Quantitative Structure–Activity Relationships of Antibacterial Agents, 7-Heterocyclic Amine Substituted 1-Cyclopropyl-6,8-difluoro-4-oxoquinoline-3-carboxylic Acids[1)]

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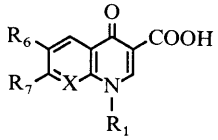
Quantitative structure–activity relationships (QSAR) of various 7-(3-substituted-azetidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids, 14—25, were studied to clarify the structural requirements for 3-substituted azetidines to potentiate antibacterial activity. A good parabolic relationship seemed to exist between the relative mean antibacterial activity indices against five representative gram-negative bacteria, *GNM*, and the calculated hydrophobic parameters, CLOG *P*, of these molecules. The CLOG *P* value of the most potent derivative was predicted to be around 2.3. On the other hand, against five representative gram-positive bacteria, the relative mean antibacterial activity indices, *GPM*, remained high and rather constant regardless of structural variation in the azetidine moiety. In order to confirm these findings, the QSAR analysis was extended with success to the quinolonecarboxylic acids, 26—34, which bear various substituted pyrrolidine, piperazine and piperidine derivatives instead of azetidines. The findings showed that the introduction of any amide substituent group to these heterocyclic amine moieties would lead to marked decrease in *GNM*, whereas incorporation of some amino substituent groups at a position two or three carbons remote from the N-1 position resulted in great enhancement of *GNM*. As azetidine quinolones exhibited somewhat low *in vivo* antibacterial activities, possibly reflecting their lesser bioavailability, we finally selected 3-amino-4-methoxypyrrolidine as one of the most promising C-7 substituent groups based on our QSAR analysis.

Keywords fluoroquinolonecarboxylic acid; azetidine derivative; QSAR analysis; antibacterial activity; log *P*; parabolic relationship

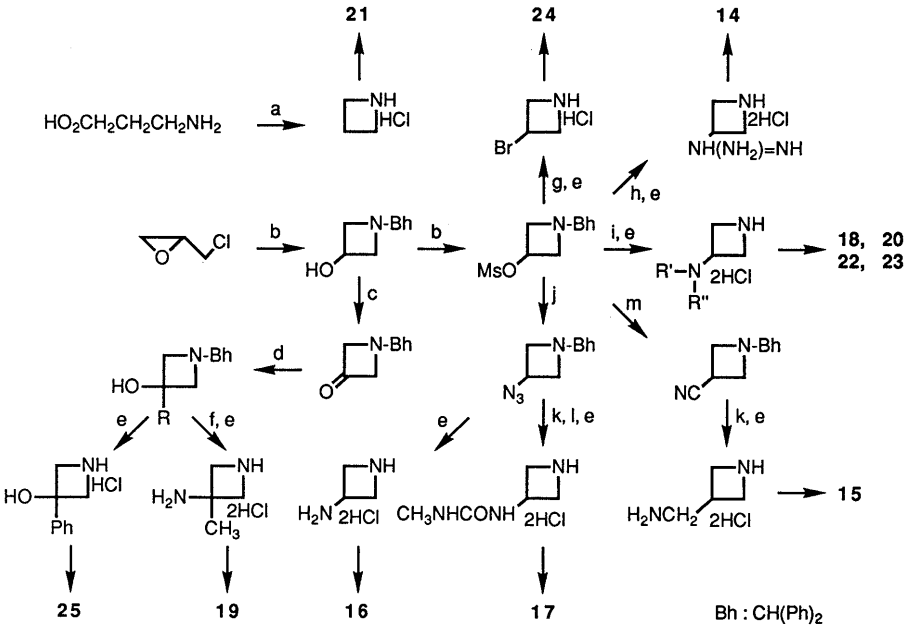
The last three decades in medicinal chemistry have been witness to the contribution of quantitative structure–activity relationships (QSAR) analysis of biologically active compounds for the discovery of diverse types of useful medicines, particularly through better understanding of pharmacological and/or toxicological properties of active compounds as well as more rational molecular design for generating new lead compounds and/or optimizing their desired properties by chemical modification.[2)] In the field of antibacterial agents, pyrridone- and quinolonecarboxylic acids, this approach has achieved remarkable success in verifying relationships between antibacterial activity and chemical structure, markedly aiding the development of some excellent therapeutic agents for clinical use. In particular, two groups, Koga *et al.*[3)] and Domagala *et al.*,[4)] have hitherto made outstanding contributions in this respect. The former group elucidated relationships between physicochemical properties of various substituents at the N-1, C-6, C-7, and C-8 positions and antibacterial activities of their quinolone derivatives against the gram-negative bacteria, *Escherichia coli* NIHJ JC-2, greatly contributing to the development of norfloxacin **2**, one of the representative new quinolone agents in wide clinical use (see some representative compounds, **1**—**12**, listed in Table I[5)]).

The structural distinction of new quinolones thus far developed was the introduction of fluorine, in most cases, at the C-6 position to greatly improve biological activities as well as pharmacodynamic and toxicological properties. Domagala *et al.* disclosed an excellent correlation between the antibacterial activities of the N-1 analogs of the compound CI-934 (**7**) and three structural parameters, the *Sterimol* length and width and the level of unsaturation of the N-1 substituent groups, finally revealing, as seen in PD 117558 (**8**), that the cyclopropyl group is one of the best N-1 substituent groups for enhancing antibacterial activity.

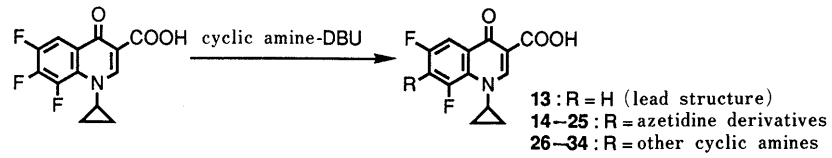
TABLE I. Clinically Significant Quinolone Type Antibacterial Agents



No.	Compd. name	R_6	R_7	X	R_1
1	Nalidixic acid	H	CH_3	N	C_2H_5–
2	Norfloxacin	F	–N⟨ ⟩N–H	CH	C_2H_5–
3	Enoxacin	F	–N⟨ ⟩N–H	N	C_2H_5–
4	Pefloxacin	F	–N⟨ ⟩N–CH_3	CH	C_2H_5–
5	Ofloxacin	F	–N⟨ ⟩N–CH_3	–$COCH_2CH(CH_3)$–	
6	Difloxacin	F	–N⟨ ⟩N–CH_3	CH	F–⟨ ⟩
7	Cl-934	F	–N⟨ ⟩($CH_2NHC_2H_5$)	CF	C_2H_5–
8	PD 117558	F	–N⟨ ⟩($CH_2NHC_2H_5$)	CF	▷
9	Ciprofloxacin	F	–N⟨ ⟩N–H	CH	▷
10	AT-3295	F	–N⟨(CH_3, NH_2)⟩	N	▷
11	Flumequine	F	H	–$CCH_2CH_2CH(CH_3)$–	
12	Tosufloxacin	F	–N⟨(NH_2)⟩	N	F–⟨F⟩



a) see ref. 8*a*. b) see ref. 8*b*. c) see ref. 8*c*. d) RMgX. e) Pd/C-H_2 in HCl/MeOH
f) 1) MsCl-Py, 2) NH_3 in H_2O/CH_3CN. g) NaBr. h) $(NH_2)_2$=NH. i) amine in H_2O/CH_3CN.
j) NaN_3. k) $LiAlH_4$. l) CH_3NCO. m) NaCN



13 : R = H (lead structure)
14–25 : R = azetidine derivatives
26–34 : R = other cyclic amines

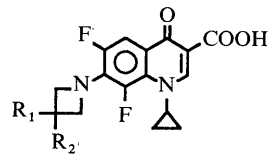
Chart 1

TABLE II. Physical Data of Azetizine Derivatives

No.	mp (dec. °C)	Formula	Analysis (%) Calcd (Found) C	H	F	N	^{1}H-NMR (200 MHz, δ from DSS in D_2O (0.5% NaOH)) J=Hz
14	>300	$C_{17}H_{17}F_2N_5O_3 \cdot 1.5H_2O$	50.49 (50.70)	4.99 (5.06)	9.40 (9.62)	17.32 (17.56)	1.20—1.45 (4H, m), 4.24 (1H, m), 4.50 (2H, m), 4.65 (1H, m), 4.95 [a] (2H, m), 7.82 (1H, d, J=13), 8.94 (1H, s)
15	227—231	$C_{17}H_{17}F_2N_3O_3 \cdot 2H_2O$	52.98 (53.22)	5.49 (5.66)	9.86 (9.66)	10.90 (10.79)	0.98—1.25 (4H, m), 2.75 (1H, m), 2.87 (2H, d, J=7), 3.84 (1H, m), 3.97 (2H, m), 4.33 (2H, m), 7.53 (1H, dd, J=2, 13), 8.41 (1H, s)
16	255—258	$C_{16}H_{15}F_2N_3O_3 \cdot H_2O$	54.39 (54.59)	4.85 (4.64)	10.75 (10.77)	11.89 (11.96)	1.00—1.25 (4H, m), 3.75—4.00 (4H, m), 4.45 (2H, m), 7.53 (1H, dd, J=2, 13), 8.42 (1H, s)
17	290—293	$C_{18}H_{18}F_2N_4O_4$	55.10 (54.92)	4.62 (4.42)	9.69 (9.93)	14.28 (14.22)	1.00—1.25 (4H, m), 2.72 (3H, s), 3.75 (1H, m), 3.95 (2H, m), 4.44 (3H, m), 7.49 (1H, dd, J=1, 13), 8.44 (1H, s)
18	270—275	$C_{17}H_{17}F_2N_3O_3$	58.45 (58.56)	4.91 (5.12)	10.88 (10.59)	12.03 (11.88)	1.00—1.25 (4H, m), 2.30 (3H, s), 3.62 (1H, tt, J=6, 6), 3.86 (1H, m), 4.04 (2H, m), 4.46 (2H, m), 7.56 (1H, dd, J=2, 13), 8.42 (1H, s)
19	270—280	$C_{17}H_{17}F_2N_3O_3$	58.45 (58.21)	4.91 (5.10)	10.88 (10.68)	12.03 (11.79)	1.00—1.20 (4H, m), 1.48 (3H, s), 3.84 (1H, m), 4.07 (2H, d, J=10), 4.20 (2H, d, J=10), 7.55 (1H, dd, J=2, 13), 8.43 (1H, s)
20	225—227	$C_{19}H_{19}F_2N_3O_3$	60.80 (60.55)	5.10 (5.10)	10.12 (10.00)	11.19 (11.17)	0.37—0.60 (4H, m), 1.00—1.22 (4H, m), 2.17 (1H, m), 3.84 (2H, m), 4.10 (2H, m), 4.47 (2H, m), 7.57 (1H, dd, J=2, 13), 8.42 (1H, s)
21	292—295	$C_{16}H_{14}F_2N_2O_3$	60.00 (60.22)	4.41 (4.52)	11.85 (11.84)	8.75 (8.48)	1.00—1.25 (4H, m), 2.35 (2H, tt, J=8, 8), 3.92 (1H, m), 4.31 (4H, m), 7.61 (1H, dd, J=2, 13), 8.43 (1H, s)
22	256—258	$C_{18}H_{19}F_2N_3O_3$	59.50 (59.77)	5.27 (5.49)	10.46 (10.19)	11.56 (11.38)	1.00—1.25 (4H, m), 2.17 (6H, s), 3.29 (1H, tt, J=7, 7), 3.88 (1H, m), 4.13 (2H, m), 4.37 (2H, m), 7.58 (1H, dd, J=2, 13), 8.48 (1H, s)
23	270—274	$C_{20}H_{21}F_2N_3O_3 \cdot 2H_2O$	56.47 (56.60)	5.92 (5.81)	8.92 (8.84)	9.88 (10.15)	1.00—1.25 (4H, m), 1.80 (4H, br s), 2.55 (4H, br s), 3.47 (1H, tt, J=6, 6), 3.90 (1H, m), 4.20 (2H, m), 4.37 (2H, m), 7.57 (1H, dd, J=2, 13), 8.42 (1H, s)
24	275—285	$C_{16}H_{13}BrF_2N_2O_3$	48.14 (48.42)	3.28 (3.41)	9.52 (9.66)	7.02 (7.28)	1.05—1.30 (4H, m), 3.95 (2H, m), 4.40 (2H, m), 4.80 (2H, m), 7.68 (1H, dd, J=2, 13), 8.42 (1H, s)
25	195—198	$C_{22}H_{18}F_2N_2O_4$	64.08 (64.22)	4.40 (4.48)	9.21 (9.01)	6.79 (7.01)	1.00—1.20 (4H, m), 3.83 (2H, d, J=6), 3.91 (2H, d, J=6), 3.87 (1H, m), 7.30—7.65 (6H, m), 8.37 (1H, s)

a) In CD_3OD (0.5% HCl, tetramethylsilane). DSS: 3-trimethylsilyl-1-propanesulfonic acid sodium salt.

TABLE III. *In Vitro* Antibacterial Activity: *MIC* (μg/ml)[a]



Compd. No.	R_1	R_2	Organism: Gram-negative Ec[b]	Kp[c]	Pm[d]	Ecl[e]	Pa[f]	Gram-positive Sa(J)[g]	Sa(S)[h]	Sa(C)[i]	Spy[j]	Spn[k]
14	$-NHC(NH_2)=NH$	$-H$	50	50	100	100	100	1.6	6.3	100	0.4	25
15	$-CH_2NH_2$	$-H$	0.1	0.2	0.4	0.4	1.6	0.1	0.1	0.4	0.4	0.4
16	$-NH_2$	$-H$	0.02	0.02	0.05	0.05	0.4	0.1	0.1	0.1	0.8	0.8
17	$-NHCONHCH_3$	$-H$	0.8	0.8	3.1	3.1	6.3	0.8	0.2	0.8	0.4	0.8
18	$-NHCH_3$	$-H$	0.05	0.05	0.1	0.1	0.8	0.2	0.1	0.1	0.8	0.8
19	$-NH_2$	$-CH_3$	0.05	0.05	0.2	0.1	0.8	0.2	0.1	0.2	1.6	0.8
20		$-H$	0.2	0.2	0.8	0.4	3.1	0.2	0.1	0.1	1.6	1.6
21	$-H$	$-H$	0.2	0.2	0.4	0.8	1.6	0.05	0.05	0.05	0.8	0.8
22	$-N(CH_3)_2$	$-H$	0.1	0.1	0.4	0.4	1.6	0.2	0.1	0.1	0.8	0.8
23		$-H$	0.2	0.2	0.8	0.2	3.1	0.2	0.2	0.2	1.6	1.6
24	$-Br$	$-H$	0.4	0.4	0.8	0.8	3.1	0.1	0.05	0.1	1.6	1.6
25	$-Ph$	$-OH$	1.6	1.6	3.1	6.3	25	0.2	0.1	0.1	1.6	1.6

a) *MIC* were determined by the agar dilution method. Inoculation was performed with one loopful of 10^6 cells per ml. *b*) *Escherichia coli* JC-2. *c*) *Klebsiella pneumoniae* SR-1. *d*) *Proteus mirabilis* PR-4. *e*) *Enterobacter cloacae* SR-233. *f*) *Pseudomonas aeruginosa* PS-24. *g*) *Staphylococcus aureus* JC-1. *h*) *Staphylococcus aureus* SMITH. *i*) *Staphylococcus aureus* C-14(R). *j*) *Streptococcus pyogenes* C-203. *k*) *Streptococcus pneumoniae* type 1.

They also found that the introduction of fluorine at the C-8 position of quinolone derivatives did not substantially improve their gyrase inhibitory activities but profoundly improved their oral efficacy.

The usefulness of QSAR information led us to examine in detail the structural effects of heterocyclic amines as C-7 substituents upon the antibacterial activity of the lead compound 1-cyclopropyl-6,8-difluoro-4-oxoquinoline-3-carboxylic acid (**13**) for two reasons. First, heterocyclic amines such as piperazine, pyrrolidine, or pyridine[6] are well known to strongly affect the antibacterial activity of quinolonecarboxylic acids but, from the QSAR viewpoint, their structural requirements had not been studied as much as the N-1 substituent groups. Second, as the lead compound **13** chosen here already possessed the cyclopropyl group at the N-1 and fluorine at the C-6 and C-8 positions, we expected to obtain highly potent derivatives from this compound by introducing a suitable C-7 substituent group. Thus, our interest was first focused on the azetidine derivatives, since substituted azetidines had been very little studied[7] despite their structural interest and the advantage of having no chiral center within the molecules. As the main subject of this study, we synthesized various 3-substituted azetidine derivatives of **13**, **14**—**25** and examined them by QSAR analysis to clarify the scope and limitations of 3-substituted azetidines as the C-7 substituent group. The findings were then extended to the prediction of promising 3,4-substituted pyrrolidine derivatives.

Synthesis and Antibacterial Activities According to the schemes shown in Chart 1, we synthesized azetidine derivatives, **14**—**25**, to subject them to QSAR analysis in order to design promising C-7 substituents.

Their analytical and spectral data are summarized in Table II and their chemical structures and biological data in Table III.

Compounds other than azetidines, **26**—**34**, were previously prepared in our laboratories and only their structures and biological data of *GNM* and *GPM* values are summarized in Table V.

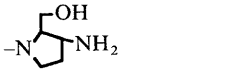
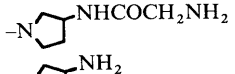
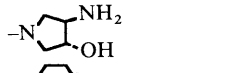
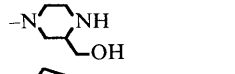
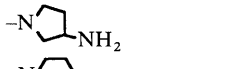
TABLE IV. The CLOG *P*, *GNM*,[a] and *GPM*[a] Values for Quinolones Bearing Azetidines

Compd. No.	CLOG *P*	*GNM* Obs.	*GNM* Deviation[b] Δ(2)	*GNM* Deviation[b] Δ(3)	*GPM* Obs.
14	−0.099	9.0	0.0	0.0	3.2
15	1.603	0.6	0.7	0.2	−1.8
16	2.120	−2.0	−1.2	−1.5	−2.0
17	2.531	3.2	3.9	3.7	−0.6
18	2.547	−1.0	−0.4	−0.5	−1.6
19	2.639	−0.8	−0.3	−0.3	−1.2
20	2.901	1.2	1.2	1.4	−1.2
21	2.971	1.0	0.8	1.1	−2.4
22	3.127	0.4	−0.2	0.1	−1.6
23	3.333	1.0	−0.4	0.2	−0.8
24	3.644	1.8	−1.0	0.0	−1.6
25	3.789	4.2	0.6	1.8	−1.2

a) The *GNM* and *GPM* values are arithmetic means of antibacterial screening index against gram-negative and gram-positive strains, respectively. See text for detailed definitions. *b*) Δ(2) and Δ(3) are deviations of the values estimated by Eqs. 2 and 3 from the observed ones, respectively.

The antibacterial activities of these compounds were tested, using standard techniques,[9] against five gram-negative bacteria, *E. coli* JC-2, *K. pneumoniae* SR-1, *P. mirabilis* PR-4, *E. cloacae* SR-233, and *P. aeruginosa* PS-24, and five gram-positive bacteria, *S. aureus* JC-1, *S. aureus* SMITH, *S. aureus* C-14(R), *S. pyogenes* C-203, and *S. pneumoniae* type 1. The minimum inhibitory concentration values (*MIC*s in μg/ml) determined were compared with that of the standard compound, ofloxacin **5**.[10] Furthermore, in order to facilitate comparison of the antibacterial activities of these different quinolone derivatives against various types of gram-negative and gram-positive bacteria, the relative mean antibacterial activity indices, *GNM* and

TABLE V. The CLOG *P*, *GNM*,[a] and *GPM*[a] Values for Quinolones Bearing Cyclic Amines Other than Azetidines

Compd. No.	R	CLOG *P*	*GNM* Obs.	*GNM* Deviation[b] *Δ*(2)	*GNM* Deviation[b] *Δ*(3)	*GPM* Obs.
26	$-NHCH_2CH(OH)-CH_2OH$	0.452	4.9	0.0	−0.3	2.5
27		1.235	3.0	2.0	1.5	2.4
28		1.440	2.6	2.3	1.8	−0.2
29		1.443	1.2	0.9	0.4	−0.8
30		1.619	0.4	0.5	0.1	0.2
31		2.111	−2.6	−1.8	−2.2	−3.8
32		2.141	6.0	6.8	6.5	5.8
33		2.340	4.2	5.0	4.8	1.6
34		4.090	2.0	−3.4	−1.9	−2.2

a, *b*) See footnotes in Table IV.

GPM, were calculated for each compound as the mean value of the corresponding relative GN_i and GP_i values defined by Eq. 1, respectively, and listed in Tables IV and V

$$GN_i \text{ or } GP_i = \log_2(MIC_i/MIC_i^{O}) \quad (1)$$

where MIC_i and MIC_i^{O} are *MIC* values of the tested compound and ofloxacin, respectively, against the *i*-th strain.

QSAR Analysis The partition coefficient values, log *P* (octanol/water) were calculated by MedChem Software (release 3.33)[11] and listed as CLOG *P* values in Tables IV and V together with *GNM* and *GPM* values of all the compounds described above. QSAR analyses were run on a Vax 6320 using our own program package. In Fig. 1, these *GNM* values are plotted against their corresponding CLOG *P* values. As clearly shown by the dotted line in Fig. 1, an excellent parabolic relationship, represented by Eq. 2, was obtained, except for compound **17** which deviated severely from the curve.

$$GNM = 1.81(\pm 0.45)[\text{CLOG } P]^2 - 8.10(\pm 1.77)[\text{CLOG } P] + 8.21(\pm 1.81) \quad (2)$$
$$n = 11, \quad r = 0.967, \quad s = 0.86$$

The four factors appearing in Eq. 2, namely the figures in parentheses, *n*, *r*, and *s*, denote the 95% confidence limits, the number of compounds, the correlation coefficient, and the standard deviation, respectively. This equation can explain 93.5% of the total variance, with no need for any additional parameter, indicating that *GNM* solely depends on CLOG *P*. The plot of *GPM* in Fig. 2 strongly suggested that the antibacterial activities of these compounds against gram-positive bacteria were almost the same values regardless of the variation of C-7 substituents, except for compound **14**.

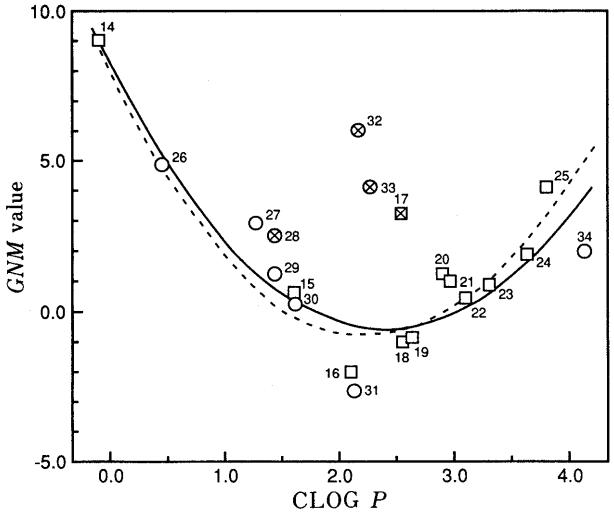


Fig. 1. Correlation of *GNM* Values with CLOG *P*

□, azetidine compounds; ○, other amine compounds; ⊠, ⊗, compounds excluded from regression analysis; ---, corresponds to Eq. 2; ——, corresponds to Eq. 3.

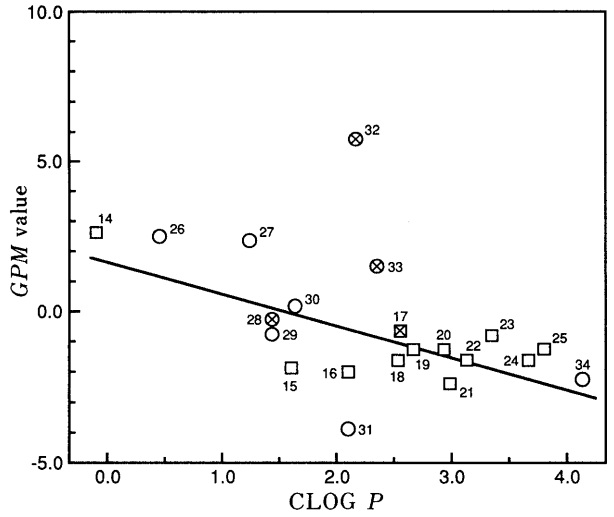


Fig. 2. Correlation of *GPM* Values with CLOG *P*

□, azetidine compounds; ○, other amine compounds; ⊠, ⊗, compounds excluded from regression analysis.

Discussion

Our QSAR analysis strongly indicated that a parabolic relationship represented by Eq. 2 existed between the relative mean antibacterial activity indices *GNM* and CLOG *P* values of azetidine compounds **14**—**25**, except in the case of compound **17**. If this relationship could be confirmed, it would strongly suggest that *GNM* of these compounds is solely dependent upon the hydrophobic properties, CLOG *P*, of these molecules. What was of most interest was the prediction that the CLOG *P* value of the compound with optimal activity would be 2.24. However, two serious questions arose in the present QSAR analysis. One was that if compound **14** having a particularly low CLOG *P* value of −0.099 and a high *GNM* value of 9.0 was excluded from the analysis, the correlation of *GNM* with CLOG *P* would be linear and not parabolic as represented by Eq. 2. The

other was that compound **17** considerably deviated from Eq. 2. In order to explain these discrepancices, we conducted further QSAR analyses by adding the data of derivatives bearing heterocyclic amines other than azetidine derivatives at the C-7 position. These analyses included various compounds having CLOG *P* values either less than 2 or more than 4 or C-7 amide substituent groups instead of amino ones. The *GNM*, *GPM*, and CLOG *P* values obtained are summarized in Table V. All of the *GNM* values of the newly added compounds were plotted against the CLOG *P* values together with those of the azetidine derivatives in Fig. 1. Next, regression analysis for *GNM* was conducted, giving the good parabolic relationship represented by Eq. 3.

$$GNM = 1.54(\pm 0.43)[\text{CLOG } P]^2 - 7.37(\pm 1.87)[\text{CLOG } P] + 8.24(\pm 1.90) \quad (3)$$
$$n=17,\ r=0.916,\ s=1.18$$

Although the compounds **28**, **32**, **33** and **17** were excluded from this regression analysis because of their extremely large *GNM* values, the newly obtained parabolic relationship confirmed the reliability of the previous one given by Eq. 2. The optimal GLOG *P* value estimated by Eq. 3 was 2.39, being quite close to the value, 2.24 estimated by Eq. 2. Also, all the coefficients for the three terms in Eq. 3 agreed well with those of the corresponding ones of Eq. 2 after consideration of the experimental errors which might be involved in the measurement of the antibacterial activities of these compounds. As for the exceptions, compounds **28**, **32**, **33** and **17**, we noted that all commonly bear certain amide or urea substituent groups on heterocyclic amine moieties, which might have caused extremely unfavorable effects on the antibacterial activity against gram-negative bacteria. As we previously noted,[7b] Shen *et al.*[12] proposed a binding model of quinolonecarboxylic acids with DNA gyrase. According to their model, the heterocyclic amine region attached to the C-7 position was designated as the drug–enzyme interaction domain. Incorporation of an amide substituent group into this region may have had a marked influence on the binding affinity of these substrates with the enzyme. In fact, Koga *et al.* had also made a similar observation on the antibacterial activity against *E. coli*.[3]

The results with gram-positive bacteria, unlike gram-negative bacteria, clearly showed that *GPM* remained rather constant, being independent of structural variation in the azetidine moiety (Table IV and Fig. 2). However, there was an exception here also. 3-Guanidino-substituted compound **14** showed much lower activity than other 3-substituted and 3-unsubstituted derivatives **15**—**25**. Therefore, like the *GNM* case, the data obtained from other heterocyclic amines were added to the analysis (Fig. 2).

There seemed to be a weak linear relationship between *GPM* and CLOG *P*. Regression analysis gave the following linear equation expressed by Eq. 4.

$$GPM = -1.13(\pm 0.63)[\text{CLOG } P] + 1.80(\pm 1.62) \quad (4)$$
$$n=17,\ r=0.703,\ s=1.38$$

This equation indicates that *GPM* decreases with an increasing CLOG *P* value. However, this correlation is quite weak due to the small *r* and large *s* values in Eq. 4, and when the CLOG *P* value is higher than 1.5, the *GPM* value will remain rather independent from the CLOG *P* value as described in the previous section.

TABLE VI. Antibacterial of Designed Compounds

No.	R	*GNM*	*GPM*
35		−0.44[a]	−0.57[b]
36		−0.6	−3.0
37		0.0	−1.6
5	Ofloxacin	0.0	0.0
12	Tosufloxacin	−1.4[c]	−3.2[c]

a) Calculated from Eq. 3. *b*) Calculated from Eq. 4. *c*) This value was obtained in our laboratory.

Our QSAR analysis predicted that the CLOG *P* value for the most potent derivative would be near 2.3 and the C-7 heterocyclic amine substituent groups should not bear an amide function. The structural details of the C-7 substituent groups involved in the potent new quinolone derivatives listed in Tables I, III and V suggest that heterocyclic amines bearing an amino group at a position two or three carbons from the nitrogen atom attached to the C-7 position possess distinctly enhanced antibacterial activity.

To discuss the scope and limitations of azetidine derivatives as a C-7 substituent group, compound **16** was chosen as an example. It had the CLOG *P* value of 2.12 and showed the highest and most balanced *in vitro* antibacterial activities among the various derivatives, as clearly shown by its *GNM* and *GPM* values listed in Table IV. Comparison of its *GNM* and *GPM* values with those of the pyrrolidine compounds listed in Table V also showed that the *in vitro* antibacterial activities of azetidine compounds were not necessarily weaker and in some cases exceeded them. However, as this series of azetidine quinolones tended to show somewhat weak *in vivo* antibacterial activities, possibly due to their reduced bioavailability, we conducted a search for pyrrolidine derivatives on the basis of our QSAR results in order to find more suitable substituent groups other than the already known 3-aminopyrrolidine.

The most promising derivative according to our QSAR analysis was the compound **35** bearing the 3′-amino-4′-methoxypyrrolidine moiety at the C-7 position. Its CLOG *P* value was 2.10 and it fulfilled the other structural requirements described above. The *GNM* and *GPM* values of this compound were estimated to be −0.44 and −0.57 by Eqs. 3 and 4, respectively, greatly superior to the values of ofloxacin which is clinically the most widely used quinoline agent today (Table VI). Further work on this compound will be described in the accompanying paper.[13]

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References and Notes

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