Synthesis and Structure−Activity Relationships of 2-Pyridones: A Novel Series of Potent DNA Gyrase Inhibitors as Antibacterial Agents

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Two novel series of 2-pyridones were synthesized by transposition of the nitrogen of 4-quinolones to the bridgehead position. This subtle interchange of the nitrogen atom with a carbon atom yielded two novel heterocyclic nuclei, pyrido[1,2-*a*]pyrimidine and quinolizine, which had not previously been evaluated as antibacterial agents and were found to be potent inhibitors of DNA gyrase. Quinolizines with a methyl group at the 9-position such as (*S*)-**45a** (ABT-719) demonstrate exceptional broad spectrum antibacterial activity. Most notably, they are active against resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant strains of enterococci, and ciprofloxacin-resistant organisms. In addition, 2-pyridones also possess favorable physiochemical and pharmacokinetic properties. These 2-pyridones were synthesized from the commercially available starting materials by 10−17 linear transformations. The structure of an adduct yielded by this sequence, (*S*)-**45a** (ABT-719), was determined by X-ray crystallographic analysis.

Introduction

Since the introduction of antibacterial fluoroquinolones in the early 1980s,[1] the utility of this class of compounds has flourished for the chemotherapeutic intervention of bacterial infections.[2] Quinolones have the advantages of being broad spectrum are orally active and are unique by virtue of their inhibition of DNA gyrase.[3] Despite their ubiquitous presence in the clinical arena, the limited spectra of activity against streptococci and anaerobes represent obstacles for the use of these drugs in the treatment of infections. The increased frequency of bacterial resistance to quinolones as well as to many other existing antibiotics has emerged as a serious problem.[4−6] Studies have shown that 80% of methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States are now resistant to ciprofloxacin,[6] and some 40% of hospital-acquired staphylococci are resistant to all forms of therapy except vancomycin.[5c] The alarming frequency of *Streptococcus pneumoniae* resistance to penicillin threatens the use of β-lactam agents for the treatment of pneumonococcal infections in the future.[4e] The National Nosocomial Infection Surveillance System[4g] revealed that the occurrence of vancomycin-resistant enterococci (VRE)[4d] in intensive care centers in the United States increased from 0.4% in 1989 to 13.6% in 1992. The absence of clinically useful drugs for the treatment of VRE strains of bacteria poses a therapeutic challenge to the medical community. The potential spread of this type of resistance to other organisms such as *Staph. aureus* underscores an urgent need for potent broad spectrum antibiotics that are efficacious against resistant microbes.

As part of a program designed to identify new DNA gyrase inhibitors, modification of the quinolone ring structure was undertaken by implementation of the methodology pioneered in the carbacephem structural motif.[7] This approach consists of transposition of the nitrogen of 4-quinolones to the bridgehead position (Figure 2). This subtle interchange of the nitrogen with a carbon atom yielded two novel heterocyclic nuclei that had not previously been evaluated as antibacterial agents.[8] This manuscript outlines the full details of the synthesis, physiochemical properties, antibacterial activities, and pharmacokinetics of these two new series of 2-pyridones.[9]

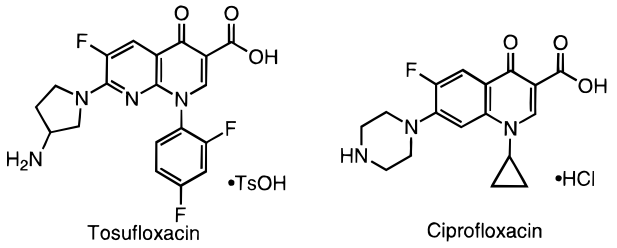

Figure 1. Structures of two clinically utilized 4-quinolones.

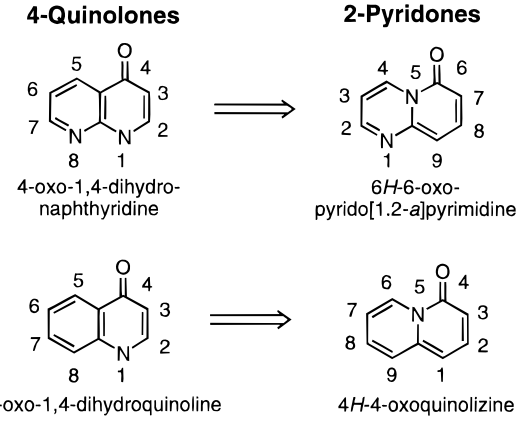

Figure 2. Structures and names of the 4-quinolone and 2-pyridone nuclei.

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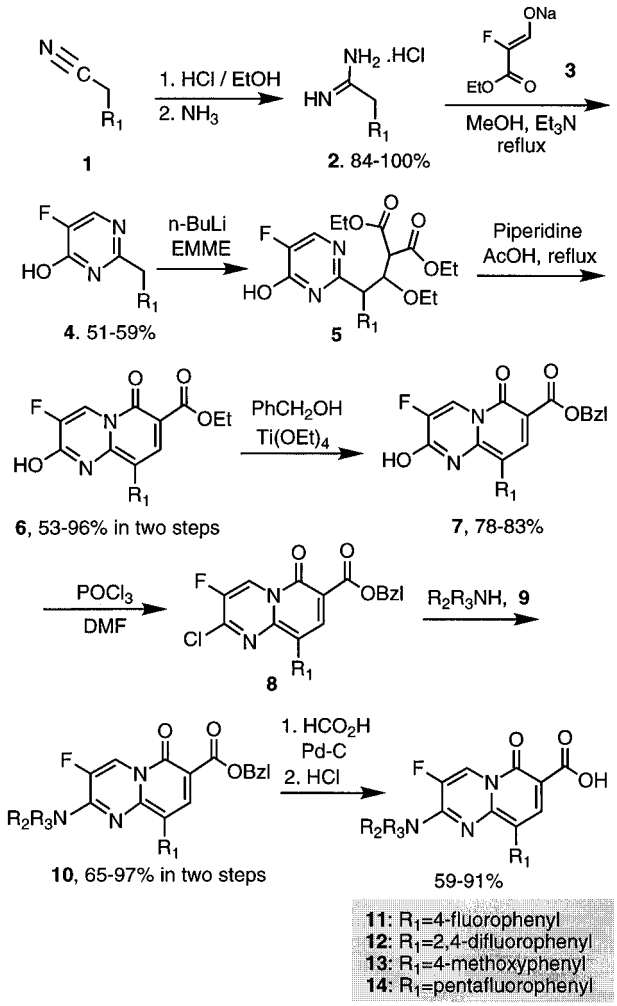
Scheme 1



Chemistry

The synthesis of pyrido[1,2-*a*]pyrimidines **11**−**14** with aromatic R_1 groups is illustrated in Scheme 1. The construction of the 5-fluoropyrimidines **4** was achieved by the cyclization of the amidines **2**, prepared from the corresponding nitriles **1**, with **3**[10] in refluxing methanol in the presence of triethylamine. Treatment of pyrimidines **4** with 2 equiv of *n*-butyllithium at −78 °C and subsequent quenching of the resulting dianions with ethyl (ethoxymethylene)malonate (EMME) yielded the addition products **5**. Cyclization of **5** was realized in refluxing ethanol in the presence of a catalytic amount of piperidine and acetic acid to give **6**. Since alkaline hydrolysis of esters **9** resulted in the destruction of the carbon−nitrogen bond at the 2-position,[11] the ethyl esters **6** were converted to the benzyl esters **7** through titanate-mediated ester exchange reactions.[12] Reaction of **7** with *N*,*N*-dimethylformamide and phosphorus oxychloride in methylene chloride at room temperature provided the 2-chloro compounds **8**. The orange-colored intermediates **8** were found to be very reactive toward nucleophiles and were titrated with amines R_2R_3NH (**9**) to afford **10**. Figure 3 depicts the R_2R_3N groups that were used. When diamines were utilized, one of the nitrogens rendered nonnucleophilic was protected with a *tert*-butyloxycarbonyl group. Removal of the benzyl groups in **10** by hydrogenolysis followed by treatment with hydrochloric acid yielded the desired final products **11**−**14**.

Attempts to extend the above sequence to the synthesis of the 9-cyclopropyl analogs resulted in opening of the adjacent cyclopropyl ring upon formation of the dianion of **4** (R_1 = cyclopropyl). Scheme 2 depicts an alternate route that was developed for the synthesis of the cyclopropyl analogs. Cyclopropylacetonitrile **15** was reacted with sodium hydride and ethyl carbonate in refluxing toluene to give the cyanoacetate **16**[13] in 77% yield. Transformation of **16** to the amidine **17**, followed by cyclization with **3** utilizing the same methods described above, provided a mixture of ethyl and methyl esters. Reduction of the esters with diisobutylaluminum hydride at −78 °C in toluene followed by cyclization with dibenzyl malonate afforded **21** in 47% yield. The same reaction sequence outlined in Scheme 1 was used to synthesize **24** from **21**.

The key synthetic challenge (Schemes 3 and 4) to the synthesis of quinolizinones **42**−**49** was the incorporation of a fluorine atom at the 7-position of the pyridone ring. The starting fluoropyridines **27**−**31**, **33**, and **35** were prepared according to the procedures depicted in Scheme 3. Treatment of the commercially available regioisomerically impure fluoropyridines (**25**, 70% pure, the remainder is 4-chlorotetrafluoropyridine)[14] with 1 equiv of sodium *tert*-butoxide[15] produced **27** in 53% yield in addition to minor quantities of the 6-*tert*-butoxypyridine, while leaving the less reactive 4-chlorotetrafluoropyridine intact. Repeating the same reaction starting with pentafluoropyridine yielded *tert*-butoxytetrafluoropyridine **28** (69%). Hydrogenolysis of **27** with 10% $Pd(OH)_2$ under hydrogen in the presence of triethylamine gave **29** in 83% yield, which followed by lithiation with lithium diisopropylamide (LDA) and subsequent alkylation with methyl iodide or ethyl iodide afforded **30** or **31**, respectively, in high yield, which was used directly in the next step without purification. Conversion of **29** to the hydroxypyridine **32** (84% yield) was achieved by lithiation with LDA followed by reaction with trimethyl borate and subsequent oxidation with hydrogen peroxide. Methylation of **32** by Mitsunobu conditions provided the methoxypyridine **33** in 91% yield. Although direct methylation of **27** with methyllithium failed, reaction with [(trimethylsilyl)methyl]lithium gave a reasonably good yield of **34** (65%). Hydrogenolysis of **34** resulted in the removal of the chlorine atom, and subsequent desilylation afforded **35** in 73% yield.

Synthesis of pyridones **42**−**49** is illustrated in Scheme 4. Selective defluorination of the 6-fluoropyridines **27**−**31** and **33**[16] was effected by replacement of the fluorine atom with hydrazine and oxidation of the hydrazino product with oxygen[17] to give **36** in 47−91% yield. Reaction of the 2-fluoropyridine **35** and **36** with cyclopropylacetonitrile anion yielded **37** in 80−96% yield. No reaction occurred when cyclopropylacetonitrile was substituted with ethyl cyclopropylacetate. All attempts to convert the nitrile **37** directly to the corresponding aldehyde failed. Thus, trifluoroacetic acid-mediated deprotection of the *tert*-butyl ether **37** provided a hydroxypyridine which was chlorinated with phosphorus oxychloride in *N*,*N*-dimethylformamide. Acidic ethanol was used to hydrolyze the nitrile to the ethyl ester **38** in 17−66% yield. Modification of the oxidation state of the oxygen-bearing carbon was achieved by lithium aluminum hydride reduction of the ester followed by Swern oxidation to produce the desired aldehyde. Condensation of the aldehyde with diethyl malonate af-

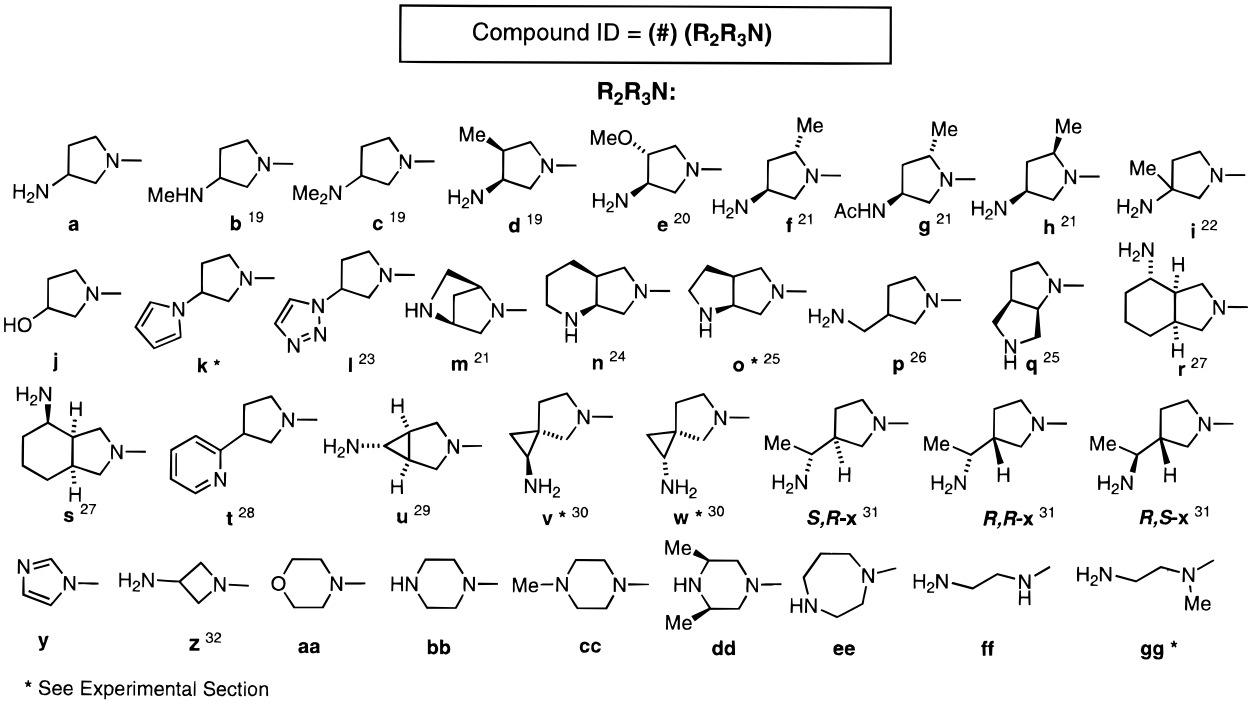
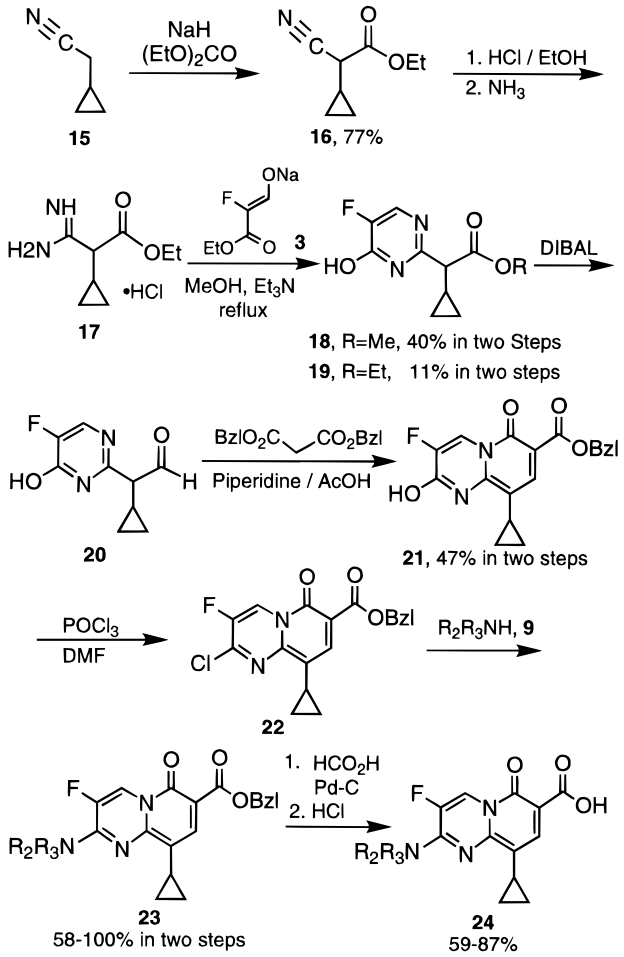


Figure 3. R_2R_3N groups used for this study.

Scheme 2



forded **39**. Thermal cyclization of **39** in Dowtherm A[18] at 240 °C furnished **40** as a yellow solid in 26−73% overall yield. Nucleophilic displacement of the chloride **40** with R_2R_3NH (**9**) in refluxing acetonitrile provided the desired coupled adduct **41**. Lithium hydroxide-mediated hydrolysis of the ester followed by acidic removal of the amine-protecting group completed the synthesis.

Synthesis of the 7-desfluoropyridones was achieved by the lithiation and ethylation of 4-chloro-2-picoline (**50**) as illustrated in Scheme 5, providing **51** in 60% yield. Lithiation of **51**, subsequent reaction with EMME, and thermal cyclization provided **53** in 54% yield. Nucleophilic displacement of the chlorine of **53** with 3-[*N*-(*tert*-butyloxycarbonyl)amino]pyrrolidine followed by acid-mediated removal of the nitrogen-protecting group and subsequent hydrolysis of the ethyl ester afforded **54** in 29% yield.

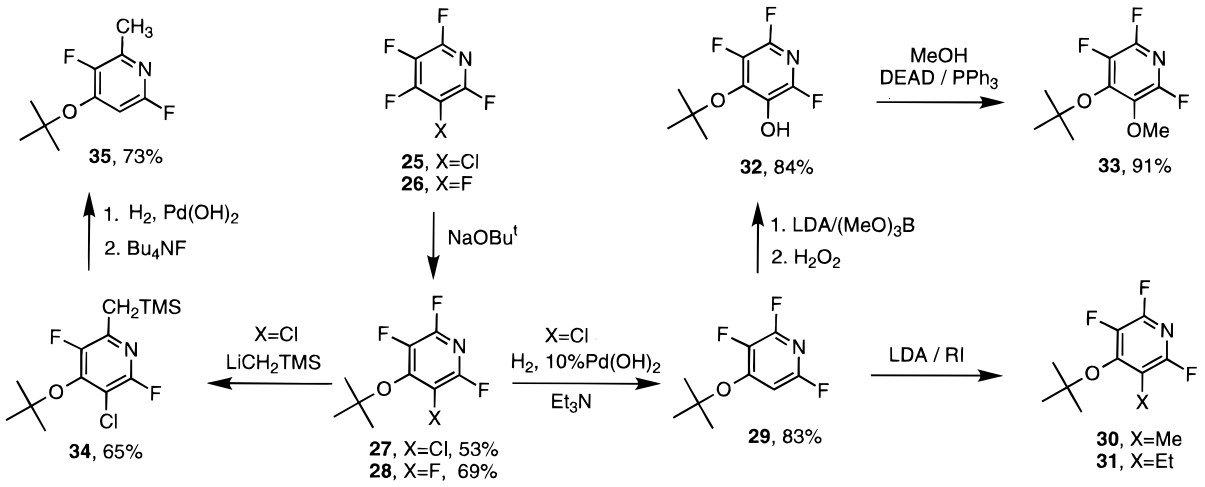
Preparation of the 3-nitromethylcarbonyl analogs was achieved by the hydrolysis of **41** (Y = H, X = CH_3) to acid **45**. Activation of the carboxylic acid moiety of **45** with carbonyldiimidazole followed by reaction with the anion of nitromethane yielded the red-colored 3-nitroacetyl analog **55** in 46% yield after removal of the amine-protecting group under acidic conditions.

The requisite R_2R_3N groups of amines **9** used for this study as discussed earlier are summarized in Figure 3. The amines which were not commercially available were prepared by literature methods as designated.

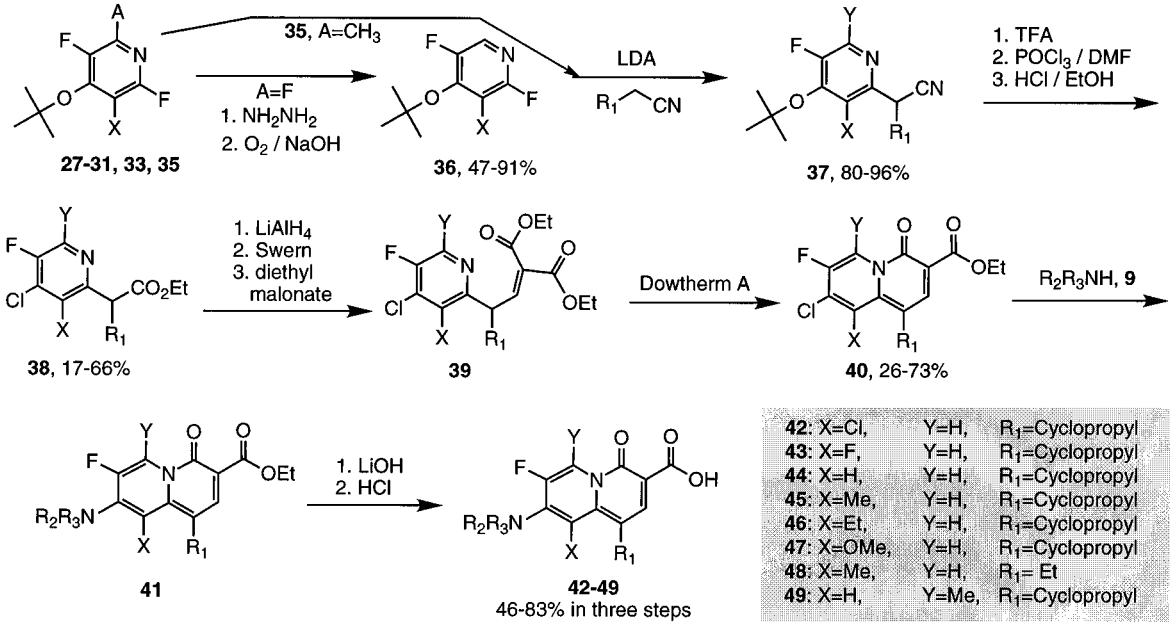
Results and Discussion

The minimum inhibitory concentrations (MICs) of the pyrido[1,2-*a*]pyrimidine analogs (Table 1) against several representative Gram-positive and Gram-negative bacteria are summarized along with data for their isosteres tosufloxacin and ciprofloxacin for comparison purposes. The most active analogs in the 6-oxopyridopyrimidine series are **12a** and **24a** which possess a 2,4-difluorophenyl group and a cyclopropyl group at the 9-position, respectively. Although the isosteric tosufloxacin and **12a** exhibited almost identical activity, the 9-cyclopropyl derivative **24a** showed improved activity against ciprofloxacin-resistant strain of *Staph. aureus* 1775. Substitution of 4-fluorophenyl (**11cc**), 4-methoxyphenyl (**13a**), or pentafluorophenyl (**14a**) at the 9-posi-

Scheme 3

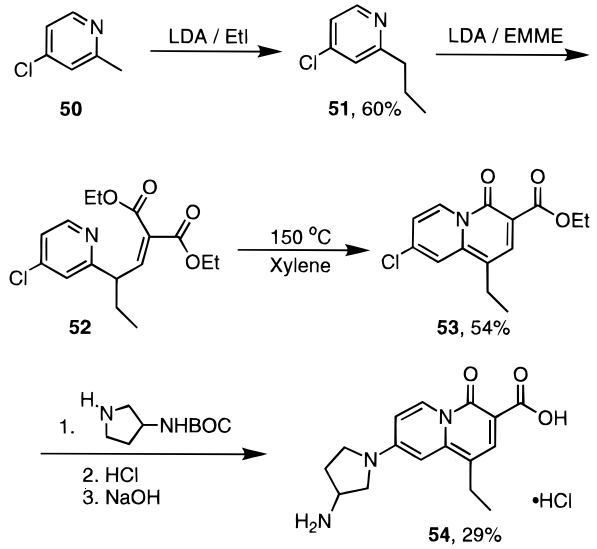


Scheme 4

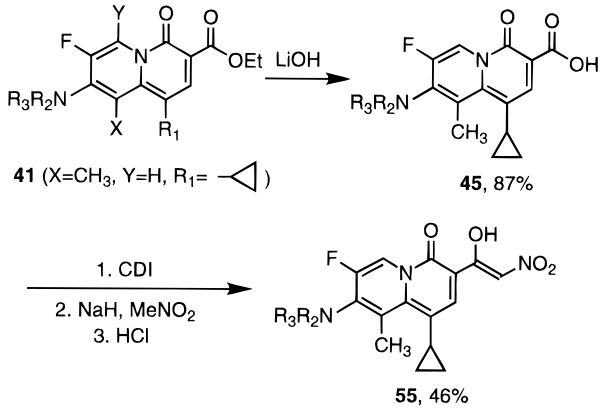


42: X=Cl,	Y=H,	R_1=Cyclopropyl
43: X=F,	Y=H,	R_1=Cyclopropyl
44: X=H,	Y=H,	R_1=Cyclopropyl
45: X=Me,	Y=H,	R_1=Cyclopropyl
46: X=Et,	Y=H,	R_1=Cyclopropyl
47: X=OMe,	Y=H,	R_1=Cyclopropyl
48: X=Me,	Y=H,	R_1= Et
49: X=H,	Y=Me,	R_1=Cyclopropyl

Scheme 5



Scheme 6



tion resulted in significant loss of activity. In general, the 2-(1-piperazinyl) derivatives are much less active than the 2-(3-amino-1-pyrrolidinyl) ones, while the 2-(1-piperazinyl) derivatives are more potent in the context of the 9-(2,4-difluorophenyl) analog versus the 9-cyclopropyl derivative.

The 4-oxoquinolizine series[33] demonstrates much higher levels of *in vitro* antibacterial potency in comparison to the 6-oxopyridopyrimidine series as the MICs are consistently lower than those of ciprofloxacin (Table 2). In general, the structure−activity relationship (SAR) is similar to that of the quinolones,[2e] with some exceptions. Deletion of the fluorine group at the 7-posi-

Table 1. *In Vitro* Antibacterial Activity of Selected Pyrido[1,2-*a*]pyrimidones

	MIC,[a] μg/mL											
	Gram-positive organisms						Gram-negative organisms					
	Staph. aureus										*Pseud. aerug.*	
compd	ATCC-6538p	NCTC-10649M	1775	*Ent. faecium* ATCC-8043	*Strep. bovis* A-5169	*Strep. pyog.* EES61	*E. coli* JUHL	*Ent. aerog.* ATCC-13048	*K. pneum.* ATCC-8045	*Prov. stuartii* CMX-640	5007	DPHD-2862
11cc	0.39	0.39	25	25	25	6.2	0.39	0.78	0.2	25	6.2	
12a	0.1	0.1	>100	0.78	1.56	0.39	0.02	0.05	0.02	1.56	0.39	100
(*S,S*)-**12f**	0.1	0.1	50	0.78	1.56	0.78	0.02	0.1	0.01	6.2	0.39	50
12g	0.1	0.2	25	1.56	3.1	0.78	0.78	3.1	0.39	25	3.1	>100
12j	0.05	0.05	100	0.78	6.2	0.78	0.1	0.39	0.05	6.2	0.78	>100
12cc	0.2	0.2	>100	6.2	12.5	3.1	0.39	0.78	0.2	25	6.2	>100
13a	50	50	100	25	25	25	25	25	12.5	>100	100	50
14a	50	50	>100	>100	>100	>100	6.2	6.2	3.1	>100	50	>100
24a	0.2	0.2	25	1.56	3.1	1.56	0.02	0.02	0.02	1.56	0.39	25
24aa	6.2	6.2	>100	>100	>100	>100	3.1	3.1	0.39	>100	25	
24bb	0.78	1.56	50	12.5	12.5	12.5	0.05	0.05	0.05	12.5	0.39	100
24cc	1.56	0.78	100	12.5	50	12.5	0.2	0.39	0.1	50	3.1	>100
tosufloxacin	0.05	0.05	>100	0.2	0.78	0.39	0.05	0.05	0.02	1.56	0.39	>100
ciprofloxacin	0.2	0.39	>100	0.78	0.78	0.78	0.02	0.02	0.02	1.56	0.2	25

[a] See Experimental Section.

tion (**54** vs **48a** and **44bb**) resulted in substantial loss of activity. The optimal substituent for the 1-position is a cyclopropyl as opposed to an ethyl group (**48** vs **45**). In contrast to the quinolones,[2e,34] the 6-methyl analog **49a** is basically devoid of activity. Judicious substitution at the 9-position of the ring resulted in substantial increase in potency, especially against ciprofloxacin-resistant bacteria. Unlike the quinolone analogs, the 9-halo derivatives[2e,35] **42a** and **43a** and the 9-methoxy derivative[2e,36] **47a** are surprisingly inactive. The 9-methyl analogs[2e,37] **45** are exceptionally active, being at least 5−10 times more potent than the 9-chloro (**42a**), 9-fluoro (**43a**), and 9-methoxy (**47a**) derivatives. The decrease in activity associated with placement of an ethyl group at the 9-position (**46a**) suggests the biological target has difficulty in accommodating bulky substituents in that region of its binding domain.

Cyclic amino substituents at the 8-position of the quinolizine nucleus are presumed to play a crucial role in the binding to gyrase in the ternary complex.[3e] Consequently, extensive modifications of this side chain have been carried out on the most active 9-methyl core. In general, the compounds containing a pyrrolidine group are much more active than piperazine (**45dd**), homopiperazine (**45ee**), azetidine (**45z**), morpholine, and noncyclic amine (**45ff**,**gg**) derivatives. The 3-(aminomethyl)pyrrolidine derivatives are usually more active than the 3-aminopyrrolidine ones, particularly against Gram-positive organisms, but are somewhat less active against *Pseudomonas aeruginosa*. The absolute configuration of the chiral carbon on the amine side chain also affects the activity. The (*S*)-3-aminopyrrolidine (*S*)-**45a**, is about 1−2-fold more active than its enantiomer (*R*)-**45a**. The difference between the potency of the two antipodes is even larger in the cases of 3-hydroxypyrrolidine **45j** and 3-(1-amino-1-ethyl)pyrrolidine **45x**. The most active analog synthesized and also perhaps the most potent antibacterial agent in this class of compounds that has been disclosed in the literature is (*R,S*)-**45x**. When evaluated against resistant bacteria, (*R,S*)-**45x** was found to be over 2000-fold more potent than ciprofloxacin against MRSA. ABT-719 ((*S*)-**45a**) and (*R,S*)-**45x** are about 10 times more potent against ciprofloxacin-sensitive and 16-fold more potent against ciprofloxacin-resistant *P. aeruginosa*. Furthermore, ABT-719 and other 2-pyridones exhibit potent antibacterial activity against strains of vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (Table 3).

According to our proposed model of the mechanism of action of DNA gyrase inhibition,[3e] the 4-carbonyl and 3-carboxylic groups of the quinolone nucleus are intimately involved in the binding of the drug to DNA in the ternary complex. It was surmised that replacement of the carboxylic acid tethered to the 3-position with an acidic nitroacetyl moiety (**55**) would produce an active analog. Biological evaluation of (*S*)-**55a** demonstrates a surprisingly good spectrum of activity against Gram-negative bacteria, and its overall activity is similar to that of ciprofloxacin.

The most potent drug candidate identified was (*R,S*)-**45x**, which exhibited extremely potent *in vitro* activity against ciprofloxacin-sensitive bacteria such as *Staphylococcus*, *Escherichia*, *Enterobacteriaceae*, and *Streptococcus*. It is also very active against organisms that are less sensitive to ciprofloxacin such as *Pseudomonas* and anaerobes.

Several of these compounds were evaluated in a DNA cleavage assay using the purified DNA gyrase isolated from *Escherichia coli* H560 (Table 4). This assay determines the drug concentration that is necessary to achieve one-half of the gyrase-mediated maximal DNA enzymatic cleavage. The poor correlation between MIC data and the cleavage concentration (CC_{50}) data may be a reflection of variables such as cell permeability, cell-killing kinetics, species variability of gyrase, and the presence of a secondary target. Compound (*R,S*)-**45x**, which was the most active compound *in vitro*, had a CC_{50} value of 0.3 μg/mL, only about equipotent *in vitro* to ciprofloxacin. Conversely, ABT-719 ((*S*)-**45a**) exhibited the most potent gyrase activity (CC_{50} = 0.03 μg/mL), approximately 8 times more potent than ciprofloxacin. The 3-nitroacetyl analog (*S*)-**55a** showed only moderate gyrase activity at 3.0 vs 0.24 μg/mL for ciprofloxacin, although they have similar MICs.

The *in vivo* efficacies of several of the compounds were determined in acute murine lethal infections. The results are shown in Table 5 against *Staph. aureus*, *Strep. pneumoniae*, *E. coli*, and *P. aeruginosa*. An interesting feature of these results is that the ED_{50} ratio of oral (po) versus subcutaneous (sc) dosage of drug for most of the selected compounds is substantially less

Table 2. *In Vitro* Antibacterial Activity of Selected Quinolizinones

	MIC,[a] μg/mL											
	Gram-positive organisms						Gram-negative organisms					
	Staph. aureus										*P. aerug.*	
compd	ATCC-6538p	NCTC-10649M	1775	*Ent. faecium* ATCC-8043	*Strep. bovis* A-5169	*Strep. pyog.* EES61	*E. coli* JUHL	*Ent. aerog.* ATCC-13048	*K. pneum.* ATCC-8045	*Prov. stuartii* CMX-640	5007	DPHD-2862
42a	0.2	0.2	6.2	0.39	0.78	0.39	0.05	0.1	0.05	3.1	0.39	6.2
43a	0.1	0.1	6.2	0.78	0.78	0.78	0.01	0.02	0.01	3.1	0.39	6.2
44bb	0.2	0.39	50	0.78	3.1	1.56	0.01	0.05	0.01	1.56	0.39	25
45a	0.01	0.01	1.56	0.02	0.02	0.02	0.002	0.005	0.002	0.2	0.05	0.78
(*S*)-**45a** (ABT-719)	0.01	0.01	0.78	0.02	0.02	0.02	0.002	0.005	0.005	0.2	0.05	0.78
(*R*)-**45a**	0.01	0.02	1.56	0.05	0.1	0.05	0.005	0.01	0.005	0.2	0.05	1.56
(*S*)-**45b**	0.0.2	0.02	1.56	0.1	0.1	0.05	0.005	0.02	0.005	0.39	0.2	1.56
(*S*)-**45c**	0.05	0.05	0.78	0.1	0.39	0.1	0.02	0.1	0.02	3.1	0.39	12.5
45d	0.02	0.02	0.78	0.05	0.02	0.05	0.005	0.02	0.005	0.78	0.1	1.56
45e	0.05	0.05	3.1	0.39	0.39	0.39	0.05	0.2	0.05	3.1	1.56	25
(*S,S*)-**45f**	0.01	0.01	1.56	0.1	0.05	0.05	0.005	0.05	0.01	0.78	0.2	3.1
(*S,R*)-**45h**	0.01	0.02	0.78	0.05	0.1	0.2	0.1	0.1	0.01	3.1	0.78	3.1
45i	0.02	0.05	1.56	0.1	0.1	0.1	0.01	0.05	0.01	0.78	0.2	6.2
45j	0.01	0.005	0.2	0.05	0.05	0.05	0.02	0.02	0.02	0.2	0.2	6.2
(*S*)-**45j**	0.005	0.005	0.39	0.05	0.1		0.02	0.1	0.01	0.39	0.39	3.1
(*R*)-**45j**	0.02	0.02	1.56	0.2	0.2		0.1	0.2	0.02	0.78	0.78	25
(*S*)-**45k**	0.02	0.01	0.39	0.1	0.2	0.1	0.1	0.39	0.05	1.56	1.56	25
45l	0.01	0.01	0.78	0.05	0.2	0.05	0.01	0.2	0.05	0.39	0.39	12.5
(*S,S*)-**45m**	0.1	0.2	6.2	0.2	0.39	0.2	0.02	0.1	0.05	0.78	0.2	6.2
45n	0.01	0.02	0.78	0.1	0.05	0.01	0.05	0.05	0.01	0.78	0.39	3.1
(*S,S*)-**45n**	0.01	0.01	0.39	0.1	0.05	0.05	0.005	0.02	0.01	0.39	0.2	3.1
(*R,R*)-**45n**	0.05	0.05	0.78	0.1	0.05	0.05	0.05	0.05	0.005	1.56	0.78	12.5
45o	0.02	0.02	0.39	0.05	0.05	0.05	0.02	0.05	0.01	0.78	0.39	6.2
(*S,S*)-**45o**[b]	0.05	0.05	3.1	0.1	0.1		0.02	0.05	0.01	0.39	0.2	3.1
(*R,R*)-**45o**[b]	0.05	0.1	6.2	0.2	0.39		0.05	0.05	0.02	0.39	0.39	6.2
45p	0.002	0.002	0.39	0.01	0.002	0.002	0.005	0.01	0.005	0.39	0. 1	1.56
45q	0.05	0.05	6.2	0.1	0.1	0.1	0.001	0.05	0.02	1.56	0.39	3.1
45r	0.005	0.005	0.39	0.02	0.01	0.02	0.02	0.1	0.02	0.78	0.39	6.2
45s	0.005	0.005	0.1	0.02	0.002	0.005	0.01	0.1	0.02	0.39	0.39	6.2
45t	0.01	0.02	0.2	0.05	0.05	0.05	0.05	0.78	0.05	1.56	0.78	12.5
45u	0.02	0.02	1.56	0.1	0.1	0.1	0.01	0.02	0.01	0.78	0.2	6.2
45v	0.002	0.02	0.39	0.05		0.01	0.01	0.05	0.005	0.39	0.39	3.1
45w	0.005	0.01	0.39	0.05		0.02	0.01	0.05	0.01	0.78	0.39	6.2
(*S,R*)-**45x**	0.002	0.002	0.2	0.01	0.005	≤0.001	0.01	0.02	0.01	0.39	0.2	3.1
(*R,R*)-**45x**	0.002	0.002	0.39	0.01	0.01	0.005	0.001	0.01	0.001	0.78	0.2	6.2
(*R,S*)-**45x**	≤0.001	≤0.001	0.05	≤0.001	≤0.001	≤0.001	≤0.001	0.01	0.005	0.2	0.05	1.56
45y	0.1	0.2	6.2	0.39		1.56	0.39	0.39	0.2	12.5	6.2	>100
45z	0.1	0.05	6.2	0.2	0.78	0.39	0.01	0.05	0.01	1.56	0.2	12.5
45dd	0.1	0.1	6.2	0.39	0.78	0.39	0.02	0.1	0.02	3.1	1.56	12.5
45ee	0.1	0.2	25	0.2	0.78	0.39	0.02	0.1	0.05	3.1	0.78	6.2
45ff	0.78	1.56	>100	3.1	12.5	6.2	0.2	0.39	0.2	6.2	0.78	50
45gg	1.56	1.56	>100	3.1	12.5	12.5	0.78	1.56	0.2	25	6.2	>100
46a	0.1	0.1	6.2	0.39		0.39	0.2	0.39	0.1	3.1	1.56	50
47a	0.05	0.05	3.1	0.2	0.39	0.2	0.02	0.05	0.01	1.56	0.39	3.1
48a	0.1	0.1	12.5	0.2	0.78	0.39	0.01	0.05	0.02	0.78	0.2	12.5
49a	0.78	1.56	50	6.2	6.2	3.1	0.2	0.39	0.1	12.5	1.56	100
54	3.1	6.2		50	25	25	3.1	3.1	3.1	25	6.2	
(*S*)-**55a**	0.05	0.1	6.2	0.39	0.2	0.2	0.02	0.1	0.02	1.56	0.39	6.2
ciprofloxacin	0.2	0.39	>100	0.78	0.78	0.78	0.02	0.02	0.02	1.56	0.2	25

[a] See Experimental Section. [b] The absolute configurations are assigned arbitrarily.

Table 3. MICs of Selected 2-Pyridones against Vancomycin-Resistant Enterococci (μg/mL)[a]

compd	*E. faecium* Van A	*E. faecalis* Van B
(*S*)-**45a** (ABT-719)	0.25	0.03
(*S*)-**45b**	0.5	0.06
45n	0.5	0.06
(*S*)-**45k**	0.5	0.03
(*S*)-**45c**	1	0.12
45p	0.03	0.015
ciprofloxacin	4	1
vancomycin	>128	32

[a] See Experimental Section.

than that of ciprofloxacin. The clinical utility of this feature in pharmacodynamic profile remains to be elucidated but is consistent with relatively high oral bioavailability. In accordance with the *in vitro* results, most compounds were significantly more effective against Gram-positive bacteria than ciprofloxacin, especially against *Strep. pneumoniae.* While the efficacy of the compounds against Gram-negative bacteria, especially against *P. aeruginosa*, is inferior compared to Gram-positive bacteria, the 2-pyridones are comparable to ciprofloxacin in most cases. Three of the most potent drug candidates *in vitro* in this series (ABT-719 ((*S*)-**45a**), (*S,S*)-**45n**, and (*R,S*)-**45x**) demonstrated also the best overall effectiveness *in vivo.* Although the hydroxypyrrolidine analog **45j** showed excellent activity *in vitro*, it was only moderately effective against Gram-positive and almost inactive against Gram-negative bacteria *in vivo.* This result suggests that a basic amine group at the 8-position is required for optimal *in vivo* efficacy. The biological properties of the molecule such as bioavailability and serum binding change as a function of this basic nitrogen and may be responsible for this enhanced efficacy. Analogous to the *in vitro* activity differences observed for compounds in opposite enantiomeric series, (*S*)-**45a**/(*R*)-**45a**, (*S,S*)-**45n**/(*R,R*)-**45n** and (*S,S*)-**45o**/(*R,R*)-**45o**, (*S,R*)-**45x**/(*R,S*)-**45x** exhibited different *in vivo* activities. Although the 9-chloro analog **42a** is substantially less potent *in vitro* in

Table 4. Activity of Gyrase-Mediated DNA Cleavage of Selected Pyridones

compd	CC_{50},[a] μg/mL	compd	CC_{50},[a] μg/mL
12a	0.5	**45n**	0.3
(*S*,*S*)-**12f**	0.5	**45o**	0.1
12g	1.3	**45p**	0.05
12j	0.5	**45q**	0.4
14a	12.5	**45r**	0.3
24a	0.15	**45s**	0.3
24aa	1.5	**45t**	2.6
24bb	2.0	**45u**	0.3
24cc	1.0	(*S*,*R*)-**45x**	0.6
42a	0.31	(*R*,*R*)-**45x**	0.4
43a	2.2	(*R*,*S*)-**45x**	0.3
44bb	0.15	**45y**	0.3
45a	0.05	**45z**	1.5
(*S*)-**45a** (ABT-719)	0.03	**45dd**	1.8
(*R*)-**45a**	0.15	**45ff**	0.8
(*S*)-**45b**	0.08	**47a**	0.3
45d	0.06	**48a**	3.2
(*S*,*S*)-**45f**	0.2	**49a**	10
(*S*)-**45k**	0.04	(*S*)-**55a**	3.0
45l	0.07	ciprofloxacin	0.24

[a] CC_{50} is defined as the drug concentration which causes 50% of the gyrase (*E. coli* H560)-mediated maximal DNA cleavage. See Experimental Section.

comparison to ABT-719, it is almost equally effective *in vivo*. The 3-nitroacetyl group does not appear to be a good pharmacophore in this SAR as (*S*)-**55a** did not exhibit significant efficacy *in vivo* despite its moderate *in vitro* activity. In the pyridopyrimidine series, the most active compound was **12a**, which possesses a 9-difluorophenyl and a 2-(3-aminopyrrolidine) group. A few simple amino acid prodrugs[38] (**12a**-*N*-Ala, **12a**-*N*-Ala-Ala, **12a**-*N*-Nov) were prepared in order to improve the solubility and perhaps also the *in vivo* efficacy. These experiments met with limited success since only **12a**-*N*-Ala-Ala demonstrated improved efficacy against *Staph. aureus*.

Solubility and Pharmacokinetic Properties. In order to optimize the *in vivo* efficacy, a limited systematic study of the pharmacokinetic properties (maximum plasma concentration (C_{max}), plasma half-life ($t_{1/2}$), and percent bioavailability (F)), as well as solubility at physiological pH (7.4 in phosphate buffer saline), was undertaken (Table 6). Almost all of the compounds tested exhibited enhanced aqueous solubility relative to ciprofloxacin. The isostere of tosufloxacin (**12a**) is 2.5 times more soluble than tosufloxacin. Synthesis of the *N*-Ala-Ala prodrug of **12a** (**12a**-*N*-Ala-Ala) significantly increased the water solubility from 0.02 to 1.0 mg/mL. Surprisingly, the least aqueous soluble analogs by virtue of their nonzwitterionic nature, **45j**,**l**, demonstrated the highest C_{max} (1.42 μg/mL). Although the 8-piperazinyl analogs **44bb** and **45dd** showed diminished levels of *in vitro* antibacterial activity, they exhibited half-lives and bioavailabilities better than the simple aminopyrrolidine analogs **45a**−**c**. As noted before, chirality has a remarkable pharmacokinetic and physiochemical effect ((*S*)-**45a**/(*R*)-**45a**, (*S*,*S*)-**45n**/(*R*,*R*)-**45n**). The *S*-isomers in both cases have 3−10 times higher C_{max} and 3 times higher bioavalability than the *R*-isomers. All three of the most potent members of this study, ABT-719 ((*S*)-**45a**), (*S*,*S*)-**45n**, and (*R*,*S*)-**45x**, showed excellent solubility and pharmacokinetic properties.

The mean plasma concentrations of ABT-719 ((*S*)-**45a**), (*R*)-**45a**, and **44bb** relative to ciprofloxacin after single oral administration in rats of 5 mg/kg are illustrated in Figure 4. The isostere of ciprofloxacin, **44bb**, was about 3 times greater in aqueous solubility, C_{max}, and bioavailability. This example is indicative of the differences between quinolones and 2-pyridones. In general, the 2-pyridones have not only exhibited enhanced aqueous solubility but are also more soluble in organic solvents. Apparently, transposition of the nitrogen of a quinolone to the bridgehead position results in a change to the overall polar nature of the molecule and perhaps a perturbation to the planarity of the core structure that is associated with molecular packing. These changes are associated with a favorable change in the solubility and pharmacokinetics of the 2-pyridones.

The regiochemistry of the substituents on the pyridone ring was verified through the X-ray structure of a single crystal of ABT-719 ((*S*)-**45a**) (Figure 5). The steric congestion created by the interaction of the methyl group with the cyclopropane forces the methyl and cyclopropyl groups out of the plane of the pyridone ring with a twist that was estimated to be approximately 30°. This deviation from planarity appears to be responsible for the enhanced solubility of the 2-pyridones. Another salient structural feature that was observed was that the nitrogen atom of the pyrrolidine that is attached to the 8-position adopts an sp^2 configuration despite the steric congestion. Figure 5 shows two molecules of ABT-719 self-assembled head to tail through $\pi-\pi$ stacking with an average distance of about 3.4 Å. It is speculated that the type of packing observed in ABT-719 is perhaps the most favorable for gyrase binding and is in accordance with a proposed ternary model.[3e]

Summary of the Results

In conclusion, the synthesis of novel substituted 2-pyridones by transposition of the nitrogen of 4-quinolines to the bridgehead position has been described. This subtle interchange of the nitrogen atom with a carbon atom yielded two novel heterocyclic nuclei that had not previously been evaluated as antibacterial agents. The 2-pyridones have been shown to be excellent DNA gyrase inhibitors. They exhibit broad spectrum antibacterial activity and are potent against organisms that are resistant to many of the clinically utilized fluoroquinolones. Most notably they were active against resistant bacteria such as MRSA, vancomycin-resistant strains of enterococci, and ciprofloxacin-resistant organisms. In addition, 2-pyridones possess favorable physiochemical and pharmacokinetic properties. The brevity and conciseness of the synthesis as well as the excellent antibacterial activity of these molecules will expedite the biological evaluation of numerous analogs of the 2-pyridones.

Experimental Section

General. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a General Electric QE300 spectrometer. A Varian Unity 500 spectrometer was used for ^{19}F NMR spectra. Chemical shifts are reported in parts per million relative to Me_4Si for ^1H NMR and $CFCl_3$ for ^{19}F NMR as internal standards. The desorption chemical ionization (DCI/NH_3) and fast atom bombardment (FAB) mass spectra were measured on a Finnigan SSQ 700 instrument and Finnigan MAT 95 instrument, respectively. IR spectra were taken on either Nicolet 5 SXC or 60 SX FT IR instruments. Column chromatography refers to flash column chromatography conducted on E. Merck silica gel 60 (230−400 mesh). THF was distilled from sodium/benzophenone ketyl. All other solvents and reagents

Table 5. *In Vivo* Efficacy of Selected Pyridones in Mice[a]

	ED$_{50}$, mg/kg[b,c]							
	Staph. aureus NCTC-10649M		*Strep. pneum.* ATCC-6303		*E. coli* JUHL		*P. aeruginosa* 5007	
compd	sc[d]	po[e]	sc	po	sc	po	sc	po
12a	4.4	12.0	–[f]	–	1.0	5.6	10.3	42.1
12a-*N*-Ala	2.7	14.4	79.8	164.2	<2.5	16.6	34.4	68.8
12a-*N*-Ala-Ala	2.8	3.0	49.7	140.5	<2.5	14.3	14.8	68.8
12a-*N*-Nov	8.0	>24.0	–	–	<2.5	25.0	11.4	29.8
12f	>8.0	12.8	>50	>70	4.8	>20.0	>50	>100
12f-*N*-Ala-Ala	11.4	25.3	–	–	3.3[g]	26.7[g]	–	–
24a	>8.0	>12.0	–	–	1.0	4.7	–	–
42a	1.6	5.7	8.5[h]	11.1[h]	1.0	5.6	3.3	17.0
43a	2.9	14.6	–	–	–	–	–	–
45a	1.0[h]	4.1[h]	6.2[h]	12.5[h]	0.4	<0.3	0.5[h]	4.6[h]
(*S*)-**45a** (ABT-719)	0.6	3.4	1.6	5.3	0.1	0.6	1.9	14.5
(*R*)-**45a**	0.9	<3.1	–	–	0.3	1.0	2.4	6.2
(*S*)-**45b**	0.9	<3.1	–	–	0.7	1.1	2.8	7.2
(*S*)-**45c**	4.7	25.0	>25.0[h]	44.1[h]	1.9	>10.0	–	–
45s	0.3	1.4	–	–	–	–	>8.0	>50
45j	11.3	15.2	7.4[g]	41.5[g]	>1.0[g]	>5.0[g]	>8.0	>50
(*S*)-**45j**	1.5	5.3	>2.0[g]	>10.0[g]	–	–	–	–
(*R*)-**45j**	6.1	11.2	>2.0[g]	>10.0[g]	–	–	–	–
45n	0.9	3.1	4.4[h]	12.5[h]	1.0[h]	3.3[h]	>8.0	36.4
(*S,S*)-**45n**	0.5[h]	2.5[h]	2.2	3.6	–	1.0	>8.0	21.4
(*R,R*)-**45n**	6.1[h]	29.3[h]	>8.0	32.2	>1.0	–	>8.0	>50
45o	0.7	5.0	4.5[g]	7.6[g]	0.4	2.5	6.4[h]	39.9[h]
(*S,S*)-**45o**	1.5	5.0	2.3[g]	11.2[g]	0.8	>10.0	18.0	>50
(*R,R*)-**45o**	0.6	1.5	–	–	0.5	1.1	5.0	17.9
45q	1.8	3.6	6.4[h]	9.5[h]	1.1[h]	3.6[h]	>8.0	42.8
45u	4.1	14.6	–	6.7	1.4	>10.0	18.0	>50
45v	1.2	6.3	–	–	–	–	–	–
45w	1.5	6.3	–	–	1.9	12.8	–	–
(*S,R*)-**45x**	0.3[g]	1.2[g]	–	–	–	–	>8.0	33.0
(*R,R*)-**45x**	<0.2	1.1	–	–	0.5[g]	5.7[g]	5.4[g]	24.4[g]
(*R,S*)-**45x**	<0.2[g]	7.2[g]	<1.3	<3.1	0.5	3.3	1.0	13.0
45dd	4.4	4.8	>8.0	49.4	1.3	2.1	>8.0	12.7
(*S*)-**55a**	>12.0	25.2	>8.0	>50	>5[g]	>10[g]	3.2	>50
ciprofloxacin	4.1	28.2	19.1	>100	0.1	1.0	0.8	21.1

[a] See Experimental Section. [b] Effective dosage that protects 50% of mice from lethal infection. [c] Unless otherwise indicated, mice were infected at 100 × LD$_{50}$. [d] sc: subcutaneously administered. [e] po: orally administered. [f] Not tested. [g] Mice were infected at 10 × LD$_{50}$. [h] Mice were infected at 1000 × LD$_{50}$.

Table 6. Aqueous Solubility and Pharmacokinetic Properties of Selected 2-Pyridones

		PK after a 5 mg/kg single oral dose in rats[a]		
compd	solubility,[b] mg/mL	C_{max},[c] μg/mL	$t_{1/2}$,[d] h	F,[e] %
12a	0.02[f]	–[g]	–	–
12a-*N*-Ala-Ala	1.0	–	–	–
44bb	0.25	0.30	3.4	46
(*S*)-**45a** (ABT-719)	0.25	0.27	1.2	32
(*R*)-**45a**	0.10	0.08	1.1	10
45b	>3.7	0.36	1.8	44
45d	–	0.17	2.1	23
(*S,S*)-**45f**	0.07	0.74	1.6	44
45j	0.003	1.42	5.4	50
45l	0.001	1.42	4.8	32
(*S,S*)-**45n**	3.1	0.53	3.5	42
(*R,R*)-**45n**	–	0.05	3.0	13
45o	–	1.13	4.1	62
45q	1.94	0.33	5.7	41
(*R,R*)-**45x**	–	0.25	5.7	40
(*R,S*)-**45x**	0.10	0.05	7.1	18
45dd	1.77	0.49	4.5	87
47a	0.35	0.18	1.3	25
ciprofloxacin	0.08	0.15	3.0	16

[a] See Experimental Section. [b] Solubility determined in pH 7.4 phosphate buffer solution (0.05 M) at 37 °C. [c] Maximal plasma concentration. [d] Plasma half-life. [e] Bioavailability. [f] Solubility for tosufloxacin at pH 7.4 is 0.008 mg/mL. [g] Not tested.

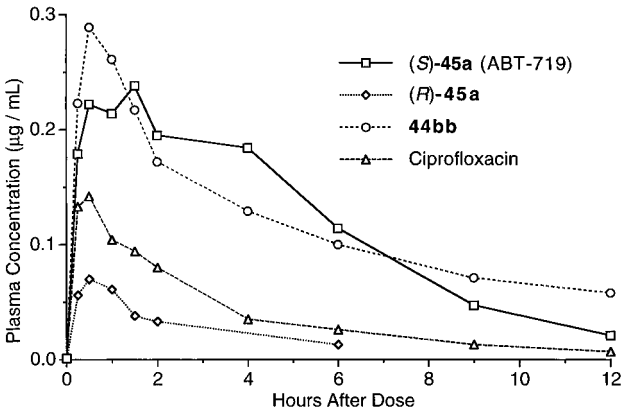


Figure 4. Mean (n = 4) plasma concentrations of selected pyridones after single oral administration of 5 mg/kg to rats in aqueous solution.

were obtained commercially and used without further purification. Unless otherwise specified, all nonaqueous reactions were carried out under a dry nitrogen atmosphere, using oven-dried glassware, and all reaction solvents were removed by rotary evaporator. All elemental analyses were within ±0.4% of the calculated values.

2-(3-Amino-1-pyrrolidinyl)-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Trifluoroacetic Acid Salt (12a). a. 2-(2,4-Difluorophenyl)-acetamidine Hydrochloride (2, R$_1$ = 2,4-difluorophenyl). To a solution of (2,4-difluorophenyl)acetonitrile (49.44 g, 0.323 mol) in absolute ethanol (20.8 mL, 0.354 mol) cooled in an ice bath was passed gaseous HCl (14.61 g, 0.400 mol). After 20 min the reaction mixture solidified. It was then allowed to warm to room temperature and held at this temperature for 72 h. To the mixture was then added ethanol (140 mL) followed by a solution of ammonia in ethanol (150 mL, 4.2 M, 0.42 mol). This mixture was stirred for an additional 3 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated to afford 65.7 g (90%) of the title compound as a white solid, mp 163−164 °C. ^{1}H NMR (DMSO-

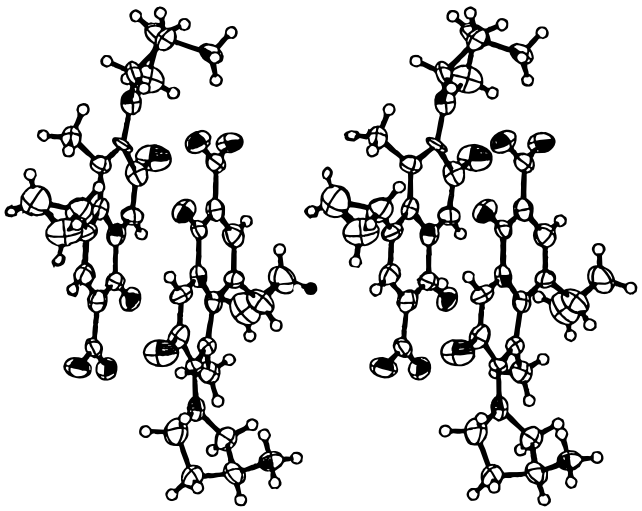


Figure 5. Stereoview of ORTEP drawing of the X-ray crystal structure of a pair of (*S*)-**45a** (ABT-719).

d_6): δ 3.72 (s, 2H), 7.16 (m, 1H), 7.33 (m, 1H), 7.50 (m, 1H), 8.95 (br, 4H). Anal. ($C_8H_9ClF_2N_2 \cdot 0.1H_2O$) C, H, N.

b. 2-(2,4-Difluorobenzyl)-5-fluoro-4-hydroxypyrimidine (4, R_1 = 2,4-difluorophenyl). A mixture of **2** (R_1 = 2,4-difluorophenyl) (68.0 g, 0.33 mol), the sodium salt of ethyl 2-fluoro-3-hydroxy-2-propenoate (**3**)[10] (0.34 mol) in anhydrous methanol (300 mL), and triethylamine (50 mL) was heated at reflux for 23 h. The solvent was removed, and water (200 mL) was added. The mixture was acidified to pH 3−4 with 10% HCl and then extracted with methylene chloride. The extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a dark oil which solidified upon standing. The solid was washed with ethyl acetate, ethyl acetate/hexane, and hexane to afford 29.8 g of the title compound as a white solid. A second crop of 10.2 g of product was obtained from the filtrates after column chromatography, eluting with 2.5% methanol in methylene chloride. Total weight was 40.0 g (50%), mp 155−156 °C. MS (DCI/NH_3): 258 (M + NH_4), 241 (M + H). ^{1}H NMR ($CDCl_3$): δ 4.02 (s, 2H), 6.88 (m, 2H), 7.33 (m, 1H), 7.89 (d, J = 3 Hz, 1H). IR (KBr): 1690, 1605 cm^{-1}. Anal. ($C_{11}H_7F_3N_2O$) C, H, N.

c. Ethyl 9-(2,4-Difluorophenyl)-3-fluoro-2-hydroxy-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylate (6, R_1 = 2,4-difluorophenyl). **4** (R_1 = 2,4-difluorophenyl) (4.80 g, 20.0 mmol) was dissolved in THF (150 mL) and cooled to −78 °C. To this was slowly added dropwise *n*-butyllithium (16.40 mL, 2.5 N in hexanes, 41.0 mmol), and the mixture was stirred for 30 min. Then diethyl (ethoxymethylene)malonate (4.85 mL, 24.0 mmol) was added, and the mixture was stirred for an additional 30 min at −78 °C. The reaction was quenched with 10% HCl until the mixture was at pH 3. It was then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed to afford the title compound as a yellow oil. This oil was dissolved in ethanol (80 mL). Piperidine (2 mL) and acetic acid (0.2 mL) were added, and the mixture was heated at reflux for 16 h. The solvent was removed, and the residue was washed with methanol and methylene chloride to give 4.79 g of a pale yellow solid. The washings were concentrated and then purified by column chromatography, eluting with 2:10:100 acetic acid:methanol:methylene chloride to afford an additional 2.22 g of the title compound as a pale yellow solid, with a total weight of 7.01 g (96%), mp 239−240 °C. MS (DCI/NH_3): 382 (M + NH_4), 365 (M + H). ^{1}H NMR (DMSO-d_6): δ 1.23 (t, J = 7 Hz, 3H), 4.14 (q, J = 7 Hz, 2H), 7.08 (m, 1H), 7.21 (m, 1H), 7.40 (m, 1H), 7.83 (s, 1H), 8.74 (d, J = 8 Hz, 1H). IR (KBr): 1710, 1675, 1620 cm^{-1}.

d. Benzyl 9-(2,4-Difluorophenyl)-3-fluoro-2-hydroxy-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylate (7, R_1 = 2,4-difluorophenyl). To a solution of the ethyl ester **6** (R_1 = 2,4-difluorophenyl) (7.00 g, 19.2 mmol) dissolved in benzyl alcohol (200 mL) was added titanium tetraethoxide (0.70 mL), and the mixture was heated with stirring at 100 °C for 2.5 h. The reaction mixture was diluted with methylene chloride and washed once with 1 N HCl and three times with water. The solution was dried over anhydrous magnesium sulfate and concentrated to leave a yellow solid. This material was triturated with ether; the solid was filtered and dried under vacuum at room temperature to afford 6.66 g (81%) of the title compound as a yellow solid, mp 218−219 °C. MS (DCI/NH_3): 427 (M + H). ^{1}H NMR (DMSO-d_6): δ 5.26 (s, 2H), 7.15−7.45 (m, 8H), 8.00 (s, 1H), 9.00 (d, J = 7 Hz, 1H). IR (KBr): 1710, 1675, 1620 cm^{-1}.

e. Benzyl 2-[3-[*N*-(*tert*-butoxycarbonyl)amino]-1-pyrrolidinyl]-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido-[1,2-*a*]pyrimidine-7-carboxylate (10, R_1 = 2,4-difluorophenyl, R_2R_3N = 3-*tert*-BOCamino-1-pyrrolidinyl). **7** (R_1 = 2,4-difluorophenyl) (1.20 g, 2.82 mmol) was stirred with DMF (2.50 mL) and $POCl_3$ (2.95 mL) in methylene chloride (45 mL) at room temperature for 2.5 h. The reaction was then quenched with ice and water and the mixture extracted with methylene chloride. The extract was washed with water until the acidity of the rinse water was above pH 3 and then dried over magnesium sulfate. To the dried solution was added an excess of 3-[*N*-(*tert*-butoxycarbonyl)amino]pyrrolidine until the color of the solution changed from orange to light yellow. The solution was then concentrated, and the product was purified by column chromatography eluting with 0.5:5:100 concentrated ammonium hydroxide:methanol:methylene chloride to afford 1.58 g (94%) of the title compound as a light yellow crystalline solid, mp 103−104 °C. MS (DCI/NH_3): 595 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 1.85−2.30 (m, 2H), 3.42−4.35 (m, 5H), 4.65 (br, 1H), 5.38 (s, 2H), 6.89 (m, 2H), 7.30−7.50 (m, 6H), 8.35 (s, 1H), 9.15 (d, J = 9 Hz, 1H), 9.16 (d, J = 9 Hz, 1H). IR (KBr): 1735, 1710, 1660 cm^{-1}. Anal. ($C_{31}H_{29}F_3N_4O_5$) C, H. N.

f. 2-[3-[*N*-(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid (12, R_2R_3N = 3-*tert*-BOCamino-1-pyrrolidinyl). A solution of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-*tert*-BOCamino-1-pyrrolidinyl) (1.77 g, 2.97 mmol) was stirred with formic acid (98%, 4.0 mL) and 10% Pd/C (0.2 g) in methanol (80 mL) at room temperature for 40 min. After filtration and evaporation of the solvent, the product was purified by column chromatography, eluting with 1:10:100 acetic acid:methanol:methylene chloride to afford, after removal of the solvent, 1.13 g (75%) of the title compound as a yellow solid, mp 209.5−210.5 °C. MS (DCI/NH_3): 505 (M + H). ^{1}H NMR ($CDCl_3$/CD_3OD): δ 1.45 (s, 9H), 1.90−2.30 (m, 2H), 3.50−4.35 (m, 5H), 6.91 (m, 2H), 7.32 (m, 1H), 8.44 (s, 1H), 9.03 (d, J = 8 Hz, 1H), 9.04 (d, J = 8 Hz, 1H). IR (KBr): 1714, 1662, 1620 cm^{-1}. Anal. ($C_{24}H_{23}F_3N_4O_5 \cdot {}^1/_4H_2O$) C, H, N.

g. 2-(3-Amino-1-pyrrolidinyl)-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Trifluoroacetic Acid Salt (12a). **12** (R_2R_3N = 3-*tert*-BOCamino-1-pyrrolidinyl) (0.100 g, 0.198 mmol) was dissolved in 4 N HCl in dioxane (2.0 mL, 8.0 mmol) and stirred at room temperature for 3 h. The solvent was removed to yield a yellow solid which was dissolved in water and neutralized to pH 7 with 5% sodium bicarbonate solution. The resulting precipitate was filtered off, washed with water, and dried to afford 75 mg (93%) of the free base of **12a** as a yellow solid, mp >250 °C. MS (DCI/NH_3): 405 (M + H). ^{1}H NMR (DMSO-d_6): δ 1.90−2.30 (m, 2H), 3.00−4.10 (m, 5H), 7.16 (m, 2H), 7.30 (m, 1H), 8.18 (s, 1H), 9.17 (d, J = 8 Hz, 1H), 9.18 (d, J = 8 Hz, 1H). IR (KBr): 1715, 1660 cm^{-1}.

A 0.879 g (2.17 mmol) portion of the above free base was dissolved in 10 mL of trifluoroacetic acid. The excess acid was then removed. The yellow residue was dissolved in 600 mL of water containing 1 mL of trifluoroacetic acid. The resulting solution was filtered through a sintered glass funnel and freeze-dried to afford 0.876 g (78%) of the title compound as a light yellow solid, mp 161−162 °C dec. MS (DCI/NH_3): 405 (M + H). ^{1}H NMR (CD_3OD): δ 2.10−2.55 (m, 2H), 3.75−4.20 (m, 5H), 7.05 (m, 2H), 7.50 (m, 1H), 8.30 (s, 1H), 9.19 (d, J = 8 Hz, 1H). IR (KBr): 1720, 1660, 1620 cm^{-1}. Anal. ($C_{19}H_{15}F_3N_4O_3 \cdot CF_3CO_2H \cdot H_2O$) C, H, N.

Following the same procedures as described for **12a**, starting from either different amines or different nitriles, the following compounds were made.

3-Fluoro-9-(4-fluorophenyl)-2-(4-methyl-1-piperazinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (11cc): mp 225−230 °C. MS (DCI/NH_3): 401 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.68 (br, 1H), 2.33 (s, 3H), 2.53 (br, 4H), 3.98 (br, 4H), 7.10 (t, 2H), 7.48 (m, 2H), 8.57 (s, 1H), 9.08 (d, 2H). Anal. ($C_{20}H_{18}F_2N_4O_3 \cdot 0.75H_2O$) C, H, N.

2-((2*S*,4*S*)-4-Amino-2-methyl-1-pyrrolidinyl)-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid hydrochloride ((*S*,*S*)-12f): mp 204 °C dec. $[\alpha]^{22}_D = +35.4°$ (c = 0.5, CH_3OH). MS (DCI/NH_3): 419 (M − Cl). ^{1}H NMR (CD_3OD): δ 1.16 and 1.41 (2d, J = 7 Hz, 3H), 2.15−2.31 (m, 2H), 3.75−4.40 (m, 4H), 7.04 (m, 2H), 7.46 (m, 1H), 8.25 and 8.30 (2s, 1H), 9.11 and 9.21 (2d, J = 9 Hz, 1H). IR (KBr): 1710, 1660, 1630 cm^{-1}. Anal. ($C_{20}H_{17}F_3N_4O_3 \cdot HCl \cdot H_2O$) C, H, N.

2-((2*S*,4*S*)-4-Acetamido-2-methyl-1-pyrrolidinyl)-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (12g): mp 163−164 °C. $[\alpha]^{23}_D$ = −50.2° (c = 0.5, $CHCl_3$). MS (DCI/NH_3): 461 (M + H). ^{1}H NMR ($CDCl_3/CD_3OD$): δ 1.09 and 1.39 (2d, J = 6 Hz, 3H), 1.92−2.15 (m, 2H), 2.00 (s, 3H), 3.97 (m, 1H), 4.16 (m, 1H), 4.32 (m, 1H), 4.72 (m, 1H), 6.90 (m, 2H), 7.25 (m, 1H), 8.17 and 8.31 (2s, 1H), 8.93 and 8.97 (2d, J = 8 Hz, 1H). IR (KBr): 1720, 1660, 1035 cm^{-1}. Anal. ($C_{22}H_{19}F_3N_4O_4 \cdot H_2O$) C, H, N.

9-(2,4-Difluorophenyl)-3-fluoro-2-(3-hydroxy-1-pyrrolidinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (12j): mp 168−170 °C dec. MS (DCI/NH_3): 406 (M + H). ^{1}H NMR (DMSO-d_6): δ 2.00−2.15 (m, 2H), 3.55−3.70 (m, 2H), 3.97−4.12 (m, 2H), 4.50−4.60 (m, 1H), 6.93 (m, 2H), 7.35 (m, 1H), 8.43 (s, 1H), 9.01 and 9.04 (2d, J = 4 Hz, 1H). IR (KBr): 1715, 1665, 1625 cm^{-1}. Anal. ($C_{19}H_{14}F_3N_3O_4 \cdot {}^1/_2H_2O$) C, H, N.

9-(2,4-Difluorophenyl)-3-fluoro-2-(4-methyl-1-piperazinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (12cc): mp 246−248 °C dec. MS (DCI/NH_3): 419 (M + H). ^{1}H NMR ($CDCl_3/CD_3OD$): δ 2.34 (s, 3H), 2.53 (m, 4H), 3.85−4.00 (m, 4H), 6.90 (m, 2H), 7.32 (m, 1H), 8.49 (s, 1H), 9.07 (d, J = 9 Hz, 1H). IR (KBr): 1720, 1660 cm^{-1}. Anal. ($C_{20}H_{17}F_3N_4O_3$) C, H, N.

2-(3-Amino-1-pyrrolidinyl)-3-fluoro-9-(4-methoxyphenyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (13a): mp 230−235 °C dec. MS (DCI/NH_3): 399 (M − Cl). ^{1}H NMR (CD_3OD): δ 2.16−2.58 (m, 2H), 3.86 (s, 3H), 3.90−4.21 (m, 5H), 6.98 (m, 2H), 7.51 (m, 2H), 8.31 (s, 1H), 9.20 (d, J = 9 Hz, 1H). Anal. ($C_{20}H_{19}FN_4O_4 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

2-(3-Amino-1-pyrrolidinyl)-3-fluoro-9-(2,3,4,5,6-pentafluorophenyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid hydrochloride salt (14a): mp 202−204 °C. MS (DCI/NH_3): 459 (M − Cl). ^{1}H NMR (CD_3OD): δ 2.12−2.54 (m, 2H), 3.70−4.36 (m, 5H), 8.42 (s, 1H), 9.21 (d, J = 9 Hz, 1H). IR (KBr): 1715, 1660, 1630 cm^{-1}. Anal. ($C_{19}H_{12}F_6N_4O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Benzyl 9-Cyclopropyl-3-fluoro-2-hydroxy-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylate (21). a. Ethyl 2-Cyano-2-cyclopropylacetate (16). A modified procedure of Carney and Wojtkunski[13] was used. To a suspension of NaH (60%, 49.6 g, 0.94 mol) and diethyl carbonate (97.2 mL, 0.800 mol) in refluxing toluene (240 mL) was added, over a period of 40 min, a solution of cyclopropaneacetonitrile (32.44 g, 0.400 mol) in toluene (120 mL). The reaction mixture was refluxed for another 2 h. Approximately 120 mL of acetic acid was added with ice bath cooling. The mixture was extracted with ethyl acetate (3×). The combined extracts were washed with saturated brine (2×), dried over $MgSO_4$, and concentrated. The product was obtained as a colorless liquid after distillation at reduced pressure (47.0 g, 77%, bp 69−72 °C at 4 mmHg).

b. 2-Cyclopropyl-2-(ethoxycarbonyl)acetamidine Hydrochloride (17). Into a stirred solution of **16** (38.72 g, 0.253 mol) in anhydrous ethanol (17.7 mL, 0.303 mol) was introduced gaseous hydrogen chloride (10.0 g, 0.274 mol) with ice cooling. The mixture was allowed to warm to room temperature and stand for 72 h. The reaction mixture was diluted with anhydrous ethanol (100 mL), and a solution of ammonia in ethanol (4.17 M, 70 mL, 0.292 mol) was added slowly at room temperature. The reaction mixture was stirred for 3 h. The reaction mixture was filtered to remove the ammonium chloride, and the solvent was removed to afford the title compound as a viscous off-white oil, which was taken directly to the next step.

c. Methyl 2-Cyclopropyl-2-(5-fluoro-4-hydroxy-2-pyrimidinyl)acetate (18) and Ethyl 2-Cyclopropyl-2-(5-fluoro-4-hydroxy-2-pyrimidinyl)acetate (19). A mixture of the above crude product **17** (0.253 mol), 0.254 mol of the sodium salt of ethyl 2-fluoro-3-hydroxy-2-propenoate (**3**),[10] and triethylamine (37.0 mL, 0.265 mol) in anhydrous methanol (250 mL) was heated at reflux for 17 h. Following removal of the solvent, 200 mL of water was added and the residue was acidified to pH 5 with acetic acid. This mixture was then extracted with methylene chloride. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give a dark brown oil. This was purified by column chromatography eluting with 1:1 ethyl acetate:hexane to afford 22.8 g (40%) of the methyl ester **18** and 6.45 g (11%) of the ethyl ester **19**, both as pale yellow viscous oils. Methyl ester **18**: MS (DCI/NH_3) 227 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.43 (m, 1H), 0.52 (m, 1H), 0.65 (m, 1H), 0.77 (m, 1H), 1.42 (m, 1H), 2.97 (d, J = 10 Hz, 1H), 3.80 (s, 3H), 7.88 (d, J = 3 Hz, 1H), 11.8 (br, 1H). IR (neat): 1740, 1690, 1615 cm^{-1}. Anal. ($C_{10}H_{11}FN_2O_3 \cdot {}^1/_4H_2O$) C, H, N. Ethyl ester **19**: MS (DCI/NH_3) 258 (M + NH_4). ^{1}H NMR ($CDCl_3$): δ 0.47 (m, 1H), 0.54 (m, 1H), 0.66 (m, 1H), 0.74 (m, 1H), 1.31 (t, J = 7 Hz, 3H), 1.34 (m, 1H), 2.96 (d, J = 10 Hz, 1H), 4.27 (m, 2H), 7.83 (d, J = 3 Hz, 1H), 11.0 (br, 1H). IR (neat): 1735, 1682, 1605 cm^{-1}. Anal. ($C_{11}H_{13}FN_2O_3 \cdot 0.3H_2O$) C, H, N.

d. 2-Cyclopropyl-2-(5-fluoro-4-hydroxy-2-pyrimidinyl)acetaldehyde (20). To a solution of the methyl ester **18** (4.96 g, 21.9 mmol) in toluene (40 mL) stirring at −70 °C was added a solution of diisobutylaluminum hydride in toluene (1.0 N, 46 mL, 46.0 mmol). The reaction mixture was stirred for 40 min, and then the reaction was quenched by acetic acid (5 mL). The mixture was allowed to warm to room temperature, and the reaction mixture was extracted with ethyl acetate. The extract was washed with water (3×), dried over anhydrous magnesium sulfate, and concentrated to afford 2.23 g of the title compound as a white solid. This compound was used directly in the next step. MS (DCI/NH_3): 214 (M + NH_4). ^{1}H NMR ($CDCl_3$): δ 0.48 (m, 2H), 0.91 (m, 2H), 1.35 (m, 1H), 7.40 (d, J = 10 Hz, 1H), 7.75 (d, J = 4 Hz, 1H), 9.61 (br, 1H), 13.64 (d, J = 10 Hz, 1H). IR (KBr): 1695, 1660, 1635 cm^{-1}.

e. Benzyl 9-Cyclopropyl-3-fluoro-2-hydroxy-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylate (21). The above crude aldehyde **18** was dissolved in anhydrous ethanol (100 mL). To this was added dibenzyl malonate (3.5 mL, 14.0 mmol), piperidine (2.5 mL), and acetic acid (0.25 mL). This reaction mixture was heated to reflux for 3 h and stirred at room temperature overnight. The solvent was removed. The residue was then dissolved in methylene chloride, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed to give a yellow oil which was purified by column chromatography, eluting with 1:5:100 acetic acid: methanol:methylene chloride. Removal of the solvent afforded 1.80 g (47%) of the title compound as a pale yellow solid, mp 225.5−226.5 °C. MS (DCI/NH_3): 355 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.64 (m, 2H), 1.08 (m, 2H), 1.62 (m, 1H), 5.37 (s, 2H), 7.35−7.48 (m, 5H), 8.28 (s, 1H), 9.00 (d, J = 6 Hz, 1H). IR (KBr): 1720, 1700, 1690 cm^{-1}. Anal. ($C_{19}H_{15}FN_2O_4 \cdot {}^1/_4H_2O$) C, H, N.

2-(3-Amino-1-pyrrolidinyl)-9-cyclopropyl-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride Salt (24a). a. Benzyl 2-Chloro-9-cyclopropyl-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylate (22). A mixture of **21** (0.200 g, 0.564 mmol), DMF (0.50 mL, 6.46 mmol), and phosphorous oxychloride (0.60 mL, 6.44 mmol) in methylene chloride (10 mL) was stirred at room temperature for 4 h. Ice was added to the reaction mixture. The mixture was extracted with methylene chloride, which was then washed with water, dried over anhydrous magnesium sulfate, and concentrated to yield the title compound as an orange residue. This compound was taken directly to the next step.

b. Benzyl 2-[3-[*N*-(*tert*-butoxycarbonyl)amino]-1-pyrrolidinyl]-9-cyclopropyl-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]-pyrimidine-7-carboxylate (23, R_2R_3N = *tert*-BOCamino-

1-pyrrolidinyl). The above crude **22** was dissolved in dry methylene chloride (5 mL) and cooled to 0 °C. To this solution was added 3-[*N*-(*tert*-butoxycarbonyl)amino]pyrrolidine (0.25 g, 1.34 mmol), and the reaction mixture was stirred at room temperature overnight. The solvent was removed, and the product was purified by column chromatography, eluting with 10% methanol in methylene chloride to afford 0.295 g (100%) of the title compound as a yellow solid, mp 159−160 °C. MS (DCI/NH_3): 523 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.60 (m, 2H), 0.87 (m, 2H), 1.46 (s, 9H), 1.90−2.40 (m, 2H), 3.70−4.45 (m, 5H), 4.94 (br, 1H), 5.37 (s, 2H), 7.29 (m, 1H), 7.37 (m, 2H), 7.50 (m, 2H), 7.99 (br, 1H), 9.10 (d, J = 10 Hz, 1H). IR (KBr): 1715, 1685, 1660 cm^{-1}. Anal. ($C_{28}H_{31}FN_4O_5 \cdot {}^1/_2H_2O$) C, H, N.

c. 2-(3-Amino-1-pyrrolidinyl)-9-cyclopropyl-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride Salt (24a). To the benzyl ester **23** (R_2R_3N = *tert*-BOCamino-1-pyrrolidinyl) (135 mg, 0.259 mmol) in methanol (20 mL) and THF (2 mL) were added formic acid (98%, 2.0 mL) and 10% Pd/C (50 mg). This mixture was stirred at room temperature for 37 min. The catalyst was removed by filtration, and the solvent was concentrated. The crude product was purified by column chromatography, eluting with 1:5:100 acetic acid:methanol:methylene chloride to afford the title compound as a yellow solid after removal of the solvent. This solid was reacted with 4 N HCl in dioxane (10 mL, 40 mmol) at room temperature for 3 h. The solvent was removed; the yellow solid was dissolved in distilled water and filtered through a sintered glass funnel. The filtrate was freeze-dried to afford 68.1 mg (71%) of the title compound as a yellow solid, mp 234 °C dec. MS (DCI/NH_3): 333 (M − Cl). ^{1}H NMR ($CDCl_3$): δ 0.64 (m, 2H), 0.96 (m, 2H), 2.20−2.65 (m, 3H), 3.58−4.35 (m, 5H), 7.80 (d, J = 10 Hz, 1H), 9.05 (br, 1H). IR (KBr): 1665, 1620 cm^{-1}. Anal. ($C_{16}H_{17}FN_4O_3 \cdot HCl \cdot H_2O$) C, H, N.

Following the same procedures as described above for **24a** and replacing the 3-BOCaminopyrrolidine with different amines, the following compounds were made.

9-Cyclopropyl-3-fluoro-2-(1-morpholinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (24aa): mp >260 °C. MS (DCI/NH_3): 334 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.68 (m, 2H), 0.95 (m, 2H), 2.19 (m, 1H), 3.90 (t, J = 6 Hz, 4H), 4.10 (t, J = 6 Hz, 4H), 8.15 (s, 1H), 9.06 (d, J = 10 Hz, 1H). IR (KBr): 1720, 1660, 1620 cm^{-1}. Anal. ($C_{16}H_{16}FN_3O_4 \cdot H_2O$) C, H, N.

9-Cyclopropyl-3-fluoro-2-(1-piperazinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (24bb): mp 198−199 °C. MS (DCI/NH_3): 333 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.67 (m, 2H), 0.94 (m, 2H), 2.19 (m, 1H), 3.08 (t, J = 6 Hz, 4H), 4.08 (m, 4H), 8.11 (s, 1H), 9.01 (d, J = 10 Hz, 1H). IR (KBr): 1710, 1660 cm^{-1}. Anal. ($C_{16}H_{17}FN_4O_3 \cdot 0.1H_2O$) C, H, N.

9-Cyclopropyl-3-fluoro-2-(4-methyl-1-piperazinyl)-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic acid (24cc): mp 219−220 °C. MS (DCI/NH_3): 347 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.67 (m, 2H), 0.95 (m, 2H), 2.18 (m, 1H), 2.39 (s, 3H), 2.65 (t, J = 6 Hz, 4H), 4.13 (m, 4H), 8.11 (s, 1H), 9.02 (d, J = 10 Hz, 1H). IR (KBr): 1720, 1660, 1620 cm^{-1}. Anal. ($C_{17}H_{19}FN_4O_3 \cdot 0.6CH_3COOH$) C, H, N.

2-[3-(*N*-(*S*)-Alanylamino)-1-pyrrolidinyl]-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride (12a-*N*-Ala). a. 2-(3-Amino-1-pyrrolidinyl)-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Benzyl Ester (10, R_1 = 2,4-difluorophenyl, R_2R_3N = 3-amino-1-pyrrolidinyl). A TFA (10 mL) solution of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-*tert*-BOCamino-1-pyrrolidinyl) (2.56 g, 4.66 mmol) was stirred at room temperature for 1 h. The solvent was removed, and the residue was suspended in methylene chloride and washed with saturated sodium bicarbonate (1×) and water (2×). The organic solution was dried over $MgSO_4$ and concentrated to give 1.98 g (86%) of the title compound, mp 185−186 °C. ^{1}H NMR ($CDCl_3$): δ 1.75−2.19 (m, 2H), 3.33−4.07 (m, 5H), 5.38 (s, 2H), 6.87 (m, 2H), 7.32 (m, 4H), 7.48 (m, 2H), 8.33 (s, 1H), 9.13 (apparent d, J = 9 Hz, 1H).

b. 12a-*N*-Ala. A suspension of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-amino-1-pyrrolidinyl) (0.982 g, 1.99 mmol) and (*S*)-*N*-[(benzyloxycarbonyl)alanyl]succinamide (0.700 g, 2.22 mmol) in THF (40 mL) was stirred at room temperature for 2 h. The solvent was evaporated off. The residue was then dissolved in methylene chloride which was washed with water (3×), dried over anhydrous magnesium sulfate, and concentrated. The product was purified by column chromatography, eluting with 5% methanol in methylene chloride, to afford 1.32 g (95%) of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-(CBZAla)amino-1-pyrrolidinyl) as a yellow crystalline solid, mp 104−107 °C. MS (DCI/NH_3): 700 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.43 (m, 3H), 1.95−2.30 (m, 2H), 3.40−4.40 (m, 5H), 4.75−5.35 (m, 5H), 6.77 (m, 2H), 7.10−7.40 (m, 1H), 8.18−8.40 (m, 2H). IR (KBr): 1720, 1660 cm^{-1}. Anal. ($C_{37}H_{32}F_3N_5O_6 \cdot {}^1/_2H_2O$) C, H, N.

The compound (1.26 g, 1.80 mmol) from the previous step was suspended in methanol (80 mL) and formic acid (98%, 4.0 mL), and 10% Pd/C (0.200 g) was added. The mixture was stirred at room temperature for 1.7 h. THF (40 mL) was then added, and the mixture was stirred for an additional 0.3 h. The catalyst was filtered off, and the filtrate was concentrated to leave a yellow solid residue. This was dissolved in 500 mL of water to which 4 mL of concentrated HCl was added. The solution was filtered through sintered glass and freeze-dried to afford 0.877 g (96%) of the title compound as a yellow solid, mp 198−200 °C dec. MS (FAB): 476 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 1.33 (apparent t, J = 7 Hz, 3H), 1.90−2.30 (m, 2H), 3.35−4.40 (m, 6H), 7.17 (m, 1H), 7.32 (m, 1H), 7.58 (m, 1H), 8.20 (d, J = 8 Hz, 1H), 9.19 (m, 1H), 13.45 (br, 1H). IR (KBr): 1715, 1665, 1620 cm^{-1}. Anal. ($C_{22}H_{21}ClF_3N_5O_4 \cdot 1.5H_2O$) C, H, N.

9-(2,4-Difluorophenyl)-3-fluoro-2-[3-(*N*-(*S*)-norvalylamino)-1-pyrrolidinyl]-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride Salt (12a-*N*-Nov). The title compound was prepared from *N*-[(benzyloxycarbonyl)-(*S*)-norvalyl]succinamide using the same procedures as described for **12a**-*N*-Ala, mp 192−194 °C. MS (FAB): 504 (M + H). ^{1}H NMR (CD_3OD): δ 0.96 (m, 3H), 1.90−2.35 (m, 6H), 3.50−4.60 (m, 5H), 7.02 (m, 2H), 7.48 (m, 1H), 8.22 (br, 1H), 8.35 (br, 2H), 9.09 (m, 1H). IR (KBr): 1710, 1665, 1610 cm^{-1}. Anal. ($C_{24}H_{25}F_3N_5O_4 \cdot 2H_2O$) C, H, N.

2-[3-(*N*-(*S*)-Alanyl-(*S*)-alanylamino)-1-pyrrolidinyl]-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride (12a-*N*-Ala-Ala). A mixture of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-amino-1-pyrrolidinyl) (0.905 g, 1.83 mmol), *N*-(benzyloxycarbonyl)-(*S*)-alanyl-(*S*)-alanine (0.81 g, 2.75 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDAC) (0.530 g, 2.76 mmol), and 1-hydroxybenzotriazole hydrate (HOBT) (0.370 g, 2.74 mmol) in DMF (10 mL) was stirred for 30 min at 0 °C and then at room temperature for 2 h. The solvent was removed using a Kugelrohr apparatus. The residue was dissolved in methylene chloride, washed with water (2×), saturated sodium bicarbonate solution (2×), and water (2×), and dried over magnesium sulfate. The solvent was removed, and the product was purified by column chromatography, eluting with 10% methanol in methylene chloride to afford 1.19 g (84%) of **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = 3-(CBZ-Ala-Ala)amino-1-pyrrolidinyl) as yellow crystals, mp 123−126 °C. MS (DCI/NH_3): 771 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.37 (m, 6H), 1.92−2.18 (m, 2H), 3.58−4.48 (m, 5H), 4.76−5.00 (m, 2H), 5.30 (s, 2H), 5.32 (s, 2H), 6.80 (m, 2H), 7.10−7.45 (m, 1H), 8.23 and 8.30 (2s, 1H), 8.87 and 8.93 (2d, J = 8 Hz, 1H). IR (KBr): 1720, 1660 cm^{-1}. Anal. ($C_{40}H_{37}F_3N_6O_7 \cdot {}^1/_2H_2O$) C, H, N.

The compound from the previous step (1.13 g, 1.47 mmol) was dissolved in methanol (80 mL). Formic acid (98%, 4.0 mL) and 10% Pd/C (0.20 g) were added. The mixture was stirred for 1 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated to leave a yellow residue. This was dissolved in 500 mL of distilled water containing 3 mL of concentrated HCl. The resulting solution was filtered through a sintered glass funnel and freeze-dried to afford 0.729 g (85%) of the title compound as a pale yellow solid, mp 217−219 °C dec. MS (FAB): 547 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 1.24 (m, 3H), 1.32 (d, J = 7 Hz, 3H), 1.80−2.20 (m, 2H), 3.40−4.50 (m, 7H), 7.17 (m, 1H), 7.31 (m, 1H), 7.57 (m, 1H), 8.20 (br, 4H), 8.47 (m, 1H), 8.66 (m, 1H), 9.19 (m, 1H), 13.45 (br, 1H). IR (KBr): 1710, 1660, 1630 cm^{-1}. Anal. ($C_{25}H_{25}F_3N_6O_5 \cdot HCl \cdot H_2O$) C, H, N.

2-[(2*S*,4*S*)-4-(*N*-(*S*)-Alanyl-(*S*)-alanylamino)-2-methyl-1-pyrrolidinyl]-9-(2,4-difluorophenyl)-3-fluoro-6*H*-6-oxopyrido[1,2-*a*]pyrimidine-7-carboxylic Acid Hydrochloride ((*S*,*S*)-12f-*N*-Ala-Ala). The compound was prepared from **10** (R_1 = 2,4-difluorophenyl, R_2R_3N = (2*S*,4*S*)-4-*tert*-BOCamino-4-methyl-1-pyrrolidinyl) using the procedures described for **12a**-*N*-Ala and **12a**-*N*-Ala-Ala, mp 198−200 °C. MS (FAB): 561 (M − Cl). ^{1}H NMR (CD_3OD): δ 1.14 and 1.40 (2d, J = 7 Hz, 3H), 1.34 and 1.35 (2d, J = 7 Hz, 3H), 1.50 and 1.51 (2d, J = 7 Hz, 3H), 1.96−2.11 (m, 2H), 3.50−4.60 (m, 6H), 7.40 (m, 2H), 7.47 (m, 1H), 8.26 and 8.29 (2s, 1H), 9.12 and 9.16 (2d, J = 9 Hz, 1H). Anal. ($C_{26}H_{27}F_3N_6O_5$·2.0HCl·2.0H_2O) C, H, N.

4-*tert*-Butoxy-3-chloro-2,5,6-trifluoropyridine (27). To a stirred solution of 2,4,5,6-tetrafluoro-3-chloropyridine (**25**; 106.0 g, 0.400 mol, 70% pure from Aldrich, remainder 4-chloro-2,3,5,6-tetrafluoropyridine) in anhydrous THF (250 mL) was added a solution of NaO-*tert*-Bu (38.30 g, 0.3985 mol) in anhydrous THF (350 mL), dropwise at −78 °C. After the addition, the reaction mixture was stirred for 2 h at −78 °C followed by ambient temperature for 16 h. The mixture was poured into 500 mL of hexane and filtered through Celite. The filtrate was concentrated *in vacuo* with a bath temperature of 30−35 °C. The residue was purified by chromatography, eluting first with hexane and then AcOEt:hexane = 1:16 to give the byproduct 6-*tert*-butoxy-3-chloro-2,4,5-trifluoropyridine as a colorless liquid (24.6 g, 26%), the mixture (9.5 g, 10%), and **27** (51.29 g, 53%) as a colorless liquid, bp 63−66 °C (1.5 mmHg). MS (DCI/NH_3): 238, 240 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.52 (d, J = 2 Hz, 9H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −73.75 (dd, J_1 = 14.2 Hz, J_2 = 23.2 Hz, 1F), −89.71 (dd, J_1 = 14.2 Hz, J_2 = 21.9 Hz, 1F), −152.42 (apparent t, J = 22 Hz, 1F).

4-*tert*-Butoxytetrafluoropyridine (28). Pentafluoropyridine (**26**) (158.5 g, 0.938 mmol) was dissolved in THF (600 mL) and cooled to −78 °C. To this was added sodium *tert*-butoxide (88.29 g, 0.919 mmol) in anhydrous THF (800 mL) over a 30 min period, with stirring while maintaining the temperature at −78 °C. The mixture was stirred for another 30 min at this temperature. The temperature of the bath was raised to −20 °C, and the reaction mixture was stirred at this temperature for 64 h. The reaction mixture was removed from the cold bath, diluted with 1.5 L of ether, and filtered through a diatomaceous earth filter aid. The solvent was removed to leave a yellow oil. The oil was purified by vacuum distillation to afford 141.34 g (69%) of the title product, bp 43−44 °C (1 mmHg). MS (DCI/NH_3): 238, 240 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −91.16 (m, 2F), −152.82 (m, 2F).

4-*tert*-Butoxy-2,5,6-trifluoropyridine (29). A mixture of **27** (90 g, 0.38 mol), triethylamine (83 g, 0.82 mol), and 10% $Pd(OH)_2$/C (dry form, 16.2 g) in ethyl acetate (1.9 L) was stirred at ambient temperature for 18 h under 4 atm of hydrogen. The mixture was filtered, and the filtrate was washed with water (2×), dried over $MgSO_4$, and concentrated. The dechlorinated product was purified by chromatography (ethyl acetate:hexane, 1:16) as a colorless liquid (65 g, 83%). MS (DCI/NH_3): 233 (M + NH_4). ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 9H), 6.51 (m, 1H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −72.60 (dd, J_1 = 14.3 Hz, J_2 = 21.0 Hz, 1F), −89.74 (dd, J_1 = 14.3 Hz, J_2 = 21.0 Hz, 1F), −164.68 (dt, J_1 = 4.2 Hz, J_2 = 21.0 Hz, 1F).

4-*tert*-Butoxy-3-methyl-2,5,6-trifluoropyridine (30). *n*-BuLi (2.5 M in hexanes, 185 mL, 0.463 mol) was added dropwise via a syringe to a stirred solution of diisopropylamine (65 mL, 0.464 mol) in anhydrous THF (250 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and at 0 °C for 15 min and then cooled back to −78 °C. The LDA solution generated above was cannulated into a stirred solution of **29** (79.55 g, 0.3877 mol) in anhydrous THF (500 mL) which was precooled to −78 °C. The reaction mixture changed from orange to brown with formation of a yellow precipitate. Stirring was continued for 25 min at −78 °C. MeI (34.5 mL, 0.554 mol) was added dropwise to the above solution. The mixture was allowed to stir at −78 °C for 30 min and at ambient temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture extracted with hexane. The extract was washed with saturated brine (1×), dried over $MgSO_4$, and concentrated *in vacuo* with a bath temperature at ∼35 °C to give **3** as a pale yellow liquid (89.13 g) which was used directly in the next step. MS (DCI/NH_3): 220 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.47 (m, 9H), 2.12 (m, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −75.91 (dd apparent, J_1 = 15.0 Hz, J_2 = 22.1 Hz, 1F), −93.17 (apparent dd, J_1 = 15.0 Hz, J_2 = 22.1 Hz, 1F), −156.54 (m, 1F).

4-*tert*-Butoxy-3-ethyl-2,5,6-trifluoropyridine (31): following the procedure for **30**, replacing the methyl iodide with ethyl iodide. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J = 7.5 Hz, 3H), 1.48 (m, 9H), 2.61 (q, J = 7.5 Hz, 2H).

4-*tert*-Butoxy-3-methoxy-2,5,6-trifluoropyridine (33). a. 4-*tert*-Butoxy-3-hydroxy-2,5,6-trifluoropyridine (32). A solution of **29** (11.16 g, 54.39 mmol) in THF (50 mL) was cooled to −78 °C. To this solution was added a solution of LDA which was generated from diisopropylamine (9.20 mL, 65.6 mmol) and *n*-butyllithium (2.5 M in hexanes, 25.0 mL, 62.5 mmol) in THF (50 mL) with stirring. The mixture was stirred for 30 min at −78 °C, during which a solid precipitated. To this mixture was added trimethoxyborane (7.5 mL, 66.0 mmol) with stirring at −78 °C. The reaction mixture was stirred at −78 °C for 25 min before adding 10 mL of acetic acid. The mixture was stirred and allowed to warm to 0 °C. Next 30% hydrogen peroxide (100 mL) and 2 N sodium hydroxide (100 mL) were added while cooling in an ice bath. The mixture was then stirred at room temperature for 16 h followed by quenching with saturated NH_4Cl solution. The mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography, eluting with 1:8 ethyl acetate:hexane to give 9.77 g (81%) of the title product as a colorless liquid. MS (EI): 221 (M). ^{1}H NMR ($CDCl_3$): δ 1.51 (m, 9H), 5.17 (br, 1H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −92.41 (m, 1F), −97.44 (m, 1F), −153.87 (m, 1F). Anal. ($C_9H_{10}FNO_2$) C, H, N.

b. 4-*tert*-Butoxy-3-methoxy-2,5,6-trifluoropyridine (33). DEAD (5.04 mL, 32.0 mmol) was added dropwise to a stirred solution of **32** (6.44 g, 29.1 mmol), triphenylphosphine (8.40 g, 32.03 mmol), and methanol (1.62 mL, 40.0 mmol) in anhydrous THF (50 mL) at room temperature. The reaction was complete in 10 min. The solvents were removed, and the residue was purified by column chromatography, eluting with 1:16 ethyl acetate:hexane to give 6.22 g (91%) of the title product as a colorless liquid. MS (DCI/NH_3): 236 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.47 (m, 9H), 3.90 (m, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −86.45 (m, 1F), −93.31 (m, 1F), −154.31 (m, 1F).

4-*tert*-Butoxy-2,5-difluoro-6-methylpyridine (35). a. 4-*tert*-Butoxy-3-chloro-2,5-difluoro-6-(trimethylsilylmethyl)pyridine (34). To a stirred solution of 4-*tert*-butoxy-3-chlorotrifluoropyridine (**27**) (7.55 g, 31.51 mmol) in THF (200 mL) at −78 °C was added [(trimethylsilyl)methyl]lithium (1.0 M in pentane, 66 mL) dropwise. The resulting solution was stirred for 1 h at −78 °C before quenching with saturated NaCl solution. The mixture was extracted with ether, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 1:32 ethyl acetate:hexane to give 6.26 g (65%) of title compound. ^{1}H NMR ($CDCl_3$): δ 0.05 (m, 9H), 1.47 (m, 9H), 2.27 (d, J = 4 Hz, 2H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −72.92 (d, J = 30.6 Hz, 1F), −136.74 (d, J = 30.6 Hz, 1F).

b. 4-*tert*-Butoxy-2,5-difluoro-6-methylpyridine (35). **34** (6.26 g, 20.35 mmol) was shaken with 10% Pd/C (1.3 g) and triethylamine (15 mL) in ethyl acetate (100 mL) under 4 atm of H_2 for 24 h. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography, eluting with 1:32 ethyl acetate:hexane to give 4.38 g (79%) of 4-*tert*-butoxy-2,5-difluoro-6-[(trimethylsilyl)-methyl]pyridine as a colorless liquid. 4-*tert*-Butoxy-2,5-difluoro-6-[(trimethylsilyl)methyl]pyridine (1.00 g, 3.66 mmol) was stirred with Bu_4NF (1.0 M in THF, 3.7 mL) in 10 mL of THF at room temperature for 2.5 h. The solvent was removed, and the residue was dissolved in ether, which was then washed with water and brine, dried over $MgSO_4$, and concentrated. The product was purified by column chromatography, eluting

with 1:32 ethyl acetate:hexane, to give 0.68 g (93%) of the title compound as a colorless liquid. This was used directly. ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 9H), 2.41 (d, J = 4 Hz, 3H), 6.45 (m, 1H).

(*S*)-8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (ABT-719, (*S*)-45a). a. 4-*tert*-Butoxy-3-methyl-2,5-difluoropyridine (36, Y = H, X = Me). The crude **30** (~0.388 mol) and hydrazine monohydrate (100 mL, 2.06 mol) were dissolved in 500 mL of *n*-propanol. The mixture was heated to reflux for 3 h. The solvent was removed *in vacuo*, and the residue was dissolved in methylene chloride which was washed with water (2×) and concentrated to give the intermediate hydrazino product as a yellow oil.

The above oil was dissolved in 700 mL of MeOH. To this was added 150 mL of a 20% NaOH solution. Air was passed through the above solution with vigorous stirring for 3 days during which time another 50 mL of a 20% NaOH solution was added. The mixture became deep blue. MeOH was removed *in vacuo* (bath temperature < 30 °C). The residue (dark brown-colored oil) was dissolved in ether which was washed with water (1×), 2% HCl (1×), and saturated brine (3×) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by column chromatography eluting first with hexane followed by AcOEt:hexane = 1:32 and 1:16 to give 71.12 g of the title compound as a colorless liquid (91% in three steps), bp 50−60 °C (1.0 mmHg). MS (DCI/NH_3): 202 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.43 (d, J = 1.5 Hz, 9H), 2.18 (d, J = 1.5 Hz, 3H), 7.85 (br, 1H). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as reference): δ −73.37 (d, J = 24.5 Hz, 1F), −142.17 (d, J = 24.5 Hz, 1F).

b. 2-(4-*tert*-Butoxy-5-fluoro-3-methyl-2-pyridinyl)cyclopropylacetonitrile (37, X = Me, Y = H, R_1 = cyclopropyl). A freshly prepared solution of LDA (0.103 mol) (14.4 mL of diisopropylamine and 40.5 mL of *n*-BuLi (2.5 M in hexanes) in 50 mL of THF) was added dropwise to a stirred solution of cyclopropylacetonitrile (8.30 g, 0.102 mol) in 50 mL of anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 15 min and then cannulated into a stirred solution of 4-*tert*-butoxy-3-methyl-2,5-difluoropyridine (**36**, X = Me, Y = H) (8.21 g, 40.80 mmol) in 40 mL of anhydrous THF at −78 °C. Stirring was continued for 1 h at −78 °C followed by 1 h at 0 °C. The reaction was then quenched with saturated aqueous NH_4Cl solution and the mixture extracted with ether (2×). The extracts were washed with saturated brine (2×), dried over $MgSO_4$, and concentrated. The product was purified by column chromatography eluting with AcOEt:hexane = 1:4 to yield **37** (X = Me, Y = H, R_1 = cyclopropyl) as a colorless liquid, which solidified on standing (10.33 g, 97%), mp 52−54 °C. MS (DCI/NH_3): 263 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.50 (m, 2H), 0.63 (m, 1H), 0.73 (m, 1H), 1.60 (m, 1H), 1.43 (d, J = 2 Hz, 9H), 2.29 (s, 3H), 3.76 (d, J = 8 Hz, 1H), 8.30 (d, J = 3 Hz, 1H). IR (neat): 2240, 1580, 1470 cm^{-1}. Anal. ($C_{15}H_{19}FN_2O$) C, H, N.

c. Ethyl 2-(4-Chloro-5-fluoro-3-methyl-2-pyridinyl)-cyclopropylacetate (38, X = Me, Y = H, R_1 = cyclopropyl). A trifluoroacetic acid solution (150 mL) of **37** (X = Me, Y = H, R_1 = cyclopropyl) (70.8 g, 0.27 mol) was stirred at room temperature for 1 h. The TFA was then removed *in vacuo*, and the residue was further dried under vacuum to give an oily material.

To the above product in 750 mL of anhydrous methylene chloride and 100 mL of DMF was added slowly $POCl_3$ (127 mL) with water bath cooling. The solution was stirred overnight. It was then poured over ice and extracted with methylene chloride (2×). The combined extracts were washed with water (1×), saturated $NaHCO_3$ solution (1×), and water (2×), dried over $MgSO_4$, and concentrated. The chloronitrile was purified by column chromatography, eluting with AcOEt:hexane = 1:4, as a pale yellow solid (45.16 g, 75%).

The above chloronitrile (16.25 g, 0.072 mol) was dissolved in 72 mL of absolute ethanol and cooled with an ice bath. Anhydrous gaseous HCl was bubbled through this solution until 38 g had been dissolved (saturated). Then water (1.6 mL, 0.089 mol) was added, and the mixture was heated to 80−85 °C for 3 h. After cooling to room temperature, 100 mL of water was added followed by cautious addition of solid $NaHCO_3$ until the pH was ~8−9. The mixture was extracted with methylene chloride (2×). The extracts were washed with water (2×), dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography eluting with AcOEt:hexane = 3:7 to give 17.26 g (88%) of the title compound as a white solid, mp 64−65 °C. MS (DCI/NH_3): 272, 274 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.12 (m, 1H), 0.38 (m, 1H), 0.53 (m, 1H), 0.76 (m, 1H), 1.20 (t, J = 7 Hz, 3H), 1.67 (m, 1H), 2.40 (s, 3H), 3.23 (d, J = 9 Hz, 1H), 4.16 (q, J = 7 Hz, 2H), 8.36 (s, 1H). Anal. ($C_{13}H_{15}ClFNO_3$) C, H, N.

d. Ethyl 8-Chloro-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylate (40, X = Me, Y = H, R_1 = cyclopropyl). To a stirred solution of **38** (X = Me, Y = H, R_1 = cyclopropyl) (5.577 g, 20.53 mmol) in anhydrous THF (10 mL) in a water bath cooling was added $LiAlH_4$ (10.5 mL, 10.5 mmol, 1.0 N in THF) dropwise. The resulting mixture was stirred at ambient temperature for 1 h, and then the reaction was carefully quenched with water. A 20% NaOH solution was added to dissolve the solid (Al_2O_3), and the mixture was extracted with ether (1×). The extract was washed with saturated brine (3×), dried over $MgSO_4$, and concentrated to give the alcohol as a pale yellow oil which was taken directly on to the next step.

A solution of oxalyl chloride (2.0 N in CH_2Cl_2, 12.3 mL, 24.6 mmol) was added dropwise to a stirred solution of anhydrous DMSO (3.6 mL, 50.73 mmol) in anhydrous methylene chloride (40 mL) at −78 °C. After the mixture was stirred for an additional 15 min, a solution of the above alcohol in 35 mL of methylene chloride was added dropwise at −78 °C. The solution was stirred for 15 min before triethylamine (14.2 mL, 102 mmol) was added. The stirring was continued at −78 °C for 5 min and at −10 °C for 10 min. The reaction was quenched with water and the mixture extracted with methylene chloride (2×). The combined extracts were washed with water (1×), dried over $MgSO_4$, and concentrated to give 4.70 g (theory: 4.67 g) of the aldehyde as a colorless oil which was taken directly on to the next step.

The above aldehyde was dissolved in 150 mL of absolute ethanol, and to this solution were added piperidine (5 mL), acetic acid (5 mL), and diethyl malonate (16 mL, 105 mmol). The solution was heated at reflux for 5 h. The solvents were removed, and the residue was dissolved in ether. The ether solution was washed with water (1×) and saturated brine (2×), dried over $MgSO_4$, and concentrated. The diethyl malonate was removed by Kugelrohr distillation at 50−60 °C at 0.1 mmHg. The remaining yellow oil (7.77 g, theory: 7.59 g) was dissolved in 30 mL of Dowtherm A (prepared from 23% of biphenyl and 77% of phenyl ether, v/v). The solution was added quickly to 100 mL of Dowtherm A preheated to 250 °C. The mixture was stirred at 235−240 °C for 30 min before cooling to room temperature. The reaction mixture was transferred to a silica gel column directly, eluting first with hexane to remove Dowtherm A and then with AcOEt:hexane = 1:2 and finally with AcOEt to give 4.86 g of **40** (X = Me, Y = H, R_1 = cyclopropyl) as a yellow solid (73% in four steps), mp 143−144 °C. MS (DCI/NH_3): 324, 326 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.75 (m, 2H), 1.07 (m, 2H), 1.42 (t, J = 7 Hz, 3H), 2.31 (m, 1H), 3.08 (s, 3H), 4.42 (q, J = 7 Hz, 2H), 8.40 (s, 1H), 9.44 (d, J = 6 Hz, 1H). Anal. ($C_{16}H_{15}ClFNO_3$) C, H, N, Cl.

(*S*)-8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (ABT-719, (*S*)-45a). A mixture of **40** (X = Me, Y = H) (7.0 g, 21.6 mmol), (3*S*)-3-(*tert*-BOCamino)pyrrolidine (8.3 g, 44.6 mmol), and sodium bicarbonate (8.5 g, 0.101 mol) in 100 mL of anhydrous acetonitrile was refluxed for 4 h. After cooling to room temperature, the reaction mixture was diluted with methylene chloride, washed with water (1×), 5% HCl (1×), and water (2×) again, dried over $MgSO_4$, and concentrated. The residue which weighed 11.25 g (theory: 10.23 g) was used directly in the next step.

A mixture of the above product (~21.6 mmol) and $LiOH\cdot H_2O$ (10.3 g, 0.245 mol) in 360 mL of THF and 185 mL of water was stirred for 10 h at 60 °C. After cooling to room temperature, 266 mL of 1.0 N HCl was added followed by 500 mL of water. The solid was filtered and washed with water until the pH of the washes became ~7. The solid was then dissolved in methylene chloride. The resulting solution was washed

with water once, dried over $MgSO_4$, and concentrated to give the product as a yellow solid (8.54 g, 89%). This material **45** (X = CH_3, Y = H, R_2R_3N = (*S*)-3-*t*-BOCamino-1-pyrrolidinyl) was taken directly to the next step, mp 129−130 °C. ^{1}H NMR ($CDCl_3$): δ 0.68 (m, 2H), 1.00 (m, 2H), 1.49 (s, 9H), 2.12 (m, 2H), 2.29 (m, 1H), 2.62 (s, 3H), 3.60 (m, 1H), 3.79 (m, 1H), 3.98 (m, 2H), 4.37 (m, 1H), 5.10 (br, 1H), 8.13 (s, 1H), 8.99 (d, J = 11 Hz, 1H). Anal. ($C_{23}H_{28}FN_3O_5 \cdot {}^1/_4H_2O$) C, H, N.

A solution of HCl in acetic acid (1.0 N, 85 mL) was added at room temperature to a stirred solution of the above crude product in 85 mL of anhydrous methylene chloride. After stirring for 10 min, a precipitate began to appear. After stirring for another 30 min, more methylene chloride was added and the precipitate was collected by filtration and washed with methylene chloride. The solid was dissolved in distilled water, filtered through a sintered glass funnel, and freeze-dried to give (*S*)-**45a** (ABT-719**)** as a yellow solid (7.16 g, 83% in three steps), mp 252−255 °C dec. MS (FAB): 346 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 0.99 (m, 2H), 2.14 (m, 1H), 2.31 (m, 2H), 2.63 (s, 3H), 3.76 (m, 2H), 3.98−4.07 (m, 3H), 7.94 (s, 1H), 8.36 (br, 3H), 9.11 (d, J = 11 Hz, 1H). Anal. $C_{18}H_{20}FN_3O_3 \cdot 1.15HCl \cdot H_2O$) C, H, N, Cl

Following the procedures described for (*S*)-**45a**, starting from either different amines (Figure 2, **a**−**gg**) or different pyridines (Scheme 4, **27**−**29**, **31**, **33**, **35**), the following compounds were made.

1-Cyclopropyl-9-chloro-7-fluoro-8-(3-amino-1-pyrrolidinyl)-4-oxo-4*H*-quinolizine-3-carboxylic acid trifluoroacetic acid salt (42a): mp 125−127 °C. MS (FAB): 366 (M − CF_3CO_2). ^{1}H NMR (DMSO-d_6): δ 0.58 (m, 2H), 0.97 (m, 2H), 2.11 (m, 1H), 2.31 (m, 1H), 2.44 (m, 1H), 3.83 (m, 1H), 3.97 (m, 2H), 4.10 (m, 1H), 4.20 (m, 1H), 8.09 (s, 1H), 8.09 (br, 3H), 9.18 (d, J = 11 Hz, 1H). Anal. ($C_{17}H_{17}ClFN_3O_3 \cdot CF_3COOH \cdot 0.5H_2O$) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7,9-difluoro-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (43a): mp 167−170 °C dec. MS (FAB): 350 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.65 (m, 2H), 0.90 (m, 2H), 2.15−2.30 (m, 3H), 3.95−4.00 (m, 3H), 4.18 (m, 2H), 7.81 (s, 1H), 8.46 (br, 3H), 9.17 (d, J = 9 Hz, 1H). Anal. ($C_{17}H_{17}F_2N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-8-(1-piperazinyl)-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (44cc): mp 219−220 °C. MS (FAB): 332 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.61 (m, 2H), 1.03 (m, 2H), 2.09 (m, 1H), 3.33 (m, 4H), 3.85 (m, 4H), 7.50 (d, J = 9 Hz, 1H), 7.87 (s, 1H), 9.26 (d, J = 11 Hz, 1H), 13.88 (br, 1H). Anal. ($C_{17}H_{18}FN_3O_3 \cdot 2HCl$) C, H, N.

(*R*)-8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*R*)-45a): mp 243−246 °C dec. MS (FAB): 346 (M − Cl). IR (KBr): 3440, 1700, 1650, 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 1.00 (m, 2H), 2.15 (m, 1H), 2.31 (m, 2H), 2.63 (s, 3H), 3.76 (m, 2H), 4.00−4.07 (m, 3H), 8.40 (br, 3H), 9.10 (d, J = 11 Hz, 1H). Anal. ($C_{18}H_{20}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45a): mp 230−232 °C dec. MS (FAB): 346 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.58 (m, 2H), 0.99 (m, 2H), 2.15 (m, 1H), 2.31 (m, 2H), 2.63 (s, 3H), 3.77 (m, 2H), 3.99−4.06 (m, 3H), 7.94 (s, 1H), 8.39 (br, 3H), 9.10 (d, J = 11 Hz, 1H), 13.85 (br, 1H). IR: 3440, 1695, 1610 cm^{-1}. Anal. ($C_{18}H_{20}FN_3O_3 \cdot HCl \cdot {}^3/_4H_2O$) C, H, N.

(*S*)-1-Cyclopropyl-7-fluoro-9-methyl-8-[3-(methylamino)-1-pyrrolidinyl]-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*S*)-45b): mp 223−225 °C dec. MS (FAB): 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.62 (m, 2H), 1.00 (m, 2H), 2.26 (m, 1H), 2.33 (m, 3H), 2.65 (s, 6H), 3.75 (m, 1H), 3.90 (m, 2H), 4.05 (m, 2H), 7.94 (s, 1H), 9.12 (d, J = 10 Hz, 1H), 9.18 (br s, 2H), 13.86 (br, 1H). IR (KBr): 3450, 1710, 1650, 1610 cm^{-1}. Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

(*S*)-1-Cyclopropyl-8-[3-(dimethylamino)-1-pyrrolidinyl]-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid ((*S*)-45c): mp 146−148 °C. MS (DCI/NH_3): 374 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.64 (m, 2H), 1.02 (m, 2H), 2.23−2.43 (m, 3H), 2.66 (s, 3H), 2.83 (s, 6H), 3.78−4.17 (m, 5H), 7.95 (s, 1H), 9.12 (d, J = 11 Hz, 1H), 11.14 (br, 1H), 13.83 (br, 1H). Anal. ($C_{20}H_{24}FN_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

8-(*cis*-3-Amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45d): mp 207−208 °C. MS (FAB): 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.99 (m, 2H), 1.18 (d, J = 7 Hz, 3H), 2.30 (m, 1H), 2.62 (s, 3H), 3.48−4.00 (m, 6H), 7.94 (s, 1H), 8.40 (m, 3H), 9.10 (d, J = 10.5 Hz, 1H). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot 1.25H_2O$) C, H, N.

8-(*trans*-3-Amino-4-methoxy-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45e): mp >250 °C dec. MS (FAB): 376 (M − Cl). ^{1}H NMR (CD_3OD): δ 0.71 (m, 2H), 1.88 (m, 2H), 2.30 (m, 1H), 2.74 (s, 3H), 3.51 (s, 3H), 3.84 (m, 2H), 3.98 (m, 1H), 4.24 (m, 3H), 8.02 (s, 1H), 9.02 (d, J = 3.5 Hz, 1H). Anal. ($C_{19}H_{22}FN_3O_4 \cdot HCl \cdot 4H_2O$) C, H; N: calcd, 8.68; found, 9.36.

8-((2*S*,4*S*)-4-Amino-2-methyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*S*,*S*)-45f): mp 185−187 °C dec. MS (DCI/NH_3): 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.51 (m, 1H), 0.63 (m, 1H), 0.90 (m, 1H), 1.09 (m, 1H), 1.17 (d, J = 6 Hz, 3H), 2.01 (m, 1H), 2.40 (m, 2H), 2.64 (s, 3H), 3.40 (m, 1H), 3.98 (m, 1H), 4.31 (m, 1H), 4.61 (m, 1H), 8.00 (s, 1H), 9.17 (d, J = 11 Hz, 1H). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-((2*S*,4*R*)-4-Amino-2-methyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*S*,*R*)-45h): mp 184−185 °C dec. MS (DCI/NH_3): 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.50 (m, 1H), 0.59 (m, 1H), 0.85 (m, 1H), 1.06 (m, 1H), 1.12 (d, J = 6 Hz, 3H), 1.22 (m, 1H), 1.75 (m, 1H), 2.33 (m, 1H), 2.57 (s, 1H), 7.98 (s, 1H), 8.48 (br, 3H), 9.02 (d, J = 10 Hz, 1H). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-(3-Amino-3-methyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45i): mp 243−247 °C dec. MS (FAB): 360 (M − Cl). ^{1}H NMR (CD_3OD): δ 0.69 (m, 2H), 1.07 (m, 2H), 1.63 (s, 3H), 2.31 (m, 3H), 2.74 (s, 3H), 3.95 (m, 4H), 8.12 (s, 1H), 9.14 (d, J = 9 Hz, 1H). Anal. ($C_{19}H_{23}ClFN_3O_3 \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-8-(3-hydroxy-1-pyrrolidinyl)-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45j): mp 232−234 °C. MS (DCI/NH_3): 346 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 0.93 (m, 1H), 1.03 (m, 1H), 1.96−2.01 (m, 3H), 2.29 (m, 1H), 2.49 (s, 3H), 3.43 (m, 1H), 3.69 (m, 1H), 4.01 (m, 2H), 4.42 (m, 1H), 5.15 (d, J = 3 Hz, 1H), 7.89 (s, 1H), 9.05 (d, J = 11 Hz, 1H), 13.86 (br, 1H). IR (KBr): 3425, 1690, 1650, 1600 cm^{-1}. Anal. ($C_{18}H_{19}FN_2O_4$) C, H, N.

1-Cyclopropyl-7-fluoro-8-(3(*S*)-hydroxy-1-pyrrolidinyl)-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid ((*S*)-45j): mp 244−245 °C. MS (DCI/NH_3): 347 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.58 (m, 2H), 0.93 (m, 1H), 1.03 (m, 1H), 1.96−2.02 (m, 2H), 2.29 (m, 1H), 2.59 (s, 3H), 3.41 (m, 1H), 3.69 (m, 1H), 4.01 (m, 2H), 4.42 (m, 1H), 5.16 (d, J = 3 Hz, 1H), 7.89 (s, 1H), 9.04 (d, J = 11 Hz, 1H), 13.86 (s, 1H). Anal. ($C_{18}H_{19}FN_2O_4$) C, H, N.

1-Cyclopropyl-7-fluoro-8-(3(*R*)-hydroxy-1-pyrrolidinyl)-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid ((*R*)-45j): mp 244−245 °C. MS (DCI/NH_3): 347 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.58 (m, 2H), 0.92 (m, 1H), 1.02 (m, 1H), 1.94−2.00 (m, 2H), 2.29 (m, 1H), 2.59 (s, 3H), 3.41 (m, 1H), 3.69 (m, 1H), 4.01 (m, 2H), 4.43 (m, 1H), 5.15 (d, J = 3 Hz, 1H), 7.88 (s, 1H), 9.03 (d, J = 11 Hz, 1H), 13.86 (s, 1H). Anal. ($C_{18}H_{19}FN_2O_4$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-4-oxo-8-[3-((*S*)-1-pyrrolyl)-1-pyrrolidinyl]-4*H*-quinolizine-3-carboxylic Acid ((*S*)-45k). A mixture of (*S*)-**45a** (25 mg, 0.070 mmol) and sodium acetate (40 mg, 0.49 mmol) in 0.7 mL of acetic acid was heated to 100 °C. To this solution was added dimethoxytetrahydrofuran (9 μL, 0.070 mmol) dropwise. The reaction mixture was stirred at 110 °C for 5 min, and then the reaction was quenched by the addition of water. The mixture was extracted twice with methylene chloride, and the extracts were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by preparative TLC, eluting with 100:10

chloroform:methanol, to give 13.6 mg (55%) of the title product as a yellow solid, mp 208−209 °C. MS (DCI/NH_3): 396 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.67 (m, 2H), 1.00 (m, 2H), 2.20 (m, 1H), 2.46 (m, 1H), 2.56 (m, 1H), 2.66 (s, 3H), 3.89 (m, 1H), 3.99 (m, 2H), 4.15 (m, 1H), 4.86 (m, 1H), 6.23 (t, J = 2 Hz, 2H), 6.79 (t, J = 2 Hz, 2H), 8.32 (s, 1H), 9.15 (d, J = 10 Hz, 1H), 13.83 (br, 1H). Anal. ($C_{22}H_{22}FN_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-[3-(1,2,3-triazol-1-yl)-1-pyrrolidinyl]-4-oxo-4*H*-quinolizine-3-carboxylic acid (45l): mp 183−184 °C. MS (DCI/NH_3): 398 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.61 (m, 2H), 0.99 (m, 2H), 2.31 (m, 1H), 2.56 (m, 2H), 2.62 (s, 3H), 3.84 (m, 1H), 3.99 (m, 1H), 4.10 (m, 1H), 4.36 (m, 1H), 5.46 (m, 1H), 7.80 (s, 1H), 7.92 (s, 1H), 8.32 (s, 1H), 9.11 (d, J = 11 Hz, 1H). Anal. ($C_{20}H_{20}FN_5O_3$) C, H, N.

1-Cyclopropyl-8-((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45m): mp 235−238 °C dec. MS (FAB): 358 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 1H), 0.93 (m, 1H), 1.06 (m, 1H), 2.05 (m, 1H), 2.31 (m, 2H), 2.59 (s, 3H), 3.45 (m, 2H), 3.61 (m, 1H), 4.09 (m, 1H), 4.51 (m, 1H), 4.96 (m, 1H), 7.97 (s, 1H), 9.07 (br, 1H), 9.20 (d, J = 10.5 Hz, 1H), 9.54 (br, 1H). Anal. ($C_{19}H_{20}FN_3O_3 \cdot 1.5HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-(2,8-diaza-8-bicyclo[4.3.0]nonyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45n): mp 250−253 °C dec. MS (FAB): 386 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.56 (m, 1H), 0.62 (m, 1H), 0.93 (m, 1H), 1.07 (m, 1H), 1.60−1.80 (m, 4H), 2.28−2.32 (m, 2H), 2.67 (s, 3H), 2.72 (m, 1H), 2.94 (m, 1H), 3.70 (m, 2H), 3.91 (m, 1H), 4.03 (m, 1H), 4.35 (m, 1H), 7.93 (s, 1H), 8.90 (br, 1H), 9.10 (d, J = 11 Hz, 1H), 9.48 (br, 1H), 13.85 (br, 1H). IR (KBr): 3400, 1690, 1650, 1600 cm^{-1}. Anal. ($C_{21}H_{26}Cl_2FN_3O_3$) C, H, N.

1-Cyclopropyl-8-((1*S*,6*S*)-2,8-diaza-8-bicyclo[4.3.0]nonyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*S*,*S*)-45n): mp 232−234 °C. $[\alpha]^{23}_D = -281.3°$ (c = 0.52, methanol). MS (FAB): 386 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.56 (m, 1H), 0.62 (m, 1H), 0.92 (m, 1H), 1.07 (m, 1H), 1.61−1.81 (m, 4H), 2.30 (m, 1H), 2.56 (m, 1H), 2.67 (s, 3H), 2.92 (m, 1H), 3.25 (m, 1H), 3.69 (m, 2H), 3.90 (m, 1H), 4.06 (m, 1H), 4.35 (m, 1H), 7.92 (s, 1H), 9.02 (br, 1H), 9.09 (d, J = 11 Hz, 1H), 9.59 (br, 1H). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot 1.25H_2O$) C, H, N.

1-Cyclopropyl-8-((1*R*,6*R*)-2,8-diaza-8-bicyclo[4.3.0]-nonanyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*R*,*R*)-45n): mp 184−185 °C. $[\alpha]^{23}_D = +275.1°$ (c = 0.53, methanol). MS (FAB): 386 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.56 (m, 1H), 0.62 (m, 1H), 0.92 (m, 1H), 1.08 (m, 1H), 1.63−1.81 (m, 4H), 2.31 (m, 1H), 2.56 (m, 1H), 2.68 (s, 3H), 2.91 (m, 1H), 3.25 (m, 1H), 3.69 (m, 2H), 3.90 (m, 1H), 4.06 (m, 1H), 4.35 (m, 1H), 7.92 (s, 1H), 9.02 (br, 1H), 9.09 (d, J = 11 Hz, 1H), 9.60 (br, 1H). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot 1.5H_2O$) C, H, N.

1-Cyclopropyl-8-(2,7-diaza-7-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45o). a. 2-CBZ-7-*tert*-BOC-2,7-diazabicyclo-[3.3.0]octane. 7-*tert*-BOC-2,7-diazabicyclo[3.3.0]octane (1.06 g, 5.00 mmol)[25] was dissolved in 12 mL of 1 N NaOH, and the solution was cooled to 0 °C. To this solution was added benzyl chloroformate (1.43 mL, 10.0 mmol) in 10 mL of ether over a 10 min period. The mixture was stirred for 4 h. The mixture was then extracted with methylene chloride, and the extract was washed with water, dried over $MgSO_4$, and concentrated to give the title compound (1.55 g, 90%).

b. 2-CBZ-2,7-diazabicyclo[3.3.0]octane. 2-CBZ-7-*tert*-BOC-2,7-diazabicyclo[3.3.0]octane (1.10 g, 3.18 mmol) was dissolved in ethyl acetate (20 mL) and treated with 4 N HCl in dioxane (5.0 mL, 20.0 mmol) at room temperature overnight. The solvent was removed, and the residue was dissolved in 5% $NaHCO_3$. The mixture was extracted with 1:3 isopropyl alcohol:methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give 0.60 g (77%) of the title compound.

c. 1-Cyclopropyl-8-(2,7-diaza-7-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45o): following the procedures as described for (*S*)-**45a** and **12a**-*N*-Ala, substituting 2-CBZ-2,7-diazabicyclo-[3.3.0]octane for the (*S*)-3-*tert*-BOCaminopyrrolidine, mp 199−202 °C. MS (FAB): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.62 (m, 2H), 1.00 (m, 2H), 1.98 (m, 1H), 2.18 (m, 1H), 2.35 (m, 1H), 2.69 (s, 3H), 3.12 (m, 1H), 3.27 (m, 1H), 3.71 (m, 2H), 3.93 (m, 1H), 4.05 (m, 1H), 4.31 (m, 1H), 8.00 (s, 1H), 9.17 (d, J = 12 Hz, 1H). Anal. ($C_{20}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-((1*S*,5*S*)-2,7-diaza-7-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride ((*S*,*S*)-45o). a. Separation of the Two Enantiomers of 2-CBZ-7-*tert*-BOC-2,7-diazabicyclo[3.3.0]-octane. The racemic 2-CBZ-7-*tert*-BOC-2,7-diazabicyclo[3.3.0]-octane prepared above in **45o** was separated by preparative HPLC using a Chiralpak column eluting with hexane:ethanol = 90:10. The compound with a lower retention time (t_R = 8.3 min on an analytical column (AD 4.6 × 250 mm) with flow rate of 1.0 mL/min) was assigned arbitrarily as (*R*,*R*)-2-CBZ-7-BOC-2,7-diazabicyclo[3.3.0]octane. The compound with higher retention time (t_R = 17.2 min on an analytical column (AD 4.6 × 250 mm) with flow rate of 1.0 mL/min) was arbitrarily assigned as (*S*,*S*)-2-CBZ-7-BOC-2,7-diazabicyclo[3.3.0]octane.

b. 1-Cyclopropyl-8-((1*S*,5*S*)-2,7-diaza-7-bicyclo[3.3.0]-octyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride ((*S*,*S*)-45o). Following the same procedures as described for **45o**, using the above arbitrarily assigned optically pure (*S*,*S*)-2-CBZ-7-*tert*-BOC-2,7-diazabicyclo-[3.3.0]octane, the title compound was obtained, mp 193−195 °C. MS (FAB): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.62 (m, 2H), 1.00 (m, 2H), 1.98 (m, 1H), 2.18 (m, 1H), 2.36 (m, 1H), 2.69 (s, 3H), 3.13 (m, 1H), 3.28 (m, 1H), 3.71 (m, 2H), 3.91 (m, 1H), 4.04 (m, 1H), 4.31 (m, 1H), 8.00 (s, 1H), 9.17 (d, J = 11 Hz, 1H). Anal. ($C_{20}H_{22}FN_3O_3 \cdot HCl \cdot 1.5H_2O$) C, H, N.

1-Cyclopropyl-8-((1*R*,5*R*)-2,7-diaza-7-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*R*,*R*)-45o): same as described for (*S*,*S*)-**45o**, using the arbitrarily assigned optically pure (*R*,*R*)-2-CBZ-7-*tert*-BOC-2,7-diazabicyclo[3.3.0]octane (see (*S*,*S*)-**45o**), mp 190−192 °C. MS (FAB): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.62 (m, 2H), 1.00 (m, 2H), 1.98 (m, 1H), 2.18 (m, 1H), 2.35 (m, 1H), 2.69 (s, 3H), 3.12 (m, 1H), 3.27 (m, 1H), 3.71 (m, 2H), 3.93 (m, 1H), 4.05 (m, 1H), 4.31 (m, 1H), 8.00 (s, 1H), 9.17 (d, J = 11 Hz, 1H). Anal. ($C_{20}H_{22}FN_3O_3 \cdot HCl \cdot 1.75H_2O$) C, H, N.

8-[3-(1-Aminomethyl)-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45p): mp 233−235 °C. MS (DCI/NH_3): 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.99 (m, 2H), 1.81 (m, 1H), 2.18 (m, 1H), 2.30 (m, 1H), 2.60 (s, 3H), 2.98 (m, 2H), 3.66−3.81 (m, 5H), 7.90 (s, 1H), 8.09 (br, 3H), 9.06 (d, J = 11 Hz, 1H), 13.85 (br, 1H). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-(2,7-diaza-2-bicyclo[3.3.0]octyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45q): mp 175−177 °C. MS (FAB): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.91 (m, 1H), 2.03−2.10 (m, 3H), 2.36 (m, 1H), 2.68 (s, 3H), 3.19 (m, 1H), 3.49 (m, 2H), 4.15 (m, 1H), 5.50 (m, 1H), 7.98 (s, 1H), 9.14 (d, J = 10 Hz, 1H), 9.40 (br, 1H). IR (KBr): 3400, 1700, 1650, 1605 cm^{-1}. Anal. ($C_{20}H_{24}Cl_2FN_3O_3$) C, H, N.

8-((1*R,2*S**,6*R**)-2-Amino-8-aza-8-bicyclo[4.3.0]nonyl)-1-cyclopropyl-7-fluoro-4*H*-9-methyl-4-oxoquinolizine-3-carboxylic acid hydrochloride (45r):** mp 209−214 °C dec. MS (FAB): 400 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.63 (m, 2H), 0.94 (m, 1H), 1.05 (m, 1H), 1.42−1.62 (m, 4H), 1.97 (m, 1H), 2.31 (m, 2H), 2.62 (s, 3H), 2.67 (m, 1H), 3.19 (m, 1H), 3.54 (m, 1H), 3.82 (m, 1H), 4.00 (m, 2H), 7.89 (s, 1H), 8.18 (br, 3H), 9.06 (d, J = 11 Hz, 1H). Anal. ($C_{22}H_{26}N_3O_3F \cdot 1.25HCl \cdot 1.5H_2O$) C, H, N.

8-((1*R,2*R**,6*R**)-2-Amino-8-aza-8-bicyclo[4.3.0]nonyl)-1-cyclopropyl-7-fluoro-4*H*-9-methyl-4-oxoquinolizine-3-carboxylic acid hydrochloride (45s):** mp 215−220 °C dec. MS (FAB): 400 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.53−0.61 (m, 2H), 0.95−1.06 (m, 2H), 1.30 (m, 2H), 1.60 (m, 2H), 1.81 (m, 2H), 2.29 (m, 1H), 2.49 (m, 1H), 2.64 (s, 3H), 2.77 (m, 1H), 3.32−3.49 (m, 3H), 4.16 (m, 2H), 7.91 (s, 1H), 8.33 (br, 3H), 9.06 (d, J = 10 Hz, 1H). Anal. ($C_{22}H_{26}N_3O_3F \cdot 1.0HCl \cdot 1.25H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-[3-(2-pyridinyl)-1-pyrrolidinyl]-4-oxo-4*H*-quinolizine-3-carboxylic acid hy-

drochloride (45t): mp 173−175 °C. MS (FAB): 408 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.99 (m, 2H), 2.30−2.40 (m, 2H), 2.60 (m, 1H), 2.64 (s, 3H), 3.86−4.16 (m, 4H), 7.80 (m, 1H), 7.90 (s, 1H), 9.07 (d, J = 11 Hz, 1H). Anal. ($C_{23}H_{23}FN_3O_3$·HCl·H_2O) C, H, N.

8-((1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hexan-3-yl)-1-cyclopropyl-9-methyl-7-fluoro-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45u): mp 190−195 °C dec. MS (FAB): 358 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.61 (m, 2H), 1.01 (m, 2H), 2.12 (br, 2H), 2.33 (m, 1H), 2.62 (s, 3H), 3.81 (m, 5H), 7.97 (s, 1H), 8.46 (br, 3H), 9.11 (d, J = 10.5 Hz, 1H), 13.83 (br, 1H). Anal. ($C_{19}H_{20}FN_3O_3$·1.5HCl·0.5H_2O) C, H, N.

8-((1*S,3*R**)-1-Amino-5-azaspiro[2.4]heptan-5-yl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45v). a. (1*S**,3*R**)-1-*tert*-BOCamino-5-azaspiro[2.4]heptane** was prepared according to literature procedures.[30] The relative stereochemistry was assigned by comparing NOE spectra of the precursors (1*S**,3*R**)-5-benzyl-1-(ethoxycarbonyl)-5-azaspiro[2.4]heptane and (1*R**,3*S**)-5-benzyl-1-(ethoxycarbonyl)-5-azaspiro[2.4]-heptane.

b. 8-((1*S,3*R**)-1-Amino-5-azaspiro[2.4]heptan-5-yl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45v).** The title compound was prepared using the procedures as described for (*S*)-**45a**, replacing 3-*t*-BOCaminopyrrolidine with (1*S**,3*R**)-1-*tert*-BOCamino-5-azaspiro[2.4]heptane to produce a solid, mp 179−182 °C dec. MS (DCI/NH_3): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.99 (m, 2H), 1.10 (m, 1H), 1.16 (m, 1H), 2.16 (m, 2H), 2.29 (m, 1H), 2.61 (s, 3H), 2.79 (m, 1H), 3.62 (m, 1H), 3.77 (m, 1H), 3.82 (m, 1H), 4.13 (m, 1H), 7.90 (s, 1H), 8.56 (br, 2H), 9.08 (d, J = 11 Hz, 1H), 13.85 (br, 1H). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·2H_2O) C, H, N.

8-((1*R,3*R**)-1-Amino-5-azaspiro[2.4]heptan-5-yl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45w).** The title compound was prepared using the procedures as described for (*S*)-**45a**, replacing 3-BOCaminopyrrolidine with (1*R**,3*R**)-1-*tert*-BOCamino-5-azaspiro[2.4]heptane (see **45v** for preparation) to produce a solid, mp 178−181 °C dec. MS (DCI/NH_3): 372 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 0.99 (m, 2H), 1.15 (m, 2H), 1.88 (m, 1H), 2.04 (m, 1H), 2.29 (m, 1H), 2.64 (s, 3H), 2.72 (m, 1H), 3.73 (m, 1H), 3.80 (m, 1H), 3.97 (m, 1H), 4.03 (m, 1H), 7.90 (s, 1H), 8.52 (br, 3H), 9.09 (d, J = 11 Hz, 1H). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·2H_2O) C, H, N.

8-[3-((3*S*,6*R*)-1-Aminoethyl)-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*S*,*R*)-45x): mp 235−240 °C dec. MS (DCI/NH_3): 374 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 1.00 (m, 2H), 1.29 (d, J = 6 Hz, 3H), 1.76 (m, 1H), 2.13 (m, 1H), 2.28 (m, 1H), 2.41 (m, 1H), 2.63 (s, 3H), 3.30 (m, 1H), 3.74 (m, 3H), 3.94 (m, 1H), 7.90 (s, 1H), 8.16 (br, 3H), 9.07 (d, J = 11 Hz, 1H). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·1.25H_2O) C, H, N.

8-[3-((3*R*,6*R*)-1-Aminoethyl)pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*R*,*R*)-45x): mp 220−222 °C. MS (DCI/NH_3): 374 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.61 (m, 2H), 0.94 (m, 1H), 1.07 (m, 1H), 1.28 (d, J = 6 Hz, 3H), 1.82 (m, 1H), 2.27 (m, 2H), 2.46 (m, 1H), 2.62 (s, 3H), 3.57 (s, 1H), 3.92 (m, 1H), 7.90 (s, 1H), 8.17 (br, 3H), 9.07 (d, J = 11 Hz, 1H), 13.84 (br, 1H). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·1.5H_2O) C, H, N.

8-[3-((3*R*,6*S*)-1-Aminoethyl)pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride ((*R*,*S*)-45x): mp 250−255 °C dec. MS (FAB): 374 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.59 (m, 2H), 1.00 (m, 2H), 1.29 (d, J = 7 Hz, 3H), 1.77 (m, 1H), 2.13 (m, 1H), 2.29 (m, 1H), 2.41 (m, 1H), 2.64 (s, 3H), 3.57 (s, 1H), 3.76 (m, 3H), 3.94 (m, 1H), 7.91 (s, 1H), 8.17 (br, 3H), 9.07 (d, J = 11 Hz, 1H), 13.83 (br, 1H). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·$^1/_2H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-8-(1-imidazolyl)-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid (45y): mp 237−240 °C dec. ^{1}H NMR ($CDCl_3$): δ 0.90 (m, 2H), 1.18 (m, 2H), 2.40 (m, 1H), 2.83 (s, 3H), 7.15 (s, 1H), 7.39 (s, 1H), 7.71 (s, 1H), 8.66 (s, 1H), 9.43 (d, J = 6 Hz, 1H). HRMS ($C_{17}H_{14}FN_3O_3$ + H): calcd, 328.1097; found, 328.1110.

8-(3-Aminoazetidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45z): mp 198−200 °C dec. MS (FAB): 332 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.61 (m, 2H), 1.00 (m, 2H), 2.30 (m, 1H), 2.61 (s, 3H), 4.15 (m, 1H), 4.56 (m, 2H), 4.86 (m, 2H), 7.89 (s, 1H), 8.51 (br s, 3H), 9.13 (d, J = 10 Hz, 1H). Anal. ($C_{17}H_{18}FN_3O_3$·1.25HCl·H_2O) C, H, N.

1-Cyclopropyl-8-(*cis*-3,5-dimethyl-1-piperazinyl)-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45dd): mp >285 °C dec. MS (FAB): 374 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.70 (m, 2H), 1.04 (m, 2H), 1.30 (d, J = 7 Hz, 6H), 2.41 (m, 1H), 2.80 (s, 3H), 3.40−3.65 (m, 6H), 8.03 (s, 1H), 9.26 (d, J = 9 Hz, 1H), 9.60 (br, 1H). IR (KBr): 3450, 1720, 1650, 1610 cm^{-1}. Anal. ($C_{20}H_{24}FN_3O_3$·HCl·0.75H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-8-(1-homopiperazinyl)-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid, acetic acid salt (45ee): mp 195−198 °C dec. MS (FAB): 360 (M + H). ^{1}H NMR (DMSO-d_6): δ 0.55 (m, 2H), 0.98 (m, 2H), 1.83 (s, 6H), 2.26−2.38 (m, 2H), 2.69 (br, 3H), 2.89 (m, 4H), 8.08 (br, 1H), 9.04 (br, 1H). Anal. ($C_{19}H_{22}FN_3O_3$·CH_3CO_2H·1.25H_2O) C, H, N.

8-[(2-Aminoethyl)amino]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (45ff): mp 197−199 °C. MS (FAB): 320 (M − Cl). ^{1}H NMR (D_2O): δ 0.60 (m, 2H), 1.02 (m, 2H), 2.02 (m, 1H), 2.64 (s, 3H), 3.40 (m, 2H), 3.99 (m, 2H), 7.40 (s, 1H), 8.80 (d, J = 10.5 Hz, 1H). Anal. ($C_{16}H_{18}N_3O_3F$·HCl·0.85H_2O) C, H, N.

8-[*N*-(2-Aminoethyl)-*N*-methylamino]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45gg). (a) *N*-[2-(Benzyloxycarbonyl)-ethyl]methylamine. (Methylamino)acetonitrile hydrochloride (2.08 g, 19.5 mmol) and sodium carbonate (2.33 g, 22.0 mmol) were suspended in methanol (24 mL) and water (8 mL). To the above mixture was added di-*tert*-butyl dicarbonate (6.7 mL, 29.3 mmol). The reaction mixture was stirred at room temperature for 2.5 h. The methanol was removed, and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over $MgSO_4$, and concentrated. The product, [*N*-(*tert*-butoxylcarbonyl)-*N*-methylamino]acetonitrile (3.33 g, 100%), was purified by column chromatography eluting with AcOEt and hexanes (1:8).

The above nitrile (19.5 mmol) was dissolved in methanol (135 mL) and hydrogenated under H_2 (4 atm) and RaNi 2800 (3.0 g) at room temperature for 3 days. The reaction mixture was filtered and concentrated to give 2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethylamine (3.02 g, 88%).

To a suspension of the above crude amine (17.3 mmol) and sodium carbonate (2.15 g, 25.9 mmol) in dioxane (15 mL) and water (15 mL) was added benzyl chloroformate (2.94 mL, 20.6 mmol) dropwise at 0 °C. The reaction mixture was then stirred for 45 min at 0−5 °C and for 3 h at room temperature before being diluted with ether. The organic phase was separated, washed with saturated $NaHCO_3$ and water, dried over $MgOS_4$, and concentrated. The residue was purified by column chromatography eluting with AcOEt and hexanes (1:4) to give [2-[*N*-(benzyloxycarbonyl)-*N*-methylamino]ethyl]-*N*-(*tert*-butoxycarbonyl)amine (2.86 g, 54%).

A 1.43 g (4.64 mmol) portion of the above BOC-protected amine was stirred with 11.5 mL of HCl in dioxane (4.0 N, 46.0 mmol) in methylene chloride (20 mL) at room temperature. The solvents were removed under vacuum, and the residue was dissolved in water and basicified with 15% NaOH. The mixture was extracted with methylene chloride and 2-propanol (3:1) (2×). The extracts were dried over $MgSO_4$ and concentrated to give the crude title product (0.98 g, 100%). It was used directly in the next step. MS (DCI/NH_3): 299 (M + H). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 9H), 2.69 (s, 3H), 2.75 (t, J = 6 Hz, 2H), 3.31 (m, 2H), 5.10 (s, 2H), 5.41 (br, 1H), 7.34 (m, 5H).

b. 8-[*N*-(2-Aminoethyl)-*N*-methylamino]-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (45gg). Following procedures described for **45o**, starting from *N*-[2-(benzyloxycarbonyl)ethyl]methylamine, the title compound was prepared, mp 205−207 °C dec. MS (DCI/NH_3): 334 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.60 (m, 2H), 0.98 (m, 2H), 2.33 (m, 1H), 2.61 (s, 3H), 2.70 (s, 3H),

3.15 (m, 2H), 3.79 (m, 2H), 7.80 (s, 1H), 9.19 (d, J = 8 Hz, 1H), 13.93 (br, 1H). Anal. ($C_{17}H_{20}FN_3O_3$·HCl·2.75H_2O) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-9-ethyl-7-fluoro-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (46a): MS (FAB) 360 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.52 (m, 2H), 0.87 (t, J = 6 Hz, 3H), 0.98 (m, 2H), 2.20 (m, 2H), 2.33 (m, 1H), 3.20 (m, 2H), 3.65−3.96 (m, 5H), 7.95 (s, 1H), 8.43 (br, 3H), 9.07 (d, J = 10.5 Hz, 1H), 13.83 (br, 1H). Anal. ($C_{19}H_{22}N_3O_3F$·1.25HCl·1.5H_2O) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methoxy-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (47a): mp 187−190 °C dec. MS (FAB): 362 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.62 (m, 2H), 0.91 (m, 2H), 2.12 (m, 1H), 2.29 (m, 1H), 2.39 (m, 1H), 3.62 (s, 3H), 3.81 (m, 1H), 3.94 (m, 2H), 4.06 (m, 2H), 7.79 (s, 1H), 8.30 (br, 3H), 9.13 (d, J = 10 Hz, 1H), 13.79 (br, 1H). IR (KBr): 3440, 1799, 1650, 1610 cm^{-1}. Anal. ($C_{18}H_{20}FN_3O_4$·2HCl·0.5H_2O) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-ethyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (48a): mp 215−217 °C. MS (FAB): 334 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 2.28 (m, 3H), 2.22 (m, 1H), 2.52 (m, 4H), 2.96 (m, 2H), 3.88−4.18 (m, 5H), 8.01 (s, 1H), 9.05 (d, J = 10 Hz, 1H). Anal. ($C_{17}H_{20}FN_3O_3$·HCl·1.5H_2O) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-6-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid hydrochloride (49a): mp >262 °C dec. MS (FAB): 346 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.53 (m, 2H), 0.99 (m, 2H), 1.87 (m, 1H), 2.20 (m, 1H), 2.34 (m, 1H), 2.87 (d, J = 5.5 Hz, 3H), 3.76−4.02 (m, 5H), 6.92 (d, J = 9 Hz, 1H), 7.72 (s, 1H), 8.38 (br, 3H). Anal. ($C_{18}H_{20}FN_3O_3$·HCl·1.5H_2O) C, H, N.

8-(3-Amino-1-pyrrolidinyl)-1-ethyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (54). a. 4-Chloro-2-propylpyridine (51). To a stirred solution of LDA in cyclohexane (100 mL, 1.5 M, 150 mmol) at −60 °C was added, dropwise over a period of 30 min, a solution of 4-chloro-2-picoline (17.47 g, 137 mmol) in 80 mL of THF. The reaction mixture was stirred for 0.5 h at −60 °C, and then a solution of ethyl iodide (10.95 mL, 137 mmol) in 30 mL of THF was added over 20 min. Stirring was continued for 0.5 h at −60 °C and for 1.5 h at −30 °C before the mixture was poured into cold brine. The aqueous mixture was extracted with methylene chloride. The organic extract was dried over anhydrous sodium sulfate and concentrated. The residue was distilled to afford 12.67 g (60%), bp 77−80 °C (10 mmHg), of the title compound.

b. Diethyl 3-(4-Chloro-2-pyridyl)-3-ethylpent-1-ene-1,1-dicarboxylate (52). To a stirred solution of LDA (89.9 mmol), prepared from diisopropylamine and *n*-butyllithium in 20 mL of THF at −60 °C, was added a solution of 4-chloro-2-propylpyridine (12.66 g, 81.9 mmol) in 100 mL of THF over a period of 30 min. The solution was stirred at −60 °C for 0.5 h, and then diethyl (ethoxymethylene)malonate (16.55 mL, 81.9 mmol) was added over 30 min. Stirring was continued at −60 °C for 0.5 h and at −20 °C for 1.5 h. The reaction mixture was then poured into cold brine, and the aqueous mixture was extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 35.48 g of the title compound. The product was carried on to the next step without purification.

c. Ethyl 8-Chloro-1-ethyl-4-oxo-4*H*-quinolizine-3-carboxylate (53). A solution of **52** (35.48 g, 99.2 mmol) in 1 L of xylene was heated at 150 °C for 24 h. The reaction mixture was then concentrated. The residue was triturated with hexane to afford 14.87 g (54%) of the title compound. MS (DCI/NH_3): 280 (M + H). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.5 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H), 2.78 (q, J = 7.5 Hz, 2H), 4.43 (q, J = 7.2 Hz, 2H), 7.10 (dd, J_1 = 2.4 Hz, J_2 = 8.1 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 8.32 (s, 1H), 9.40 (d, J = 8.1 Hz, 1H).

d. 8-(3-Amino-1-pyrrolidinyl)-1-ethyl-4-oxo-4*H*-quinolizine-3-carboxylic Acid Hydrochloride (54). A mixture of **53** (1.20 g, 4.3 mmol), 3-[*N*-(*tert*-butoxycarbonyl)amino]-pyrrolidine (1.04 g, 5.59 mmol), and triethylamine (1.8 mL, 12.9 mmol) in 15 mL of dry pyridine was heated at 60 °C for 12 h. The reaction mixture was then concentrated. The residue was triturated with ethanol to give 0.42 g of the desired product. The filtrate was concentrated and the residue purified by column chromatography eluting with 2% methanol in methylene chloride followed by 5% methanol in methylene chloride to afford an additional 1.27 g of the desired product. The total weight of the BOC-protected compound was 1.69 g (92%).

A solution of the above solid (1.69 g, 3.94 mmol) in 25 mL of trifluoroacetic acid (TFA) was stirred for 2 h at room temperature. The TFA was evaporated, and the residue was dissolved in 200 mL of methanol. To the resultant solution was added 25 g of a strongly basic ion exchange resin, and the mixture was stirred at room temperature for 2 h. The mixture was filtered, and the filtrate was concentrated to afford ethyl 8-(3-amino-1-pyrrolidinyl)-1-ethyl-4-oxo-4*H*-quinolizine-3-carboxylate which was then dissolved in 6 mL of THF and 10.5 mL of a 1 M aqueous solution of sodium hydroxide. The reaction mixture was heated at 60 °C for 2 h. After the THF was removed, the reaction mixture was poured into water, and the pH of the resultant solution was adjusted to ∼2 with concentrated hydrochloric acid. The solid was filtered to afford 0.365 g (29%) of the title compound, mp 196−198 °C. MS (DCI/NH_3): 302 (M − Cl). ^{1}H NMR (TFA-*d*): δ 1.41 (t, J = 7.5 Hz, 3H), 2.39 (q, J = 7.5 Hz, 2H), 2.70 (m, 3H), 4.0 (m, 3H), 4.53 (m, 1H), 6.93 (d, J = 1.5 Hz, 1H), 7.33 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1H), 7.93 (s, 1H), 9.08 (d, J = 9 Hz, 1H). IR (KBr): 3440, 2960, 1650. Anal. ($C_{16}H_{19}N_3O_3$·HCl) C, H, N.

8-((*S*)-3-Amino-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-3-(nitroacetyl)-4-oxo-4*H*-quinolizine Hydrochloride ((*S*)-55a). A mixture of **45** (X = CH_3, Y = H, R_2R_3N = (*S*)-3-*tert*-BOCamino-1-pyrrolidinyl) (1.23 g, 2.76 mmol) (see (*S*)-**45a** for preparation) and carbonyldiimidazole (0.90 g, 5.55 mmol) in 30 mL of THF was refluxed for 8 h. The reaction mixture was diluted with methylene chloride, and the solution was washed with water (2×), dried over $MgSO_4$, and concentrated. The residue dissolved in 50 mL of DMF was added to a solution of the anion of nitromethane in DMF (made from the addition of nitromethane (1.0 mL, 11.1 mmol) to NaH (0.39 g, 60% dispersion in mineral oil, 9.75 mmol) in 20 mL of DMF at room temperature for 2 h). The mixture was heated to 40 °C for 8 h. The DMF was removed under vacuum. The residue was dissolved in methylene chloride, washed with 1 N HCl (1×) and water (1×), and dried over $MgSO_4$. The residue, after removal of the solvent, was purified by column chromatography, eluting with 3% methanol in methylene chloride. This BOC-protected compound was dissolved in methylene chloride (40 mL). HCl in dioxane (10 mL, 4.0 N, 40 mmol) was added. The reaction mixture was stirred at room temperature for 24 h before adding more methylene chloride. The precipitate was collected by filtration and washed with methylene chloride. The solid was dissolved in distilled water and filtered through a sintered glass funnel. The filtrate was freeze-dried to give (*S*)-**55a** as a dark red solid (0.722 g, 46%), mp 195−198 °C dec. MS (DCI/NH_3): 389 (M − Cl). ^{1}H NMR (DMSO-d_6): δ 0.56 (m, 2H), 0.96 (m, 2H), 2.13 (m, 1H), 2.29 (m, 2H), 2.61 (s, 3H), 3.77 (m, 2H), 3.96−4.07 (m, 3H), 6.00 (s, 1H), 7.25 (s, 1H), 8.33 (br, 3H), 9.09 (d, J = 11 Hz, 1H), 12.25 (s, 1H). Anal. ($C_{19}H_{21}FN_4O_4$·1.5HCl·H_2O) C, H, N.

Single-Crystal X-ray Analysis of ABT-719. The crystal was grown in a mixture of ethanol and water. Crystallographic data were collected on a Rigaku AFC5R single-crystal diffractometer with Cu Kα radiation and a nickel filter. Data were collected at ambient temperature, and cell constants and orientation matrices for data collection were obtained from a least-squares refinement using the setting angles of 18 accurately centered reflections in the range 43° < 2θ < 82°, using the $\omega - 2\theta$ scan technique with stationary background and a scan speed of 16.0°/min. Space group was determined from systematic absences or structure determination. Limits of data collection were 6° ≤ 2θ ≤ 120°. No decay was observed in the intensities of three representative reflections measured after every 150 reflections. Data were reduced to a unique set of intensities and associate σ values in the usual manner using the TEXSCAN programs. The structure was solved by a combination of direct methods using program SHELX86 and Fourier techniques. All non-hydrogen atoms were anisotropically refined. H atom contributions were idealized. The absolute configuration was also determined by X-ray. Crystal

data for $C_{18}H_{21}ClFN_3O_3$ (ABT-719): yellow crystals, orthorhombic, $P2_12_12_1$; $a = 10.319(2)$ Å, $b = 29.785(8)$ Å, $c = 6.778(2)$ Å; $V = 2083.1(8)$ Å^3; $Z = 4$; $D_{calc} = 1.217$. Of 3710 reflections collected ($T = 296$ K, $2\theta_{max} = 120.1°$), 1894 were unique and observed; $R = 6.9\%$ and $R_w = 6.5\%$.

***In Vitro* Antibacterial Activity.** MICs were determined as described by the National Committee for Clinical Laboratory Standards[39] except brain−heart infusion agar was used. The MIC was defined as the lowest concentration resulting in inhibition of visible bacterial growth after incubation at 37 °C for 18−24 h.[33a]

***In Vivo* Antibacterial Efficacy.** *In vivo* efficacy was determined as previously described.[33c,40] Mice were treated at several concentrations with a single dose administered either subcutaneously (sc) or orally (po). The ED_{50} is the calculated dose that results in protecting 50% of the treated animals.

Gyrase Inhibition. Gyrase-mediated DNA cleavage of a compound is expressed by a CC_{50} value that is defined as the drug concentration which causes 50% of the maximal gyrase-mediated DNA cleavage. The assay procedures were described previously, using the gyrase from *E. coli* H560 and supercoiled ColE1 DNA.[41]

Solubility Studies. Known excess weights of the compounds in known volume of sodium phosphate buffer (0.05 M, pH 7.4) containing 0.9% sodium chloride by weight were capped, vortexed, and agitated overnight. The contents were filtered through 0.45 μm filters. The filtrates were analyzed by HPLC (column, 5 cm × 4.6 mm 3 μm Spherisorb OD-2; mobile phase, acetonitrile:0.04 M H_3PO_4:0.01 M NaH_2PO_4: 0.005 M acetohydroxamic acid:0.2% SDS) at a flow rate of 1.0 mL/min with detection at 420 nm. The concentration of compounds was calculated by least-squares linear regression analysis of the peak area of spiked mobile phase standards versus concentration.

Pharmacokinetic Studies. Compounds were administered orally and intravenously to male Sprague−Dawley rats (250−350 g) at a 5 mg/kg dose in water (the non-hydrochloride compounds were dissolved in water with 1−2 mol equiv of sodium hydroxide). Rats were fasted overnight prior to and throughout the duration of study but allowed free access to water. At the selected time points after dosing, sequential blood samples were collected from a tail vein of each rat. The plasma was separated from the red cells by centrifugation. The compounds of interest were extracted into a mixed solvent of methylene chloride and ethanol (9:1, by volume) at neutral pH. The compounds were analyzed by HPLC (column, 5 cm × 4.6 mm 5 μm Inertsil; mobile phase, acetonitrile:0.04 M H_3PO_4:0.01 M NaH_2PO_4:0.005 M acetohydroxamic acid:0.2% SDS) at a flow rate of 1.0 mL/min with detection at 420 nm. The plasma concentration of compound was calculated by least-squares linear regression analysis of the peak area ratio (parent/internal standard) of the spiked rat plasma versus concentration.

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Supporting Information Available: X-ray crystallographic data of ABT-719 (tables of atomic coordinates, thermal parameters, bond lengths, bond angles, torsion angles, intermolecular distances, and crystal packing diagram) and yields, melting points, and spectroscopic data of intermediates for Scheme 1 (12 pages). Ordering information is given on any current masthead page.

References

(1) Kojima, T.; Mitsuhashi, S. History of Quinolone Antibacterials. *Prog. Drug Res.* **1992**, *38*, 11−17.

(2) For recent reviews about quinolones, see: (a) Chu, D. T. W.; Shen, L. L. Quinolones: Synthetic Antibacterial Agents. In *50 Years of Microbials*; Darby, G. K., Hunter, P. A., Russell, A. D., Eds.; Cambridge University Press: Cambridge, 1995; pp 111−137. (b) Chambers, S. T. Quinolones. *New Zealand Med. J.* **1995**, *108*, 273−277. (c) Hendershot, E. F. Fluoroquinolones. *Infect. Dis. Clin. North Am.* **1995**, *9*, 715−730. (d) Suh, B.; Lorber, B. Quinolones. *Med. Clin. North Am.* **1995**, *79*, 869−894. (e) Domagala, J. M. Structure-activity and Structure-side-effect Relationships for the Quinolone Antibiotics. *J. Antimicrob. Chemother.* **1994**, *33*, 685−706. (f) Guyay, D. R. P. Quinolones. *Infect. Dis. Ther.* **1994**, *9*, 237−310. (g) New, H. C. Major Advances in Antibacterial Quinolone Therapy. *Adv. Pharmacol.* **1994**, *29A*, 227−262. (h) *Quinolone Antibacterial Agents*, 2nd ed.; Hooper, D. C., Wolfson, J. C., Eds.; American Society of Microbiology: Washington, DC, 1993. (i) Asahina, Y.; Ishizaki, T.; Suzue, S. Recent Advances in Structure-Activity Relationships in New Quinolones. *Prog. Drug Res.* **1992**, *38*, 57−106. (j) Stanislav, R.; Bouzard, D. Recent Advances in the Synthesis of Antibacterial Quinolones. *Heterocycle* **1992**, *34*, 2143−2177. (k) Chu, D. T. W. Recent Developments in the Field of Quinolone Antibacterial Agents. *Adv. Drug Res.* **1991**, *21*, 39−144. (l) Leysen, D. C.; Zhang, M. Q.; Haemers, A.; Bolaert, W. Synthesis of Antibacterial 4-Quinolone-3-Carboxylic Acids and Their Derivatives. Part 1 & 2. *Pharmazie* **1991**, *46*, 485−501, 557−572. (m) Mitscher, L. A.; Zavod, R. M.; Devasthale, P. V.; Chu, D. T. W.; Shen, L. L.; Sharma, P. N.; Pernet, A. G. Microbes Beware: Quinolones. Part 1 & 2. *CHEMTECH* **1991**, *21*, 50−56, 249−255. (n) *The New Generation of Quinolones*; Siporin, C., Heifetz, C. L., Domagala, J. M., Eds.; Marcel Dekker: New York, 1990. (o) *The 4-Quinolones: Antibacterial Agents in vitro*; Crumplin, G. C., Ed.; Springer-Verlag: London, 1990. (p) Rosen, T. The Fluoroquinolone Antibacterial Agents. *Prog. Med. Chem.* **1990**, *27*, 235−295.

(3) For recent reviews about topoisomerases, see: (a) Roca, J. The Mechanisms of DNA Topoisomerases. *Trends Biochem. Sci.* **1995**, *20*, 156−160. (b) Luttinger, A. The Twisted 'Life' of DNA in the Cell: Bacterial Topoisomerases. *Mol. Microbiol.* **1995**, *15*, 601−606. (c) Sharma, A.; Mondragon, A. DNA Topoisomerases. *Curr. Opin. Str. Biol.* **1995**, *5*, 39−47. (d) Orphanides, G.; Maxwell, A. In One Gate, Out the Other. *Curr. Biol.* **1994**, *4*, 1006−1009. (e) Shen, L. L. Molecular Mechanisms of DNA Gyrase Inhibition by Quinolone Antibacterials. *Adv. Pharmacol.* **1994**, *29a*, 285−304. (f) Fostel, J.; Shen, L. L. DNA Topoisomerases. In *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: Oxford, 1994; Vol. 2, pp 564−624. (g) *DNA Topoisomerases: Biochemistry and Molecular Biology*; Liu, L. F., Ed.; Academic Press: New York, 1994; Vol. 29A. (h) *DNA Topoisomerases: Topoisomerase-Targeting Drugs*; Liu, L. F., Ed.; Academic Press: New York, 1994; Vol. 29B. (i) *Molecular Biology of DNA Topoisomerase and Its Application to Chemotherapy*; Andoh, T., Ikeda, H., Oguro, M., Eds.; CRC Press: Ann Arbor, 1991.

(4) For recent reviews about bacterial resistance, see: (a) Amábile-Cuevas, C. F.; Cárdenas-García, M.; Ludgar, M. Antibiotic Resistance. *Am. Sci.* **1995**, *83*, 320−329. (b) Berkowitz, F. E. Antibiotic Resistance in Bacteria. *South. Med. J.* **1995**, *88*, 797−804. (c) Bartlett, J. G.; Froggatt, J. W. Antibiotic Resistance. *Arch. Otolaryngol. Head Neck Surg.* **1995**, *121*, 392−396. (d) Jones, R. N.; Sader, H. S.; Erwin, M. E.; Anderson, S. C. Emerging Mutiply Resistant Enterococci among Clinical Isolates. *Diagn. Microbiol. Infect. Dis.* **1995**, 85−93. (e) Lonks, J. R.; Medeiros, A. A. The Growing Threat of Antibiotic-Resistant *Streptococcus pneumoniae*. *Med. Clin. North Am.* **1995**, *79*, 523−535. (f) Longman, R. The Antibiotics Dilemma. *In Vivo* **1995**, 41−48. (g) Centers for Disease Control and Prevention. Nosocomial Enterococci: Resistance to Vancomycin-United States, 1989−1993. *MMWR Mob. Morb. Wkly. Rep.* **1993**, *42*, 597−599. (h) Rubinstein, E., Ed. *Science* **1994**, *264*, 360−393. (i) Pechere, J. C. Bacterial Resistance: New Threats, New Challenges. *Support Care Cancer* **1993**, *1*, 124−129. (j) Acar, J. F.; O'Brien, T. F. F.; Goldstein, W.; Jones, R. N. The Epidemiology of Bacterial Resistance to Quinolones. *Drugs* **1993**, *45* (Suppl. 3), 24−28. (k) Rubinstein, E., Ed. *Science* **1992**, *257*, 1036−1082. (l) Amyes, S. G. B.; Gemmell, C. G. Antibiotic Resistance in Bacteria. *J. Med. Microbiol.* **1992**, *36*, 4−29. (m) Lederberg, J., Shope, R. E., Oaks, S. C., Eds. *Emerging Infections: Microbial Threats to Health in the United States*; National Academy Press: Washington, DC, 1992.

(5) For recent news media coverage about bacterial resistance, see: (a) Lemonick, M. D. The Killers All Around. *Time* **1994**, *144*, 62−69. (b) Bylinsky, G. Killer Microbes. *Fortune* **1994**, 74−82. (c) Begley, S. The End of Antibiotics. *Newsweek* **1994**, 46−51.

(6) (a) Yee, Y. C.; Thornsberry, C. A Survey of Ciprofloxacin and 11 Other Antimicrobial Agent Susceptibility Data of United States Bacterial Isolates from 1990 to 1992. *Antimicrob. Infect. Dis. Newslett.* **1995**, *14*, 1−18. (b) Voss, A.; Doebbeling, B. N. The Worldwide Prevalence of Methicillin-Resistant *Staphylococcus aureus*. *Int. J. Antimicrob. Agents* **1995**, 101−106. (c) Brumfitt, W.; Hamilton-Miller, J. M. T. The Challenge of Methicillin-Resistant Staphylococcus aureus. *Drugs Exp. Clin. Res.* **1994**, *20*, 215−224. (d) Neu, H. C. The Crisis in Antibiotic Resistance. *Science* **1992**, *257*, 1064−1073.

(7) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. Total Synthesis of β-Lactam Antibiotics. VIII. Stereospecific Total Synthesis of (±)-1-Carbacephalothin. *J. Am. Chem. Soc.* **1974**, *96*, 7584−7585.

(8) During the course of our study, a similar patented work by Merck scientists appeared, claiming one compound with 7-defluoro-2-pyridone structure. However, the compound is almost inactive. Heck, J.; Thorsett, U. D. 4-Oxo-4H-Quinolizine-3-carboxylic Acids and Derivatives Thereof. U.S. Patent 4,921,857, 1990.

(9) This paper has been presented in part in preliminary forms at the following meetings: (a) Li, Q.; Claiborne, A.; Chu, D. T. W.; Lee, C. M.; Raye, K. A.; Berst, K.; Ma, Z.; Wang, W.; Shen, L. L.; Flamm, R.; Nilius, A.; Alder, J.; Marsh, K.; Shortridge, V. D.; Tanaka, S. K.; Seif, L.; Cooper, C. S.; Fung, A.; Tufano, M.; Melcher, L. M.; Henry, R.; Klein, L.; Plattner, J. J. Synthesis and In Vitro Antibacterial Activity of Novel DNA Gyrase Inhibitors. 35th ICAAC, 1995; Abstract F8. (b) Chu, D. T. W.; Li, Q.; Claiborne, A.; Raye, K. A.; Cooper, C. S.; Fung, A.; Lee, C. M.; Tanaka, S. K.; Shen, L. L.; Donner, P.; Armiger, Y. L.; Plattner, J. J. Synthesis and Antibacterial Activity of A-86719.1 and Related 2-Pyridones: A Novel Series of Potent DNA Gyrase Inhibitors. 34th ICAAC, 1994; Abstract F41. (c) Li, Q.; Chu, D. T. W.; Lee, C. M.; Raye, K. A.; Shen, L. L.; Tanaka, S. K.; Plattner, J. J. Synthesis and Activity of the Bioisosteres of Naphthyridine Antibacterial Agents. 32nd ICAAC, 1992; Abstract 764. (d) Chu, D. T. W.; Li, Q.; Lee, C. M.; Raye K. A.; Tanaka, S. K.; Alder, J.; Plattner, J. J. Novel Quinolone Antibacterial Agents: Synthesis and Biological Activity of 6*H*-6-Oxopyrido[1, 2-*a*]pyrimidine-7-carboxylic Acids. In *Recent Advances in the Chemistry of Anti-infective Agents*; Bentley, P. H., Ponsford, R., Eds.; Royal Society of Chemistry: Cambridge, England, 1993; pp 94−105.

(10) Elkik, P. E.; Imbeaux-Oudotte, M. No. 212-Formyl fluoro cétones et esters. I.-Préparation et dérivés acétylés. (No. 212-Formyl Fluoroketones and -esters. I. Preparation of Acetyl Derivatives.) *Bull. Soc. Chim. Fr.* **1975**, 1165−1169.

(11) Hydrolysis of **10** to **7** was so easy that the reaction took place at room temperature in 1.0 N solution of LiOH in THF and water.

(12) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schaurrenberger, P.; Weidmann, B.; Zuger, M. Titanate-Mediated Transesterifications with Functionalized Substrates. *Synthesis* **1982**, 138−141.

(13) Carney, R. W. J.; Wojtkunski, J. Diethyl Cyclopropropanemalonate. *Org. Prep. Proc.* **1973**, *5*, 25−29.

(14) Chambers, R. D.; Hutchinson, J.; Muscrave, W. K. R. Polyfluoroheterocyclic Compounds. Part I. The Preparation of Fluoro-, Chlorofluoro-, and Chlorofluorohydropyridines. *J. Chem. Soc.* **1964**, 3573−3576. **25** is commercially available from Aldrich as 70% pure, the remainder is 4-chlorotetrafluoropyridine.

(15) The *tert*-butoxy group serves as a protecting group. Using less hindered groups such as benzyloxy and thiophenoxy resulted in displacement of the protecting groups rather than 2-fluorine by the anion of cyclopropylacetonitrile.

(16) The structures of **27** and **36** were determined by comparison of ^{19}F NMR; see: Chambers, R. D.; Hutchinson, J.; Musgrave, W. K. R. Polyfluoro-heterocyclic Compounds. Part III. Hydroxy-derivatives of Pentafluoro- and Chlorofluoropyridines. *J. Chem. Soc.* **1964**, 5634−5640.

(17) Camparini, A.; Ponticelli, F. New Derivatives of 3-Methylisoxazolo[5.4-*b*]pyridine. *J. Heterocycl. Chem.* **1977**, *14*, 435−438.

(18) Dowtherm A is a mixture of biphenyl and diphenyl ether (23:77).

(19) Cesare, P. D.; Bouzard, D.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Kiechel, J. R.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. Fluoronaphthyridines and -quinolones as Antibacterial Agents. 5. Synthesis and Antibacterial Activity of Chiral 1-tert-Butyl-6-fluoro-7-substituted-naphthyridones. *J. Med. Chem.* **1992**, *35*, 4205−4213.

(20) Okada, T.; Sato, H.; Tsuji, T.; Tsushima, T.; Nakai, H.; Yoshida, T.; Matsuura, S. Synthesis and Structure-Activity Relationships of 7-(3′-Amino-4′-methoxypyrrolidin-1′-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. *Chem. Pharm. Bull.* **1993**, *41*, 132−138.

(21) (a) Li, Q.; Chu, D. T. W.; Raye, K.; Claiborne, A.; Seif, L.; Macri, B.; Plattner, J. J. A Practical Stereoselective Synthesis of (2*S*, 4*S*)-4-*tert*-Butoxycarbonylamino-2-Methylpyrrolidine. *Tetrahedron Lett.* **1995**, *36*, 8391−8394. (b) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. Design, Synthesis, and Properties of (4*S*)-7-(4-Amino-2-substituted-pyrrolidin-1-yl)quinolone-3-carboxylic Acids. *J. Med. Chem.* **1988**, *31*, 1598−1611.

(22) Hagen, S. E.; Domagala, J. M.; Heifetz, C. L.; Sanchez, J. P.; Solomon, M. New Quinolone Antibacterial Agents. Synthesis and Biological Activity of 7-(3,3- or 3,4-Disubstituted-1-pyrrolidinyl)-quinoline-3-carboxylic Acids. *J. Med. Chem.* **1990**, *33*, 849−854.

(23) Singh, R.; Singh, I. P.; Fathi-Afshar, R.; Thomas, G.; Doerkson, T.; Gandhi, A.; Singh, M. P.; Higashitani, F.; Hyodo, A.; Micetich, R. G. Synthesis and Structure-Activity Relationship of Novel Quinolones with Triazolyl-Pyrrolidinyl Moiety at C-7. 32nd ICAAC, 1992; Abstract 761.

(24) Petersen, U.; Bremm, K. D.; Krebs, A.; Metzger, K. G.; Philipps, T.; Schenke, T. Bay Y3118, a Novel 4-Quinolones: Synthesis and In Vitro Activity. 32nd ICAAC, 1992; Abstract 642.

(25) Schenke, T.; Petersen, U. Preparation of 2,7-Diazabicyclo[3.3.0]-octanes. U.S. Patent 5,071,999, 1991.

(26) Scarborough, H. C.; Minielli, J. L.; Lawes, B. C.; Lobeck, W. G., Jr.; Corrigan, J. R.; Wu, Y. H. Pyrrolidines. V. 3-Pyrrolidinylmethylamines and Quinoline Derivatives. *J. Org. Chem.* **1961**, *26*, 4955−4959.

(27) Ogata, M.; Matsumoto, H.; Shimizu, S.; Kida, S.; Nakai, H.; Motokawa, K.; Miwa, H.; Matsuura, S.; Yoshida, T. Synthesis and Antibacterial Activity of New 7 (Aminoazabicycloalkanyl)-quinolonecarboxylic Acids. *Eur. J. Med. Chem.* **1991**, *26*, 889−906.

(28) Edgardo, L. 3-Arylpyrrolidines via Azomethine Ylide 1,3-Dipolar Cycloaddition to Styrenes. *Tetrahedron Lett.* **1992**, *33*, 6607−6610.

(29) Gootz, T. D.; Brighty, K. E.; Anderson, M. R.; Haskell, S. L.; Sutclitte, J. A.; Castaldi, M. J.; Miller, S. A. In Vitro Activity and Synthesis of CP-99,219, A Novel 7-(3-Aza-Bicyclo[3.1.0]-Hexyl)-Naphthyridone. 32nd ICAAC, 1992; Abstract 751.

(30) Kim, W. J.; Park, M. H.; Ha, J. D.; Baik, K. U. EP Application 550016-A1, 1993.

(31) Schroeder, M. C.; Kiely, J. S.; Laborde, E.; Johnson, D. R.; Szotek, D. L.; Domagala, J. M.; Stickney, T. M. Synthesis of the Four Stereoisomers of Several 3-(1-Aminoethyl)pyrrolidines. Important Intermediates in the Preparation of Quinolone Antibacterials. *J. Heterocycl. Chem.* **1992**, *29*, 1481−1498.

(32) Nisato, D.; Frigerio, M. Synthesis of 3-Aminoazetidine. *J. Heterocycl. Chem.* **1995**, *22*, 961−963.

(33) For *in vitro* and *in vivo* activity and a review on ABT-719, see: (a) Flamm, R. K.; Vojtko, C.; Chu, D. T.; Li, Q.; Beyer, J.; Hensey, D.; Ramer, N.; Clement, J. J.; Tanaka, S. K. *In Vitro* Evaluation of ABT-719, A Novel DNA Gyrase Inhibitor. *Antimicrob. Agents Chemother.* **1995**, *39*, 964−970. (b) Eliopoulos, G. M.; Wennersten, C. B.; Cole, G.; Chu, D.; Pizzuti, D.; Moellering, R. C., Jr. In Vitro Activity of A-86719.1, a Novel 2-Pyridone Antimicrobial Agent. *Antimicrob. Agents Chemother.* **1995**, *39*, 850−853. (c) Alder, J.; Clement, J.; Meulbroek, J.; Shipkowitz, N.; Mitten, M.; Jarvis, K.; Oleksijew, A.; Hutch, T., Sr.; Paige, L.; Flamm, R.; Chu, D.; Tanaka, K. Efficacies of ABT-719 and Related 2-Pyridones, Members of a New Class of Antibacterial Agents, against Experimental Bacterial Infections. *Antimicrob. Agents Chemother.* **1995**, *39*, 971−975. (d) ABT-719. Futured by Fromtling, R. A. *Drugs Future* **1995**, *20*, 1103−1108.

(34) (a) Hagen, S. E.; Domagala, J. M.; Heigetz, C. L.; Johnson, J. Synthesis and Biological Activity of 5-Alkyl-1,7,8-trisubstituted-6-fluoroquinoline-3-carboxylic Acids. *J. Med. Chem.* **1991**, *34*, 1155−1161. (b) Ohguro, K.; Ohnishi, H.; Kubo, A.; Ohmori, K.; Tamaoka, H.; Kikuchi, M. OPC-17116, A Novel Broad Spectrum 5-Methyl Quinolones Derivative; Antibacterial Activity in vitro. 31st ICAAC, 1991; Poster 1461.

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

(36) Am-1155. *Drugs Future* **1993**, *18*, 203−205.

(37) Miyamoto, H.; Ueda, H.; Otsuka, T.; Aki, S.; Tamaoka, H.; Tominaga, M.; Nakagawa, K. Studies on Bacterial Agents. III. Synthesis and Antibacterial Activities of Substituted 1,4-Dihydro-8-methyl-4-oxoquinolone-3-carboxylic Acids. *Chem. Pharm. Bull.* **1990**, *38*, 2472−2475.

(38) (a) Chu, D. T. W.; Marsh, K.; Hallas, R.; Shipkowitz, N.; Plattner, J. J. Synthesis and Bilogical Properties of A-70826: A Prodrug of Tosufloxacin. 31st ICAAC, 1991; Poster 1440. (b) Marsh, K.; Eiden, E.; Hernandez, L.; Chu, D. T. W.; Hallas, R.; Borodkin, S. *In vitro* and *In vivo* Evaluation of a Series of Amino Acid Prodrugs of Tosufloxacin. 31st ICAAC, 1991; Poster 1441.

(39) (a) *National Committee for Clinical Laboratory Standards 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3*; National Committee for Clinical Laboratory Standards: Villanova, PA.

(40) Clement, J. C.; Tanaka, S. K.; Alder, J. D.; Vojtko, C.; Beyer, J.; Hensey, D.; Ramer, N.; McDaniel, D.; Chu, D. T. W. In Vitro and In Vivo Evaluations of A-80556, A New Fluoroquinolone. *Antimicrob. Agents Chemother.* **1994**, *38*, 1071−1078.

(41) (a) Shen, L. L.; Baranowski, J.; Fostel, J.; Montgomery, D. A.; Lartey, P. A. DNA Topoisomerases from Pathogenic Fungi: Targets for the Discovery of Antifungal Drugs. *Antimicrob. Agents Chemother.* **1992**, *36*, 2778−2784. (b) Shen, L. L.; Kohlbrenner, W. E.; Weigl, D.; Baranowski, J. Mechanism of Quinolone Inhibition of DNA Gyrase. Appearance of Unique Norfloxacin Binding Sites in Enzyme-DNA Complexes. *J. Biol. Chem.* **1989**, *264*, 2973−2978.

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