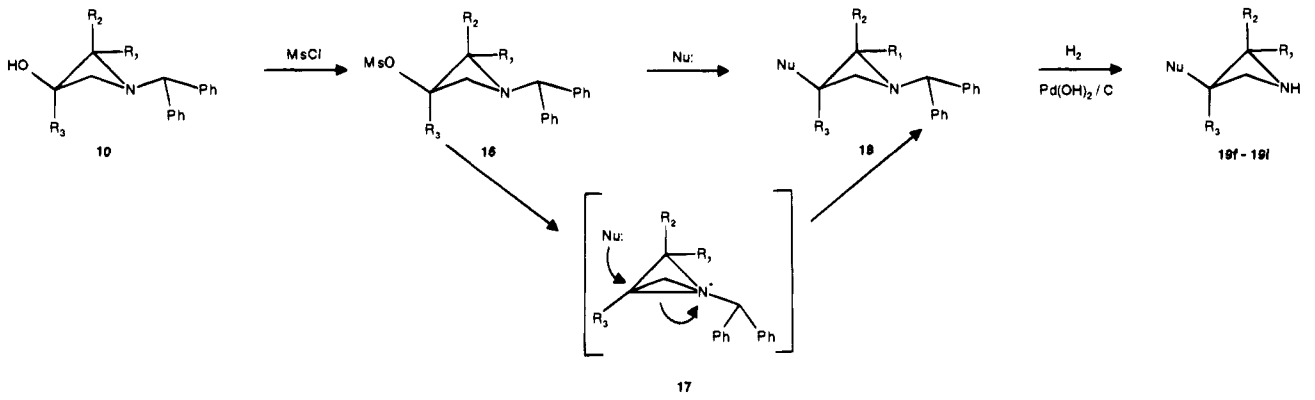
Chemistry

The 2,3-disubstituted, 2,2,3-trisubstituted, and 2,3,3-trisubstituted aminoazetidines used in this study are new compounds that we have prepared in our laboratories.[16] 3-Azetidinols are key compounds in 3-aminoazetidines synthesis. Most 3-azetidinols **10** (Table 1) have been synthesized in good yields from the corresponding α-hydroxyalkene **7** (Scheme 1) *via* a common methodology involving generation of epoxide **9**, opening of the epoxide with benzhydrylamine **11**, and cyclization,

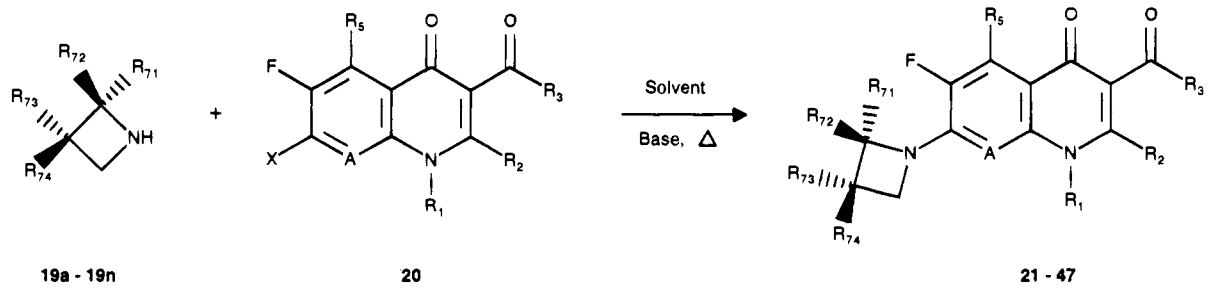
Scheme 2



Scheme 3



Scheme 4



X = F, Cl (See Tables II and III for Structures)

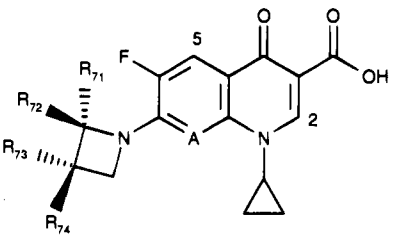
following, with slight modifications, the procedure described by Gaertner.[17] This reaction proceeds in a stereospecific way as described for *trans*-1-cyclohexyl-2-methylazetidin-3-ol,[18] thus differing from 1-*tert*-butyl-2-methylazetidin-3-ols which were obtained as two diastereomeric pairs.[17b]

The synthesis of 2,2-dimethyl-1-(diphenylmethyl)-azetidin-3-ol **10e** was not possible following the procedure mentioned above, because of the instability of the epoxide **9e** at room temperature. The synthesis was carried out (Scheme 2) by bromination of the 3-methylbutanone tertiary carbon and substitution by benzhydrylamine to obtain **13**, followed by bromination of the α-methyl and cyclization in basic medium to afford **15**. The final step was achieved by reduction of ketone **15** with $NaBH_4$ in good yield.

An amino group, primary and secondary amines, as well as other nucleophiles were introduced at the 3-position of 1-benzhydrylazetidine by sequential methanesulfonate ester formation (**16**) and displacement with the nucleophiles to obtain **18** (Scheme 3). The methanesulfonyloxy substitution proceeded with stereospecific retention of configuration due to the participation of the ring nitrogen *via* the 1-azabicyclo[1.1.0]butyl cation **17**. Kinetic and stereochemical studies[19] with 1-*tert*-butylazetidine 3-tosylates and (1-cyclohexyl)-2-phenylazetidine 3-mesylate have shown conclusively that reactions with nucleophiles proceed *via* a double-inversion process, resulting in a net retention of configuration. NOE studies on compounds **10**, **16**, and **18** demonstrate unambiguously that nucleophilic displacements in 1-benzhydrylazetidines occur with retention of configuration.

Some of the 3-aminoazetidines listed in Table 2 needed to be protected before displacement of the quinolone 7-fluoro group in order to avoid reaction of the exocyclic amino group. Thus, the reaction of **18m** with trifluoroacetic anhydride provided compound **18p** in 82% 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. Following this procedure,[20] the corresponding salts **19a–n** were obtained and could be condensed with the quinolone nuclei. Compounds **21a–n**, **22a–n**, **25i**, and **21f–47f** prepared for this study were synthesized as summarized in Scheme 4. The general method used for the preparation of 4-oxoquinolines, naphthyridines, and isothiazolopyridones **20** was adapted from synthetic routes previously reported.[1,21] The regiospecific nucleophilic aromatic

Table 2. Synthetic and Physical Data of the Quinolone Antibacterials Prepared for This Study[a]



compd	A	R_{71}	R_{72}	R_{73}	R_{74}	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]	log k′
21a	CH	H	Me	OH	H	239–242	$C_{17}H_{17}FN_2O_4 \cdot 1.0H_2O$	A (83)	8.52	7.74	0.4068
21b	CH	Me	H	OH	H	236–240	$C_{17}H_{17}FN_2O_4 \cdot 0.4H_2O$	A (76)	8.58	7.79	0.3299
21c	CH	Et	H	OH	H	250–255	$C_{18}H_{19}FN_2O_4 \cdot 0.3H_2O$	A (96)	8.55	7.74	0.5288
21d	CH	H	Me	OH	Me	284–290	$C_{18}H_{19}FN_2O_4 \cdot 0.1H_2O$	A (88)	8.57	7.77	0.5993
21g	CH	Me	H	NH_2	H	222–225	$C_{17}H_{18}FN_3O_3 \cdot 0.7H_2O$	A (73)	8.52	7.75	0.0457
21h	CH	Et	H	NH_2	H	236–237	$C_{18}H_{20}FN_3O_3 \cdot 0.4H_2O$	A (57)	8.57	7.81	0.1708
21j	CH	H	Me	NH_2	Me	269–272	$C_{18}H_{20}FN_3O_3 \cdot 0.9H_2O$	A (85)	8.61	7.86	0.1421
21k	CH	H	Me	NHMe	H	208–212	$C_{18}H_{20}FN_3O_3 \cdot 1.3H_2O$	B (51)	8.65	7.85	0.1790
21l	CH	H	Me	NMe_2	H	181–185	$C_{19}H_{22}FN_3O_3$	A (77)	8.64	7.90	0.6680
21m	CH	H	Me	CH_2NH_2	H	222–227	$C_{18}H_{20}FN_3O_3$	B (35)	8.58	7.81	−0.0607
21n	CH	H	Me	CH_2NHEt	H	219–225	$C_{20}H_{24}FN_3O_3 \cdot 0.5H_2O$	B (83)	8.49	7.73	−0.0042
22a	CF	H	Me	OH	H	215–218	$C_{17}H_{16}F_2N_2O_4 \cdot 1.1H_2O$	A (67)	8.57	7.69	0.5176
22b	CF	Me	H	OH	H	235–238	$C_{17}H_{16}F_2N_2O_4 \cdot 0.1H_2O$	A (83)	8.59	7.69	0.4618
22c	CF	Et	H	OH	H	259–261	$C_{18}H_{18}F_2N_2O_4 \cdot 0.9H_2O$	A (92)	8.58	7.65	0.6791
22d	CF	H	Me	OH	Me	246–251	$C_{18}H_{18}F_2N_2O_4 \cdot 0.1H_2O$	A (84)	8.59	7.68	0.6899
22g	CF	Me	H	NH_2	H	215–218	$C_{17}H_{17}F_2N_3O_3 \cdot 0.6H_2O$	A (73)	8.57	7.69	0.0813
22h	CF	Et	H	NH_2	H	230–234	$C_{18}H_{19}F_2N_3O_3$	A (55)	8.60	7.64	0.1399
22i	CF	Me	Me	NH_2	H	214–216	$C_{18}H_{19}F_2N_3O_3 \cdot 0.7H_2O$	A (39)	8.56	7.64	0.1903
22j	CF	H	Me	NH_2	Me	265–268	$C_{18}H_{19}F_2N_3O_3 \cdot 0.2H_2O$	A (75)	8.63	7.77	0.1312
22k	CF	H	Me	NHMe	H	241–246	$C_{18}H_{19}F_2N_3O_3 \cdot 0.9H_2O$	B (36)	8.65	7.77	0.2923
22l	CF	H	Me	NMe_2	H	149–151	$C_{19}H_{21}F_2N_3O_3$	A (78)	8.61	7.75	0.7694
22m	CF	H	Me	CH_2NH_2	H	196–203	$C_{18}H_{19}F_2N_3O_3 \cdot 0.8H_2O$	B (58)	8.51	7.69	−0.0397
22n	CF	H	Me	CH_2NHEt	H	209–212	$C_{20}H_{23}F_2N_3O_3 \cdot 1.5H_2O$	B (56)	8.55	7.65	0.0250
25i	N	Me	Me	NH_2	H	190–195	$C_{17}H_{19}FN_4O_3 \cdot 0.7H_2O$	A (35)	8.53	7.95	−0.0223

[a] Abbreviations: Me = methyl, Et = ethyl. [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.

substitution at C-7 of 6,7-difluoroquinolones, 6,7-difluoroisothiazoloquinolones, and 7-chloro-6-fluoro-naphthyridines **20** with the appropriate azetidine **19a–n** (Scheme 4) proceeded smoothly at temperatures between 80 °C and reflux conditions, according to the general procedures A and B, to give compounds **21–47**. When a trifluoroacetylated intermediate was used, this protecting group was removed in the final step. Physical properties of compounds **a–d** and **g–n** and the structures of their substituents are summarized in Table 2, and physical properties of 7-(*trans*-3-amino-2-methyl-1-azetidinyl)quinolones **f** in Table 3. The 3-mono- and 3,3-disubstituted (azetidinyl)quinolones **21B–Q**, **22B–Q**, **23E–49E**, and **23I–49I**, prepared as described previously,[1] are shown in Table 4.

X-ray Crystallographic Study

Among the thousands of synthesized quinolones, only a few structures have been reported using X-ray crystallography, e.g., nalidixic acid,[22] oxolinic acid,[23] pipemidic acid,[24] pefloxacin salts,[25] sparfloxacin,[11] and ofloxacin perchlorate.[26] Concerning 7-azetidinylquinolones only **6b**, **6c**, and **6d** afforded suitable crystals for X-ray analysis. We have studied the crystal structure of these compounds to improve our understanding of the drug action of quinolones. The single-crystal X-ray structures of **6b**, **6c**, and **6d** are shown in Figures 1–3, and the cell parameters and characteristics are described in Table 5. The main structural features are summarized here.

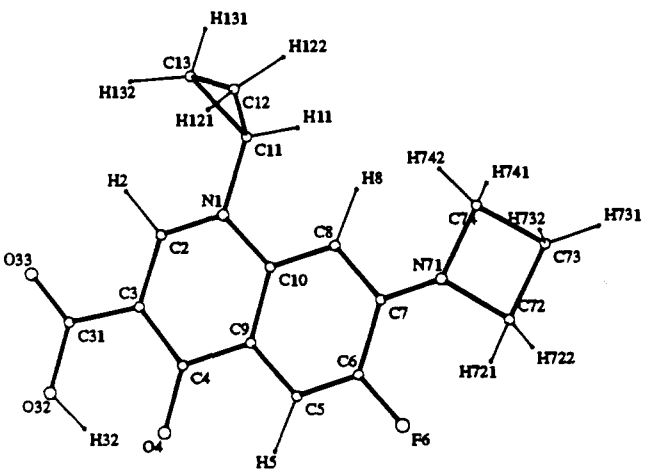
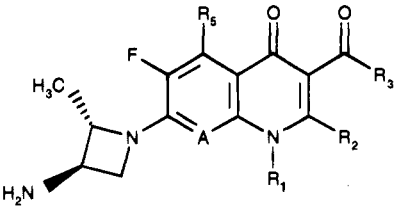


Figure 1. Single-crystal X-ray structure of **6b**.

The quinoline ring is almost planar for all three compounds. The cyclopropyl ring is out of the plane of the quinoline ring. The angle between the cyclopropyl and the quinoline least-square planes measures 126.3(4)° (**6b**), 123.8(1)° (**6c**), and 129.8(2)° (**6d**). The azetidine ring is slightly off the plane determined by the quinoline. The dihedral angle between the mean plane of this ring and the quinoline ring is 9.2(3)° (**6b**), 16.0(1)° (**6c**), and 12.5(3)° (**6d**).

The carboxylic group has a nonionic form in compounds **6b** and **6c**, which is characterized by the lack of substituents in the azetidine ring. An intramolecular hydrogen bond between the carboxylic and the carbonyl

Table 3. 7-(*trans*-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]	log k′
21f	CH	c-C_3H_5	H	OH	H	241–244	$C_{17}H_{18}FN_3O_3 \cdot 0.2H_2O$	A (72)	8.61	7.86	−0.0132
22f	CF	c-C_3H_5	H	OH	H	234–237	$C_{17}H_{17}F_2N_3O_3 \cdot 0.2H_2O$	A (79)	8.61	7.70	0.0755
23f	CF	c-C_3H_5	H	OH	NH_2	206–210	$C_{17}H_{18}F_2N_4O_3 \cdot 0.7H_2O$	A (51)	8.33		0.0828
24f	CCl	c-C_3H_5	H	OH	H	226–230	$C_{17}H_{17}ClFN_3O_3$	A (89)	8.73	7.80	0.1361
25f	N	c-C_3H_5	H	OH	H	213–218	$C_{16}H_{17}FN_4O_3$	A (85)	8.60	7.95	−0.0304
26f	CH	c-C_3H_5	−SNH−		H	264–267	$C_{17}H_{17}FN_4O_2S \cdot 1.3H_2O$	A (78)		7.75	0.0650
27f	CF	c-C_3H_5	−SNH−		H	268–270	$C_{17}H_{16}F_2N_4O_2S \cdot 0.9H_2O$	A (62)		7.66	0.1134
28f	CH	C_2H_5	H	OH	H	232–235	$C_{16}H_{18}FN_3O_3 \cdot 0.4H_2O$	A (70)	8.83	7.80	−0.0915
29f	CF	C_2H_5	H	OH	H	215–217	$C_{16}H_{17}F_2N_3O_3 \cdot 1.2H_2O$	A (67)	8.86	7.80	0.0145
30f	CCl	C_2H_5	H	OH	H	230–232	$C_{16}H_{17}ClFN_3O_3 \cdot 0.7H_2O$	A (83)	8.80	7.84	0.1600
31f	N	C_2H_5	H	OH	H	212–215	$C_{15}H_{17}FN_4O_3$	A (73)	8.94	8.10	−0.1061
32f	CH	CH_2CH_2F	H	OH	H	215–220	$C_{16}H_{17}F_2N_3O_3 \cdot 0.5H_2O$	A (64)	8.83	7.90	−0.1459
33f	CF	CH_2CH_2F	H	OH	H	222–224	$C_{16}H_{16}F_3N_3O_3$	A (62)	8.80	7.90	−0.1024
34f	CCl	CH_2CH_2F	H	OH	H	232–236	$C_{16}H_{16}ClF_2N_3O_3 \cdot 0.3H_2O$	A (83)	8.46	7.90	0.0166
35f	N	CH_2CH_2F	H	OH	H	268–271	$C_{15}H_{16}F_2N_4O_3 \cdot 0.8H_2O$	A (74)	8.79	7.81	−0.2166
36f	CH	*t*-C_4H_9	H	OH	H	225–227	$C_{18}H_{22}FN_3O_3 \cdot 1.2H_2O$	A (80)	8.86	7.91	0.1399
37f	CF	*t*-C_4H_9	H	OH	H	263–266	$C_{18}H_{21}F_2N_3O_3 \cdot 0.1H_2O$	A (78)	8.96	7.81	0.2616
38f	N	*t*-C_4H_9	H	OH	H	223–225	$C_{17}H_{21}FN_4O_3$	A (82)	8.88	8.14	0.1644
39f	CH	4-FPh	H	OH	H	235–239	$C_{20}H_{17}F_2N_3O_3 \cdot 0.5H_2O$	A (80)	8.10	8.64	0.0755
40f	CF	4-FPh	H	OH	H	223–229	$C_{20}H_{16}F_3N_3O_3 \cdot 0.8H_2O$	A (84)	8.45	7.80	0.1875
41f	CCl	4-FPh	H	OH	H	245–247	$C_{20}H_{16}ClF_2N_3O_3 \cdot 0.4H_2O$	A (72)	8.48	7.90	0.2581
42f	N	4-FPh	H	OH	H	239–244	$C_{19}H_{16}F_2N_4O_3 \cdot 0.9H_2O$	A (70)	8.67	8.12	0.0681
43f	CH	2,4-F_2Ph	H	OH	H	203–205	$C_{20}H_{16}F_3N_3O_3 \cdot 0.1H_2O$	A (71)	8.70	8.00	0.1875
44f	CF	2,4-F_2Ph	H	OH	H	200–204	$C_{20}H_{15}F_4N_3O_3$	A (64)	8.61	7.81	0.2644
45f	CCl	2,4-F_2Ph	H	OH	H	182–186	$C_{20}H_{15}ClF_3N_3O_3 \cdot 0.9H_2O$	A (57)	8.60	7.80	0.3553
46f	N	2,4-F_2Ph	H	OH	H	220–222	$C_{19}H_{15}F_3N_4O_3$	A (89)	8.83	8.14	0.1417
47f		$CSCH_2CH_2$	H	OH	H	192–195	$C_{16}H_{16}FN_3O_3S \cdot 0.6H_2O$	A (62)	8.81	7.75	−0.1195

[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–e] See Table 2.

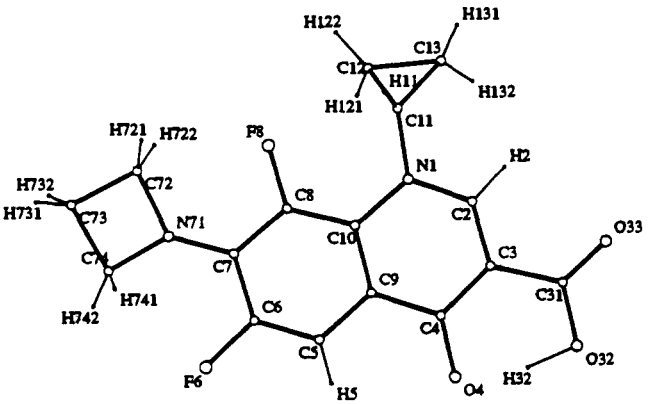


Figure 2. Single-crystal X-ray structure of **6c**.

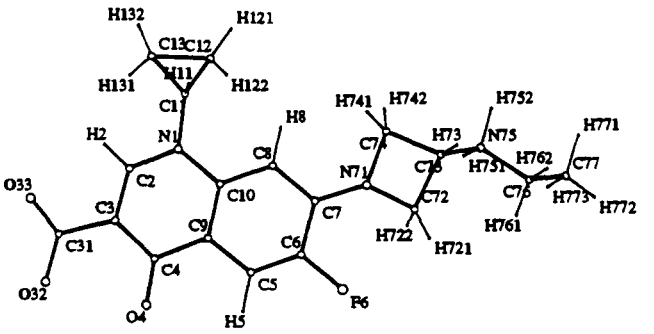


Figure 3. Single-crystal X-ray structure of **6d**.

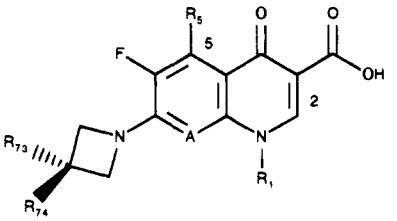
groups forms a pseudo-six-membered ring [**6b**, O(32)–H(32) 1.00(5) Å, O(4)–H(32) 1.67(6) Å, ∠O–H–O 142.0(5)°; **6c**, O(32)–H(32) 1.08(3) Å, O(4)–H(32) 1.47(2) Å, ∠O–H–O 163.4(2)°]. However, the amino acid **6d** has a zwitterionic character exhibiting four intermolecular hydrogen bonds [N(75)–H(751) 1.01(6) Å, H(751)–O(32) 1.73(5) Å, H(751)–O(4) 2.66(5) Å, N(75)–H(752) 1.03(5) Å, H(752)–O(32) 2.10(6) Å, H(752)–O(4) 1.94(5) Å] as shown in the crystal structure (Figure 4). On the other hand, the plane determined by the carbonyl and the carboxylic acid group and the plane of the quinoline ring are both almost coincident for compounds **6b** and **6c** [1.8(8)° and 1.0(2)°, respectively]. However, the angle between these planes is 13.9(5)° for the zwitterionic compound **6d**.

Results and Discussion

In vitro antibacterial activity of the new compounds described in this paper 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 Table 6. Data for five Gram-positive and six Gram-negative bacteria are reported in the table as representative examples. The data for ciprofloxacin (**1b**) are included for comparison.

When comparing data of *trans*-3-amino-2-methyl series **f** with those of *cis*-3-amino-2-methyl series **g**, it appears that *cis* compounds are 1–4 times less active

Table 4. 3-Substituted- and 3,3-Disubstituted-1-azetidinylquinolones[a,b]



compd	A	R_1	R_5	R_{73}	R_{74}	log *k'*	compd	A	R_1	R_5	R_{73}	R_{74}	log *k'*
21A	CH	c-C_3H_5	H	H	H	0.7188	**24E**	CCl	c-C_3H_5	H	NH_2	H	−0.0264
21B	CH	c-C_3H_5	H	OH	H	0.1906	**24F**	CCl	c-C_3H_5	H	NHMe	H	0.1150
21C	CH	c-C_3H_5	H	OH	Me	0.2148	**24I**	CCl	c-C_3H_5	H	NH_2	Me	0.1061
21D	CH	c-C_3H_5	H	OH	Et	0.6222	**25F**	N	c-C_3H_5	H	NHMe	H	−0.0773
21E	CH	c-C_3H_5	H	NH_2	H	−0.0607	**25H**	N	c-C_3H_5	H	NMe_2	H	0.4643
21F	CH	c-C_3H_5	H	NHMe	H	0.0215	**25I**	N	c-C_3H_5	H	NH_2	Me	−0.1606
21G	CH	c-C_3H_5	H	NHEt	H	0.0844	**25J**	N	c-C_3H_5	H	NHMe	Me	0.0408
21H	CH	c-C_3H_5	H	NMe_2	H	0.4820	**28I**	CH	C_2H_5	H	NH_2	Me	−0.1805
21I	CH	c-C_3H_5	H	NH_2	Me	−0.1249	**29I**	CF	C_2H_5	H	NH_2	Me	−0.0757
21J	CH	c-C_3H_5	H	NHMe	Me	0.0875	**30I**	CCl	C_2H_5	H	NH_2	Me	0.1210
21K	CH	c-C_3H_5	H	NMe_2	Me	0.5153	**31I**	N	C_2H_5	H	NH_2	Me	−0.2296
21N	CH	c-C_3H_5	H	CH_2NH_2	H	−0.1549	**32I**	CH	CH_2CH_2F	H	NH_2	Me	0.0374
21O	CH	c-C_3H_5	H	CH_2NHEt	H	−0.1060	**33I**	CF	CH_2CH_2F	H	NH_2	Me	−0.1871
21P	CH	c-C_3H_5	H	CH_2NH_2	Me	−0.0782	**34I**	CCl	CH_2CH_2F	H	NH_2	Me	−0.0332
21Q	CH	c-C_3H_5	H	CH_2NHEt	Me	−0.0356	**35I**	N	CH_2CH_2F	H	NH_2	Me	−0.1706
21R[c]	CH	c-C_3H_5	H	$^+NMe_2EtI^-$	H		**36I**	CH	*t*-C_4H_9	H	NH_2	Me	0.0294
22A	CF	c-C_3H_5	H	H	H	0.9074	**36J**	CH	*t*-C_4H_9	H	NHMe	Me	0.3030
22B	CF	c-C_3H_5	H	OH	H	0.3264	**37I**	CF	*t*-C_4H_9	H	NH_2	Me	0.1751
22C	CF	c-C_3H_5	H	OH	Me	0.5451	**38I**	N	*t*-C_4H_9	H	NH_2	Me	0.0128
22D	CF	c-C_3H_5	H	OH	Et	0.7591	**38J**	N	*t*-C_4H_9	H	NHMe	Me	0.2107
22E	CF	c-C_3H_5	H	NH_2	H	−0.0438	**39I**	CH	4-FPh	H	NH_2	Me	−0.0223
22F	CF	c-C_3H_5	H	NHMe	H	0.0390	**40I**	CF	4-FPh	H	NH_2	Me	0.1106
22G	CF	c-C_3H_5	H	NHEt	H	0.0996	**41I**	CCl	4-FPh	H	NH_2	Me	0.2546
22H	CF	c-C_3H_5	H	NMe_2	H	0.5843	**42I**	N	4-FPh	H	NH_2	Me	−0.0388
22I	CF	c-C_3H_5	H	NH_2	Me	−0.0177	**43I**	CH	2,4-F_2Ph	H	NH_2	Me	0.0969
22J	CF	c-C_3H_5	H	NHMe	Me	0.1055	**44I**	CF	2,4-F_2Ph	H	NH_2	Me	0.2380
22K	CF	c-C_3H_5	H	NMe_2	Me	0.6039	**45E**	CCl	2,4-F_2Ph	H	NH_2	H	0.1280
22N	CF	c-C_3H_5	H	CH_2NH_2	H	−0.1960	**45F**	CCl	2,4-F_2Ph	H	NHMe	H	0.2500
22O	CF	c-C_3H_5	H	CH_2NHEt	H	0.2742	**45I**	CCl	2,4-F_2Ph	H	NH_2	Me	0.3448
22P	CF	c-C_3H_5	H	CH_2NH_2	Me	−0.0438	**46E**	N	2,4-F_2Ph	H	NH_2	H	0.0063
22Q	CF	c-C_3H_5	H	CH_2NHEt	Me	−0.0118	**46I**	N	2,4-F_2Ph	H	NH_2	Me	0.0792
22S[c]	CF	c-C_3H_5	H	$^+NMe_3I^-$	Me		**48E**	CF	C_2H_5	NH_2	NH_2	H	−0.1033
23B	CF	c-C_3H_5	NH_2	OH	H	0.3487	**48I**	CF	C_2H_5	NH_2	NH_2	Me	0.0367
23E	CF	c-C_3H_5	NH_2	NH_2	H	−0.0505	**49E**	CF	2,4-F_2Ph	NH_2	NH_2	H	0.1424
23I	CF	c-C_3H_5	H	NH_2	Me	0.0094	**49I**	CF	2,4-F_2Ph	NH_2	NH_2	Me	0.3189

[a] Previously described compounds.[1] [b] Abbreviations: c-C_3H_5 = cyclopropyl, 2,4-F_2Ph = 2,4-difluorophenyl, Me = methyl, Et = ethyl, *t*-C_4H_9 = *tert*-butyl, 4-FPh = 4-fluorophenyl. [c] See the Experimental Section.

than *trans* compounds (**21g** vs **21f**; **22g** vs **22f**). Addition of a methyl group to the *trans*-3-amino-2-methyl series (**21f**, **22f**) to obtain either the *r*-3-amino-*trans*-2,3-dimethyl derivatives (**21j**, **22j**) or the 3-amino-2,2-dimethyl derivatives (**22i**) resulted in a significant overall decrease in activity. When a 2-methyl group was substituted by a 2-ethyl group in the azetidine ring, an overall decrease in activity was also observed (**21g** vs **21h**; **22g** vs **22h**).

The 1-cyclopropyl-7-(*trans*-3-amino-2-methyl-1-azetidinyl) series **21f**–**25f** proved to be two times more active *in vitro* than its 3-amino-1-azetidinyl **21E**–**24E** and 3-amino-3-methyl-1-azetidinyl **21I**–**25I** counterparts, respectively. Conversely, a different effect was observed in the 1-(2,4-difluorophenyl) series; for instance, 7-(*trans*-3-amino-2-methyl-1-azetidinyl)-8-chloroquinolone **45f** was 2–8 times less active than its 3-amino-1-azetidinyl counterpart **45E**.[1]

In summary, the *in vitro* activity of the **f** (*trans*-3-amino-2-methyl) series with an N-1 cyclopropyl group compares very favorably with ciprofloxacin (**1b**), and with the 3-monosubstituted and 3,3-disubstituted azetidinylquinolones previously described.[1] In particular, the 5-amino-8-fluoroquinolone **23f** and 8-chloroquinolone **24f** showed an outstanding broad spectrum.

Quantitative Structure–Activity Relationships. Chemical structures of 116 compounds (those listed in Tables 2–4, except **26f**, **27f**, **47f**, **21*R***, and **22*S***) included in this paper were built using the molecular modeling software Chem-X,[27] and their structures were optimized initially by molecular mechanics using the MM2-derived force field within Chem-X, and later by semiempirical AM1 method[28] interfaced with Chem-X. The conformation selected for each compound was that with the minimum energy in AM1, which coincided with the X-ray structure for compounds **6b**, **6c**, and **6d**. The ESP option within the molecular orbital package MOPAC[29] was used to calculate the electrostatic potentials of the compounds. A database containing experimental (activities, capacity factors) and calculated (energetic, structural, electronic) parameters for all the compounds was built within Chem-X and transferred to the SAS[30] program package for statistical analysis. A principal component analysis was used to select *Escherichia coli*

Table 5. Crystal and Refinement Parameters for Compounds **6b–d**

	6b (PYR)[a]	**6c** (DMF)[a]	**6d** (DMSO)[a]
formula	$C_{16}H_{15}FN_2O_3$	$C_{16}H_{14}F_2N_2O_3$	$C_{18}H_{20}FN_3O_3$
crystal habit	colorless needles	colorless prisms	colorless plates
crystal size/mm	0.20 × 0.10 × 0.07	0.36 × 0.26 × 0.10	0.13 × 0.13 × 0.07
symmetry	monoclinic, $P2_1/c$	triclinic, $P\bar{1}$	monoclinic, $P2_1/c$
unit cell determination	least-squares fit from 25 reflections		
	(15° < θ < 20°)	(20° < θ < 25°)	(9° < θ < 19°)
unit cell dimension			
a/Å	7.4211(2)	7.9223(4)	7.035(3)
b/Å	15.8286(4)	9.5568(5)	18.883(9)
c/Å	12.5161(7)	10.2450(6)	11.920(7)
α/deg		111.788(5)	
β/deg	107.555(5)	99.081(4)	93.59(7)
g/deg		96.142(6)	
packing: V/Å, Z	1401.23(6), 4	699.54(7), 2	1580 (1), 4
D_c/g cm^{-3}, M, F(000)	1.43, 302.30, 632	1.58, 332.31, 344	1.45, 345.37, 728
μ/cm^{-1}	1.02	1.20	1.02
λ/Å	0.71073	0.71073	0.71073
technique	diffractometer: Enraf-Nonius CAD-4 single-crystal		
	graphite crystal monochromator: Mo Kα, ω − 2θ scans, 1 min per reflection		
number of reflections			
measured	8788	9013	4901
independent	4101	4083	4567
observed	422 [2σ(I) criterion]	1937 [3σ(I) criterion]	1348 [2.5σ(I) criterion]
R_{int}	0.036	0.062	0.020
standard reflections	three reflections every 60 min		
range hkl	0, −22, −17 to 10, 22, 16	−11, −13, −14 to 11, 13, 14	−9, 0, 0 to 9, 26, 16
drift correction	0.97–1.01	0.97–1.02	0.98–1.01
absorption corr; ψ scans	0.94–1.00	0.74–1.00	not applied
difabs	0.27–1.22	0.66–1.93	0.66–1.30
solution and refinement	direct methods; full matrix least-squares on F_o		
Parameters: no. of var	231	264	289
degrees of freedom	491	1673	1059
ratio of freedom	2.12	6.34	3.66
H atoms	difference Fourier synthesis		
final shift/error	0.002	0.001	0.002
weighting scheme	$\sum w(F_o - F_c)^2$, $w = 1/[\sigma^2(F_o) + gF_o^2]$ with $\sigma(F_o)$ from counting statistics		
g	0.00050	0.00080	0.00030
max. thermal value	U_{33}[O(33)] = 0.144(6) Å^2	U_{11}[C(13)] = 0.080(2) Å^2	U_{11}[O(4)] = 0.063(3) Å^2
final ΔF peaks/e Å^{-3}	0.24, −0.17 e Å^{-3}	0.23, −0.28 e Å^{-3}	0.24, −0.21 e Å^{-3}
final R and R_w	0.049, 0.043	0.052, 0.058	0.046, 0.043

[a] Solvent of recrystallization: DMSO, dimethyl sulfoxide; DMF, dimethylformamide; PYR, pyridine.

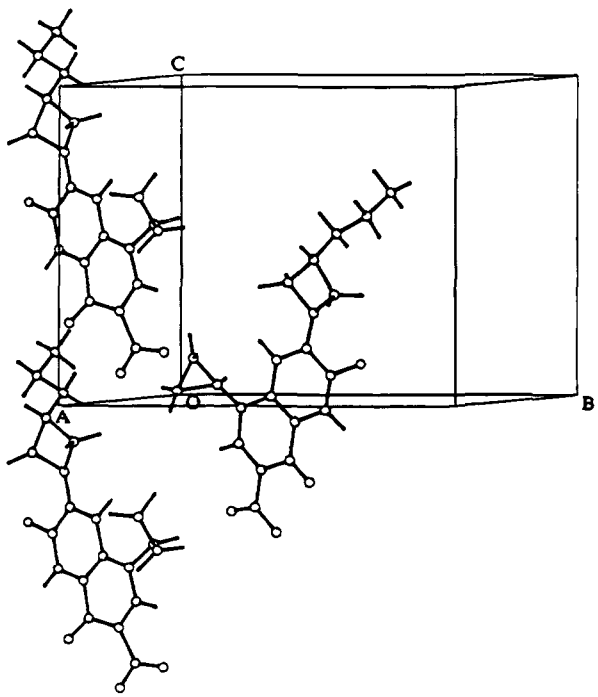


Figure 4. Molecular packing in the crystal structure of **6d**.

ATCC 10799 (Ec in Table 6) as the reference activity among all tested Gram-positive and Gram-negative bacterial strains. A factorial analysis on experimental and calculated parameters in the database was carried out to select the less intercorrelated parameters, the more correlated ones with factors explaining most of the variance, those with a higher correlation with the reference activity, and those most chemically meaningful. A stepwise regression analysis, with selected parameters as independent variables (normalized) and $\log_{10}$(1/MIC)Ec as dependent variable led to the following best-correlated equation for all the compounds:

$$\log_{10}(1/\mathrm{MIC})\ \mathrm{Ec} = (0.69 \pm 0.12) - (1.37 \pm 0.29)(\log k')^2 - (1.27 \pm 0.26)Q_{8R} + (0.76 \pm 0.21)Q_{R73} + (0.57 \pm 0.24)Q_{C5} + (0.46 \pm 0.11)Y + (0.45 \pm 0.11)C \quad (1)$$

$$n = 116 \quad r^2 = 0.49 \quad F = 18\ (99.99\%) \quad s = 0.35$$

where k' is the capacity factor; Q_{8R}, Q_{R73}, and Q_{C5} are respectively the calculated charges of the atom plus the substituent at position 8 of the quinolone ring, of the heteroatom appended at position 3 of the azetidine, and of the carbon at position 5 of the quinolone ring; Y and C are indicator parameters ($Y = 0.5$ for amines, $Y = -0.5$ for hydroxyl, $C = 0.5$ for an heteroatom (O, N), $C = -0.5$ for carbon, as substituents at position 3 of the azetidine moiety).

The application of the stepwise regression procedure on several structure-dependent subsets of compounds

Table 6. *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
21a	0.015	0.06	2	0.12	0.06	2	0.25	0.06	0.015	0.25	0.12
21b	0.015	0.25	2	0.25	0.25	4	0.5	0.25	0.25	0.5	0.25
21c	0.06	1	8	1	0.5	8	1	0.5	0.5	2	0.5
21d	0.03	0.12	2	0.25	0.12	2	0.5	0.25	0.12	0.25	0.25
21f	0.03	0.06	0.25	0.12	0.12	0.25	0.03	0.06	0.03	0.03	0.03
21g	0.03	0.06	0.5	0.12	0.06	0.5	0.03	0.06	0.03	0.06	0.03
21h	0.015	0.25	4	0.25	0.25	2	0.25	0.25	0.015	0.12	0.12
21j	0.015	0.25	2	0.25	0.12	2	0.06	0.25	0.03	0.06	0.015
21k	0.03	0.12	0.25	0.12	0.06	0.5	0.06	0.12	0.03	0.06	0.03
21l	0.06	0.5	4	0.25	0.12	4	0.5	0.5	0.06	0.5	0.5
21m	0.06	1	1	0.25	0.25	2	1	1	0.06	0.12	0.12
21n	0.06	1	4	0.5	0.5	4	0.5	1	0.06	0.12	0.12
22a	0.015	0.06	1	0.12	0.06	2	0.25	0.12	0.015	0.25	0.12
22b	0.015	0.25	2	0.25	0.25	8	0.5	0.25	0.015	0.5	0.25
22c	0.12	0.5	8	1	0.5	8	1	0.5	0.5	1	0.5
22d	0.015	0.12	0.5	0.12	0.12	2	0.5	0.25	0.015	1	0.5
22f	0.03	0.06	0.25	0.06	0.06	0.25	0.03	0.06	0.03	0.015	0.03
22g	0.06	0.12	1	0.012	0.12	1	0.012	0.25	0.12	0.12	0.06
22h	0.015	0.12	2	0.12	0.12	2	0.12	0.25	0.015	0.12	0.12
22i	0.015	0.12	0.5	0.12	0.12	2	0.12	0.25	0.03	0.12	0.06
22j	0.06	0.25	1	0.25	0.12	2	0.12	0.5	0.03	0.12	0.06
22k	0.03	0.06	0.5	0.06	0.06	0.5	0.06	0.12	0.03	0.06	0.03
22l	0.015	1	1	0.12	0.06	2	0.25	0.25	0.06	0.25	0.12
22m	0.06	0.25	0.25	0.12	0.12	0.5	0.25	0.25	0.12	0.06	0.06
22n	0.12	0.25	2	0.25	0.25	4	0.5	0.5	0.06	0.25	1
23f	0.015	0.015	0.06	0.015	0.015	0.25	0.015	0.06	0.015	0.03	0.015
24f	0.03	0.03	0.06	0.03	0.03	0.12	0.03	0.03	0.007	0.007	0.03
25f	0.03	0.06	0.25	0.12	0.12	0.5	0.03	0.06	0.03	0.03	0.03
25i	0.06	0.06	2	0.12	0.12	2	0.25	0.5	0.06	0.25	0.12
26f	0.015	0.06	0.25	0.06	0.03	0.25	0.03	0.12	0.015	0.03	0.015
27f	0.06	0.06	0.25	0.12	0.12	1	0.06	0.12	0.03	0.12	0.03
28f	0.12	1	2	1	0.25	2	0.25	1	0.06	0.25	0.12
29f	0.06	0.25	1	0.25	0.12	1	0.06	0.25	0.015	0.12	0.06
30f	0.03	0.12	0.5	0.12	0.12	0.5	0.03	0.25	0.03	0.06	0.06
31f	0.12	0.5	2	0.5	0.5	2	0.25	0.5	0.12	0.25	0.12
32f	0.25	1	2	1	1	2	0.12	1	0.12	0.25	0.12
33f	0.12	0.5	2	0.5	0.5	1	0.06	0.5	0.03	0.12	0.12
34f	0.06	0.25	0.5	0.12	0.12	1	0.03	0.25	0.03	0.03	0.03
35f	0.12	0.5	4	1	0.5	2	0.06	0.5	0.06	0.12	0.06
36f	0.06	0.25	0.5	0.25	0.25	2	0.25	0.25	0.015	0.25	0.12
37f	0.06	0.25	0.5	0.25	0.25	2	0.25	0.25	0.06	0.25	0.25
38f	0.015	0.12	1	0.12	0.12	2	0.12	0.25	0.015	0.06	0.06
39f	0.06	0.25	0.5	0.25	0.25	1	0.06	0.25	0.015	0.12	0.06
40f	0.12	0.25	2	0.25	0.12	2	0.25	0.5	0.12	0.12	0.12
41f	0.03	0.03	0.25	0.03	0.06	0.25	0.06	0.25	0.03	0.06	0.06
42f	0.06	0.25	4	0.25	0.25	2	0.25	2	0.06	0.12	0.12
43f	0.03	0.25	1	0.12	0.12	2	0.25	0.5	0.015	0.12	0.12
44f	0.06	0.12	1	0.12	0.12	1	0.25	0.5	0.06	0.12	0.06
45f	0.03	0.03	0.25	0.12	0.06	0.5	0.25	0.25	0.12	0.06	0.12
46f	0.06	0.25	1	0.12	0.25	1	0.25	1	0.06	0.25	0.12
47f	0.25	1	8	1	0.5	2	0.25	1	0.25	0.5	0.25
1b	0.06	0.25	0.5	0.25	0.5	0.12	0.06	0.06	0.03	0.12	0.03

[a] Structures are shown in Tables 2 and 3. [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 10799; Ecl, *Enterobacter cloacae* ATCC 23355.

(i.e., all the compounds with a cyclopropyl ring at position 1 of the quinolone ring, eq 2) led to equations where the majority of the selected parameters in eq 1 for all the compounds were statistically significant and the parameter coefficients had the same sign and comparative values as those indicated in eq 1:

$$\log_{10}(1/\mathrm{MIC})\ \mathrm{Ec} = (0.53 \pm 0.10) - (1.24 \pm 0.22)(\log k')^2 - (0.65 \pm 0.23)Q_{8R} + (0.67 \pm 0.25)Q_{C5} + (0.50 \pm 0.09)Y + (0.59 \pm 0.10)C \quad (2)$$

$$n = 69 \qquad r^2 = 0.70 \qquad F = 30\ (99.99\%) \qquad s = 0.29$$

We should note here that the set of compounds analyzed in this regression analysis has a very strong antibacterial activity. Therefore, the range of values for $\log_{10}(1/\mathrm{MIC})$ Ec is very small and, consequently, the correlation coefficient r is not very large. A more detailed statistical analysis of these azetidinyl quinolones will be published elsewhere.

Equations 1 and 2 indicate that better activity would be obtained for those compounds that have a combination of the following characteristics: a small $(\log k')^2$ value, meaning a small capacity factor or a low lipophilicity; a low total-charge value on the atom at position 8 of the quinolone ring plus the charge of its substituent; a large value of charge at position C5 of the quinoline ring; a large value of charge of the heteroatom at position 3 of the azetidine ring; and the presence of an amine substituent instead of an hydroxyl or an alkylamine substituent at position 3 of the azetidine ring. Although not significantly improving the

Table 7. 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
21f	22.3	3.5	108.2
21g	36.7	20.0	277.0
21k	23.3	2.0	80.4
21l	62.1	4.5	135.0
21m	95.0	60.5	355.0
21n	60.5	28.4	265.0
22f	9.0	2.0	22.1
22g	18.6	6.2	123.0
22k	11.2	2.3	70.5
22l	17.9	3.1	163.9
22m	20.0	31.0	70.0
22n	37.5	4.7	61.0
23f	8.7	4.2	102.0
24f	9.6	2.8	38.0
25f	13.8	3.5	95.4
29f	5.1	4.0	56.3
39f	7.5	2.9	109.0
40f	5.7	2.5	54.6
41f	1.3	3.6	37.9
42f	11.9	3.1	>400.0
43f	8.1	6.0	77.9
44f	10.0	2.3	61.0
45f	4.3	3.6	86.9
46f	8.9	3.3	140.0
1b	45.1	3.0	70.3

correlation, other parameters that contributed to a better activity for these azetidinylquinolones were as follows: a volume reduction of substituent at C-7; a low value of charge on the azetidine nitrogen bonded to C-7; and a low value of charge on quinolone ring N-1.

QSAR studies on a variety of quinolones have been reported.[31] Each study concentrates on a particular zone of the quinolones structure, and some of their conclusions are confirmed by our results. Okada et al.[31d] analyzed a smaller set of azetidine and pyrrolidine C-7-substituted quinolones and found a negative parabolic correlation between a calculated value of the partition coefficient (clogP) and the observed activity against Gram-negative bacteria. When we tried to use clogP for our compounds as a measure of lipophilicity, we did not find a statistically significant correlation, while the use of the experimental capacity factor (log k') resulted in a better equation. We also found a negative quadratic correlation between (log k') and the antimicrobial activity, indicating that more lipophilic molecules tend to be less active.

***In Vivo* Activity and Pharmacokinetic Properties.** To determine *in vivo* efficacy, several of these compounds were evaluated in mouse protection tests. Ciprofloxacin (**1b**) was used as a reference compound. Data on oral administration are given for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *E. coli* (Table 7). Most of the *trans*-2-methyl-3-amino derivatives (series **f**) and *trans*-2-methyl-3-methylamino derivatives (series **k**) exhibit analogous or higher *in vivo* efficacy against *E. coli* and *P. aeruginosa* when compared with **1b**. As described for 3-amino- and 3-amino-3-methylazetidine derivatives,[1] series **f** and **k** showed efficacies 4–40 times greater than that of ciprofloxacin. The observed decrease of the overall *in vivo* efficacy for dimethylamino-, aminomethyl-, and (ethylamino)methyl-monosubstituted azetidinylquinolones and 3-methyl-disubstituted azetidinylquinolones,[1] was also present in the corresponding *trans*-2-methyl series **l**, **m**, and **n**.

The trends observed in the *in vitro* activity of *cis*-2-methyl-3-amino- (**g**) and *trans*-2-methyl-3-amino- (**f**) series were also reflected in their *in vivo* efficacy. For instance, 7-(*cis*-2-methyl-3-aminoazetidinyl)-8-fluoroquinolone **22g** was 2–5 times less active, in the mouse protection model, than the corresponding *trans*-substituted analog **22f**.

Table 8. Blood Level of Selected Quinolones after Oral Administration in Mice[a] (50 mg/kg)

compd	AUC[b]	compd	AUC
21f	9.2	**22n**	11.8
21g	3.7	**23f**	12.3
21h	3.6	**24f**	5.2
21j	3.8	**25f**	27.2
21k	10.3	**29f**	16.2
21l	12.1	**33f**	6.9
21m	0.0	**36f**	2.0
21n	3.2	**38f**	16.5
22f	24.5	**39f**	16.9
22g	9.0	**40f**	31.4
22h	14.7	**43f**	30.2
22j	20.6	**44f**	22.3
22k	20.8	**45f**	32.3
22l	23.2	**46f**	25.8
22m	2.3	**1b**[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 recorded at 0.5, 1, 2, and 4 h after dosing (AUC, 0–4 h), μg/mL/h. [c] Ciprofloxacin.

As noted before, the presence of a halogen at position 8 of the quinolone ring improves *in vivo* efficacy for piperazinyl and aminopyrrolidinyl derivatives[32] and for 3-aminoazetidinyl and 3-amino-3-methylazetidinyl derivatives.[1] The results in Table 7 confirm this reported trend regarding *trans*-3-amino-2-methyl-1-azetidinyl derivatives. Overall *in vivo* efficacy in the 1-cyclopropyl series increases in this order: 8-CH < 8-N < 8-CF-5-NH_2 < 8-CCl ≤ 8-CF (**21f** < **25f** < **23f** < **24f** ≤ **22f**); in the 1-(4-fluorophenyl) series the order is 8-N < 8-CH < 8-CF < 8-CCl (**42f** < **39f** < **40f** < **41f**); and in the 1-(2,4-difluorophenyl) series the order of increase is 8-N < 8-CH < 8-CF ≤ 8-Cl (**46f** < **43f** < **44f** < **45f**).

Results of preliminary pharmacokinetic studies of selected compounds in mice are displayed in Table 8. Several selected compounds showed areas under the plasma level curves 10–14 times greater than the reference compound **1b**. Based on data from 1-cyclopropyl derivatives in the **f** (*trans*-3-amino-2-methyl) series, the contribution to oral absorption of the 8-position substituent increases in the order 8-CCl < 8-CH < 8-CF < 8-N (**24f** < **21f** < **22f** < **25f**), which is in agreement with previously reported results[1] for the 3-amino-3-methyl series. The maximum AUCs were observed with the 1-(2,4-difluorophenyl) series, where the contribution of the 8-position substituent to oral absorption increases in the order 8-CF < 8-N < 8-CH < 8-CCl (**44f** < **46f** < **43f** < **45f**). In the 7-(*trans*-3-amino-2-methyl-1-azetidinyl)-8-unsubstituted-quinolone series, the contribution of the 1-substituent to plasma levels increased in the same order reported for 3-amino-3-methyl series:[1] *tert*-butyl < cyclopropyl < 4-fluorophenyl < 2,4-difluorophenyl (**36f** < **21f** < **39f** < **43f**). In this respect, the basic substituent appended at the 3-position of *trans*-2-methylazetidine was critical in the enhancement of blood levels, as observed with monosubstituted and 3-methyl-3-substituted-azetidines.[1] Thus, AUC values for 8-CH quinolones **21** and 8-CF quinolones **22** showed the following increasing trend: aminomethyl < (ethylamino)methyl < amino ≤ methylamino ≤ dimethylamino. Finally, *cis*-2,3-disubstituted

Table 9. Aqueous Solubility of Selected Compounds

compd	solubility,[a] μg/mL	compd	solubility,[a] μg/mL
21f	9.9	**45f**	16.5
21g	6.1	**46f**	10.4
21h	42.2	**21E**	1.5
21j	1.3	**21F**	1.3
21k	9.2	**21H**	44.5
21l	96.3	**21I**	0.8
22f	23.2	**21J**	0.7
22g	23.6	**21K**	9.7
22h	55.9	**22E**	1.8
22j	3.3	**22F**	1.7
22k	13.1	**22H**	58.0
22l	97.1	**22I**	0.8
23f	37.7	**22J**	0.5
24f	12.0	**22K**	23.6
25f	20.3	**23I**	15.3
40f	11.2	**24I**	1.7
43f	31.0	**25I**	13.9
44f	23.4	**1b**	90.0

[a] Solubility determined at 25 °C in a pH 7.4 buffer. See the Experimental Section.

derivatives showed a dramatic AUCs decrease in comparison with their *trans*-2,3-disubstituted counterparts (**21g** and **21h** vs **21f**; **22g** and **22h** vs **22f**).

In summary, 8-haloquinolones bearing a *trans*-3-amino-2-methylazetidine ring at C-7 exhibited very good *in vivo* efficacy against Gram-negative and especially Gram-positive organisms. 1-Cyclopropyl derivatives showed the best *in vitro* overall profile (**22f**, **23f**, **24f**), and 1-(4-fluorophenyl) derivatives (**40f**, **41f**) and 1-(2,4-difluorophenyl) derivatives (**44f**, **45f**) displayed promising pharmacokinetic properties.

Physicochemical Properties. The zwitterionic character displayed by quinolones having a basic substituent at position 7 (as showed in the X-ray structure of **6d**) causes a low water solubility. However, data shown in Table 9 indicate that there are some azetidinylquinolones over 100 times more soluble than others. As shown, all *trans*-2-methylazetidine derivatives (**21f**–**25f**, **21k**–**22k**, and **21l**–**22l**) exhibit improved solubility relative to the corresponding unsubstituted derivatives (**21E**–**22E**, **21F**–**22F**, and **21H**–**22H**), and these, in turn, exhibit enhanced solubility with respect to 3-methylazetidine derivatives (**21I**–**25I**, **21J**–**22J**, and **21K**–**22K**, respectively). The *cis*-2-methyl group exhibits poorer or equal solubility compared to the *trans*-2-methyl group: **21g** < **21f** and **22g** = **22f**. Enlargement of the azetidine alkyl chain from methyl to ethyl led to a large increase in solubility (**21g** < **21h** and **22g** < **22h**), but addition of a methyl group at C-3 led to a large decrease in solubility (**21j** < **21f** and **22j** < **22f**). Based on data from *trans*-2-methyl-3-aminoazetidine derivatives **f** of the 1-cyclopropylquinolones and naphthyridines, the contribution of the 8-position substituent to solubility increases in the order 8-CH < 8-CCl < 8-N < 8-CF (**21f** < **24f** < **25f** < **22f** < **23f**). This arrangement is completely different for 1-(2,4-difluorophenyl)-quinolones and naphthyridines: 8-N < 8-CCl < 8-CF < 8-CH (**46f** < **45f** < **44f** < **43f**).

The influence of lipophilicity of drugs on their *in vivo* biological activities is well-known.[33] Reversed-phase high-performance liquid chromatography (RP-HPLC) has been developed in recent years to predict the classical octanol–water partition coefficient, log *P*.[34] In this work the logarithm of capacity factor (log *k'*) is used as index of lipophilicity and is also directly correlated

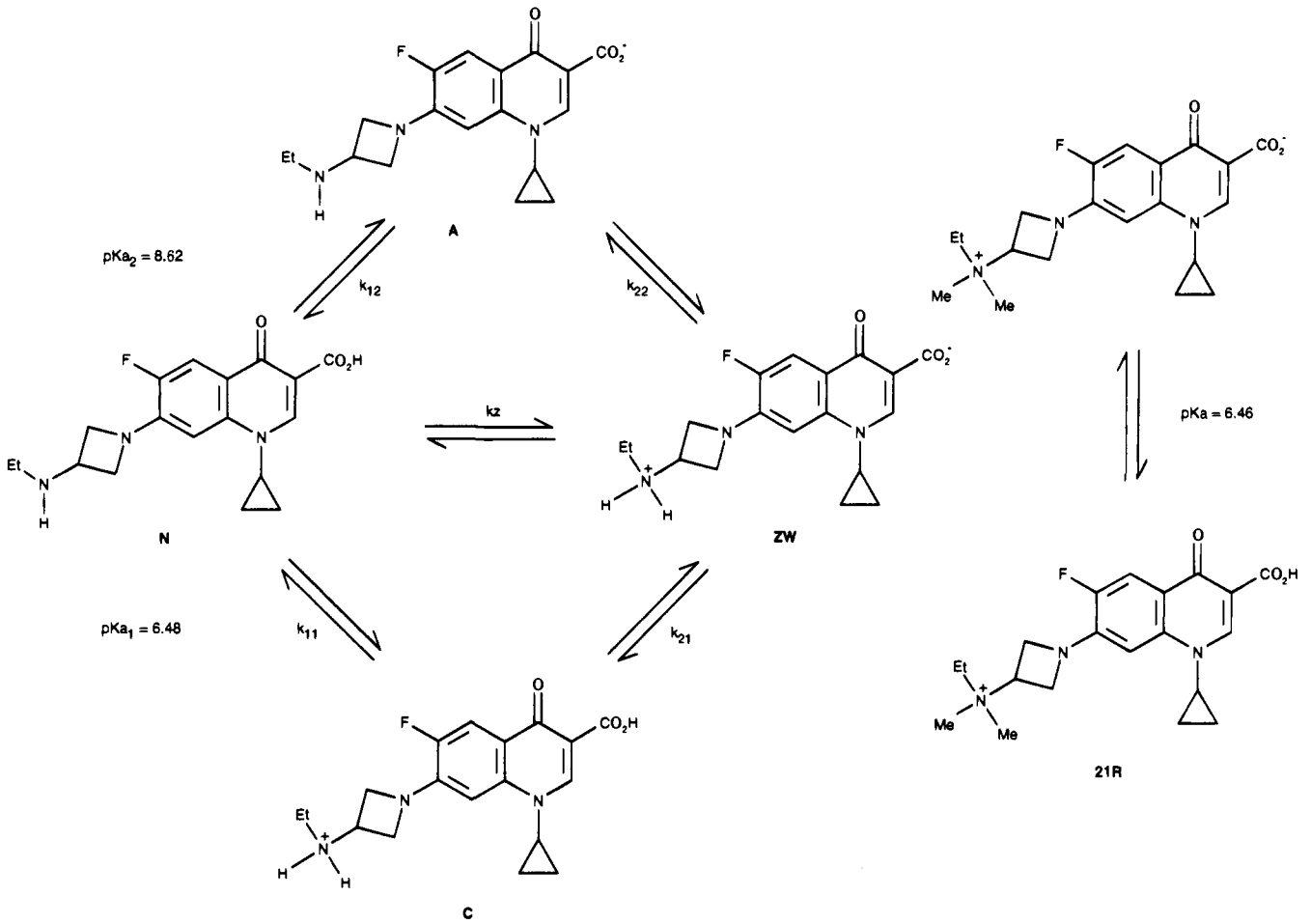
Table 10. Ionization Constants of Selected Compounds

compd	pK_{a_1}	pK_{a_2}	compd	pK_{a_1}	pK_{a_2}
6d	6.48	8.62	**21K**	6.47	7.90
21f	6.46		**21R**	6.46	–
21k	6.50	8.60	**22E**	6.12	8.20
21l	6.29	7.90	**22F**	6.18	8.44
22f	6.13	8.35	**22G**	6.20	8.57
22k	6.13	8.50	**22H**	6.00	8.14
22l	6.08	8.20	**22I**	6.23	8.33
23f	6.65		**22J**	6.26	8.58
24f	6.04	8.47	**22K**	6.05	8.12
25f	6.26	8.31	**22S**	6.03	–
21E	6.49		**23E**	6.65	
21F	6.54	8.56	**23I**	6.71	8.51
21H	6.44	7.81	**24E**	5.96	
21I	6.58	8.55	**24I**	6.08	8.45
21J	6.47	8.65	**25I**	6.38	8.21

with biological activity (see above), as described previously[35] for other classes of compounds. The experimentally determined log *k'* values are summarized in Tables 2–4. Addition of a methyl group on the azetidine ring led to an increase in lipophilicity for 3-methyl and mainly for *trans*-2-methyl, in 1-cyclopropyl 8-unsubstituted, 8-fluoro, 8-fluoro-5-amino, and 8-chloro series (3-aminoazetidine, **21E** < **21I** < **21f**, **22E** < **22I** < **22f**, **23E** < **23I** < **23f**, and **24E** < **24I** < **24f**; 3-(methylamino)azetidine, **21F** < **21J** < **21k** and **22F** < **22J** < **22k**; 3-(dimethylamino)azetidine, **21H** < **21K** < **21l** and **22H** < **22K** < **22l**). Methylation of the exocyclic nitrogen of the azetidine led to an increase in lipophilicity in the order NH_2 < MeNH < Me_2N (**21f** < **21k** < **21l**, **22f** < **22k** < **22l**, etc). An increase in lipophilicity was also observed, when N-1 had a cyclopropyl or a 2,4-difluorophenyl group, from naphthyridines to 8-unsubstituted quinolones, 8-fluoroquinolones, and 8-chloroquinolones (**25f** < **21f** < **22f** < **23f** < **24f**, **46f** < **43f** < **44f** < **45f**). While the *trans*-2-methyl-3-aminoazetidine at C-7 remained constant, the contribution of the radical appended at N-1 to lipophilicity increases in the order fluoroethyl < ethyl < cyclopropyl < 4-fluorophenyl < *tert*-butyl < 2,4-difluorophenyl (**32f** < **28f** < **21f** < **39f** < **36f** < **43f**, **33f** < **29f** < **22f** < **40f** < **37f** < **44f**). An analogous correlation was observed for C-7 3-amino-3-methylazetidinyl-substituted compounds (**28I** < **21I** < **39I** < **36I** < **43I**, **33I** < **29I** < **22I** < **40I** < **37I** < **44I**).

Ionization constants of several compounds were determined by a spectrophotometric method, and results are collected in Table 10. Most of the new azetidinylfluoroquinolones have two ionizable groups at physiologically relevant pH values: the carboxylic acid function at position 3 and the amino group attached to the azetidine ring. Obtained acid ionization constants are in the same range as those recently reported for piperazinylquinolones.[36] The ionization of the azetidinylquinolones can be illustrated (Scheme 5) using **6d** as an example. The X-ray analysis of **6d** has demonstrated that the structure in the solid state shows the zwitterionic form **ZW**. Since **6d** might tautomerize to an uncharged form **N** in solution, we examined which species predominated in the tautomeric equilibrium. To decide to which tautomer cation **C** would dissociate, the pK_a value of quaternary salt **21R** was measured. The pK_a value for **21R** (6.46) was in good agreement with the pK_{a_1} for **6d** (6.48), which corresponds to the dissociation constant of cation **C**, and so pK_{a_2} (8.62) refers to the dissociation of aminoazetidinyl group. On the other hand, since ionizable groups in fluoroquinolones

Scheme 5



are spatially separated, it is reasonable to assume that the charge on one functional group will not affect significantly the dissociation constant of the other ionizable function.[36e] Therefore, if we assume that the microscopic dissociation constants $k_{11} = k_{22}$ and $k_{21} = k_{12}$ (Scheme 5), the resulting values are $k_{21} = 3.28 \times 10^{-7}$, $k_{11} = 2.42 \times 10^{-9}$, and $k_z = 136$, thus showing that **6d** exists mainly in the zwitterionic form **ZW**. The fraction of zwitterionic species and neutral species can then be calculated at any pH; for instance at pH = 7.4 the zwitterionic species is present in 84%.

On the basis of data from the *trans*-3-amino-2-methylazetidine series (**f**), the 3-amino-3-methylazetidine series (**I**), and the 3-aminoazetidine series (**E**) of the 1-cyclopropylquinolones and naphthyridines, the contribution of the 8-position substituent to the acid character of the carboxylic group (pK_{a_1}) increases in the order 5-NH_2-8-CF < 8-CH < 8-N < 8-CF < 8-CCl (**23f** < **21f** < **25f** < **22f** < **24f**; **23I** < **21I** < **25I** < **22I** < **24I**; **23E** < **21E** < **22E** < **24E**). On the other hand, methylation of the azetidine exocyclic nitrogen of 1-cyclopropylquinolones, led to an increase of basic character (pK_{a_2}) in the order Me_2N < NH_2 < MeNH (**22I** < **22f** < **22k**; **22K** < **22I** < **22J**; **22H** < **22E** < **22F**).

The introduction of a methyl substituent to 3-aminopyrrolidine ring of quinolone and naphthyridinone compounds has been shown to be important in modifying their physicochemical and pharmacokinetic properties.[37] The effect of adding a methyl group at different carbons of bridged piperazinylnaphthyridines on physicochemical properties has also been pointed out.[12] In the 1-cyclopropyl-7-azetidinyl series, addition of a methyl group at the 3-aminoazetidine ring (**22E**) led to an increase in lipophilicity of N-methylated (**22F**), 3-methylated (**22I**), and 2-methylated (**22f**) compounds. The solubility of **22F** was not affected; for **22I** a decrease was observed, while for **22f** the increase in solubility was by a factor of 12. The basicity of the azetidine exocyclic nitrogen increased in all three cases, but mainly for **22F**. The pharmacokinetic profiles and chemotherapeutic efficacies depended on the above-mentioned changes in physicochemical properties. Thus, **22I** maintained the overall efficacy of **22E**, but **22F** (3-methylaminoazetidine) and **22f** (*trans*-3-amino-2-methylazetidine) increased *in vivo* potency. At first sight, one would expect a high potency for the *trans*-2-methyl-3-(methylamino)azetidine derivative, but **22k** resulted in a decrease both in efficacy and AUC. If we look at the physicochemical properties of **22k**, we can observe a large increase in lipophilicity and basicity, as well as a decrease in solubility with respect to **22F** and **22f**.

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 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 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 Azetidinols (Scheme 1). *threo*-3-Bromo-1,2-epoxypentane (9c). To a solution of *cis*-2-penten-1-ol (**7c**, 25 g, 0.29 mol) in $CHCl_3$ (24 mL) was added dropwise bromine (15 mL) at room temperature. The reaction mixture was concentrated to dryness to obtain an oil (71.3 g) that was dissolved in diethyl ether (150 mL) and stirred together with a solution of KOH (16.2 g, 0.29 mol) in H_2O (172 mL) for 2 h. The organic phase was concentrated to dryness to give 50 g of an oil that was distilled (70 °C, 14 mmHg) to afford **9c** (35.97 g, 75%): ^{1}H-NMR ($CDCl_3$) δ 1.10 (t, J = 7.1 Hz, 3H), 1.60–2.30 (a.c., 2H), 2.63 (dd, J = 6.0 Hz, J' = 2.3 Hz, 1H), 2.90 (dd, J = 4.6 Hz, J' = 3.9 Hz, 1H), 3.17 (m, 1H), 3.42 (m, 1H).

***trans*-1-(Diphenylmethyl)-2-methyl-3-azetidinol (10a).** A solution of *threo*-3-bromo-1,2-epoxybutane[38] (**1a**, 9.8 g, 64.9 mmol) and diphenylmethylamine (11.8 g, 64.5 mmol) in MeOH (70 mL) was stirred for 80 h at room temperature and then was refluxed for 72 h. The solvent was removed *in vacuo*, and the residue was partitioned with Et_2O and water. The aqueous layer was alkalinized with Na_2CO_3 and was extracted with Et_2O to give **10a** as an oil (9.4 g, 61%): mp hydrochloride 100–103 °C; IR (film) 3400–1450, 1156, 749, 702 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.75 (d, J = 6 Hz, 3H), 2.40 (br, 1H), 2.56 (t, J = 6 Hz, 1H), 3.02 (q, J = 6 Hz, 1H), 3.64 (t, J = 6 Hz, 1H), 3.87 (quint, J = 6 Hz, 1H), 4.43 (s, 1H), 7.25 (m, 10H).

An analogous procedure was used to obtain compounds **10b–d**. Physical and spectral data are given below.

***cis*-1-(Diphenylmethyl)-2-methyl-3-azetidinol (10b)** was obtained from *erythro*-3-bromo-1,2-epoxybutane:[39] mp hydrochloride 112–116 °C; IR (KBr) 3400–3000, 1512, 1449, 1175, 751, 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.73 (d, J = 6.5 Hz, 3H), 2.62 (br, 1H), 3.21 (m, 4H), 4.36 (s, 1H), 7.25 (m, 10H).

***cis*-1-(Diphenylmethyl)-2-ethyl-3-azetidinol (10c):** mp 105–107 °C; IR (KBr) 3200, 2966, 2844, 1600, 1500, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.6 (m, 3H), 1.52 (m, 2H), 2.80–3.30 (m, 4H), 4.32 (s, 1H), 7.00–7.60 (m, 10H).

***trans*-1-(Diphenylmethyl)-2,3-dimethyl-*r*-3-hydroxyazetidine (10d)** was obtained from 3-bromo-2-methyl-1,2-epoxybutane:[40] mp 139–144 °C; IR (KBr) 3330, 1491, 1451, 1183, 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.56 (d, J = 6 Hz, 3H), 1.25 (s, 3H), 2.03 (br, 1H), 2.67 (t, J = 7 Hz, 1H), 3.07 (q, J = 6 Hz, 1H), 3.26 (t, J = 7 Hz, 1H), 4.34 (s, 1H), 7.24 (m, 10H).

Preparation of Azetidinols (Scheme 2). 3-[(Diphenylmethyl)amino]-3-methyl-2-butanone (13). A solution of 3-bromo-3-methyl-2-butanone (**12**,[41] 46.52 g, 0.28 mol), diphenylmethylamine (51 g, 0.215 mol), and triethylamine (43.4 g, 0.43 mol) in methanol (180 mL) was refluxed overnight. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (200 mL), washed with a 10% acetic acid solution (200 mL), and then washed several times with a solution of Na_2CO_3. The organic layer was dried, and the solvent was removed *in vacuo* to obtain **13** as an oil (46 g, 61%): IR (film) 2979, 1708, 1493, 1451, 1121 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.64 (s, 6H), 2.06 (s, 3H), 4.74 (s, 1H), 7.00–7.42 (m, 10H).

2,2-Dimethyl-1-(diphenylmethyl)-3-azetidone (15). To a stirred solution of **13** (21.7 g, 0.081 mol) in acetic acid saturated with HCl (75 mL) was added dropwise bromine (13.01 g, 0.082 mol), and then the solution was stirred for 4 h at room temperature. The solution was poured on a 40% NaOH–ice mixture and extracted with CCl_4 and the organic layer evaporated to dryness. The precipitate was dissolved in DMF (125 mL), and an aqueous $NaHCO_3$ solution (21.3 g) was added. CCl_4 was added and the organic layer washed several times with water. The organic layer was dried and evaporated to dryness to yield **15** (20.9 g, 96%): mp 124–126 °C; IR (KBr) 2972, 1804, 1453, 1206, 1075 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (s, 6H), 3.96 (s, 2H), 4.87 (s, 1H), 7.10–7.80 (m, 10H).

2,2-Dimethyl-1-(diphenylmethyl)-3-azetidinol (10e). To a cooled (0 °C) solution of **15** (20.9 g, 0.078 mol) in methanol (150 mL) was slowly added $NaBH_4$ (25 g, 0.66 mol). Then it was refluxed for 3 h, and some drops of H_2O were added after cooling. The solvent was removed *in vacuo*, and the residue was partitioned with $CHCl_3$ and water. From the organic layer **10e** was obtained as an oil (21.0 g, 100%): mp hydrochloride 179–182 °C; IR (film) 3400, 1493, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.07 (s, 3H), 2.71 (dd, J = 7.7 Hz, J' = 5.8 Hz, 1H), 3.31 (dd, J = 7.7 Hz, J' = 6.4 Hz, 1H), 3.97 (t, J = 6.1 Hz, 1H), 4.57 (s, 1H), 7.00–7.80 (m, 10H).

Preparation of Aminoazetidines (Scheme 3). *trans*-1-(Diphenylmethyl)-2-methyl-3-[(methylsulfonyl)oxy]azetidine (16a). To a stirred solution of **10a** (77.33 g, 0.329 mol) and triethylamine (50 g, 0.495 mol) in CH_2Cl_2 (600 mL) was added dropwise a solution of methanesulfonyl chloride (50 g, 0.437 mol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 24 h at room temperature. The organic solution was washed several times with water (300 mL), and the solvent was removed *in vacuo* to obtain an oil, which was crystallized with petroleum ether to afford **16a** (104.6 g, 96%): mp 70–71 °C; IR (KBr) 1361, 1178, 1152, 708 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.87 (d, J = 6 Hz, 3H), 2.80 (s, 3H), 2.82 (m, 1H), 3.43 (t, J = 7 Hz, 1H), 3.74 (t, J = 7 Hz, 1H), 4.46 (s, 1H), 4.60 (m, 1H), 7.32 (m, 10H).

An analogous procedure was used to obtain compounds **16b–e**. Physical and spectral data are given below.

***cis*-1-(Diphenylmethyl)-2-methyl-3-[(methylsulfonyl)oxy]azetidine (16b):** mp 76–79 °C; ^{1}H-NMR ($CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3H), 3.01 (s, 3H), 3.17 (m, 1H), 3.63 (m, 2H), 4.41 (s, 1H), 5.15 (dt, J = 6.5 and 2.3 Hz, 1H), 7.29 (m, 10H).

***cis*-1-(Diphenylmethyl)-2-ethyl-3-[(methylsulfonyl)oxy]azetidine (16c):** Oil, ^{1}H-NMR ($CDCl_3$) δ 0.64 (m, 3H), 1.60 (m, 2H), 2.70–3.70 (m, 3H), 3.01 (s, 3H), 4.35 (s, 1H), 5.19 (t, J = 5.8 Hz, 1H), 7.00–7.60 (m, 10H).

(*trans*)-1-(Diphenylmethyl)-2,3-dimethyl-*r*-3-[(methylsulfonyl)oxy]azetidine (16d): mp 83–85 °C; IR (KBr) 3299, 1459, 1320, 1301, 1150, 744, 699 cm^{-1}.

2,2-Dimethyl-1-(diphenylmethyl)-3-[(tolylsulfonyl)oxy]azetidine (16e): IR (KBr) 1453, 1366, 1190, 1177, 1031 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.16 (s, 3H), 2.42 (s, 3H), 2.87 (dd, J = 7.9 Hz, J' = 6.5 Hz, 1H), 4.52 (m, 2H), 3.25 (dd, J = 7.9 Hz, J' = 6.5 Hz, 1H), 4.52 (m, 2H), 7.00–7.85 (m, 14H).

***trans*-3-Amino-1-(diphenylmethyl)-2-methylazetidine (18f).** A mixture of **16a** (31 g, 93.65 mmol), 2-propanol (150 mL), and ammonium hydroxide (30%, 100 mL) was heated at 70 °C for 3 h. 2-Propanol was removed *in vacuo*, and the resulting solution was alkalinized with Na_2CO_3 and extracted with CH_2Cl_2 to give **18f** (16.3 g, 70%): mp 68–69 °C; IR (KBr) 3270, 1450, 702 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.64 (d, J = 7 Hz, 3H), 2.20 (q, J = 7 Hz, 1H), 2.63 (t, J = 7 Hz, 1H), 2.90 (quint, J = 7 Hz, 1H), 3.50 (t, J = 7 Hz, 1H), 4.20 (s, 1H), 7.20 (m, 10H).

An analogous procedure was used to obtain compounds **18g–l**. Physical and spectral data are given below.

***cis*-3-Amino-1-(diphenylmethyl)-2-methylazetidine (18g):** mp dihydrochloride 70–71 °C; IR dihydrochloride (KBr) 3350, 1492, 1451, 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.63 (d, J = 6 Hz, 3H), 1.64 (br, 2H), 2.09 (d, J = 4 Hz, 2H), 3.35 (m, 2H), 4.34 (s, 1H), 7.29 (m, 10H).

***cis*-3-Amino-1-(diphenylmethyl)-2-ethylazetidine (18h):** bp 215–235 °C (6.5×10^{-2} mbar); mp dihydrochloride 123–125 °C; IR (film) 3380, 3312, 3025, 2954, 2828, 1600, 1492 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.54 (m, 3H), 1.47 (m, 2H), 1.71 (s, 2H), 3.04 (m, 3H), 3.43 (dt, J = 6.1 Hz, J' = 2.5 Hz, 1H), 4.29 (s, 1H), 7.00–7.60 (m, 10H).

3-Amino-2,2-dimethyl-1-(diphenylmethyl)azetidine (18i): mp 103–106 °C; mp hydrochloride 150–152 °C; IR (KBr) 2964, 1493, 1452, 745, 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.00 (s, 6H), 2.51 (t, J = 6.1 Hz, 1H), 3.27 (m, 2H), 4.54 (s, 1H), 7.00–7.65 (m, 10H).

***r*-3-Amino-1-(diphenylmethyl)-*trans*-2,3-dimethylazetidine (18j):** mp dihydrochloride 172–174 °C; IR dihydrochlo-

ride (KBr) 3500–2200, 1457, 1390, 753, 704 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.53 (d, J = 6.5 Hz, 3H), 1.26 (s, 3H), 1.51 (br, 2H), 2.41 (d, J = 7 Hz, 1H), 2.84 (q, J = 7 Hz, 1H), 3.25 (d, J = 7 Hz, 1H), 4.27 (s, 1H), 7.26 (m, 10H).

***trans*-1-(Diphenylmethyl)-2-methyl-3-(methylamino)-azetidine (18k):** mp 93–95 °C; IR (KBr) 2920, 1960, 1470, 705 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.8 (d, J = 6 Hz, 3H), 1.2 (br, 1H), 2.28 (s, 3H), 2.29 (m, 1H), 2.85 (m, 2H), 3.5 (m, 1H), 4.25 (s, 1H), 7.25 (m, 10H).

***trans*-3-(Dimethylamino)-1-(diphenylmethyl)-2-methylazetidine (18l):** mp dihydrochloride 149–152 °C; IR dihydrochloride (KBr); ^1H-NMR ($CDCl_3$) 0.75 (d, J = 6 Hz, 3H), 2.05 (s, 6H), 2.35 (q, J = 6.5 Hz, 1H), 2.6 (t, J = 6.5 Hz, 1H), 3.15 (quint, J = 6.5 Hz, 1H), 3.5 (t, J = 6.5 Hz, 1H), 4.4 (s, 1H), 7.3 (m, 10H).

***trans*-3-Cyano-1-(diphenylmethyl)-2-methylazetidine (18o).** A mixture of **16a** (16.55 g, 50 mmol) and sodium cyanide (5.5 g, 112.5 mmol) in DMF (45 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 **18o** (10.58 g, 81%): mp 99–104 °C; IR (KBr) 2845, 2240, 1453, 749, 705 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.78 (d, J = 6 Hz, 3H), 2.86 (m, 2H), 3.48 (m, 2H), 4.35 (s, 1H), 7.23 (m, 10H).

***trans*-3-(Aminomethyl)-1-(diphenylmethyl)-2-methylazetidine (18m).** A solution of **18o** (14.35 g, 53.7 mmol) in THF (100 mL) was slowly added to a suspension of LAH (4.07 g, 107 mmol) in THF (170 mL), and the mixture was stirred overnight at room temperature. Excess hydride reagent was eliminated by careful addition of EtOH. The mixture was filtered and evaporated, and the residue was dissolved with $CHCl_3$, washed with water, dried, and evaporated to give **18m** (10.85 g, 76%): mp 84–87 °C; IR (KBr) ^1H-NMR ($CDCl_3$) 0.75 (d, J = 7 Hz, 3H), 1.36 (br, 2H), 2.11 (quint, J = 7 Hz, 1H), 2.42 (t, J = 7 Hz, 1H), 2.72 (d, J = 7 Hz, 2H), 1.94 (q, J = 7 Hz, 1H), 3.46 (t, J = 7 Hz, 1H), 7.26 (m, 10H).

***trans*-1-(Diphenylmethyl)-2-methyl-3-[[(trifluoroacetyl)-amino]methyl]azetidine (18p).** To a stirred solution of **18m** (12.40 g, 46.5 mmol) in $CHCl_3$ (100 mL) was added dropwise a solution of trifluoroacetic anhydride (12.5 g, 58.1 mmol) in $CHCl_3$ (50 mL). The reaction mixture was stirred at room temperature for 2 h, washed with water, 10% $NaHCO_3$, and saturated NaCl, dried, and evaporated to afford **18p** (13.88 g, 82%): mp 122–125 °C; IR (KBr) 3292, 1726, 1705, 1228, 1180, 703 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.85 (d, J = 6 Hz, 3H), 2.24 (q, J = 7 Hz, 1H), 2.54 (t, J = 7 Hz, 1H), 3.16 (quint, J = 7 Hz, 1H), 3.48 (m, 3H), 4.42 (s, 1H), 6.98 (br, 1H), 7.29 (m, 10H).

***trans*-1-(Diphenylmethyl)-2-methyl-3-[[*N*-ethyl-*N*-(trifluoroacetyl)amino]methyl]azetidine (18q).** To a solution of **18p** (3.51 g, 9.7 mmol) in a mixture of 1,4-dioxane (110 mL) and DMF (30 mL) was added sodium hydride (55%, 0.43 g, 9.7 mmol), and the reaction was stirred at 70 °C for 2 h. The mixture was cooled to room temperature, and ethyl iodide (2.0 g, 12.5 mmol) was added. The reaction mixture was then stirred at 70 °C for 4 h, the solvent was evaporated, and the residue was partitioned with $CHCl_3$ and water. The organic layer was dried and concentrated to give **18q** (2.85 g, 76%): mp (hydrochloride) 97–104 °C; IR (film) 1685, 1218, 1144, 704 cm^{-1}.

***trans*-3-Amino-2-methylazetidine Dihydrochloride (19f).** A mixture of **18f** (11.0 g, 33.8 mmol) and 10% $Pd(OH)_2/C$ (1.1 g) in ethanol (200 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 **19f** (4.2 g, 78%): mp 165–168 °C; IR (KBr) 3500–2100, 1561, 1451, 1365, 1403 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.51 (d, J = 7 Hz, 3H), 3.92 (m, 3H), 4.60 (m, 1H), 9.2 (br, 5H).

An analogous procedure was used to obtain compounds **19g–l**, **19p**, and **19q**. Physical and spectral data are given below.

***cis*-3-Amino-2-methylazetidine dihydrochloride (19g):** mp 181–183 °C; IR (KBr) 3300–2300, 1561, 1338, 1188, 1051 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.59 (d, 3H), 4.09 (m, 3H), 4.59 (m, 1H), 9.2 (br, 5H).

***cis*-3-Amino-2-ethylazetidine dihydrochloride (19h):** IR (KBr) 3387, 1462, 1387, 1325 cm^{-1}.

3-Amino-2,2-dimethylazetidine dihydrochloride (19i): mp 168–171 °C; IR (KBr) 3431, 2968, 1581, 1543, 1512 cm^{-1}.

***r*-3-Amino-*trans*-2,3-dimethylazetidine dihydrochloride (19j):** mp 180–183 °C; IR (KBr) 3300–2300, 1596, 1554, 1159 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.38 (d, 3H), 1.53 (s, 3H), 3.57 (d, J = 9.5 Hz, 1H), 4.13 (d, J = 9.5, 1H), 4.67 (m, 1H), 9.2 (br, 5H).

***trans*-2-Methyl-3-(methylamino)azetidine dihydrochloride (19k):** IR (film) 2925, 1618, 1450, 1075 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.61 (d, 3H), 2.63 (s, 3H), 3.50 (m, 1H), 4.03 (m, 2H), 4.84 (m, 1H), 9.7 (br, 2H), 10.2 (br, 2H).

***trans*-3-(Dimethylamino)-2-methylazetidine dihydrochloride (19l):** mp 170–174 °C; IR (KBr) 3300–2300, 1473, 1382, 1252 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.51 (d, 3H), 2.70 (s, 6H), 4.04 (m, 3H), 4.60 (m, 1H), 9.9 (br, 3H).

***trans*-2-Methyl-3-[[(trifluoroacetyl)amino]methyl]azetidine hydrochloride (19p):** mp 130–132 °C; IR (KBr) 3300–2300, 1728, 1492, 1215, 1184, 1158 cm^{-1}.

***trans*-2-Methyl-3-[[*N*-ethyl-*N*-(trifluoroacetyl)amino]-methyl]azetidine hydrochloride (19q):** mp 180–183 °C; IR (KBr) 3210, 1686, 1223, 1191, 1145 cm^{-1}.

General Procedures for the Preparation of Quinolones and Naphthyridines (Scheme 4). Method A. Preparation of 7-(*trans*-3-Amino-2-methyl-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (22f). A mixture containing 1.12 g (3.95 mmol) of 1-cyclopropyl-1,4-dihydro-6,7,8-trifluoro-4-oxo-3-quinolinecarboxylic acid,[21] 0.82 g (5.16 mmol) of *trans*-3-amino-2-methylazetidine dihydrochloride, and 2.03 g (20 mmol) of triethylamine in 20 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 concentrated NH_4OH, and filtered, and the pH was adjusted to 7.2 by elimination of NH_3. The precipitated solid was collected and washed successively with water and ethanol to give **22f** (1.09 g, 79%): mp 234–237 °C; IR (KBr): 3300–2500, 1630, 1579, 1466, 1402, 1319 cm^{-1}; ^1H-NMR (DMSO-d_6, TFA) δ 1.16 (m, 4H), 1.53 (d, J = 6 Hz, 3H), 3.72 (m, 1H), 4.09 (m, 2H), 4.76 (m, 2H), 7.69 (d, J = 2 Hz, 1H), 7.82 (d, J = 2 Hz, 1H), 8.32 (br, 2H), 8.61 (s, 1H).

Method B. Preparation of 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[*trans*-2-methyl-3-(methylamino)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic Acid (22k). A mixture containing 2.6 g (9.2 mmol) of 1-cyclopropyl-1,4-dihydro-6,7,8-trifluoro-4-oxo-3-quinolinecarboxylic acid,[21] 2.57 g (11 mmol) of *trans*-2-methyl-3-(*N*-methyltrifluoroacetamido)azetidine hydrochloride, and 3 g (30 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-[*trans*-2-methyl-3-(*N*-methyltrifluoroacetamido)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic acid (2.25 g, 53%).

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[*trans*-2-methyl-3-(*N*-methyltrifluoroacetamido)-1-azetidinyl]-4-oxo-3-quinolinecarboxylic acid (2.05 g, 4.5 mmol) was treated with 20 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 **22k** (1.1 g, 67%): mp 241–246 °C; IR (KBr) 2930, 1625, 1460, 1322 cm^{-1}; ^1H-NMR (DMSO-d_6, TFA) δ 1.19 (m, 4H), 1.58 (d, J = 6 Hz, 3H), 2.66 (s, 3H), 3.77 (m, 1H), 4.07 (m, 2H), 4.87 (m, 2H), 7.77 (d, J = 13 Hz, 1H), 8.65 (s, 1H).

Method C. Preparation of 3-Carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-[3-(*N*,*N*-dimethyl-*N*-ethylammonio)-1-azetidinyl]quinoline Iodide (21R). To a solution of 1-cyclopropyl-1,4-dihydro-7-[3-(ethylamino)-1-azetidinyl]-6-fluoro-4-oxo-3-quinolinecarboxylic acid[1] (0.52 g, 1.5 mmol) in chloroform (10 mL) and ethanol (30 mL) was added methyl iodide (2.1 g, 15 mmol) and then the mixture was

heated to reflux for 24 h. The precipitate was collected, washed with ethanol, dried, and recrystallized from water to give **21R** (0.44 g, 58%): mp 247–251°C; IR (KBr) 1706, 1626, 1512, 1474, 1391 cm^{-1}; ^1H-NMR (DMSO-d_6, TFA) δ 1.20 (m, 4H), 1.33 (t, 3H), 3.17 (s, 6H), 3.49 (q, 2H), 3.74 (m, 1H), 4.52 (m, 2H), 4.70 (m, 3H), 7.03 (d, 1H), 7.90 (d, 1H), 8.65 (s, 1H).

An analogous procedure was used to obtain compound **22S**. Physical and spectral data are given below.

3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[3-methyl-3-(trimethylammonio)-1-azetidinyl]quinoline iodide (22S): mp 275–282 °C; IR (KBr) 1719, 1625, 1540, 1460, 1336 cm^{-1}; ^1H-NMR (DMSO-d_6, TFA) δ 1.17 (m, 4H), 1.79 (s, 3H), 3.21 (s, 9H), 4.03 (s, 1H), 4.41 (d, 2H), 4.95 (d, 2H), 7.77 (d, 1H), 8.63 (s, 1H).

Single-Crystal X-ray Analysis of 6b–d. Crystallographic data were collected on an Enraf-Nonius CAD4 single-crystal diffractometer with Mo Kα radiation and a graphite crystal monochromator. Unit cell dimensions were determined from the angular settings of 25 reflections within the θ ranges shown in Table 5. Space groups were determined from systematic absences or structure determination. The reflections were measured using the $\omega - 2\theta$ scan technique with a variable scan rate and a maximum scan time of 60 s per reflection. The intensity was checked throughout data collection by monitoring three standard reflections every 60 min. Final drift corrections are shown in Table 5. A profile analysis was performed on all reflections.[42a,b] A semiempirical absorption correction, ψ-scan based, was applied. Symmetry equivalent and double measured reflections were averaged, $R_{int} = \Sigma(|I| - \langle I \rangle)/\Sigma I$. Lorentz and polarization corrections were applied and the data were reduced to $|F_c|$ values. The structure was solved by Direct Methods using the program SHELX86[42c] and Fourier synthesis. Isotropic least-squares refinement, using SHLX76,[42d] was performed until convergence. An empirical absorption correction was applied.[42e] Maximum and minimum correction factors are shown in Table 5. Further refinements included anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms were isotropically refined with a common thermal parameter or individual in some cases. The function minimized was $\Sigma w(F_o - F_c)^2$, $w = 1./(\sigma^2(F_o) + gF_o^2)$ with $\sigma(F_o)$ from counting statistics. Atomic scattering factors were taken from ref 42. The plots were made with the PLUTO program.[42g] Geometrical calculations were made with PARST.[42h] All crystallographic calculations were carried out on a MicroVax-3400. Fractional coordinates, bond distances, bond angles, structure amplitudes, anisotropic thermal parameters, H-atom parameters, distances and angles involving H atoms, distances, angles, and least-squares-planes data and torsion angles are available as supplementary material.

Structure–Activity Relationships. Chem-X[27] and AM1 (MOPAC)[28,29] calculations were run on either a Digital Equipment Corporation (DEC) VAX-8350 or a Silicon Graphics Personal Iris computer. Statistical analyses were carried out using the SAS[30] program package running on either a DEC VAX-8350 or a PC486 computer.

Capacity Factor Studies. A reversed-phase high-performance liquid chromatography (RP-HPLC) procedure was performed on a Waters HPLC system consisting of an M-45 solvent delivery system and a WISP 710B automatic injector. The compounds studied on this system were detected by a Waters 441 absorbance spectrophotometric detector at 280 nm. Retention times were measured using a Merck D-2000 integrator. A 300 × 3.9 mm i.d. stainless-steel column packed with Spherisorb ODS-2 of particle size 10 μm was used. A guard column filled with an RP material was placed just before the column. Capacity factors were determined at 45 °C using an ion-pairing mobile phase composed of 10 mM 1-heptanesulfonic acid sodium salt and 50 mM potassium dihydrogen phosphate aqueous buffer–methanol (45:55, v/v). The pH of the aqueous phase was previously adjusted to 3.5 with orthophosphoric acid. The flow rate was 1 mL/min. Compounds were dissolved in DMF at a concentration of 100 μg/mL. A 10 μL injection was made in duplicate. The capacity factors were calculated according to $k' = (t_R - t_o)/t_o$, where t_R is the retention time of the compound and t_o is that of the solvent front.

Solubility Studies. A known excess weight of the compound was added to pH = 7.4, 0.05 M phosphate buffer, into a suitable container. The solution was shaken for 24 h in a Heto shaking water bath, at 25 °C. The suspension was filtered (0.22-μm filter) and the first portion discarded to ensure saturation of the filter. An aliquot of the filtrate was diluted with either 0.1 N HCl or 0.1 N NaOH and analyzed spectrophotometrically at the wavelength corresponding to the maximum absorbance of the compound.

pK_a Measurements. Ionization constants were determined spectrophotometrically[43] at 20 ± 1 °C. The pH values were measured with a Crison 2001 pH meter and the spectral measurements were carried out with a Hewlett-Packard UV-HP 8452A spectrophotometer in the wavelength range of 200–400 nm. The pH of the fluoroquinolone aqueous solution, at constant 0.1 M ionic strength, was varied by means of acidic (H_2SO_4) and basic (NaOH) solutions diluted in the same compound stock solution. Optimum wavelengths were chosen (for each compound) where the absorbance of all the species varied significantly. The change of absorbance with pH, at the selected wavelength, was monitored. The curve $A = f(pH)$ (at each wavelength) shows two steps. The pH at the inflection points are pK_{a_1} and pK_{a_2}.

Microbiology. General Procedures for *in Vitro* Studies. The *in vitro* antibacterial activity was studied by side-by-side comparison with **1b** 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 four 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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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, bond angles, anisotropic temperature factors, torsion angles, and angles between planes for compounds **6b** (E-4516), **6c** (E-4419), and **6d** (E-4605) and mass spectral data of 7-azetidinylquinolones and naphthyridinones (27 pages). Ordering information is given on any current masthead page.

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