

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 Acids¹

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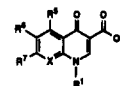
A series of 6-fluoroquinolone- and 6-fluoro-1,8-naphthyridone-3-carboxylic acids possessing a [3-amino (or aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl] group at C-7 were synthesized and evaluated for their antimicrobial activity. The effect of the relative stereochemistry of the pyrrolidinyl 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



Compd	Name	X	R ¹	R ²	R ³	R ⁴	Ref.
1	Norfloxacin	CH	Et	H			3
2	Enoxacin	N	Et	H			4
3	Ciprofloxacin	CH	<i>o</i> -Pr	H			5
4	Lomefloxacin	CF	Et	H			6
5	Ofloxacin	C-O-CH ₂ -CH-CH ₃		H			7
6	Sparfloxacin	CF	<i>o</i> -Pr	NH ₂			8
7	Tosufloxacin	N	2,4-F ₂ Ph	H			9
8	Clinefloxacin	CCl	<i>o</i> -Pr	H			10
9	---	N	2,4-F ₂ Ph	H			11
10	AT-3295	N	<i>o</i> -Pr	H			12
11	---	CF	<i>o</i> -Pr	H			13
12	---	CF	<i>o</i> -Pr	H			14

Figure 1. Clinically significant quinolones and reference agents.

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}

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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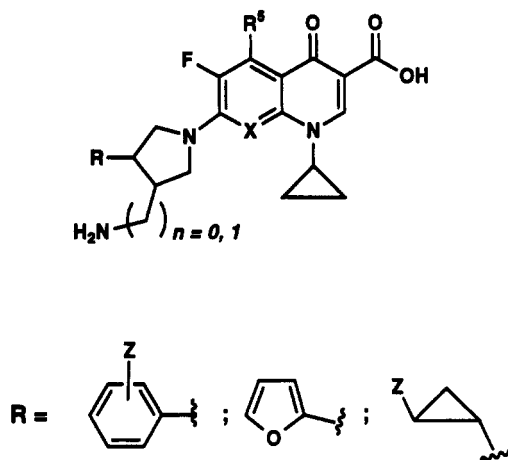


Figure 2. 7-[3-Amino (or aminomethyl)-4-aryl (or cyclopropyl)-1-pyrrolidinyl]quinolones.

the ((2*S*,4*S*)-4-amino-2-methylpyrrolidinyl)naphthyridine 9¹¹ and the (*trans*-3-amino-4-methylpyrrolidinyl)naphthyridine 10¹² 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

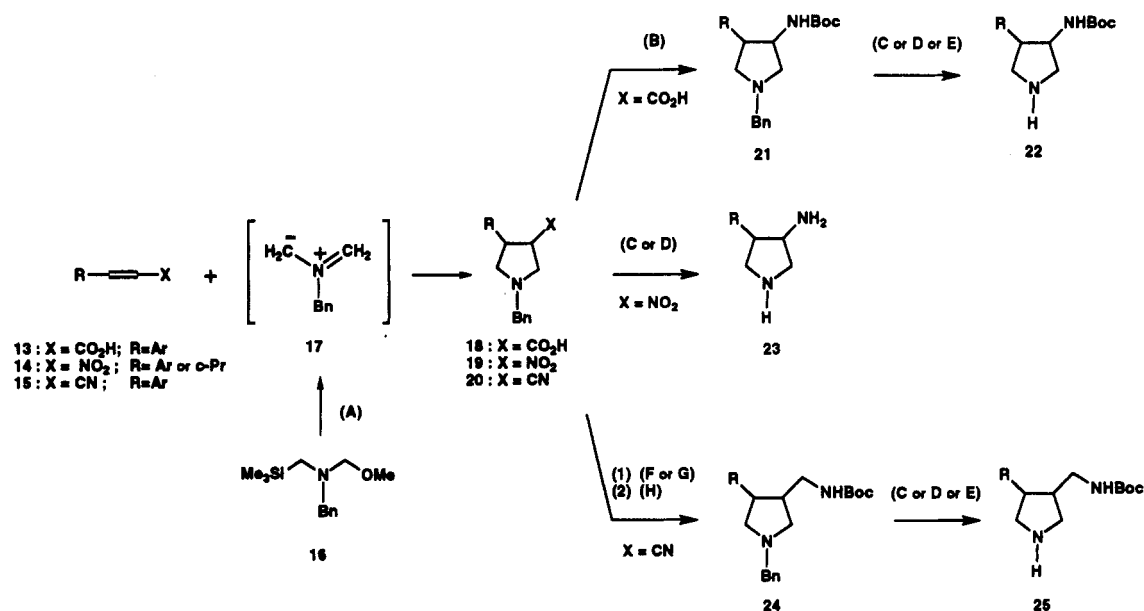
Scheme 1^a

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 nitromethane¹⁸ 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



^a Reagents: (A) TFA (cat.), CH₂Cl₂; (B) DPPA, Et₃N, t-BuOH; (C) H₂, 20% Pd/C, MeOH; (D) HCO₂NH₄, 10% Pd/C, MeOH/H₂O; (E) TMSCH₂OCOC₂H₅, THF; then, Et₃N, CH₃CN; (F) LiAlH₄, THF; (G) Ra-Ni, NH₃/MeOH; (H) Boc₂O, Et₃N or i-Pr₂EtN, CH₂Cl₂.

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 ₂ H	58		C ₁₉ H ₂₁ NO ₃ (C, H, N)
18c	trans-2-OMe-Ph	CO ₂ H	62	197–202	C ₁₉ H ₂₁ NO ₃ ·0.2H ₂ O (C, H, N)
18e	trans-3,4-Cl ₂ -Ph	CO ₂ H	77	167–168	C ₁₈ H ₁₇ Cl ₂ NO ₂ (C, H, N, Cl)
18k	trans-4-NO ₂ -Ph	CO ₂ H	65	164–166	C ₁₈ H ₁₈ N ₂ O ₄ (C, H, N)
19a	trans-Ph	NO ₂	51	177–179	C ₁₇ H ₁₈ N ₂ O ₂ ·HCl (C, H, N)
19d	trans-3-CN-Ph	NO ₂	70	151–156	C ₁₈ H ₁₇ H ₃ O ₂ ·HCl·0.25H ₂ O (C, H, N, Cl) ^c
19f	trans-4-(i-Pr)-Ph	NO ₂	83	181–183	C ₂₀ H ₂₄ N ₂ O ₂ ·HCl (C, H, N)
19g	trans-4-F-Ph	NO ₂	86	183–185	C ₁₇ H ₁₇ FN ₂ O ₂ ·HCl (C, H, N)
19h	trans-4-OH-Ph	NO ₂	65	224–227	C ₁₇ H ₁₈ N ₂ O ₃ ·HCl (C, H, N, Cl)
19i	trans-4-OMe-Ph	NO ₂	81	75–80	C ₁₈ H ₂₀ N ₂ O ₃ ·H ₂ O (C, H, N)
19l	trans-4-NMe ₂ -Ph	NO ₂	42		C ₁₉ H ₂₃ H ₃ O ₂ ·1.05HCl (C, H, N, Cl)
19m	trans-4-CO ₂ Me-Ph	NO ₂	95	oil	
19o	trans-c-Pr	NO ₂	84	oil	C ₁₄ H ₁₈ N ₂ O ₂ (C, H, N)
20p	trans-(trans-2-CO ₂ Et)-c-Pr	NO ₂	71	oil	C ₁₇ H ₂₂ N ₂ O ₄ (C, H, N)
20a	trans-Ph	CN	86	204–206	C ₁₈ H ₁₈ N ₂ ·HCl (C, H, N, Cl)
20d	trans-3-CN-Ph	CN	66	158–165	C ₁₉ H ₁₇ N ₃ ·HCl·H ₂ O (C, H, N, Cl)
20j	cis-4-NO ₂ -Ph	CN	20	216–218	C ₁₈ H ₁₇ N ₃ O ₂ ·HCl·0.25H ₂ O (C, H, N)
20k	trans-4-NO ₂ -Ph	CN	65	211–214	C ₁₈ H ₁₇ N ₃ O ₂ ·HCl (C, H, N, Cl)
20n	trans-2-Furanyl	CN	60	oil	C ₁₆ H ₁₆ N ₂ O (C, H, N) ^d

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

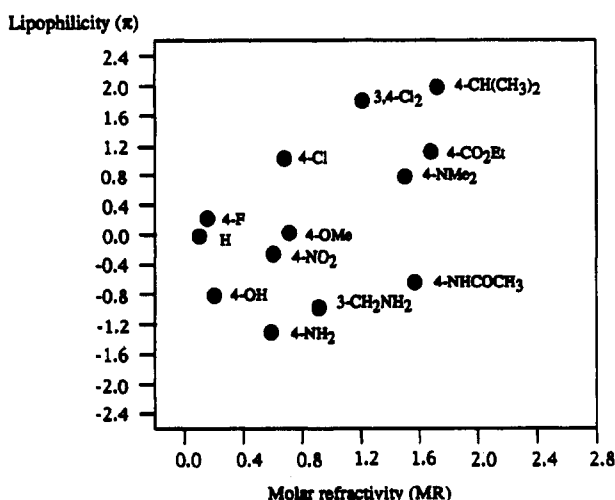


Figure 3. Aromatic ring substituents selected for this study. good (Table I). Worthy of note is the observation that the cinnamic acids 13 proved themselves to be good dipolarophiles in this reaction, making it unnecessary to resort to their ester derivatives. This result expedited the introduction of 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

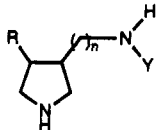
debenzylation was carried out by the method of Campbell, using 2-(trimethylsilyl)ethyl chloroformate.²¹

Catalytic hydrogenation (3 atm of H₂, 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 LiAlH₄. 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 29²⁴ (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 ₁₆ H ₂₄ H ₂ O ₃ ·1.2H ₂ O (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 ₂ N ₂ O ₂ ·0.25H ₂ O (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 ·2.05HCl·0.5H ₂ O (C,H,N,Cl)
23d	0	trans-(CH ₂ NHBoc)-Ph	Boc	G,H,C	70	68–71	C ₂₁ H ₃₃ N ₃ O ₄ ·0.4H ₂ O (C,H,N ^d)
23f	0	trans-4-(i-Pr)-Ph	H	C	77	163–166	C ₁₃ H ₂₀ N ₂ ·1.1HCl (C,H,N)
23g	0	trans-4-F-Ph	H	C	90	>275	C ₁₀ H ₁₃ FN ₂ ·2HCl (C,H,N,Cl)
23h	0	trans-4-OH-Ph	H	C	87	>275	C ₁₀ H ₁₄ N ₂ O·2HCl·0.75H ₂ O (C,H,N,Cl)
23i	0	trans-4-OMe-Ph	H	C	61	247–249	C ₁₁ H ₁₆ N ₂ O·HCl·H ₂ O (C,H,N,Cl)
23l	0	trans-4-NMe ₂ -Ph	H	C	78	117–121	C ₁₂ H ₁₉ N ₃ ·1.4HCl·0.25H ₂ O (C,H,N,Cl)
23m	0	trans-4-CO ₂ Me-Ph	H	C	88	93–96	C ₁₂ H ₁₆ N ₂ O ₂ ·HCl·0.77H ₂ O (C,H,N,Cl)
23o	0	trans-c-Pr	H	D	14	oil	
23p	0	trans-(trans-2-CO ₂ Et)-c-Pr	H	D	77	oil	C ₁₀ H ₁₈ N ₂ O ₂ ·0.9H ₂ O (C,H ^e ,N)
25a	1	trans-Ph	Boc	F,H,C	97	oil	C ₁₆ H ₂₄ N ₂ O ₂ ·0.6H ₂ O (C,H,N)
25d	1	trans-3-(CH ₂ NHBoc)-Ph	Boc	G,H,C	77	62–65	C ₂₂ H ₃₅ N ₃ O ₄ ·0.5H ₂ O (C,H,N ^f)
25j	1	cis-4-NH ₂ -Ph	Boc	G,H,D	67	198–202	C ₁₆ H ₂₅ N ₃ O ₂ ·H ₂ O (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 ₂ O ₃ ·0.8H ₂ O (C,H ^h ,N)

^a Overall yield from 18, 19, or 20. ^b Symbols refer to those elements analyzed. Analyses were within $\pm 0.4\%$ 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 precipitation²⁵ 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, $\mu\text{g/mL}$) 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 (PD₅₀, 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, $\mu\text{g/mL}$) of the compounds prepared in this study are shown in Table IV. The mouse protection doses (PD₅₀, 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'-NH₂, and 4'-NMe₂Ph derivatives (31-0g,h,i,k,l) were all essentially equipotent with the unsubstituted phenyl compound, 31-0a. Interestingly, the 4'-NMe₂Ph 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'-NH₂Ph derivatives 31-1j and 31-1k, respectively, were 2–3 times less potent *in vitro* than the corresponding unsubstituted phenyl analog 31-1a.

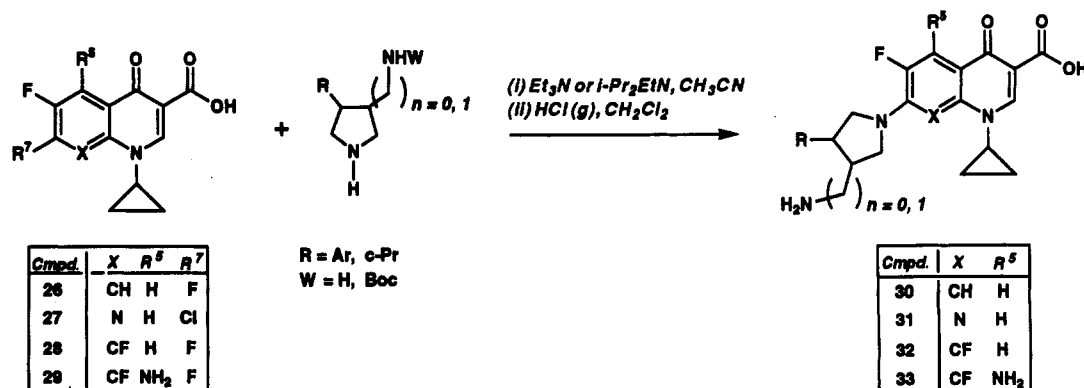
(3) Bulky, lipophilic groups at the 4'-position of the phenyl ring decreased activity by 2–4-fold. This effect was more pronounced for the Gram-negative than for the Gram-positive organisms (*cf.*, 31-0f,l,m), which is the reason why we think it may be related to transport or permeability factors.

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 ₃ O ₃ ·0.3H ₂ O (C,H,N)
30-0p	H	CH	0	trans-(trans-2-CO ₂ Et)-c-Pr	45	200–203	C ₂₃ H ₂₆ FN ₃ O ₅ ·1.5H ₂ O (C,H,N)
31-0a	H	N	0	trans-Ph	75	>295	C ₂₂ H ₂₁ FN ₄ O ₃ ·HCl·1.2H ₂ O (C,H,N,Cl)
31-0b	H	N	0	cis-2-OMe-Ph	89	225–232	C ₂₃ H ₂₃ FN ₄ O ₄ ·HCl·2.5H ₂ O (C,H,N)
31-0c	H	N	0	trans-2-OMe-Ph	77	>280	C ₂₃ H ₂₃ FN ₄ O ₄ ·HCl·0.7H ₂ O (C,H,N)
31-0d	H	N	0	trans-3-(CH ₂ NH ₂)-Ph	87	>270	C ₂₃ H ₂₄ FN ₅ O ₃ ·2HCl·2H ₂ O (C,H,N)
31-0e	H	N	0	trans-3,4-Cl ₂ -Ph	54	226–230	C ₂₂ H ₁₉ Cl ₂ FN ₄ O ₃ ·1.2HCl·H ₂ O (C,H,N,Cl)
31-0f	H	N	0	trans-4-(i-Pr)-Ph	30	220–225	C ₂₅ H ₂₇ FN ₄ O ₃ ·1.75HCl·H ₂ O (C,H,N)
31-0g	H	N	0	trans-4-F-Ph	81	220–223	C ₂₂ H ₂₀ F ₂ N ₄ O ₃ ·0.5H ₂ O (C,H,N)
31-0h	H	N	0	trans-4-OH-Ph	22	276–280	C ₂₂ H ₂₁ FN ₄ O ₄ ·0.75H ₂ O (C,H,N)
31-0i	H	N	0	trans-4-OMe-Ph	62	233–235	C ₂₃ H ₂₃ FN ₄ O ₄ ·0.5H ₂ O (C,H,N)
31-0k	H	N	0	trans-4-NH ₂ -Ph	82	>255	C ₂₂ H ₂₂ FN ₅ O ₃ ·1.8HCl·2H ₂ O (C,H,N,Cl)
31-0l	H	N	0	trans-4-NMe ₂ -Ph	85	236–238	C ₂₄ H ₂₆ FN ₅ O ₃ ·0.2H ₂ O (C,H,N)
31-0m	H	N	0	trans-4-CO ₂ Me-Ph	35	282	C ₂₄ H ₂₃ FN ₄ O ₅ ·0.5H ₂ O (C,H,N)
31-0p	H	N	0	trans-(trans-2-CO ₂ Et)-c-Pr	30	230–235	C ₂₂ H ₂₆ FN ₄ O ₅ ·1.7H ₂ O (C,H,N ^d)
32-0a	H	CF	0	trans-Ph	53	206–208	C ₂₃ H ₂₁ F ₂ N ₃ O ₃ ·0.75H ₂ O (C,H,N)
32-0c	H	CF	0	trans-2-OMe-Ph	78	255–257	C ₂₄ H ₂₃ F ₂ N ₃ O ₄ ·1.1HCl·1.75H ₂ O (C,H,N,Cl)
32-0e	H	CF	0	trans-3,4-Cl ₂ -Ph	45	238–243	C ₂₃ H ₁₉ Cl ₂ F ₂ N ₃ O ₃ ·HCl·1.5H ₂ O (C,H ^e ,N,Cl)
32-0f	H	CF	0	trans-4-(i-Pr)-Ph	72	194–196	C ₂₆ H ₂₇ F ₂ N ₃ O ₃ ·0.25H ₂ O (C,H,N,F)
32-0g	H	CF	0	trans-4-F-Ph	90	210–212	C ₂₃ H ₂₀ F ₃ N ₃ O ₃ ·0.75H ₂ O (C,H,N)
32-0h	H	CF	0	trans-4-OH-Ph	49	222–225	C ₂₃ H ₂₁ F ₂ N ₃ O ₄ ·1.2H ₂ O (C,H,N)
32-0i	H	CF	0	trans-4-OMe-Ph	83	202–205	C ₂₄ H ₂₃ F ₂ N ₃ O ₄ ·1.1H ₂ O (C,H,N,F)
32-0k	H	CF	0	trans-4-NH ₂ -Ph	74	>255	C ₂₃ H ₂₂ F ₂ N ₄ O ₃ ·2HCl·2H ₂ O (C,H,N,Cl)
32-0l	H	CF	0	trans-4-NMe ₂ -Ph	79	240–243	C ₂₆ H ₂₆ F ₂ N ₄ O ₃ ·0.25H ₂ O (C,H,N)
32-0m	H	CF	0	trans-4-CO ₂ Me-Ph	25	196	C ₂₅ H ₂₃ F ₂ N ₃ O ₅ ·H ₂ O (C,H,N)
33-0a	NH ₂	CF	0	trans-Ph	66	212–215	C ₂₃ H ₂₂ F ₂ N ₄ O ₃ ·H ₂ O (C,H,N)
33-0g	NH ₂	CF	0	trans-4-F-Ph	87	204–206	C ₂₃ H ₂₁ F ₃ N ₄ O ₃ ·1.6H ₂ O (C,H,N)
33-0h	NH ₂	CF	0	trans-4-OH-Ph	87	231–237	C ₂₃ H ₂₂ F ₂ N ₄ O ₄ ·1.6H ₂ O (C,H,N)
33-0k	NH ₂	CF	0	trans-4-NMe ₂ -Ph	91	229–231	C ₂₅ H ₂₇ F ₂ N ₅ O ₃ (C,H,N,F)
31-1a	H	N	1	trans-Ph	96	>270	C ₂₃ H ₂₃ FN ₄ O ₃ ·2HCl·H ₂ O (C,H,N,Cl)
31-1d	H	N	1	trans-3-(CH ₂ NH ₂)-Ph	90	>270	C ₂₄ H ₂₆ FN ₅ O ₃ ·2HCl·2.4H ₂ O (C,H,N)
31-1j	H	N	1	cis-4-NH ₂ -Ph	36	>270	C ₂₃ H ₂₄ FN ₅ O ₃ ·2HCl·0.35H ₂ O (C,H,N ^f)
31-1k	H	N	1	trans-4-NH ₂ -Ph	66	>270	C ₂₃ H ₂₄ FN ₅ O ₃ ·2HCl·2.5H ₂ O (C,H,N)
31-1n	H	N	1	trans-2-furanyl	82	255–260	C ₂₁ H ₂₁ FN ₄ O ₄ ·HCl·0.75H ₂ O (C,H,N)
32-1a	H	CF	1	trans-Ph	62	265–269	C ₂₄ H ₂₃ F ₂ N ₃ O ₃ ·1.5HCl·1.5H ₂ O (C,H,N,Cl ^g)
32-1d	H	CF	1	trans-3-(CH ₂ NH ₂)-Ph	73	>270	C ₂₆ H ₂₆ F ₂ N ₄ O ₃ ·2HCl·3H ₂ O (C,H,N)
32-1k	H	CF	1	trans-4-NH ₂ -Ph	53	>270	C ₂₄ H ₂₄ F ₂ N ₄ O ₃ ·2HCl·2.1H ₂ O (C,H,N)
32-1n	H	CF	1	trans-2-furanyl	72	234–242	C ₂₂ H ₂₁ F ₂ N ₃ O ₄ ·HCl·0.5H ₂ O (C,H,N,Cl)
33-1a	NH ₂	CF	1	trans-Ph	6.5	217–220	C ₂₄ H ₂₄ F ₂ N ₄ O ₃ ·1.25HCl·1.25H ₂ O (C,H,N,Cl)
33-1k	NH ₂	CF	1	trans-4-NH ₂ -Ph	34	>270	C ₂₄ H ₂₆ F ₂ N ₅ O ₃ ·HCl·3.5H ₂ O (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 $\pm 0.4\%$ 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



(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'-Cl₂Ph)],

Table IV. *In Vitro* Antibacterial Activity

		minimum inhibitory concentration (MIC), $\mu\text{g/mL}$											
		Gram-negative organisms					Gram-positive organisms						
compd	R	<i>Entero. cloacae</i> MA-2646	<i>Esch. coli</i> Vogel	<i>Klebs. pneum.</i> MGH-2	<i>Prov. rettgeri</i> M-1771	<i>Pseudo. aerug.</i> UI-18	<i>Staph. aureus</i> H-228	<i>Staph. aureus</i> UC-76	<i>Entero. faecalis</i> MGH-2	<i>Strep. pneum.</i> SV-1	<i>Strep. pyog.</i> C-203	geometric means	
												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 ₂ Et]-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 ₂ NH 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 ₂ Me-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 ₂ Et]-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 ₂ NH 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 ₂ Me-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 ₂ NH 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

compd	PD ₅₀ (mg/kg) po/sc	
	<i>E. coli</i> Vogel	<i>S. pyogenes</i> 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'-CH₂NH₂Ph)], and [3-(aminomethyl)-4-(3'-CH₂NH₂Ph)] 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'-NH₂-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'-NH₂-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'-NH₂-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. Tetrahydrofuran 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 F₂₅₄ 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 Bruker 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 CH₂Cl₂ (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 CH₂Cl₂ (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 Et₂O 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 (CD₃OD) 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 (CD₃OD) 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 (CDCl₃) 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 (CHCl₃) 1246, 1256, 1454, 1515, 1612 cm⁻¹; MS *m/z* (relative intensity) 313 (M + 1, 40), 266 (43), 147 (100), 91 (46); ¹H NMR (CDCl₃) 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 (CHCl₃) 1285, 1553, 1721, 2976 cm⁻¹; MS *m/z* (relative intensity) 341 (M + 1, 100), 294 (24), 325 (3); ¹H NMR (CDCl₃) 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 (1H, 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 [3 α ,4 β (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 ($\text{DMSO}-d_6$) 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-pyrrolidinecarboxonitrile hydrochloride (20a): IR (KBr) 702, 765, 1457, 2243 cm^{-1} ; MS m/z (relative intensity) 263 ($M + 1$, 100), 185 (4), 133 (91), 91 (23); ^1H NMR ($\text{DMSO}-d_6$) 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-pyrrolidinecarboxonitrile 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 ($\text{DMSO}-d_6$) 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-pyrrolidinecarboxonitrile 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 ($\text{DMSO}-d_6$) 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-pyrrolidinecarboxonitrile 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 ($\text{DMSO}-d_6$) 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-pyrrolidinecarboxonitrile (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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) 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 $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2$ 277.1790, found 277.1800; ^1H NMR ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 $\text{CHCl}_3/\text{MeOH}/\text{concentrated NH}_3$) 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); ^1H 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) 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); ^1H 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); ^1H 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); ^1H NMR ($\text{DMSO}-d_6$) 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); ^1H NMR ($\text{DMSO}-d_6$) 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); ^1H NMR ($\text{DMSO}-d_6$) 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); ^1H NMR ($\text{DMSO}-d_6$) 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); ^1H NMR ($\text{DMSO}-d_6$) 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); ^1H NMR ($\text{DMSO}-d_6$) 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 $\text{CHCl}_3/\text{MeOH}/\text{concentrated NH}_3$) 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); ^1H NMR

($\text{DMSO}-d_6$) 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 [3 α ,4 β (*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); ^1H NMR ($\text{DMSO}-d_6$) 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 filtrate was concentrated and chromatographed (75:25 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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): ^1H 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); ^1H 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 $i\text{-Pr}_2\text{EtN}$ (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 $i\text{-PrOH}/\text{MeOH}$ (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); ^1H 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).

[3 α ,4 β -(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); ^1H 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 ($\text{Et}_3\text{NH}^+\text{Cl}^-$) was removed by filtration. The filtrate was concentrated and the crude product recrystallized from $\text{MeOH}/\text{Et}_2\text{O}$ to give the $N\text{-Boc}$ -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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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).

[3 α ,4 β (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-Op): MS m/z (relative intensity) 444 (M, 3), 400 (15), 218 (25), 189 (11), 44 (100); ^1H 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-Oa): IR (KBr) 1461, 1521, 1626, 1727 cm^{-1} ; MS m/z (relative intensity) 426 (M + 1, 27), 408 (2), 321 (4), 115 (100); ^1H 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-Ob): IR (KBr) 1458, 1496, 1522, 1627, 1725 cm^{-1} ; MS m/z (relative intensity) 456 (M + 1, 3); ^1H 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-Of): IR (KBr) 1459, 1520, 1626, 1726, 2891 cm^{-1} ; MS m/z (relative intensity) 496 (M + 2, 9), 494 (M + 1, 13), 476 (5); ^1H 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-Of): IR (KBr) 1459, 1519, 1627, 1728, 2956 cm^{-1} ; MS m/z (relative intensity) 468 (M + 1, 52), 322 (14), 277 (14); ^1H 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-Og): IR (KBr) 1459, 1464, 1513, 1626, 1727 cm^{-1} ; MS m/z (relative intensity) 444 (M + 1, 9), 181 (17), 164 (16), 115 (100); ^1H 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-Oh): IR (KBr) 1464, 1521, 1627, 1734 cm^{-1} ; MS m/z (relative intensity) 442 (M + 1, 100), 424 (13), 322 (23), 147 (33); ^1H 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-Oi): IR (KBr) 1464, 1471, 1515, 1626, 1727 cm^{-1} ; MS m/z (relative intensity) 456 (M + 1, 100), 438 (34), 395 (8); ^1H 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-Oj): IR (KBr) 1466, 1521, 1628, 1717 cm^{-1} ; MS m/z (relative intensity) 441 (M + 1, 100), 423 (24); ^1H 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-Ol): IR (KBr) 1376, 1458, 1538, 1626, 1728 cm^{-1} ; MS m/z (relative intensity) 469 (M + 1, 100), 452 (24),

206 (63), 189 (51); ^1H 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-Of): IR (KBr) 1281, 1456, 1611, 1626, 1722 cm^{-1} ; MS m/z (relative intensity) 484 (M + 1, 100), 466 (48), 423 (8); ^1H 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-Oa): IR (KBr) 1350, 1435, 1516, 1631, 1723 cm^{-1} ; MS m/z (relative intensity) 441 (M + 1, 100), 423 (66), 397 (12), 380 (11); ^1H 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-Og): IR (KBr) 1437, 1512, 1636, 1725 cm^{-1} ; MS m/z (relative intensity) 459 (M + 1, 10), 181 (5), 115 (72); ^1H 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-Oh): IR (KBr) 1352, 1436, 1517, 1631, 1727 cm^{-1} ; MS m/z (relative intensity) 457 (M + 1, 100), 439 (38), 413 (10); ^1H 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-Ok): IR (KBr) 1349, 1435, 1520, 1630, 1724 cm^{-1} ; MS m/z (relative intensity) 484 (M + 1, 100), 466 (15), 440 (14), 147 (88); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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-aminophenyl)-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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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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