Korean J. of Med. Chem., Vol. 2, No. 2, 1992

Quantitative Structure-Activity Relationship Study on Quinolones and Naphthyridines

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(Received August 13, 1992)

ABSTRACT

Quantitative structure-activity relationship(QSAR) study was carried out for a series of N-1-(mono-,-(di- and -(trifluoro-tert-butyl)quinolones and naphthyridines. The relationship between the activity and the localized electron population(LEP) at selected atomic sites was studied. The LEPs for 10 quinolone derivatives and 14 naphthyridine ones were calculated by AM1 method. The results show that the LEP is a good structural parameter to predict the activity for naphthyridines but not for quinolones.

INTRODUCTION

In recent years, there has been considerable excitement concerning the development and clinical use of the newer quinolone antimicrobial agents.[1-7] These agents, also called fluoroquinolones, 4-quinolones, and quinolone carboxylic acids, include norfloxacin, ciprofloxacin, ofloxacin, pefloxacin, enoxacin etc.[8] Nalidixic acid and oxolinic acid were the first marketed quinolone agents.[9] In contrast to these earlier drugs, the newer agents are more potent, broader in spectrum of activity *in vitro*. The new agents have additional advantageous pharmacokinetic properties, including relatively long half-lives in serum, allowing generally for twice daily administration, excellent penetration into many tissues, and permeation into human cells, resulting in antimicrobial activity against intracellular pathogens.

In 1977, Gellert *et al.*[10] and Sugino *et al.*[11] reported experiments that defined the A unit of DNA gyrase as a primary target of nalidixic acid and oxolinic acid, using a combined biochemical and genetic approach. These drugs, including other quinolone agents, antagonize almost all of the activities of purified DNA gyrase, including introduction of negative supertwists, catenation-decatenation, and unknotting.[12-14] Many previous studies indicated that modification of the quinolone structure affected its antibacterial activity.[15-17]

So far, almost all QSAR[18] studies have used exclusively experimental parameters i.e. hydrophobicity, distribution coefficient(P), cavity surface area(CSA), solubility, Hammetts constant(σ) and etc.[19-22]

We conjecture that those quantities are implicitly related to the electronic structure of the system. So, we introduce the localized electron population(LEP)[23] which directly represents electronic structure as structural parameter. The study of the correlation between activity and LEP is the aim of this work. The LEP calculations have been carried out for 10 quinolone derivatives and 14 naphthyridine's by AM1 method[24] and regression analysis[25] has been performed by SPSS[26]. The drug activity data used here are obtained from Remuzon *et al.*'s report.[27]

CALCULATION AND RESULTS

The skeletons of N-1-(mono-, -(di- and -(trifluoro-tert-butyl)quinolones and naphthyridines (briefly quinolones and naphthyridines) used here are given in Figure 1 and susbstituents are given in Figure 2 and the code name of their derivatives are listed in Table 1. As shown in Table 1, the number of data is 10 for quinolones and 14 for naphthyridines. The input geometries are taken from the x-ray crystallographic data and fully optimized with AM1 method. The AM1 calculations are performed in ALLIANT FX/2800 at the computing center of the Seoul National University.

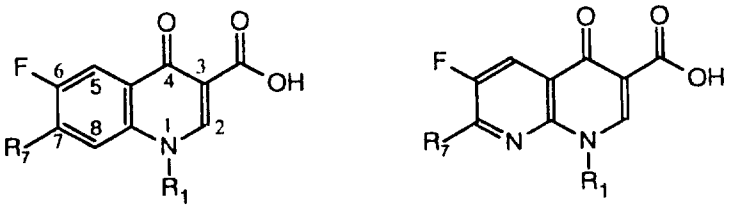


Figure 1. The structures of the quinolones(A) and naphthyridines(B).

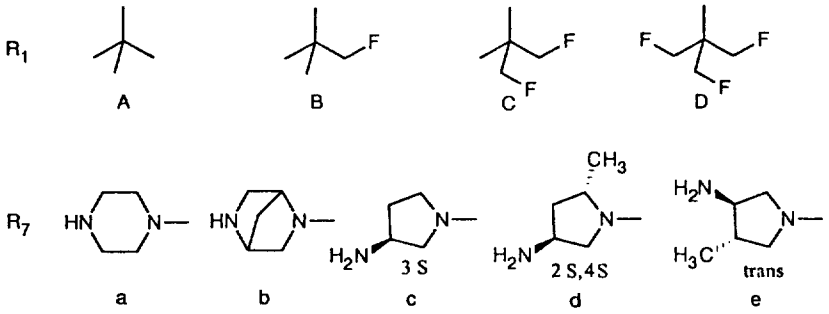


Figure 2. The substituents considered in this work.

1. LEP calculation by AM1

The LEP for atom A is defined as follows:

$$\text{LEP of atom A} = P_{AA} + \sum_{B} P_{AB}/2 \tag{1}$$

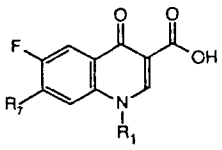
$$P_{AA} = \sum_{i(A)} \sum_{k} n_k C_{ki}^2 \tag{2}$$

$$P_{AB} = 2 \sum_{i(A)} \sum_{j(B)} \sum_{k} n_k C^*_{ki} S_{ij} C_{jk} \tag{3}$$

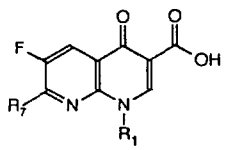
where P_{AA} and P_{AB} are the reduced overlap populations, S_{ij} is the overlap matrix element and n_k is the occupation number. The LEP is similar to Mulliken's net charge(NC). The definition of NC is

$$\text{NC} = \text{LEP} - \text{the number of valence electrons.} \tag{4}$$

Table 1. Substituted Quinolones and Naphthyridines



quinolones



naphthyridines

No.	quinolones code name	R_1	R_7	naphthyridines code name	R_1	R_7
1	Q1	A	a	N1	A	a
2	Q2	B	a	N2	B	a
3	Q3	C	a	N3	C	a
4	Q4	A	b	N4	D	a
5	Q5	B	b	N5	A	b
6	Q6	A	c	N6	B	b
7	Q7	B	c	N7	C	b
8	Q8	C	c	N8	D	b
9	Q9	B	d	N9	A	c
10	Q10	B	e	N10	B	c
11				N11	C	c
12				N12	D	c
13				N13	B	d
14				N14	D	e

Table 2 shows the 13 organisms used in test and the activity data for them are listed in Table 3. In Table 2, the first four organisms(V1-V4) are Gram positive bacteria and the others are negative.

Table 2. Organisms Selected for Activity Test

		Full Name
V1	S. pn.	*Streptococcus pneumoniac* A9585
V2	E. fa.	*Enterococcus faecalis* A 9809
V3	S. au. I	*Staphylococcus aureus* A9537
V4	S. au. II	*Staphylococcus aureus* A24227
V5	E. co.	*Escherichia coli* A15119
V6	K. pn.	*Klebsellia pneunomiae* A9664
V7	E. cl.	*Enterobacter. cloacae* A9656
V8	P. mi.	*Proteus mirabilis* A9900
V9	M. mo.	*Morganella morganii* A15153
V10	S. ma.	*Serratia marcescens* A20019
V11	P. ae.	*Pseudomonas aeruginosa* A9845
V12	H. in.	*Haemophilus influenzae* A21515
V13	B. fr.	*Bacillus fragilis* A22862

Table 3-a. In Vitro Antibacterial Activity of Substituted Quinolones (MIC, μg/mL)[a]

	V1[b]	V2	V3	V4[b]	V5	V6	V7	V8	V9	V10	V11	V12[b]	V13[b]
Q1	—	2	0.25	—	0.06	0.06	0.13	0.25	0.25	0.5	0.5	—	—
Q2	1	0.25	0.13	0.06	0.016	0.016	0.03	0.03	0.016	0.06	0.25	0.016	8
Q3	8	1	1	2	0.13	0.13	0.25	0.13	0.06	0.5	1	0.06	16
Q4	—	2	0.5	—	0.5	0.13	0.25	4	2	4	0.5	—	—
Q5	1	0.5	0.5	0.25	0.016	0.06	0.06	0.06	0.13	0.13	0.25	0.008	8
Q6	0.06	0.13	0.008	0.03	0.016	0.5	0.06	0.06	0.13	0.13	0.25	0.008	8
Q7	0.06	0.13	0.03	0.016	0.002	0.004	0.004	0.004	0.002	0.016	0.13	0.016	2
Q8	0.5	0.5	0.06	0.13	0.008	0.13	0.06	0.03	0.016	0.13	0.25	0.001	4
Q9	0.25	0.25	0.03	0.03	0.03	0.13	0.06	0.13	0.5	0.25	1	0.016	4
Q10	0.25	0.25	0.03	0.03	0.008	0.13	0.03	0.06	0.06	0.13	0.5	0.008	4

[a]Obtained from reference 27.
[b]Two activity data were not given in reference 27.

Table 3-b. In Vitro Antibacterial Activity of Substituted Naphthyridines(MIC, μg/mL)[a]

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12[b]	V13[b]
N1	1	1	0.06	0.25	0.016	0.03	0.06	0.13	0.06	0.06	0.5	0.016	8
N2	0.5	2	0.25	0.5	0.13	0.25	0.25	0.25	0.13	0.25	1	0.13	16
N3	16	16	4	4	0.13	0.25	0.25	1	0.13	0.5	4	0.25	125
N4	32	16	8	8	0.5	1	0.5	2	0.5	1	16	0.5	125
N5	0.13	0.5	0.003	0.03	0.008	0.016	0.016	0.06	0.06	0.06	0.25	0.03	—
N6	0.5	2	0.25	2	0.06	0.25	0.13	0.5	0.25	0.25	0.5	0.13	8
N7	8	4	2	2	0.13	0.5	0.13	0.5	0.13	0.5	1	0.016	32
N8	32	32	4	4	0.25	0.5	0.25	1	0.25	1	4	0.06	125
N9	0.008	0.06	0.004	0.002	0.016	0.03	0.03	0.13	0.13	0.25	0.25	—	1
N10	0.03	4	0.03	0.13	0.03	0.03	0.13	0.5	0.06	0.25	1	0.5	16
N11	16	16	8	4	0.5	2	0.5	4	0.5	2	8	0.25	125
N12	32	32	4	8	0.5	2	2	2	2	2	32	0.25	125
N13	0.13	0.13	0.008	0.008	0.016	0.06	0.06	0.13	0.13	0.13	1	0.016	16
N14	8	4	0.5	1	0.5	2	1	4	2	2	32	0.5	125

[a]Obtained from reference 27.
[b]One activity was not given in reference 27.

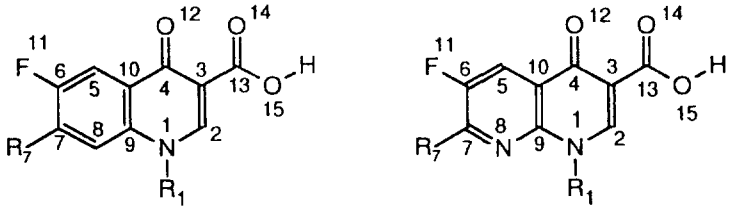
Even if the LEP calculations for the drugs at all atomic sites performed, the LEP's only at 12 atomic sites which we concentrated our concerns on, are given in Table 4. The numberings of the drugs used in calculations are shown in Figure 3.

Table 4-a. Localized Electron Populations of Substituted Quinolones at 12 Atomic Sites

	N-1	C-3	C-4	C-6	C-7	C-8	C-9	F-11	O-12	C-13	O-14	O-15
Q1	5.1768	4.2716	3.6825	3.9179	3.9866	4.1734	3.9467	7.0881	6.2638	3.6381	6.3262	6.3462
Q2	5.1742	4.2585	3.6836	3.9152	3.9873	4.1708	3.9511	7.0868	6.2574	3.6396	6.3213	6.3458
Q3	5.1691	4.2551	3.6841	3.9133	3.9890	4.1765	3.9572	7.0855	6.2550	3.6403	6.3201	6.3463
Q4	5.1671	4.2741	3.6858	3.9588	3.9673	4.1180	3.9670	7.1012	6.2622	3.6374	6.3250	6.3426
Q5	5.1659	4.2622	3.6850	3.9531	3.9740	4.1169	3.9694	7.0993	6.2582	3.6407	6.3218	6.3420
Q6	5.1994	4.2903	3.6784	3.9875	3.9233	4.2397	3.8951	7.1046	6.2791	3.6373	6.3318	6.3476
Q7	5.2027	4.2772	3.6782	3.9932	3.9202	4.2272	3.8964	7.1059	6.2755	3.6368	6.3252	6.3482
Q8	5.2018	4.2728	3.6831	3.9891	3.9239	4.2313	3.8996	7.1044	6.2757	3.6362	6.3226	6.3479
Q9	5.1991	4.2753	3.6781	4.0016	3.8886	4.2362	3.8935	7.1075	6.2777	3.6366	6.3258	6.3495
Q10	5.1987	4.3206	3.6697	3.9527	3.9602	4.1963	3.9129	7.0813	6.2489	3.6185	6.2929	6.3661

Table 4-b. Localized Electron Populations of Substituted Naphthyridines at 12 Atomic Sites

	N-1	C-3	C-4	C-6	C-7	N-8	C-9	F-11	O-12	C-13	O-14	O-15
N1	5.1619	4.2704	3.6784	3.9758	3.9083	5.2034	3.8788	7.0805	6.2653	3.6387	6.3274	6.3444
N2	5.1589	4.2625	3.6800	3.9718	3.9062	5.2035	3.8805	7.0788	6.2604	3.6384	6.3207	6.3440
N3	5.1617	4.2644	3.6780	3.9741	3.8932	5.2080	3.8740	7.0796	6.2619	3.6365	6.3190	6.3473
N4	5.1555	4.2552	3.6841	3.9669	3.9017	5.2107	3.8891	7.0749	6.2541	3.6394	6.3150	6.3434
N5	5.1544	4.2719	3.6766	4.0161	3.8954	5.1367	3.8928	7.0913	6.2633	3.6373	6.3237	6.3459
N6	5.1519	4.2609	3.6805	4.0114	3.8936	5.1398	3.8925	7.0903	6.2598	3.6376	6.3212	6.3436
N7	5.1488	4.2578	3.6816	4.0097	3.8909	5.1477	3.8948	7.0888	6.2571	3.6383	6.3202	6.3422
N8	5.1486	4.2552	3.6844	4.0066	3.8887	5.1459	3.9004	7.0869	6.2534	3.6381	6.3139	6.3434
N9	5.1790	4.2901	3.6748	4.0391	3.8668	5.2154	3.8454	7.0963	6.2788	3.6381	6.3241	6.3395
N10	5.1856	4.2790	3.6734	4.0405	3.8548	5.2247	3.8393	7.0973	6.2761	3.6361	6.3209	6.3473
N11	5.1799	4.2764	3.6758	4.0372	3.8586	5.2293	3.8429	7.0957	6.2750	3.6360	6.3143	6.3460
N12	5.1951	4.2663	3.6782	4.0456	3.8300	5.2443	3.8363	7.0963	6.2785	3.6368	6.3224	6.3445
N13	5.1893	4.2884	3.6661	4.0508	3.8289	5.2353	3.8320	7.0968	6.2718	3.6311	6.3128	6.3522
N14	5.1950	4.2680	3.6759	4.0478	3.8170	5.2471	3.8346	7.0957	6.2761	3.6367	6.3214	6.3456



A B

Figure 3. The numberings for the quinolones(A) and naphthyridines(B).

2. Regression Analysis by SPSS

The regression equation is assumed as follows:

$$A = \sum_i B_i X_i + C \qquad (5)$$

where the A is activity as dependent variable, the B_i are fitting parameter and the X_i is the LEP of i-th atom as independent variable, and C is constant as intercept. The best fitting parameters are obtained by regression method.[25] The SPSS(statistical package for social science) is used for the calculation.[26]

Since the balancing the number of data with the number of independent variable is very important to increase the confidence of the regression, we restrict the number of independent variable to six. So, the only 6 LEP's should be included in the calculation. The six atoms are selected intuitively with reference to Shen *et al*'s report.[28] They proposed that the substituent attached to C-7 was the binding site with DNA gyrase, and the near carbonyl domain seemed to be the binding site with DNA. So, the charges near C-7 domain and near carbonyl domian may be regarded as the kernel parameters related with the activity. The lists of the atoms included in these domains are shown in Table 5.

Table 5. The Atomic Lists Included in Two Domains

	six atomic sites
Domain I	N-1, C-6, C-7, C-8[a], C-9, F-11
Domain II	C-3, C-4, O-12, C-13, O-14, O-15

[a]Replaced by N-8 for naphthyridines.

The result of regression analysis for them is given in Table 6.

Table 6-a. The Results of Regression Analysis for the LEP's at Domain I

		quinolones			naphthyridines		
		r[a]	s[b]	F[c]	r	s	F
V1	S.pn.	0.9571	2.0680	1.8181	0.8081	10.4054	2.1964
V2	E.fa.	0.6644	0.9461	0.9461	0.6690	11.4874	0.9449
V3	S.au.I	0.9483	0.1779	4.4597	0.8090	2.3434	2.2105
V4	S.au.II	0.9508	0.5610	1.5680	0.7385	2.5882	1.3997
V5	E.co.	0.6583	0.1727	0.6118	0.9189	0.1120	6.3292*
V6	K.pn.	0.9001	0.1054	2.1336	0.9021	0.4619	5.0965*
V7	E.cl.	0.7576	0.1003	0.6736	0.9033	0.3134	5.1723*
V8	P.mi.	0.6724	1.1245	1.6504	0.8411	1.0039	2.8221
V9	M.mo.	0.7020	0.5832	1.2144	0.9522	0.2793	11.3471*
V10	S.ma.	0.6572	1.1187	1.5205	0.9219	0.3948	6.6059*
V11	P.ae.	0.9160	0.2165	2.6055	0.9584	4.4084	13.1449*
V12	H.in.	0.8713	0.0238	0.5254	0.6655	0.2015	0.7948
V13	B.fr.	0.9999	0.1526	969.8127*	0.8819	38.7227	3.5001

[a]Multiple linearity. [b]Standard error. [c]F-value used in statistical F-test.
*The regression for the organism is significant statistically within the confidence limit 95%.

The significance levels(or confidence limits) generally used in statistical test, are 0.05 and 0.01. We have used significance level 0.05 through this work. In our case, the F-value corresponding to significance level 0.05(confidence limit 95%) is 8.9402 for quinolones and 3.8660 for naphthyridines. If the F-value in Table 6 is greater than these values, the regression result is meaningful statistically within the confidence limit 95%.

For the domain I(Table 6-a), except only V13 case, all calculations for quinolones are not significant, but some significant results are shown for naphthyridines. For the naphthyridine case, linearities and reliabilities of the calculations for Gram negative organisms are good but not for Gram positive ones. This may be understood as follows: for Gram positive organisms, the charges(i.e. LEP's) near C-7 domain are not important factor to decide the activities of the drugs.

Table 6-b. The Results of Regression Analysis for the LEP's at Domain II

		quinolones			naphthyridines		
		r	s	F[a]	r	s	F
V1	S.pn.	0.9967	0.5783	25.2135	0.9271	0.1064	7.1399*
V2	E.fa.	0.9061	0.5357	2.2622	0.9472	4.9561	10.1777*
V3	S.au.I	0.8090	0.3294	0.9468	0.8837	1.8659	4.1691*
V4	S.au.II	0.9965	0.1517	23.5615	0.8343	2.1163	2.6717
V5	E.co.	0.8502	0.1395	1.3040	0.9271	0.1064	7.1399*
V6	K.pn.	0.9310	0.0883	3.2514	0.9126	0.4374	5.8154*
V7	E.cl.	0.7595	0.1000	0.6816	0.9102	0.2831	7.7240*
V8	P.mi.	0.9012	0.9313	2.1611	0.8740	0.9020	3.7748
V9	M.mo.	0.8827	0.4968	1.7645	0.9083	0.3826	5.5022*
V10	S.ma.	0.8928	0.9455	1.9640	0.9375	0.3526	8.4622*
V11	P.ae.	0.5646	0.3856	0.3744	0.8764	7.4372	3.8617
V12	H.in.	0.9937	0.0054	13.1223	0.9061	0.1142	4.5847*
V13	B.fr.	0.9125	3.3669	1.9906	0.8822	35.8167	4.9119*

[a]It is noted that even if some F-values are greater than 8.9402, their results are not significant yet within confidence limit 95% because the number of data for V1, V4, V12, and V13 is not 10 but 8.

In Table 6-b, for the quinolones, all the results are not significant. But, in the case of naphthyridine, most of the results are significant as shown in the table. These good correlations for naphthyridines between activity and charge(LEP) mean that the charges near carbonyl domain are important factor to decide the activities both for Gram positive organisms and for negative ones.

The fitting parameter B_i's are given in Table 7. For the sake of convenience, the result for a set of 4 randomly selected bacteria is given.

Table 7-a. The Fitting Parameter B_i's for Domain I calculation

	quinolones				naphthyridines			
	[a]V3	[a]V4	[b]V5	[b]V6	V3	V4	V5	V6
N1	-6.623317	-4.633454	0.0	-92.04172	-634.9287	-174.1385	-15.59570	-51.99528
C6	35.18318	101.4615	4.153281	19.95745	-168.2786	-168.2535	-16.04526	-108.7346
C7	5.771010	14.95367	-0.741313	19.50721	-113.9555	-109.4801	-10.53316	-51.13384
C8	29.41792	88.98456	0.954701	-1.423307	437.0259	332.7695	31.01777	114.3339
C9	60.62480	172.1619	7.306783	-54.07317	496.4750	587.8196	53.71914	203.6495
F11	-49.86425	-156.3931	-3.934027	-20.51619	1741.724	1410.748	137.5748	691.4573
const.	-135.0215	-375.7303	-18.22011	685.3202	-12134.87	-12002.23	-1158.267	-5379.887

Gram [a]positive and [b]negative bacteria. [a,b]These bacteria were selected randomly.

Table 7-b. The Fitting Parameter B_i's for Domain II calculation

	quinolones				naphthyridines			
	[a]V3	[a]V4	[b]V5	[b]V6	V3	V4	V5	V6
C3	13.76737	290.0562	-14.49898	34.91389	201.2760	105.4701	-22.78491	-94.53079
C4	54.87577	259.1066	1.247704	69.16850	1146.276	1456.882	-24.84585	-73.70375
O12	-16.13600	214.1151	-13.06143	1.470483	228.4993	261.8761	29.16523	121.2356
C13	99.98014	2641.928	-135.6291	148.9828	592.0475	-941.1950	100.0895	161.4741
O14	-13.79051	-790.2679	41.10307	-12.40376	-522.0954	-150.6112	-42.23964	-110.1040
O15	49.38704	1019.541	-47.38782	84.36211	789.9185	477.9694	10.04125	-17.52928
const.	-749.3931	-14619.25	673.4871	-1411.832	-10370.38	-6104.529	-154.7201	135.2863

Gram [a]positive and [b]negative bacteria. [a,b]These bacteria were selected randomly.

Table 8. Activity Predictions for Derivative N14 Assumed Unknown Drug

		[a]N12		Unknown([b]N14)	
		calc.	exp.	calc.	exp.
V1	S. pn.	0.47	32	0.5	8
V2	E. fa.	30	32	40	4
V3	S. au. I	4	4	5	0.5
V4	S. au. II	7	8	8	1
V5	E. co.	0.5	0.5	0.5	0.5
V6	K. pn.	2	2	2	2
V7	E. cl.	2	2	2	1
V8	P. mi.	2	2	2	4
V9	M. mo.	2	2	2	2
V10	S. ma.	2	2	2	2
V11	P. ae.	29	32	29	32
V12	H. in.	0.30	0.25	0.3	0.5
V13	B. fr.	121	125	166	125

[a,b]These derivatives are selected arbitrarily. The results for derivative N12 are obtained by interpolation, but those of derivative N14 obtained by extrapolation.

In Table 7, the larger the B_i value is, the more important the variable is. The further discussion will be given later.

Finally, as an example, activity prediction calculation has been performed for the unknown drug. The scheme is as follows: we assume the derivative N14 as an unknown drug and the optimized regression equation is obtained from the rest 13 data set which does not include the data for the derivative N14, and then the activity of the derivative N14 is evaluated by the equation. It is noted that the fitting parameters of the domain I are used. The result for this is given in Table 8.

In Table 8, the data for derivative N12 is given as an example to test out the accuracy of the regression equation. the predicted activities for Gram negative organisms(\5-\13) show better agreements than those for Gram positive ones with experiment's. In fact, these results can be infered from the Table 6-a. That is, the activity predictions evaluated by the equations with good confidence show good agreements with experiment's and others are not.

DISCUSSION and CONCLUSION

The merits of the use of the LEP as a parameter are as follows: it is very familiar concept to medicinal chemists and its evaluation is rather easy, and it is a independent parameter which is related to the major physicochemical parameters i.e. partition coefficient, hydrophobicity, and steric parameters etc. with which the activity is commonly described.

Even though the linearity for V1 bacteria(Table 6-a) is good, the result of activity predictions(Table 8) is not. This means that in the regression, the reliability is more important than its linearity. The Table 6 shows that most of the regressions for quinolones is not significant within the confidence limit 95% statistically. It means that the LEP is not correlated to the activity for the quinolones. That is, the LEP is meaningless parameter to evaluate the activity for this case. But in case of naphthyridines, most of the results are significant. This implies that the LEP can be regarded as a good structural parameter within the same confidence.

From now on, we restrict the discussion to the naphthyridines. In Table 6-a, the LEP dependence on the activity is not good for Gram positive organisms for the domain I, but good correlations are shown for the domain II. It means that the charges of the near C-7 domain are important for Gram negative organisms to decide the activity of the drug, but the charges of the near carbonyl domain are important both for Gram positive and negative bacteria. That is, the charges of the near C-7 domain are important to one type bacteria and are not to the other. It may imply that the near C-7 domain is the discriminative position for the bacteria. The essential difference of these two type bacteria is the cell wall structure. The structure of Gram negative bacteria is more complex than those of positive ones. So, our results may suggest that the near C-7 position is important site to interact with cell wall.

In Table 7-a, the LEP's of F-11 are most important for the domain I, and those of C-13, O-12, and O-14 are important for the domain II. It was proposed by Shen *et al* that those positions were the binding sites with the DNA of the bacteria.[28] If their suggestion can be accepted, the following may be also suggested: the binding between drug and DNA is the most important step to decide the activity of the drug.

In conclusion, the LEP is a good structural parameter to predict activity for naphthyridines but not for quinolones. And it is suggested that the near C-7 position is important site to interact with cell wall.

A C K N O W L E D G E M E N T

This work has been supported by the Ministry of Science and Technology and by the Ministry of Education.

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