New Quinolone Antibacterial Agents. Synthesis and Biological Activity of 7-(3,3- or 3,4-Disubstituted-1-pyrrolidinyl)quinoline-3-carboxylic Acids

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Received February 8, 1989

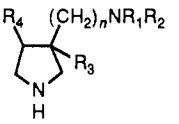
A series of 7-(3-amino- or 3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids was synthesized and tested for antibacterial activity. Unique to these quinolones was the presence of a methyl or phenyl group in the pyrrolidine ring. Although the in vitro activity of these agents was usually equal to or less than that of their unsubstituted counterparts, one quinolone, 7-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, displayed exceptional potency both in vitro and in vivo, particularly against Gram-positive organisms.

In the search for potent, orally effective antibacterials, the quinolones in particular have generated much well-deserved enthusiasm. Although early members of this class suffered from poor Gram-positive activity and inferior blood levels, subsequent structure–activity relationship (SAR) correlations have delineated several features necessary for improved efficacy.[1] These features include a fluorine atom at C-6, a basic group at C-7,[2,6] a halogen atom at C-8,[3,4] and a cyclopropyl or difluorophenyl moiety at the quinolone ring nitrogen.[5] Different combinations of these functionalities resulted in a variety of new chemotherapeutic agents exemplified by enoxacin (**1**),[6] ofloxacin (**2**),[7] and ciprofloxacin (**3**),[8] all of which contain a piperazine group at C-7. More recently, this piperazine has been replaced with two appropriate mimics, namely, a (3-aminomethyl)pyrrolidine and a 3-aminopyrrolidine. These modifications engendered a dramatic improvement in Gram-positive activity and culminated in the discovery of 1-ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**4**)[3] and 7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**5**),[4] two very potent Gram-positive quinolones with exceptional in vivo efficacy.

Since our previous efforts have proven that the aminopyrrolidines are excellent replacements for the standard piperazine moiety, our attention then shifted to the question of side chain substitution: in other words, what effect would alkyl or aryl groups on the pyrrolidine ring have on the overall antibacterial potency of the molecule. Of particular interest was the role steric bulk might play when said groups were in close proximity to the exocyclic amine and if an aromatic group would confer any special activity. A similar study on a 1,8-naphthyridine series undertaken by Matsumoto et al.[9] revealed that methyl substitution on the pyrrolidine ring did not significantly affect the minimum inhibitory concentrations (MICs), regardless of the position of the methyl group in the ring; however, introduction of this alkyl moiety markedly increased the solubility of the compound, an effect that was found to be isomer-dependent. The culmination of this research was compound **6**, a naphthyridine with a *trans*-4-amino-3-methylpyrrolidine at the 7-position.

In this paper we report the synthesis and biological activity of a series of quinolones containing alkyl- and aryl-substituted pyrrolidines at C-7. Both the 3-aminopyrrolidines and the 3-(aminomethyl)pyrrolidines are examined in this context, with particular emphasis on the 3,3-disubstituted heterocycles. Of major importance was the discovery of 7-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**20b**), a very active Gram-positive agent with excellent in vivo activity.

Table I. Pyrrolidine Starting Materials Synthesized for This Study



compd	*n*	R_1	R_2	R_3	R_4	synthesis
15a	1	H	H	Ph	H	Scheme I
15b	1	H	Et	Ph	H	Scheme I
15c	1	Me	Me	Ph	H	Scheme I
15d	0	H	H	Ph	H	Scheme I
15e	0	H	H	H	Ph	ref 12
15f	1	H	H	H	Ph	ref 14[a]
18a	0	H	Ac	CH_3	H	ref 13[b]
18b	1	H	H	CH_3	H	Scheme II

[a] The reference cited contains the starting material for this pyrrolidine; procedures for the reduction and deprotection to give **15f** are included in the Experimental Section. [b] This N-acylated pyrrolidine was coupled in the normal fashion and then deprotected, see the Experimental Section.

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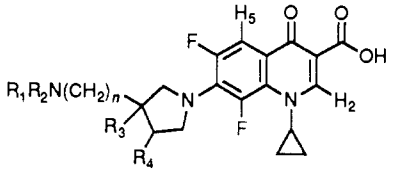
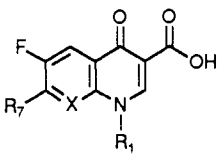
Table II. Synthetic and Physical Data of the Quinolone Antibacterials Prepared for This Study



compd	n	R_1	R_2	R_3	R_4	mp, °C	analysis[a]	purification[b]	yield,[c] %	NMR (TFA), δ C_2H[d]	NMR (TFA), δ C_5H[e]
19a	1	H	H	Ph	H	233–235	$C_{24}H_{23}F_2N_3O_3 \cdot 0.15H_2O$ (C, H, N)	none	89	9.3	8.05
19b	1	H	Et	Ph	H	194–195	$C_{26}H_{27}F_2N_3O_3 \cdot 0.5H_2O$ (C, H, N)	none	65	9.3	8.1
19c	1	Me	Me	Ph	H	186–188	$C_{26}H_{27}F_2N_3O_3 \cdot HCl$ (C, H, N)	recryst *i*-PrOH	58	9.3	8.1
19d	0	H	H	Ph	H	237–239	$C_{23}H_{21}F_2N_3O_3$ (C, H, N)	none	83	9.35	8.15
19e	0	H	H	H	Ph	185–187	$C_{23}H_{21}F_2N_3O_3 \cdot 0.5H_2O$ (C, H, N)	isoelect prec	65	9.4	8.2
19f	1	H	H	H	Ph	231–233	$C_{24}H_{23}F_2N_3O_3 \cdot 0.5H_2O$ (C, H, N)	none	64	8.6[f]	7.7[f]
20a	0	H	H	CH_3	H	>300	$C_{18}H_{19}F_2N_3O_3 \cdot 1.2HCl \cdot 1.3H_2O$ (C, H, N, Cl)	recryst 2-PrOH	53	9.3	8.15
20b	1	H	H	CH_3	H	245–247	$C_{19}H_{21}F_2N_3O_3 \cdot 0.4H_2O$ (C, H, N)	none	78	8.55[f]	7.6[f]

[a] Symbols refer to those elements analyzed for. Analyses were ±0.4% of theoretical values. [b] Isoelectric precipitation refers to dissolving the solid in aqueous base, adjusting the pH to 7.2, and filtering the solid that precipitates. [c] Yields are those obtained from the coupling step to final product, including deprotections when appropriate. [d] Singlet. [e] Doublet. [f] DMSO-d_6 used as NMR solvent.



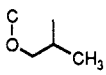
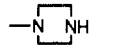
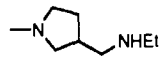
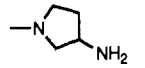
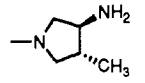
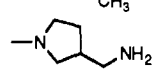
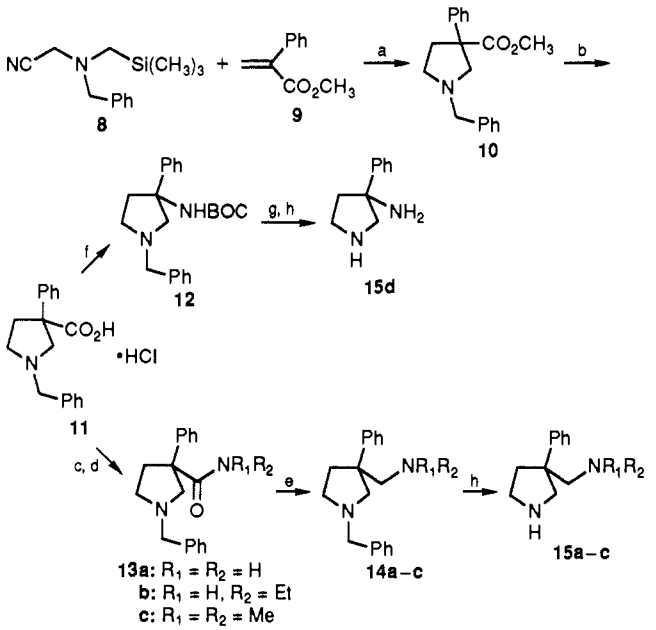
compd	name	X	R_1	R_7	ref
1	enoxacin	N	Et		6
2	ofloxacin				7
3	ciprofloxacin	CH			8
4		CF	Et		3
5		CF			4
6		N			9
7		CF			4

Figure 1. Clinically significant quinolone type antibacterial agents and reference compounds.

Chemistry

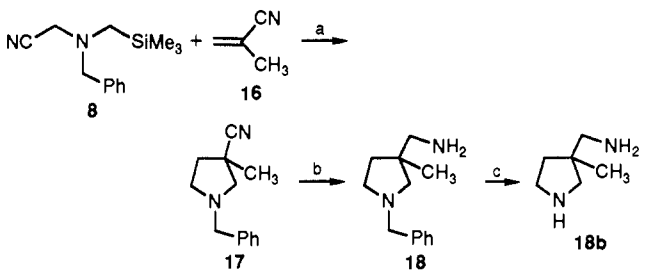
The compounds prepared for this study (Table II) were synthesized in the usual manner[10] from the appropriate pyrrolidine (Table I) and 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[11] (see General Method B in the Experimental Section). 4-Phenyl-3-pyrrolidinamine (**15e**)[12] and *N*-(3-methyl-3-pyrrolidinyl)-acetamide (**18a**)[13] used for compounds **19e** and **20a** were prepared according to literature procedures. For the synthesis of 4-phenyl-3-pyrrolidinemethanamine (**15f**), the readily accessible 4-phenyl-1-(phenylmethyl)-3-pyrrolidinecarbonitrile[14] was reduced to the 4-phenyl-1-(phenylmethyl)-3-pyrrolidinemethanamine and then debenzylated to give the desired pyrrolidine **15f**.

Scheme I[a]



[a] (a) AgF, CH_3CN; (b) HCl, Δ; (c) NEt_3, CDI; (d) NHR_1R_2; (e) $LiAlH_4$; (f) DPPA, NEt_3; (g) 6 M HCl; (h) H_2, Pd–C.

Scheme II[a]



[a] (a) AgF, CH_3CN; (b) $LiAlH_4$; (c) H_2, Pd–C.

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Table III. Biological Testing Results from the Drug-Induced Cleavage Assay, Antibacterial Screening, and Mouse Protection Assay

	minimum inhibitory concentrations (MIC), μg/mL[a]											protective dose (PD_{50}), mg/kg[b]			gyrase–drug[c] induced cleavage, μg/mL:
	Gram-negative organisms						Gram-positive organisms								
	E. cloacae HA 2646	*E. coli* Vogel	*E. coli* H560	*K. pneum.* MGH-2	*P. rettgeri* H1771	P. *aeruginosa* UI-18	*S. aureus* H228	*S. aureus* UC-76	*S. faecalis* MGH-2	*S. pneum.* SV-1	*S. pyogenes* C203	*E. coli* H560 (PO/SC)	*S. pyog.* (PO/SC)	*S. pneu.* (PO/SC)	*E. coli*
5	0.025	0.013	0.006	0.025	0.05	0.1	0.05	0.025	0.05	0.05	0.05	1/0.2	7.5/2	15/6	0.1
7	0.05	0.025	0.006	0.05	0.1	0.2	0.025	0.003	0.025	0.006	0.013	6/1	4/0.4	10/1	0.25
19a	0.05	0.05	0.013	0.1	0.2	0.8	0.025	0.013	0.05	0.013	0.05	14/4	21/7		2.62
19b	0.8	0.4	0.1	0.8	1.6	3.1	0.10	0.05	0.2	0.025	0.1	37/24			2.62
19c	0.05	0.05	0.013	0.1	0.1	0.4	0.05	0.05	0.05	0.006	0.025	50/24			2.62
19d	0.006	0.025	0.013	0.05	0.05	0.2	0.013	0.006	0.05	0.013	0.05	12/3.1	12/6.5		0.55
19e	0.2	0.1	0.025	0.2	0.4	1.6	0.05	0.025	0.1	0.1	0.1				2.75
19f	0.2	0.1	0.013	0.1	0.4	1.6	0.013	0.006	0.013	0.006	0.013	27/5.2	11/2	25/4	2.62
20a	0.2	0.2	0.2	0.4	0.8	3.1	0.8	0.2	1.6	0.8	0.8				0.8
20b	0.025	0.05	0.013	0.1	0.2	0.4	0.013	0.003	0.013	0.006	0.025	2.1/.7	9/3	5/2	2.62

[a] Standard microdilution techniques; see ref 16. [b] Dose required to protect 50% of mice from lethal infection. [c] Minimum concentration of drug needed to produce linear DNA at an intensity relative to oxolinic acid at 10 μg/mL.

3-Phenyl-3-pyrrolidinamine (**15d**) and the analogous 3-phenyl-3-pyrrolidinemethanamines (**15a**, **15b**, and **15c**) (Scheme I) were derived from common intermediate **11**. The acid **11** was prepared via the reaction of an azomethine ylide[15] (generated in situ from **8**) with methyl atropate (**9**) followed by acid hydrolysis of the resulting ester; although this methodology has been widely exploited in the construction of numerous 3,4-disubstituted pyrrolidines, its application to the 3,3-isomer has not been previously explored. The pyrrolidine acid obtained was then converted to amine **15d** by Curtius rearrangement and subsequent deprotection of the amine moieties. Alternatively, the acid functionality was transformed into several N-substituted 3-phenyl-3-pyrrolidinemethanamines via conversion to the requisite amide, reduction of the carbonyl, and debenzylation, affording the desired pyrrolidines **15a–c**.

In a similar fashion, an azomethine ylide reaction between precursor **8** and methacrylonitrile produced the pyrrolidinecarbonitrile **17** (Scheme II). Reduction with lithium aluminum hydride and subsequent debenzylation gave the target compound **18b**. Reaction of pyrrolidine **18b** with the trifluoroquinolone occurred almost exclusively at the pyrrolidine nitrogen, thereby avoiding the need for protection of the exocyclic amine; however, a protecting group (such as a *tert*-butoxycarbonyl) can be used if desired and is eadily appended prior to the debenzylation step.

Biological Assays

The series of quinolones prepared for this study was tested against a variety of Gram-negative and Gram-positive organisms by using standard microtitration techniques;[16] their minimum inhibitory concentrations (MICs in micrograms/milliliter) were compared to two standard compounds (**5** and **7**), and the results are presented in Table III. The geometric means of these MICs (for both the Gram-negative and Gram-positive strains) were also calculated to facilitate comparisons in activity between the different quinolone derivatives. A summary of the geometric means is found in Table IV. In addition, the quinolones were tested for their ability to inhibit the target enzyme DNA gyrase via a process described previously;[2a] these values are also included in Table III.

Table IV. Calculated Geometric Means of MICs[a]

compd	gram-negative mean[b]	gram-positive mean
5	0.019	0.044
7	0.033	0.010
19a	0.057	0.025
19b	0.53	0.075
19c	0.050	0.028
19d	0.022	0.019
19e	0.13	0.066
19f	0.10	0.0095
20a	0.30	0.70
20b	0.050	0.0095

[a] The geometric means were calculated by multiplying the MICs together and taking the fifth root. [b] Calculated by excluding *P. aeruginosa*.

The in vivo potency, expressed as the median protective dose (PD_{50}, milligrams/kilogram), was determined in acute, lethal systemic infections in female Charles River CD-1 mice. This method is described elsewhere,[3,17] and the results are listed in Table III. When the in vitro activity was particularly poor, no in vivo testing was performed; similarly, if the in vivo activity against *E. coli* H560 was low, no additional strains were tested.

Discussion of Results

The quinolone nucleus chosen for this study contained fluorine atoms at C-6 and C-8 and a cyclopropyl moiety at N-1, features necessary for good in vitro and in vivo activity. Therefore, these modifications were kept constant while varying the substitution pattern in the pyrrolidine ring. The resulting antibacterial potencies were interpreted from two perspectives. In the first, the exocyclic amine was kept constant, either as a 3-amino or as a 3-(aminomethyl) functionality, while the R group was varied. Conversely, the R group itself was kept constant while modifying the nature of the amine moiety. By using both approaches, some general conclusions could be drawn.

Using the first approach, the 3-(aminomethyl)-pyrrolidinyl quinolone **7** was compared to the analogous compounds containing 3-methyl (**20b**), 3-phenyl (**19a**), and 4-phenyl (**19f**) substituents. Evaluation of the appropriate geometric means revealed little if any change in in vitro efficacy, regardless of the nature or position of the substituent. The Gram-negative activity of the 3-methyl analogue **20b** was identical with that of the 3-phenyl compound **19a**, and both were only slightly less active than the 3-hydrogen parent (**7**); the 4-phenyl derivative was the

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(16) (a) Heifetz, C. L.; Chodubski, J. A.; Pearson, I. A.; Silverman, C. A.; Fisher, M. W. *Antimicrob. Agents Chemother.* **1974**, *6*, 124. (b) Cohen, M. A.; Griffin, T. J.; Bien, P. A.; Heifetz, C. L.; Domagala, J. M. *Antimicrob. Agents Chemother.* **1985**, *28*, 766.
(17) Miller, L. C.; Tainter, M. L. *Proc. Soc. Exp. Biol. Med.* **1944**, *57*, 261.

least potent of the four (by approximately 3-fold). Even less affected by alkyl and aryl substitution were the Gram-positive organisms: three of the four compounds—the 3-hydrogen, the 3-methyl, and the 4-phenyl derivatives—were equipotent, with geometric means of 0.01. Apparently there is no deleterious interaction between the amine group and the substituent, at least in vitro.

In contrast, the 3-amino analogues, in which the methylene spacer between the amino moiety and the ring was removed, *were* dependent on the nature of the substituent. The 3-phenyl-3-aminopyrrolidinyl compound **19d** showed a slight improvement over the 3-aminopyrrolidinyl parent (**5**) for Gram-positive bacteria and no change in activity against Gram-negative strains; however, the 3-methyl-3-aminopyrrolidinyl derivative **20a** proved inferior to either **19d** or **5**, with a 15-fold decrease in Gram-negative activity and a 35-fold decrease in Gram-positive activity.

A logical inference from these observations concerns the relationship between the distance from the amine to the substituent and the potency of the resulting compound. When R = phenyl and the amine group is varied, it becomes evident that the closer the phenyl group is to the amine, the more active the compound in vitro. For example, the 3-amino-3-phenylpyrrolidinyl compound **19d** was slightly more active than the 3-aminomethyl-3-phenyl isostere **19a**, in which the amino group is further away from the phenyl moiety; more apparent were the differences between the 4-phenyl-3-aminopyrrolidinyl derivative **19e** and the 4-phenyl-3-(aminomethyl)pyrrolidinyl quinolone **19f**, which were 6- and 2-fold less active, respectively, than their 3,3-disubstituted analogues. However, this general relationship between proximity and activity does not hold when the aryl moiety is changed to an alkyl group. The 3-methyl-3-aminopyrrolidinyl quinolone **20a** was 6 times *less* potent in vitro versus Gram-negative strains (and 7 times less potent versus Gram-positive organisms) than the homologous 3-methyl-3-(aminomethyl)pyrrolidine compound **20b**.

A theory that accounts for these contradictions and that explains the correlation between proximity and potency is not readily apparent. However, it has been postulated that the efficacy of those quinolones containing 3-amino- and 3-(aminomethyl)pyrrolidines arises from the ability of the side chain to assume a piperazinyl conformation in space. If this assumption is valid, then further substitution on the pyrrolidine ring could seriously interfere with the overlap needed for activity and result in a loss of antibacterial potency. The steric effect may therefore explain why the 3-aminopyrrolidinyl quinolone is more sensitive to substitution than is the corresponding 3-(aminomethyl)pyrrolidinyl analogue. The amine moiety in the aminomethyl compound possesses more degrees of freedom than does the amine in the aminopyrrolidine, enabling it to maneuver more easily in space to bypass any steric interference. For this reason, substitution on the pyrrolidine ring does not significantly affect the antibacterial potency of the pyrrolidinemethanamines. Conversely, the amino group in the aminopyrrolidinyl compounds is more restricted in its movements and is more susceptible to any substituent (such as a methyl group) that may prohibit the desired interactions, although this hindrance can be overcome if said substituent is aromatic. This hypothesis, though only conjecture at this point, nevertheless explains the observations gathered from this limited data set.

All compounds in this study possess gyrase cleavage values that are less than 3 μg/mL (Table III), making them excellent inhibitors of the target enzyme. Previous studies[2a,5] have shown that the correlation between gyrase inhibition and antibacterial efficacy is a general one in that agents having gyrase values <5 μg/mL are usually (but not always) potent antifectives. Moreover, gyrase values of 0.1 or 0.2 μg/mL, while desirable, do not necessary correspond to MICs that are orders of magnitude better than those compounds possessing gyrase values of 3 or 4 μg/mL. In light of this observation, it is not particularly surprising that compounds **19a–f** and **20a,b**, while displaying similar activity against the gyrase enzyme, display widely different antibacterial potencies.

Until now, only the in vitro activity of these compounds has been addressed. As a general rule, the alkyl- or aryl-substituted pyrrolidine derivatives were all less active in vivo than the analogous unsubstituted compounds (e.g., **5** and **7**). Only the 3-(aminomethyl)-3-methylpyrrolidinyl quinolone **20b** was more active than the unsubstituted parent compound against *Strep. pneumonia*, *Strep. pyogenes*, and *E. coli*. In this one surprising case, the quinolone containing the 3,3-disubstituted pyrrolidine was generally 2–3 times more potent. This anomaly in the data did not seem to be a function of improvement in solubility, and factors such as transport or other post-gyrase events could presumably be at work.

A series of 3-phenyl-*N*-substituted-3-pyrrolidinemethanamines (**19b** and **19c**) was synthesized, tested, and compared to **19a**, the parent 3-phenyl-3-pyrrolidinemethanamine. The *N,N*-dimethyl compound **19c** proved to be equipotent with the unsubstituted amino parent **19a**, while the *N*-ethyl analogue **19b** showed a 10-fold decrease in Gram-negative activity and a 3-fold decrease in Gram-positive activity. All N-substituted compounds were inferior to the parent quinolone in vivo. These observations contradict the trends reported for the desphenyl series,[4] where the N-substituted pyrrolidinemethanamines display a 2–3-fold *enhancement* in in vivo activity over the unsubstituted pyrrolidinemethanamines.

In conclusion, substitution on the pyrrolidine ring of (3-pyrrolidinylmethyl)amino quinolones (such as **7**) does not significantly affect antibacterial activity in vitro, while substitution in the analogous 3-aminopyrrolidine system either decreases the potency (when said substituent is a methyl group) or increases the efficacy (when that substituent is aromatic). The in vivo activity of the alkyl- and aryl-substituted pyrrolidine derivatives decreases in comparison to the unsubstituted derivatives in all cases save one: the quinolone containing a 3-(aminomethyl)-3-methylpyrrolidine at the 7-position (**20b**). This particular agent is equipotent with the unsubstituted analogue against Gram-negative strains, 4 times more potent against Gram-positive organisms, and 2–3 times more potent in vivo against representative bacteria. In fact, the 7-[3-(aminomethyl)-3-methyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**20b**) showed the best Gram-positive efficacy in vitro and in vivo of any quinolone in this study.

Experimental Section

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Nicolet FT IR SX-20. Proton magnetic resonance (NMR) were recorded on either a Varian XL-200 or IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Column chromatography was performed with E. Merck silica gel, 230–400 mesh ASTM; solutions were dried over magnesium sulfate. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer, and all compounds had analytical results ±0.4% of theoretical values. Compounds **19a–f** and **20a,b** were assayed for purity with a Perkin-Elmer LC-95 HPLC system equipped with a 5-μm Ul-

trasphere ODS column and a mobile phase consisting of 25% THF: 75% 0.05 M $NH_4H_2PO_4$ (adjusted to pH 5.0 with H_3PO_4); in all cases, the purity exceeded 97.0%. All concentrations were performed in vacuo at 10–30 mmHg. *tert*-Butyl alcohol was distilled from CaH_2, while all other solvents were used without purification. The structures of all compounds were consistent with their spectral properties.

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinecarboxylic Acid Methyl Ester (10). A suspension of 32.5 g (140 mmol) of 8,[15] 27.7 g (170 mmol) of methyl atropate, 21.6 g (170 mmol) of silver(I) fluoride, and 400 mL of CH_3CN was stirred for 18 h in the dark. The reaction mixture was diluted with $HCCl_3$ and filtered through Celite. The filtrate was concentrated, and the residue was chromatographed on silica gel, eluting with 80:20 $HCCl_3$/EtOAc, to give 8.2 g (20%) of the title compound: IR (film) 1773 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (m, 10 H), 3.7 (m, 3 H, CH_3), 3.55 (m, 3 H, benzyl and pyrrol), 3.05 (m, 3 H), 2.4 (m, 3 H), 2.2 (m, 1 H).

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinecarboxylic Acid Hydrochloride (11). A solution of 7.7 g (26.1 mmol) of 10, 75 mL of 6 M HCl, and 75 mL of MeOH was refluxed for 3 h and then stirred at room temperature for 18 h. The mixture was concentrated, and the residue was triturated with 2-propanol and filtered. The crude product was recrystallized from 2-propanol to give 5.0 g (60%) of the desired product as the hydrochloride salt: mp 228–230 °C: IR 3400 (br), 1724 cm^{-1}; NMR (DMSO-d_6) δ 7.65 (m, 2 H), 7.4 (m, 8 H), 4.4 (s, 2 H, benzyl), 4.2 (m, 1 H), 3.5 (m, 4 H), 2.9 (m, 1 H). Anal. Calcd for $C_{17}H_{19}NO_2$·HCl: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.97; H, 6.28; N, 4.65.

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinecarbamic Acid Butyl Ester (12). A suspension of 4.8 g (15.1 mmol) of 11, 3.05 g (30.2 mmol) of triethylamine, and 200 mL of dry *tert*-butyl alcohol was stirred at room temperature for 1 h. To the mixture was added 4.15 g (15.1 mmol) of diphenyl phosphorazidate dropwise. The solution was refluxed for 18 h and then concentrated to a syrup. The residue was dissolved in H_2CCl_2, washed with 5% $NaHCO_3$ and H_2O, and dried. Concentration gave 5.2 g of the title compound, which was used without purification in the next step: IR (film) 1698 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 10 H), 3.7 (q, 2 H, benzyl), 2.95 (m, 4 H), 2.4 (m, 2 H), 1.3 (s, 9 H, BOC).

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinamine. A solution of 5.0 g (13.6 mmol) of crude 12, 50 mL of THF, and 40 mL of 6 M HCl was stirred at 60 °C for 3 h and then at room temperature for 18 h. The solution was concentrated to give a viscous oil which was dissolved in 15 mL of EtOH and treated with ether to precipitate a white solid. This solid was filtered, washed with ether, and dissolved in H_2O. The solution was made basic (pH 10) and filtered to remove a trace of insoluble material; the filtrate was extracted with ether and the extracts dried and concentrated to give 1.5 g (44%) of yellow oil: NMR ($CDCl_3$) δ 7.3 (m, 10 H), 3.7 (s, 2 H, benzylic), 3.1 (m, 1 H), 2.8 (d, 2 H), 2.5 (m, 3 H), 1.95 (s, 2 H, NH_2).

3-Phenyl-3-pyrrolidinamine (15d). A mixture of 1.1 g (4.4 mmol) of 3-phenyl-1-(phenylmethyl)-3-pyrrolidinamine, 0.2 g of 20% palladium on carbon, and 100 mL of MeOH was shaken in a hydrogen atmosphere of 50 psi for 18 h. The catalyst was filtered, and the filtrate was concentrated to give 0.69 g of a tan oil. This material was used without purification in the displacement reactions.

General Procedure. Syntheses of 3-Phenyl-3-pyrrolidinemethanamines 15a–c. In a typical experiment, a suspension of 4.3 g (13.5 mmol) of 11, 1.36 g (13.5 mmol) of triethylamine, and 100 mL of CH_3CN was treated with 2.4 g (14.8 mmol) of 1,1′-carbonyldiimidazole and heated at 60 °C for 90 min. The solution was then cooled to room temperature. To this mixture was added the requisite amine as follows: for ethylamine, the condensed liquid (1.1 equiv) was added portionwise, and for ammonia and dimethylamine, the gaseous material was bubbled through the reaction mixture for 30 min. In all cases, the resulting solution was stirred overnight at room temperature once amine addition was complete. The solution was then concentrated, and the residue was dissolved in H_2CCl_2, washed with H_2O, and dried. Concentration gave the appropriate N-substituted amides in good yields (65–90%).

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinecarboxamide (13a): IR (film) 3200, 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (m, 10 H, arom), 3.8 (s, 2 H, benzyl), 3.5 (d, 1 H, pyrrol), 3.1 (m, 1 H, pyrrol), 2.75 (m, 3 H, pyrrol), 2.35 (m, 1 H, pyrrol). The NMR spectrum of the *N*-ethyl analogue (**13b**) displayed the characteristic ethyl resonances at δ 3.2 (m, 2 H) and δ 1.1 (t, 3 H). Similarly, the spectrum of the *N,N*-dimethyl compound (**13c**) contained a diagnostic singlet at δ 2.75 corresponding to the $N(CH_3)_2$ protons.

The amides were reduced to the corresponding amines as follows: To a suspension of the amide (13.0 mmol) in dry THF was added 1.0 g (26.0 mmol) of lithium aluminum hydride under argon. The mixture was stirred overnight at room temperature and then refluxed for 2 h. The solution was carefully treated with 0.8 mL of H_2O, 1.0 mL of 40% NaOH, and 3.5 mL of H_2O. The grainy precipitate was filtered and the filtrate concentrated to give the desired pyrrolidine amines in moderate to good yields.

3-Phenyl-1-(phenylmethyl)-3-pyrrolidinemethanamine (14a): IR (film) 2800, 1496, 1453 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (m, 10 H), 3.65 (s, 2 H, benzyl), 3.0 (m, 4 H, CH_2NH_2 and pyrrol), 2.65 (d, 1 H), 2.45 (q, 1 H), 2.2 (m, 2 H), 1.9 (m, 2 H, NH_2). The NMR spectrum of the *N*-ethyl analogue (**14b**) displayed characteristic ethyl resonances at δ 3.2 (m, 2 H) and δ 1.1 (t, 3 H), while the *N,N*-dimethyl compound (**14c**) contained a singlet at δ 2.3 indicative of the $N(CH_3)_2$ protons.

The benzyl groups were removed as follows: A solution of 10.2 mmol of the appropriate 1-benzyl pyrrolidine, 0.5 g of 20% palladium on carbon, and 100 mL of MeOH was shaken in a hydrogen atmosphere of 50 psi at 25 °C for 24 h. The catalyst was filtered, and the filtrate was concentrated to give the debenzylated pyrrolidine in excellent (>90%) yields.

3-Phenyl-3-pyrrolidinemethanamine (15a): IR (film) 3400 (br); NMR ($CDCl_3$) δ 7.3 (m, 5 H, arom), 3.3 (d, 1 H), 3.1 (m, 3 H, pyrrol and CH_2NH_2), 2.8 (m, 2 H), 2.1 (t, 2 H), 1.95 (bs, 2 H, NH_2). Again, the NMR spectrum of the *N*-ethyl analogue (**15b**) displayed the predicted signals at δ 2.55 (m, 2 H) and δ 1.0 (t, 3 H).

4-Phenyl-1-(phenylmethyl)-3-pyrrolidinemethanamine. To a solution of 5.7 g (21.8 mmol) of 4-phenyl-1-(phenylmethyl)-3-pyrrolidinecarbonitrile[14] in 150 mL of dry THF was added 0.83 g (21.8 mmol) of lithium aluminum hydride in portions under argon. The mixture was stirred for 18 h at room temperature and then treated with 0.9 mL of H_2O, 0.8 mL of 40% NaOH, and 3.0 mL of H_2O. The precipitate was filtered and the filtrate concentrated to give 5.5 g (95%) of the title compound: IR 2913 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 10 H), 3.7 (s, 2 H, benzyl), 2.8 (m, 8 H, CH_2NH_2 and pyrrol), 1.5 (bs, 2 H, NH_2).

4-Phenyl-3-pyrrolidinemethanamine (15f). A solution of 4.4 g (16.5 mmol) of crude 4-phenyl-1-(phenylmethyl)-3-pyrrolidinemethanamine, 0.5 g of 20% palladium on carbon, 100 mL of MeOH, and 1 mL of AcOH was shaken in an atmosphere of hydrogen at about 50 psi and at room temperature for 18 h. The catalyst was filtered and the filtrate concentrated to give 2.4 g (84%) of the title compound: NMR ($CDCl_3$) δ 7.3 (m, 5 H), 3.9 (m, 1 H), 3.7 (m, 1 H), 3.45 (s, 2 H, CH_2NH_2), 3.3 (m, 4 H), 2.8 (m, 2 H, NH_2).

3-Methyl-1-(phenylmethyl)-3-pyrrolidinecarbonitrile (17). A suspension of 11.6 g (50.0 mmol) of 8,[15] 3.5 g (52.0 mmol) of methacrylonitrile, 7.0 g (55.0 mmol) of silver fluoride, and 150 mL of CH_3CN was stirred for 18 h at room temperature in the dark. The mixture was diluted with $HCCl_3$ and filtered through Celite. Concentration of the filtrate gave an oil which was chromatographed on silica gel, eluting with an 80:20 $HCCl_3$/EtOAc mixture, to give 2.5 g (18%) of the title compound: IR (film) 2237 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5 H), 3.6 (s, 2 H, benzyl), 2.95 (d, 1 H), 2.75 (m, 1 H), 2.5 (m, 1 H), 2.3 (d, 1 H), 2.2 (m, 1 H), 1.85 (m, 1 H), 1.4 (s, 3 H, CH_3).

3-Methyl-1-(phenylmethyl)-3-pyrrolidinemethanamine (18). To a solution of 2.0 g (10 mmol) of 17 in 40 mL of THF was added 0.38 g (10 mmol) of lithium aluminum hydride in portions under argon. The reaction mixture was stirred at room temperature for 18 h and then treated with 0.3 mL of H_2O, 0.4 mL of 40% NaOH, and 1.4 mL of H_2O. The grainy precipitate was filtered, and the filtrate was concentrated to give 1.9 g (88%) of the title compound: bp 100–102 °C 0.1 (mmHg); NMR ($CDCl_3$) δ 7.2 (s, 5 H), 3.55 (s, 2 H, benzyl), 2.6 (s, 2 H, CH_2NH_2), 2.2 (d, 1 H), 1.5 (m, 4 H, pyrrol and NH_2), 1.05 (s, 3 H, CH_3).

3-Methyl-3-pyrrolidinemethanamine (18b). A suspension of 1.87 g (9.0 mmol) of crude 18, 1.0 g of 20% palladium on carbon,

and 100 mL of MeOH was shaken in an atmosphere of hydrogen at about 50 psi and at room temperature for 20 h. The catalyst was filtered and the filtrate concentrated to give 1.0 g (95%) of the title compound: NMR ($CDCl_3$) δ 3.0 (t, 2 H, CH_2NH_2), 2.5 (m, 7 H, pyrrol and amine protons), 1.5 (m, 2 H), 1.05 (s, 3 H, CH_3).

General Method B. Synthesis of 7-[3-(Aminomethyl)-3-phenyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (19a). To 1.13 g (4.00 mmol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[11] in 40 mL of CH_3CN were added 0.88 g (5.00 mmol) of **15a** and 1.03 g (10.0 mmol) of triethylamine. The mixture was refluxed for 3 h and then stirred at room temperature for 18 h. The solids were filtered and washed with CH_3CN and ether to give 1.55 g (89%) of the title compound: mp 233-235 °C; IR (KBr) 1723, 1626 cm^{-1}; NMR (TFA) δ 9.3 (s, 1 H, C_2H), 8.1 (d, J = 13 Hz, 1 H, C_5H), 7.5 (m, 5 H, phenyl), 4.5 (m, 4 H, pyrrol), 4.1 (m, 1 H, cyclopr), 3.8 (s, 2 H, CH_2NH_2), 2.65 (m, 2 H, pyrrol), 1.5 (m, 4 H, cyclopr). Anal. Calcd for $C_{24}H_{23}F_2N_3O_3 \cdot 0.15H_2O$: C, 65.19; H, 5.31; N, 9.50. Found: C, 65.13; H, 5.19; N, 9.65.

Compound **20a** was prepared in a similar fashion, using **18a**,[13] the trifluoroquinolone, and triethylamine to give 7-[3-(acetylamino)-3-methyl-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. A suspension of 1.05 g (2.59 mmol) of this product in 35 mL of 6 N HCl and 20 mL of AcOH was refluxed for 18 h and then cooled and concentrated. The residue was triturated with *i*-PrOH, and the solids were filtered and recrystallized from *i*-PrOH to give 0.85 g (53% over two steps) of **20a**.

N-Phenyl-*N'*-pyridinylureas as Anticonvulsant Agents[1]

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A series of *N*-phenyl-*N'*-pyridinylureas was examined for anticonvulsant activity. Extensive structure/activity investigations revealed optimal activity in the *N*-(2,6-disubstituted-phenyl)-*N'*-(4-pyridinyl)urea series, with **37** exhibiting the best overall anticonvulsant profile. Compound **37** was effective against seizures induced by maximal electroshock but did not protect mice from clonic seizures produced by the convulsant pentylenetetrazol. The overall pharmacological profile suggests that **37** would be of therapeutic use in the treatment of generalized tonic-clonic and partial seizures. Compound **37** was selected for Phase 1 clinical trials.

The search for new anticonvulsant drugs remains an active area of investigation since available antiepileptic drugs are effective in only 60%-80% of patients.[2] While absence (petit mal) seizures are well treated in most instances, significant therapeutic improvement is still needed for the treatment of partial-complex (focal) and generalized tonic-clonic (grand mal) seizures.[3] In addition, most marketed anticonvulsants suffer from a broad range of undesirable side effects[4] such as sedation, teratogenicity, cognitive dulling, blood dyscrasia, and hepatotoxicity. Failure to achieve control of seizures is frequently due to use-limiting side effects seen with increasing doses of the drugs before a satisfactory therapeutic dose is reached.

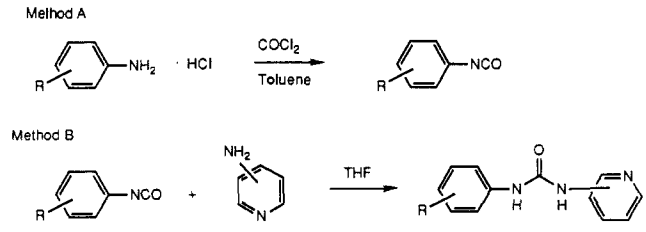
In collaboration with the NIH-NINCDS Antiepileptic Drug Discovery Program,[5] we discovered the potent anticonvulsant effects of a series of *N*-phenyl-*N'*-(4-pyridinyl)ureas.[6] While this class of compounds has been described to promote cell growth and differentiation in plants,[7-10] we are unaware of reports of these compounds displaying anticonvulsant activity.

Initially, anticonvulsant activity was observed with *N*-(2,6-dimethylphenyl)-*N'*-(4-pyridinyl)urea (**1**). While this compound was effective in blocking seizures in mice induced by maximal electroshock (an accepted model for generalized tonic-clonic seizures), we sought both an improvement in potency as well as greater separation between the doses affording protection from seizures and those exhibiting undesirable behavioral side effects. To achieve these goals, we systematically examined structural modifications using **1** as a starting point.

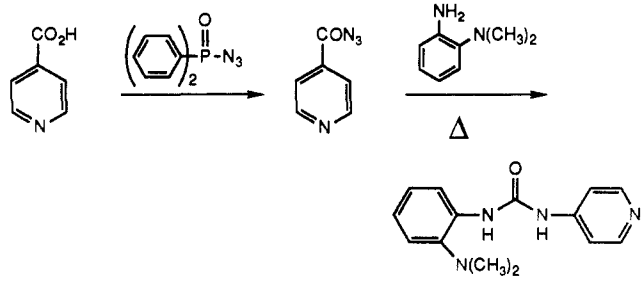
Chemistry

The ureas were prepared by reaction of an isocyanate with an amine (method B, Scheme I). In most cases the isocyanates were commercially available or were prepared by reaction of an aniline hydrochloride with excess phosgene[11] (method A, Scheme I). The two exceptions were compounds **17** and **44**. In the former case, attempts to

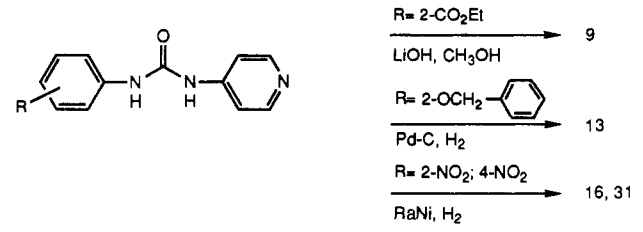
Scheme I



Scheme II



Scheme III



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(1) Presented in part at 194th American Chemical Society Meeting, New Orleans, LA, 1987.

0022-2623/90/1833-0854$02.50/0 © 1990 American Chemical Society