Articles

Synthesis and Antimicrobial Evaluation of a Series of 7-[3-Amino (or Aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl]-4-quinolone- and -1,8-naphthyridone-3-carboxylic Acids[1]

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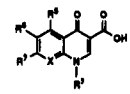
A series of 6-fluoroquinolone- and 6-fluoro-1,8-naphthyridone-3-carboxylic acids possessing a [3-amino (or aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl] group at C-7 were synthesized and evaluated for their antimicrobial activity. The effect of the relative stereochemistry of the pyrrolidinyl substituents, as well as the presence of different functional groups on the 4-aryl (or cyclopropyl) moiety, was investigated in conjunction with their attachment to several quinolone or naphthyridone nuclei. In general, the incorporation of substituents on the aryl (or cyclopropyl) ring decreased *in vitro* and *in vivo* activity, regardless of the nature and relative position of the substituent. Bulky, lipophilic groups and substitution at the 2- and 3-position of the aromatic ring were particularly deleterious. Within a limited subset of derivatives, *cis* substitution of the pyrrolidine ring was less favorable than *trans* substitution. The majority of these effects were more apparent against the *Enterobacteriaceae* than against any other Gram-negative or Gram-positive organism and could be associated with negative interactions related to permeability or transport factors.

Introduction

The challenge associated with fighting bacterial infections has become an increasingly complex one, partly because of the fast development of resistance to the classic antibiotics, but also due to the changing nature of the infections observed in the elderly and other immunocompromised patients. In this context, the quinolone antibacterials have aroused much expectation owing to their broad spectrum of activity, high potency, and oral efficacy and novel mechanism of action.[2] Several of these agents are already on the market, while many others have been described or await further development.

The majority of the currently marketed quinolones contain a piperazine or substituted piperazine at C-7 of the quinolone nucleus (*e.g.*, 1–6, Figure 1).[3-8] These agents possess excellent activity against most members of the *Enterobacteriaceae* family (*e.g.*, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Serratia marcescens*, etc.) and other Gram-negative organisms, including in some cases *Pseudomonas aeruginosa*. Their activity against important Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci, and hemolytic streptococci, however, is only fair.

In the search for new analogs with higher potency and a broad spectrum of activity, it was found that replacement of the C-7 piperazine by a 3-amino (or aminomethyl)-1-pyrrolidine (*e.g.*, 7–12, Figure 1)[9-14] provides a dramatic improvement in Gram-positive activity, while still maintaining the good levels of potency against Gram-negative organisms characteristic of the piperazinyl substituted quinolones.[13,15] This improvement, however, is more notorious *in vitro* than *in vivo*, a fact that has been attributed to the relatively lower solubility of the pyrrolidinyl-substituted compounds.[11,12]



Cmpd	Name	X	R^1	R^5	R^7	Ref.
1	Norfloxacin	CH	Et	H		3
2	Enoxacin	N	Et	H		4
3	Ciprofloxacin	CH	c-Pr	H		5
4	Lomefloxacin	CF	Et	H		6
5	Ofloxacin	C-O-CH_2-CH-CH_3		H		7
6	Sparfloxacin	CF	c-Pr	NH_2		8
7	Tosufloxacin	N	2,4-F_2Ph	H		9
8	Clinafloxacin	CCl	c-Pr	H		10
9	---	N	2,4-F_2Ph	H		11
10	AT-3295	N	c-Pr	H		12
11	---	CF	c-Pr	H		13
12	---	CF	c-Pr	H		14

Figure 1. Clinically significant quinolones and reference agents.

Several structural modifications were therefore sought to improve upon the solubility and/or pharmacokinetic properties of the pyrrolidinyl-substituted quinolones. Among these modifications, methyl substitution on the pyrrolidine ring was found to have a beneficial effect in this respect, in a manner similar to that previously observed with the piperazinyl-substituted quinolones. For example,

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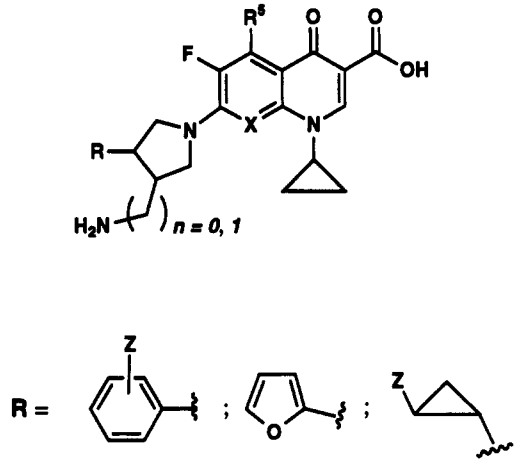


Figure 2. 7-[3-Amino (or aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl]quinolones.

the ((2*S*,4*S*)-4-amino-2-methylpyrrolidinyl)naphthyridine **9**[11] and the (*trans*-3-amino-4-methylpyrrolidinyl)naphthyridine **10**[12] both have an *in vitro* activity comparable to that of the corresponding desmethyl analog, but are significantly (*i.e.*, 20 and 40 times, respectively) more soluble in pH 7 phosphate buffer solution. The enhanced solubility, in turn, translates into improved oral absorption and better pharmacokinetic profile (*e.g.*, the peak plasma concentration of **9** in the dog is 5 times higher than that of its desmethyl analog).

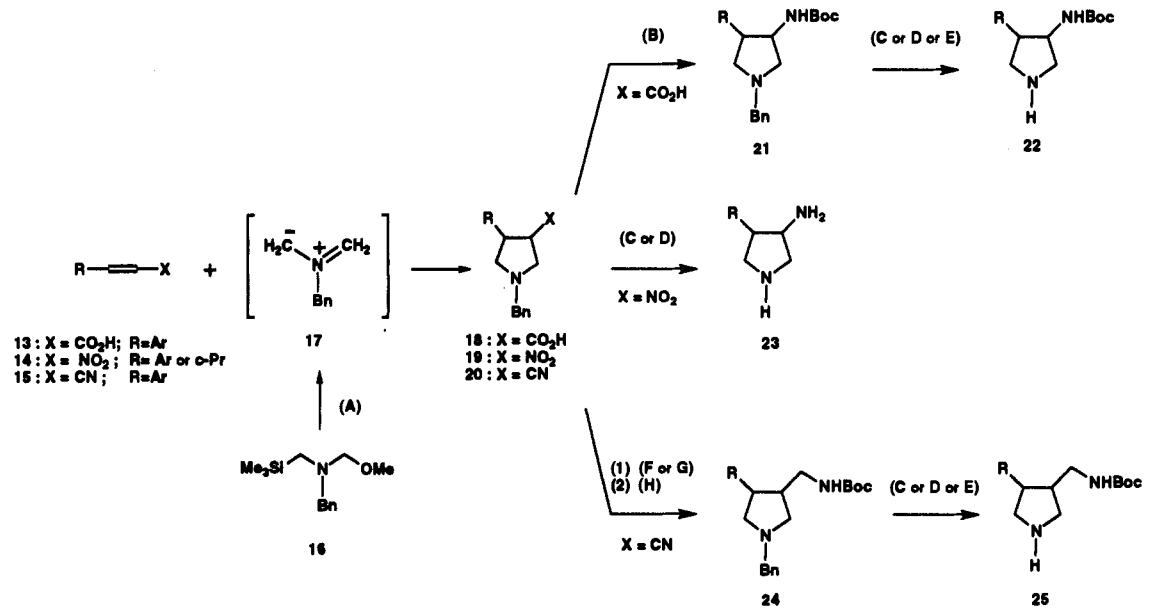
In contrast with the above observations, a previous study from our laboratories had shown that, with the exception of the (3-(aminomethyl)-3-methylpyrrolidinyl)quinolone **12**, the *in vivo* activity of several other 3- or 4-methyl (or phenyl)-substituted (3-amino- or 3-(aminomethyl)pyrrolidinyl)-6,8-difluoroquinolones *decreased* in comparison to the corresponding unsubstituted compound.[14] These results, along with the observed dependence of the 2- and 4-methyl-3-aminopyrrolidinyl derivatives on the relative stereochemistry of the substituents for optimal activity (*e.g.*, the C-2 epimer of **9** is at least 10 times less active than **9**, both at the bacterial and enzymatic levels, yet it is twice as soluble and has better pharmacokinetics, whereas the *cis* isomer of **10** is twice as potent as **10**, albeit 10 times less soluble), suggest that substitution on the pyrrolidine ring has also a more intrinsic effect on the overall bacterial inhibitory process. Therefore, in an effort to expand upon previous structure–activity relationships,[14] we undertook a systematic study of the effect upon antibacterial activity of different substituents on the 4-position of a (3-amino (or aminomethyl)-4-substituted-1-pyrrolidinyl)quinolone.[16] The 4-substituents, which included functionalized phenyl, heteroaryl, and to a lesser extent, cyclopropyl rings, were chosen because of their unique steric and electronic properties (Figure 2). The functional groups on these rings, on the other hand, were selected so as to provide a wider range of log *P* values, as well as fine tuning of steric and electronic parameters (Figure 3). Additionally, we looked at the effect of *cis* versus *trans* substitution on the pyrrolidine ring and to the interplay that different quinolone and naphthyridone nuclei may have upon the overall activity of the final compounds.

Chemistry

The 3,4-disubstituted pyrrolidines utilized in this study were synthesized *via* a common methodology involving a 1,3-dipolar cycloaddition of the nonstabilized azomethine ylide **17**, generated by desilylation of ((silylmethyl)amino)-methyl ether **16**,[17] and a cinnamic acid, 2-nitro- or 2-cyanostyrene derivative (Scheme I). The required olefins, in turn, were either obtained from commercial sources or prepared by condensation of the corresponding aldehyde with nitromethane[18] or acetonitrile.[19] In these cases, the thermodynamically more stable *trans*-substituted compounds were produced exclusively or predominantly. Where mixtures of *cis* and *trans* isomers were obtained, chromatographic separation of the olefins (or of their corresponding cycloadducts) provided stereochemically homogeneous material.

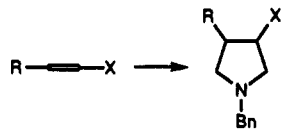
The 1,3-dipolar cycloadditions were performed according to a modification of the procedure reported by Achiwa.[17b] The yields of cycloadducts were generally very

Scheme I[a]



[a] Reagents: (A) TFA (cat.), CH_2Cl_2; (B) DPPA, Et_3N, t-BuOH; (C) H_2, 20% Pd/C, MeOH; (D) HCO_2NH_4, 10% Pd/C, MeOH/H_2O; (E) $TMSCH_2OCOCl$, THF; then, Et_4NF, CH_3CN; (F) $LiAlH_4$, THF; (G) Ra-Ni, NH_3/MeOH; (H) Boc_2O, Et_3N or i-Pr_2EtN, CH_2Cl_2.

Table I. 3,4-Disubstituted Pyrrolidines via Dipolar Cycloaddition



compd	R	X	yield (%)[a]	mp (°C)	formula (analysis)[b]
18b	cis-2-OMe-Ph	CO_2H	58		$C_{19}H_{21}NO_3$ (C,H,N)
18c	trans-2-OMe-Ph	CO_2H	62	197–202	$C_{19}H_{21}NO_3 \cdot 0.2H_2O$ (C,H,N)
18e	trans-3,4-Cl_2-Ph	CO_2H	77	167–168	$C_{18}H_{17}Cl_2NO_2$ (C,H,N,Cl)
18k	trans-4-NO_2-Ph	CO_2H	65	164–166	$C_{18}H_{13}N_2O_4$ (C,H,N)
19a	trans-Ph	NO_2	51	177–179	$C_{17}H_{18}N_2O_2 \cdot HCl$ (C,H,N)
19d	trans-3-CN-Ph	NO_2	70	151–156	$C_{18}H_{17}H_3O_2 \cdot HCl \cdot 0.25H_2O$ (C,H,N,Cl[c])
19f	trans-4-(i-Pr)-Ph	NO_2	83	181–183	$C_{20}H_{24}N_2O_2 \cdot HCl$ (C,H,N)
19g	trans-4-F-Ph	NO_2	86	183–185	$C_{17}H_{17}FN_2O_2 \cdot HCl$ (C,H,N)
19h	trans-4-OH-Ph	NO_2	65	224–227	$C_{17}H_{18}N_2O_3 \cdot HCl$ (C,H,N,Cl)
19i	trans-4-OMe-Ph	NO_2	81	75–80	$C_{18}H_{20}N_2O_3 \cdot H_2O$ (C,H,N)
19l	trans-4-NMe_2-Ph	NO_2	42		$C_{19}H_{23}H_3O_2 \cdot 1.05HCl$ (C,H,N,Cl)
19m	trans-4-CO_2Me-Ph	NO_2	95	oil	
19o	trans-c-Pr	NO_2	84	oil	$C_{14}H_{18}N_2O_2$ (C,H,N)
20p	trans-(*trans*-2-CO_2Et)-c-Pr	NO_2	71	oil	$C_{17}H_{22}N_2O_4$ (C,H,N)
20a	trans-Ph	CN	86	204–206	$C_{18}H_{18}N_2 \cdot HCl$ (C,H,N,Cl)
20d	trans-3-CN-Ph	CN	66	158–165	$C_{18}H_{17}N_3 \cdot HCl \cdot H_2O$ (C,H,N,Cl)
20j	cis-4-NO_2-Ph	CN	20	216–218	$C_{18}H_{17}N_3O_2 \cdot HCl \cdot 0.25H_2O$ (C,H,N)
20k	trans-4-NO_2-Ph	CN	65	211–214	$C_{18}H_{17}N_3O_2 \cdot HCl$ (C,H,N,Cl)
20n	trans-2-Furanyl	CN	60	oil	$C_{16}H_{18}N_2O$ (C,H,N[d])

[a] Overall yield from **13**, **14**, or **15**. [b] Symbols refer to those elements analyzed. Analyses were within ±0.4% of theoretical values, except where indicated. [c] Calcd/found 10.16/9.66. [d] Calcd/found 11.10/10.62.

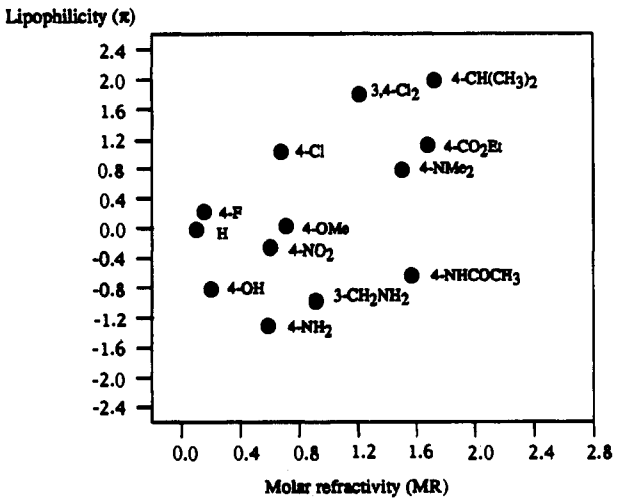


Figure 3. Aromatic ring substituents selected for this study.

good (Table I). Worthy of note is the observation that the cinnamic acids **13** proved themselves to be good dipolarophiles in this reaction, making it unnecessary to resort to their ester derivatives. This result expedited the introduction of the 3-amino group *via* a subsequent Curtius rearrangement. Alternatively, access to the 3-amino substituent was gained by using a nitro olefin as the dipolarophile component of the cycloaddition. In a similar fashion, vinyl nitriles were convenient starting materials for the preparation of the 3-(aminomethyl)-substituted pyrrolidines (Scheme I). In all cases, the relative stereochemistry of the substituents on the pyrrolidine ring was ensured by the use of stereochemically pure olefins (*vide supra*) and by the well-established stereospecificity of the cycloaddition.

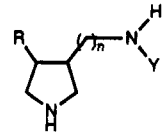
Curtius rearrangement of the 3-carboxy-4-substituted-pyrrolidines **18** using diphenyl phosphorazidate (DPPA) and triethylamine in t-BuOH gave the corresponding Boc-protected amines **21**.[20] Removal of the benzyl group by catalytic hydrogenation afforded pyrrolidines **22** (Scheme I). Due to the lability of the aromatic chlorine atoms contained in **18e** toward catalytic hydrogenation, the debenzylation was carried out by the method of Campbell, using 2-(trimethylsilyl)ethyl chloroformate.[21]

Catalytic hydrogenation (3 atm of H_2, 20% Pd/C) of *N*-benzyl-3-nitropyrrolidines **19** provided the 3-amino-4-arylpyrrolidines **23** in one step by effecting simultaneous reduction of the nitro moiety and removal of the benzyl protecting group (Scheme I). In the case of the cyclopropyl-substituted pyrrolidines **19o,p**, however, these two transformations were best achieved by transfer hydrogenolysis (aqueous ammonium formate, 10% Pd/C), which maintained the integrity of the cyclopropyl ring. The *m*-cyanophenyl derivative **19d**, on the other hand, was first hydrogenated in the presence of Raney nickel; the resulting 3-amino-4-[3-(aminomethyl)phenyl]-1-benzylpyrrolidine was reacted with an excess of di-*tert*-butyl dicarbonate, followed by debenzylation, to give the bis-Boc-protected pyrrolidine **23d**.

Selective reduction of the 3-cyano-4-substituted-pyrrolidines **20**, without debenzylation, was accomplished with Raney nickel in methanol saturated with ammonia, except for the parent 4-phenyl compound **20a**, which was reduced with $LiAlH_4$. It should be noted that this operation also reduced the aromatic cyano and nitro groups present in **20d** and **20j,k**, respectively. The resulting 3-(aminomethyl)-4-arylpyrrolidines were protected with di-*tert*-butyl dicarbonate to afford compounds **24**. This protection affected only the aliphatic and benzylic amino groups and was necessary to avoid any interference of these groups in the subsequent coupling reaction. Finally, catalytic debenzylation provided pyrrolidines **25** (Scheme I).

The quinolones reported in this study were all prepared by well-established procedures,[13] starting with the appropriate pyrrolidine and either the 6,7-difluoroquinolone **26**,[22] the 7-chloro-1,8-naphthyridine **27**,[13] the 6,7,8-trifluoroquinolone **28**,[23] or the 5-amino-6,7,8-trifluoroquinolone **29**[24] (Scheme II). In those cases where the distal nitrogen of the pyrrolidine was protected as a *tert*-butoxycarbonyl (Boc) derivative, subsequent removal of the protecting group with HCl gas and purification of the

Table II. [3-Amino (or aminomethyl)-4-substituted]pyrrolidines



compd	n	R	Y	method(s) of preparation	yield (%)[a]	mp (°C)	formula (analysis)[b]
22b	0	cis-2-OMe-Ph	Boc	B,C	95		$C_{18}H_{24}H_2O_3 \cdot 1.2H_2O$ (C,H[c],N)
22c	0	trans-2-OMe-Ph	Boc	B,C	85	170–172	
22e	0	trans-3,4-Cl_2-Ph	Boc	B,E	64		$C_{15}H_{20}Cl_2N_2O_2 \cdot 0.25H_2O$ (C,H,N)
22k	0	trans-4-NH_2-Ph	Boc	B,C	88	207–210	HRMS: calcd 277.1790, found 277.1800
23a	0	trans-Ph	H	C	82	>275	$C_{10}H_{14}N_2 \cdot 2.05HCl \cdot 0.5H_2O$ (C,H,N,Cl)
23d	0	trans-(CH_2NHBoc)-Ph	Boc	G,H,C	70	68–71	$C_{21}H_{33}N_3O_4 \cdot 0.4H_2O$ (C,H,N[d])
23f	0	trans-4-(i-Pr)-Ph	H	C	77	163–166	$C_{13}H_{20}N_2 \cdot 1.1HCl$ (C,H,N)
23g	0	trans-4-F-Ph	H	C	90	>275	$C_{10}H_{13}FN_2 \cdot 2HCl$ (C,H,N,Cl)
23h	0	trans-4-OH-Ph	H	C	87	>275	$C_{10}H_{14}N_2O \cdot 2HCl \cdot 0.75H_2O$ (C,H,N,Cl)
23i	0	trans-4-OMe-Ph	H	C	61	247–249	$C_{11}H_{16}N_2O \cdot HCl \cdot H_2O$ (C,H,N,Cl)
23l	0	trans-4-NMe_2-Ph	H	C	78	117–121	$C_{12}H_{19}N_3 \cdot 1.4HCl \cdot 0.25H_2O$ (C,H,N,Cl)
23m	0	trans-4-CO_2Me-Ph	H	C	88	93–96	$C_{12}H_{16}N_2O_2 \cdot HCl \cdot 0.77H_2O$ (C,H,N,Cl)
23o	0	trans-c-Pr	H	D	14	oil	
23p	0	trans-(*trans*-2-CO_2Et)-c-Pr	H	D	77	oil	$C_{10}H_{18}N_2O_2 \cdot 0.9H_2O$ (C,H[e],N)
25a	1	trans-Ph	Boc	F,H,C	97	oil	$C_{16}H_{24}N_2O_2 \cdot 0.6H_2O$ (C,H,N)
25d	1	trans-3-(CH_2NHBoc)-Ph	Boc	G,H,C	77	62–65	$C_{22}H_{35}N_3O_4 \cdot 0.5H_2O$ (C,H,N[f])
25j	1	cis-4-NH_2-Ph	Boc	G,H,D	67	198–202	$C_{16}H_{25}N_3O_2 \cdot H_2O$ (C,H,N[g])
25k	1	trans-4-NH_2-Ph	Boc	G,H,D	79		
25n	1	trans-2-Furanyl	Boc	G,H,C	45	163–169	$C_{14}H_{22}N_2O_3 \cdot 0.8H_2O$ (C,H[h],N)

[a] Overall yield from **18**, **19**, or **20**. [b] Symbols refer to those elements analyzed. Analyses were within ±0.4% of theoretical values, except where indicated. [c] Calcd/found = 8.47/7.85. [d] Calcd/found = 10.54/10.03. [e] Calcd/found = 9.31/8.86. [f] Calcd/found = 10.17/7.05. [g] Calcd/found = 13.58/12.72. [h] Calcd/found = 8.42/7.87.

product by recrystallization or isoelectric precipitation[25] provided the target compound.

Biological Evaluation of New Compounds

***In Vitro* Assays.** The series of quinolones and naphthyridones prepared for this study was tested *in vitro* against an assortment of five Gram-negative and five Gram-positive organisms using standard microdilution techniques.[26] The minimum inhibitory concentration (MICs, μg/mL) for each strain was recorded, and the geometric means of the MICs for both Gram-negative (except *P. aeruginosa*) and Gram-positive organisms were calculated to facilitate comparison in activity.

***In Vivo* Assays.** The *in vivo* potency, expressed as the median protective dose (PD_{50}, mg/kg), was determined in acute, lethal systemic infections in female Charles River CD-1 mice, with a single dose of the compound administered orally (po) or subcutaneously (sc) at the time of challenge.[28]

Results and Discussion

The minimum inhibitory concentrations (MICs, μg/mL) of the compounds prepared in this study are shown in Table IV. The mouse protection doses (PD_{50}, mg/kg) for some of the more active agents are presented in Table V.

The quinolone nuclei utilized in this study all contained a fluorine atom at C-6 and a cyclopropyl group at N-1, features associated with potent antibacterial activity. We chose to center our synthetic efforts on the 1,8-naphthyridine, 6,8-difluoroquinolone, and 5-amino-6,8-difluoroquinolone series due to the additional beneficial attributes imparted by these nuclei. Indeed, it has been shown that, while the *in vitro* activity of 7-pyrrolidinyl-substituted naphthyridines is roughly equal to that of the corresponding 8-H quinolones, their *in vivo* efficacy is generally superior, due in part to the inherent better oral absorption and tissue penetration of the naphthyridine nucleus.[13] Similarly, incorporation of a second fluorine atom at C-8 of 7-pyrrolidinyl-substituted quinolones has been demonstrated to increase not only the *in vitro* potency against Gram-positive organisms, but also the overall *in vivo* efficacy of the resulting agents.[13] This particular combination, however, has been associated with undesirable side effects, the most notorious of which is phototoxicity.[29] The additional presence of an amino group at C-5 of a 6,8-difluoroquinolone, on the other hand, not only boosts *in vitro* potency relative to the 5-H analogues, but also reduces phototoxic risk.[24,30]

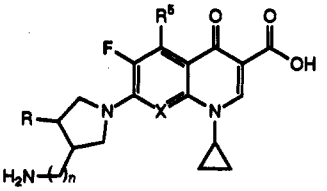
An examination of the MICs for naphthyridine series of compounds (**31-0** and **31-1**) revealed the following trends:

(1) The incorporation of functional groups on the phenyl ring of the pyrrolidine either had no effect on or decreased antibacterial activity *in vitro*. These effects were dependent on (a) the nature and position of the functional group(s) on the aromatic nucleus, (b) the relative stereochemistry of the substituents on the pyrrolidine ring (*i.e.*, *cis* vs *trans*), and (c) whether the pyrrolidine had an amino or an aminomethyl moiety.

(2) Small, polar groups at the 4′-position of the phenyl ring had no effect upon activity in the aminopyrrolidinyl series. Thus, the 4′-F, 4′-OH, 4′-OMe, 4′-NH_2, and 4′-NMe_2Ph derivatives (**31-0g,h,i,k,l**) were all essentially equipotent with the unsubstituted phenyl compound, **31-0a**. Interestingly, the 4′-NMe_2Ph analog **31-0l** was moderately more active versus staphylococcus than any of the other 4-substituted phenyl derivatives. In the (aminomethyl)pyrrolidinyl series, however, both the *cis*- and *trans*-4′-NH_2Ph derivatives **31-1j** and **31-1k**, respectively, were 2–3 times less potent *in vitro* than the corresponding unsubstituted phenyl analog **31-1a**.

(3) Bulky, lipophilic groups at the 4′-position of the phenyl ring decreased activity by 2–4-fold. This effect was more pronounced for the Gram-negative than for the Gram-positive organisms (*cf.*, **31-0f,l,m**), which is the reason why we think it may be related to transport or permeability factors.

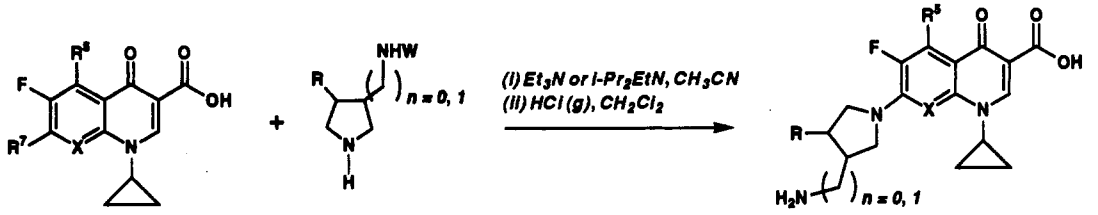
Table III. Physical Data of the Quinolone and Naphthyridone Antibacterials Prepared for This Study



compd	R^5	X	*n*	R[a]	yield (%)[b]	mp (°C)	formula (analysis)[c]
30-0o	H	CH	0	trans-c-Pr	57	236–240	$C_{20}H_{22}FN_3O_3 \cdot 0.3H_2O$ (C,H,N)
30-0p	H	CH	0	trans-(*trans*-2-CO_2Et)-c-Pr	45	200–203	$C_{23}H_{26}FN_3O_5 \cdot 1.5H_2O$ (C,H,N)
31-0a	H	N	0	trans-Ph	75	>295	$C_{22}H_{21}FN_4O_3 \cdot HCl \cdot 1.2H_2O$ (C,H,N,Cl)
31-0b	H	N	0	cis-2-OMe-Ph	89	225–232	$C_{23}H_{23}FN_4O_4 \cdot HCl \cdot 2.5H_2O$ (C,H,N)
31-0c	H	N	0	trans-2-OMe-Ph	77	>280	$C_{23}H_{23}FN_4O_4 \cdot HCl \cdot 0.7H_2O$ (C,H,N)
31-0d	H	N	0	trans-3-(CH_2NH_2)-Ph	87	>270	$C_{23}H_{24}FN_5O_3 \cdot 2HCl \cdot 2H_2O$ (C,H,N)
31-0e	H	N	0	trans-3,4-Cl_2-Ph	54	226–230	$C_{22}H_{19}Cl_2FN_4O_3 \cdot 1.2HCl \cdot H_2O$ (C,H,N,Cl)
31-0f	H	N	0	trans-4-(i-Pr)-Ph	30	220–225	$C_{25}H_{27}FN_4O_3 \cdot 1.75HCl \cdot H_2O$ (C,H,N)
31-0g	H	N	0	trans-4-F-Ph	81	220–223	$C_{22}H_{20}F_2N_4O_3 \cdot 0.5H_2O$ (C,H,N)
31-0h	H	N	0	trans-4-OH-Ph	22	276–280	$C_{22}H_{21}FN_4O_4 \cdot 0.75H_2O$ (C,H,N)
31-0i	H	N	0	trans-4-OMe-Ph	62	233–235	$C_{23}H_{23}FN_4O_4 \cdot 0.5H_2O$ (C,H,N)
31-0k	H	N	0	trans-4-NH_2-Ph	82	>255	$C_{22}H_{22}FN_5O_3 \cdot 1.8HCl \cdot 2H_2O$ (C,H,N,Cl)
31-0l	H	N	0	trans-4-NMe_2-Ph	85	236–238	$C_{24}H_{26}FN_5O_3 \cdot 0.2H_2O$ (C,H,N)
31-0m	H	N	0	trans-4-CO_2Me-Ph	35	282	$C_{24}H_{23}FN_4O_5 \cdot 0.5H_2O$ (C,H,N)
31-0p	H	N	0	trans-(*trans*-2-CO_2Et)-c-Pr	30	230–235	$C_{22}H_{25}FN_4O_5 \cdot 1.7H_2O$ (C,H,N[d])
32-0a	H	CF	0	trans-Ph	53	206–208	$C_{23}H_{21}F_2N_3O_3 \cdot 0.75H_2O$ (C,H,N)
32-0c	H	CF	0	trans-2-OMe-Ph	78	255–257	$C_{24}H_{23}F_2N_3O_4 \cdot 1.1HCl \cdot 1.75H_2O$ (C,H,N,Cl)
32-0e	H	CF	0	trans-3,4-Cl_2-Ph	45	238–243	$C_{23}H_{19}Cl_2F_2N_3O_3 \cdot HCl \cdot 1.5H_2O$ (C,H[e],N,Cl)
32-0f	H	CF	0	trans-4-(i-Pr)-Ph	72	194–196	$C_{26}H_{27}F_2N_3O_3 \cdot 0.25H_2O$ (C,H,N,F)
32-0g	H	CF	0	trans-4-F-Ph	90	210–212	$C_{23}H_{20}F_3N_3O_3 \cdot 0.75H_2O$ (C,H,N)
32-0h	H	CF	0	trans-4-OH-Ph	49	222–225	$C_{23}H_{21}F_2N_3O_4 \cdot 1.2H_2O$ (C,H,N)
32-0i	H	CF	0	trans-4-OMe-Ph	83	202–205	$C_{24}H_{23}F_2N_3O_4 \cdot 1.1H_2O$ (C,H,N,F)
32-0k	H	CF	0	trans-4-NH_2-Ph	74	>255	$C_{23}H_{22}F_2N_4O_3 \cdot 2HCl \cdot 2H_2O$ (C,H,N,Cl)
32-0l	H	CF	0	trans-4-NMe_2-Ph	79	240–243	$C_{25}H_{26}F_2N_4O_3 \cdot 0.25H_2O$ (C,H,N)
32-0m	H	CF	0	trans-4-CO_2Me-Ph	25	196	$C_{25}H_{23}F_2N_3O_5 \cdot H_2O$ (C,H,N)
33-0a	NH_2	CF	0	trans-Ph	66	212–215	$C_{23}H_{22}F_2N_4O_3 \cdot H_2O$ (C,H,N)
33-0g	NH_2	CF	0	trans-4-F-Ph	87	204–206	$C_{23}H_{21}F_3N_4O_3 \cdot 1.6H_2O$ (C,H,N)
33-0h	NH_2	CF	0	trans-4-OH-Ph	87	231–237	$C_{23}H_{22}F_2N_4O_4 \cdot 1.6H_2O$ (C,H,N)
33-0k	NH_2	CF	0	trans-4-NMe_2-Ph	91	229–231	$C_{25}H_{27}F_2N_5O_3$ (C,H,N,F)
31-1a	H	N	1	trans-Ph	96	>270	$C_{23}H_{23}FN_4O_3 \cdot 2HCl \cdot H_2O$ (C,H,N,Cl)
31-1d	H	N	1	trans-3-(CH_2NH_2)-Ph	90	>270	$C_{24}H_{26}FN_5O_3 \cdot 2HCl \cdot 2.4H_2O$ (C,H,N)
31-1j	H	N	1	cis-4-NH_2-Ph	36	>270	$C_{23}H_{24}FN_5O_3 \cdot 2HCl \cdot 0.35H_2O$ (C,H,N[f])
31-1k	H	N	1	trans-4-NH_2-Ph	66	>270	$C_{23}H_{24}FN_5O_3 \cdot 2HCl \cdot 2.5H_2O$ (C,H,N)
31-1n	H	N	1	trans-2-furanyl	82	255–260	$C_{21}H_{21}FN_4O_4 \cdot HCl \cdot 0.75H_2O$ (C,H,N)
32-1a	H	CF	1	trans-Ph	62	265–269	$C_{24}H_{23}F_2N_3O_3 \cdot 1.5HCl \cdot 1.5H_2O$ (C,H,N,Cl[g])
32-1d	H	CF	1	trans-3-(CH_2NH_2)-Ph	73	>270	$C_{25}H_{26}F_2N_4O_3 \cdot 2HCl \cdot 3H_2O$ (C,H,N)
32-1k	H	CF	1	trans-4-NH_2-Ph	53	>270	$C_{24}H_{24}F_2N_4O_3 \cdot 2HCl \cdot 2.1H_2O$ (C,H,N)
32-1n	H	CF	1	trans-2-furanyl	72	234–242	$C_{22}H_{21}F_2N_3O_4 \cdot HCl \cdot 0.5H_2O$ (C,H,N,Cl)
33-1a	NH_2	CF	1	trans-Ph	6.5	217–220	$C_{24}H_{24}F_2N_4O_3 \cdot 1.25HCl \cdot 1.25H_2O$ (C,H,N,Cl)
33-1k	NH_2	CF	1	trans-4-NH_2-Ph	34	>270	$C_{24}H_{25}F_2N_5O_3 \cdot HCl \cdot 3.5H_2O$ (C,H,N)

[a] Cis and trans indicate the relative stereochemistry between the pyrrolidine substituents. [b] Yields are those obtained from the coupling step to final product isolation, including deprotection where applicable. [c] Symbols refer to those elements analyzed. Unless otherwise noted, analyses were within ±0.4% of theoretical values. [d] Calcd/found = 11.79/10.99. [e] Calcd/found = 4.16/3.71. [f] Calcd/found = 13.55/12.77. [g] Calcd/found = 10.20/9.72.

Scheme II



Cmpd.	X	R^5	R^7
26	CH	H	F
27	N	H	Cl
28	CF	H	F
29	CF	NH_2	F

Cmpd.	X	R^5
30	CH	H
31	N	H
32	CF	H
33	CF	NH_2

(4) Substitution at the 2′- or 3′-position of the phenyl ring also had a detrimental effect upon *in vitro* activity, particularly against Gram-negative organisms. Indeed, the *cis*- and *trans*-[3-amino-4-(2′-OMePh)] derivatives **31-0b** and **31-0c**, respectively, both were less potent than the unsubstituted phenyl compound **31-0a**. In contrast, the [3-amino-4-(4′-OMePh)] analog **31-0i** had the same overall activity as **31-0a**. Similarly, the [3-amino-4-(3′,4′-Cl_2Ph)],

Table IV. *In Vitro* Antibacterial Activity

		minimum inhibitory concentration (MIC), μg/mL											
		Gram-negative organisms					Gram-positive organisms					geometric means	
compd	R	*Entero. cloacae* MA-2646	*Esch. coli* Vogel	*Klebs. pneum.* MGH-2	*Prov. rettgeri* M-1771	*Pseudo. aerug.* UI-18	*Staph. aureus* H-228	*Staph. aureus* UC-76	*Entero. faecalis* MGH-2	*Strep. pneum.* SV-1	*Strep. pyog.* C-203	Gram-negat.	Gram-posit.
30-0o	trans-c-Pr	0.1	0.05	0.05	0.1	0.8	0.1	≤0.025	0.1	0.1	0.1	0.071	0.076
30-0p	trans-[trans-2-CO_2Et]-c-Pr	0.2	0.2	0.4	0.8	3.1	1.6	0.2	0.8	0.8	0.8	0.336	0.696
31-0a	trans-Ph	0.1	0.1	0.2	0.4	1.6	0.1	0.05	0.2	0.1	0.2	0.168	0.115
31-0b	cis-2-OMe-Ph	0.8	0.8	1.6	3.1	>3.1	0.4	0.2	0.8	0.8	1.6	1.33	0.606
31-0c	trans-2-OMe-Ph	0.2	0.2	0.4	0.8	3.1	0.1	0.05	0.2	0.1	0.2	0.336	0.115
31-0d	trans-3-(CH_2NH_2)-Ph	0.8	0.8	0.8	1.6	3.1	3.1	0.4	0.8	0.2	0.2	0.951	0.524
31-0e	trans-3,4-Cl_2-Ph	0.4	0.4	0.4	0.8	3.1	0.1	0.05	0.2	0.2	0.4	0.476	0.152
31-0f	trans-4-(i-Pr)-Ph	0.8	0.4	0.8	1.6	6.3	0.2	0.1	0.4	0.4	0.4	0.80	0.264
31-0g	trans-4-F-Ph	0.1	0.1	0.2	0.4	1.6	0.1	0.025	0.1	0.2	0.2	0.168	0.10
31-0h	trans-4-OH-Ph	0.1	0.1	0.2	0.4	1.6	0.4	0.1	0.1	0.2	0.2	0.168	0.174
31-0i	trans-4-OMe-Ph	0.1	0.1	0.2	0.4	1.6	0.1	0.05	0.2	0.1	0.1	0.168	0.10
31-0k	trans-4-NH_2-Ph	0.1	0.1	0.2	0.4	1.6	0.2	0.05	0.2	0.2	0.2	0.168	0.152
31-0l	trans-4-NMe_2-Ph	0.2	0.2	0.4	0.4	3.1	0.05	0.025	0.2	0.2	0.2	0.282	0.10
31-0m	trans-4-CO_2Me-Ph	0.4	0.4	0.4	0.8	3.1	0.2	0.1	0.4	0.8	0.8	0.476	0.348
31-0p	trans-[trans-2-CO_2Et]-c-Pr	1.6	1.6	3.1	6.3	2.5	1.6	0.4	1.6	1.6	1.6	2.659	1.913
31-1a	trans-Ph	0.05	0.05	0.05	0.1	0.8	0.025	0.006	0.025	0.013	0.025	0.059	0.016
31-1d	trans-3-(CH_2NH_2)-Ph	3.1	3.1	3.1	6.3	12.5	3.1	0.8	1.6	0.8	0.2	3.70	0.913
31-1j	cis-4-NH_2-Ph	0.2	0.2	0.4	0.8	1.6	0.2	0.025	0.1	0.05	0.05	0.336	0.066
31-1k	trans-4-NH_2-Ph	0.2	0.2	0.2	0.4	1.6	0.4	0.05	0.1	0.05	0.05	0.238	0.087
31-1n	trans-2-furanyl	0.2	0.1	0.1	0.2	0.4	0.05	0.013	0.05	0.025	0.05	0.150	0.033
32-0a	trans-Ph	0.025	0.025	0.05	0.1	0.8	0.025	0.013	0.1	0.1	0.1	0.042	0.050
32-0c	trans-2-OMe-Ph	0.4	0.2	0.4	0.8	3.1	0.05	0.025	0.1	0.1	0.1	0.40	0.066
32-0e	trans-3,4-Cl_2-Ph	0.2	0.1	0.2	0.2	1.6	0.05	0.013	0.1	0.1	0.1	0.168	0.058
32-0f	trans-4-(i-Pr)-Ph	0.4	0.4	0.4	0.4	3.1	0.05	0.025	0.2	0.2	0.2	0.40	0.100
32-0g	trans-4-F-Ph	0.1	0.1	0.1	0.2	1.6	0.025	0.013	0.1	0.1	0.1	0.199	0.050
32-0h	trans-4-OH-Ph	0.1	0.1	0.1	0.2	1.6	0.1	0.025	0.1	0.1	0.1	0.119	0.076
32-0i	trans-4-OMe-Ph	0.1	0.1	0.2	0.4	1.6	0.025	0.013	0.1	0.05	0.05	0.168	0.038
32-0k	trans-4-NH_2-Ph	0.05	0.05	0.1	0.2	0.8	0.1	0.025	0.1	0.1	0.1	0.084	0.076
32-0l	trans-4-NMe_2-Ph	0.2	0.2	0.2	0.4	3.1	0.025	0.013	0.1	0.1	0.1	0.238	0.050
32-0m	trans-4-CO_2Me-Ph	0.4	0.4	0.8	1.6	3.1	0.1	0.05	0.4	0.4	0.4	0.673	0.200
32-1a	trans-Ph	0.05	0.05	0.05	0.1	0.8	0.013	0.003	0.013	0.013	0.013	0.059	0.0097
32-1d	trans-3-(CH_2NH_2)-Ph	1.6	1.6	1.6	3.1	6.3	1.6	0.2	0.8	0.2	0.1	1.89	0.348
32-1k	trans-4-NH_2-Ph	0.1	0.1	0.2	0.2	1.6	0.1	0.025	0.05	0.05	0.05	0.141	0.050
32-1n	trans-2-furanyl	0.05	0.05	0.1	0.1	0.4	0.025	0.003	0.013	0.006	0.013	0.071	0.014
33-0a	trans-Ph	0.025	0.025	0.05	0.1	0.8	0.013	0.006	0.05	0.05	0.1	0.042	0.029
33-0g	trans-4-F-Ph	0.1	0.1	0.1	0.2	1.6	0.025	0.013	0.1	0.1	0.1	0.119	0.05
33-0h	trans-4-OH-Ph	0.05	0.05	0.05	0.1	0.8	0.05	0.013	0.05	0.05	0.1	0.059	0.044
33-1a	trans-Ph	0.05	0.025	0.05	0.1	0.8	0.006	0.003	0.013	0.003	0.006	0.05	0.005
33-1k	trans-4-NH_2-Ph	0.1	0.1	0.2	0.2	0.8	0.025	0.006	0.025	0.013	0.025	0.141	0.016

Table V. *In Vivo* Efficacy of Selected Compounds in Mouse Protection Tests

	PD_{50} (mg/kg) po/sc	
compd	*E. coli* Vogel	*S. pyogenes* C-203
31-0a	11/6.5	
31-0c	37/28	44/22
31-0g	18/9	
31-0k	24/3.1	
31-1a		27/4.5
31-1n		36/4.2
32-0a	15.5/7	10/1.6
32-0f		100/90
32-0g		44/40
32-0h	100/50	
32-0k	10/1.6	
32-1a		10/1.6

[3-amino-4-(3′-CH_2NH_2Ph)], and [3-(aminomethyl)-4-(3′-CH_2NH_2Ph)] derivatives **31-0e**, **31-0d**, and **31-1d** all were significantly less active than the corresponding unsubstituted phenyl analogs **31-0a** and **31-1a**. Interestingly, removal of the pyrrolidinyl amino or aminomethyl substituent in **31-0d** or **31-1d** (data not shown) brings about a dramatic increase in *in vitro* potency, particularly against Gram-positive pathogens.[31]

(5) *Cis* substitution on the pyrrolidine ring had a more dramatic effect on the amino- than on the (aminomethyl)-pyrrolidinyl series. For example, the *cis*-[3-amino-4-(2′-OMePh)] derivative **31-0b** was 2–3 times less active across the spectrum than the corresponding *trans*-substituted analog **31-0c**, whereas the *cis*-[3-(aminomethyl)-4-(4′-NH_2-Ph)] compound **31-1j** was essentially equipotent to its *trans*-substituted counterpart, **31-1k**.

(6) Replacement of the phenyl ring in **31-0m** by a cyclopropane (*cf.* **31-0p**)[32] decreased overall activity by 2-fold. Replacement of the phenyl ring in **31-1a** by a 2′-furanyl moiety (*cf.* **31-1n**), on the other hand, resulted in a slight reduction in activity against the *Enterobacteriaceae*, but essentially retained the activity against the other Gram-negative and all of the Gram-positive strains.

Most of the trends observed for the naphthyridine compounds were also present in the 6,8-difluoro- and 5-amino-6,8-difluoroquinolone series. However, the intrinsic high potency of these difluoroquinolones, particularly against Gram-positive organisms, more than compensated for the negative effect resulting from introduction of a substituent on the phenyl ring of the pyrrolidine side chain. Such an effect, therefore, was more apparent within the Gram-negative strains, especially those belonging to the *Enterobacteriaceae* family.

The trends observed in the *in vitro* activity of the substituted phenyl derivatives prepared for this study were also reflected in their *in vivo* efficacy. For instance, the *trans*-[3-amino-4-(2′-OMePh)]naphthyridine **31-0c** was 3–4 times less active in the mouse protection model against *E. coli* Vogel than the parent compound **31-0a**, whereas

the 4′-F-Ph and 4′-NH_2-Ph analogs **31-0g** and **31-0k** were roughly equally efficacious, particularly by the subcutaneous route of administration.

Replacement of the phenyl ring by a 2′-furanyl group had also no effect on *in vivo* potency against *S. pyogenes* (*cf.* **31-1a** *vs* **31-1n**).

In the 6,8-difluoroquinolone series, however, there was a more striking difference between *in vitro* and *in vivo* activity. Thus, while the 4′-OH-Ph and 4′-NH_2-Ph derivatives **32-0h** and **32-0k** were almost equipotent *in vitro*, the latter turned out to be 10–30 times more active *in vivo*. This anomaly may be related to a negative effect of the hydroxyl substituent associated with transport or permeability.

In summary, we have shown that the activity of [3-amino (or aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl]-quinolones can be modulated by the introduction of functionality on the 4-substituent of the pyrrolidine ring. However, most of the substituents tested had little or no beneficial effect upon both *in vitro* and *in vivo* antibacterial activity, in spite of the ample variation in their physicochemical parameters. These results suggest that this portion of the quinolone molecule may be involved in mechanisms associated with permeability or transport rather than bacterial killing. Alternatively, the presence of several functional groups within the pyrrolidinyl side chain could disrupt whatever interaction is usually established with a single amino (or aminomethyl) substituent.

Experimental Section

Air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of nitrogen or argon. Tetyrahydrofuran was distilled from sodium benzophenone ketyl, dioxane from sodium, and dimethylformamide from calcium hydride. Unless otherwise indicated, organic solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on E. Merck silica gel 60 F_{254} precoated glass plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel 60, 230–400-mesh ASTM, according to Still.[33] Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX-1 FTIR spectrometer. Proton and carbon-13 magnetic resonance spectra were obtained on either a Varian XL 200 or a Brüker AM 250 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Low- (MS) and high-resolution (HRMS) mass spectra were recorded on either a Finnigan 4500 or a VG analytical 7070E/HF mass spectrometer. Elemental analyses were performed on a CEC 240XA elemental analyzer.

***cis*-4-(2-Methoxyphenyl)-1-(phenylmethyl)-3-pyrrolidinecarboxylic Acid (18b). Method A.** A solution of *N*-(methoxymethyl)-*N*-(phenylmethyl)-*N*-(trimethylsilyl)methylamine (11.87 g, 50 mmol) in CH_2Cl_2 (25 mL) was added dropwise, over a 30-min period, to a stirred solution of *cis*-2-methoxycinnamic acid (4.45 g, 25 mmol) and trifluoroacetic acid (2.5 mL, 2.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated to a yellow oil, which was triturated with Et_2O to give the title compound as an off-white solid. (In some cases, the pyrrolidine was isolated as its hydrochloride salt, by treating an ether solution of the crude material with 6 N HCl.): IR (KBr) 1243, 1496, 1588, 1603 cm^{-1}; MS *m/z* (relative intensity) 311 (M, 20), 220 (13), 147 (11), 133 (51), 91 (100); ^1H NMR (CD_3OD) δ 3.29–3.51 (2H, m), 4.44 (2H, s), 6.82 (1H, dd, *J* = 7.3, 8.1 Hz), 6.91 (1H, d, *J* = 8.1 Hz), 7.17 (2H, dd, *J* = 6.9, 7.4 Hz), 7.42–7.44 (3H, m), 7.46–7.54 (2H, m).

***trans*-4-(2-Methoxyphenyl)-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid (18c)**: IR (KBr) 1242, 1494, 1602, 1635 cm^{-1}; MS *m/z* (relative intensity) 311 (M, 19), 220 (16), 133 (72), 91 (100); ^1H NMR (DMSO-d_6) δ 2.48 (1H, t, *J* = 8.0 Hz), 2.83–2.95 (3H, m), 3.03–3.12 (1H, m), 3.58 (1H, d, *J* = 13.0 Hz), 3.67 (1H, d, *J* = 13.0 Hz), 3.75 (3H, s), 3.87 (1H, q, *J* = 7.1 Hz), 6.88–6.97 (2H, m), 7.17–7.34 (7H, m).

***trans*-4-(3,4-Dichlorophenyl)-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid (18e)**: IR (KBr) 1388, 1473, 1598, 1605, 1701, 1718 cm^{-1}; MS *m/z* (relative intensity) 351 (M + 2, 6), 349 (9), 258 (10), 133 (48), 91 (100); ^1H NMR (DMSO-d_6) δ 2.66 (1H, dd, *J* = 5.9, 9.2 Hz), 2.80 (1H, dd, *J* = 6.4, 7.8 Hz), 2.88–3.07 (3H, m), 3.50–3.59 (1H, m), 3.65 (2H, dd, *J* = 13.0, 17.2 Hz), 7.22–7.50 (8H, m).

***trans*-4-(4-Nitrophenyl)-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid (18k)**: IR (KBr) 1348, 1519, 1602 cm^{-1}; MS *m/z* (relative intensity) 326 (M, 14), 280 (5), 235 (29), 133 (28), 91 (100); ^1H NMR (DMSO-d_6) δ 2.62 (1H, dd, *J* = 9.2, 15.6 Hz), 2.84 (1H, dd, *J* = 8.2, 14.2 Hz), 2.92–3.17 (3H, m), 3.58–3.71 (3H, m), 7.25–7.35 (5H, m), 7.62 (2H, d, *J* = 8.8 Hz), 8.18 (2H, d, *J* = 8.8 Hz).

***trans*-3-Nitro-4-phenyl-1-(phenylmethyl)pyrrolidine hydrochloride (19a)**: IR (KBr) 1379, 1458, 1558 cm^{-1}; MS *m/z* (relative intensity) 283 (M + 1, 100), 236 (81), 117 (47), 91 (45); ^1H NMR (DMSO-d_6) δ 3.40–3.60 (1H, m), 3.62–3.92 (2H, m), 3.93–4.28 (3H, m), 4.31–4.64 (2H, m), 5.55–5.70 (1H, m), 7.30–7.56 (8H, m), 7.60–7.77 (2H, m).

***trans*-3-[4-Nitro-1-(phenylmethyl)-3-pyrrolidinyl]benzonitrile hydrochloride (19d)**: IR (KBr) 1561, 2233, 2284 cm^{-1}; MS *m/z* (relative intensity) 308 (M + 1, 100), 261 (51), 91 (57); ^1H NMR (CD_3OD) δ 3.71 (1H, t, *J* = 11.8 Hz), 4.03 (1H, dd, *J* = 3.3, 11.0 Hz), 4.18 (1H, dd, *J* = 4.5, 9.2 Hz), 4.25–4.40 (2H, m), 4.61 (2H, s), 5.66 (1H, dt, *J* = 3.6, 8.9 Hz), 7.42–7.55 (3H, m), 7.60–7.65 (3H, m), 7.76 (1H, d, *J* = 7.7 Hz), 7.84 (1H, d, *J* = 7.8 Hz), 7.94 (1H, s).

***trans*-3-[4-(1-Methylethyl)phenyl]-4-nitro-1-(phenylmethyl)pyrrolidine hydrochloride (19f)**: IR (KBr) 1458, 1559, 2960 cm^{-1}; MS *m/z* (relative intensity) 325 (M + 1, 100), 278 (33), 159 (14), 117 (10), 91 (10); ^1H NMR ($CDCl_3$) δ 1.18 (6H, d, *J* = 6.5 Hz), 2.8–3.0 (1H, m), 3.76–3.90 (2H, m), 4.15–4.70 (5H, m), 5.44–5.56 (1H, m), 7.15–7.25 (2H, m), 7.30–7.52 (5H, m), 7.70–7.82 (2H, m).

***trans*-3-(4-Fluorophenyl)-4-nitro-1-(phenylmethyl)pyrrolidine hydrochloride (19g)**: IR (KBr) 1225, 1385, 1518, 1560, 1609 cm^{-1}; MS *m/z* (relative intensity) 301 (M + 1, 100), 254 (42), 135 (21), 91 (17); ^1H NMR (DMSO-d_6) δ 3.38–3.66 (4H, m), 3.70–3.88 (1H, m), 3.90–4.30 (3H, m), 4.35–4.70 (2H, m), 5.50–5.70 (1H, m), 7.26 (2H, t, *J* = 8.8 Hz), 7.40–7.50 (2H, m), 7.60–7.80 (5H, m).

***trans*-4-[4-Nitro-1-(phenylmethyl)-3-pyrrolidinyl]phenol hydrochloride (19h)**: IR (KBr) 1519, 1558, 1616, 2577 cm^{-1}; MS *m/z* (relative intensity) 299 (M + 1, 100), 252 (89), 133 (74), 120 (36), 91 (59); ^1H NMR (DMSO-d_6) δ 3.25–3.80 (2H, m), 3.90–4.30 (3H, m), 4.40–4.70 (2H, m), 5.40–5.60 (1H, m), 6.79 (2H, d, *J* = 8.2 Hz), 7.25 (2H, d, *J* = 8.2 Hz), 7.45–7.60 (3H, m), 7.62 (2H, m).

***trans*-3-(4-Methoxyphenyl)-4-nitro-1-(phenylmethyl)pyrrolidine (19i)**: IR ($CHCl_3$) 1246, 1256, 1454, 1515, 1612 cm^{-1}; MS *m/z* (relative intensity) 313 (M + 1, 40), 266 (43), 147 (100), 91 (46); ^1H NMR ($CDCl_3$) δ 2.66 (1H, dd, *J* = 7.6, 9.1 Hz), 3.09 (1H, dd, *J* = 7.8, 10.8 Hz), 3.27 (1H, t, *J* = 8.6 Hz), 3.39 (1H, dd, *J* = 4.0, 10.8 Hz), 3.72 (1H, dd, *J* = 13.1, 18.2 Hz), 3.79 (3H, s), 3.92–4.02 (1H, m), 4.85–4.95 (1H, m), 6.87 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.6 Hz), 7.28–7.35 (5 H, m).

***trans*-N,N-Dimethyl-4-[4-nitro-1-(phenylmethyl)-3-pyrrolidinyl]benzenamine hydrochloride (19l)**: IR (KBr) 1444, 1458, 1528, 1556, 1616 cm^{-1}; MS *m/z* (relative intensity) 325 (M, 3), 160 (100), 144 (7), 91 (15); ^1H NMR (DMSO-d_6) δ 2.90 (6H, s), 3.35–3.60 (2H, m), 3.62–3.75 (1H, m), 3.85–4.15 (2H, m), 4.40–4.60 (2H, m), 5.44–5.58 (1H, m), 6.72–6.85 (2H, m), 7.24–7.36 (2H, m), 7.44–7.53 (3H, m), 7.58–7.67 (2H, m).

Methyl *trans*-4-[4-nitro-1-(phenylmethyl)-3-pyrrolidinyl]benzoate (19m): IR ($CHCl_3$) 1285, 1553, 1721, 2976 cm^{-1}; MS *m/z* (relative intensity) 341 (M + 1, 100), 294 (24), 325 (3); ^1H NMR ($CDCl_3$) δ 2.71 (1H, dd, *J* = 6.9, 9.4 Hz), 3.17 (1H, dd, *J* = 7.8, 10.9 Hz), 3.27 (1H, t, *J* = 8.6 Hz), 3.38 (1 H, dd, *J* = 4.3, 10.9 Hz), 3.72 (2H, dd, *J* = 13.0, 15.8 Hz), 3.91 (3H, s), 4.07 (1H, dd, *J* = 7.2, 12.5 Hz), 4.89–4.96 (1H, m), 7.25–7.35 (5H, m), 7.38 (2H, d, *J* = 8.4 Hz), 8.01 (2H, d, *J* = 8.4 Hz).

***trans*-3-Cyclopropyl-4-nitro-1-(phenylmethyl)pyrrolidine (19o)**: IR (LF) 1349, 1371, 1454, 1496, 1548 cm^{-1}; MS *m/z* (relative intensity) 247 (M + 1, 13), 246 (66), 200 (51), 199 (54), 170 (15), 158 (19), 91 (100); ^1H NMR ($CDCl_3$) δ 0.12–0.21 (1H, m), 0.23–0.38 (1H, m), 0.53 (2H, dd, J = 19.3, 11.4 Hz), 0.81–0.97 (1H, m), 2.12–2.26 (1H, m), 2.31–2.38 (1H, m), 2.89 (1H, dd, J = 11.0, 7.5 Hz), 3.03 (1H, dist. t, J = 8.0, 8.4 Hz), 3.29 (1H, dd, J = 3.6, 11.0 Hz), 3.64 (2H, AB quartet, J_{AB} = 13.1 Hz), 4.73–4.80 (1H, m), 7.23–7.32 (5H, m).

Ethyl [3α,4β(R^*)]-2-[4-nitro-1-(phenylmethyl)-3-pyrrolidinyl]cyclopropanecarboxylate (19p): IR (LF) 1182, 1205, 1269, 1343, 1371, 1454, 1550, 1723 cm^{-1}; MS *m/z* (relative intensity) 319 (M + 1, 100), 272 (48), 134 (31), 91 (60); ^1H NMR (DMSO-d_6) δ 0.90–1.08 (2H, m), 1.12–1.21 (3H, m), 1.46–1.58 (1H, m), 1.59–1.71 (1H, m), 2.16 (1H, dd, J = 8.5, 19.0 Hz), 2.26–2.38 (1H, m), 2.76 (1H, dd, J = 7.3, 11.2 Hz), 2.99 (1H, dd, J = 8.3, 16.3 Hz), 3.25–3.37 (1H, m), 3.59 (2H, s), 3.99–4.11 (2H, m), 4.98–5.07 (1H, m), 7.20–7.40 (5H, m).

***trans*-4-Phenyl-1-(phenylmethyl)-3-pyrrolidinecarbonitrile hydrochloride (20a)**: IR (KBr) 702, 765, 1457, 2243 cm^{-1}; MS *m/z* (relative intensity) 263 (M + 1, 100), 185 (4), 133 (19), 91 (23); ^1H NMR (DMSO-d_6) δ 3.40–3.58 (2H, m), 3.60–4.10 (4H, m), 4.40–4.60 (2H, m), 7.35–7.55 (8H, m), 7.60–7.70 (2H, m).

***trans*-4-(3-Cyanophenyl)-1-(phenylmethyl)-3-pyrrolidinecarbonitrile hydrochloride (20d)**: IR (KBr) 1486, 2230, 2251, 2569, 3455 cm^{-1}; MS *m/z* (relative intensity) 288 (M + 1, 100), 210 (3), 133 (6), 91 (13); ^1H NMR (DMSO-d_6) δ 3.30–4.20 (6H, m), 4.33–4.60 (2H, m), 7.40–7.50 (3H, m), 7.55–7.72 (3H, m), 7.80–7.95 (2H, m), 8.02–8.15 (1H, bs).

***cis*-4-(4-Nitrophenyl)-1-(phenylmethyl)-3-pyrrolidinecarbonitrile hydrochloride (20j)**: IR (KBr) 702, 1458, 1525, 1609 cm^{-1}; MS *m/z* (relative intensity) 308 (M + 1, 100), 278 (45), 133 (27), 91 (25); ^1H NMR (DMSO-d_6) δ 3.60–4.00 (4H, m), 4.10–4.35 (2H, m), 4.48–4.62 (2H, m), 7.40–7.52 (3H, m), 7.62–7.80 (4H, m), 8.22–8.32 (2H, m).

***trans*-4-(4-Nitrophenyl)-1-(phenylmethyl)-3-pyrrolidinecarbonitrile hydrochloride (20k)**: IR (KBr) 699, 704, 1349, 1522, 1601 cm^{-1}; MS *m/z* (relative intensity) 308 (M + 1, 100), 278 (42), 133 (32), 91 (31); ^1H NMR (DMSO-d_6) δ 3.70–4.20 (4H, m), 4.45–4.65 (2H, m), 7.38–7.50 (3H, m), 7.60–7.75 (2H, m), 7.80–7.92 (2H, m), 8.22–8.35 (2H, m).

***trans*-4-(2-Furanyl)-1-(phenylmethyl)-3-pyrrolidinecarbonitrile (20n)**: IR (neat) 1454, 1507, 2242, 2806 cm^{-1}; MS *m/z* (relative intensity) 253 (M + 1, 100), 175 (3), 133 (10), 91 (9); ^1H NMR ($CDCl_3$) δ 2.74 (1H, dd, J = 2.0, 7.5 Hz), 2.95–3.22 (4H, m), 3.68–3.83 (3H, m), 6.19 (1H, d, J = 3.3 Hz), 6.35 (1H, d, J = 3.3 Hz), 7.29–7.42 (6H, m).

1,1-Dimethylethyl *cis*-[4-(2-Methoxyphenyl)-1-(phenylmethyl)-3-pyrrolidinyl]carbamate (21b). Method B. Diphenyl phosphorazidate (4.40 g, 16 mmol) was added dropwise to a stirred suspension of pyrrolidinecarboxylic acid **18b** (4.81 g, 15 mmol) and CuI (30 mg, 0.2 mmol) in a mixture of dry t-BuOH (65 mL) and dioxane (15 mL). The suspension was heated at reflux under N_2 for 26 h, allowed to cool to room temperature, diluted with $CHCl_3$, and washed successively with saturated $NaHCO_3$ and brine. The organic layer was dried, filtered through a short pad of Florisil, and concentrated. The solid that crystallized was filtered, washed with hexanes, and dried *in vacuo* to give the title compound (2.26 g). The filtrate and washings were concentrated and chromatographed (8:1 hexanes/i-PrOH) to afford a second crop of product (1.5 g, 63% combined yield): MS *m/z* (relative intensity) 383 (M + 1, 15), 327 (61), 265 (74), 91 (95); ^1H NMR ($CDCl_3$) δ 1.20 (9H, s), 2.50–2.60 (1H, m), 2.72–2.88 (1H, m), 2.90–3.05 (2H, m), 3.68 (2H, m), 3.79 (3H, s), 4.38–4.66 (2H, m), 6.81–6.93 (2H, m), 7.17–7.35 (7H, m).

1,1-Dimethylethyl *trans*-[4-(2-methoxyphenyl)-1-(phenylmethyl)-3-pyrrolidinyl]carbamate (21c): IR (KBr) 1494, 1541, 1699, 2967 cm^{-1}; MS *m/z* (relative intensity) 383 (M + 1, 21), 265 (21), 91 (86), 57 (100); ^1H NMR ($CDCl_3$) δ 1.11 (9H, s), 2.12–2.28 (1H, m), 2.35–2.50 (1H, m), 2.60–2.72 (1H, m), 2.72–2.88 (1H, m), 3.12–3.22 (1H, m), 3.36 (2H, s), 3.50 (3H, s), 3.84–4.05 (1H, m), 5.30–5.40 (1H, m), 6.55–6.66 (2H, m), 6.88–7.03 (7H, m).

1,1-Dimethylethyl *trans*-[4-(3,4-dichlorophenyl)-1-(phenylmethyl)-3-pyrrolidinyl]carbamate (21e): IR (KBr) 1292, 1365, 1471, 1560, 1693 cm^{-1}; MS *m/z* (relative intensity) 420 (M, 1), 363 (3), 347 (5), 303 (57), 133 (22), 91 (100); ^1H NMR ($CDCl_3$) δ 1.41 (9H, s), 2.38–2.50 (1H, m), 2.50–2.75 (1H, m), 2.90–3.18 (3H, m), 3.63 (2H, s), 4.02–4.25 (1H, m), 4.88–5.02 (1H, m), 7.11–7.15 (1H, m), 7.27–7.37 (7H, m).

1,1-Dimethylethyl *trans*-[4-(4-nitrophenyl)-1-(phenylmethyl)-3-pyrrolidinyl]carbamate (21k): IR ($CHCl_3$) 1216, 1349, 1520, 1708 cm^{-1}; MS *m/z* (relative intensity) 398 (M + 1, 100), 342 (65), 280 (22); ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 2.57 (1H, dd, J = 6.0, 8.0 Hz), 2.60–2.75 (1H, m), 3.04 (1H, dd, J = 7.5, 9.7 Hz), 3.10–3.30 (2H, m), 3.68 (2H, s), 4.08–4.30 (1H, m), 4.88–5.18 (1H, m), 7.25–7.40 (5H, m), 7.46 (2H, d, J = 8.7 Hz), 8.15 (2H, d, J = 8.7 Hz).

1,1-Dimethylethyl *cis*-[4-(2-Methoxyphenyl)-3-pyrrolidinyl]carbamate (22b). Method C. A suspension of **21b** (1.14 g, 3 mmol) and 20% Pd/C (0.5 g) in MeOH (75 mL) was hydrogenated in a Parr apparatus at 50 psi for 25 min. The catalyst was filtered through a pad of Celite, the filtrate was concentrated, and the residue was triturated with Et_2O. The resulting solid was filtered, washed with Et_2O, and dried to give the title compound; IR (KBr) 1243, 1497, 1684, 2972, 3387 cm^{-1}; MS *m/z* (relative intensity) 293 (M + 1, 2), 237 (10), 219 (11), 175 (100); ^1H NMR ($CDCl_3$) δ 1.24 (9H, s), 2.98–3.16 (1H, m), 3.38 (2H, d, J = 8.5 Hz), 3.42–3.48 (1H, m), 3.69–3.82 (1H, m), 3.84 (3H, s), 4.40–4.52 (1H, m), 4.54–4.66 (1H, m), 4.68–4.82 (1H, m), 6.87–6.96 (2H, m), 7.16–7.27 (2H, m) .

1,1-Dimethylethyl *trans*-[4-(2-Methoxyphenyl)-3-pyrrolidinyl]carbamate (22c): IR (KBr) 1170, 1247, 1528, 1712, 2972 cm^{-1}; MS *m/z* (relative intensity) 293 (M + 1, 19), 265 (8), 237 (64), 175 (100); ^1H NMR ($CDCl_3$) δ 1.13 (9H, s), 2.88–3.11 (2H, m), 3.28–3.50 (3H, m), 3.60 (3H, s), 4.14–4.38 (1H, m), 5.98–6.12 (1H, m), 6.64–6.70 (2H, m), 6.97–7.04 (2H, m).

1,1-Dimethylethyl *trans*-[4-(3,4-Dichlorophenyl)-3-pyrrolidinyl]carbamate (22e). Method E. To a solution of β-trimethylsilyl chloroformate (4.12 g, 25 mmol) in THF (70 mL), at −50 °C, was added a solution of **21e** (3.51 g, 8.3 mmol) in THF (50 mL). The mixture was stirred at −50 °C for 40 min and then allowed to warm to 25 °C. The solvent was evaporated, and the crude product was chromatographed (9:1 CH_2Cl_2/MeOH) to give 1-[[[2-(trimethylsilyl)ethoxy]carbonyl]oxy]-1,1-dimethylethyl *trans*-[4-(3,4-dichlorophenyl)-3-pyrrolidinyl]carbamate (3.91 g, 98%): IR ($CHCl_3$) 1473, 1504, 1696, 2957 cm^{-1}; MS *m/z* (relative intensity) 475 (M, 3), 463 (19), 391 (100); ^1H NMR ($CDCl_3$) δ 0.97 (2H, t, J = 8.4 Hz), 1.35 (9H, s), 3.08–3.28 (2H, m), 3.38–3.55 (1H, m), 3.72–3.89 (2H, m), 4.05–4.19 (3H, m), 4.48–4.62 (1H, m), 7.08 (1H, d, J = 7.4 Hz), 7.31–7.38 (2H, m).

To a solution of the above intermediate in CH_3CN (100 mL) was added Et_4NF (3.73 g, 25 mmol). The mixture was heated at reflux for 5 h, cooled to room temperature, and diluted with EtOAc. It was then washed with saturated $NaHCO_3$, dried (K_2CO_3), and concentrated to give the title compound: IR (KBr) 1558, 1682, 2974, 3309 cm^{-1}; MS *m/z* (relative intensity) 333 (M + 2, 81), 331 (98), 277 (77), 275 (100); ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 2.85–3.10 (3H, m), 3.35–3.52 (2H, m), 4.00–4.15 (1H, m), 4.76–4.86 (1H, m), 7.12 (1H, d, J = 7.4 Hz), 7.30–7.39 (2H, m).

1,1-Dimethylethyl *trans*-[4-(4-aminophenyl)-3-pyrrolidinyl]carbamate (22k): IR ($CHCl_3$) 1165, 1282, 1520, 1684 cm^{-1}; HRMS calcd for $C_{15}H_{23}N_3O_2$ 277.1790, found 277.1800; ^1H NMR (DMSO-d_6) δ 1.38 (9H, s), 3.17–3.32 (1H, m), 3.35–3.50 (1H, m), 3.53–3.67 (2H, m), 3.70–3.82 (1H, m), 4.22–4.40 (1H, m), 7.43 (4H, s).

***trans*-4-Phenyl-3-pyrrolidinamine hydrochloride (23a)**: IR (KBr) 764, 1496, 1506, 1603 cm^{-1}; MS *m/z* (relative intensity) 163 (M + 1, 100), 146 (93), 120 (25), 104 (20); ^1H NMR (DMSO-d_6) δ 3.27 (1H, t, J = 10.2 Hz), 3.30–3.50 (1H, m), 3.67–3.83 (3H, m), 3.90–4.05 (1H, m), 7.33–7.48 (5H, m), 8.80–9.00 (2H, bs).

1,1-Dimethylethyl *trans*-[4-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]phenyl]-3-pyrrolidinyl]carbamate (23d). Method G. A suspension of *trans*-3-[4-nitro-1-(phenylmethyl)-3-pyrrolidinyl]benzonitrile hydrochloride, **19d** (4.97 g, 14.5 mmol), and Raney nickel (2.0 g) in MeOH saturated with ammonia (100 mL) was hydrogenated in a Parr apparatus at 50 psi for 20 h. The suspension was filtered through a pad of Celite, the filtrate was concentrated, and the oily residue was chromatographed (75:25:5 $CHCl_3$/MeOH/concentrated NH_3) to give *trans*-4-[3-(aminomethyl)phenyl]-1-(phenylmethyl)-3-pyrrolidinamine (2.41 g, 59%): IR ($CHCl_3$) 1518, 1623, 2796, 2919,

3380 cm^{-1}; MS m/z (relative intensity) 282 (M + 1, 100), 265 (11), 204 (2), 149 (4); ^{1}H NMR ($CDCl_3$) δ 2.54–2.67 (2H, m), 2.85–3.03 (2H, m), 3.11 (1H, t, J = 8.5 Hz), 3.42–3.54 (1H, m), 3.62 (1H, d, J = 12.9 Hz), 3.70 (1H, d, J = 12.9 Hz), 7.11–7.38 (9H, m).

Method H. To a solution of the above compound (2.30 g, 8.2 mmol) and Et_3N (2.23 g, 22 mmol) in CH_2Cl_2 (150 mL) was added dropwise, over a 20-min period, a solution of di-*tert*-butyl dicarbonate (4.37 g, 20 mmol) in CH_2Cl_2 (100 mL). The solution was stirred at room temperature for an additional 3 h and concentrated, and the residue was chromatographed (90:10 CH_2Cl_2/MeOH) to give 1,1-dimethylethyl *trans*-[4-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]phenyl]-1-(phenylmethyl)-3-pyrrolidinyl]carbamate (3.61 g, 91%): IR (KBr) 1525, 1700, 2977, 3360 cm^{-1}; MS m/z (relative intensity) 482 (M + 1, 100), 426 (48), 382 (19), 370 (49); ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.53 (9H, s), 2.42 (1H, t, J = 8.6 Hz), 2.70–2.82 (1H, m), 2.91 (1H, dd, J = 7.0, 9.5 Hz), 3.05 (1H, dd, J = 7.3, 13.4 Hz), 3.17 (1H, t, J = 9.2 Hz), 3.63 (2H, s), 4.19–4.23 (1H, m), 4.28 (2H, d, J = 6.1 Hz), 4.78–4.88 (1H, m, NH), 4.90–5.02 (1H, m, NH), 7.10–7.36 (9H, m).

Removal of the benzyl protecting group according to method C afforded the title compound: IR (KBr) 1558, 1695, 1700, 2977 cm^{-1}; MS m/z (relative intensity) 392 (M + 1, 68), 336 (47), 280 (100), 236 (50), 218 (24); ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 3.04–3.98 (2H, m), 3.34–3.48 (1H, m), 3.72–3.97 (2H, m), 4.15–4.25 (1H, m), 4.28 (2H, d, J = 5.2 Hz), 4.68–4.80 (1H, m, NH), 4.85–5.00 (1H, m, NH), 7.12–7.40 (4H, m).

***trans*-4-[4-(1-Methylethyl)phenyl]-3-pyrrolidinamine hydrochloride (23f)**: IR (KBr) 1516, 1548, 1609, 2959 cm^{-1}; MS m/z (relative intensity) 205 (M + 1, 100), 188 (83), 146 (48), 131 (26); ^{1}H NMR (DMSO-d_6) δ 1.23 (6H, d, J = 7.0 Hz), 2.89 (1H, quintet, J = 7.0 Hz), 3.10–3.25 (2H, m), 3.37 (1H, t, J = 11.0 Hz), 3.60–3.70 (2H, m), 3.74 (1H, dd, J = 8.2, 11.0 Hz), 5.20–5.60 (2H, bs), 7.23 (4H, s).

***trans*-4-(4-Fluorophenyl)-3-pyrrolidinamine hydrochloride (23g)**: IR (KBr) 1229, 1515, 1590, 1607 cm^{-1}; MS m/z (relative intensity) 181 (M + 1, 100), 164 (86), 135 (12), 122 (16); ^{1}H NMR (DMSO-d_6) δ 3.23 (1H, t, J = 9.3 Hz), 3.30–3.50 (2H, m), 3.65–3.82 (3H, m), 3.96 (1H, q, J = 7.4 Hz), 7.25 (2H, t, J = 8.8 Hz), 7.52 (2H, dd, J = 5.4, 8.8 Hz).

***trans*-4-(4-Amino-3-pyrrolidinyl)phenol hydrochloride (23h)**: IR (KBr) 1235, 1455, 1493, 1520 cm^{-1}; MS m/z (relative intensity) 179 (M + 1, 100), 162 (100), 150 (5), 133 (13); ^{1}H NMR (DMSO-d_6) δ 3.16 (1H, t, J = 10.5 Hz), 3.30–3.40 (1H, m), 3.48–3.60 (1H, m), 3.67–3.75 (2H, m), 3.80–3.88 (1H, m), 6.79 (2H, d, J = 8.5 Hz), 7.23 (2H, d, J = 8.6 Hz), 8.73 (2H, bs), 9.59 (1H, s).

***trans*-4-(Methoxyphenyl)-3-pyrrolidinamine hydrochloride (23i)**: IR ($CHCl_3$) 1035, 1097, 1516, 1612 cm^{-1}; MS m/z (relative intensity) 193 (M + 1, 57), 176 (70), 147 (20), 134 (100); ^{1}H NMR (DMSO-d_6) δ 3.02–3.20 (2H, m), 3.34 (1H, t, J = 11.0 Hz), 3.53–3.70 (2H, m), 3.72–3.78 (1H, m), 3.79 (3H, s), 6.89 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz).

***trans*-4-[4-(Dimethylamino)phenyl]-3-pyrrolidinamine hydrochloride (23l)**: IR (KBr) 1352, 1526, 1615 cm^{-1}; MS m/z (relative intensity) 206 (M + 1, 46), 189 (83), 160 (24), 147 (100); ^{1}H NMR (DMSO-d_6) δ 2.87 (6H, s), 3.02–3.14 (2H, m), 3.18–3.24 (1H, m), 3.45–3.62 (3H, m), 6.72 (2H, d, J = 8.7 Hz), 7.18 (2H, d, J = 8.7 Hz).

Methyl *trans*-4-(4-aminopyrrolidinyl)benzoate hydrochloride (23m): IR ($CHCl_3$) 1286, 1719, 2930, 2973 cm^{-1}; MS m/z (relative intensity) 221 (M + 1, 100), 204 (49), 189 (10), 163 (19); ^{1}H NMR (DMSO-d_6) δ 2.76 (1H, dd, J = 6.5, 11.1 Hz), 2.93 (1H, dd, J = 8.8, 19.2 Hz), 3.03 (1H, dd, J = 7.2, 14.8 Hz), 3.20 (1H, dd, J = 6.7, 11.1 Hz), 3.35–3.49 (2H, m), 3.85 (3H, s), 7.46 (2H, d, J = 8.2 Hz), 7.91 (2H, d, J = 8.2 Hz).

***trans*-4-Cyclopropyl-3-pyrrolidinamine (23o). Method D.** To a suspension of **19o** (17.92 g, 73 mmol) and 10% Pd/C (1.00 g) in MeOH (250 mL) was added dropwise a solution of ammonium formate (18.92 g, 300 mmol) in water (50 mL). The resulting black suspension was heated at gentle reflux for 1.5 h. It was then allowed to cool to room temperature and filtered, and the filtrate was concentrated. The residue was chromatographed (75:25:5 $CHCl_3$/MeOH/concentrated NH_3) to give the title compound (1.26 g, 14%) as a light orange oil; MS m/z (relative intensity) 127 (M + 1, 11), 126 (6), 96 (12), 84 (100); ^{1}H NMR (DMSO-d_6) δ −0.03 to 0.08 (1H, m), 0.17–0.49 (3H, m), 0.50–0.70 (1H, m), 0.95–1.06 (1H, m), 2.36–2.51 (2H, m), 2.82–3.06 (3H, m).

Ethyl [3α,4β(*R)]-2-(4-amino-3-pyrrolidinyl)cyclopropanecarboxylate (23p)**: IR (LF) 1182, 1206, 1372, 1413, 1714 cm^{-1}; MS m/z (relative intensity) 199 (M + 1, 77), 156 (100), 139 (53), 111 (39), 82 (65), 67 (72); ^{1}H NMR (DMSO-d_6) δ 0.73–0.81 (1H, m), 0.86–1.01 (2H, m), 1.15–1.20 (4H, m), 1.39–1.45 (1H, m), 1.58–1.66 (1H, m), 2.32–2.50 (2H, m), 2.83–3.02 (3H, m), 4.00–4.08 (2H, m).

1,1-Dimethylethyl *trans*-[[4-Phenyl-1-(phenylmethyl)-3-pyrrolidinyl]methyl]carbamate (24a). Method F. To a solution of **20a** (11.23 g, 42.8 mmol) in dry THF (200 mL) at 0 °C was added $LiAlH_4$ (1.90 g, 50 mmol) in small portions. The cooling bath was removed, and the suspension was stirred at 25 °C for 18 h and at reflux for an additional 5 h. It was then allowed to cool to room temperature and quenched by careful addition of water (2 mL), 50% NaOH (2 mL), and again water (7 mL). The mixture was filtered through a pad of Celite and the filtrate was dried (K_2CO_3) and concentrated. The oily residue was dissolved in a small volume of EtOAc and the solution treated with concentrated HCl and poured onto an excess of Et_2O. A small amount of a white solid that precipitated out of the solution was filtered and discarded. The filtrated was concentrated and chromatographed (75:25 CH_2Cl_2/MeOH) to give *trans*-4-phenyl-1-(phenylmethyl)-3-pyrrolidinemethanamine as its hydrochloride salt (14.50 g, 100%): IR (KBr) 700, 1494, 2926, 3400 cm^{-1}; MS m/z (relative intensity) 267 (M + 1, 100), 249 (55), 236 (10), 91 (67); ^{1}H NMR (CD_3OD) δ 3.13 (1H, d, J = 11.6 Hz), 3.24–3.38 (1H, m), 3.48 (2H, s), 3.52–3.75 (2H, m), 3.80–4.02 (2H, m), 4.67 (2H, s), 7.44–7. 70 (8H, m), 7.72–7.98 (2H, m).

The above intermediate was protected according to method H to give the title compound (13.70 g, 100%) as a white solid: IR (KBr) 1525, 1680, 3382 cm^{-1}; MS m/z (relative intensity) 367 (M + 1, 100), 311 (66), 293 (21), 267 (26); ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s), 2.35–2.48 (1H, m), 2.50–2.70 (2H, m), 2.81 (1H, dd, J = 8.3, 8.8 Hz), 2.98–3.26 (4H, m), 3.62 (1H, d, J = 2.9 Hz), 3.69 (1H, d, J = 12.9 Hz), 5.02–5.14 (1H, m, NH), 7.15–7.40 (10H, m).

1,1-Dimethylethyl *trans*-[[3-[4-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-1-(phenylmethyl)-3-pyrrolidinyl]-phenyl]methyl]carbamate (24d): IR (KBr) 1513, 1522, 1699, 1707, 3005 cm^{-1}; MS m/z (relative intensity) 496 (M + 1, 100), 440 (39), 396 (30), 384 (28); ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s), 1.47 (9H, s), 2.33–2.42 (1H, m), 2.43–2.62 (2H, m), 2.79 (1H, dd, J = 8.2, 8.9 Hz), 2.96–3.24 (4H, m), 3.64 (2H, q, J = 2.9 Hz), 4.28 (2H, d, J = 5.8 Hz), 4.80–4.92 (1H, m, NH), 5.08–5.15 (1H, m, NH), 7.10–7.69 (9H, m).

1,1-Dimethylethyl *cis*-[[4-(4-aminophenyl)-1-(phenylmethyl)-3-pyrrolidinyl]methyl]carbamate (24j): IR (KBr) 1517, 1701, 3364, 3432 cm^{-1}; MS m/z (relative intensity) 382 (M + 1, 51), 326 (58), 251 (56), 91 (100); ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s), 2.46–3.04 (6H, m), 3.08 (1H, t, J = 8.4 Hz), 3.42–3.55 (1H, m), 3.68–3.83 (2H, m), 4.45–4.55 (1H, m, NH), 6.62 (2H, d, J = 8.2 Hz), 7.05 (2H, d, J = 8.2 Hz), 7.30–7.42 (5H, m).

1,1-Dimethylethyl *trans*-[[4-(4-aminophenyl)-1-(phenylmethyl)-3-pyrrolidinyl]methyl]carbamate (24k): IR (KBr) 1518, 1699 cm^{-1}; MS m/z (relative intensity) 382 (M + 1, 35), 326 (45), 251 (45), 91 (100); ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.28–2.42 (1H, m), 2.43–2.52 (1H, m), 2.59–2.68 (1H, m), 3.05–3.28 (3H, m), 3.61 (1H, d, J = 13.1 Hz), 3.67 (1H, d, J = 12.8 Hz), 5.06–5.18 (1H, m, NH), 6.63 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.20–7.37 (5H, m).

1,1-Dimethylethyl *trans*-[[4-(2-furanyl)-1-(phenylmethyl)-3-pyrrolidinyl]methyl]carbamate (24n): IR (neat) 1366, 1688, 1708, 2976 cm^{-1}; MS m/z (relative intensity) 357 (M + 1, 100), 301 (79), 283 (15), 257 (11); ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 2.46–2.68 (2H, m), 2.70–2.84 (2H, m), 3.10–3.30 (4H, m), 3.64 (1H, d, J = 12.8 Hz), 3.73 (1H, d, J = 12.8 Hz), 5.20–5.33 (1H, m, NH), 6.05 (1H, d, J = 3.0 Hz), 6.27 (1H, t, J = 2.4 Hz), 7.22–7.41 (6H, m).

1,1-Dimethylethyl *trans*-[(4-phenyl-3-pyrrolidinyl)methyl]carbamate (25a): IR ($CHCl_3$) 702, 1167, 1508, 1708 cm^{-1}; MS m/z (relative intensity) 277 (M + 1, 55), 221 (100), 177 (38); ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.32–2.46 (1H, m), 2.83–2.92 (2H, m), 2.98–3.09 (2H, m), 3.13–3.25 (2H, m), 3.33 (1H, dd, J = 8.0, 11.0 Hz), 3.44 (1H, dd, J = 8.0, 10.4 Hz), 4.53–4.68 (1H, m, NH), 7.18–7.34 (5H, m).

1,1-Dimethylethyl *trans*-[[4-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]phenyl]-3-pyrrolidinyl]methyl]carbamate (25d): IR (KBr) 1446, 1631, 1715 cm^{-1}; MS *m/z* (relative intensity) 406 (M, 3), 292 (10), 276 (28), 57 (100); ^{1}H NMR ($CDCl_3$) δ 1.40 (9H, s), 1.46 (9H, s), 2.30–2.44 (1H, m), 2.83–2.99 (3H, m), 3.05–3.20 (2H, m), 3.31 (1H, dd, J = 7.9, 11.0 Hz), 3.42 (1H, dd, J = 7.9, 10.4 Hz), 4.88–5.02 (1H, bs, NH), 7.12–7.22 (3H, m), 7.24–7.30 (1H, m).

1,1-Dimethylethyl *cis*-[[4-(4-aminophenyl)-3-pyrrolidinyl]methyl]carbamate (25j): IR (KBr) 1705, 1700, 1521 cm^{-1}; MS *m/z* (relative intensity) 292 (M + 1, 80), 236 (100), 192 (14); ^{1}H NMR ($CDCl_3$) δ 1.14 (9H, s), 2.41–2.58 (2H, m), 2.60–2.72 (1H, m), 3.00–3.28 (3H, m), 3.30–3.48 (2H, m), 3.70–3.90 (2H, m, NH_2), 5.32–5.45 (1H, m, NH), 6.38 (2H, d, J = 8.3 Hz), 6.69 (2H, d, J = 8.3 Hz).

1,1-Dimethylethyl *trans*-[[4-(4-aminophenyl)-3-pyrrolidinyl]methyl]carbamate (25k): ^{1}H NMR ($CDCl_3$) δ 1.36 (9H, s), 2.38–2.65 (1H, m), 2.88–3.34 (5H, m), 3.54–3.78 (2H, m), 4.98–5.18 (1H, m, NH), 6.63 (2H, d, J = 8.2 Hz), 7.01 (2H, d, J = 8.2 Hz).

1,1-Dimethylethyl *trans*-[[4-(2-furanyl)-3-pyrrolidinyl]methyl]carbamate (25n): IR ($CHCl_3$) 1508, 1708, 2980, 3455 cm^{-1}; MS *m/z* (relative intensity) 267 (M + 1, 24), 211 (100), 193 (8); ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s), 2.40–2.84 (2H, m), 2.95–3.60 (6H, m), 4.88–5.02 (1H, m, NH), 6.10 (1H, d, J = 3.0 Hz), 6.26–6.31 (1H, m), 7.27–7.34 (1H, m).

trans-7-(3-Amino-4-cyclopropyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (30-0o). **Coupling Procedure 1.** A suspension of 6,7-difluoroquinolone **26** (1.88 g, 7.1 mmol), pyrrolidine **23o** (1.07 g, 8.5 mmol), and i-Pr_2EtN (3.88 g, 30.0 mmol) in CH_3CN (60 mL) was heated at reflux for 6 h. Upon cooling, the solids were filtered, washed with cold CH_3CN and Et_2O, and triturated with boiling i-PrOH/MeOH (5:1) to give the title compound (1.50 g, 56%): IR (KBr) 1471, 1511, 1630, 1719 cm^{-1}; MS *m/z* (relative intensity) 372 (M + 1, 12), 371 (19), 327 (100), 259 (22); ^{1}H NMR (TFA-*d*) δ 0.38–0.48 (2H, m), 0.67–0.82 (2H, m), 0.83–1.00 (1H, m), 1.37–1.43 (2H, m), 1.60–1.72 (2H, m), 2.04–2.18 (1H, m), 3.82–4.07 (2H, m), 4.21–4.39 (3H, m), 4.42–4.58 (1H, m), 7.43 (1H, d, J = 6.8 Hz), 8.19 (1H, d, J = 13.3 Hz), 9.23 (1H, s).

[3α,4β(*R**)]-7-[3-Amino-4-[2-(ethoxycarbonyl)cyclopropyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (30-0p): IR (KBr) 1472, 1510, 1630, 1719 cm^{-1}; MS *m/z* (relative intensity) 443 (M, 24), 399 (74), 259 (55), 215 (24), 84 (55), 66 (100); ^{1}H NMR (DMSO-d_6) δ 0.85–1.40 (10H, m), 1.50–1.68 (1H, m), 1.69–1.80 (1H, m), 3.15–3.50 (3H, m), 3.67–3.88 (3H, m), 4.00–4.10 (2H, m), 7.01 (1H, d, J = 7.3 Hz), 7.76 (1H, d, J = 14.0 Hz), 8.55 (1H, s).

trans-7-(3-Amino-4-phenyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (31-0a). **Coupling Procedure 2.** A suspension of 7-chloronaphthyridine **27** (0.79 g, 2.8 mmol), pyrrolidine **23a** (0.98 g, 3.7 mmol), and Et_3N (0.91 g, 9.0 mmol) in acetonitrile (60 mL) was heated at reflux for *ca.* 15 h, cooled to room temperature, and concentrated. The residue was taken up in CH_2Cl_2 (*ca.* 20 mL) and treated with an excess of Et_2O, and the white solid that precipitated out ($Et_3NH^+Cl^-$) was removed by filtration. The filtrate was concentrated and the crude product recrystallized from MeOH/Et_2O to give the *N*-Boc-protected derivative of the title compound (0.63 g, 41%).

Deprotection Procedure. Anhydrous HCl(g) was bubbled through a solution of the above compound (0.55 g, 1.1 mmol) in CH_2Cl_2 (150 mL) for 1.5 h. The reaction vessel was then stopped and the mixture stirred at room temperature overnight. Upon concentration, the residue was dissolved in a small volume of MeOH and the solution poured onto Et_2O; a white solid precipitated, which was filtered, washed with Et_2O, and dried *in vacuo* to afford the title compound (0.36 g, 75%): IR (KBr) 1455, 1496, 1506, 1630, 1718 cm^{-1}; MS *m/z* (relative intensity) 409 (M + 1, 100), 391 (25), 365 (6), 323 (12); ^{1}H NMR (DMSO-d_6) δ 1.03–1.28 (4H, m), 3.60–3.73 (1H, m), 3.74–3.88 (1H, m), 3.90–4.18 (3H, m), 4.20–4.58 (2H, m), 7.30–7.50 (5H, m), 8.07 (1H, d, J = 12.6 Hz), 8.59 (1H, s).

cis-7-[3-Amino-4-(2-methoxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0b): IR (KBr) 1630, 1506, 1496, 1456, 1448 cm^{-1}; MS *m/z* (relative intensity) 439 (M + 1, 6), 395 (12), 260 (33), 134 (100); ^{1}H NMR (DMSO-d_6) δ 1.05–1.30 (4H, m), 3.65–3.80 (2H, m), 3.87 (3H, s), 3.98–4.43 (5H, m), 7.02 (1H, dd, J = 7.4, 7.6 Hz), 7.11 (1H, d, J = 8.2 Hz), 7.33–7.41 (2H, m), 8.07 (1H, d, J = 12.6 Hz), 8.61 (1H, s).

trans-7-[3-Amino-4-(2-methoxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0c): IR (KBr) 1457, 1496, 1506, 1631 cm^{-1}; MS *m/z* (relative intensity) 439 (M + 1, 19); ^{1}H NMR (DMSO-d_6) δ 1.05–1.25 (4H, m), 3.62–3.74 (1H, m), 3.85 (3H, s), 3.90–4.05 (3H, m), 4.07–4.20 (1H, m), 4.22–4.48 (2H, m), 6.93–7.04 (1H, m), 7.09 (1H, d, J = 8.3 Hz), 7.34 (2H, t, J = 7.8 Hz), 8.07 (1H, d, J = 12.5 Hz), 8.60 (1H, s).

trans-7-[4-[3-(Aminomethyl)phenyl]-3-amino-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0d): IR (KBr) 1458, 1632, 1701 cm^{-1}; MS *m/z* (relative intensity) 438 (M + 1, 55), 407 (4), 189 (20), 125 (100); ^{1}H NMR (TFA-*d*) δ 1.18–1.40 (2H, m), 1.42–1.71 (2H, m), 4.02–4.32 (2H, m), 4.35–4.74 (5H, m), 4.76–5.05 (2H, m), 7.48–7.70 (3H, m), 7.78–7.96 (1H, m), 8.14–8.32 (1H, m), 9.18–9.28 (1H, m).

trans-7-[3-Amino-4-(3,4-dichlorophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0e): IR (KBr) 1357, 1449, 1506, 1630, 1719 cm^{-1}; MS *m/z* (relative intensity) 479 (M + 2, 74), 477 (M, 100), 459 (7), 432 (15); ^{1}H NMR (DMSO-d_6) δ 0.93–1.28 (4H, m), 3.57–4.24 (5H, m), 4.24–4.58 (2H, m), 7.40–7.57 (1H, m), 7.60–7.68 (1H, m), 7.68–7.88 (1H, m), 8.06 (1H, d, J = 12.2 Hz), 8.59 (1H, s).

trans-7-[3-Amino-4-[4-(1-methylethyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0f): IR (KBr) 1449, 1507, 1630, 1724, 2960 cm^{-1}; MS *m/z* (relative intensity) 451 (M + 1, 100), 433 (45), 416 (13), 406 (12); ^{1}H NMR (DMSO-d_6) δ 1.02–1.38 (4H, m), 1.21 (6H, d, J = 6.8 Hz), 2.80–2.95 (1H, m), 3.60–4.15 (4H, m), 4.25–4.55 (2H, m), 7.20–7.45 (4H, m), 8.03 (1H, d, J = 12.9 Hz), 8.59 (1H, s).

trans-7-[3-Amino-4-(4-fluorophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0g): IR (KBr) 1455, 1511, 1632, 1719, 1724 cm^{-1}; MS *m/z* (relative intensity) 427 (M + 1, 10), 181 (4), 164 (4), 115 (100); ^{1}H NMR (DMSO-d_6) δ 1.03–1.34 (4H, m), 3.62–3.80 (2H, m), 3.82–3.98 (2H, m), 4.00–4.18 (1H, m), 4.25–4.50 (2H, m), 7.26 (2H, dd, J = 8.5, 9.2 Hz), 7.51 (2H, dd, J = 5.5, 8.6 Hz), 8.07 (1H, d, J = 12.2 Hz), 8.61 (1H, s).

trans-7-[3-Amino-4-(4-hydroxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0h): MS *m/z* (relative intensity) 425 (M + 1, 5), 381 (3), 115 (100); ^{1}H NMR (DMSO-d_6) δ 1.01–1.32 (4H, m), 3.50–3.75 (2H, m), 3.80–4.10 (3H, m), 4.25–4.50 (2H, m), 6.84 (2H, d, J = 8.3 Hz), 7.25 (2H, d, J = 8.3 Hz), 8.61 (1H, s).

trans-7-[3-Amino-4-(4-methoxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0i): IR (KBr) 1475, 1509, 1577, 1635, 1728 cm^{-1}; MS *m/z* (relative intensity) 439 (M + 1, 100), 421 (29), 395 (6), 323 (12); ^{1}H NMR (TFA-*d*) δ 1.20–1.43 (2H, m), 1.45–1.63 (2H, m), 3.95–4.20 (1H, m), 4.05 (3H, s), 4.25–4.40 (2H, m), 4.42–4.62 (2H, m), 4.65–5.05 (2H, m), 7.17 (2H, d, J = 8.3 Hz), 7.45 (2H, d, J = 8.3 Hz), 8.05 (1H, d, J = 12.8 Hz), 9.23 (1H, s).

trans-7-[3-Amino-4-(4-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0k): IR (KBr) 1453, 1507, 1633, 1719 cm^{-1}; MS *m/z* (relative intensity) 424 (M + 1, 2); ^{1}H NMR (DMSO-d_6) δ 0.98–1.29 (4H, m), 3.60–3.75 (1H, m), 3.80–4.15 (4H, m), 4.30–4.52 (2H, m), 7.36 (2H, d, J = 8.3 Hz), 7.54 (2H, d, J = 8.3 Hz), 8.07 (1H, d, J = 12.5 Hz), 8.59 (1H, s).

trans-7-[3-Amino-4-[4-(dimethylamino)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0l): IR (KBr) 1456, 1505, 1523, 1631, 1724 cm^{-1}; MS *m/z* (relative intensity) 452 (M + 1, 100), 434 (12), 147 (40); ^{1}H NMR (TFA-*d*) δ 1.22–1.41 (2H, m), 1.45–1.70 (2H, m), 3.51 (6H, s), 4.05–4.55 (3H, m), 4.55–4.75 (2H, m), 4.75–5.00 (2H, m), 7.78 (4H, s), 9.23 (1H, s).

trans-7-[3-Amino-4-[4-(methoxycarbonyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0m): MS *m/z* (relative in-

tensity) 467 (M + 1, 100), 449 (40), 423 (5); ^{1}H NMR (DMSO-d_6) δ 1.02–1.27 (4H, m), 3.62–3.74 (1H, m), 3.79–3.88 (1H, m), 3.97 (3H, s), 3.95–4.07 (2H, m), 4.08–4.24 (1H, m), 4.26–4.58 (2H, m), 7.62 (2H, d, J = 8.5 Hz), 8.02 (2H, d, J = 8.5 Hz), 8.05 (1H, d, J = 14.6 Hz), 8.61 (1H, s).

[3α,4β(*R)]-7-[3-Amino-4-[2-(ethoxycarbonyl)cyclopropyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-0p)**: MS m/z (relative intensity) 444 (M, 3), 400 (15), 218 (25), 189 (11), 44 (100); ^{1}H NMR (TFA-d) δ 1.17–1.38 (6H, m), 1.46–1.63 (3H, m), 1.77–1.88 (1H, m), 1.89–2.14 (1H, m), 2.30–2.48 (1H, m), 4.07–4.75 (8H, m), 8.21 (1H, d, J = 8.9 Hz), 9.22 (1H, s).

***trans*-7-(3-Amino-4-phenyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0a)**: IR (KBr) 1461, 1521, 1626, 1727 cm^{-1}; MS m/z (relative intensity) 426 (M + 1, 27), 408 (2), 321 (4), 115 (100); ^{1}H NMR (DMSO-d_6) δ 1.08–1.32 (4H, m), 3.57–3.65 (1H, m), 3.90–4.00 (2H, m), 4.12–4.25 (4H, m), 7.36–7.55 (5H, m), 7.80 (1H, d, J = 13.4 Hz), 8.67 (1H, s).

***trans*-7-[3-Amino-4-(2-methoxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0c)**: IR (KBr) 1458, 1496, 1522, 1627, 1725 cm^{-1}; MS m/z (relative intensity) 456 (M + 1, 3); ^{1}H NMR (DMSO-d_6) δ 1.12–1.32 (4H, m), 3.85 (3H, s), 3.78–4.02 (2H, m), 4.03–4.28 (5H, m), 6.95–7.05 (1H, m), 7.09 (1H, d, J = 8.1 Hz), 7.31–7.42 (2H, m), 7.78 (1H, d, J = 13.7 Hz), 8.64 (1H, s).

***trans*-7-[3-Amino-4-(3,4-dichlorophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0e)**: IR (KBr) 1459, 1520, 1626, 1726, 2891 cm^{-1}; MS m/z (relative intensity) 496 (M + 2, 9), 494 (M + 1, 13), 476 (5); ^{1}H NMR (TFA-d) δ 1.38–1.52 (2H, m), 1.54–1.75 (2H, m), 3.90–4.05 (1H, m), 4.27–4.74 (6H, m), 7.32 (1H, d, J = 7.9 Hz), 7.56 (2H, d, J = 7.3 Hz), 8.13 (1H, d, J = 13.0 Hz), 9.32 (1H, s).

***trans*-7-[3-Amino-4-[4-(1-methylethyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0f)**: IR (KBr) 1459, 1519, 1627, 1728, 2956 cm^{-1}; MS m/z (relative intensity) 468 (M + 1, 52), 322 (14), 277 (14); ^{1}H NMR (DMSO-d_6) δ 1.20 (6H, d, J = 6.9 Hz), 1.06–1.23 (4H, m), 2.88 (1H, septet, J = 6.9 Hz), 3.06 (1H, q, J = 8.6 Hz), 3.49–3.68 (2H, m), 3.83–3.94 (2H, m), 3.97–4.12 (2H, m), 7.26 (4H, dd, J = 8.0, 16.2 Hz), 7.70 (1H, d, J = 13.8 Hz), 8.60 (1H, s).

***trans*-7-[3-Amino-4-(4-fluorophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0g)**: IR (KBr) 1459, 1464, 1513, 1626, 1727 cm^{-1}; MS m/z (relative intensity) 444 (M + 1, 9), 181 (17), 164 (16), 115 (100); ^{1}H NMR (DMSO-d_6) δ 1.10–1.32 (4H, m), 3.54–3.68 (1H, m), 3.83–3.98 (2H, m), 4.00–4.28 (4H, m), 7.26 (2H, t, J = 8.6 Hz), 7.42–7.58 (2H, m), 7.80 (1H, d, J = 14.7 Hz), 8.67 (1H, s).

***trans*-7-[3-Amino-4-(4-hydroxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0h)**: IR (KBr) 1464, 1521, 1627, 1734 cm^{-1}; MS m/z (relative intensity) 442 (M + 1, 100), 424 (13), 322 (23), 147 (33); ^{1}H NMR (TFA-d) δ 1.38–1.65 (4H, m), 3.78–3.91 (1H, m), 4.29–4.76 (6H, m), 7.10 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 8.12 (1H, d, J = 13.4 Hz), 9.30 (1H, s).

***trans*-7-[3-Amino-4-(4-methoxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0i)**: IR (KBr) 1464, 1471, 1515, 1626, 1727 cm^{-1}; MS m/z (relative intensity) 456 (M + 1, 100), 438 (34), 395 (8); ^{1}H NMR (TFA-d) δ 1.35–1.50 (2H, m), 1.55–1.65 (2H, m), 3.80–3.95 (1H, m), 4.06 (3H, s), 4.25–4.65 (6H, m), 7.17 (2H, d, J = 8.5 Hz), 7.44 (2H, d, J = 8.5 Hz), 8.13 (1H, d, J = 12.9 Hz), 9.31 (1H, s).

***trans*-7-[3-Amino-4-(4-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0k)**: IR (KBr) 1466, 1521, 1628, 1717 cm^{-1}; MS m/z (relative intensity) 441 (M + 1, 100), 423 (24); ^{1}H NMR (DMSO-d_6) δ 1.08–1.28 (4H, m), 3.65–3.80 (2H, m), 3.80–4.25 (5H, m), 7.33 (2H, d, J = 8.2 Hz), 7.53 (2H, d, J = 8.2 Hz), 7.78 (1H, d, J = 13.7 Hz), 8.64 (1H, s).

***trans*-7-[3-Amino-4-[4-(dimethylamino)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0l)**: IR (KBr) 1376, 1458, 1538, 1626, 1728 cm^{-1}; MS m/z (relative intensity) 469 (M + 1, 100), 452 (24), 206 (63), 189 (51); ^{1}H NMR (TFA-d) δ 1.35–1.50 (2H, m), 1.52–1.68 (2H, m), 3.51 (6H, s), 4.00–4.15 (1H, m), 4.25–4.42 (1H, m), 4.45–4.80 (5H, m), 7.77 (4H, s), 8.14 (1H, d, J = 12.9 Hz), 9.32 (1H, s).

***trans*-7-[3-Amino-4-[4-(methoxycarbonyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (32-0m)**: IR (KBr) 1281, 1456, 1611, 1626, 1722 cm^{-1}; MS m/z (relative intensity) 484 (M + 1, 100), 466 (48), 423 (8); ^{1}H NMR (TFA-d) δ 1.35–1.50 (2H, m), 1.50–1.65 (2H, m), 4.12 (3H, s), 3.98–4.22 (1H, m), 4.35–4.70 (5H, m), 7.61 (2H, d, J = 8.2 Hz), 8.14 (1H, d, J = 12.9 Hz), 8.22 (2H, d, J = 8.2 Hz), 9.32 (1H, s).

***trans*-5-Amino-7-(3-amino-4-phenyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (33-0a)**: IR (KBr) 1350, 1435, 1516, 1631, 1723 cm^{-1}; MS m/z (relative intensity) 441 (M + 1, 100), 423 (66), 397 (12), 380 (11); ^{1}H NMR (DMSO-d_6) δ 1.02–1.18 (4H, m), 3.55–3.68 (1H, m), 3.85–4.23 (6H, m), 7.30–7.50 (5H, m), 8.51 (1H, s).

***trans*-5-Amino-7-[3-amino-4-(4-fluorophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (33-0g)**: IR (KBr) 1437, 1512, 1636, 1725 cm^{-1}; MS m/z (relative intensity) 459 (M + 1, 10), 181 (5), 115 (72); ^{1}H NMR (DMSO-d_6) δ 1.03–1.25 (4H, m), 3.48–3.68 (1H, m), 3.70–4.25 (6H, m), 7.26 (2H, t, J = 8.7 Hz), 7.52 (2H, dd, J = 5.6, 8.4 Hz), 8.47 (1H, s).

***trans*-5-Amino-7-[3-amino-4-(4-hydroxyphenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (33-0h)**: IR (KBr) 1352, 1436, 1517, 1631, 1727 cm^{-1}; MS m/z (relative intensity) 457 (M + 1, 100), 439 (38), 413 (10); ^{1}H NMR (TFA-d) δ 1.20–1.39 (2H, m), 1.40–1.55 (2H, m), 3.77–3.87 (1H, m), 4.18–4.62 (6H, m), 7.10 (2H, d, J = 8.3 Hz), 7.37 (2H, d, J = 8.3 Hz), 9.14 (1H, s).

***trans*-5-Amino-7-[3-amino-4-[4-(dimethylamino)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (33-0k)**: IR (KBr) 1349, 1435, 1520, 1630, 1724 cm^{-1}; MS m/z (relative intensity) 484 (M + 1, 100), 466 (15), 440 (14), 147 (88); ^{1}H NMR (TFA-d) δ 1.22–1.38 (2H, m), 1.41–1.57 (2H, m), 3.50 (6H, s), 4.02–4.16 (1H, m), 4.19–4.38 (2H, m), 4.41–4.68 (4H, m), 7.76 (4H, s), 9.15 (1H, s).

***trans*-7-[3-(Aminomethyl)-4-phenyl-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-1a)**: IR (KBr) 1526, 1637, 3420 cm^{-1}; MS m/z (relative intensity) 423 (M + 1, 100), 405 (3), 378 (5); ^{1}H NMR (TFA-d) δ 1.10–1.72 (4H, m), 3.14–3.66 (4H, m), 3.92–4.35 (2H, m), 4.58–5.00 (2H, m), 7.37–7.60 (5H, m), 8.05–8.14 (1H, m), 9.17 (1H, s).

***trans*-7-[3-(Aminomethyl)-4-[3-(aminomethyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-1d)**: IR (KBr) 1449, 1457, 1653, 1701, 1717 cm^{-1}; MS m/z (relative intensity) 451 (M, 4), 421 (12), 377 (6), 280 (11), 206 (100); ^{1}H NMR (TFA-d) δ 1.20–1.29 (2H, m), 1.40–1.52 (1H, m), 1.55–1.63 (1H, m), 3.30–3.60 (4H, m), 3.90–4.27 (3H, m), 4.51 (2H, bs), 4.59–4.79 (1H, m), 4.81–5.00 (1H, m), 7.58 (3H, bs), 7.81 (1H, s), 8.13–8.17 (1H, m), 9.16 (1H, s).

***cis*-7-[3-(Aminomethyl)-4-(4-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-1j)**: IR (KBr) 1458, 1617, 1631, 1652, 1700 cm^{-1}; MS m/z (relative intensity) 438 (M + 1, 100), 394 (28), 264 (23), 217 (56), 163 (67); ^{1}H NMR (TFA-d) δ 1.20–1.80 (4H, m), 2.90–3.70 (2H, m), 4.00–5.10 (7H, m), 7.40–7.90 (4H, m), 8.18–8.30 (1H, m), 9.23 (1H, bs), 11.39 (1H, bs).

***trans*-7-[3-(Aminomethyl)-4-(4-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-1k)**: IR (KBr) 1450, 1457, 1506, 1632, 1718 cm^{-1}; MS m/z (relative intensity) 438 (M + 1, 18), 437 (38), 300 (30), 283 (52), 277 (74), 145 (77), 119 (100); ^{1}H NMR (TFA-d) δ 1.19–1.34 (2H, m), 1.39–1.49 (1H, m), 1.57–1.66 (1H, m), 3.20–3.72 (4H, m), 3.90–4.30 (3H, m), 4.55–5.10 (2H, m), 7.70 (4H, bs), 8.13–8.22 (1H, m), 9.17 (1H, bs), 11.45 (1H, bs).

***trans*-7-[3-(Aminomethyl)-4-(2-furanyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (31-1n)**: IR (KBr) 1630, 1718, 1722 cm^{-1}; MS m/z (relative intensity) 413 (M + 1, 100), 395 (8), 368 (9); ^{1}H NMR (DMSO-d_6) δ 1.00–1.34 (4H, m), 2.69–2.88 (1H, m), 2.90–3.08 (2H, m), 3.46–3.62 (1H, m), 3.65–3.81 (1H, m), 3.65–3.81

(2H, m), 3.83–3.98 (1H, m), 4.15–4.40 (2H, m), 6.46 (2H, dist. d, J = 3.1 Hz), 7.69 (1H, s), 8.02 (1H, d, J = 12.4 Hz), 8.08–8.30 (3H, bs, NH_3^+), 8.58 (1H, s).

***trans*-7-[3-(Aminomethyl)-4-phenyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (32-1a)**: IR (KBr) 1626, 1719, 1728, 3428 cm^{-1}; MS m/z (relative intensity) 440 (M + 1, 100), 422 (9), 274 (4); ^{1}H NMR (TFA-d) δ 1.25–1.68 (4H, m), 3.04–3.23 (1H, m), 3.25–4.02 (1H, m), 3.44–3.60 (2H, m), 4.14–4.32 (1H, m), 4.35–4.63 (4H, m), 7.38–7.58 (5H, m), 9.26 (1H, s).

***trans*-7-[3-(Aminomethyl)-4-[3-(aminomethyl)phenyl]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (32-1d)**: IR (KBr) 1453, 1465, 1522, 1626, 1701, 1718 cm^{-1}; MS m/z (relative intensity) 468 (M, 5), 438 (10), 274 (16), 206 (20), 129 (45), 44 (100); ^{1}H NMR (TFA-d) δ 1.30–1.60 (4H, m), 3.20–3.60 (4H, m), 4.22–4.71 (7H, m), 7.15–7.47 (3H, m), 7.72–7.85 (1H, bs), 9.26 (1H, d, J = 12.4 Hz), 9.26 (1H, s), 11.39 (1H, s).

***trans*-7-[3-(Aminomethyl)-4-(3-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (32-1k)**: IR (KBr) 1457, 1517, 1607, 1626, 1718 cm^{-1}; MS m/z (relative intensity) 454 (M, 5), 392 (3), 294 (27), 211 (18), 145 (57), 119 (100); ^{1}H NMR (DMSO-d_6) δ 1.35–1.67 (4H, m), 3.14–3.35 (1H, m), 3.42–3.58 (3H, m), 4.20–4.54 (4H, m), 4.56–4.70 (1H, m), 7.68–7.71 (4H, m), 8.08 (1H, d, J = 13.1 Hz), 9.26 (1H, s), 11.45 (1H, bs).

***trans*-7-[3-(Aminomethyl)-4-(2-furanyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (32-1n)**: IR (KBr) 1521, 1627, 1701, 1719 cm^{-1}; MS m/z (relative intensity) 430 (M + 1, 100), 412 (10), 386 (2); ^{1}H NMR (DMSO-d_6) δ 1.11–1.30 (4H, m), 2.64–2.84 (1H, m), 2.90–3.10 (2H, m), 3.48 (1H, q, J = 8.4 Hz), 3.73–3.87 (1H, m), 3.90–4.18 (4H, m), 6.43–6.48 (2H, m), 7.67 (1H, s), 7.74 (1H, d, J = 13.4 Hz), 8.10–8.35 (3H, bs, NH_3^+), 8.62 (1H, s).

***trans*-5-Amino-7-[3-(aminomethyl)-4-phenyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (33-1a)**: IR (KBr) 1516, 1633, 1718 cm^{-1}; MS m/z (relative intensity) 455 (M + 1, 100), 437 (6), 411 (2); ^{1}H NMR (TFA-d) δ 1.28–1.58 (4H, m), 3.00–3.22 (1H, m), 3.25–3.42 (1H, m), 3.44–3.59 (2H, m), 4.09–4.24 (1H, m), 4.25–4.40 (3H, m), 4.42–4.58 (1H, m), 7.35–7.56 (5H, m), 9.15 (1H, s).

***trans*-5-Amino-7-[3-(aminomethyl)-4-(4-aminophenyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid (33-1k)**: IR (KBr) 1304, 1570, 1634, 1718 cm^{-1}; MS m/z (relative intensity) 470 (M + 1, 89), 452 (30), 299 (100), 159 (33); ^{1}H NMR (TFA-d) δ 1.20–1.68 (4H, m), 3.09–3.32 (1H, m), 3.40–3.60 (3H, m), 3.78–4.13 (1H, m), 4.15–4.41 (3H, m), 4.45–4.70 (1H, m), 7.66 (4H, bs), 9.16 (1H, s), 11.50 (1H, bs).

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References

(1) A portion of this work has been presented in preliminary form: Bucsh, R. A.; Laborde, E.; Domagala, J. M.; Sesnie, J. C. Synthesis and Biological Evaluation of 7-[3-Amino-4-aryl- and 3-(aminomethyl)-4-aryl-1-pyrrolidinyl]quinolones. *23rd National Medicinal Chemistry Symposium*, Buffalo, NY, June 14-18, 1992; Abstr. 63.

(2) Reviews: (a) Andriole, V. T. *The Quinolones*; Academic Press: London, 1988. (b) Wentland, M. P. Structure-Activity Relationships of Fluoroquinolones. In *The New Generation of Quinolones*; Siporin, C., Heifetz, C. L., Domagala, J. M., Eds.; Marcell Dekker, Inc.: New York, 1990; pp 1–44. (c) Chu, D. T. W.; Fernandes, P. B. Recent Developments in the Field of Quinolone Antibacterial Agents. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press: New York, 1991; Vol. 21, pp 39–144. (c) Hooper, D. C.; Wolfson, J. S. Fluoroquinolone Antimicrobial Agents. *N. Engl. J. Med.* 1991, *324*, 384–394. (d) Maple, P.; Brumfitt, W.; Hamilton-Miller, J. M. T. A Review of the Antimicrobial Activity of the Fluoroquinolones. *J. Chemother.* 1990, *2*, 280–294.

(3) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-Alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. *J. Med. Chem.* 1980, *23*, 1358–1363.

(4) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. Pyridonecarboxylic Acids as Antibacterial Agents. 2. Synthesis and Structure-Activity Relationships of 1,6,7-Trisubstituted-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids, Including Enoxacin, A New Antibacterial Agent. *J. Med. Chem.* 1984, *27*, 292–301.

(5) Wise, R.; Andrews, J. M.; Edwards, L. J. In Vitro Activity of BAY 09867, A New Quinolone Derivative, Compared with Those of Other Antimicrobial Agents. *Antimicrob. Agents Chemother.* 1983, *23*, 559–564.

(6) (a) Wise, R.; Andrews, J. M.; Ashby, J. P.; Matthews, R. S. In Vitro Activity of Lomefloxacin, A New Quinolone Antimicrobial Agent, in Comparison with Those of Other Agents. *Antimicrob. Agents Chemother.* 1988, *32*, 617–622. (b) Chin, N. X.; Novelli, A.; Neu, H. C. In Vitro Activity of Lomefloxacin (SC-4711; NY-198), a Difluoroquinolone-3-carboxylic Acid, Compared with Those of Other Quinolones. *Antimicrob. Agents Chemother.* 1988, *32*, 656–662.

(7) (a) Hayakawa, I.; Hiramatsu, Y.; Tanaka, Y. Synthesis and Antibacterial Activities of Substituted 7-Oxo-2,3-dihydro-7*H*-pyridol[1,2,3-*de*]-[1,3]benzoxazine-6-carboxylic Acids. *Chem. Pharm. Bull.* 1984, *32*, 4907–4913. (b) Sato, K.; Matsuura, Y.; Inoue, M.; Une, T.; Osada, Y.; Ogawa, H.; Mitsuhashi, S. In Vitro and In Vivo Activity of DL-8280, a New Oxazine. *Antimicrob. Agents Chemother.* 1982, *22*, 548–553.

(8) Miyamoto, T.; Matsumoto, J.; Chiba, K.; Egawa, H.; Shibamori, K.; Minamide, A.; Nishimura, Y.; Okada, H.; Kataoka, M.; Fujita, M.; Hirose, T.; Nakano, J. Synthesis and Structure-Activity Relationships of 5-Substituted 6,8-Difluoroquinolones, Including Sparfloxacin, a New Quinolone Antibacterial Agent with Improved Potency. *J. Med. Chem.* 1990, *33*, 1645–1656.

(9) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. Synthesis and Structure-Activity Relationships of New Arylfluoronaphthyridine Antibacterial Agents. *J. Med. Chem.* 1986, *29*, 2363–2369. See also: Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Shen, L.; Borodkin, S.; Pernet, A. G. Asymmetric Synthesis and Properties of the Enantiomers of the Antibacterial Agent 7-(3-Aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride. *J. Med. Chem.* 1988, *31*, 1586–1590.

(10) (a) Wise, R.; Ashby, J. P.; Andrews, J. M. In Vitro Activity of PD 127391, an Enhanced-Spectrum Quinolone. *Antimicrob. Agents Chemother.* 1988, *32*, 1251–1256. (b) Norrby, S. R.; Jonsson, M. Comparative In Vitro Activity of PD 127391, a New Fluorinated 4-Quinolone Derivative. *Antimicrob. Agents Chemother.* 1988, *32*, 1278–1281.

(11) 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 (*4S*)-7-(4-Amino-2-substituted-pyrrolidin-1-yl)quinolone-3-carboxylic Acids. *J. Med. Chem.* 1988, *31*, 1598–1611.

(12) Matsumoto, J.; Nakano, J.; Miyamoto, T.; Hirose, T.; Minamida, A.; Egawa, H.; Nishimura, Y.; Chiba, K.; Okada, H.; Shibamori, K.; Kataoka, M.; Uno, H. AT-3295, A New Pyridonecarboxylic Acid Derivative with Potent Antibacterial Activity: Synthesis and Structure-Activity Relationships. *Proceedings of the 14th International Congress of Chemotherapy*; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, 1985; pp 1519–1520.

(13) 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.

(14) 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.

(15) (a) Chu, D. T. W.; Fernandes, P. B.; Akiyo, K. C.; Pihuleac, E.; Nordeen, C. W.; Maleczka, R. E.; Pernet, A. G. Synthesis and Structure-Activity Relationships of Novel Arylfluoroquinolone Antibacterial Agents. *J. Med. Chem.* 1985, *28*, 1558–1564. (b) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid. New Quinolone Antibacterial with Potent Gram-Positive Activity. *J. Med. Chem.* 1986, *29*, 445–448. (c) Culbertson, T. P.; Domagala, J. M.; Hagen, S. E.; Hutt, M. P.; Nichols, J. B.; Mich, T. F.; Sanchez, J. P.; Schroeder, M. C.; Solomon, M.; Worth, D. F. Structure-Activity Relationships of the Quinolone Antibacterials. The Nature of the C_7-Side Chain. In *Quinolones*; Fernandez, P. B., Ed.; J. R. Prous: Barcelona, Spain, 1989; pp 47–71.

(16) For a related study involving 3,3-disubstituted pyrrolidines, see: Stier, M. A.; Suto, M. J.; Emery, L. A.; Sesnie, J. C.; Domagala, J. M. Synthesis and Evaluation of a Series of 7-(3-Amino-3-aryl-1-pyrrolidinl)-4-naphthyridones As Antimicrobial Agents. *202th ACS National Meeting*, New York, NY, August 25–30, 1991; Abstr. 61.

(17) (a) Hosomi, A.; Sakata, Y.; Sakurai, H. N-(Trimethylsilylmethyl)-aminomethyl Ethers as Azomethine Ylide Synthons. A New Convenient Access to Pyrrolidine Derivatives. *Chem. Lett.* **1984**, 1117–1120. (b) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. Trifluoroacetic Acid-Catalyzed 1,3-Cycloaddition of the Simplest Iminium Ylide Leading to 3- or 3,4-Substituted Pyrrolidines and 2,5-Dihydropyrroles. *Chem. Pharm. Bull.* **1985**, *33*, 2762–2766. (c) Padwa, A.; Dent, W. On the Use of N-[(Trimethylsilyl)methyl]-amino Ethers as Capped Azomethine Ylide Equivalents. *J. Org. Chem.* **1987**, *52*, 235–244.

(18) (a) Worrall, D. E. Nitrostyrene. Organic Syntheses; Wiley: New York, 1941; Collect. Vol. I, pp 413–415. (b) Lerner, O. M. Ethylenediamine as a Catalyst in the Synthesis of Unsaturated Nitro Compounds of the Aromatic Series. *Zhur. Priklad. Khim.* **1958**, 663–664. (c) Gairaud, C. B.; Lappin, G. R. The Synthesis of ω-Nitrostyrenes. *J. Org. Chem.* **1953**, *18*, 1–3.

(19) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. Direct Synthesis of α,β-Unsaturated Nitriles from Acetonitrile and Carbonyl Compounds: Survey, Crown Effects, and Experimental Conditions. *J. Org. Chem.* **1979**, *44*, 4640–4649.

(20) Shiori, T.; Ninomiya, K.; Yamada, S. Diphenylphosphoryl Azide. A New Convenient Reagent for a Modified Curtius Reaction and for the Peptide Synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.

(21) (a) Campbell, A. L.; Pilipauskaus, D. R.; Khanna, I. K.; Rhodes, R. A. The Mild and Selective N-debenzylation of Tertiary Alkylamines Using β-Trimethylsilylethyl Chloroformate. *Tetrahedron Lett.* **1987**, *28*, 2331–2334. (b) Rich, D.; Shute, R. E. Synthesis and Evaluation of Novel Activated Mixed Carbonate Reagents for the Introduction of the 2-(Trimethylsilyl)ethoxycarbonyl (Teoc) Protecting Group. *Synthesis* **1987**, 346–349.

(22) Mich, T. F.; Sanchez, J. P.; Domagala, J. M.; Trehan, A. K. U.S. Pat. 4,663,457, 1987.

(23) (a) Culbertson, T. P.; Domagala, J. M.; Mich, T. F.; Nichols, J. B. U.S. Pat. 4,665,079, 1987. (b) Domagala, J. M.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Nichols, J. B.; Solomon, M.; Worth, D. F. 1-Substituted 7-[3-(Ethylamino)methyl-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. New Quantitative Structure-Activity Relationships at N_1 for the Quinolone Antibacterials. *J. Med. Chem.* **1988**, *31*, 991–1001.

(24) Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Trehan, A. K. 7-Substituted 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids: Synthesis and Biological Activity of a New Class of Quinolone Antibacterials. *J. Med. Chem.* **1988**, *31*, 503–506.

(25) Refers to dissolving the solid in aqueous base, adjusting the pH to 5–7, and filtering the solid that precipitates.

(26) Cohen, M. A.; Griffin, T. J.; Bien, P. A.; Heifetz, C. L.; Domagala, J. M. In Vitro Activity of Cl-934, a Quinolone Carboxylic Acid Active Against Gram-Positive and -Negative Bacteria. *Antimicrob. Agents Chemother.* **1985**, *28*, 766–772.

(27) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. New Structure-Activity Relationships of the Quinolone Antibacterials Using the Target Enzyme. The Development and Application of a DNA Gyrase Assay. *J. Med. Chem.* **1986**, *29*, 394–404.

(28) Sesnie, J. C.; Fritsch, P. W.; Griffin, T. J.; Heifetz, C. L.; Leopold, E. T.; Malta, T. E.; Shapiro, M. A.; Vincent, P. W. Comparative Chemotherapeutic Activity of New Fluorinated 4-Quinolones and Standard Agents Against a Variety of Bacteria in a Mouse Infection Model. *J. Antimicrob. Chemother.* **1989**, *23*, 729–736 and references therein.

(29) (a) Sesnie, J. C.; Heifetz, C. L.; Joannides, E. T.; Malta, T. E.; Shapiro, M. A. Comparative Phototoxicity of Quinolones In A Mouse Phototolerance Model. *30th ICAAC*, Atlanta, Georgia, October 21–24, 1990; Abstr. 399. (b) Sanchez, J. P.; Bridges, A. J.; Domagala, J. M.; Szotek, D. L. New 8-(Trifluoromethyl)substituted Quinolones. The Benefits of the 8-Fluoro Group with Reduced Phototoxic Risk. *J. Med. Chem.* **1992**, *35*, 361–367. (c) Suto, M. J.; Domagala, J. M.; Roland, G. E.; Mailloux, G. B.; Cohen, M. A. Fluoroquinolones: Relationships Between Structural Variations, Mammalian Cell Cytotoxicity, and Antimicrobial Activity. *J. Med. Chem.* **1992**, *35*, 4745–4750.

(30) Sesnie, J. C.; et al. Unpublished results.

(31) Colbry, N. L.; Domagala, J. M.; Hydorn, M. B.; Johnson, D. R.; Laborde, E.; Sesnie, J. C. New Quinolone Antibacterials. Design, Synthesis and Biological Evaluation of 7-(3-Aryl-1-pyrrolidinyl)-quinolones. Manuscript in preparation. For a preliminary communication, see: Laborde, E.; Domagala, J. M.; Schroeder, M. C.; Sesnie, J. C.; Joannides, E. T.; Shapiro, M. A.; VanderRoest, S. New Quinolone Antibacterials. Synthesis and Biological Evaluation of 7-(3-Aryl-1-pyrrolidinyl)quinolones. *23rd National Medicinal Chemistry Symposium*, Buffalo, NY, June 14–18, 1992; Abstr. 64.

(32) For related compounds possessing a 3-amino-4-spirocyclopropylpyrrolidine, see: Hayakawa, I.; Atarashi, S.; Kimura, Y.; Kawakami, K.; Saito, T.; Yafune, T.; Sato, K.; Une, T.; Sato, M. Design and Structure-Activity Relationships of New N_1-cis-2-Fluorocyclopropylquinolones. *31st ICAAC*, Chicago, IL, 1991; Abstr. 1504.

(33) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.