Synthesis and Antimicrobial Activity of 4*H*-4-Oxoquinolizine Derivatives: Consequences of Structural Modification at the C-8 Position

Zhenkun Ma,* Daniel T. W. Chu, Curt S. Cooper, Qun Li, Anthony K. L. Fung, Sanyi Wang, Linus L. Shen, Robert K. Flamm, Angela M. Nilius, Jeffery D. Alder, Jonathan A. Meulbroek, and Yat Sun Or

Infectious Disease Research, Abbott Laboratories, 200 Abbott Park Road, Abbott Park, Illinois 60064-3537

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The antibacterial 4*H*-4-oxoquinolizines were introduced recently to overcome bacterial resistance to fluoroquinolones. They exhibit potent antibacterial activity against Gram-positive, Gram-negative, and anaerobic organisms and are highly active against some quinolone-resistant bacteria including quinolone-resistant MRSA. Preliminary studies indicated that oxoquinolizines possess distinct activity and toxicity profiles as compared with their parent quinolones. In order to develop a potent antibacterial agent with the desired spectrum of activity, good tolerability, and balanced pharmacokinetic profile, we synthesized and evaluated a series of oxoquinolizines with various substituents at the C-8 position. Most compounds tested in this study demonstrated better activity against Gram-positive bacteria than ciprofloxacin and exhibited good susceptibility against ciprofloxacin- and methicillin-resistant *S. aureus*. While maintaining potent in vitro activity, several compounds showed improved in vivo efficacy over ABT-719 as indicated by the mouse protection test. As an example, the oral ED_{50} values for the *cis*-3-amino-4-methylpiperidine analogue **3ss** against *S. aureus* NCTC 10649M, *S. pneumoniae* ATCC 6303, and *E. coli* JUHL were 0.8, 2.0, and 1.4 mg/kg, compared to 3.0, 10.0, and 8.3 mg/kg for ABT-719. The current study revealed that the steric and electronic environment, conformation, and absolute stereochemistry of the C-8 group are very important to the antibacterial profiles. Structural modifications of the C-8 group provide a useful means to improve the antibacterial activities, physicochemical properties, and pharmacokinetic profiles. Manipulation of the C-8 group also allows us to generate analogues with the desired spectrum of activity, such as analogues that are selective against respiratory pathogens.

Introduction

The discovery of nalidixic acid in 1962 shed the first light on a new avenue for the treatment of bacterial infections by inhibiting bacterial DNA synthesis. To date many quinolone antibacterial agents have been introduced into clinical use, and significant improvements in antibacterial spectrum and activity have been achieved. The prototype quinolone, nalidixic acid, is active only against Gram-negative organisms and is indicated primarily for urinary tract infections.[1] This situation did not change until the early 1980s, when the first fluoroquinolone, norfloxacin, was launched. Introduction of norfloxacin and other fluoroquinolones, such as: ofloxacin, enoxacin, ciprofloxacin, tosufloxacin, sparfloxacin, grepafloxacin, and levofloxacin, has changed the landscape of antimicrobial chemotherapy. Fluoroquinolones are active against a wide range of Gram-negative and Gram-positive pathogens and possess improved oral absorption and systemic distribution. Therefore, their clinical applications have been extended to the treatment of lower respiratory tract infections, skin and soft tissue infections, sexually transmitted diseases, and urinary tract infections.[2] One of the most recent fluoroquinolones, trovafloxacin, is reported to have improved antibacterial activity against Gram-positive bacteria and anaerobes with improved pharmacokinetic profiles.[3]

Despite many advances, the current fluoroquinolones have shown several deficiencies. First, they generally have low intrinsic activity against a number of clinically important Gram-positive pathogens, such as: *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Enterococcus*. Second, extensive clinical use of fluoroquinolones, especially ciprofloxacin, has resulted in increasing quinolone resistance among many pathogens. High-level resistance to ciprofloxacin and many other antibiotics has developed among methicillin-resistant *S. aureus* (MRSA).[4,5] To address the deficiencies of the current fluoroquinolones, we directed our research attention to the core modification of fluoroquinolones and identified a series of potent antibacterial agents with a 4*H*-4-oxoquinolizine core structure.[6] Oxoquinolizines exhibit potent activity against Gram-positive, Gram-negative, and anaerobic organisms. In addition, they show excellent activity against resistant bacteria such as quinolone-resistant MRSA.[6] Oxoquinolizines are bioisosteres of quinolones and possess the same mechanism of action.[7] They exert their bactericidal effect by inhibiting type II bacterial DNA topoisomerases, including two highly homologous enzymes, topoisomerase II (gyrase) and topoisomerase IV. The change in the core structure has resulted in significant enhancement of gyrase and topoisomerase IV inhibition activities.[7] Recent studies suggest that mutations of the target enzymes in the quinolone resistance-determining region (QRDR) appear to be the main factor leading to quinolone resistance.[5] Our preliminary study indicated that oxoquinolizines exhibited

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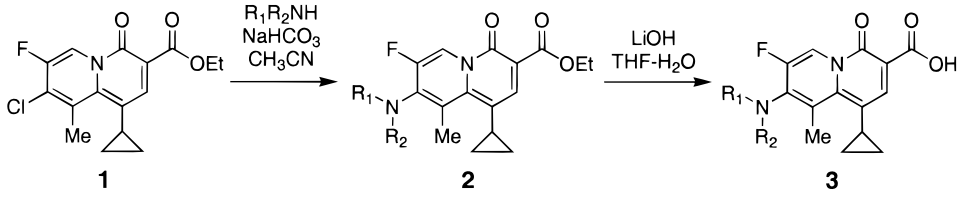
Scheme 1



good inhibition activities to both gyrase and topoisomerase IV isolated from resistant bacteria. In contrast, quinolones such as ciprofloxacin showed very low-level inhibition activities against resistant enzymes. These results suggested that our oxoquinolizines have the ability to bind to mutated enzymes and thus behave differently from the fluoroquinolones.[8] Although progress has been made recently on the structure determination and on the mechanism of DNA topoisomerase,[9] we have very limited knowledge of how the drug, DNA, and topoisomerase integrate.[10] Without a clear picture of drug−receptor interaction, we pursued a systemic structural modification of oxoquinolizine in order to optimize the antibacterial profiles based on this new platform.

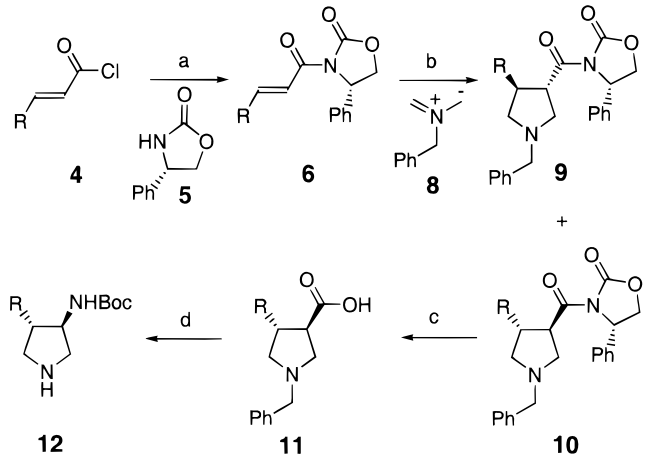
Since the discovery of nalidixic acid, thousands of quinolones have been synthesized and evaluated. One useful conclusion from the earlier work is that the structure of the C-7 moiety of quinolones plays an essential role in their antibacterial activity. This conclusion is consistent with a drug−DNA−gyrase ternary cooperative binding model suggesting that the quinolone inserts itself into the complex formed between DNA and gyrase in such a way that the C-3 carboxylic acid and the C-4 ketone interact with the cleaved or perturbed DNA while the C-7 group interacts with DNA gyrase.[10,11] Due to a different numbering system, the C-8 moiety of oxoquinolizines occupys the same position as the C-7 group of quinolones. In order to identify an antibacterial agent with the desired spectrum of activity, good tolerability and balanced pharmacokinetic profiles, we carried out an extensive modification of the C-8 moiety of the oxoquinolizine. Herein, we would like to discuss in detail the consequences of the structural variation of the C-8 moiety on the in vitro and in vivo antibacterial activity.

Chemistry

The synthesis of the 4*H*-4-oxoquinolizine core **1** has been reported earlier[6] and served as our key intermediate. Aromatic nucleophilic substitution of the 8-chloro group with an appropriate cyclic amine produced the coupling product **2**. Hydrolysis of the 3-ethyl ester provided the oxoquinolizines **3** with the desired C-8 moiety (Scheme 1). In the cases where diamines were used, the amino groups were differentiated using a protecting group prior to coupling. After coupling to the core and hydrolysis of the ester, the protecting group was removed to give the desired compounds.

The amines used in this study were obtained from commercial sources or prepared according to literature procedures.[12] Optically active chiral amines were obtained by chiral HPLC separation or by asymmetric synthesis. We developed a practical and efficient synthesis as a general route to optically active *trans*-3-amino-4-alkyl(aryl)pyrrolidines utilizing an asymmetric

Scheme 2[a]



[a] (a) **5**, *n*-BuLi, THF, −78 °C; (b) *N*-benzyl-*N*-(methoxymethyl)-(trimethylsilyl)methylamine (**7**), 0.1 equiv TFA, toluene; (c) LiOH, H_2O_2, THF−H_2O, rt; (d) (1) DPPA, Et_3N, *t*-BuOH, 95 °C, (2) HCO_2NH_4, 10% Pd−C, MeOH, reflux.

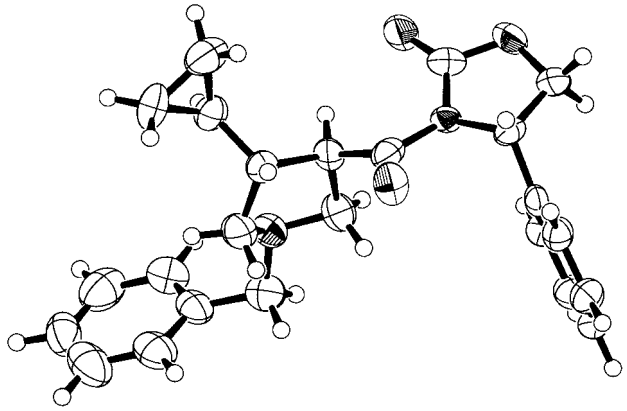


Figure 1. X-ray single-crystal structure of compound **10** (R = cyclopropyl group).

dipolar cycloaddition reaction (Scheme 2).[13] The major diastereomer **10** produced was determined to have the 3*R*,4*R* configuration by single-crystal X-ray crystallography (Figure 1). Utilizing this methodology, the opposite enatiomers of **12** were conveniently obtained from the chiral auxiliary (**5**) of opposite stereochemistry.

The structures of the C-8 groups used in this study are listed in Charts 1 and 2. These amines were selected with the intention of studying the effects of ring size, substitution, conformation, and stereochemistry on the antibacterial activity and efficacy.

Microbiology

In Vitro Antibacterial Activity. The C-8-modified oxoquinolizines used in this study and the reference agent, ciprofloxacin, were tested against representative Gram-positive and Gram-negative bacteria from the

Chart 1. Structures of the C-8 Group of Oxoquinolizines **3**

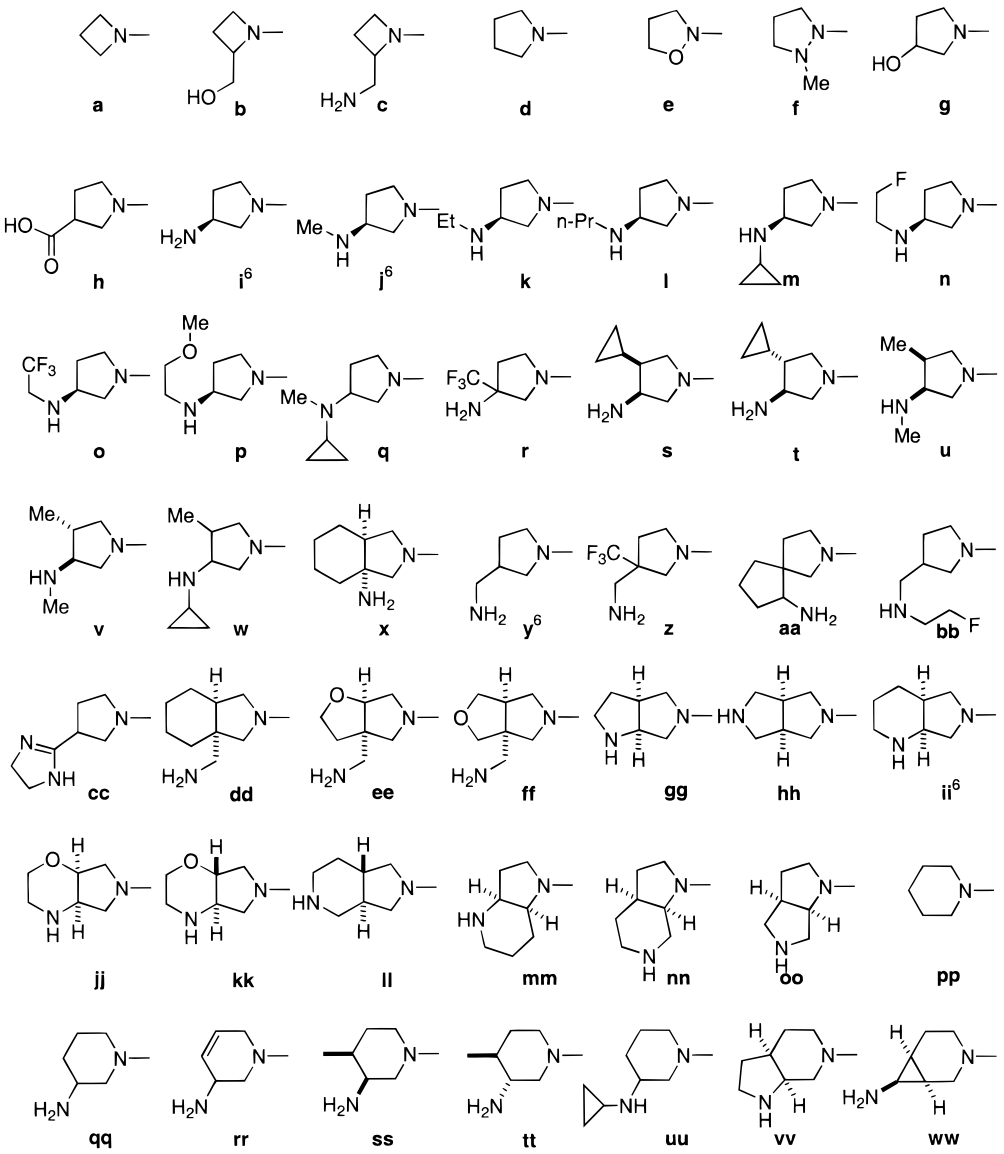
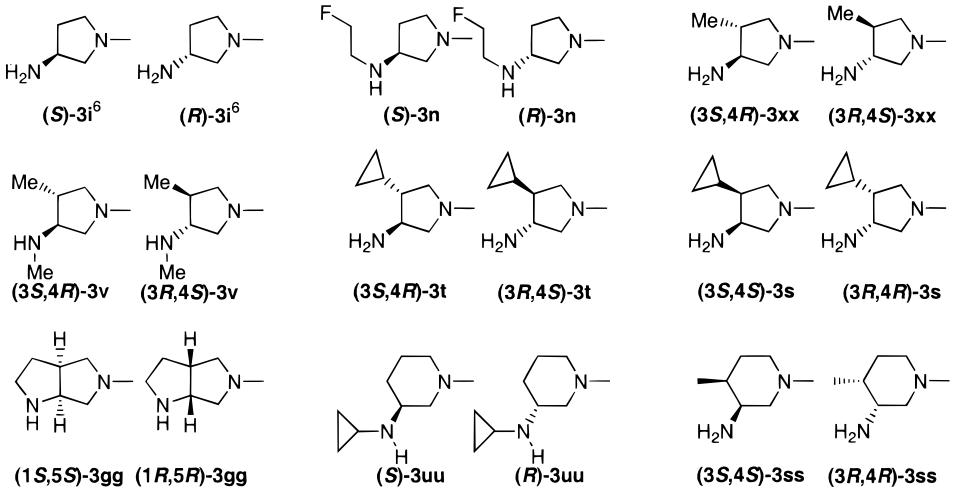


Chart 2. Stereochemical Structures of the Selected C-8 Group of Oxoquinolizines **3**



Abbott clinical culture collection. The ciprofloxacin-resistant and less susceptible isolates such as *Staphylococcus aureus* 1775, *Escherichia coli* KNK 437, *Pseudomonas cepacia*, and *Pseudomonas aeruginosa* DPHD-5263 were included in this test in order to identify potent analogues that could overcome ciprofloxacin resistance. The in vitro antibacterial activity is reported as the minimum inhibitory concentrations

Table 1. In Vitro Antibacterial Activity of Compounds **3a**−**3ww**

	MIC (μg/mL)							
	Gram-positive organism[a]				Gram-negative organism[b]			
compd	*S. aureus* NCTC 10649M	*S. aureus* 1775	*E. faecium* ATCC 8043	*S. pyogenes* 930	*E. coli* KNK 437	*P. cepacia* 2961	*P. aeruginosa* 5007	*P. aeruginosa* DPHP 5263
ciprofloxacin	0.39	>100	0.39	0.78	0.2	6.2	0.1	12.5
3a	0.2	3.1	0.78	0.78	3.1	3.1	3.1	>100
3d	0.02	0.78	0.2	0.2	0.39	0.78	0.78	>100
3e	0.78	>100	3.1	6.2	6.2	6.2	6.2	>100
3f	0.02	3.1	0.39	0.39	3.1	1.56	3.1	>100
3g	0.005	0.2	0.05	0.05	0.2	0.1	0.2	6.2
3i	0.02	0.78	0.02	0.02	0.02	0.39	0.05	0.78
3j	0.02	1.56	0.1	0.05	0.05	1.56	0.2	1.56
3k	0.05	1.56	0.1	0.1	0.2	3.1	0.39	6.2
3l	0.1	1.56	0.39	0.2	0.2	3.1	1.56	12.5
3m	0.02	0.39	0.2	0.05	0.2	0.39	0.39	12.5
3o	0.02	0.78	0.39	0.39	1.56	3.1	3.1	>100
3p	0.05	1.56	0.39	0.39	0.39	0.78	1.56	12.5
3q	0.05	1.56	0.2	0.2	0.39	3.1	0.78	100
3s	0.02	0.39	0.1	0.1	0.2	0.78	0.39	12.5
3t	0.01	0.78	0.1	0.05	0.1	0.78	0.78	6.2
3u	0.02	0.39	0.1	0.1	0.1	1.56	0.39	6.1
3v	0.02	1.56	0.2	0.2	0.2	1.56	0.39	12.5
3x	0.05	1.56	0.2	0.2	0.78	1.56	1.56	25
3y	0.002	0.39	0.01	0.002	0.05	0.39	0.1	1.56
3z	0.02	0.39	0.2	0.1	0.39	6.2	1.56	25
3aa	0.05	0.78	0.1		0.2	3.1	0.78	6.2
3bb	0.002	0.1	0.02	0.002	0.2	3.1	0.78	12.5
3dd	0.002	0.2	0.02	0.02	1.56	3.1	3.1	50
3ee	0.005	0.78	0.05		0.2	3.1	0.39	6.2
3ff	0.01	3.1	0.05	0.02	0.1	6.2	6.2	6.2
3gg	0.02	0.39	0.05	0.05	0.2	1.56	0.39	6.2
3hh	0.05	6.2	0.1	0.1	0.2	3.1	0.2	6.2
3ii	0.02	0.78	0.1	0.05	0.1	1.56	0.39	3.1
3jj	0.002	0.78	0.1	0.1	0.78	6.2	1.56	100
3kk	0.05	0.78	0.2	0.2	0.78	3.1	1.56	25
3ll	0.05	6.2	0.2	0.05	0.2	0.39	0.39	6.2
3mm	0.2	12.5	3.1	1.56	0.78	25	3.1	100
3nn	0.05	6.2	0.2		0.39	3.1	0.78	6.2
3oo	0.05	6.2	0.1	0.1	0.2	3.1	0.39	3.1
3pp	0.05	0.78	0.39	0.2	3.1	3.1	3.1	>100
3qq	0.01	0.39	0.05	0.02	0.1	0.78	0.2	3.1
3ss	0.05	1.56	0.2	0.1	0.39	1.56	0.78	12.5
3tt	0.01	0.39	0.05	0.02	0.39	3.1	0.39	
3uu	0.01	1.56	0.05	0.05	0.2	3.1	0.39	25
3ww	0.02	1.56	0.05	0.05	0.2	3.1	0.39	6.2

[a] *S aureus* 1775 is a ciprofloxacin-, erythromycin-, and methicillin-resistant strain, and *S. pyogenes* 930 is an erythromycin-resistant strain. [b] *E. coli* KNK 437 is a ciprofloxacin less sensitive strain, and *P. cepacia* 2961 and *P. aeruginosa* DPHP 5263 are ciprofloxacin-resistant strains.

(MICs), which were determined by the agar dilution method as recommended by the National Committee for Clinical Laboratory Standards.

In Vivo Efficacy. The in vivo efficacies of a selected group of compounds were assessed by mouse protection test. The mice were inoculated intravenously with a 100-fold LD_{50} of representative organisms. Tested compounds were administered by either subcutaneous injection or oral gavage at 1 and 5 h post-inoculation. Mortality rates of the mice were monitored for a period of 7 days post-inoculation with a 100% mortality rate for untreated controls. The efficacy of each compound, based on the survival rates over a dose range, was reported as the drug dose resulting in a survival of 50% of treated mice over the duration of the trial (ED_{50}).

Results and Discussion

The effects of C-1[14] and C-9[6] modifications of oxoquinolizine on antibacterial activity have been discussed elsewhere. A cyclopropyl group at the C-1 position and a methyl group at the C-9 position appear to be optimum. Therefore, we selected 1-cyclopropyl-7-fluoro-9-methyl-4-oxoquinolizine-3-carboxylic acid as our template.[15] The structures of the C-8 groups are shown in Charts 1 and 2. The in vitro activities of the corresponding oxoquinolizines are shown in Tables 1 and 2, and the in vivo efficacies for selected compounds are shown in Table 3. A panel of Gram-positive and Gram-negative bacteria was selected for the in vitro testing to assess the potency and spectrum of activity. Among the organisms, *S. aureus* 1775 represents a quinolone-resistant MRSA. The structures of the C-8 groups were carefully selected so that the effects of the ring size, functionality, substitution, conformation, and stereochemistry of the C-8 moiety could be assessed. In general, most compounds tested demonstrated better activity than ciprofloxacin against Gram-positive organisms and exhibited good susceptibility against methicillin- and ciprofloxacin-resistant *S. aureus*. The activities against Gram-negative organisms were retained in some cases and reduced in others depending on the structure of the C-8 substituents.

Table 2. In Vitro Antibacterial Activity of Selected Optically Active Compounds

	MIC (μg/mL)							
	Gram-positive organism[a]				gram-negative organism[b]			
compd	*S. aureus* NCTC 10649M	*S. aureus* 1775	*E. faecium* ATCC 8043	*S. pyogenes* 930	*E. coli* KNK 437	*P. cepacia* 2961	*P. aeruginosa* 5007	*P. aeruginosa* DPHP 5263
ciprofloxacin	0.39	>100	0.39	0.78	0.2	6.2	0.1	12.5
(*S*)-3i	0.01	0.78	0.02	0.02	0.02	0.39	0.05	0.39
(*R*)-3i	0.02	1.56	0.05	0.05	0.05	0.78	0.05	1.56
(*S*)-3n	0.01	0.39	0.1	0.1	0.2	3.1	0.78	12.5
(*R*)-3n	0.02	0.39	0.1	0.05	1.56	1.56	1.56	25
(3*S*,4*R*)-3xx	0.02	0.78	0.05	0.05	0.05	0.78	0.2	1.56
(3*R*,4*S*)-3xx	0.05	0.78	0.2	0.1	0.1	0.78	0.39	3.1
(3*S*,4*R*)-3v	0.01	0.39	0.1	0.02	0.05	0.78	0.2	3.1
(3*R*,4*S*)-3v	0.05	0.78	0.2	0.1	0.2	0.78	3.1	12.5
(3*S*,4*R*)-3t	0.05	0.78	0.1	0.05	0.2	1.56	0.39	3.1
(3*R*,4*S*)-3t	0.02	0.78	0.1	0.1	0.2	1.56	0.39	12.5
(3*S*,4*S*)-3s	0.005	0.39	0.05	0.02	0.1		0.39	12.5
(3*R*,4*R*)-3s	0.02	0.78	0.1	0.1	0.2	1.56	0.39	12.5
(1*S*,5*S*)-3gg	0.05	3.1	0.1		0.1	0.78	0.2	3.1
(1*R*,5*R*)-3gg	0.1	6.2	0.2		0.39	0.78	0.39	6.2
(*S*)-3uu	0.01	0.39	0.1	0.02	0.05	0.78	0.2	3.1
(*R*)-3uu	0.01	3.1	0.05	0.02	0.1	6.2	0.78	25
(3*S*,4*S*)-3ss	0.05	1.56	0.2	0.1	0.2	1.56	0.78	
(3*R*,4*R*)-3ss	0.1	3.1	0.39	0.39	0.78	6.2	1.56	12.5

[a] *S. aureus* 1775 is a ciprofloxacin-, erythromycin-, and methicillin-resistant strain, and *S. pyogenes* 930 is an erythromycin-resistant strain. [b] *E. coli* KNK 437 is a ciprofloxacin less sensitive strain, and *P. cepacia* 2961 and *P. aeruginosa* DPHP 5263 are ciprofloxacin-resistant strains.

Table 3. In Vivo Efficacy of Selected Compounds

	mouse protection test, ED_{50} (mg/kg)							
	S. aureus NCTC 10649M		*S. pneumoniae* ATCC 6303		*E. coli* JUHL		*P. aeruginosa* 5007	
compd	sc[a]	po[b]	sc	po	sc	po	sc	po
ciprofloxacin	3.6	25.0	37.4	>100	0.2	1.3	2.4	20.0
3d	>12				>50			
3e	>12				>5			
3i	0.8	3.0	2.6	10.0	0.3	8.3	0.5	2.9
3k	1.0	7.7	2.9	7.9	0.6	3.0	>8	>50
3l	4.3	25.4			1.1	>10	>8	>50
3m	3.6	25.0	>8	23.1	5.0	16.5	>32	>50
(*S*)-3n	1.1	7.5		9.9	4.9	17.2	>32	>50
(*R*)-3n	2.1	9.6	8.0	30.7	4.4	34.1	>32	>50
3p	6.1	18.1			2.5	>10		
3s	1.5	3.4			3.7	6.6		
(3*S*,4*R*)-3t	1.5	10.9	8.0	25.0	3.4	10.0	>32	>50
(3*R*,4*S*)-3t	3.0	11.2	>8.0	>50.0	1.2	>10	>32	>50
3u	1.3				0.5	2.7		
3v	1.6	6.3	5.0	13.0	2.8	9.1	16.1	>50
3dd	1.8	17.7			>5	>20	>32	>50
3gg	0.7	5.0	4.5	7.6	0.4	2.5	6.4	39.1
(1*S*,5*S*)-3gg	0.6	1.5			0.5	1.1	5.0	17.9
(1*R*,5*R*)-3gg	1.5	5.0	2.3	11.2	0.8	10	18.0	>50
3hh	1.2	12.5	1.3	25.2	0.7	5.0	6.4	58.7
3jj	2.7	4.8			>5	>20		
3kk	6.0	11.5			>5	>20	>32	>50
3mm	7.0	23.9			4.4	>10	>32	>50
3ss	3.3	0.8	1.0	2.0	0.6	1.4		
(3*S*,4*R*)-3ss	1.0	4.3	2.1	1.0	0.6	3.0	24.5	>50
(3*R*,4*S*)-3ss	1.2	6.3	8.0	5.2	2.0	12.5	>32	>50
3tt	0.5	1.9			1.7	2.3		
3uu	0.4	2.1	1.0	2.5	2.8	8.0	>32	>50
(*S*)-3uu	0.8		4.3		>5		>32	
(*R*)-3uu	1.8		>16				>32	
3ww	1.2	4.1			0.9	5.0		

[a] sc represents subcutaneous injection. [b] po represents oral gavage.

The ring size of the C-8 group appeared to be an important factor for the antibacterial activity. The optimum ring sizes are five and six with the five-membered ring being somewhat more active. This trend is clearly illustrated by comparing the MICs of compounds **3a**, **3d**, and **3pp**. The antibacterial activity, especially against Gram-negative organisms, was greatly enhanced by introducing a hydroxy or an amino group onto the five- or six-membered ring cyclic amine as exemplified by compounds **3d**, **3g**, and **3i** or compounds **3pp** and **3qq**. Moreover, the amino group appeared to be the key element in giving good in vivo efficacy (Table 3). When an additional heteroatom was integrated into the ring, as in compounds **3e** and **3f**, no improvement in activity was observed.

Manipulation of the C-7/C-8 (C-7 for quinolones and

C-8 for oxoquinolizines) structure has been a useful tool to achieve the right balance of antibacterial activity, physiochemical properties, and pharmacokinetics.[16] Furthermore, modification of the C-7/C-8 group has been used to improve the toxicity profiles. It has been illustrated that introducing substituents on the piperazine ring at the C-7 position of a quinolone increased the selectivity between bacterial gyrase and mammalian topoisomerase II.[17] In our case, introduction of an alkyl group to the amino nitrogen of the (3*S*)-3-aminopyrrolidine moiety diminished the in vitro antibacterial activity. The activities decreased with the increase of the size of alkyl groups (see MICs for compounds **3i**−**3l**). However, the in vivo efficacy did not directly correlate to the size of the alkyl groups (Table 3). The ethyl-substituted analogue **3k** showed comparable or better efficacy than its unsubstituted parent compound **3i** in three of the four organisms tested. Substitutions on the neighboring carbon of the amino group gave a series of analogues with excellent antibacterial activities, especially against Gram-positive bacteria. Although the configuration of this neighboring alkyl group had insignificant effects on the in vitro activity as exemplified by *cis*- and *trans*-3-amino-4-alkylpyrrolidines (Table 1, **3s** and **3t**, **3u** and **3v**), the *cis* compounds (Table 3, **3s**, **3u**) demonstrated better in vivo efficacy than their *trans* counterparts (**3t**, **3v**).

Among the oxoquinolizine analogues, the 3-(aminomethyl)pyrrolidine series (**3y**−**3ff**) displayed the best activity against Gram-positive bacteria. For example, compound **3dd** is 10 times more potent than **3x** against Gram-positive bacteria. It is worth noting that the proper substitution on the amino nitrogen or the ring can provide analogues with a defined spectrum of activity. One such compound, **3dd**, exhibited excellent activity against all Gram-positive bacteria but showed very weak activity against Gram-negative pathogens. This compound did not show any in vivo efficacy in the mouse protection model against Gram-negative bacteria. Such compounds with a defined spectrum of activity may be advantageous for the treatment of Gram-positive infections, such as respiratory infections.

In the bicyclic series (**3gg**−**3oo**), two 3,4-fused pyrrolidine analogues, 2,7-diazobicyclo[3.3.0]octane derivative **3gg** and 2,8-diazobicyclo[4.3.0]nonane derivative **3ii**, are among the most potent compounds. In fact, compound **3gg** showed better in vivo efficacies than ABT-719 (**3i**) against *S. aureus*, *S. pneumoniae*, and *E. coli* and was one of the most efficacious compounds in vivo. Compound **3jj**, the oxygen isostere of **3ii**, exhibited excellent Gram-positive activity but had reduced Gram-negative activity. This compound showed excellent in vivo efficacy against *S. aureus* but failed against *E. coli* in the mouse protection test. Compound **3kk**, the *trans* isomer of **3jj**, was less active both in vitro and in vivo. Bicyclic compounds with a 2,3-fused pyrrolidine moiety such as **3mm**−**3oo** were less active and gave weak activities against quinolone-resistant MRSA.

Several substituted 3-aminopiperidine derivatives also exhibited excellent activity. *trans*-3-Amino-4-methylpiperidine derivative **3tt** is 5 times more active against Gram-positive bacteria than its *cis* counterpart **3ss**. Both compounds showed better in vivo efficacy than ABT- 719 against Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) infections. Compound **3uu**, the 3-cyclopropylaminopiperidine derivative, demonstrated excellent activity. The in vitro activities against Gram-positive bacteria were similar to those of ABT-719, but the oral efficacies against Gram-positive bacteria (*S. aureus* and *S. pneumoniae*) were much better as illustrated by the mouse protection test.

Chirality also appeared to be an important factor for antibacterial activity. According to the proposed drug−DNA−gyrase ternary cooperative binding model, the C-8 group of oxoquinolizine interacts directly with DNA gyrase and topoisomerase IV.[11] Due to the chiral nature of gyrase and topoisomerase IV, the chirality of the C-8 moiety would have a direct effect on the binding affinity. To test this hypothesis, we synthesized a series of optically pure analogues of selected racemic compounds by asymmetric synthesis or by chiral separation. The structures of these chiral derivatives are listed in Chart 2. The absolute stereochemistry of enantiomers of **3i**, **3n**, **3v**, **3t**, and **3xx** were unambiguously assigned based on single-crystal X-ray analysis or their chemical sources. The assignments for the enantiomers of **3s**, **3gg**, **3uu**, and **3ss** were arbitrary. Nevertheless, the difference in antibacterial activities and efficacies between enantiomers was apparent, ranging from 2 times for some organisms to 10 times for others (Tables 2 and 3). Compound **(3*S*,4*R*)-3v**, for example, is on average 5-fold more active than **(3*R*,4*S*)-3v** against the tested strains. The activity is inferentially correlated to the stereochemistry of the 3-amino group, suggesting that the 3-amino group may be directly involved in the interaction with a chiral binding site of receptors. For those compounds with defined stereochemical structure, the 3*S* isomers always displayed better in vitro activities and in vivo efficacies than the 3*R* forms (Table 3).

Conclusion

We have demonstrated that the structure of the C-8 moiety of oxoquinolizines is important to the antibacterial profiles. Many factors such as ring size, substitution, conformation, and stereochemistry influence the in vitro activity and in vivo efficacy. Oxoquinolizines derived from five- and six-membered ring cyclic amines with proper substituents demonstrated the best activity and efficacy. Many of these compounds showed improved in vivo efficacy over ABT-719 against Gram-positive bacteria. We also observed that the spectrum of antibacterial activity can be altered by controlling the substitution and configuration of the C-8 group.

Experimental Section

The key intermediate, ethyl 8-chloro-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizinecarboxylate (**1**), was provided by the Abbott Process Research Department. The synthesis of this compound has been reported in our previous paper.[6] Tetrahydrofuran was distilled from sodium/benzophenone. All other solvents and reagents were obtained from commercial sources and used without further purification. All nonaqueous reactions were carried out under a nitrogen atmosphere using oven- or flame-dried glassware unless otherwise indicated. Flash column chromatography was performed on Merck silica gel 60 (230−400 mesh). Chiral separations were performed on preparative high-performance liquid chromatography (HPLC) by the Abbott Process Research Department, and the separation conditions will be specified in the experimental procedures. Melting points were recorded on a Fisher-Johns appa-

ratus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin-Elmer 241 polarimeter. All elemental analyses were performed by Robertson Microlite Laboratories, and the data for carbon, hydrogen, and nitrogen reported are within 0.4% of theoretical values.

8-(1-Azetidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3a). General Procedure A. Azetidine (1.00 g, 17.54 mmol) was added to a stirred mixture of **1** (1.29 g, 4.00 mmol) and sodium bicarbonate (1.68 g, 20.00 mmol) in acetonitrile (40 mL) under nitrogen. The reaction mixture was heated with stirring at 60 °C for 20 h. After cooling to room temperature, the reaction mixture was taken up in CH_2Cl_2 (100 mL) and washed with water (50 mL), 1 N HCl (50 mL), water (50 mL), and brine (50 mL). The resulting solution was dried over Na_2SO_4 and the solvent was evaporated. The yellow solid obtained was purified by flash column chromatography eluting with CH_2Cl_2/MeOH (95:5) to give **2a** as a yellow solid (1.29 g).

To a solution of the above product **2a** (1.29 g, 3.75 mmol) in THF (100 mL) was added a solution of $LiOH·H_2O$ (1.57 g, 37.5 mmol) in water (40 mL). The reaction mixture was heated to 80 °C and stirred at this temperature for 6 h. After cooling to room temperature, the mixture was neutralized to pH 3 with 1 N HCl (40 mL) solution and diluted with water (300 mL). The precipitate was collected by filtration, washed three times with cold water, and dried in a vacuum desiccator to give a yellow solid **3a** (0.705 g, 2.37 mmol, 60%): mp 245−247 °C; MS (APCI) *m*/*e* 317 $(M + H)^+$; high-resolution MS (APCI) obsd 317.1290, calcd for $C_{17}H_{17}FN_2O_3$ 317.1301; ^1H NMR ($CDCl_3$) δ 13.86 (1H, s, COOH), 8.97 (1H, d, J = 9.3 Hz, H-6), 8.09 (1H, s, H-2), 4.63 (4H, m), 2.62 (3H, s, CH_3), 2.53 (2H, m), 2.12 (1H, m), 0.97 (2H, m), 0.69 (2H, m).

1-Cyclopropyl-7-fluoro-8-(2-hydroxymethyl-1-azetidinyl)-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3b). General Procedure B. To a solution of (±)-2-(hydroxymethyl)azetidinium trifluoroacetate[18] (540 mg, 2.68 mmol) and **1** (434 mg, 1.34 mmol) in DMF (10 mL) was added triethylamine (1.00 mL, 7.19 mmol). The reaction mixture was stirred at 50 °C under a nitrogen atmosphere for 48 h and cooled to room temperature. The reaction mixture was taken up in ethyl acetate (50 mL) and washed with water (30 mL), 1 N HCl (30 mL), water (30 mL), and brine (30 mL). The resulting ethyl acetate solution was dried over Na_2SO_4 and evaporated to dryness. Flash column chromatography eluting with CH_2Cl_2/MeOH (90:10) provided **2b** as a yellow glass (160 mg).

To a solution of the above product **2b** (150 mg, 0.40 mmol) in THF (8 mL) was added a solution of $LiOH·H_2O$ (168 mg, 4.00 mmol) in water (4 mL). The reaction mixture was heated to 80 °C and stirred at this temperature for 4 h. After cooling to room temperature, the mixture was neutralized to pH 3 with 1 N HCl solution (5 mL) and diluted with water (30 mL). The solid formed was collected by filtration and purified by flash column eluting with CH_2Cl_2/MeOH/HOAc (90:10:1) to give **3b** (102 mg, 0.29 mmol, 74%) as a yellow solid: mp 235−237 °C; MS (DCI/NH_3) *m*/*e* 347 $(M + H)^+$; ^1H NMR (DMSO) δ 13.80 (1H, br s, COOH), 9.04 (1H, d, J = 10.0 Hz, H-6), 7.86 (1H, s, H-2), 4.92 (1H, m), 4.68 (1H, m), 4.25 (1H, m), 3.76 (1H, m), 3.63 (1H, m), 3.31 (3H, s, CH_3), 2.55 (1H, m), 2.27 (2H, m), 1.05 (1H, m), 0.88 (1H, m), 0.58 (2H, m). Anal. ($C_{18}H_{19}FN_2O_4·0.25H_2O$) C, H, N.

8-(2-Aminomethyl-1-azetidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3c). General Procedure C. A mixture of **1** (150 mg, 0.46 mmol), (±)-2-(*tert*-butoxycarbonyl)aminomethylazetidine (173 mg, 0.93 mmol), and $NaHCO_3$ (195 mg, 2.32 mmol) in acetonitrile (5 mL) was heated to reflux under nitrogen for 16 h. The reaction mixture was taken up in ethyl acetate (50 mL) and sequentially washed with water (30 mL), 1 N HCl (30 mL), water (30 mL), and brine (30 mL). The resulting ethyl acetate solution was dried over Na_2SO_4 and evaporated to dryness. Flash column chromatography eluting with CH_2Cl_2/MeOH (90:10) provided ethyl 8-[2-(*tert*-butoxycarbonyl)aminomethyl-1-azetidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizinecarboxylate (**2c**) as a yellow solid (215 mg).

To a solution of the above product (215 mg, 0.45 mmol) in THF (8 mL) was added a solution of $LiOH·H_2O$ (191 mg, 4.55 mmol) in water (4 mL). The reaction mixture was heated to 80 °C and stirred at this temperature for 4 h. After cooling to room temperature, the mixture was neutralized to pH 3 with 1 N HCl (4.6 mL) solution followed by addition of water (30 mL). The solid formed was collected by filtration and purified by flash column eluting with CH_2Cl_2/MeOH/HOAc (90:5:0.5) to give 8-[2-(*tert*-butoxycarbonyl)aminomethyl-1-azetidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizinecarboxylic acid (162 mg) as a yellow solid.

To a solution of the above product (162 mg, 0.37 mmol) in CH_2Cl_2 was added a solution of HCl in dioxane (4 N, 2 mL). The reaction mixture was stirred at room temperature for 4 h and treated with ethyl ether (20 mL). The precipitate was collected by filtration, washed with ether, and dissolved in distilled water. The resulting yellow solution was filtered through a sintered glass funnel and freeze-dried to give **3c** as a yellow solid (123 mg, 0.32 mmol, 88%): mp 181−183 °C; MS (DCI/NH_3) *m*/*e* 346 $(M + H)^+$; ^1H NMR (DMSO) δ 13.8 (1H, s, COOH), 9.25 (1H, d, J = 10.0 Hz, H-6), 8.15 (1H, s, H-2), 3.80 (1H, m), 3.64 (1H, m), 3.10−3.40 (3H, m), 2.80 (3H, s, CH_3), 2.38 (1H, m), 2.20 (2H, m), 1.05 (2H, m), 0.60 (2H, m). Anal. ($C_{18}H_{20}FN_3O_3·HCl·H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-(1-pyrrolidinyl)-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3d). By following general procedure A, starting from **1** (656 mg, 2.00 mmol) and pyrrolidine (568 mg, 8.00 mmol), **3d** was obtained as a yellow solid (400 mg, 1.21 mmol, 61% in 2 steps): mp 220−221 °C; MS (DCI/NH_3) *m*/*e* 331 $(M + H)^+$; high-resolution MS (APCI) obsd 331.1465, calcd for $C_{18}H_{20}FN_2O_3$ 331.1458; ^1H NMR ($CDCl_3$) δ 13.89 (1H, s, COOH), 9.06 (1H, d, J = 10.5 Hz, H-6), 8.22 (1H, s, H-2), 3.75 (4H, m), 2.61 (3H, s, CH_3), 2.17 (1H, m), 2.06 (4H, m), 0.98 (2H, m), 0.65 (2H, m).

1-Cyclopropyl-7-fluoro-8-(1-isoxazolinyl)-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3e). By following general procedure A, starting from **1** (771 mg, 2.39 mmol) and isoxazoline hydrochloride[19] (1.31 g, 11.95 mmol), **3e** was obtained as a yellow solid (260 mg, 0.78 mmol, 33% in 2 steps): mp 174−175 °C; MS (DCI/NH_3) *m*/*e* 333 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 13.83 (1H, s, COOH), 9.21 (1H, d, J = 10.5 Hz, H-6), 8.37 (1H, s, H-2), 4.18 (2H, t, J = 6.3 Hz), 3.78 (2H, m), 2.88 (3H, s, CH_3), 2.50 (2H, m), 2.30 (1H, m), 1.05 (2H, m), 0.72 (2H, m). Anal. ($C_{17}H_{17}FN_2O_4$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-(2-methyl-1-pyrazolidinyl)-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3f). By following general procedure A, starting from **1** (646 mg, 2.00 mmol) and *N*-methylpyrazolidine[20] (344 mg, 4.00 mmol), **3f** was obtained as a yellow solid (156 mg, 0.45 mmol, 23% in 2 steps): mp 185−187 °C; MS (DCI/NH_3) *m*/*e* 346 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 13.93 (1H, s, COOH), 9.14 (1H, d, J = 10.2 Hz, H-6), 8.28 (1H, s, H-2), 3.78 (2H, m), 3.14 (2H, t, J = 6.9 Hz), 2.72 (3H, s, CH_3), 2.53 (3H, s), 2.32 (2H, m), 2.25 (1H, m), 1.02 (2H, m), 0.68 (2H, m).

8-(3-Carboxy-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3h). By following general procedure A, starting from **1** (323 mg, 1.00 mmol) and 3-carbamoylpyrrolidine (190 mg, 1.75 mmol), **3h** was obtained as a yellow solid (44 mg, 0.12 mmol, 12% in 2 steps): mp 180 °C dec; MS (DCI/NH_3) *m*/*e* 375 $(M + H)^+$; ^1H NMR (DMSO) δ 9.08 (1H, d, J = 10.5 Hz, H-6), 7.91 (1H, s, H-2), 3.90 (2H, m), 3.78 (2H, m), 3.20 (1H, m), 2.61 (3H, s, CH_3), 2.10−2.30 (3H, m), 0.98 (2H, m), 0.62 (2H, m). Anal. ($C_{19}H_{19}FN_2O·0.5H_2O$) C, H, N.

1-Cyclopropyl-8-[(3*S*)-3-ethylamino-1-pyrrolidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3k). By following general procedure C, starting from **1** (535 mg, 1.65 mmol) and (3*S*)-3-ethyl(*tert*-butoxycarbonyl)aminopyrrolidine (708 mg, 3.31 mmol), **3k** was obtained as a yellow solid (412 mg, 1.01 mmol, 61% in 3 steps): mp 260 °C dec; MS (DCI/NH_3) *m*/*e* 374 $(M + H)^+$; ^1H

NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.12 (1H, d, $J = 10.2$ Hz, H-6), 7.95 (1H, s, H-2), 3.90-4.10 (7H, m), 2.64 (3H, s, CH_3), 2.33 (2H, m), 2.20 (1H, m), 1.24 (3H, t, $J = 6.9$ Hz), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-[(3*S*)-3-propylamino-1-pyrrolidinyl]-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3l). By following general procedure C, starting from **1** (476 mg, 1.47 mmol) and (3*S*)-3-propyl(*tert*-butoxycarbonyl)aminopyrrolidine (500 mg, 2.21 mmol), **3l** was obtained as a yellow solid (340 mg, 0.80 mmol, 55% in 3 steps): mp 249 °C dec; MS (DCI/NH_3) *m/e* 388 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.83 (1H, br s, COOH), 9.12 (1H, d, $J = 10.5$ Hz, H-6), 7.94 (1H, s, H-2), 3.75-4.05 (5H, m), 2.97 (2H, m), 2.65 (3H, s, CH_3), 2.32 (2H, m), 2.25 (1H, m), 1.68 (2H, m), 1.00 (2H, m), 0.95 (3H, t, $J = 8.0$ Hz), 0.62 (2H, m). Anal. ($C_{21}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-(3-cyclopropylamino-1-pyrrolidinyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3m). (±)-3-Cyclopropyl(*tert*-butoxycarbonyl)-aminopyrrolidine was obtained in three steps by following the literature procedure.[21] By following general procedure C, starting from **1** (808 mg, 2.50 mmol) and 3-cyclopropyl(*tert*-butoxycarbonyl)aminopyrrolidine (1.13 g, 5.00 mmol), **3m** was obtained as a yellow solid (863 mg, 2.04 mmol, 82% in 3 steps): mp 218 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, $J = 10.5$ Hz, H-6), 7.94 (1H, s, H-2), 3.95-4.15 (4H, m), 3.81 (1H, m), 2.85 (1H, m), 2.65 (3H, s, CH_3), 2.25-2.45 (3H, m), 0.95−1.05 (4H, m), 0.82 (2H, m), 0.62 (2H, m). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-[(3*S*)-(2-fluoroethyl)amino-1-pyrrolidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 1-Cyclopropyl-8-[(3*R*)-(2-fluoroethyl)amino-1-pyrrolidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(*S*)-3n and (*R*)-3n]. The optically pure amines were prepared from commercially available (*S*)-3-amino-1-benzylpyrrolidine and (*R*)-3-amino-1-benzylpyrrolidine. By following general procedure C, starting from **1** (808 mg, 2.50 mmol) and (3*S*)-(2-fluoroethyl)(*tert*-butoxycarbonyl)aminopyrrolidine (1.16 g, 5.00 mmol), **(*S*)-3n** was obtained as a yellow solid (553 mg, 1.24 mmol, 50% in 3 steps): mp 249 °C dec; MS (DCI/NH_3) *m/e* 392 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.84 (1H, br s, COOH), 9.10 (1H, d, $J = 10.6$ Hz, H-6), 7.93 (1H, s, H-2), 4.91 (1H, m), 4.75 (1H, m), 3.93−4.10 (4H, m), 3.82 (1H, m), 3.49 (1H, m), 3.36 (1H, m), 2.64 (3H, s, CH_3), 2.25−2.40 (3H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{23}F_2N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

By following general procedure C, starting from **1** (808 mg, 2.50 mmol) and (3*R*)-(2-fluoroethyl)(*tert*-butoxycarbonyl)aminopyrrolidine (1.16 g, 5.00 mmol), **(*R*)-3n** was obtained as a yellow solid (601 mg, 1.33 mmol, 54% in 3 steps): mp 252 °C dec; MS (DCI/NH_3) *m/e* 392 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.13 (1H, d, $J = 10.6$ Hz, H-6), 7.94 (1H, s, H-2), 4.89 (1H, m), 4.73 (1H, m), 3.93-4.10 (4H, m), 3.82 (1H, m), 3.48 (1H, m), 3.36 (1H, m), 2.64 (3H, s, CH_3), 2.25−2.40 (3H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{23}F_2N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-[(3*S*)-(2,2,2-trifluoroethyl)amino-1-pyrrolidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3o). By following general procedure C, starting from **1** (646 mg, 2.00 mmol) and (3*S*)-(2,2,2-trifluoroethyl)(*tert*-butoxycarbonyl)aminopyrrolidine (1.07 g, 4.00 mmol), **3o** was obtained as a yellow solid (493 mg, 1.15 mmol, 58% in 3 steps): mp 163−165 °C; MS (DCI/NH_3) *m/e* 428 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.06 (1H, d, $J = 10.5$ Hz, H-6), 7.89 (1H, s, H-2), 3.93 (2H, m), 3.76 (1H, m), 3.55 (2H, m), 2.60 (3H, s, CH_3), 2.29 (1H, m), 2.12 (1H, m), 1.93 (1H, m), 0.98 (2H, m), 0.60 (2H, m). Anal. ($C_{20}H_{21}F_4N_3O_3 \cdot 0.25H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-8-[(3*S*)-(2-methoxyethyl)amino-1-pyrrolidinyl]-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3p). By following general procedure C, starting from **1** (810 mg, 2.50 mmol) and (3*S*)-(2-methoxyethyl)(*tert*-butoxycarbonyl)aminopyrrolidine (1.22 g, 5.00 mmol), **3p** was obtained as a yellow solid (272 mg, 0.62 mmol, 25% in 3 steps): mp 204−205 °C; MS (DCI/NH_3) *m/e* 404 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, $J = 10.5$ Hz, H-6), 7.95 (1H, s, H-2), 3.90-4.10 (4H, m), 3.82 (1H, m), 3.65 (2H, t, $J = 4.8$ Hz), 3.34 (3H, s, OCH3), 3.24 (2H, m), 2.63 (3H, s, CH_3), 2.20−2.40 (3H, m), 1.01 (2H, m), 0.62 (2H, m). Anal. ($C_{21}H_{26}FN_3O_4 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-8-[3-methyl(cyclopropyl)amino-1-pyrrolidinyl]-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3q). By following general procedure A, starting from **1** (206 mg, 0.64 mmol) and (±)-3-methyl(cyclopropyl)aminopyrrolidine (180 mg, 1.28 mmol), **3q** was obtained as a yellow solid (49 mg, 0.11 mmol, 18% in 3 steps): mp 192 °C dec; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.13 (1H, d, $J = 10.5$ Hz, H-6), 7.95 (1H, s, H-2), 3.90−4.20 (5H, m), 2.85 (1H, m), 2.93 (3H, s, NCH3), 2.64 (3H, s, CH_3), 2.20−2.45 (3H, m), 1.25 (1H, m), 0.90−1.10 (4H, m), 0.85 (1H, m), 0.62 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3 \cdot HCl \cdot 2.25H_2O$) C, H, N.

8-(3-Amino-3-trifluoromethyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3r). By following general procedure C, starting from **1** (162 mg, 0.50 mmol) and (±)-3-(*tert*-butoxycarbonyl)-amino-3-trifluoromethylpyrrolidine (254 mg, 1.00 mmol), **3r** was obtained as a yellow solid (79 mg, 0.19 mmol, 38% in 3 steps): mp 150 °C dec; MS (DCI/NH_3) *m/e* 414 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, $J = 10.2$ Hz, H-6), 7.97 (1H, s, H-2), 4.15 (2H, m), 3.78 (2H, m), 2.65 (3H, s, CH_3), 2.35 (2H, m), 2.19 (1H, m), 1.02 (2H, m), 0.62 (2H, m). Anal. ($C_{19}H_{19}F_4N_3O_3$) C, H, N.

8-(*cis*-3-Amino-4-cyclopropyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3s). By following general procedure C, starting from **1** (307 mg, 0.95 mmol) and (±)-*cis*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (215 mg, 0.95 mmol), **3s** was obtained as a yellow solid (212 mg, 0.50 mmol, 52% in 3 steps): mp 254 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.10 (1H, d, $J = 10.5$ Hz, H-6), 7.95 (1H, s, H-2), 4.20 (1H, m), 3.95 (2H, m), 3.80 (2H, m), 2.64 (3H, s, CH_3), 2.35 (1H, m), 1.86 (1H, m), 1.38 (1H, m), 0.90−1.10 (4H, m), 0.60 (2H, m), 0.32 (2H, m). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-[(3*S*,4*S*)-*cis*-3-Amino-4-cyclopropyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 8-[(3*R*,4*R*)-*cis*-3-Amino-4-cyclopropyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(3*S*,4*S*)-3s and (3*R*,4*R*)-3s]. The optically pure amines were obtained by a chiral separation of racemic *cis*-1-benzyloxycarbonyl-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine on a Chiralpak column eluting with 90:10 hexane:ethanol. The enantiomer with a longer retention time was arbitrarily assigned as 3*S*,4*S*-isomer. By following general procedure C, starting from **1** (128 mg, 0.40 mmol) and (3*S*,4*S*)-*cis*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (143 mg, 0.40 mmol), **(3*S*,4*S*)-3s** was obtained as a yellow solid (16 mg, 0.04 mmol, 10% in 3 steps): mp 252 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.11 (1H, d, $J = 10.8$ Hz, H-6), 7.94 (1H, s, H-2), 4.18 (1H, m), 3.95 (2H, m), 3.81 (2H, m), 2.64 (3H, s, CH_3), 2.32 (1H, m), 1.87 (1H, m), 1.05 (1H, m), 0.95 (1H, m), 0.82 (1H, m), 0.59 (3H, m), 0.34 (1H, m), 0.28 (1H, m). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

By following general procedure C, starting from **1** (84 mg, 0.26 mmol) and (3*R*,4*R*)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (94 mg, 0.26 mmol), **(3*R*,4*R*)-3s** was obtained as a yellow solid (57 mg, 0.14 mmol, 52% in 3 steps): mp 250 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.11 (1H, d, $J = 10.5$ Hz, H-6), 7.93 (1H, s, H-2), 4.18 (1H, m), 3.94 (2H, m), 3.81 (2H, m), 2.64 (3H, s, CH_3), 2.34 (1H, m), 1.87 (1H, m), 1.05 (1H, m), 0.96 (1H, m), 0.82 (1H, m), 0.59 (3H, m), 0.35 (1H, m), 0.29 (1H, m). Anal. ($C_{21}H_{24}FN_3O_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

8-(*trans*-3-Amino-4-cyclopropyl-1-pyrrolidinyl)-1-cy-

clopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3t). By following general procedure C, starting from **1** (533 mg, 1.65 mmol) and (±)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (745 mg, 3.30 mmol), **3t** was obtained as a yellow solid (369 mg, 0.88 mmol, 53% in 3 steps): mp 199 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, J = 10.5 Hz, H-6), 7.95 (1H, s, H-2), 4.16 (1H, m), 4.05 (1H, m), 3.78 (2H, m), 3.64 (1H, m), 2.64 (3H, s, CH_3), 2.34 (1H, m), 1.82 (1H, m), 1.00 (2H, m), 0.90 (1H, m), 0.62 (2H, m), 0.54 (1H, m), 0.36 (1H, m), 0.24 (1H, m). Anal. ($C_{21}H_{24}FN_3O_3$·HCl·0.75H_2O) C, H, N.

8-[(3*S*,4*R*)-*trans*-3-Amino-4-cyclopropyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 8-[(3*R*,4*S*)-*trans*-3-Amino-4-cyclopropyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(3*S*,4*R*)-3t and (3*R*,4*S*)-3t]. The optically pure amines were prepared according to the procedure described by ref 13. By following general procedure C, starting from **1** (7.11 g, 22.0 mmol) and (3*S*,4*R*)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (5.80 g, 25.6 mmol), **(3*S*,4*R*)-3t** was obtained as a yellow solid (3.94 g, 9.36 mmol, 43% in 3 steps): mp 220 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.08 (1H, d, J = 10.5 Hz, H-6), 7.93 (1H, s, H-2), 4.18 (1H, m), 4.07 (1H, m), 3.79 (2H, m), 3.62 (1H, m), 2.62 (3H, s, CH_3), 2.33 (1H, m), 1.84 (1H, m), 1.00 (2H, m), 0.90 (1H, m), 0.61 (2H, m), 0.53 (1H, m), 0.38 (1H, m), 0.22 (1H, m). Anal. ($C_{21}H_{24}FN_3O_3$·HCl·1.50H_2O) C, H, N.

By following general procedure C, starting from **1** (652 mg, 2.02 mmol) and (3*R*,4*S*)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-cyclopropylpyrrolidine (640 mg, 2.02 mmol), **(3*R*,4*S*)-3t** was obtained as a yellow solid (380 mg, 0.90 mmol, 45% in 3 steps): mp 218 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, J = 10.5 Hz, H-6), 7.96 (1H, s, H-2), 4.18 (1H, m), 4.06 (1H, m), 3.78 (2H, m), 3.62 (1H, m), 2.64 (3H, s, CH_3), 2.33 (1H, m), 1.82 (1H, m), 1.00 (2H, m), 0.89 (1H, m), 0.61 (2H, m), 0.53 (1H, m), 0.38 (1H, m), 0.22 (1H, m). Anal. ($C_{21}H_{24}FN_3O_3$·HCl·0.25H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-(*cis*-4-methyl-3-methylamino-1-pyrrolidinyl)-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3u). By following general procedure C, starting from **1** (481 mg, 1.49 mmol) and (±)-*cis*-3-(*tert*-butoxycarbonyl)methylamino-4-methylpyrrolidine[22] (637 mg, 2.98 mmol), **3u** was obtained as a yellow solid (378 mg, 0.92 mmol, 62% in 3 steps): mp 227 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.13 (1H, d, J = 10.2 Hz, H-6), 7.94 (1H, s, H-2), 4.08 (2H, m), 3.90 (1H, m), 3.40−3.60 (2H, m), 2.66 (6H, br s, CH_3, N-CH_3), 2.56 (1H, m), 2.30 (1H, m), 1.18 (3H, d, J = 6.6 Hz, CH_3), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-(*trans*-4-methyl-3-methylamino-1-pyrrolidinyl)-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3v). By following general procedure C, starting from **1** (323 mg, 1.00 mmol) and (±)-*trans*-3-(*tert*-butoxycarbonyl)methylamino-4-methylpyrrolidine[22] (320 mg, 1.49 mmol), **3v** was obtained as a yellow solid (218 mg, 0.53 mmol, 53% in 3 steps): mp 160 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.12 (1H, d, J = 10.2 Hz, H-6), 7.92 (1H, s, H-2), 4.11 (1H, m), 4.00 (1H, m), 3.84 (2H, m), 3.72 (1H, m), 2.72 (1H, m), 2.67 (3H, br s, N-CH_3), 2.64 (3H, s, CH_3), 2.32 (1H, m), 1.17 (3H, d, J = 6.6 Hz, CH_3), 1.01 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·1.25H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-[(3*S*,4*R*)-*trans*-4-methyl-3-methylamino-1-pyrrolidinyl]-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 1-Cyclopropyl-7-fluoro-9-methyl-8-[(3*R*,4*S*)-*trans*-4-methyl-3-methylamino-1-pyrrolidinyl]-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(3*S*,4*R*)-3v and (3*R*,4*S*)-3v]. Optically pure amines were obtained by methylation of (3*S*,4*R*)- and (3*R*,4*S*)-*trans*-1-benzyloxycarbonyl-3-(*tert*-butoxycarbonyl)amino-4-methylpyrrolidines.[13] By following general procedure C, starting from **1** (366 mg, 1.13 mmol) and (3*S*,4*R*)-*trans*-3-(*tert*-butoxycarbonyl)methylamino-4-methylpyrrolidine (243 mg, 1.13 mmol), **(3*S*,4*R*)-3v** was obtained as a yellow solid (94 mg, 0.22 mmol, 20% in 3 steps): mp 161−163 °C; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.82 (1H, s, COOH), 9.12 (1H, d, J = 10.6 Hz, H-6), 7.93 (1H, s, H-2), 4.12 (1H, m), 3.98 (1H, m), 3.84 (2H, m), 3.72 (1H, m), 2.72 (1H, m), 2.68 (3H, s, N-CH_3), 2.66 (3H, s, CH_3), 2.32 (1H, m), 1.18 (3H, d, J = 6.6 Hz, CH_3), 1.01 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·H_2O) C, H, N.

By following general procedure C, starting from **1** (386 mg, 1.19 mmol) and (3*R*,4*S*)-*trans*-3-(*tert*-butoxycarbonyl)methylamino-4-methylpyrrolidine (255 mg, 1.19 mmol), **(3*R*,4*S*)-3v** was obtained as a yellow solid (98 mg, 0.23 mmol, 19% in 3 steps): mp 162−164 °C; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.82 (1H, s, COOH), 9.12 (1H, d, J = 10.5 Hz, H-6), 7.93 (1H, s, H-2), 4.10 (1H, m), 3.98 (1H, m), 3.84 (2H, m), 3.73 (1H, m), 2.72 (1H, m), 2.67 (3H, s, N-CH_3), 2.64 (3H, s, CH_3), 2.30 (1H, m), 1.18 (3H, d, J = 6.6 Hz, CH_3), 1.00 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3$·HCl·H_2O) C, H, N.

1-Cyclopropyl-8-(3-cyclopropylamino-4-methyl-1-pyrrolidinyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3w). By following general procedure C, starting from **1** (241 mg, 0.74 mmol) and 3-(*tert*-butoxycarbonyl)cyclopropylamino-4-methylpyrrolidine (269 mg, 1.12 mmol), **3w** was obtained as a yellow solid (182 mg, 0.42 mmol, 57% in 3 steps): mp 194 °C dec; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.13 (1H, d, J = 10.6 Hz, H-6), 7.95 (1H, s, H-2), 3.90−4.20 (3H, m), 3.70 (1H, m), 3.49 (1H, m), 2.83 (1H, m), 2.66 (3H, s, CH_3), 2.54 (1H, m), 2.38 (1H, m), 1.21 (3H, d, J = 6.6 Hz, CH_3), 1.01 (2H, m), 0.93 (2H, m), 0.82 (2H, m), 0.62 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3$·HCl·H_2O) C, H, N.

8-(*cis*-1-Amino-8-aza-8-bicyclo[4.3.0]nonyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3x). By following general procedure C, starting from **1** (317 mg, 0.98 mmol) and *cis*-**1**-(*tert*-butoxycarbonyl)amino-8-aza-8-bicyclo[4.3.0]nonane (550 mg, crude), **3x** was obtained as a yellow solid (66 mg, 0.15 mmol, 15% in 3 steps): mp 194−196 °C; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.10 (1H, d, J = 10.6 Hz, H-6), 7.94 (1H, s, H-2), 4.27 (1H, m), 4.16 (1H, m), 3.67 (1H, d, J = 12.0 Hz), 3.56 (1H, d, J = 12.0 Hz), 2.65 (3H, s, CH_3), 2.39 (1H, m), 2.32 (1H, m), 2.07 (1H, m), 1.82 (1H, m), 1.60−1.80 (3H, m), 1.51 (1H, m), 1.20−1.40 (2H, m), 1.01 (2H, m), 0.62 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3$·HCl·2H_2O) C, H, N.

8-(3-Aminomethyl-3-trifluoromethyl-1-pyrrolidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3z). By following general procedure C, starting from **1** (133 mg, 0.41 mmol) and (±)-3-(*tert*-butoxycarbonyl)aminomethyl-3-trifluoromethylpyrrolidine (222 mg, 0.62 mmol), **3z** was obtained as a yellow solid (47 mg, 0.10 mmol, 25% in 3 steps): mp 181−183 °C; MS (DCI/NH_3) *m/e* 428 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.16 (1H, d, J = 10.6 Hz, H-6), 7.99 (1H, s, H-2), 3.98 (2H, m), 3.85 (2H, m), 2.68 (3H, s, CH_3), 2.32 (3H, m), 1.02 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{21}F_4N_3O_3$·HCl·1.75H_2O) C, H, N.

8-(5-Amino-2-aza-2-spiro[4.4]nonyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3aa). By following general procedure C, starting from **1** (116 mg, 0.36 mmol) and 5-(*tert*-butoxycarbonyl)amino-2-aza-2-spiro[4.4]nonane (105 mg, 0.44 mmol), **3aa** was obtained as a yellow solid (57 mg, 0.13 mmol, 36% in 3 steps): mp 196−198 °C; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, s, COOH), 9.09 (1H, d, J = 10.6 Hz, H-6), 7.93 (1H, s, H-2), 3.92 (1H, m), 3.81 (2H, m), 3.58 (1H, m), 3.47 (1H, m), 2.63 (3H, s, CH_3), 1.65−2.35 (8H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3$·HCl·1.50H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-8-[3-(2-fluoroethyl)aminomethyl-

1-pyrrolidinyl]-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3bb). By following general procedure C, starting from **1** (262 mg, 0.81 mmol) and (±)-3-(2-fluoroethyl)(*tert*-butoxycarbonyl)aminomethylpyrrolidine (200 mg, 0.81 mmol), **3bb** was obtained as a yellow solid (85 mg, 0.19 mmol, 23% in 3 steps): mp 229 °C dec; MS (DCI/NH_3) *m*/*e* 406 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.08 (1H, d, $J = 10.6$ Hz, H-6), 7.92 (1H, s, H-2), 4.89 (1H, m), 4.73 (1H, m), 3.65-3.90 (4H, m), 3.35 (2H, m), 3.16 (2H, m), 2.70 (1H, m), 2.63 (3H, s, CH_3), 2.28 (1H, m), 2.20 (1H, m), 1.85 (1H, m), 1.00 (2H, m), 0.60 (2H, m). Anal. ($C_{21}H_{25}F_2N_3O_3$·HCl·1.25H_2O) C, H, N.

1-Cyclopropyl-7-fluoro-8-[3-(2-imidazolin-2-yl)-1-pyrrolidinyl]-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid, Trifluoroacetic Acid Salt (3cc). By following general procedure C, starting from **1** (610 mg, 1.89 mmol) and (±)-3-[1-(*tert*-butoxycarbonyl)-2-imidazolin-2-yl]pyrrolidine (907 mg, 3.79 mmol), **3cc** was obtained as a yellow solid (230 mg, 0.45 mmol, 24% in 3 steps): mp 107−108 °C; MS (DCI/NH_3) *m*/*e* 399 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 10.12 (2H, br s), 9.14 (1H, d, $J = 10.6$ Hz, H-6), 7.95 (1H, s, H-2), 3.80−4.00 (8H, m), 3.45 (2H, m), 2.62 (3H, s, CH_3), 2.40 (1H, m), 2.30 (1H, m), 2.19 (1H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{21}H_{23}FN_4O_3$·CF_3CO_2H·H_2O) C, H, N.

8-(*cis*-1-Aminomethyl-8-aza-8-bicyclo[4.3.0]nonyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3dd). By following general procedure C, starting from **1** (355 mg, 1.10 mmol) and *cis*-(±)-1-(*tert*-butoxycarbonyl)aminomethyl-8-azabicyclo[4.3.0]-nonane (560 mg, 2.20 mmol), **3dd** was obtained as a yellow solid (298 mg, 0.66 mmol, 60% in 3 steps): mp 194−196 °C; MS (DCI/NH_3) *m*/*e* 414 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.90 (1H, s, COOH), 9.08 (1H, d, $J = 10.5$ Hz, H-6), 7.90 (1H, s, H-2), 3.88 (2H, m), 3.60−3.80 (4H, m), 3.12 (1H, m), 2.93 (1H, m), 2.63 (3H, s, CH_3), 2.28 (1H, m), 2.17 (1H, m), 1.40−1.60 (7H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{23}H_{28}FN_3O_3$·HCl·1.25H_2O) C, H, N.

8-(*cis*-5-Aminomethyl-7-aza-2-oxo-7-bicyclo[3.3.0]octyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3ee). By following general procedure C, starting from **1** (464 mg, 1.43 mmol) and *cis*-(±)-5-(*tert*-butoxycarbonyl)aminomethyl-7-aza-2-oxobicyclo-[3.3.0]octane (978 mg, 4.00 mmol), **3ee** was obtained as a yellow solid (258 mg, 0.59 mmol, 41% in 3 steps): mp 181−184 °C; MS (DCI/NH_3) *m*/*e* 402 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.86 (1H, s, COOH), 9.17 (1H, d, $J = 10.5$ Hz, H-6), 7.98 (1H, s, H-2), 3.90−4.00 (3H, m), 3.60−3.90 (3H, m), 3.18 (2H, m), 2.89 (1H, m), 2.68 (3H, s, CH_3), 2.35 (1H, m), 2.18 (1H, m), 1.88 (1H, m), 1.02 (2H, m), 0.63 (2H, m). Anal. ($C_{21}H_{24}$-FN_3O_4·HCl·H_2O) C, H, N.

8-(*cis*-1-Aminomethyl-7-aza-3-oxo-7-bicyclo[3.3.0]octyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3ff). By following general procedure C, starting from **1** (172 mg, 0.53 mmol) and *cis*-(±)-1-(*tert*-butoxycarbonyl)aminomethyl-7-aza-3-oxobicyclo-[3.3.0]octane (260 mg, 1.06 mmol), **3ee** was obtained as a yellow solid (87 mg, 0.20 mmol, 37% in 3 steps): mp 214 °C dec; MS (DCI/NH_3) *m*/*e* 402 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.87 (1H, s, COOH), 9.18 (1H, d, $J = 10.5$ Hz, H-6), 8.00 (1H, s, H-2), 4.02 (1H, m), 3.90 (2H, m), 3.76 (2H, m), 3.50−3.70 (3H, m), 3.14 (2H, m), 2.80 (1H, m), 2.72 (3H, s, CH_3), 2.37 (1H, m), 1.02 (2H, m), 0.63 (2H, m). Anal. ($C_{21}H_{24}FN_3O_4$·HCl·2.25H_2O) C, H, N.

1-Cyclopropyl-8-(*cis*-2,7-diaza-7-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3gg). By following general procedure C, starting from **1** (482 mg, 1.49 mmol) and *cis*-(±)-2-benzyloxycarbonyl-2,7-diazabicyclo[3.3.0]octane (550 mg, 2.24 mmol), **3gg** was obtained as a yellow solid (336 mg, 0.82 mmol, 55% in 3 steps): mp 190−192 °C; MS (DCI/NH_3) *m*/*e* 372 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.16 (1H, d, $J = 10.5$ Hz, H-6), 8.00 (1H, s, H-2), 4.32 (1H, m), 4.05 (1H, m), 3.93 (1H, m), 3.72 (2H, m), 3.28 (2H, m), 3.14 (1H, m), 2.69 (3H, s, CH_3), 2.36 (1H, m), 2.18 (1H, m), 1.97 (1H, m), 1.02 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·H_2O) C, H, N.

1-Cyclopropyl-8-[(1*S*,5*S*)-*cis*-2,7-diaza-7-bicyclo[3.3.0]-octyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 1-Cyclopropyl-8-[(1*R*,5*R*)-*cis*-2,7-diaza-7-bicyclo[3.3.0]octyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(1*S*,5*S*)-3gg and (1*R*,5*R*)-3gg]. Optically pure amines were obtained by a chiral separation of racemic 2-benzyloxycarbonyl-7-(*tert*-butyloxycarbonyl)-2,7-diazabicyclo[3.3.0]octane on a Chiralpak column eluting with hexane:ethanol (90:10). The enantiomer with a longer retention time was arbitrarily assigned as 1*S*,5*S* isomer. By following general procedure C, starting from **1** (438 mg, 1.36 mmol) and 1*S*,5*S*)-*cis*-2-benzyloxycarbonyl-2,7-diazabicyclo[3.3.0]octane (500 mg, 2.03 mmol), **(1*S*,5*S*)-3gg** was obtained as a yellow solid (263 mg, 0.65 mmol, 48% in 3 steps): mp 194 °C dec; MS (DCI/NH_3) *m*/*e* 372 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.84 (1H, br s, COOH), 9.17 (1H, d, $J = 10.5$ Hz, H-6), 7.99 (1H, s, H-2), 4.32 (1H, m), 4.05 (1H, m), 3.93 (1H, m), 3.72 (2H, m), 3.28 (2H, m), 3.13 (1H, m), 2.69 (3H, s, CH_3), 2.36 (1H, m), 2.18 (1H, m), 1.97 (1H, m), 1.02 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·1.50H_2O) C, H, N.

By following general procedure C, starting from **1** (464 mg, 1.44 mmol) and (1*R*,5*R*)-*cis*-2-benzyloxycarbonyl-2,7-diazabicyclo[3.3.0]octane (530 mrg, 2.15 mmol), **(1*R*,5*R*)-3gg** was obtained as a yellow solid (194 mg, 0.48 mmol, 33% in 3 steps): mp 192 °C dec; MS (DCI/NH_3) *m*/*e* 372 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.84 (1H, br s, COOH), 9.18 (1H, d, $J = 10.5$ Hz, H-6), 8.01 (1H, s, H-2), 4.32 (1H, m), 4.05 (1H, m), 3.90 (1H, m), 3.72 (2H, m), 3.28 (2H, m), 3.13 (1H, m), 2.70 (3H, s, CH_3), 2.36 (1H, m), 2.18 (1H, m), 1.97 (1H, m), 1.02 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·1.75H_2O) C, H, N.

1-Cyclopropyl-8-(*cis*-3,7-diaza-3-bicyclo[3.3.0]octyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3hh). By following general procedure C, starting from **1** (646 mg, 2.00 mmol) and *cis*-3-(*tert*-butoxycarbonyl)-3,7-diazabicyclo[3.3.0]octane (636 mg, 3.00 mmol), **3hh** was obtained as a yellow solid (522 mg, 1.28 mmol, 64% in 3 steps): mp 220 °C dec; MS (DCI/NH_3) *m*/*e* 372 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.13 (1H, d, $J = 10.5$ Hz, H-6), 7.97 (1H, s, H-2), 3.85 (2H, m), 3.72 (2H, m), 3.44 (2H, m), 3.12 (4H, m), 2.68 (3H, s, CH_3), 2.35 (1H, m), 1.00 (2H, m), 0.62 (2H, m). Anal. ($C_{20}H_{22}FN_3O_3$·HCl·H_2O) C, H, N.

1-Cyclopropyl-8-(*cis*-5,8-diaza-2-oxo-8-bicyclo[4.3.0]-nonyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3jj). By following general procedure C, starting from **1** (468 mg, 1.45 mmol) and *cis*-(±)-5-benzyl-5,8-diaza-2-oxobicyclo[4.3.0]nonane (634 mg, 2.91 mmol), **3jj** was obtained as a yellow solid (223 mg, 0.53 mmol, 36% in 3 steps): mp 194 °C dec; MS (DCI/NH_3) *m*/*e* 388 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.12 (1H, d, $J = 10.5$ Hz, H-6), 7.96 (1H, s, H-2), 4.42(1H, m), 4.26 (2H, m), 4.05 (2H, m), 3.82 (2H, m), 3.58 (1H, m), 3.40 (1H, m), 3.14 (1H, m), 2.64 (3H, s, CH_3), 2.33 (1H, m), 1.08 (1H, m), 0.90 (1H, m), 0.62 (2H, m). Anal. ($C_{20}H_{22}FN_3O_4$·HCl·H_2O) C, H, N.

1-Cyclopropyl-8-(*trans*-5,8-diaza-2-oxo-8-bicyclo[4.3.0]-nonyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3kk). By following general procedure C, starting from **1** (585 mg, 1.81 mmol) and *trans*-(±)-5-benzyloxycarbonyl-5,8-diaza-2-oxobicyclo[4.3.0]nonane (620 mg, 2.71 mmol), **3kk** was obtained as a yellow solid (363 mg, 0.86 mmol, 47% in 3 steps): mp 214 °C dec; MS (DCI/NH_3) *m*/*e* 388 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.12 (1H, d, $J = 10.5$ Hz, H-6), 7.96 (1H, s, H-2), 4.10−4.30 (4H, m), 3.70−4.00 (5H, m), 3.20 (1H, m), 2.62 (3H, s, CH_3), 2.32 (1H, m), 1.09 (1H, m), 0.91 (1H, m), 0.62 (2H, m). Anal. ($C_{20}H_{22}FN_3O_4$·HCl·$2H_2O$) C, H, N.

1-Cyclopropyl-8-(*trans*-3,8-diaza-8-bicyclo[4.3.0]nonyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3ll). By following general procedure C, starting from **1** (323 mg, 1.00 mmol) and *trans*-(±)-3-benzyl-3,8-diazabicyclo[4.3.0]nonane (380 mg, 1.76 mmol), **3ll** was

obtained as a yellow solid (20 mg, 0.052 mmol, 5.2% in 3 steps): mp 170 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^1H NMR (DMSO) δ 13.85 (1H, br s, COOH), 9.08 (1H, d, $J = 10.5$ Hz, H-6), 7.90 (1H, s, H-2), 3.70-4.00 (4H, m), 3.20 (3H, m), 3.04 (1H, m), 2.62 (3H, s, CH_3), 2.50−2.70 (2H, m), 2.30 (1H, m), 1.90 (1H, m), 1.78 (1H, m), 0.98 (2H, m), 0.62 (2H, m).

1-Cyclopropyl-8-(*cis*-3,9-diaza-9-bicyclo[4.3.0]nonyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3nn) and 1-Cyclopropyl-8-(*cis*-3,9-diaza-3-bicyclo[4.3.0]nonyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3vv). By following general procedure C, starting from **1** (323 mg, 1.00 mmol) and *cis*-(±)-3,9-diazabicyclo[4.3.0]nonane dihydrochloride (crude), **3nn** was obtained as a yellow solid (174 mg, 0.41 mmol, 41% in 3 steps): mp 176 °C dec; MS (DCI/NIH_3) *m/e* 386 $(M + H)^+$; ^1H NMR (DMSO) δ 13.83 (1H, br s, COOH), 9.18 (1H, d, $J = 10.5$ Hz, H-6), 8.00 (1H, s, H-2), 3.60−3.80 (3H, m), 3.30−3.60 (3H, m), 3.23 (1H, m), 2.72 (3H, s, CH_3), 2.52 (1H, m), 2.38 (1H, m), 2.04 (1H, m), 1.88 (2H, m), 1.65 (1H, m), 0.97 (2H, m), 0.60 (2H, m). Anal. ($C_{21}H_{24}FN_3O_4 \cdot HCl \cdot 2H_2O$) C, H, N.

Compound **3vv** was obtained as a minor product (34 mg, 0.081 mmol, 8% in 3 steps): mp 180 °C dec; MS (DCI/NH_3) *m/e* 386 $(M + H)^+$; ^1H NMR (DMSO) δ 13.83 (^1H, br s, COOH), 9.16 (1H, d, $J = 10.8$ Hz, H-6), 8.00 (1H, s, H-2), 5.21 (1H, m), 4.11 (1H, m), 3.15-3.50 (5H, m), 2.85 (1H, m), 2.68 (3H, s, CH_3), 2.56 (1H, m), 2.38 (1H, m), 2.12 (1H, m), 1.84 (2H, m), 1.73 (1H, m), 1.10 (1H, m), 0.91 (1H, m), 0.61 (2H, m). Anal. ($C_{21}H_{24}FN_3O_4 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-fluoro-9-methyl-8-(1-piperidinyl)-4(*H*)-4-oxoquinolizine-3-carboxylic Acid (3pp). By following general procedure A, starting from **1** (1.27 g, 3.94 mmol) and piperidine (1.60 mL, 16.00 mmol), **3d** was obtained as a yellow solid (831 mg, 2.42 mmol, 61% in 2 steps): mp 260−261 °C; MS (DCI/NH_3) *m/e* 345 $(M + H)^+$; high-resolution MS (APCI) obsd 345.1613, calcd for $C_{19}H_{22}FN_2O_3$ 345.1614; ^1H NMR ($CDCl_3$) δ 13.89 (1H, s, COOH), 9.17 (1H, d, $J = 10.5$ Hz, H-6), 8.32 (1H, s, H-2), 3.41 (4H, m), 2.78 (3H, s, CH_3), 2.26 (1H, m), 1.76 (6H, m), 1.02 (2H, m), 0.68 (2H, m).

8-(5-Amino-1-aza-3-cyclohexen-1-yl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3rr). By following general procedure C, starting from **1** (323 mg, 1.00 mmol) and (±)-5-(*tert*-butoxycarbonyl)amino-1-aza-3-cyclohexene dihydrochloride (crude), **3rr** was obtained as a yellow solid (25 mg, 0.070 mmol, 7% in 3 steps): mp 185 °C dec; MS (DCI/NH_3) *m/e* 358 $(M + H)^+$; ^1H NMR (DMSO) δ 13.83 (1H, br s, COOH), 9.25 (1H, d, $J = 10.5$ Hz, H-6), 8.08 (1H, s, H-2), 6.22 (1H, m), 5.95 (1H, m), 4.05 (2H, m), 3.88 (2H, m), 3.50 (1H, m), 2.78 (3H, s, CH_3), 2.42 (1H, m), 1.04 (2H, m), 0.65 (2H, m).

8-(*cis*-3-Amino-4-methyl-1-piperidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3ss). By following general procedure C, starting from **1** (137 mg, 0.42 mmol) and (±)-*cis*-3-(*tert*-butoxycarbonyl)amino-4-methylpiperidine (110 mg, 0.51 mmol), **3ss** was obtained as a yellow solid (69 mg, 0.17 mmol, 40% in 3 steps): mp 195 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.22 (1H, d, $J = 10.5$ Hz, H-6), 8.05 (1H, s, H-2), 3.64 (2H, m), 3.48 (2H, m), 3.24 (1H, m), 2.80 (3H, s, CH_3), 2.43 (1H, m), 2.15 (1H, m), 1.82 (1H, m), 1.70 (1H, m), 1.04 (3H, d, $J = 6.0$ Hz, CH_3), 1.00 (2H, m), 0.65 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3 \cdot HCl \cdot 3H_2O$) C, H, N.

8-[(3*S*,4*S*)-*cis*-3-Amino-4-methyl-1-piperidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 8-[(3*R*,4*R*)-*cis*-3-Amino-4-methyl-1-piperidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(3*S*,4*S*)-3ss and (3*R*,4*R*)-3ss]. Optically pure amines were obtained by a chiral separation of racemic *cis*-1-benzyloxycarbonyl-3-(*tert*-butoxycarbonyl)amino-4-methylpiperidine on a Chiralpak column eluting with 90:10 hexane:methanol. The enantiomer with longer retention time was arbitrarily assigned as 3*S*,4*S* isomer. By following general procedure C, starting from **1** (403 mg, 1.25 mmol) and (3*S*,4*S*)-*cis*-3-(*tert*-butoxycarbonyl)amino-4-methylpiperidine (640 mg, 2.50 mmol), **(3*S*,4*S*)-3ss** was obtained as a yellow solid (332 mg, 0.81 mmol, 65% in 3 steps): mp 198 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.24 (1H, d, $J = 10.5$ Hz, H-6), 8.07 (1H, s, H-2), 3.62 (2H, m), 3.44 (2H, m), 3.24 (1H, m), 2.80 (3H, s, CH_3), 2.43 (1H, m), 2.14 (1H, m), 1.82 (1H, m), 1.71 (1H, m), 1.05 (3H, d, $J = 6.0$ Hz, CH_3), 1.00 (2H, m), 0.65 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3 \cdot HCl \cdot 1.25H_2O$) C, H, N.

By following general procedure C, starting from **1** (403 mg, 1.25 mmol) and (3*R*,4*R*)-*cis*-3-(*tert*-butoxycarbonyl)amino-4-methylpiperidine (636 mg, 2.50 mmol), **(3*R*,4*R*)-3ss** was obtained as a yellow solid (391 mg, 0.96 mmol, 76% in 3 steps): mp 198 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.24 (1H, d, $J = 10.5$ Hz, H-6), 8.07 (1H, s, H-2), 3.63 (2H, m); 3.45 (2H, m), 3.24 (1H, m), 2.80 (3H, s, CH_3), 2.43 (1H, m), 2.14 (1H, m), 1.82 (1H, m), 1.71 (1H, m), 1.05 (3H, d, $J = 6.0$ Hz, CH_3), 1.00 (2H, m), 0.65 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3 \cdot HCl \cdot 1.75H_2O$) C, H, N.

8-(*trans*-3-Amino-4-methyl-1-piperidinyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3tt). By following general procedure C, starting from **1** (323 mg, 1.00 mmol) and (±)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-methylpiperidine (300 mg, 1.40 mmol), **3tt** was obtained as a yellow solid (241 mg, 0.59 mmol, 59% in 3 steps): mp 205 °C dec; MS (DCI/NH_3) *m/e* 374 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.23 (1H, d, $J = 10.5$ Hz, H-6), 8.04 (1H, s, H-2), 3.82 (1H, m), 3.48 (2H, m), 3.25 (1H, m), 3.02 (1H, m), 2.78 (3H, s, CH_3), 2.40 (1H, m), 1.83 (2H, m), 1.48 (1H, m), 1.10 (3H, d, $J = 6.0$ Hz, CH_3), 1.02 (2H, m), 0.63 (2H, m). Anal. ($C_{20}H_{24}FN_3O_3 \cdot HCl \cdot 1.50H_2O$) C, H, N.

1-Cyclopropyl-8-(3-cyclopropylamino-1-piperidinyl)-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3uu). By following general procedure C, starting from **1** (1.01 g, 3.12 mmol) and (±)-3-cyclopropyl(*tert*-butoxycarbonyl)aminopiperidine (1.50 g, 6.25 mmol), **3uu** was obtained as a yellow solid (630 mg, 1.44 mmol, 46% in 3 steps): mp 222 °C dec; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.22 (1H, d, $J = 10.5$ Hz, H-6), 8.04 (1H, s, H-2), 3.90 (1H, m), 3.49 (2H, m), 3.39 (2H, m), 3.25 (1H, m), 2.78 (3H, s, CH_3), 2.42 (1H, m), 2.28 (1H, m), 1.94 (1H, m), 1.70 (2H, m), 1.05 (2H, m), 0.90 (2H, m), 0.82 (2H, m), 0.63 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-8-[(*S*)-3-cyclopropylamino-1-piperidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 1-Cyclopropyl-8-[(*R*)-3-cyclopropylamino-1-piperidinyl]-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(*S*)-3uu and (*R*)-3uu]. Optically pure amines were obtained by a chiral separation of racemic 3-(*tert*-butoxycarbonyl)(cyclopropyl)-amino-1-benzyloxycarbonylpiperidine on a Chiralpak column eluting with 90:10 hexane:methanol. The enantiomer with longer retention time was arbitrarily assigned as *R* isomer. By following general procedure C, starting from **1** (646 mg, 2.00 mmol) and (*S*)-3-cyclopropyl(*tert*-butoxycarbonyl)amino-piperidine (1.05 g, 2.78 mmol), **(*S*)-3uu** was obtained as a yellow solid (508 mg, 1.16 mmol, 58% in 3 steps): mp 210 °C dec; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.22 (1H, d, $J = 10.5$ Hz, H-6), 8.05 (1H, s, H-2), 3.92 (1H, m), 3.49 (2H, m), 3.40 (2H, m), 3.25 (1H, m), 2.79 (3H, s, CH_3), 2.42 (1H, m), 2.29 (1H, m), 1.92 (1H, m), 1.69 (2H, m), 1.03 (2H, m), 0.90 (2H, m), 0.81 (2H, m), 0.64 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

By following general procedure C, starting from **1** (600 mg, 1.86 mmol) and (*R*)-3-cyclopropyl(*tert*-butoxycarbonyl)amino-piperidine (672 mg, 2.80 mmol), **(*R*)-3uu** was obtained as a yellow solid (514 mg, 1.18 mmol, 63% in 3 steps): mp 208 °C dec; MS (DCI/NH_3) *m/e* 400 $(M + H)^+$; ^1H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.24 (1H, d, $J = 10.5$ Hz, H-6), 8.06 (1H, s, H-2), 3.92 (1H, m), 3.49 (2H, m), 3.39 (2H, m), 3.25 (1H, m), 2.79 (3H, s, CH_3), 2.42 (1H, m), 2.28 (1H, m), 1.94

(1H, m), 1.70 (2H, m), 1.03 (2H, m), 0.88 (2H, m), 0.82 (2H, m), 0.65 (2H, m). Anal. ($C_{22}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-(7-Amino-3-aza-3-bicyclo[4.1.0]heptyl)-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride (3ww). By following general procedure C, starting from **1** (426 mg, 1.32 mmol) and (±)-7-(*tert*-butoxycarbonyl)amino-3-azabicyclo[4.1.0]heptane (560 mg, 2.64 mmol), **3ww** was obtained as a yellow solid (160 mg, 0.39 mmol, 30% in 3 steps): mp 198 °C dec; MS (DCI/NH_3) *m*/*e* 372 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.86 (1H, br s, COOH), 9.18 (1H, d, J = 10.8 Hz, H-6), 8.04 (1H, s, H-2), 3.85 (1H, m), 3.61 (1H, m), 3.21 (2H, m), 2.72 (3H, s, CH_3), 2.55 (1H, m), 2.36 (1H, m), 2.10 (1H, m), 1.92 (1H, m), 1.59 (2H, m), 1.02 (2H, m), 0.65 (2H, m). Anal. ($C_{20}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

8-[(3*S*,4*R*)-*trans*-3-Amino-4-methyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride and 8-[(3*R*,4*S*)-*trans*-3-Amino-4-methyl-1-pyrrolidinyl]-1-cyclopropyl-7-fluoro-9-methyl-4(*H*)-4-oxoquinolizine-3-carboxylic Acid Hydrochloride [(3*S*,4*R*)-3xx and (3*R*,4*S*)-3xx]. The optically pure amines were prepared according to the procedure described by ref 13. By following general procedure C, starting from **1** (420 mg, 1.30 mmol) and (3*S*,4*R*)-*trans*-3-(*tert*-butoxycarbonyl)-amino-4-methylpyrrolidine (350 mg, 1.50 mmol), **(3*S*,4*R*)-3xx** was obtained as a yellow solid (263 mg, 0.64 mmol, 49% in 3 steps): mp 198 °C dec; MS (DCI/NH_3) *m*/*e* 360 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.82 (1H, br s, COOH), 9.07 (1H, d, J = 10.8 Hz, H-6), 7.93 (1H, s, H-2), 4.02 (2H, m), 3.89 (1H, m), 3.55 (2H, m), 2.63 (3H, s, CH_3), 2.52 (1H, m), 2.30 (1H, m), 1.18 (3H, d, J = 6.3 Hz, CH_3), 0.99 (2H, m), 0.60 (2H, m). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

By following general procedure C, starting from **1** (420 mg, 1.30 mmol) and (3*R*,4*S*)-*trans*-3-(*tert*-butoxycarbonyl)amino-4-methylpyrrolidine (541 mg, 2.70 mmol), **(3*R*,4*S*)-3xx** was obtained as a yellow solid (246 mg, 0.60 mmol, 46% in 3 steps): mp 199 °C dec; MS (DCI/NH_3) *m*/*e* 360 $(M + H)^+$; ^{1}H NMR (DMSO) δ 13.82 (1H, br s, COOH), 9.11 (1H, d, J = 10.8 Hz, H-6), 7.96 (1H, s, H-2), 4.02 (2H, m), 3.84 (1H, m), 3.55 (2H, m), 2.63 (3H, s, CH_3), 2.50 (1H, m), 2.33 (1H, m), 1.19 (3H, d, J = 6.3 Hz, CH_3), 1.00 (2H, m), 0.61 (2H, m). Anal. ($C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

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