titioned between CH_2Cl_2 and water. The organic layer was separated, dried, and concentrated to give 4.52 g of crude product. A solution of this material in 100 mL of EtOH was hydrogenated over 0.5 g of Raney nickel at 51 psig and 26 °C for 18 h. The mixture was filtered, and the filtrate was concentrated to a yellow solid. This solid was suspended in 50 mL of EtOH and 50 mL of 6 M HCl, refluxed for 3 h, and cooled to room temperature. The solution was concentrated, and the residue was triturated with 2-propanol and filtered to give 3.43 g (68% from 4) of **5f** as a hygroscopic solid: IR 1735, 1630 cm^{-1}; NMR (DMSO-d_6) δ 8.8 (s, 1 H, C_2H), 7.3 (d, J = 12 Hz, 1 H, C_5H), 6.1 (s, 2 H, C_8NH_2), 4.6 (m, 1 H, cyclopropyl), 3.25 (m, 6 H, CH_2NMe_2 and pyrrolidine), 2.8 (s, 6 H, $N(CH_3)_2$), 2.25 (m, 2 H, pyrrolidine), 1.9 (m, 1 H, pyrrolidine), 1.2 (m, 4 H, cyclopropyl). Anal. Calcd for $C_{20}H_{25}FN_4O_3\cdot2.75H_2O\cdot1.65HCl$: C, 48.21; H, 6.50; N, 11.25; Cl, 11.75. Found: C, 47.98; H, 6.59; N, 11.09; Cl, 11.73.

7-[3-[(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-6-fluoro-8-nitro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester (4.4 g, 5.7 mmol), was prepared from 4, 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, and triethylamine as described above. The nitro group was reduced as before with Raney nickel in DMF at 55 psig and 25 °C. The final hydrolysis in 6 M HCl and EtOH removed the protecting group from the amine and hydrolyzed the ester to the acid to give, upon trituration and filtration, 2.4 g (68% from 4) of **5a**.

General Method E. Preparation of 10-[3-(Aminomethyl)-1-pyrrolidinyl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (7b). To 0.75 g (2.7 mmol) of 7 in 40 mL of CH_3CN was added 0.80 g (8.0 mmol) of 3-pyrrolidinemethanamine, and the mixture was refluxed overnight. The solution was concentrated, and the residue was triturated with 40 mL of 1:1 EtOH/ether. The solids were filtered and washed with ether to give 0.95 g (93%) of **7b**, mp 213-216 °C: IR 1730 cm^{-1}; NMR (TFA) δ 9.3 (s, 1 H, C_5H), 8.15 (d, J = 12 Hz, 1 H, C_5H), 7.2 (s, 3 H, NH_3^+), 5.2 (m, 1 H, C_8H), 4.8 (m, 2 H, C_2H), 4.3 (m, 4 H, CH_2NH_2 and pyrrolidine), 3.5 (m, 3 H, pyrrolidine), 2.75 (m, 1 H, pyrrolidine), 2.5 (m, 1 H, pyrrolidine), 2.2 (m, 1 H, pyrrolidine), 1.85 (d, 3 H, CH_3). Anal. Calcd for $C_{18}H_{20}FN_3O_4\cdot1.5H_2O$: C, 55.66; H, 5.95; N, 10.82. Found: C, 55.41; H, 5.66; N, 10.90.

Compound **7c** was prepared as above, and the residue was dissolved in water at pH 1. Concentration of the solution gave a solid, which was recrystallized from EtOH to give the desired product as the hydrochloride.

10-[3-[(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (1.3 g, 2.9 mmol) was prepared from **7**, 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, DBU, and DMF at 60 °C as outlined above. The solution was concentrated, and the residue was triturated with water to give a crystalline solid. This material was then filtered, suspended in 5 mL of 6 M HCl and 10 mL of acetic acid, and stirred at room temperature for 18 h. Concentration followed by trituration with EtOH/ether, 1:1, and filtration gave 0.80 g (49% from **7**) of **7a**.

Registry No. 1, 93107-30-3; **1a**, 113533-52-1; **1a** (*N*-BOC, free base), 99724-20-6; **1b**, 104455-75-6; **1c**, 104455-80-3; **1d**, 104455-77-8; **1d**·HCl, 104455-76-7; **1e**, 113533-53-2; **1e**·HCl, 113533-54-3; **1f**, 113533-55-4; **1g**, 85721-33-1; **2**, 94695-52-0; **2a**, 106797-94-8; **2a** (*N*-BOC, free base), 99724-13-7; **2b**, 99734-96-0; **2c**, 99735-00-9; **2d**, 99734-97-1; **2e**, 99735-02-1; **2f**, 104456-07-7; **2g**, 94242-53-2; **3**, 101987-89-7; **3a**, 105956-99-8; **3a** (*N*-BOC free base), 105956-96-5; **3d**, 104456-00-0; **3f**, 104456-06-6; **3g**, 99696-22-7; **4**, 111453-55-5; **4a**, 113533-56-5; **4d**, 113533-57-6; **4g**, 113533-58-7; **5a**, 113533-59-8; **5c**, 113533-60-1; **5d**, 113533-61-2; **5f**, 113533-62-3; **5g**, 113533-63-4; **6**, 100361-18-0; **6a**, 96568-33-1; **6a** (*N*-BOC), 113533-64-5; **6b**, 99735-09-8; **6c**, 113533-65-6; **6d**, 99735-10-1; **6e**, 99735-11-2; **6f**, 113533-66-7; **6g**, 99735-41-8; **7**, 82419-35-0; **7a**, 113533-67-8; **7a** (*N*-BOC, free base), 113533-68-9; **7b**, 91188-21-5; **7c**, 91188-22-6; **7c**·HCl, 113533-69-0; **7d**, 91196-82-6; **7f**, 113533-70-3; **16**, 327-52-6; **17**, 446-17-3; **22**, 106809-17-0; cyclopropylamine, 765-30-0; ethyl 2'-(ethoxymethylene)-3'-[4-chloro-2-(cyclopropylamino)-5-fluoro-3-nitrophenyl]-3'-oxopropionate, 113533-71-4; *N*,*N*-dimethyl-3-pyrrolidinemethanamine, 99724-17-1; 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, 99724-19-3; *N*-methyl-3-pyrrolidinemethanamine, 91187-81-4; *N*-ethyl-3-pyrrolidinemethanamine, 91187-83-6; 7-[3-[(*tert*-butoxycarbonyl)amino]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-8-nitro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, 113533-72-5; 1-cyclopropyl-7-[3-[(dimethylamino)methyl]-1-pyrrolidinyl]-6-fluoro-8-nitro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, 113548-08-6; 3-pyrrolidinemethanamine, 67318-88-1; *N*-isopropyl-3-pyrrolidinemethanamine, 91187-87-0; piperazine, 110-85-0.

1-Substituted 7-[3-[(Ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. New Quantitative Structure–Activity Relationships at N_1 for the Quinolone Antibacterials[1]

John M. Domagala,* Carl L. Heifetz, Marland P. Hutt, Thomas F. Mich, Jeffry B. Nichols, Marjorie Solomon, and Donald F. Worth

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.
Received August 7, 1987

A series of 18 1-substituted 7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (N_1 analogues of CI-934) were synthesized and evaluated for antibacterial activity and DNA-gyrase inhibition. Correlations between the inhibition of DNA gyrase and antibacterial potency were established. A quantitative structure–activity relationship (QSAR) was derived by using the antibacterial potency for each of 11 strains of bacteria and the Gram-negative mean. The equations indicated that antibacterial potency was strongly dependent on STERIMOL length and width and the level of unsaturation of the N_1 substituent. Some strains also showed a dependence on the presence of heteroatoms (O, N, S) in the N_1 group. No significant correlations between gyrase inhibition and combinations of these parameters were found. These QSAR results are discussed in conjunction with the conformational analyses from molecular modeling studies. The substituent that most enhanced the activity of the quinolone in all regards was the cyclopropyl group. This analogue, 1-cyclopropyl-7-[3-[(ethylamino)-methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (PD 117558), demonstrated outstanding broad spectrum activity both in vitro and in vivo when compared to relevant standards.

The quinolone antiinfectives, represented generically by 1, have aroused much interest because of their potency and oral efficacy.[2] While many excellent agents have been described or are under development[3] (Figure 1), only a few

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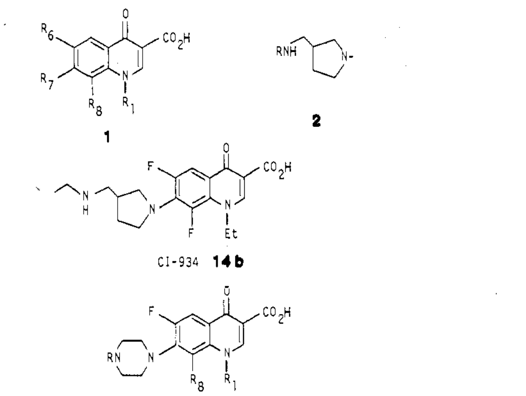


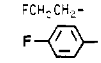
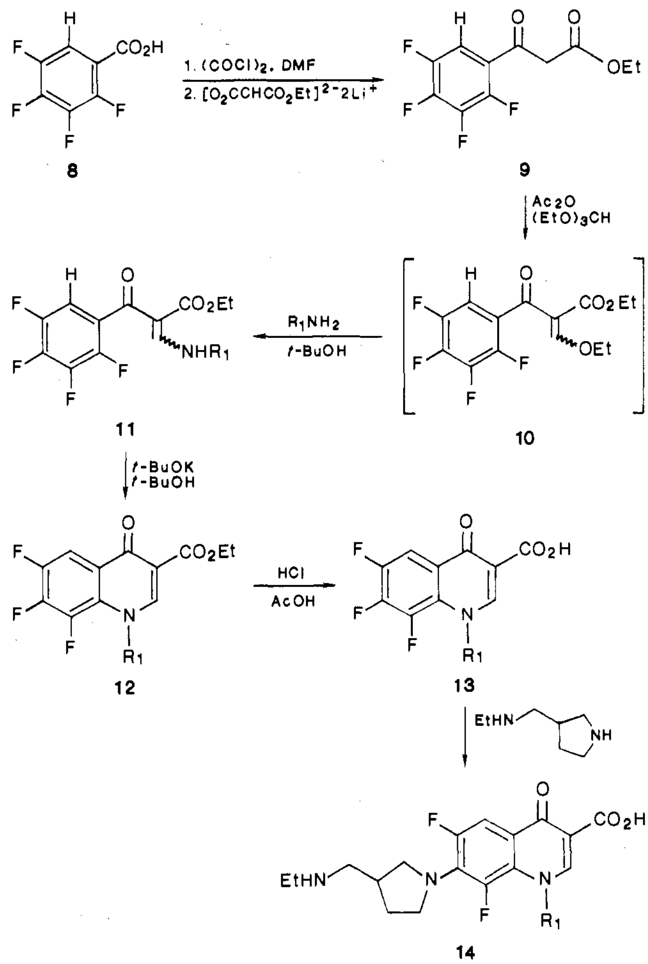
Compd #	Compd Name	R_1	R_8	R	Ref.
3	ciprofloxacin		H	H	10
4	AM 833	FCH_2CH_2-	F	CH_3	11
5	difloxacin (A56619)		H	CH_3	12
6	norfloxacin	Et	H	H	4a
7	amifloxacin	CH_3NH-	H	CH_3	4b

Figure 1. Clinically significant quinolones chosen as reference agents for this study.

Scheme I



detailed structure–activity relationships (SAR) have been published.[3c,4,5] It is generally accepted that a fluorine at R_6 is optimal[4,5] and is a feature common to all of the most potent agents. Many substituents have been synthesized at R^7 with various degrees of activity,[2c,d] but systematic studies by Koga,[4a] Matsumoto,[6a] and in our laboratories[5] have clearly identified a preference for five- and six-membered rings. Fewer studies have centered around R_8.[2d,4d] In the early development of the quinolones, a large variety of lower alkyl and simple aromatic substituents were tested at R_1,[2d] including cyclopropyl.[6b] Only a few studies have utilized the potent 6-fluorinated quinolones,[4a–c,6a] and in these the variety of alkyl groups at R_1 was limited. Most literature reports generally lack sufficient data or alter too many variables to be useful in a quantitative SAR (QSAR). Today, the cyclopropyl radical is accepted as one of the most effective substituents,[3] but the reason for this efficacy is largely unknown.

Studies from our laboratories have indicated that the antibacterial activity of the quinolones may have two components. The first and simplest component conceptually is the ability of the drug to inhibit the target enzyme DNA gyrase. The second, less defined component has been attributed to transport effects[5] or other post-gyrase events.[7] Developing an SAR using traditional minimum inhibitory concentrations (MICs), without considering the target enzyme, could be misleading.

To sort out these variables, we have employed a DNA-gyrase assay combined with traditional antibacterial screens. This approach helped us to predict that a 3-(aminomethyl)pyrrolidine (2) might mimic the more commonly used piperazinyl side chain at R_7, leading to the synthesis of CI-934[8] (**14b**) with the unexpected benefit of increased staphylococci and streptococci activity.[9] This

(1) A portion of this work has been presented in preliminary form at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 29–Oct 1, 1986, New Orleans, LA. Abstracts 422–424.

(2) (a) Wolfson, J. S.; Hooper, D. C. *Antimicrob. Agents Chemother.* **1985**, *28*, 581 and 716. (b) Hoiby, N. *Eur. J. Clin. Microbiol.* **1986**, *5*, 138. (c) Janknegt, R. *Pharm. Weekbl., Sci. Ed.* **1986**, *8*, 6. (d) Albrecht, R. *Prog. Drug Res.* 1977, *21*, 9. (e) Bergan, T. *Antimicrobial Agents Annual I*; Peterson, P. K., Verhoef, J., Eds.; Elsevier: *Amsterdam*, 1986; Chapter 14, pp 164–178.

(3) Many reports on newer quinolines have been presented at the (a) 23rd, (b) 24th, (c) 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct 24–26, 1983, Las Vegas, NV; Oct 8–10, 1984, Washington, DC; Sept 29–Oct 2, 1985, Minneapolis, MN.

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(6) (a) Egawa, H.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Okada, H.; Uno, H.; Matsumoto, J. *J. Med. Chem.* **1984**, *27*, 1543. (b) Grohe, K.; Zeiler, H. J.; Metzger, K. U.S. Pat. 4284629, 1981.

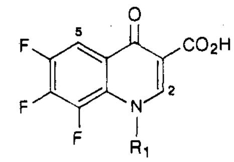
(7) In addition to permeability and transport, it is quite possible that another component of activity involves post-gyrase events. Smith, J. T. *Fortschr. Antimikrob. Antineoplast. Chemother.* **1984**, *3–5*, 493. Crumplin, G. C.; Kenwright, M.; Hirst, T. *J. Antimicrob. Chemother.* **1984**, *13*, Suppl. B, 9. See also abstract 946, ref 1.

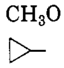
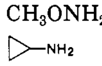
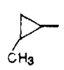
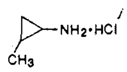
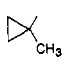
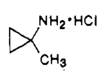
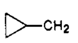
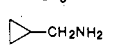
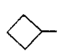
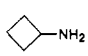
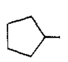
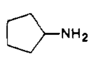
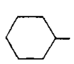
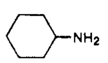
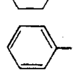
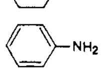
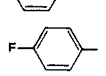
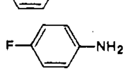
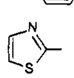
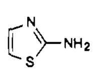
(8) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. *J. Med. Chem.* **1986**, *29*, 445.

(9) Cohen, M. A.; Griffin, T. J.; Bien, P. A.; Heifetz, C. L.; Domagala, J. M. *Antimicrob. Agents Chemother.* **1985**, *28*, 766.

(10) Wise, R.; Andrews, J. M.; Edwards, L. *Antimicrob. Agents Chemother.* **1983**, *23*, 559.

Table I. Synthetic and Physical Data of the 1-Substituted Trifluoroquinolone Starting Materials



compd	R_1	starting amine	% yield from **9**	mp, °C	NMR data (δ), TFA: C_2H[a]	C_5H[b]	R_1	mp, °C: **11**[c]	**12**[c]
13a	CH_3	CH_3NH_2(g)	67	271–273[e]	9.3	8.25	4.6 (d, J = 9 Hz, 3 H)		198–200
13b	CH_3CH_2	*d*		258–259[d]	9.5	8.45	5.1 (m, 2 H), 1.84 (t, J = 7 Hz, 3 H)		202–205
13c	$CH_2{=}CH$	*f*		185–186	9.2	8.25	7.65 (m, 1 H), 5.9 (m, 2 H)		135–136
13d	FCH_2CH_2	$FCH_2CH_2NH_2{\cdot}HCl$	43	211–213[g]	9.5	8.5	5.6 (m, 1 H), 5.2 (m, 2 H), 4.85 (m, 1 H)		199–201
13e	CF_3CH_2	$CF_3CH_2NH_2{\cdot}HCl$	37	205–207	9.4	8.35	5.65 (q, J = 7 Hz, 2 H)		161–163
13f	CH_3NH	$CH_3N(NH_2)CO_2$-t-Bu[i]	49	237–238	8.96	8.16	7.25 (q, J = 7 Hz, 1 H), 2.9 (d, J = 7 Hz, 3 H)	130–131	99.5–102
13g	CH_3O	$CH_3ONH_2{\cdot}HCl$	25	223–224	9.5	8.3	4.3 (s, 3 H)		
13h			82	226–228	8.65	8.05	4.05 (m, 1 H), 1.2 (m, 4 H)	64–65	170–171
13i	$(CH_3)_2CH$	$(CH_3)_2CHNH_2$	70	256–260	9.5	8.4	5.9 (5, 1 H), 1.9 (d, J = 6 Hz, 6 H)	69–71	157–159
13j			53	167–180	9.5	8.4	4.2 (m, 1 H), 1.8 (m, 2 H), 1.5 (m, 4 H)		154–156
13k			60	292–294	9.8	8.5	2.1 (d, J = 2 Hz, 3 H), 1.8 (m, 4 H)		
13l			42	223–255 (sl dec)	9.1[h]	8.2	4.5 (dd, J = 8, 3 Hz, 2 H), 1.4 (m, 1 H), 0.65 (m, 4 H)	116–117	158–160
13m			30	192–194	9.35	8.3	5.55 (m, 1 H), 2.7 (m, 4 H), 2.1 (m, 2 H)	100–101	156–158
13n			79	206–207	9.4	9.3	5.9 (m, 1 H), 2.7–2.0 (m, 8 H)	98–100	177–178
13o			58	261–264	9.4	8.4	5.5 (m, 1 H), 2.0 (m, 10 H)		
13p			59	264–267.5	8.57[h]	8.25	7.73 (m, 5 H)	101–103	190.5–192
13q			32	255–257	9.3	8.49	7.66 (m, 2 H), 7.42 (m, 2 H)		219–220
13r			48	198.5–200	9.3	8.3	8.12 (d, J = 3 Hz, 1 H), 8.0 (d, J = 3 Hz, 1 H)		172–174

[a] Singlet. [b] Multiplet. [c] Melting points are given for those cases where **11** or **12** were isolated and analytically pure. [d] Prepared from Scheme II, see ref 15. [e] Lit. mp 255–258 °C, see ref 15. [f] Prepared from Scheme II. [g] Lit. mp 208–210 °C, see ref 15. [h] DMSO used as NMR solvent. [i] See ref 33. [j] See ref 34.

work also demonstrated that the C_8 fluorine of **14b** (and 4) did not substantially influence gyrase inhibition or antibacterial potency, but had a profound effect on oral efficacy. Keeping the arrangement of the functional groups (R_6–R_8) of CI-934 constant, we decided to explore the nature of the R_1 group.

In this paper, we report the systematic variation of R_1 and its influence on the inhibition of DNA gyrase and bacterial cell growth. We also describe our efforts to define a quantitative structure–activity relationship involving R_1 and the synthesis and biological activity of the optimum agent resulting from this study.

Chemistry. The trifluoroquinolone starting materials (Table I), with the exception of **13b** and **13c**, were prepared as shown in Scheme I. The 2,3,4,5-tetrafluorobenzoic acid[13] (**8**) was converted to the keto ester **9** by reacting the acid chloride of **8** with the dianion of malonic acid half ethyl ester.[14] The active methylene of **9** was then reacted with acetic anhydride and triethyl orthoformate to give **10**, which was reacted without isolation to produce **11** by addition of the appropriate amine R_1NH_2. The enamine **11** was readily cyclized with base to yield the trifluoro ester **12**. Hydrolysis with acid gave the starting materials **13** in excellent purity. The vinyl substrate **13c** was prepared by an alkylative route (Scheme II). At elevated temperatures, the initial bromoethyl product eliminates to produce the vinyl product in one step. The ethyl derivative **13b** was prepared in a similar manner.[15]

All of the trifluoro substrates **13** were appended to the *N*-ethyl-3-pyrrolidinemethanamine side chain in refluxing acetonitrile[8] to give the final products **14** (Table II). The products all precipitated during the reacton and were readily purified by washing with aqueous acetonitrile and ether. Compound **14b** has been previously reported.[8]

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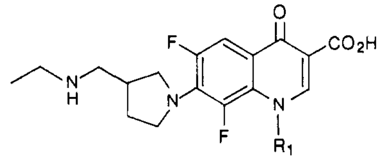
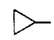
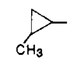
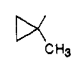
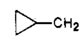
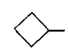
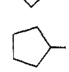
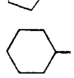
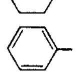
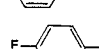
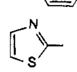
Table II. Synthetic and Physical Data of the 1-Substituted 7-[3-[(Ethylamino)methyl]-1-pyrrolidinyl]quinolone Products



compd	R_1	% yield from 13[a]	mp, °C	formula (anal.)[b]
14a	CH_3	97	238–240	$C_{18}H_{21}F_2N_3O_3 \cdot 0.5H_2O$ (C, H, N)
14b	CH_3CH_2[c]	80	200–202	$C_{19}H_{23}F_2N_3O_3 \cdot 0.45H_2O$ (C, H, N, H_2O)
14c	$CH_2{=}CH$	87	217–220	$C_{19}H_{21}F_2N_3O_3 \cdot 0.9H_2O$ (C, H, N, H_2O)
14d	FCH_2CH_2	86	221–223	$C_{19}H_{22}F_3N_3O_3$ (C, H, N)
14e	CF_3CH_2	76	222–224	$C_{19}H_{20}F_5N_3O_3$ (C, H, N)
14f	CH_3NH	65	222–224	$C_{18}H_{22}F_2N_4O_3 \cdot 0.37H_2O$ (C, H, N, H_2O)
14g	CH_3O	29	192–194	$C_{18}H_{21}N_2F_3O_4 \cdot 0.35H_2O$ (C, H, N)
14h		87	257–258	$C_{20}H_{23}F_2N_3O_3$ (C, H, N)
14i	$(CH_3)_2CH$	74	230–231	$C_{20}H_{25}F_2N_3O_3$ (C, H, N)
14j		81	225–228	$C_{21}H_{25}F_2N_3O_3 \cdot 0.55H_2O$ (C, H, N, F)
14k		69	261–263	$C_{21}H_{25}F_2N_3O_3$ (C, H, N)
14l		69	185–188	$C_{21}H_{25}F_2N_3O_3 \cdot 0.33H_2O$ (C, H, N, H_2O)
14m		68	223–225	$C_{21}H_{25}F_2N_3O_3 \cdot 0.16H_2O$ (C, H, N, H_2O)
14n		74	214–217	$C_{22}H_{27}F_2N_3O_3 \cdot 0.61H_2O$ (C, H, N)
14o		81	194–196	$C_{23}H_{29}F_2N_3O_3 \cdot 0.46H_2O$ (C, H, N)
14p		64	258–260	$C_{23}H_{23}F_2N_3O_3 \cdot 0.16H_2O$ (C, H, N)
14q		87	248–251	$C_{23}H_{22}F_3N_3O_3 \cdot 0.5H_2O$ (C, H, N, H_2O)
14r		45	200–207 (dec)	$C_{20}H_{20}F_2N_4O_3S \cdot 0.46H_2O$ (C, H, N, S)

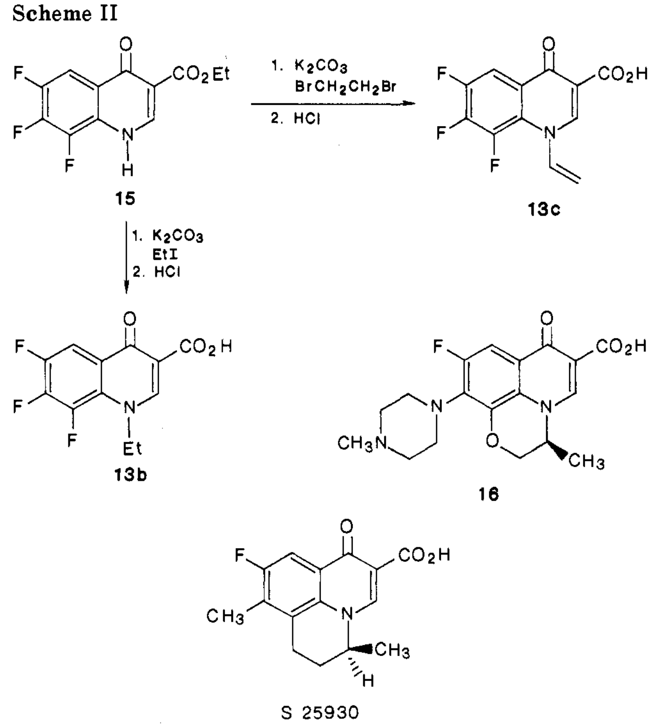
[a] Yields are from the largest scale run. [b] All analyses were ±0.4% for the atoms listed. Samples were dried at 80 °C for 2 h at 0.1 mmHg before analysis. [c] Prepared in a previous study; see ref 8.

Biology. The pyrrolidinyl quinolones 14 were tested against an assortment of 11 organisms by using standard techniques,[9] and their MICs were compared against the reference agents in Figure 1. The compounds were also tested for their inhibition of DNA gyrase as previously described.[5,8] The concentrations of drug (μg/mL) required to induce the gyrase-mediated cleavage of DNA and the 50% inhibition concentrations (I_{50}) were recorded. These combined results are shown in Table III. Aqueous stock solutions were prepared with 0.1 N sodium or potassium hydroxide. The in vivo potency expressed as the median protective dose (PD_{50}, mg/kg) was determined in acute, lethal, systemic infections in female Charles River CD-1 mice as previously described.[8,16] Single doses of compound were administered with challenge. These results are listed in Table IX.

Quantitative Structure–Activity Relationships. Two aspects were investigated quantitatively. First, correlations were sought among the various antibacterial MICs and between these and the two measures of gyrase inhibition. Second, by use of multiple regression analysis, relationships between the biological potencies and various physicochemical descriptors were studied. For this, the potencies listed in Table III were converted to log (1/molar potency) (see Table VIII and supplementary material).

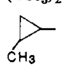
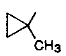
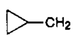
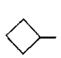
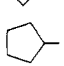
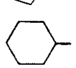
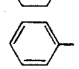
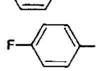
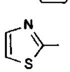
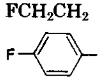
For QSAR regressions, parameters were chosen to reflect the bulk, hydrophobicity, and electronic effects due to changes in R_1. The values used in regressions are shown in Table IV. The STERIMOL[17,18] length (L), minimum

Scheme II



(16) Miller, L. C.; Tainter, M. L. *Proc Soc. Exp. Biol. Med.* **1944**, *57*, 261.

Table III. Biological Testing Results from the Supercoiling Inhibition Assay and the Antibacterial Screen

				antibacterial activity (MICs),[b] μg/mL											
		gyrase cleavage,[a] μ/mL	gyrase 50% inhib, μg/mL	*E. coli*		*K. pneum.*	*P. rettg.*	*E. cloac.*	*P. aerug.*	*S. aureus*		*S. faecalis*	*S. pneum.*	*S. pyog.*	geometric mean of Gram-neg org[c]
compd	R_1			H560	vogel	MGH-2	M1771	MA2646	UI-18	H-228	UC76	MGH-2	SV-1	C203	
14a	CH_3	5.0	7.5	0.1	0.4	0.4	1.6	1.6	1.6	1.6	0.2	1.6	0.4	0.4	0.53
14b	CH_3CH_2	2.5	14	0.1	0.1	0.2	0.4	0.2	1.6	0.1	0.05	0.1	0.1	0.1	0.17
14c	$CH_2{=}CH$	0.8	2.9	0.1	0.2	0.4	1.6	0.2	1.6	0.4	0.1	0.4	0.2	0.1	0.30
14d	FCH_2CH_2	2.5	7.5	0.1	0.1	0.4	0.8	0.2	1.6	0.4	0.1	0.2	0.1	0.1	0.23
14e	CF_3CH_2	2.5	26	0.4	0.8	0.8	3.1	1.6	6.3	0.4	0.1	0.2	0.4	0.4	1.05
14f	CH_3NH	2.5	27	0.2	0.2	0.2	1.6	0.2	0.8	0.4	0.2	0.4	0.1	0.2	0.30
14g	CH_3O	2.5	27	0.4	0.4	0.2	1.6	0.4	6.3	0.8	0.2	0.8	0.8	0.8	0.46
14h		0.25	1.4	0.013	0.05	0.05	0.2	0.1	0.4	0.05	0.006	0.025	0.025	0.025	0.06
14i	$(CH_3)_2CH$	5.0	28	0.2	0.8	0.8	6.3	1.6	12.5	0.4	0.2	1.6	0.8	0.2	1.05
14j		2.5	13	0.8	0.8	1.6	6.3	1.6	6.3	0.8	0.2	0.4	0.8	0.8	1.59
14k		2.5	6.3	1.6	0.8	0.8	1.6	3.1	3.1	0.4	0.1	0.2	0.8	0.8	1.38
14l		10	30	0.8	0.8	1.6	12.5	3.1	25	0.2	0.1	0.8	0.8	0.4	2.09
14m		2.5	26	0.1	0.2	0.4	3.1	0.4	3.1	0.1	0.05	0.2	0.1	0.2	0.40
14n		5.0	28	0.8	3.1	3.1	12.5	6.3	12.5	0.4	0.1	0.4	0.2	0.4	3.60
14o		10	30	3.1	6.3	12.5	>100	25	>100	6.3	3.1	6.3	3.1	6.3	16.5
14p		7.5	29	0.8	1.6	1.6	6.3	1.6	6.3	0.8	0.2	0.8	1.6	1.6	1.83
14q		2.5	14	0.1	0.8	1.6	1.6	0.8	1.6	0.1	0.2	0.2	0.4	0.4	0.70
14r		10	30	3.1	1.6	3.1	12.5	1.6	25	25	1.6	6.3	12.5	6.3	3.14
3 (cipro.)		0.5	5.3	0.025	0.05	0.1	0.1	0.05	0.4	3.1	0.2	0.8	1.6	0.8	0.06
4 (AM833)	FCH_2CH_2	1.0	4.6	0.1	0.2	0.2	0.4	0.2	1.6	0.8	0.2	3.1	6.3	6.3	0.20
5 (diflox.)		1.0	5.5	0.05	0.4	0.4	1.6	0.8	0.8	1.6	0.4	3.1	1.6	1.6	0.40
6 (norflox.)	Et	1.0	5.5	0.1	0.025	0.05	0.05	0.1	0.2	0.8	0.05	1.6	1.6	0.8	0.06
7 (amifl.)	CH_3NH	2.5	6.3	0.025	0.1	0.2	0.2	0.1	0.8	1.6	0.4	3.1	12.5	12.5	0.10

[a] Lowest concentration necessary to induce the gyrase-mediated cleavage of DNA. Initial inhibition, see ref 5. All gyrase data are from duplicate experiments with a ± 50% reproducibility. [b] Standard microtitration techniques, see ref 8 and 9. [c] Geometric mean calculated for the Gram-negative Enterobacteriaceae. These include the two *E. coli* strains, *K. pneumonia*, *P. rettgeri*, and *E. cloacae*.

Table IV. Parameters for Regression Analyses

compd	R_1	L^a	$B_1{}^a$	$B_5{}^a$	MR^b	π	UNSAT	HACCEPT	SIGMA[c]
14a	CH_3	2.87	1.52	2.04	5.67	0.47	0	0	−0.17
14b	C_2H_5	4.11	1.52	3.17	10.30	1.00	0	0	−0.15
14c	$CH{=}CH_2$	4.29	1.60	3.09	10.81	0.46	2	0	−0.04
14d	$(CH_2)_2F$	4.26	1.65	3.78	10.46	0.27	0	0	−0.09
14e	CH_2CF_3	4.70	1.52	3.70	10.77	0.40	0	0	0.09
14f	$NHCH_3$	3.53	1.35	3.08	9.35	0.42	0	1	−0.84
14g	OCH_3	3.98	1.35	3.07	7.20	0.36	0	1	−0.27
14h	$CH(CH_2)_2$	4.14	1.55	3.24	13.57	0.82	1	0	−0.21
14i	$CH(CH_3)_2$	4.11	1.90	3.17	14.94	1.30	0	0	−0.15
14j	2-CH_3-c-propyl	5.21	1.46	3.88	18.21	1.34	1	0	−0.21
14k	1-CH_3-c-propyl	4.29	2.11	3.27	18.21	1.34	1	0	−0.25
14l	$CH_2CH(CH_2)_2$	5.17	1.63	4.41	18.21	1.44	0	0	−0.15
14m	$CH(CH_2)_3$	4.77	1.77	3.82	17.81	1.38	0	0	−0.15
14n	$CH(CH_2)_4$	4.90	1.90	4.09	22.44	1.94	0	0	−0.02
14o	$CH(CH_2)_5$	6.17	1.91	3.49	27.08	2.50	0	0	−0.22
14p	C_6H_5	6.28	1.71	3.11	26.14	2.38	6	0	−0.01
14q	C_6H_4-4-F	6.87	1.71	3.11	26.30	2.59	8	0	0.06
14r	2-thiazolyl	5.91	1.66	3.18	22.12	1.26	4	1	0.29

[a] References 17 and 18. [b] Reference 19. [c] Reference 35.

Table V. Interparameter Correlations

	L	B_1	B_5	MR	π	UNSAT	HACCEPT
L	1.00						
B_1	0.33	1.00					
B_5	0.35	0.21	1.00				
MR	0.91	0.60	0.35	1.00			
π	0.82	0.63	0.23	0.92	1.00		
UNSAT	0.71	0.10	−0.23	0.58	0.54	1.00	
HACCEPT	−0.12	−0.46	−0.23	−0.22	−0.42	0.01	1.00
SIGMA	0.51	0.28	0.12	0.38	0.44	0.45	−0.28

width (B_1), and maximum width (B_5) as well as molar refractivity (MR)[19] were examined as descriptors of bulk. Distributional/hydrophobic bonding effects from the R_1 substituents were modeled by calculated π (octanol/water) values.[19]

As noted by other workers,[20] it rapidly became apparent that the bulk descriptors alone[4c] were inadequate for the range of R_1 substituents encompassed by this compound set. Attempts to use molecular orbital calculations to pinpoint the precise set of operative electronic parameters and contending with the plethora of values[21] and the attendant problems of statistical interpretation[22] seemed most undesirable.

Some measure of electron availability seemed important. Thus, an unsaturation index, denoted UNSAT, was devised. This index was given the value of 1 for pseudoaromatic substituents (cyclopropyl) directly attached to nitrogen and twice the number of double bonds for unsaturated substituents (vinyl, aromatic) plus two for electron-rich substituents (F) attached to phenyl. HACCEPT, an indicator variable, was used to account for possible potency variations due to hydrogen bonding when R_1 contained an oxygen or nitrogen atom. Finally, σ values were considered in order to provide a continuous electronic variable. Squared values for L, MR, and π were also used in regressions. Counting these, a total of 11 parameters was used. This is somewhat large for an 18-membered compound set.[22] Therefore, limitations were applied to reduce the risk of finding spurious relationships. Perhaps most important, L, MR, and π were not considered simultaneously because they are highly correlated (Table V) and are all essentially descriptors of bulk for this compound set. Combinations with squared terms were not allowed unless both the variable and its square met the significance criterion. No combinations containing more than four terms were considered.

Preliminary surveys of r^2 values[23] indicated that L generally gave higher correlations than either MR or π. Further, σ was rarely significant. Thus, only L, L^2, B_1, B_5, UNSAT, and HACCEPT were considered in final regressions.

Molecular Modeling. Modeling of the 6,8-difluoroquinolones was performed by using the SYBYL[25] program package. Models were constructed with ring systems and substituents available in this package and from the X-ray

(17) Verloop, A.; Hoogenotraaten, W.; Tipker, J. *Drug Design*; Ariens, E. J., Ed., Academic: New York, 1976; Vol. VIII, Chapter 4. Verloop, A. *IUPAC Pesticide Chem, Human Welfare and Environment*; Migamoto, et al., Ed.; Pergamon: New York, 1983.

(18) The values used in regressions were obtained from the phenyl analogues, built by using fragments available within SYBYL in extended conformations and relaxed with MAXIMIN, with a program kindly supplied by A. Verloop and interfaced with the SYBYL programs by D. Moreland, unpublished.

(19) Calculated by using the CLOGP (Ver. 3.33) program from Medicinal Chemistry Project, Pomona College, Claremont, CA.

(20) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Prihuleac, E.; Nordeen, C. W.; Maleczka, R. E., Jr.; Pernet, A. G. *J. Med. Chem.* **1985**, *28*, 1558.

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(22) Topliss, J. G.; Edwards, R. P. *J. Med. Chem.* **1979**, *22*, 1238.

(23) *SAS User's Guide: Statistics, Version 5 Edition*; SAS Institute: Cary, NC, 1985.

(24) For an English summary of Koga's original work see Fujita, T. In *Drug Design: Fact or Fantasy*; Jolles, G., Woolridge, K. R. H., Eds.; Academic: New York, 1984; p 19.

(25) (a) *SYBYL Molecular Modeling System VAX-Evans & Sutherland Manual*; Tripos Associates: St. Louis, MO, Release 3.2, May 1985. (b) Motoc, I.; Dammkoehler, R. A.; Mayer, D.; Labanowski, J. *Quant. Struct.-Act. Relat. Pharmacol, Chem. Biol.* **1986**, *5*, 99. (c) Labanowski, J.; Motoc, I.; Naylor, C. B.; Mayer, D.; Dammkoehler, R. A. *Ibid.* **1986**, *5*, 138.

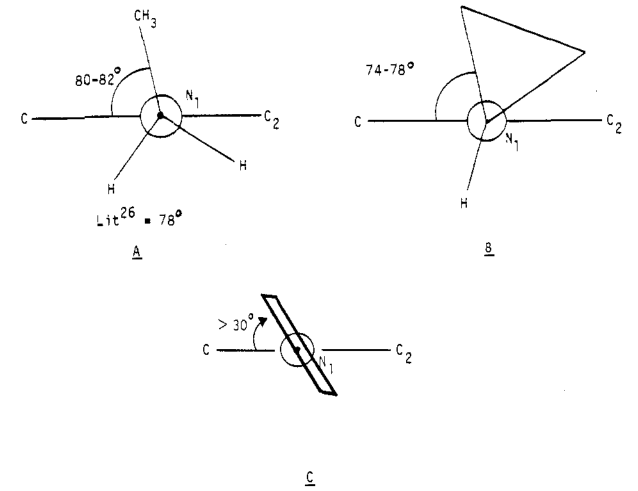

Figure 2. Newman projection looking down the R_1–N_1 bond showing the most favored conformations, calculated for models of **14b**, **14h**, and **14p**.

data[26] of oxolinic acid. Conformations were initially screened without consideration of electrostatic interactions by using the rigid rotor SEARCH[25a] routine, rotating the N_1–R_1 bond. Selected conformations were then optimized by using the molecular mechanics based MAXIMIN[25b] routine while retaining the internal geometry except for the R_1 substituents. These models were then verified by using the molecular orbital AM1 program[36] with geometry optimization for appropriate valence and torsion angles involving N_1 and R_1.

The preliminary modeling compared the ethyl (**14b**), cyclopropyl (**14b**), and phenyl (**14p**) derivatives with emphasis on the energetically preferred orientations of these substituents.

Results and Discussion

In all other previous literature reports where R_1 was studied, an optimum requirement for a two-atom fragment was demonstrated.[2d,4,6] In each study, ethyl, fluoroethyl, or vinyl appeared near the optima, and each additional modification brought a gradual reduction of MIC.

These trends were confirmed in a quantitative structure–activity relationship reported by Koga[4c] for eight variations of N_1 in a series of 7-piperazinyl derivatives. From his limited set of N_1 substituents, a powerful relationship was demonstrated between the MICs and the STERIMOL length of the R_1 group with an optimum near the ethyl moiety.[24]

The existing R_1 literature seemed to suggest that the influence of R_1 was strictly steric. A two-atom fragment was optimal possibly because the second atom is required to permit a slight but beneficial penetration of the space above (or below) the ring system. X-ray data from oxolinic acid[26] was consistent with such a geometrical picture. In oxolinic acid, the methyl of the N_1-ethyl group is aligned above (or below) the plane of the essentially flat quinolone nucleus (Figure 2a). With this preliminary geometrical picture in mind, the data in Table III can be analyzed.

Examination of the gyrase cleavage values (associated with initial inhibition) shows a range of concentrations from 0.25 to 10 μg/mL. Our previous reports[5,8] have proposed that gyrase cleavage values of $\leq$5 μg/mL represent very good inhibitors. By this criterion the only agents in Table III that are not good gyrase inhibitors are the cyclopropylmethyl (**14l**), cyclohexyl (**14o**), phenyl (**14p**), and thiazolyl (**14r**). The most active choices for R_1 in the cleavage assay are cyclopropyl (**14h**) and vinyl (**14c**). The gyrase cleavage value of $\leq$5 μg/mL appears to be a very good predictor of useful antibacterial activity in both Gram-negative and Gram-positive bacteria for this data set.[5] The gyrase I_{50}'s are a measure of the ability of the drug to shut off supercoiling completely.[5] When these data are considered, the vinyl (**14c**) and cyclopropyl (**14h**) groups are again superior, with most of the remaining quinolones all 1–2 times less active than the ethyl **14b**. While many changes at R_1 permit initial inhibition of gyrase comparable to ethyl (2.5 μg/mL), only a few permit the 50% inhibition at concentrations $\leq$14 μg/mL. The biological significance of shutting supercoiling off 100% (giving lower I_{50}'s) has not been established. Certainly a low I_{50} is considered to be ideal, but the "initial inhibitory power" of the compound may be sufficient to result in substantial antibacterial effect.[27]

A correlation matrix of the gyrase and antibacterial potencies (supplementary material) shows significant relationships between gyrase cleavage concentrations ($p <$ 0.05) and each of the 11 bacterial MICs. The r^2 values for the correlations with *Escherichia coli* H560 and the Gram-negative mean are 0.56 and 0.62, respectively. Even the potency against gram-positive organisms correlates significantly (r^2 = 0.37–0.64) with results from the Gram-negative enzyme. That the potency is not completely predicted by the gyrase cleavage is consistent with the presumption that the interactions at gyrase are not always the sole governing interaction. The correlation of potency and gyrase I_{50} values was not as strong.

Extending the examination of the data to the antibacterial potency (especially as expressed in the geometric mean), only the cyclopropyl analogue **14h** is clearly superior to the ethyl group. The fluoroethyl (**14d**), cyclobutyl (**14m**), and the methylamino of **14f** are about equal to the ethyl group, and all the other substituents confer less activity.

The cyclopropyl group is associated with the most potent gyrase and antibacterial potency. Both the cleavage value and I_{50} are 10 times better than the ethyl-containing quinolone **14b**, and the MICs improve by an average of 3-fold. The vinyl group in **14c** confers good but less spectacular improvement. When compared to ethyl, the

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(27) One generally approximates that the arguments made regarding gyrase from *E. coli* are at least somewhat applicable to the other members of Enterobacteriaceae.
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Table VI. Preferred Equations for Each Antibacterial Potency[a,b]

eq no.	log (1/molar MIC)	r^2	F	s
3	*E. coli* (H560) = −0.44 (±0.16)L + 0.14 (±0.07)UNSAT − 1.22 (± 0.65)B_1 − 0.84 (±0.32)HACCEPT + 10.2	0.58	4.4	0.45
4	Gram-negative mean = −0.79 (± 0.19)L + 0.25 (±0.08)UNSAT + 0.50 (±0.28)B_5 + 7.5	0.59	6.8	0.39
5	*E. coli* (vogel) = −0.70 (±0.20)L + 0.20 (±0.08)UNSAT + 0.50 (±0.29)B_5 + 7.3	0.52	5.0	0.41
6	*K. pneumoniae* = −0.55 (±0.12)L + 0.11 (± 0.05)UNSAT + 8.2	0.60	11.3	0.37
7	*P. rettgeri* = −1.01 (±0.20)L + 0.35 (±0.09)UNSAT + 0.64 (±0.29)B_5 + 7.3	0.68	9.9	0.41
8	*E. cloacae* = 1.88 (±0.91)L − 0.25 (±0.10)L^2 + 0.25 (±0.07)UNSAT − 1.3 (±0.51)B_1 + 4.3	0.68	6.9	0.39
9	*P. aeruginosa* = −0.99 (±0.18)L + 0.37 (±0.07)UNSAT + 0.61 (±0.25)B_5 + 7.1	0.73	12.8	0.36
10	*S. aureus* (UC76) = −0.77 (±0.24)L + 0.28 (±0.10)UNSAT + 0.96 (±0.35)B_5 − 0.72 (±0.32)HACCEPT + 6.1	0.56	4.1	0.49
11	*S. aureus* (MGH-2) = −0.81 (±0.18)L + 0.26 (±0.08)UNSAT + 0.88 (±0.26)B_5 − 0.55 (±0.24)HACCEPT + 7.1	0.67	6.6	0.37
12	*S. faecalis* = −0.75 (±0.23)L + 0.27 (±0.10)UNSAT + 0.91 (±0.33)B_5 − 0.52 (±0.31)HACCEPT[c] + 6.2	0.52	3.5	0.47
13	*S. pneumoniae* = −0.76 (±0.24)L + 0.19 (±0.10)UNSAT + 0.70 (±0.35)B_5 − 0.52 (±0.32)HACCEPT[d] + 7.1	0.53	3.7	0.49
14	*S. pyogenes* = −0.86 (±0.19)L + 0.24 (±0.08)UNSAT + 0.76 (±0.27)B_5 − 0.56 (±0.25)HACCEPT + 7.3	0.69	7.1	0.38

[a] Parameters chosen from L, L^2, B_1, B_5, UNSAT, HACCEPT. [b] All parameters included in equations are significant at ≥90% level, unless otherwise indicated. [c] Significant at 88% level. [d] Significant at 87% level.

Table VII. Development of Eq 3 and 4

eq no.	log (1/molar MIC)	r^2	F	s
	E. coli (H560) = −0.26 (±0.13)L + 7.4	0.19	3.7	0.57
	E. coli (H560) = −0.49 (±0.18)L + 0.14 (±0.08)UNSAT + 8.3	0.34	3.8	0.53
	E. coli (H560) = −0.54 (±0.17)L + 0.16 (±0.07)UNSAT − 0.58 (± 0.32)HACCEPT + 8.6	0.46	4.0	0.49
3	*E. coli* (H560) = −0.44 (±0.16)L + 0.14 (±0.07)UNSAT − 0.84 (±0.32)HACCEPT − 1.22 (±0.65)B_1 + 10.2	0.58	4.4	0.45
	Gram-negative mean = −0.30 (±0.11)L + 7.1	0.31	7.1	0.48
	Gram-negative mean = −0.54 (±0.14)L + 0.15 (±0.06)UNSAT + 8.1	0.50	7.5	0.42
4	Gram-negative mean = −0.79 (±0.19)L + 0.25 (±0.08)UNSAT + 0.50 (±0.28)B_5 + 7.5	0.59	6.8	0.39

phenyl (**14p**) and *p*-fluorophenyl (**14q**) are not remarkable, but compared to cyclohexyl (**14o**), their saturated counterpart, both of these quinolones show marked increases in gyrase inhibition and antibacterial potency.

In all of these cases the activity against the enzyme was greater than expected on steric grounds alone, suggesting that electronic interactions between the quinolone nucleus and the Walsh orbitals[28] of the cyclopropane or the p orbitals of the vinyl or aromatic group may be important. Our first approach was to test the conclusions from the work of Koga[4c] to see if the relationship demonstrated between size (STERIMOL length) at R_1 and antibacterial potency applied to our compounds, whose substituents at C_7 and C_8 were optimized and very different from Koga's set. To imitate Koga's study, all compounds with π- or pseudo-π-electron density (**14c,h,j,k,p–r**) were excluded in this phase of the analysis. Equations 1 and 2 show the relationship derived for STERIMOL length vs the potency against *E. coli* H560 and the Gram-negative mean.

$$\log (1/\text{molar MIC } E.\ coli \text{ H560}) = -0.4\ (\pm 0.1)L + 7.9 \quad (1)$$

$$n = 11,\ r^2 = 0.55,\ F = 11,\ s = 0.34$$

$$\log (1/\text{molar MIC Gram-negative mean}) = 1.8\ (\pm 0.9)L - 0.2\ (\pm 0.1)L^2 + 2.9 \quad (2)$$

$$n = 11,\ r^2 = 0.74,\ F = 11,\ s = 0.33$$

A very strong relationship between antibacterial potency and the length of the R_1 substituent existed. Other STERIMOL parameters such as the minimum width (B_1) and the maximum width (B_5) were not significant for *E. coli* H560 or for the Gram-negative mean but were significant for certain other strains. The relationship with length was in complete agreement with Koga's results.[4c] The lack of an L^2 term for the *E. coli* H560 (parabolic relationship) was probably due to a lack of sufficient data for R_1 groups smaller than ethyl. The parabolic relationship depends heavily on the potency of the methyl group in **14a** relative to the ethyl group of **14b**. A parabolic relationship was obtained in seven of 11 strains.

While the correlation between potency and STERIMOL parameters is significant ($r^2 \geq 0.60$) for eight of the remaining 10 strains, such is not the case for the gyrase inhibition. This lack of correlation between gyrase activity and bulk at N_1 is disturbing. A priori, one would like to believe that the enzyme is strongly influenced by the groupings at N_1, especially because of recent reports regarding the profound effect of chirality at this position. Ofloxacin **16**[29,31c] and S-25930 **17**[30] have been resolved, and only one enantiomer possesses virtually all of the activity at the MIC level and 10-fold more activity at the enzyme level.[29b] The absolute configuration for the active enantiomer of both derivatives has been determined,[30,31c] and in each case the methyl moiety is above the plane of the quinolone ring as depicted in **16** and **17**. In fact, the presence of two methyl groups at C_3 (in **16**, one up and one down) was as inactive as the wrong enantiomer.[31a] The lack of correlation between gyrase and STERIMOL length in our work may merely reflect an insufficient spread of the gyrase data (0.25–10 μg/mL), since the data set did not cover enough steric bulk to preclude all the gyrase activity. Put another way, all the compounds tested possess optimum features at C_6–C_8, and even the larger R_1 groups do not diminish the intrinsic gyrase activity.

When the entire 18-compound set is employed, the correlation between potency against *E. coli* H560 and STERIMOL length is very low (r^2 = 0.19). Furthermore, addition of L^2, B_1, or B_5 to the equation is not justified (90% level). The STERIMOL parameters are clearly failing to adequately predict the activity of the cyclopropyl and phenyl data points. Clearly, new parameters are required to derive useful equations. The additional parameters examined for these equations were chosen to reflect electronic effects and are described in the QSAR methods section. The equations derived for the various strains are given in Table VI. These are the best equations (highest r^2 values) found by using all 18 compounds and limiting the parameters to no more than four chosen from L, L^2, B_1, B_5, UNSAT, and HACCEPT. The degree of fit ranges from strong trends (*E. coli*, *Streptococcus faecalis*, *Streptococcus pneumoniae*) to a potentially predictive level *Providencia rettgeri*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Streptomyces pyogenes*). The development, the effect of adding successive parameters, of eq 3 and 4 and a listing of calculated and found potencies

Table VIII. Comparison of Found and Calculated Potencies[a,b] for *E. coli* (H560) and the Gram-Negative Mean

	E. coli (H560)			Gram-negative mean		
compd	found	calcd eq 3	residual	found	calcd eq 4	residual
14a	6.57	7.09	-0.52	5.85	6.21	-0.36
14b	6.59	6.54	0.04	6.35	5.79	0.56
14c	6.60	6.65	-0.05	6.11	6.11	0.00
14d	6.60	6.32	0.28	6.24	5.98	0.26
14e	6.03	6.28	-0.25	5.62	5.59	-0.03
14f	6.29	6.17	0.12	6.11	6.21	-0.10
14g	5.99	5.97	0.02	5.93	5.84	0.08
14h	7.48	6.63	0.84	6.83	6.05	0.77
14i	6.29	6.08	0.21	5.57	5.79	-0.22
14j	5.71	6.27	-0.55	5.42	5.52	-0.11
14k	5.41	5.88	-0.47	5.48	5.95	-0.47
14l	5.71	5.94	-0.23	5.29	5.57	-0.27
14m	6.65	5.95	0.70	6.05	5.59	0.45
14n	5.73	5.73	0.00	5.08	5.62	-0.55
14o	5.15	5.15	-0.00	4.43	4.32	0.11
14p	5.73	6.19	-0.46	5.37	5.55	-0.18
14q	6.66	6.21	0.45	5.81	5.59	0.23
14r	5.15	5.29	-0.14	5.15	5.38	-0.23

[a] log (1/molar MIC). [b] A complete tabulation is included in the supplementary material.

for *E. coli* H560 and Gram-negative mean are shown in Tables VII and VIII. Comparable data for the other bacterial strains are included in the supplementary material.

$$\log(1/\text{molar MIC } E.\ coli\ \text{H560}) = -0.4\ (\pm 0.2)L + 0.1\ (\pm 0.07)\text{UNSAT} - 0.8\ (\pm 0.3)\text{HACCEPT} - 1.2\ (\pm 0.6)B_1 + 10.2 \quad (3)$$

$$n = 18,\ r^2 = 0.58,\ F = 4,\ s = 0.45$$

$$\log(1/\text{molar MIC Gram-negative mean}) = -0.8\ (\pm 0.2)L + 0.3\ (\pm 0.08)\text{UNSAT} + 0.5\ (\pm 0.3)B_5 + 7.5 \quad (4)$$

$$n = 18,\ r^2 = 0.59,\ F = 7,\ s = 0.39$$

The most obvious difference between the complete data set (eq 3 and 4) and the data set minus the electron donors (eq 1 and 2) is the significance of the unsaturation term UNSAT, which added to the overall potency. This term, from those examined, best approximates the electronic effects of R_1 and is important to QSAR analysis as intuitively postulated from the cyclopropyl and phenyl results. Again, in these equations there is no significant dependency on L^2. Another difference from eq 1 and 2 is the significance of the minimum and maximum widths. Throughout the equations in Table VI, the coefficient for minimal width (B_1) is always negative while the coefficient for maximal width (B_5) is always positive. These results imply that steric bulk is desirable in one but not two directions perpendicular to the N–R_1 bond. This concept is crucial. These STERIMOl widths are significant in 11 of 12 equations. The variable HACCEPT was significant in six of 12 equations appearing more important against Gram-positive organisms (5/5). The coefficients for HACCEPT are always negative, indicating a reduced activity when a heteroatom is attached directly to or one atom removed from N_1. The same regression analysis was applied to the gyrase cleavage and I_{50} values, but no useful correlation was found.

While it is clear that steric bulk and unsaturation are important descriptors for calculating potency, it is not clear how these variables interact in real terms. What makes the cyclopropyl and phenyl substituents so much more effective than the isopropyl or cyclohexyl groups? Can the π-electron density of the cyclopropyl and phenyl groups be mediated through the quinolone ring system or does the electron density of these moieties interact directly with the enzyme surface or some other receptor? Within this data set, no significant differences or trends could be discerned when looking at charge densities or pKa's of the carboxyl functionality. This result alone implies that the π-electronic character of the R_1 group is not mediated into the quinolone ring system. Molecular modeling results further substantiate this notion.

Modeling of the ethyl and cyclopropyl derivatives showed a preference for each group to orient above (or below) the plane of the quinolone ring (Figure 2A,B). The cyclopropyl group in Figure 2B would not be capable of electron donation into the quinolone π system.[32] Because the barriers to rotation were not large, the cyclopropyl could, in the environment of the receptor, revert to a configuration that would permit π delocalization through the ring. Such is not the case for the phenyl ring (Figure 2C). The minimum energy conformations never permit a configuration allowing delocalization between the rings. Clearly, the beneficial unsaturation effect for the phenyl ring must be mediated through space, and the same is likely to be true for the cyclopropyl as well.

The results described earlier for chiral ofloxacin **16** and S-25930 **17** are also significant in this discussion. Having a methyl group above the plane of the quinolone nucleus (as depicted in **16** and **17**) is vital for potent activity, and a methyl below the plane is deleterious. Groups that can fill limited space above the plane without simultaneously occupying space below will be favored. Since all two-atom groups can accomplish this requirement, most have activity close to ethyl. The isopropyl group of **14i** fills volume above and below the plane and is less active as are the 1-methylcyclopropyl analogue **14k** and the larger ring derivatives from cyclobutyl **14m** to cyclohexyl **14o**. The phenyl group cannot confer the potency obtained with cyclopropyl because it simultaneously fills volume above and below the quinolone plane. One ortho substituent is acceptable, but two are not.[31b] The unsaturation of the phenyl group in **14p** (**14q**) provides added potency over cyclohexyl where bulk is comparable. The modeling work and discussions thus far indicate a favorable volume requirement above the plane of the ring. This requirement may partially be described by B_5 (and the negative coefficient for B_1). The "magic" of the cyclopropyl group may well be a fortuitous blend of through-space electronic interactions mixed with exactly the right combination of volume filled above the plane for optimal activity.

When the reference agents are analyzed, some additional interesting concepts evolve. Ciprofloxacin (**3**) with a cy-

Table IX. Mouse Chemotherapy Results PD_{50} (mg/kg) for **14h** (PD 117 558) and Selected Standards

compd	*E. coli*		*P. aerug*		*S. pyogenes*		*S. pneum*	
	po	sc	po	sc	po	sc	po	sc
14h	4	1	40	13	2	0.5	3	2
14b (CI-934)	12	2	>200	76	9	3	20	4
3 (ciprofloxacin)	1	0.3	25	5	>100	20	>100	29
5 (difloxacin)	2	2	14	14	7	7	16	13
6 (norfloxacin)	4	0.6	76	11	>100	45	>100	>100

clopropyl at N_1 is only 2 times better than the ethyl-containing norfloxacin (**6**) vs gyrase cleavage, while in the pyrrolidine series a 10 times improvement is witnessed. The mean MIC values of ciprofloxacin and norfloxacin were identical. The key feature in this analysis is that norfloxacin (**6**) has a mean MIC of 0.06 μg/mL while **14b** is 0.17 μg/mL. When the piperazine side chain, known for Gram-negative potency, is employed, the addition of cyclopropyl at N_1 manifests only a slight improvement in Gram-negative antibacterial activity. In the pyrrolidine series, a 10-fold improvement against *E. coli* was observed with a 3-fold improvement in the mean MICs vs Gram-negative organisms. These data imply that the piperazine common to all the reference agents carries with it good Gram-negative activity and that adding a cyclopropyl does not greatly enhance this feature. In the pyrrolidine case, **14b** was weak in Gram-negative activity and was the weakest of the reference agents vs gyrase. The addition of the cyclopropyl group had a major impact in this case, improving both measures of activity by substantial amounts.

The final point related to this discussion is that the Gram-positive MICs for the reference agents are relatively constant for all changes of R_1. In this study, 12 of the 17 entries maintain their Gram-positive potency (≤0.8 μg/mL) regardless of the choice of R_1, again demonstrating a controlling role of the side chain. The choice of cyclopropyl for R_1 produced an agent that not only improved its Gram-negative potency 2- to 10-fold over the N_1 quinolone ethyl but showed a 2- to 4-fold improvement against Gram-positive organisms as well. This agent, PD 117558 (**14h**), is the most potent quinoline of all the compounds tested in this or previously reported studies.[5,8,9] The excellent in vitro activity carries over to the in vivo mouse protection tests as seen in Table IX.

In this study we have demonstrated the sensitivty of gyrase and antibacterial activity to the R_1 group. The gyrase inhibition while useful does not provide a clear understanding of the subtle interactions between the enzyme and the N_1 position. Transport or permeability variables do not seem to be a major consideration. The differences between R_1 are amplified slightly when the geometric mean vs Enterobacteriaceae is evaluated. As in the case of ciprofloxacin, a clear winner among R_1 groups is cyclopropyl, which is superior in every category. Electronic π-donation (UNSAT) has been shown to be a factor in the activity of this group, along with ideal spatial effects. The major accomplishment of this work is the synthesis of 1-cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (PD 117558), which is the most potent quinolone tested in both the gyrase and the antibacterial assays. Complete microbiological evaluations of this agent will be forthcoming.

Experimental Section

All melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr on a Nicolet FT IR SX-20 instrument. Proton NMR spectra were recorded on either a Varian XL 200 or an IBM 100 WP 100 SY spectrometer. Shifts are reported in δ units relative to internal tetramethylsilane. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. All compounds prepared had analytical results within ±0.4% of theoretical values. All organic solutions were dried with $MgSO_4$. Column chromatography was performed with E. Merck silica gel 60, 70–230 mesh ASTM. All amines in Table I were commercially available or were prepared by literature methods. Acetonitrile was used without drying. DMF was distilled from calcium hydride. *n*-Butyllithium was obtained from Aldrich. The indicator used in the reaction precluded the need for titration.

2,3,4,5-Tetrafluoro-β-oxobenzenepropanoic Acid Ethyl Ester (9). To 30.0 g (0.155 mol) of **8** in 750 mL of H_2CCl_2 was added 14.8 mL (1.1 equiv) of oxalyl chloride. The mixture was treated with three drops of dry DMF, and the initially vigorous reaction was stirred overnight. Concentration, a toluene chase, and reconcentration gave the crude acid chloride of **8**, which was used in the next step.

Via the published procedure,[14] 40.9 g (0.310 mol) of propanedioic acid monoethyl ester was converted to the dilithium salt in 800 mL of THF with 280 mL of 2.21 N *n*-butyllithium in hexane. To this solution at −78 °C was added the acid chloride of **8** (prepared above) in 100 mL of THF. The reaction mixture was stirred for 45 min, warmed to −35 °C, and poured into 155 mL of 2 N HCl, 1 L of H_2O, and 1 L of H_2CCl_2. The water layer was extracted with another liter of H_2CCl_2, and the combined extracts were washed with 50% saturated $NaHCO_3$. The H_2CCl_2 layer was dried and concentrated to give 37.8 g (93%) of the slow-forming solid: mp 63–65 °C; IR 1742, 1700, 1648 cm^{-1}; NMR (DMSO-d_6) δ 12.5 (s, 0.2 H, enol O*H*), 7.9 (m, 0.8 H, C_2H), 7.7 (m, 0.2 H, C_2H), 5.8 (s, 0.2 H, enol C*H*), 4.3 (q, J = 7 Hz, 0.4 H, CH_2CH_3), 4.15 (q, J = 7 Hz, 1.6 H, CH_2CH_3), 3.3 (s, 1.6 H, CH_2), 1.25 (t, J = 7 Hz, 0.6 H, CH_3), 1.15 (t, J = 7 Hz, 2.4 H, CH_3). Anal. Calcd for $C_{11}H_8F_4O_3$: C, 50.00; H, 3.03. Found: C, 50.10; H, 2.87.

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (13h). General Procedure. To 17.6 g (66.6 mmol) of **9** were added 14.6 g (1.5 equiv) of triethyl orthoformate and 16.19 g (2.4 equiv) of acetic anhydride. The mixture was refluxed 2 h on an oil bath at 150 °C. It was cooled to 80 °C and concentrated in vacuo to a thick residue. The mixture was diluted with 120 mL of *tert*-butyl alcohol and cooled to 10 °C, and 3.8 g (1.05 equiv) of cyclopropylamine was added in 15 mL of *tert*-butyl alcohol. After being stirred for 30 min at 10 °C, the mixture was warmed at 45 °C overnight. The solids that formed could be isolated and washed pure with cold ethanol to give **11h** in 40% yield, or the crude solids could be collected without washing 75–85% yield. The pure crystals were collected to give α-[(cyclopropylamino)methylene]-2,3,4,5-tetrafluoro-β-oxobenzenepropanoate (**11h**): mp 64–65 °C; IR 1700, 1686, 1629 cm^{-1}; NMR ($DCCl_3$) δ 10.8 (br s, 1 H, N*H*), 8.1 (d, J = 13 Hz, 1 H, C*H*=C), 6.9 (m, 1 H, C_6H), 3.95 (q, J = 7 Hz, 2 H, CH_2CH_3), 2.9 (m, 1 H, C*H*N), 1.05 (t, J = 7 Hz, 3 H, CH_2CH_3), 0.9 (m, 4 H, CH_2CH_2). The remaining solids were treated with 7.5 g (1.0 equiv) of potassium *tert*-butoxide in 50 mL of *tert*-butyl alcohol, and the mixture was stirred for 18 h at 50 °C. Filtration of the cooled mixture gave **12** as a tan solid. A small portion of crude **12** was crystallized from hot dioxane to give pure cyclized ethyl ester **12**: mp 170–171 °C; IR 1732, 1619 cm^{-1}; NMR ($DCCl_3$) δ 8.5 (s, 1 H, C_2H), 8.0 (dd, J = 8, 2 Hz, 1 H, C_5H), 4.28 (q, J = 7 Hz, 2 H, CH_2CH_3), 3.8 (m, 1 H, cyclopropyl C*H*), 1.35 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.2 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_{15}H_{12}F_3NO_3$: C, 57.88; H, 3.86; N, 4.50. Found: C, 57.67; H, 3.86; N, 4.58.

The remaining solid was dissolved in hot acetic acid and a half volume of 3 N HCl was added over 2 h at 100 °C. The mixture was stirred an additional 2 h at this temperature and cooled slowly.

The solids were filtered and washed with cold water, 2-propanol, and ether to give 15.44 g (82% overall from **9**) of **13h**: mp 226–228 °C; IR 3108, 1729, 1622 cm^{-1}. Anal. Calcd for $C_{13}H_7F_3NO_3$: C, 55.12; H, 2.83; N, 4.95. Found: C, 55.08; H, 2.96; N, 5.06.

1-Ethenyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (13c). To 5.89 g (21.7 mmol) of **15**[15] were added 7.5 g (2.5 equiv) of K_2CO_3 and 300 mL of dry DMF. After the mixture was stirred for 30 min at 50 °C, 45 g (11.0 equiv) of 1,2-dibromoethane was added. The temperature was raised to 80 °C, and the mixture stirred vigorously for 48h. It was concentrated to dryness and the residue was partitioned between H_2O and H_2CCl_2. The organic layer was extracted twice more with water. It was dried and concentrated to a dark oil, which was purified by column chromatography ($HCCl_3$/hexane/2-propanol, 4:5:1) to give 2.58 g (40%) of the ethyl ester **12c**, mp 135–136 °C. To 2.2 g (7.4 mmol) of this material were added 40 mL of AcOH and 20 mL of 3 N HCl, and the mixture was heated for 4 h. Dilution with water and filtration gave 1.35 g (68%) of **13c**: mp 185–186 °C; IR 1728, 1648 cm^{-1}. Anal. Calcd for $C_{12}H_{16}F_3NO_3{\cdot}0.2H_2O$: C, 52.94; H, 2.35; N, 5.14; H_2O, 1.32. Found: C, 52.77; H, 2.41; N, 5.24; H_2O, 0.96.

1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid 14h. General Coupling Procedure. To 5.00 g (17.65 mmol) of **13h** in 50 mL of CH_3CN was added a solution of 2.7 g (1.0 equiv) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.4 g (1.05 equiv) of *N*-ethyl-3-pyrrolidinemethanamine in 25 mL of CH_3CN. The mixture was refluxed for 2.5 h and was stirred at room temperature overnight. The solids were filtered and washed with 50 mL of CH_3CN, 20 mL of 80% aqueous CH_3CN, 50 mL of ethanol, and 200 mL of ether to give 6.01 g (87%) of **14h** as a white solid: mp 257–258 °C; IR 1730, 1623, 1584 cm^{-1}; NMR (TFA) δ 9.15 (s, 1 H, C_2H), 8.0 (d, J = 12 Hz, 1 H, C_5H), 7.1 (br s, 1 H, N*H*), 4.1 (m, 5 H, $CH_2NHCH_2CH_3$ and cyclopropyl C*H*), 3.4 (m, 4 H, pyrrolidine CH_2N), 2.8 (m, 1 H, pyrrolidine C_3H), 2.4 (m, 1 H, pyrrolidine C_4H), 1.9 (m, 1 H, pyrrolidine C_4H), 1.45 (m, 7 H, CH_3 and CH_2CH_2). Anal. Calcd for $C_{20}H_{23}F_2N_3O_3$: C, 61.38; H, 5.88; N, 10.74. Found: C, 61.08; H, 5.94; N, 10.93.

Data Processing. QSAR analyses were run on an IBM 3081 using the SAS[35] program package. In eq 1–14, the figures in parentheses are the standard errors of the regression coefficients. For each equation, n is the number of compounds, r is the correlation coefficient, F is a significance test, and s is the standard error of the estimate. Molecular modeling used the SYBYL program package[25] operating on a VAX 11/780.

Acknowledgment. We thank J. Topliss for helpful discussions on the QSAR analysis and particularly the concept for the UNSAT parameter. We also thank our chemotherapy group for the test results, especially J. Sesnie, M. Shapiro, and T. Leopold.

Registry No. 8, 1201-31-6; 8 (acid chloride), 94695-48-4; **9**, 94695-50-8; **11a**, 113220-15-8; **11d**, 113220-16-9; **11e**, 113220-17-0; **11f**, 113220-18-1; **11g**, 113220-19-2; **11h**, 94695-51-9; **11i**, 113220-20-5; **11j**, 113220-21-6; **11k**, 113220-22-7; **11l**, 113220-23-8; **11m**, 113220-24-9; **11n**, 113220-25-0; **11o**, 113220-26-1; **11p**, 106809-20-5; **11q**, 105859-07-2; **11r**, 113220-27-2; **12a**, 113220-28-3; **12c**, 91188-95-3; **12d**, 93969-13-2; **12e**, 113220-29-4; **12f**, 100276-66-2; **12g**, 113249-33-5; **12h**, 94242-51-0; **12i**, 113220-30-7; **12j**, 113220-31-8; **12k**, 113220-32-9; **12l**, 113220-33-0; **12m**, 113220-34-1; **12n**, 113220-35-2; **12o**, 113220-36-3; **12p**, 104599-93-1; **12q**, 105859-09-4; **12r**, 106464-85-1; **13a**, 79660-45-0; **13b**, 75338-42-0; **13c**, 91187-99-4; **13d**, 79660-52-9; **13e**, 113220-10-3; **13f**, 100276-67-3; **13g**, 113220-11-4; **13h**, 94695-52-0; **13i**, 98079-84-6; **13j**, 113220-12-5; **13k**, 99724-24-0; **13l**, 113220-13-6; **13m**, 99724-27-3; **13n**, 99724-28-4; **13o**, 99724-30-8; **13p**, 104599-99-7; **13q**, 103994-87-2; **13r**, 106464-84-0; **14a**, 91188-03-3; **14b**, 91188-00-0; **14c**, 91188-02-2; **14d**, 91188-01-1; **14e**, 99735-14-5; **14f**, 103490-74-0; **14g**, 113220-14-7; **14h**, 99734-97-1; **14i**, 99735-25-8; **14j**, 99735-16-7; **14k**, 99735-15-6; **14l**, 99735-19-0; **14m**, 99735-20-3; **14n**, 99735-21-4; **14o**, 99735-24-7; **14p**, 106464-87-3; **14q**, 106486-83-3; **14r**, 106464-86-2; **15**, 79660-46-1; H_3CNH_2, 74-89-5; $F(CH_2)_2NH_2{\cdot}HCl$, 460-08-2; $F_3CCH_2NH_2{\cdot}HCl$, 373-88-6; $H_3CN(NH_2)CO_2Bu$-*t*, 21075-83-2; $H_3CONH_2{\cdot}HCl$, 593-56-6; $(H_3C)_2CHNH_2$, 75-31-0; $C_6H_5NH_2$, 62-53-3; 4-$FC_6H_4NH_2$, 371-40-4; cyclopropylamine, 765-30-0; 2-methylcyclopropanamine hydrochloride, 89123-14-8; 1-methylcyclopropanamine hydrochloride, 88887-87-0; cyclopropanemethanamine, 2516-47-4; cyclobutanamine, 2516-34-9; cyclopentanamine, 1003-03-8; cyclohexanamine, 108-91-8; 2-thiazolylamine, 96-50-4; *N*-ethyl-3-pyrrolidinemethanamine, 91187-83-6; propanedioic acid monoethyl ester, 1071-46-1.

Supplementary Material Available: Correlation matrix for the biological potencies, a tabulation showing the development of eq 5–14, and comparisons of calculated and found potencies for all organisms (5 pages). Ordering information is given on any current masthead page.

Potential Anticonvulsants. 11. Synthesis and Anticonvulsant Activity of Spiro[1,3-dioxolane-2,3′-indolin]-2′-ones and Structural Analogues

Milind Rajopadhye† and Frank D. Popp*

Department of Chemistry, University of Missouri—Kansas City, Kansas City, Missouri 64110. *Received October 22, 1987*

A number of spiro[1,3-dioxolane-2,3′-indolin]-2′-ones were synthesized and tested for anticonvulsant activity in the maximal electroshock seizure (MES) and pentylenetetrazole seizure threshold (sc-Met) tests. 5′-Chlorospiro[1,3-dioxolane-2,3′-indolin]-2′-one was the most active compound in the MES test and had ED_{50} = 27.97 mg/kg. Structural analogues spiro[1,3-dioxane-2,3′-indolin]-2′-one, spiro[1,3-dithiolane-2,3′-indolin]-2′-one, spiro[indoline-3,2′-[1,3]-oxathiolan]-2-one, and 3,3-dimethoxyindolin-2-one were also evaluated for anticonvulsant activity. Almost all compounds submitted for screening exhibited the ability to protect mice against electrically and chemically induced seizures. The ED_{50} and TD_{50} values for some of the title compounds are reported. Anticonvulsant screenings were carried out through NINCDS, NIH.

The search for potent antiepileptic drugs has resulted in the synthesis and evaluation of compounds having diverse chemical structures.[1,2] Many of these compounds have structural features quite different from the more popular antiepileptic drugs viz. carbamazepine, phenytoin, phenobarbital, and primidone.[3] A closer look reveals the presence of an amide moiety (cyclic or otherwise) and a tetrahedral carbon in most anticonvulsants. Unique structural features, such as an amide linkage and a β carbonyl (a site for structural modification), make isatin

† Present address: Department of Chemistry, Dartmouth College, Hanover, NH 03755.

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0022-2623/88/1831-1001$01.50/0