Table 1. Recoveries of cyanide and sulfide after three different sample treatments

added amount	Conway Microdiffusion		dialysis membrane filtration		aeration	
(ppm)	cyanide	sulfide	cyanide	sulfide	cyanide	sulfide
0.20	0.19	0.18	0.10	0.13	0.18	0.18
0.40	0.36	0.36	0.25	0.25	0.34	0.37
0.60	0.58	0.54	0.39	0.53	0.53	0.56
0.80	0.73	0.73	0.54	0.57	0.72	0.73
ave. recovery	93.7± 2.6	91.5± 0.7	66.8± 2.6	72.6± 5.4	88.8± 1.5	92.5± 0.5

their recoveries are shown in Table 1. The filtration method is simple and fast compared with the other two methods. However, the recoveries of cyanide are lower than the others because the cyanide binds with heme, hemoglobin or methemoglobin that could not pass through the pores of the dialysis membrane. The recoveries of sulfide are also decreased because sulfide could adsorb on the large protein molecule.

References

1. Fleet, B.; Strop, H. V. *Anal. Lett.* **1971**, *4*, 425.
2. Tse, Y.; Janda, P.; Lever, A. B. *Anal. Chem.* **1994**, *66*, 384.
3. Joo, C. N.; Choi, S. D. *Korean Biochem. Journal* **1992**, *25*, 397.
4. Peramunage, D.; Forouzan, F.; Licht, S. *Anal. Chem.* **1994**, *66*, 378.
5. Zamecnik, Z.; Tam, T. *J. Anal. Toxicology* **1987**, *11*, 47.
6. Nagata, T.; Kage, S.; Kimura, K.; Kudo, K.; Noda, M. *J. Forensic Sciences* **1990**, *35*, 706.
7. Leung, L. K.; Bartak, D. E. *Anal. Chim. Acta.* **1981**, *131*, 167.
8. Wallingford, R. A.; Ewing, A. G. *Anal. Chem.* **1987**, *59*, 1762.
9. O'Shea, T. J.; Lunte, S. M. *Anal. Chem.* **1993**, *65*, 948.
10. Rucki, R. J. *Talanta* **1980**, *27*, 147.
11. Lu. W.; Cassidy, R. M. *Anal. Chem.* **1993**, *65*, 1649.
12. Johonson, D. C.; LaCourse, W. R. *Anal. Chem.* **1990**, *62*, 589A.
13. Chen, T. K.; Lau, Y. Y.; Wong, D. K. Y.; Ewing, A. G. *Anal. Chem.* **1992**, *64*, 1264.
14. Kissinger, P. T. *Anal. Chem.* **1977**, *49*, 447A.
15. Vandeberg, P. J.; Johonson, D. C. *Anal. Chem.* **1993**, *65*, 2713.
16. Shimizu, K.; Osteryoung. R. A. *Anal. Chem.* **1981**, *53*, 2350.
17. Philar, B.; Kosta, L. *Anal. Chim. Acta.* **1980**, *114*, 275.
18. Philar, B.; Kosta, L. Hristovski, B. *Talanta* **1979**, *26*, 805.
19. Koch, W. F. *J. of Research of the National Bureau of Standards* **1983**, *88*, May-June, 157.
20. Rocklin, R. D.; Johonson, E. L. *Anal. Chem.* **1983**, *55*, 4.
21. Shimizu, K.; Aoki, K; Osteryoung, R. A. *J. Electroanal. Chem.* **1981**, *129*, 159.

Quantitative Structure-Activity Relationships (QSAR) Study on C-7 Substituted Quinolone

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Received August 26, 1995

To see the quantitative relationship between the structures of the C-7 substituted quinolones and their antibacterial activities, theoretical parameters such as the molecular van der Waals volume, surface area and some electrostatic parameters based on the molecular electrostatic potential, which represent lipophilicity , and some quantum mechanical parameters are introduced as descriptors. The sixteen substituted quinolone derivatives and twenty bacteria are used for the study. It is found that the QSARs of C-7 substituted quinolones are obtained for eleven bacteria and our descriptors are more useful for Gram positive organisms than negative ones. It is also shown that molecular surface area (or molecular Waals volume) of the C-7 substituent and net charge of C-7 atom of the quinolones are the descriptors of utmost importance.

Introduction

The basic assumption of Quantitative Structure-Activity Relationships (QSAR) is that there are some quantitative relationships between the microscopic (molecular structure) and the macroscopic (empirical) properties (particularly biological activity) of a molecule.[1] The term structure does not necessarily mean the spatial arrangement of atoms in a mo-

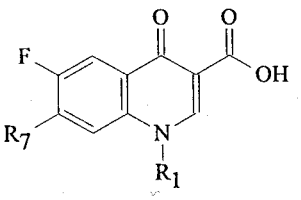

Figure 1. The structure of quinolone.

lecule itself, but rather the chemical and physicochemical properties inherent in that arrangement.

Quinolones (Figure 1) have become a major class of antibacterial agents which are under extensive clinical development.[2~4] They have an attraction because of their extremely potent activity, rapid bactericidal effects, and low incidence of resistance development.[2] According to the inhibition mechanisms of the quinolone, proposed by Shen *et al.*,[5~8] the site near the C-7 substituent is regarded as drug-enzyme interaction domain. In addition, Klopman *et al.*[9] also concluded that the cell permeability is dominantly controlled by C-7 substituent. These facts motivate our concern for QSAR between the activity and the C-7 substituent of quinolone.

Most of the QSAR studies have frequently used empirical parameters, *i.e.* lipophilicity, cavity surface area (CSA), solubility, and Hammetts constant (σ).[10~13] Especially, lipophilicity, expressed by the logarithm of partition coefficient (log P), is a very important physicochemical parameter which describes a partitioning equilibrium of solute molecules between water and an immiscible organic solvent. It is of particular importance in drug design not only because it is correlated with the biological data but also because it encodes a wealth of structural information.[1] In spite of its success in describing hydration-dehydration effect, log P has the bias of all empirical parameter. It can be determined either from the costly and time-consuming experiment, or from the approximate empirical formula with limited reliability.[14]

Therefore, it is quite meaningful to seek the theoretical parameters which may replace log P. It has been believed that the partition coefficients encode two major structural contributions, namely a cavity and a polarity term.[15~18] The cavity term reflecting the energy needed to create a cavity in the solvent, may be expressed in terms of volume or surface area of a molecule in general. And the polarity term may be represented by molecular electrostatic potential (MEP or ESP) parameters because the ESP is a powerful tool for characterizing the essential stereoelectronic features of biomolecules and drugs.[20~24]

Our main objectives in the present work are to find the theoretical descriptors to which the activities of the C-7 substituted quinolones are tightly correlated and to investigate the QSARs of C-7 substituted quinolones with them.

Methods and Calculation

At first, the eight descriptors given in Table 1 are selected for the QSAR study. The molecular total van der Waals volume (TVV) and total surface area (TSA) are selected to represent cavity term of partition coefficient and Π, σ_+ and σ_- of Murray *et al.*,[25], defined in Equations (1)-(4) respectively, to present polarity. Π is given by

Table 1. Theoretical Descriptor Sets Used in the Present Work No abbr

No.	abbr.	physicochemical quantities	unit
1	TVV	Total Van der Waals Volume	Å^3
2	TSA	Total Surface Area	Å^2
3	σ_+	std. deviation of positive electrostatic potential	kT/e
4	σ_-	std. deviation of negative electrostatic potential	kT/e
5	Π	average deviation of electrostatic potential	kT/e
6	BO1	bond order between C-6 and C-7	
7	BO2	bond order between C-7 and C-8	
8	C7	net charge of C-7 atom	electron charge

$$\Pi=\frac{1}{n}\sum_{i=1}^{n}\left|V(r_i)-\overline{V}_s\right|, \tag{1}$$

where $V(r_i)$ is the value of $V(r)$ at the grid point i on the molecular surface and $\overline{V}_s$ is the average of the $V(r_i)$ on the surface. The electrostatic potential $V(r)$ itself is defined by

$$V(r)=\sum_A \frac{Z_A}{|r_A-r|}-\int\frac{\rho(r')dr}{|r'-r'|}, \tag{2}$$

where Z_A is the charge on nucleus A located at r_A, (r) is the electronic density function. The electrostatic potential $V(r)$ is a real physical property and well established as an effective measure of molecular interaction[26]; it is particularly useful in studies of long range interactions that do not involve any significant degree of charge transfer. The first term on the right side of Equation (2) gives the contribution of the nuclei, which is positive; the second term reflects that of the electrons and is negative. Π is viewed as a measure of charge separation or local polarity; by definition, it is the average deviation of the surface electrostatic potential. [27] The standard deviation of the electrostatic potential for positive charge, σ_+, and that for negative charge, σ_-, are defined as follows[28,29]:

$$\sigma_+=\left[\frac{1}{m}\sum_{i=1}^{m}\left|V^+(r_i)-\overline{V}_s^+\right|^2\right]^{1/2} \tag{3}$$

and

$$\sigma_-=\left[\frac{1}{m}\sum_{i=1}^{m}\left|V^-(r_i)-\overline{V}_s^-\right|^2\right]^{1/2}, \tag{4}$$

where $V^+(r_i)$ and $V^-(r_i)$ are the positive and negative value of $V(r)$ on the molecular surface and $\overline{V}_s^+$ and $\overline{V}_s^-$ are their averages. In addition to these five parameters related to lipophilicity, the net charge of C-7 atom (C7) and bond orders (BO1, BO2) near C-7 atom are chosen to take the electrostatic interactions into account.

The structures of the quinolone and sixteen C-7 substituents used in this study are shown in Figure 2. Note that the second fluorine atom is attached to C-8 atom.

All the calculations about eight descriptors are performed on several modules of BIOSYM's *InsightII* package[30] for the

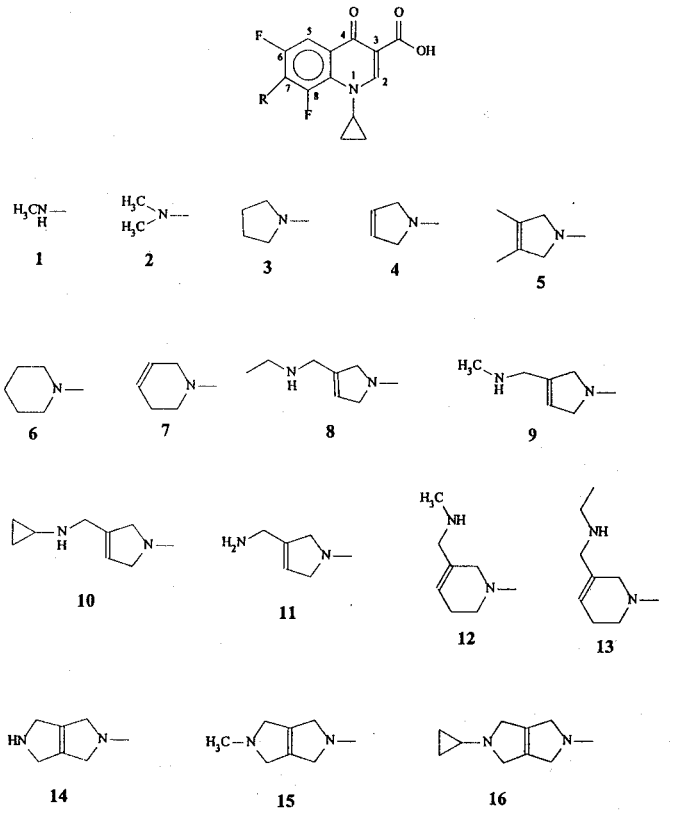

Figure 2. The structure of quinolone and sixteen C-7 substituents used in the present study.

AM1 optimized geometries. The molecular van der Waals volume is calculated on Search/Compare module and molecular solvent accessible surface area calculations are performed on Surface module which uses the Connolly algorithm.[31,32] The three terms related to the electrostatic potentials (ESP) are obtained at Del Phi module, which calculates the electrostatic potential in and around molecules using a finite difference solution to the non-linear Poisson-Bolzman equation.[33] Finally, the atomic net charge of C-7 atom and bond orders are obtained by AM1 calculations on Ampac/Mopac module.[34] The calculated values of the descriptors are listed in Table 2.

Anti-bacterial activities against twenty bacteria are expressed in terms of averaged minimum inhibitory concentration (MIC, μg/mL), and the twenty bacteria used for the test are listed in Table 3. The first six are Gram-positive(G(+)) bacteria and the others are Gram-negative(G(−)) ones. The ac-

Table 3. Twenty Organisms Selected for Activity Test

No	abbr.	organisms
1	**S.py.1*	*Streptococcus pyogenes 308*
2	**S.py.2*	*Streptococcus pyogenes 77*
3	**S.fa.*	*Streptococcus faecium MD 8b*
4	**S.au.1*	*Staphylococcus aureus SG 511*
5	**S.au.2*	*Staphylococcus aureus 285*
6	**S.au.3*	*Staphylococcus aureus 503*
7	*E.co.1*	*Escherichia coli O 55*
8	*E.co.2*	*Escherichia coli DC 0*
9	*E.co.3*	*Escherichia coli DC 2*
10	*E.co.4*	*Escherichia coli TEM*
11	*E.co.5*	*Escherichia coli 1507E*
12	*P.ae.1*	*Pseudomonas aeruginosa 9027*
13	*P.ae.2*	*Pseudomonas aeruginosa 1592E*
14	*P.ae.3*	*Pseudomonas aeruginosa 1771*
15	*P.ae.4*	*Pseudomonas aeruginosa 1771M*
16	*S.ty.*	*Salmonella typhimurium*
17	*K.ae.1*	*Klebsiella aerogenes 1082E*
18	*K.ae.2*	*Klebsiella aerogenes 1522E*
19	*E.cl.1*	*Enterobacter cloacae P 99*
20	*E.cl.2*	*Enterobacter cloacae 1321E*

*Gram-positive bacteria and the others are negative ones.

Table 2. Values of Descriptors for Each Quinolone Compound

compound	TVV	TSA	σ_+	σ_-	Π	BO1	BO2	C7
1	203.63	280	17.3946	51.6078	3.3436	1.28566	1.36632	−0.0528
2	219.13	282	16.0595	49.4744	3.1644	1.31144	1.40712	−0.0704
3	239.44	310	17.2272	60.3807	3.7465	1.28721	1.35760	−0.0156
4	234.14	307	17.9683	57.7838	3.5355	1.27827	1.35548	−0.0058
5	262.87	340	15.5106	58.6922	3.5120	1.28921	1.37964	−0.0328
6	253.99	322	16.0051	55.4518	3.3879	1.29499	1.35663	−0.0284
7	248.37	317	16.3310	52.0457	3.2402	1.30909	1.39709	−0.0598
8	287.52	378	12.8732	49.1299	3.0465	1.27752	1.35525	−0.0052
9	273.02	363	14.1954	60.8371	3.5098	1.30063	1.37485	−0.0359
10	295.79	386	11.2179	52.0912	2.9781	1.27775	1.35625	−0.0054
11	258.80	340	15.4582	61.4628	3.4593	1.27732	1.35589	−0.0063
12	289.04	373	15.1774	51.0111	2.9855	1.33090	1.39503	−0.0761
13	303.21	393	12.9418	50.0165	2.8283	1.31466	1.41572	−0.0792
14	264..49	342	16.1459	55.2910	3.0376	1.30001	1.37917	−0.0380
15	279.48	362	14.1192	59.1145	3.2712	1.30640	1.37219	−0.0408
16	301.99	387	13.2254	60.2160	3.0463	1.31235	1.41519	−0.0729

Table 4. *In Vitro* Antibacterial Activity (MIC, μg/mL) Data against Gram-Positive Bacteria

No.	*S.py.1*	*S.py.2*	*S.fa*	*S.au.1*	*S.au.2*	*S.au.3*
1	6.25	6.25	3.125	0.195	0.195	0.195
2	3.125	0.781	0.391	0.049	0.049	0.049
3	0.391	0.195	0.098	0.007	0.007	0.007
4	0.781	0.195	0.098	0.013	0.013	0.013
5	0.781	0.195	0.195	0.025	0.025	0.007
6	0.781	0.391	0.195	0.025	0.025	0.025
7	1.563	0.195	0.195	0.025	0.025	0.025
8	0.098	0.025	0.025	0.007	0.007	0.007
9	0.098	0.049	0.049	0.001	0.007	0.001
10	0.098	0.004	0.025	0.007	0.007	0.007
11	0.195	0.025	0.049	0.025	0.049	0.025
12	0.391	0.098	0.095	0.025	0.098	0.049
13	0.195	0.098	0.098	0.049	0.049	0.049
14	0.391	0.098	0.098	0.025	0.049	0.049
15	0.391	0.195	0.195	0.025	0.049	0.025
16	0.781	0.391	0.391	0.098	0.098	0.098

Table 5. *In Vitro* Antibacterial Activity (MIC, μg/mL) Data against Gram-Negative Bacteria

No	*E.co.1*	*E.co.2*	*E.co.3*	*E.co.4*	*E.co.5*	*P.ae.1*	*P.ae.2*
1	0.049	6.25	0.391	0.098	0.098	3.125	3.125
2	0.049	6.25	0.391	0.195	0.098	3.125	1.563
3	0.025	1.563	0.098	0.049	0.049	0.781	0.781
4	0.049	3.125	0.195	0.098	0.098	1.563	0.781
5	0.098	12.5	1.563	0.195	0.195	1.563	1.563
6	0.098	6.25	0.781	0.195	0.195	3.125	1.563
7	0.098	1.563	1.563	0.195	0.195	3.125	1.563
8	0.007	0.195	0.025	0.025	0.025	1.563	0.781
9	0.001	0.195	0.025	0.007	0.013	0.781	0.391
10	0.013	0.391	0.049	0.049	0.049	3.125	1.563
11	0.004	0.195	0.049	0.025	0.025	1.563	0.781
12	0.013	0.781	0.098	0.098	0.098	3.125	1.563
13	0.049	0.781	0.098	0.195	0.195	6.25	3.125
14	0.004	0.098	0.025	0.013	0.013	0.781	0.195
15	0.001	0.195	0.049	0.013	0.013	1.563	0.781
16	0.098	0.195	0.391	0.391	0.195	6.25	3.125

No	*P.ae.3*	*P.ae.4*	*S.ty.*	*K.ae.1*	*K.ae.2*	*E.cl.1*	*E.cl.2*
1	3.125	0.781	0.098	0.013	0.098	0.049	0.025
2	1.563	0.391	0.049	0.025	0.098	0.049	0.049
3	0.781	0.195	0.049	0.013	0.098	0.049	0.013
4	0.781	0.195	0.098	0.025	0.195	0.049	0.025
5	1.563	0.391	0.195	0.195	0.781	0.391	0.098
6	3.125	0.391	0.195	0.098	0.391	0.195	0.049
7	3.125	0.195	0.195	0.195	0.391	0.195	0.049
8	1.563	0.391	0.013	0.001	0.049	0.025	0.013
9	0.781	0.195	0.007	0.001	0.025	0.013	0.007
10	3.125	0.781	0.025	0.025	0.098	0.049	0.025
11	0.781	0.195	0.013	0.025	0.049	0.025	0.013
12	3.125	0.781	0.049	0.049	0.098	0.049	0.013
13	6.25	1.563	0.098	0.098	0.195	0.098	0.049
14	0.391	0.098	0.007	0.013	0.025	0.025	0.007
15	0.781	0.195	0.013	0.013	0.025	0.013	0.001
16	6.25	1.563	0.195	0.098	0.391	0.195	0.049

tivity data are listed in Table 4 and 5. They are obtained from Korea Research Institute of Chemical Technology (KRICT) through a private communication.[35]

The statistical analysis is performed with SPSS/PC+(Statistical Package for Social Science). The regression equation in QSAR is as follows[36]:

$$-\log_{10}\mathrm{MIC}=\sum B_iX_i+C=\mathbf{B}\cdot\mathbf{X}+C \quad (5)$$

where X_i and B_i are i-th descriptor and fitting parameter (regression coefficient), respectively and C is constant.

Results and Discussion

The correlation for eight descriptors is listed in Table 6. It shows that the TVV and TSA are highly correlated (0.9890) and BO1, BO2, and C7 have good correlation. It means that they are not independent variables for the other one(s). And by definition, σ_+ and σ_- are slightly correlated to Π. In general, two or more variables which have highly interrelated are not used simultaneously in regression analysis.

Results of regression analysis for six G(+) bacteria and fourteen G(−) ones are given in Table 7. The regression equations are obtained for only eleven bacteria. Unfortunately for nine organisms, the regression equations are not obtained in general confidence limit (95%). It is noted that the nine ones are all G(−) bacteria. The multiple linearity and stability show better results for G(+) organisms. It

Table 6. Correlation Table for Eight Descriptors

	BO1	BO2	C7	Π	σ_-	σ_+	TSA	TVV
BO1	1.0000							
BO2	.8337	1.0000						
C7	−.9014	−.9185	1.0000					
Π	−.4628	−.5402	.4894	1.0000				
σ_-	−.2297	−.2686	.3439	.6705	1.0000			
σ_+	−.0866	−.1845	.0306	.6362	.1811	1.0000		
TSA	.2183	.2109	−.0632	−.5774	.0146	−.8693	1.0000	
TVV	.2812	.2628	−.1018	−.5868	.0165	−.8487	.9890	1.0000

Table 7. The Results of Regression Analysis

No	abbr.	regression equation	r	F	Sig. F
1	**S.py.1*	$-\log_{10}MIC = 0.0114\ TSA + 9.48\ C7 - 3.23$	0.914	33.0	0.0000
2	**S.py.2*	$-\log_{10}MIC = 0.0135\ TSA + 14.2\ C7 - 3.23$	0.858	18.1	0.0002
3	**S.fa.*	$-\log_{10}MIC = 0.00862\ TSA + 11.0\ C7 - 1.64$	0.820	13.3	0.0007
4	**S.au.1*	$-\log_{10}MIC = 31.4\ C7 + 38.0\ BO1 - 46.4$	0.748	8.24	0.0049
5	**S.au.2*	$-\log_{10}MIC = 11.7\ C7 + 1.99$	0.685	12.4	0.0034
6	**S.au.3*	$-\log_{10}MIC = 12.0\ C7 + 2.15$	0.583	7.22	0.0177
7	*E.co.1*				
8	*E.co.2*	$-\log_{10}MIC = 0.0125\ TSA - 4.24$	0.670	11.4	0.0045
9	*E.co.3*				
10	*E.co.4*	$-\log_{10}MIC = -11.9\ BO2 + 17.6$	0.504	4.76	0.0466
11	*E.co.5*				
12	*P.ae.1*	$-\log_{10}MIC = 0.678\ \Pi - 2.53$	0.601	7.92	0.0138
13	*P.ae.2*				
14	*P.ae.3*	$-\log_{10}MIC = 7.40\ C7 + 0.0578$	0.551	6.09	0.0271
15	*P.ae.4*	$-\log_{10}MIC = 0.767\ \Pi - 2.07$	0.555	6.22	0.0258
16	*S.ty.*				
17	*K.ae.1*				
18	*K.ae.2*				
19	*E.cl.1*				
20	*E.cl.2*				

*Gram positive bacteria and the others are negative ones.

means that our descriptors have more effectiveness for G(+) than G(−) ones. These difference of the QSARs for G(+) and G(−) bacteria can be understood by taking their cell wall structures into account. In general, the cell envelope structures of G(−) bacteria are more complicated than those of G(+) ones, and so it can be expected that the drug-transport mechanisms for G(−) ones are relatively complex. Therefore, it is inferred that it is relatively difficult to obtain the QSAR for G(−) ones. That is, more descriptors may be needed to express the QSAR for G(−) cases.

In Table 7, the TSA (Total Surface Area of the molecule) and C7 (net charge of C-7 atom) are confirmed as very important descriptors to express the activities. It is noticed that the difference of TSA with different quinolones is almost the difference of surface area of only C-7 substituents because the surface area of main body is changed a little by changing C-7 substituents. That is, the surface area of C-7 substituents is tightly connected with the activity of quinolone. Since TVV is highly correlated to TSA (Table 6), it can be said that the van der Waals volume of C-7 substituents is also important descriptor to show the QSAR of our molecule.

In general, the activity of any molecule is explained by following three effects.[1] The first is electrostatic effect which expresses the electrostatic interactions between drug and target molecule, and the next is steric effect which shows very weak or non electrostatic interaction without any chemical bond, that is van der Waals interaction etc. Finally, the third is transfer effect which implies many problems associated with the process through which the drug molecule meets with the target. The TSA and TVV can be classified as the parameters which are related to steric effect. And the C7 is also important descriptor which can describe electrostatic interaction.

The sign of the regression coefficient, B, is important because it can contribute to the understanding of the drug-action mechanism and/or give us the useful information about the drug design. In Table 7, the signs of the coefficient for descriptor TSA and C7 are positive. It means that these quantities should be large for good potency of the drug. That is, to have higher potency the quinolone molecule should have the C-7 substituent of which the surface area becomes large and/or of which the net charge of C-7 atom becomes large by the introduction. The net charge is the difference between the charge of the atom embedded in molecule and that of the atom alone. To have a large net charge, the C-7 atom should lose their electrons to neighbor atoms.

In conclusion, it is demonstrated that the theoretical parameters which represent lipophilicity and quantum mechanical properties could be applied to the QSAR study of C-7 substituted quinolone. The results of regression analysis for G(+) bacteria are relatively good but are not for G(−) case. It is found that the surface area of C-7 substituent and the net charge of C-7 atom are most important descriptors in the present study.

Acknowledgment. Some computational results are obtained from the software of Biosym Technologies in San Diego. Authors thank Dr. Wan Joo Kim for providing the activity data of C-7 substituted quilonones. This work has been supported by the Ministry of Science and Technology and the Ministry of Education of Republic of Korea, Seoul National University (SNU) Daewoo Fund, and NON DIRECTED RESEARCH FUND of Korea Research Foundation, 1993.

Reference

1. Hanch, C. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: New York, 1971.
2. Hooper, D. C.; Wolfson, J. C. *Antimicrob. Agents Chemother.* **1985**, *28*, 716.
3. Neu, H. C. *Antimicrob. Newsl.* **1987**, *4*, 9.
4. Fernandes, P. B. *J. Clin. Pharmcol.* **1988**, *28*, 156.
5. Shen, L. L.; Mitscher, L. A.; Sharma, P. N.; ODonnell, T. T.; Chu, D. W. T.; Cooper, C. S.; Rosen, T.; Pernet, A. G. *Biochemistry* **1989**, *28*, 3886.
6. Shen, L. L.; Pernet, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 307.
7. Shen, L. L.; Kohlbrenner, W. E.; Weigl, D.; Baranowski, J. *J. Biol. Chem.* **1989**, *264*, 2973.
8. Shen, L. L.; Baranowski, J.; Pernet, A. G. *Biochemistry* **1989**, *28*, 3879.
9. Klopman, G.; Macina, O. T.; Levinson, M. E.; Rosenkranz, H. S. *Antimicrobial Agents and Chemotherapy* **1987**, *Nov*, 1831.
10. Herman, R. B. *J. Phys. Chem.* **1972**, *76*, 2754.
11. Herman, R. B. *J. Phys. Chem.* **1976**, *79*, 263.
12. Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1.
13. Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175.
14. Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.
15. Moriguchi, I.; Kanada, Y.; Komatsu, K. *Chem. Pharm. Bull.* **1976**, *24*, 1799.
16. Cramer III, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 1837.
17. Testa, B.; Seiler, P. *Arzneim.-Forsch.* **1981**, *31*, 1053.
18. Grnbauer, H. J. M.; Tomlinson, E. *Int. J. Pharm.* **1984**, *21*, 61.
19. Taft, R. W.; Abraham, M. H.; Doherty, R. M.; Kamlet, M. J. *Nature* **1985**, *313*, 384.
20. Murray, J. S.; Brinck, T.; Polizer, P. *J. Phys. Chem.* **1993**, *97*, 13807.
21. Georges, G.; Vercauteren, D. P.; Vanderveken, D. J.; Horin, R.; Evrard, G.; Fripiat, J. G.; Andre, J. M.; Durent, F. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1990**, *17*, 1.
22. Greco, G.; Novellino, E.; Silipo, C.; Vittoria, A. *Quant. Struct.-Act. Relat.* **1991**, *10*, 289.
23. Kumar, A.; Bhattacharjee, A. K.; Mishra, P. C. *J. Mol. Struct. (Theochem)* **1991**, *251*, 359.
24. Sanz, F.; Manaut, F.; Saanchez, J. A.; Lozoya, E. *J. Mol. Struct. (Theochem)* **1991**, *230*, 431.
25. Murray, J. S.; Brinck, T.; Lane, P. *et al. J. Mol. Struct. (Theochem)* **1994**, *307*, 55.
26. Politzer, P.; Murray, J. S. In: *Reviews in Computationl Chemistry*; Vol. 2: Lipkowitz, K. B.; Boyd, D. B., Ed.; VCH Publishers: New York, 1991.
27. Brinck, T.; Murray, J. S.; Politzer, P. *Mol. Phys.* **1992**, *76*, 609.
28. Murray, J. S.; Lane, P.; Brinck, T.; Politzer, P. *J. Phys. Chem.* **1993**, *97*, 5144.
29. Murray, J. S.; Lane, P.; Brinck, T.; Paulsen, K.; Grice, M. E.; Politzer, P. *J. Phys. Chem.* **1993**, *97*, 9369.
30. *InsightII Reference Guide*; version 2.1.0, San Diego: Biosym Technologies, 1992.
31. Connolly, M. L. *Science* **1983**, *221*, 709.
32. Connolly, M. L. *J. Am. Chem. Soc.* **1985**, *107*, 1118.
33. *Del Phi User Guide*; version 2.3 San Diego: Biosym Technologies, 1992.
34. Dewar, M. J. S. *et al. J. Am. Chem. Soc.* **1985**, *107*, 3092.
35. Kim, W. J. Korea Research Institute of Chemical Technology (KRICT), private communication.
36. Draper, N.; Smith, H. *Applied Regression Analysis* 2nd Ed.; John Wiley and Sons: New York, 1981.