Quantitative Structure-Activity Relationship (QSAR) Study by Use of Theoretical Descriptors: Quinolone and Naphthyridine

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Quantitative Structure-Activity Relationship (QSAR) studies are performed for the sets of 40 quinolones and 47 naphthyridines. Net charge, van der Waals volume, polarizability, and dipole moment are empolyed as theoretical descriptors (independent variables) to find the relationship between activity and physicochemical propreties such as electrostatic effect, steric effect, and transferability. The results are analyzed by the regression and the factor analysis. It is found that for Gram-negative bacteria, the QSAR of quinolone and naphthyridine are substantially different: to describe the activity, the electrostatic effect is the most important for quinolone, and the steric effect and the transferability for naphthyridine.

Introduction

Quantitative structure-activity relationship (QSAR)[1] has been used extensively in correlating molecular structural features of compounds to their biological, chemical, and physical properties. The preferability of QSAR is that there is quantitative connection between the microscopic (molecular structure) and the macroscopic (empirical) properties (particularly biological activity) of a molecule. Furthermore, this connection can be used to predict empirical properties of a compound with its molecular structure given.

Quinolones, a series of nalidixic acid analogues, have become a major class of synthetic antibacterial agents which are under extensive clinical development.[2-4] These drugs have an attraction because of their extremely potent antibacterial activity, rapid bactericidal effects, and low incidence of resistance development.[2] For quinolones, many studies have reported that modification of the structure affects its antibacterial activity.[5-8] Most QSAR studies have used exculsively the experimental descriptors, *i.e.* hydrophobicity, distribution coefficient (P), cavity surface area (CSA), solubility, and Hammetts constant (σ.[9-12] However, the observations on quantitative relationship between activity and microscopic properties theoretically calculated (*i.e.* theoretical descriptors) are not sufficient. The relationship can serve to investigate the mechanism of drug action and also contribute to find new derivatives of quinolones.

In general, the naphthyridine (Figure 1) is regarded as quinolone by its structural analogy and comparable activity.

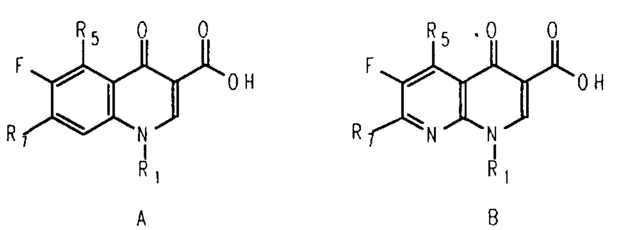


Figure 1. The structure of quinolone (A) and naphthyridine (B).

Table 1. Gram-negative Bacteria Selected for Activity Test

Abbrev.	Full name
E. co.	*Escherichia coli* A15119
K. pn.	*Klebsellia pneunomiae* A9664
E. cl.	*Enterobacter cloacae* A9656
M. mo.	*Morganella morganii* A15153
P. ae.	*Pseudomonas aeruginosa* A9845

But it is expected that the electronic structure of the two molecules are quite different because the nitrogen atom has nonbonding orbital. So, our concern here is to compare the QSAR of quinolone with that of naphthyridine.

The electrostatic interaction, bulk or steric effect, and transfer property (transferability) of the molecules are considered as microscopic properties. Theoretical descriptors used here are as follows: net charge for electrostatic interaction; molecular van der waals volume for bulk or steric effect; polarizability volume for transferability; and dipole moment. The AM1 calculations[13] are performed for 40 quinolones and 47 naphthyridines. The results are statistically analyzed by multiple regression and factor analysis.[14,15]

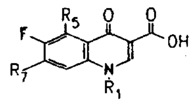
Method

The structure of quinolone and naphthyridine are illustrated in Figure 1.

The X-ray structure for the basic skeleton of the drug molecule[16] is used for the input of the AM1 calculation from which net charge, polarizability, and dipole moment are evaluated. The molecular van der Waals volume calculations are performed on Biosym's *InsightII*.

The activity data taken from a set of serial papers.[17-20] Because the given data are almost Gram-negative, the bacteria used for calculation are all Gram-negative ones (listed in Table 1). The selected data are given in Table 2 and 3.

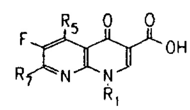
Table 2. *In Vitro* Antibacterial Activity of Substituted Quinolones (MIC, μg/mL)[a]



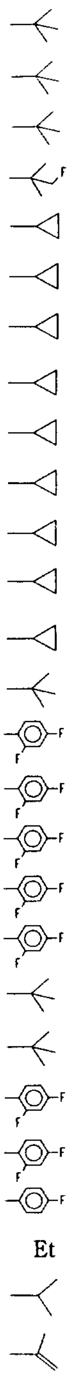
No.	R_1	R_5	R_7	E. co.	K. pn.	E. cl.	M. mo.	P. ae.
Q01	C_2H_5	H		0.13	0.03	0.06	0.015	0.5
Q02		H		0.5	2.	4.	1.	4.
Q03		H		0.25	0.5	0.5	4.	0.5
Q04		H		0.5	1.	2.	0.25	1.
Q05		H		0.13	0.25	0.06	0.13	0.5
Q06		H		2.	4.	4.	16.	32.
Q07		H		0.06	0.13	0.13	0.25	0.5
Q08		H		0.5	1.	1.	4.	4.
Q09		H		0.03	0.03	0.008	0.015	0.13
Q10		H		0.06	2.	0.13	1.	2.
Q11		H		0.13	1.	0.5	0.25	1.
Q12		H		1.	2.	4.	8.	32.
Q13		H		0.06	0.25	0.5	0.25	0.5
Q14		H		0.13	0.25	0.25	0.25	4.
Q15		H		0.13	0.13	1.	0.5	1.
Q16		H		2.	4.	32.	16.	32.
Q17		H		0.25	2.	1.	0.5	8.
Q18		H		1.	1.	8.	8.	8.
Q19		H		2.	8.	4.	32.	63.
Q20		H		0.008	0.13	0.06	0.016	0.25
Q21		H		0.25	1.	0.5	2.	8.
Q22		H		0.03	0.25	0.25	0.25	0.5
Q23		H		0.008	0.015	0.03	0.5	1.
Q24		H		0.13	0.5	0.13	1.	4.
Q25		H		0.06	0.25	0.13	0.5	1.
Q26		H		0.25	0.13	0.13	0.5	4.
Q27		H		0.5	0.13	0.13	1.	4.
Q28		H		0.5	0.25	0.25	1.	2.
Q29		H		0.03	0.13	0.06	0.5	1.
Q30		H		0.25	0.25	0.25	2.	0.5
Q31		H		0.008	0.06	0.03	0.008	0.25
Q32		H		0.03	0.13	0.13	0.03	2.
Q33		H		0.008	0.13	0.03	0.06	0.5
Q34		H		0.016	0.016	0.03	0.016	0.25
Q35		H		0.13	0.13	0.25	0.06	1.
Q36		H		0.5	0.13	0.25	2.	0.5
Q37		H		0.016	0.06	0.06	0.13	0.25
Q38		H		0.004	0.016	0.06	0.016	0.5
Q39		H		0.016	0.5	0.06	0.13	0.25
Q40		H		0.002	0.004	0.004	0.002	0.13

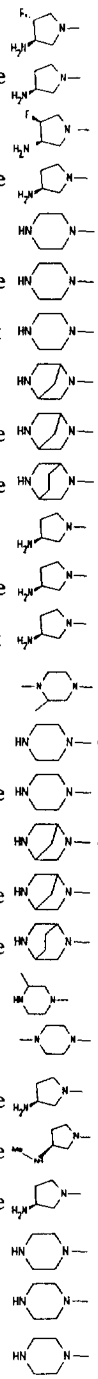
[a]Obtained from the references [18-21].

Table 3. *In Vitro* Antibacterial Activity of Substitued Naphthyridines (MIC, μg/mL)[a]



No.	R_1	R_5	R_7	E. co.	K. pn.	E. cl.	M. mo.	P. ae.
N01		H		0.016	0.03	0.06	0.06	0.5
N02		H		0.13	0.25	0.25	0.13	1.
N03		H		0.13	0.25	0.25	0.13	4.
N04		H		0.5	1.	0.5	0.5	16.
N05		H		0.008	0.016	0.016	0.06	0.25
N06		H		0.06	0.25	0.13	0.25	0.5
N07		H		0.5	0.25	0.5	1.	1.
N08		H		0.06	0.06	0.13	0.5	2.
N09		H		0.016	0.03	0.03	0.13	0.25
N10		H		0.03	0.03	0.13	0.06	1.
N11		H		0.5	2.	0.5	0.5	8.
N12		H		0.13	0.13	0.06	1.	1.
N13		H		0.5	0.1	0.25	2.	4.
N14		H		0.13	0.13	0.25	0.5	4.
N15	Et	Me		0.002	0.016	0.008	0.03	1.
N16	2-F-Et	Me		0.001	0.002	0.002	0.016	0.25
N17		H		0.03	0.06	0.03	0.25	1.
N18		Me		0.06	0.06	0.25	0.25	4.
N19		H		0.25	0.03	0.13	0.5	0.5
N20		Me		0.03	0.06	0.13	0.13	2.





N21		H		0.5	0.5	0.5	0.5	2.
N22		Me		0.004	0.03	0.03	0.06	1.
N23		H		0.25	0.06	0.25	0.5	2.
N24		Me		0.016	0.03	0.25	0.5	2.
N25		H		0.03	0.06	0.06	0.06	0.5
N26		Me		0.008	0.02	0.03	0.06	0.5
N27		Et		0.5	1.	1.	4.	16.
N28		H		0.06	0.06	0.03	0.06	0.25
N29		Me		0.002	0.002	0.002	0.016	0.25
N30		Me		0.008	0.016	0.06	0.06	0.5
N31		H		0.002	0.004	0.016	0.004	0.25
N32		Me		0.002	0.004	0.002	0.016	0.25
N33		Et		0.25	0.25	0.25	0.5	4.
N34		H		0.03	0.13	0.06	1.	4.
N35		H		0.016	0.03	0.03	0.13	0.5
N36		Me		0.016	0.03	0.03	0.13	1.
N37		H		0.004	0.008	0.016	0.06	0.25
N38		Me		0.008	0.06	0.03	0.13	0.5
N39		Me		0.008	0.008	0.008	0.13	0.5
N40		H		0.5	2.	1.	4.	8.
N41		H		0.06	0.06	0.06	0.5	1.
N42		Me		0.002	0.002	0.002	0.03	0.25
N43		Me		0.016	0.016	0.03	0.06	1.
N44		Me		0.002	0.002	0.002	0.008	0.25
N45	Et	H		0.13	0.5	0.5	0.13	0.5
N46		H		0.25	1.	0.5	1.	4.
N47		H		0.13	0.13	0.25	0.5	2.

[a] Obtained from the references [18-21].

The regression and factor analysis are performed with SPSS[x] (Statistical Package for Social Science).[21] The regression equation used here is as follows.

$$\log_{10} A = \sum_i B_i X_i + C \qquad (1)$$

where the X_i is the i-th independent variable (descriptor) and B_i is the fitting parameter for the variable, the A is biological activity of the drug, and C is a constant. The descriptors used for the molecule are listed in Table 4.

The numbering needed for indicating net charge is given in Figure 2. The number of data set is 40 for quinolone and 47 for naphthyridiene, respectively.

Table 4. Theoretical Descriptors used in Calculation

Descriptor	Meaning	Unit
V1	van der Waals volume of R_1	cubic angstrong
V7	van der Waals volume of R_7	cubic angstrong
V	van der Waals volume	cubic angstrong
D	dipole moment	debye
P	polarizability volume	cubic angstrong
N1	net charge of no. 1 atom	electron charge
C2	net charge of no. 2 atom	electron charge
C3	net charge of no. 3 atom	electron charge
C4	net charge of no. 4 atom	electron charge
C5	net charge of no. 5 atom	electron charge
C6	net charge of no. 6 atom	electron charge
C7	net charge of no. 7 atom	electron charge
X8	net charge of no. 8 atom (N or C)	electron charge
C9	net charge of no. 9 atom	electron charge
C10	net charge of no. 10 atom	electron charge
F11	net charge of no. 11 atom	electron charge
O12	net charge of no. 12 atom	electron charge
C13	net charge of no. 13 atom	electron charge
O14	net charge of no. 14 atom	electron charge
O15	net charge of no. 15 atom	electron charge

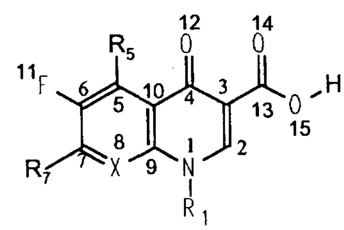


Figure 2. The numbering system used in regression.

Result and Discussion

The values of descriptors obtained by computation are listed in Table 5 and 6.

The results of the regression analysis are given in Table 7 and 8. For each descriptor, the magnitude of fitting parameter B indicates the amount of the contribution of the descriptor to the activity. That is, the larger is the magnitude of B, the more important it is to the activity. The fitting parameter B's should be standardized for the rational comparison. The results for this standardization are given as β's (Table 7 and 8).

The results show that for five kinds of bacteria, multiple r's are about 0.82 for quinolone and naphthyridine, respectively (Table 7 and 8). For the detailed observation of the data characteristics, factor analysis is performed. Factor analysis is a multivariate technique for reducing matrices of data to their lowest dimensionality by use of orthogonal factor space and transformations that yield predictions and/or recognizable factors.[15] It also can classify the total variables (descriptors) into several groups. In general, the factor mat-

Table 5a. The Results of Descriptor Calculations for Quinolone

No.	V1	V7	V	D	P	N1	C2	C3	C4	C5
Q01	37.99	79.54	237.92	10.2747	38.0880	−.1949	.1058	−.2918	.3240	−.0549
Q02	60.59	79.54	260.55	10.7038	41.4191	−.1938	.1104	−.2911	.3214	−.0505
Q03	84.54	79.54	285.47	10.0644	46.7021	−.1812	.0936	−.2788	.3202	−.0583
Q04	52.19	79.54	251.75	10.2811	39.9010	−.1936	.1034	−.2890	.3233	−.0523
Q05	46.98	79.54	247.10	15.7033	44.3399	−.1692	.0002	−.1513	.3027	−.0466
Q06	99.20	79.54	300.11	10.9032	48.6013	−.1915	.0984	−.2789	.3197	−.0471
Q07	66.61	79.54	267.81	10.2550	41.7521	−.2011	.0999	−.2861	.3224	−.0501
Q08	81.35	79.54	282.92	10.3449	43.7058	−.2013	.1002	−.2869	.3220	−.0506
Q09	45.79	79.54	246.83	9.3359	38.9204	−.1453	.0862	−.2700	.3212	−.0627
Q10	60.59	79.54	261.04	9.4692	40.9556	−.1410	.0860	−.2701	.3215	−.0622
Q11	60.59	79.54	261.04	9.3351	40.9049	−.1438	.0858	−.2747	.3241	−.0633
Q12	75.17	79.54	275.16	9.5223	42.7667	−.1531	.0922	−.2722	.3237	−.0580
Q13	60.59	79.54	261.39	9.3973	40.7012	−.1398	.0865	−.2703	.3212	−.0616
Q14	106.89	79.54	307.93	11.0630	49.7077	−.1656	.1277	−.3030	.3223	−.0534
Q15	59.24	79.54	260.14	9.8557	41.0015	−.1633	.0869	−.2770	.3213	−.0607
Q16	60.59	79.54	274.54	10.1587	43.1062	−.1665	.0847	−.2737	.3215	−.0551
Q17	73.44	79.54	273.97	9.7079	42.7016	−.1536	.0851	−.2763	.3190	−.0626
Q18	67.18	79.54	268.19	9.9089	42.6183	−.1749	.0871	−.2793	.3196	−.0600
Q19	128.93	79.54	330.24	9.8826	51.0436	−.1703	.0899	−.2828	.3189	−.0700
Q20	73.95	78.41	274.70	8.9103	41.8145	−.2018	.0945	−.2728	.3169	−.0574
Q21	66.61	108.03	310.20	10.3810	45.8314	−.1784	.0949	−.2939	.3195	−.0577
Q22	66.61	94.34	283.10	10.4706	43.9214	−.1974	.1029	−.2906	.3247	−.0528
Q23	66.61	93.69	281.93	10.2984	43.7444	−.2006	.1054	−.2939	.3252	−.0583
Q24	66.61	108.49	296.11	10.4994	45.6756	−.1986	.1061	−.2908	.3215	−.0581
Q25	66.61	140.83	328.94	11.1203	52.8027	−.1870	.1009	−.2908	.3190	−.0527
Q26	66.61	97.09	284.93	9.8364	43.8921	−.2000	.1054	−.2935	.3247	−.0576
Q27	66.61	115.21	303.45	9.2201	47.0350	−.1925	.1006	−.2930	.3238	−.0523
Q28	66.61	100.63	288.82	8.5078	44.5511	−.1917	.1000	−.2920	.3220	−.0591
Q29	69.63	92.42	284.26	9.7061	43.8366	−.1991	.0921	−.2753	.3219	−.0544
Q30	66.61	93.13	281.50	10.2804	43.5748	−.1793	.0947	−.2938	.3193	−.0604
Q31	45.79	79.54	246.48	9.1805	38.8326	−.1408	.0826	−.2688	.3223	−.0634
Q32	40.90	94.34	256.72	7.9744	37.6755	−.1819	.0831	−.2640	.3230	−.0589
Q33	69.63	93.12	285.44	10.8723	46.1760	−.1987	.1192	−.3206	.3303	−.0796
Q34	69.63	79.54	270.78	6.9497	40.8668	−.1742	.0722	−.2585	.3164	−.0973
Q35	73.95	79.54	274.51	5.4966	41.0003	−.1691	.0729	−.2551	.3159	−.0967
Q36	66.61	84.70	272.73	6.5595	41.7655	−.1671	.0819	−.2741	.3142	−.0952
Q37	69.63	84.70	277.67	5.8777	41.8182	−.1659	.0725	−.2622	.3150	−.0951
Q38	69.63	64.93	257.09	9.9337	39.5381	−.1817	.1031	−.3015	.3214	−.0603
Q39	66.61	78.41	266.71	9.4935	41.5955	−.1994	.1014	−.2903	.3216	−.0642
Q40	69.63	78.41	269.92	9.6598	41.6600	−.2027	.0925	−.2772	.3218	−.0563

Table 5b. The Results of Descriptor Calculations for Quinolone

No.	C6	C7	C8	C9	C10	F11	O12	C13	O14	O15
Q01	.0030	.1251	−.2554	.1123	−.1894	−.1089	−.2871	.3663	−.3282	−.3494
Q02	.0056	.1075	−.2460	.1121	−.1898	−.1057	−.2876	.3687	−.3279	−.3531
Q03	.0076	.1123	−.2378	.0992	−.1963	−.1060	−.2816	.3660	−.3240	−.3508
Q04	.0022	.1098	−.2462	.1106	−.1876	−.1065	−.2870	.3675	−.3302	−.3524
Q05	.0388	.1400	−.2568	.0632	−.1739	−.0790	−.2026	.3424	−.2652	−.3435
Q06	−.0157	.1468	−.2548	.1213	−.2046	−.1098	−.2823	.3623	−.3317	−.3452
Q07	−0.026	.1077	−.2467	.1177	−.1878	−.1068	−.2813	.3658	−.3289	−.3523
Q08	−0.028	.1080	−.2461	.1170	−.1884	−.1069	−.2815	.3655	−.3287	−.3519
Q09	.0161	.0858	−.2109	.0729	−.1839	−.1042	−.2721	.3638	−.3231	−.3477

Q10	.0155	.0870	−.2116	.0737	−.1838	−.1040	−.2729	.3647	−.3243	−.3498
Q11	.0190	.0743	−.2059	.0737	−.1806	−.1026	−.2758	.3681	−.3245	−.3547
Q12	.0095	.0947	−.2196	.0800	−.1862	−.1048	−.2724	.3650	−.3236	−.3505
Q13	.0129	.0908	−.2129	.0766	−.1883	−.1054	−.2732	.3634	−.3245	−.3474
Q14	−.0083	.1400	−.2529	.1174	−.2035	−.1104	−.2858	.3660	−.3291	−.3455
Q15	.0112	.0982	−.2306	.0888	−.1910	−.1051	−.2770	.3645	−.3248	−.3483
Q16	−.0022	.1306	−.2442	.1001	−.2033	−.1076	−.2784	.3634	−.3251	−.3466
Q17	.0127	.0921	−.2230	.0862	−.1903	−.1038	−.2781	.3653	−.3259	−.3499
Q18	.0099	.1013	−.2406	.1015	−.1921	−.1049	−.2800	.3636	−.3265	−.3475
Q19	.0143	.0718	−.2019	.0810	−.1854	−.1034	−.2795	.3671	−.3279	−.3533
Q20	.0109	.0761	−.2313	.1004	−.1884	−.1044	−.2757	.3638	−.3226	−.3479
Q21	.0052	.0997	−.2506	.1218	−.1948	−.1019	−.2895	.3670	−.3292	−.3513
Q22	.0003	.1007	−.2445	.1131	−.1881	−.1062	−.2826	.3655	−.3331	−.3509
Q23	.0057	.0968	−.2394	.1149	−.1919	−.1064	−.2849	.3678	−.3280	−.3526
Q24	.0051	.0951	−.2383	.1128	−.1874	−.1067	−.2864	.3658	−.3315	−.3490
Q25	.0029	.1130	−.2415	.1172	−.1896	−.1093	−.2977	.3702	−.3359	−.3581
Q26	.0056	.0960	−.2381	.1150	−.1905	−.1065	−.2846	.3680	−.3274	−.3529
Q27	−.0125	.1255	−.2592	.1256	−.1979	−.1078	−.2882	.3668	−.3303	−.3520
Q28	.0058	.0791	−.2407	.1201	−.1872	−.1049	−.2836	.3656	−.3301	−.3490
Q29	−.0016	.1114	−.2362	.1065	−.2001	−.1075	−.2777	.3634	−.3258	−.3495
Q30	.0107	.0955	−.2477	.1194	−.1929	−.1008	−.2886	.3674	−.3285	−.3518
Q31	.0179	.0781	−.2036	.0667	−.1811	−.1032	−.2720	.3654	−.3226	−.3506
Q32	.0129	.0989	−.2291	.0783	−.1848	−.1026	−.2673	.3622	−.3223	−.3472
Q33	.0473	.0398	−.1963	.0871	−.2107	−.0813	−.2489	.3815	−.2929	−.3661
Q34	.0848	.0127	−.1708	.0489	−.1560	−.0868	−.2574	.3604	−.3213	−.3458
Q35	.0867	.0110	−.1765	.0428	−.1544	−.0855	−.2550	.3597	−.3201	−.3463
Q36	.0412	.0327	−.1180	.0330	−.1511	−.1012	−.2622	.3626	−.3250	−.3426
Q37	.0469	.0260	−.1169	.0306	−.1524	−.0993	−.2582	.3593	−.3218	−.3420
Q38	.0147	.0645	−.2314	.1092	−.1846	−.1016	−.2860	.3690	−.3225	−.3532
Q39	.0125	.0767	−.2397	.1049	−.1929	−.1046	−.2791	.3627	−.3318	−.3476
Q40	.0068	.0798	−.2272	.1036	−.1944	−.1059	−.2755	.3632	−.3252	−.3482

Table 6a. The Results of Descriptor Calculations for Naphthyridine

No.	V1	V7	V8	D	P	N1	C2	C3	C4	C5
N01	66.61	79.54	262.82	6.2298	40.6092	−.1619	.0837	−.2704	.3216	−.0585
N02	69.63	79.54	266.92	5.9360	40.7966	−.1589	.0765	−.2625	.3200	−.0594
N03	66.61	79.54	270.51	5.2266	40.9655	−.1617	.0800	−.2644	.3220	−.0591
N04	76.82	79.54	273.94	4.8220	41.1326	−.1555	.0714	−.2552	.3159	−.0586
N05	66.61	84.70	268.19	5.1406	41.4966	−.1544	.0833	−.2719	.3234	−.0582
N06	69.63	84.70	272.51	4.7688	41.6856	−.1519	.0748	−.2609	.3195	−.0570
N07	66.61	93.12	276.75	9.1046	42.3843	−.1772	.1067	−.3007	.3324	−.0251
N08	66.61	93.56	275.89	10.1243	43.2403	−.1769	.1068	−.2986	.3268	−.0281
N09	66.61	78.41	261.87	7.8771	40.7082	−.1790	.1031	−.2901	.3252	−.0300
N10	69.63	78.41	266.84	7.9978	40.9404	−.1856	.0950	−.2790	.3266	−.0298
N11	73.95	78.41	269.33	7.6310	41.0924	−.1799	.0971	−.2764	.3242	−.0291
N12	66.61	100.63	284.28	7.3849	44.3179	−.1808	.1042	−.2912	.3244	−.0348
N13	66.61	115.21	298.21	8.0704	46.7106	−.1818	.1032	−.2914	.3276	−.0234
N14	66.61	100.09	284.61	9.8608	47.0418	−.1611	.0849	−.2656	.3072	.0039
N15	37.99	78.41	247.73	4.9553	39.0782	−.1863	.0712	−.2534	.3209	.0601
N16	40.90	78.41	251.53	4.4267	39.3258	−.1822	.0756	−.2565	.3228	.0540
N17	66.61	107.89	291.98	9.8602	45.1497	−.1745	.1054	−.3008	.3268	−.0307
N18	66.61	79.54	278.94	8.6399	43.5351	−.1914	.1019	−.2877	.3270	.0621
N19	66.61	93.12	277.13	8.4185	43.4077	−.1762	.1061	−.3007	.3277	−.0213
N20	66.61	84.70	283.74	7.9569	44.8556	−.1775	.1049	−.3012	.3272	.0487
N21	66.61	82.11	265.36	8.5495	41.4758	−.1789	.1087	−.2962	.3247	−.0225

N22	66.61	79.54	277.05	7.6735	43.3684	−.1809	.1072	−.3006	.3273	.0583
N23	66.61	82.11	265.36	7.9930	41.5287	−.1793	.1092	−.3007	.3280	−.0233
N24	69.63	78.41	281.39	5.9604	43.5311	−.1819	.0999	−.2967	.3257	.0562
N25	45.79	79.54	242.62	8.5015	38.6142	−.1507	.0968	−.2749	.3291	−.0218
N26	45.79	79.54	257.01	7.5903	40.6913	−.1302	.0876	−.2796	.3287	.0499
N27	45.79	79.54	271.65	7.8924	42.6174	−.1554	.0917	−.2695	.3258	.0682
N28	45.79	84.70	247.99	8.1322	40.3876	−.1602	.1202	−.2961	.3255	−.0295
N29	45.79	84.70	262.44	7.4831	42.4112	−.1595	.1176	−.2978	.3255	.0517
N30	45.79	100.63	278.15	6.1065	43.9075	−.1550	.1078	−.2912	.3308	.0470
N31	45.79	78.41	240.30	7.2037	38.6209	−.1309	.0879	−.2709	.3267	−.0327
N32	45.79	78.41	255.93	5.8596	40.0532	−.1365	.0901	−.2757	.3261	.0475
N33	45.79	78.41	271.54	6.6067	42.6076	−.1431	.0931	−.2767	.3237	.0594
N34	66.61	109.16	292.98	9.3810	45.7855	−.1819	.1044	−.2940	.3257	−.0256
N35	76.63	79.54	272.97	8.5015	45.3035	−.1362	.1123	−.2783	.3245	−.0382
N36	76.63	79.54	287.55	7.7720	47.2950	−.1361	.1098	−.2840	.3266	.0474
N37	76.63	84.70	278.59	7.2098	46.2647	−.1403	.1187	−.2822	.3270	−.0262
N38	76.63	84.70	293.08	6.5720	48.2930	−.1411	.1165	−.2850	.3268	.0550
N39	76.63	100.63	308.64	5.8538	50.7872	−.1436	.0977	−.2745	.3282	.0396
N40	66.61	93.69	277.34	7.9649	43.5210	−.1841	.1043	−.2936	.3290	−.0277
N41	66.61	115.21	278.05	9.3471	43.6950	−.1883	.1069	−.2933	.3307	−.0233
N42	76.63	78.41	286.85	6.6517	47.7404	−.1390	.1015	−.2702	.3225	.0664
N43	76.63	93.64	302.43	6.5327	49.7164	−.1376	.1017	−.2777	.3263	.0597
N44	73.87	78.41	283.69	5.4176	47.4400	−.1360	.0981	−.2781	.3257	.0643
N45	37.99	79.54	234.23	8.9111	37.6437	−.1813	.1067	−.2954	.3285	−.0304
N46	52.19	79.54	248.24	9.1926	39.6447	−.1813	.1024	−.2911	.3256	−.0303
N47	46.98	79.54	242.87	8.4361	39.6660	−.1277	.1052	−.2877	.3282	−.0335

Table 6b. The Results of Descriptor Calculations for Naphthyridine

No.	C6	C7	N8	C9	C10	F11	O12	C13	O14	O15
N01	.0242	.0917	−.2034	.1212	−.2047	−.0805	−.2653	.3613	−.3274	−.3444
N02	.0282	.0938	−.2035	.1195	−.2032	−.0788	−.2604	.3616	−.3207	−.3440
N03	.0259	.1068	−.2080	.1260	−.2114	−.0796	−.2619	.3635	−.3190	−.3473
N04	.0331	.0983	−.2107	.1109	−.2031	−.0749	−.2541	.3606	−.3150	−.3434
N05	−.0161	.1046	−.1367	.1072	−.2048	−.0913	−.2633	.3627	−.3237	−.3459
N06	−.0114	.1064	−.1398	.1075	−.2031	−.0903	−.2598	.3624	−.3212	−.3436
N07	−.0506	.1751	−.2607	.1789	−.2536	−.0980	−.2806	.3643	−.3332	−.3455
N08	−.0421	.1752	−.2586	.1781	−.2455	−.0980	−.2871	.3655	−.3307	−.3466
N09	−.0391	.1332	−.2154	.1546	−.2478	−.0963	−.2788	.3619	−.3241	−.3395
N10	−.0405	.1452	−.2247	.1607	−.2466	−.0973	−.2761	.3639	−.3209	−.3473
N11	−.0372	.1414	−.2293	.1571	−.2438	−.0957	−.2750	.3640	−.3143	−.3460
N12	−.0345	.1434	−.2467	.1787	−.2318	−.0963	−.2877	.3663	−.3287	−.3476
N13	−.0583	.1882	−.2676	.1895	−.2485	−.0997	−.2893	.3666	−.3291	−.3496
N14	.0008	.0777	−.2954	.1222	−.2296	−.1095	−.2892	.3583	−.3248	−.3392
N15	−.0766	.1928	−.2071	.1491	−.2765	−.1019	−.2676	.3583	−.3206	−.3369
N16	−.0684	.1869	−.2066	.1428	−.2724	−.0987	−.2671	.3644	−.3210	−.3418
N17	−.0338	.1598	−.2516	.1757	−.2427	−.0957	−.2899	.3688	−.3294	−.3508
N18	−.0702	.1928	−.2754	.1920	−.2412	−.1017	−.2895	.3667	−.3290	−.3507
N19	−.0516	.1902	−.2710	.1824	−.2533	−.0965	−.2898	.3677	−.3278	−.3505
N20	−.0468	.1485	−.2600	.1753	−.2308	−.0982	−.2940	.3689	−.3288	−.3520
N21	−.0471	.1849	−.2627	.1800	−.2447	−.0963	−.2877	.3645	−.3304	−.3457
N22	−.0731	.1997	−.2766	.1885	−.2528	−.0997	−.2921	.3647	−.3331	−.3458
N23	−.0476	.1866	−.2635	.1813	−.2498	−.0958	−.2857	.3663	−.3281	−.3478
N24	−.0562	.1767	−.2627	.1798	−.2448	−.0960	−.2913	.3680	−.3268	−.3503
N25	−.0440	.1709	−.2404	.1543	−.2426	−.0975	−.2725	.3631	−.3236	−.3437
N26	−.0392	.1449	−.2354	.1436	−.2249	−.0973	−.2799	.3687	−.3222	−.3527

N27	−.0584	.1809	−.2498	.1632	−.2538	−.0987	−.2810	.3592	−.3301	−.3397
N28	−.0372	.1570	−.2424	.1655	−.2357	−.0971	−.2856	.3662	−.3281	−.3468
N29	−.0530	.1587	−.2461	.1681	−.2341	−.0993	−.2928	.3678	−.3290	−.3482
N30	−.0404	.1434	−.2415	.1565	−.2306	−.0983	−.2899	.3736	−.3230	−.3580
N31	−.0290	.1595	−.2316	.1474	−.2433	−.0949	−.2770	.3662	−.3204	−.3495
N32	−.0437	.1549	−.2322	.1499	−.2372	−.0967	−.2843	.3682	−.3216	−.3501
N33	−.0505	.1678	−.2392	.1560	−.2447	−.0974	−.2867	.3655	−.3227	−.3472
N34	−.0449	.1735	−.2621	.1813	−.2352	−.0972	−.2918	.3701	−.3242	−.3544
N35	−.0140	.1702	−.2546	.1625	−.2228	−.0905	−.2788	.3662	−.3250	−.3441
N36	−.0293	.1621	−.2520	.1648	−.2252	−.0929	−.2877	.3695	−.3246	−.3490
N37	−.0359	.1605	−.2584	.1644	−.2279	−.0956	−.2748	.3640	−.3265	−.3413
N38	−.0524	.1660	−.2634	.1697	−.2318	−.0974	−.2824	.3668	−.3228	−.3450
N39	−.0252	.1302	−.2542	.1716	−.2237	−.0905	−.2714	.3680	−.3250	−.3411
N40	−.0426	.1736	−.2622	.1849	−.2418	−.0977	−.2895	.3702	−.3263	−.3549
N41	−.0487	.1811	−.2640	.1859	−.2433	−.0986	−.2862	.3681	−.3256	−.3521
N42	−.0740	.2115	−.2915	.1973	−.2485	−.0978	−.2853	.3631	−.3264	−.3386
N43	−.0557	.1854	−.2750	.1891	−.2430	−.0960	−.2844	.3689	−.3227	−.3465
N44	−.0666	.2006	−.2791	.1931	−.2478	−.0974	−.2833	.3636	−.3236	−.3453
N45	−.0289	.1551	−.2575	.1671	−.2308	−.0962	−.2879	.3701	−.3259	−.3546
N46	−.0336	.1609	−.2623	.1776	−.2305	−.0964	−.2866	.3649	−.3299	−.3471
N47	−.0268	.1490	−.2444	.1700	−.2295	−.0938	−.2851	.3708	−.3242	−.3559

Table 7. The Results of the Regression Analysis for Quinolone ($n=40$)

	E. co.	K. pn.	E. cl.	M. mo.	P. ae.
Multiple R	.8614	.8176	.8322	.8581	.8506
Std Error	.5676	.6103	.6591	.7264	.5172
F	2.7334	1.9159	2.1400	2.6536	2.4875
Signif F	.0164	.0812	.0516	.0190	.0261
		Fitting parameter B			
V1	−.0116	−.0505	−.0398	.0008	.0008
V7	−.0403	−.0726	−.0803	−.0344	−.0284
V	.0148	.0561	.0578	.0370	.0617
D	−.0761	.0655	−.0633	.1601	.1186
P	.0939	.0588	.0842	−.0189	−.1908
N1	4.6837	.7682	−11.1284	2.7727	−.9319
C2	−45.0149	−4.0648	−116.6938	−108.8672	−47.3505
C3	57.0900	23.8593	−69.8757	−18.6436	16.8225
C4	−23.4272	−130.0064	−38.0337	8.1760	66.7902
C5	−182.7403	−91.5649	2.7458	−171.1416	−75.0862
C6	−73.2991	−80.8934	17.9484	−32.5304	−18.3234
C7	24.0326	2.4466	28.6883	28.3393	18.3094
C8	−58.4046	−59.0440	−61.9006	−55.9875	−41.6674
C9	25.5080	−40.5277	−40.0447	23.3799	−6.4752
C10	89.6420	37.2780	78.6084	80.0583	55.4705
F11	−20.8939	52.0697	−120.0559	−182.8171	−59.6246
O12	123.3645	125.1033	125.9491	161.6772	59.6704
C13	608.5090	344.7850	509.8009	497.7500	390.1018
O14	−104.3330	−154.9143	−79.1403	−84.8589	−22.1049
O15	159.3283	8.1640	200.1465	113.5249	157.8874
(Constant)	−155.2487	−101.3183	−125.9679	−161.9953	−108.3725
		β(Standardized B)			
V1	−.2441	−1.1206	−.7887	.0141	.0195
V7	−.6957	−1.3216	−1.3039	−.4700	−.5570
V	.3977	1.5888	1.4603	.7851	1.8819
D	−.1591	.1444	−.1244	.2644	.2819

P	.4072	.2691	.3432	−.0648	−.9402
N1	.1197	.0207	−.2674	.0559	−.0270
C2	−1.0971	−.1044	−2.6739	−2.0959	−1.3110
C3	1.7947	.7908	−2.0652	−.4629	.6008
C4	−.1259	−.7366	−.1921	.0347	.4077
C5	−3.0607	−1.6170	.0432	−2.2643	−1.4287
C6	−2.0392	−2.3729	.4694	−.7149	−.5791
C7	.9854	.1057	1.1060	.9179	.8529
C8	−2.4452	−2.6064	−2.4365	−1.8516	−1.9818
C9	.8396	−1.4066	−1.2393	.6079	−.2421
C10	1.5261	.6691	1.2582	1.0766	1.0728
F11	−.1929	.5069	−1.0421	−1.3333	−.6254
O12	2.4852	2.6573	2.3855	2.5728	1.3656
C13	3.9883	2.3827	3.1415	2.5770	2.9047
O14	−1.5424	−2.4147	−1.0999	−.9909	−.3712
O15	.8713	.0470	1.0291	.4904	.9810

Table 8. The Results of the Regression Analysis for Naphthyridine ($n=47$)

	E. co.	K. pn.	E. cl.	M. mo.	P. ae.
Multiple R	.8196	.8020	.8327	.7814	.8513
Std Error	.6221	.6248	.5566	.5560	.3580
F	2.6617	2.3435	2.9403	2.0387	3.4249
Signif F	.0101	.0213	.0053	.0444	.0019
		Fitting parameter B			
V1	−.0734	−.0757	−.0603	.0486	.0437
V7	−.0543	−.0597	−.0723	−.0343	−.0359
V	.1303	.1171	.1055	.0999	.0828
D	−.0568	.1216	−.0677	.0939	.1295
P	−.4214	−.3472	−.2557	−.3059	−.2437
N1	2.3855	−9.5251	−9.5280	−4.0100	−3.1212
C2	8.4834	6.7888	1.4787	4.3221	8.6937
C3	−17.6759	−11.5128	−3.8424	8.4821	3.8751
C4	−32.4178	−3.3164	31.9673	−6.1959	−45.5819
C5	−10.9504	−7.6759	−10.7199	−8.9811	.3690
C6	46.7924	48.2035	37.4105	21.9044	32.0852
C7	15.2217	19.8946	12.2072	9.9278	10.8099
N8	−1.5860	2.4341	−7.5252	−.4563	2.2545
C9	40.3686	36.0693	15.3360	20.0497	28.4608
C10	18.6606	35.6023	15.6020	17.5757	7.1747
F11	−143.0226	−145.0101	−128.8049	−80.1783	−74.0815
O12	52.2755	36.9295	38.6346	9.1894	36.0834
C13	−93.3238	−84.5707	−91.2530	−9.4761	−89.1831
O14	51.9503	92.4703	24.9366	7.4992	38.9266
O15	−26.1106	2.2384	−67.6182	14.2781	−66.2088
(Constant)	35.0204	46.5551	−7.1263	−.2984	29.9280
		β(Standardized B)			
V1	−1.1032	−1.1812	−.9787	−.8909	−1.0459
V7	−.7009	−.7995	−1.0077	−.5397	−.7374
V	2.6710	2.4925	2.3367	2.4961	2.6997
D	.1041	.2315	.1341	.2098	.3778
P	−1.5972	−1.3665	−1.0471	−1.4134	−1.4701
N1	.0568	−.2358	−.2454	−.1165	−.1184
C2	.1312	.1090	.0247	.0815	.2140
C3	−.2996	−.2026	−.0703	.1752	.1045
C4	−.1621	−.0172	.1727	−.0377	−.3628

C5	−.6072	−.4420	−.6422	−.6070	.0325
C6	1.4868	1.5904	1.2841	.8483	1.6223
C7	.5906	.8016	.5117	.4695	.6675
N8	−.0623	.0994	−.3197	−.0218	.1410
C9	1.1820	1.0967	.4851	.7155	1.3261
C10	.3790	.7509	.3423	.4351	.2319
F11	−1.0681	−1.1245	−1.0392	−.7298	−.8804
O12	.6521	.4784	.5207	.1397	.7163
C13	−.3853	−.3626	−.4070	−.0476	−.5860
O14	.2630	.4862	.1364	.0462	3136
O15	.1528	.0136	−.4276	.1018	.6167

Table 9. The Rotated Factor Matrix for Quinolone (n=40)

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
[a]pct of var	41.8	20.2	12.6	10.1	5.6
V1	−.03159	−.07654	−.13471	.93372	−.22610
V7	.05890	−.08641	−.09312	.18481	.91474
V	.02243	−.11516	−.17344	.86684	.42826
D	.85477	.02239	.41011	.10702	.05150
P	.24834	−.04202	.04867	.87986	.35749
N1	−.27031	.25962	.06965	−.06103	−.51562
C2	.12006	−.76703	−.53801	.16805	.07384
C3	.01532	.81181	.51906	−.16026	−.10974
C4	.14544	−.86186	−.32757	−.12201	−.00788
C5	.96689	−.02067	−.15617	−.06518	.07253
C6	−.80119	.14938	.50779	−.07719	−.04189
C7	.93753	.14280	−.16254	.06772	.04470
C8	−.91912	.10948	.08568	.02011	−.16931
C9	.75158	−.36859	−.32430	.12237	.30768
C10	−.77364	.49494	.07316	−.17794	−.00129
F11	−.41731	.10048	.86684	−.05707	.01841
O12	−.23991	.43695	.81013	−.10732	−.16173
C13	−.02799	−.94449	−.20996	.10736	.11580
O14	.04787	.23157	.93895	−.09559	−.10330
O15	−.17030	.83731	−.25509	−.05641	−.27017

[a]Percentage of variance, the percentage for contribution of the factor to describe total variance.

Table 10. The Rotated Factor Matrix for Naphthyridibe (n=47)

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
[a]pct of var	39.9	15.4	13.6	8.9	5.4
V1	.25898	−.09584	.82055	−.17926	−.04714
V7	.04987	−.18838	.53577	.33933	−.46797
V	−.07446	−.04713	.97392	.04908	−.03811
D	.02971	−.86049	−.05591	.11154	−.23753
P	−.16670	−.16619	.92712	.01671	.23165
N1	.15163	.18526	.06757	.03113	.88443
C2	−.19514	−.77467	.18853	.37815	.10178
C3	.14064	.75137	−.06623	−.50946	.23093
C4	−.35287	−.25940	−.06541	.68914	−.07282
C5	−.77454	.07911	.15656	.01850	.43710
C6	.94287	.20583	−.00754	−.12533	.06955
C7	.84628	−.29271	.03706	.15847	−.05107
N8	.42269	.68719	−.31905	−.07428	−.14572
C9	−.61911	−.58064	.28020	.30314	.08229
C10	.88039	.15305	.14384	.09217	.27854
F11	.68900	.41305	.05961	−.00761	.08213
O12	.43261	.71296	−.11173	−.38511	−.02736
C13	−.10482	−.21338	.10908	.93172	.12241
O14	.21502	.75950	−.07718	−.02120	.19100
O15	−.09384	.17564	.11424	−.91381	.06783

[a]Percentage of variance, the percentage for contribution of the factor to describe total variance.

rix is transformed to rotated factor matrix for clear distinction of the factors. So, as a result, the rotated factor matrices are given in Table 9 and 10.

The rotated factor matrix can show to which factor each descriptor is subjected. for example, Table 9 shows that descriptor V1 belongs to Factor 4: the magnitude of matrix element of Factor 4 is about 1, but the other are nearly zero.

In Table 9 and 10, the principal factors are a series of the net charges of atoms located in the left ring of the quinolone plateau, *i.e.* C5, C6, C7, C8, C9, and C10 for naphthydidine and especially quinolone. It also shows that the characteristics of the classification are qualitatively different for both.

The standardized B (β)'s are compared to study the weighting of the descriptor to the activity. It can be expected that the larger is the absolute value of β for the descriptor, the more important to the activity is the descriptor. In Table 7 and 8, the hierachy of magnitude of β's have a similar tendency for the 5 Gram-negative bacteria. The β's for each descriptor are averaged over the 5 bacteria. The averaged values of β's are listed in Table 11 and it shows how important each descriptor is to describle the activity for quinolone and naphthyridine respectively.

According to Table 11, the descriptors which represent net charges are principal to describe activity for quinolone. But in the case of naphthyridine, V1, V, and P are importent. This means that for quinolone, the electrostatic interaction is important to determine the activity, but the steric effect and the transferability for naphthyridine. In other word, the QSARs for both are fundamentally different. This result is compatible with the previous factor analysis result.

It may be pointed out that net charge changes of the atoms

Table 11. The Averaged β's for 5 Bacteria

	Quinolone	Naphthyridine
V1	.4374	1.0400
V7	.8696	.7570
V	1.2228	2.5392
D	.1948	.2115
P	.4049	1.3789
N1	.0981	.1546
C2	1.4565	.1121
C3	1.1429	.1704
C4	.2994	.1505
C5	1.6828	.4662
C6	1.2351	1.3664
C7	.7936	.6082
X8	2.2643	.1288
C9	.8671	.9611
C10	1.1206	.4278
F11	.7401	.9684
O12	2.2933	.5014
C13	2.9988	.3577
O14	1.2838	.2491
O15	.6838	.2625

which are located in the right ring of quinolone plateau, such as N1, are not so important as V1. It may be interpreted as follows. That is, the change of the substitutent R_1 has steric importance rather than electrostatic one to determine activity. However, in opposition to these trends, the net charge changes of the atoms located near the substituent R_7 are important but V7 is not. It can be inferred that the change of the substituent R_7 is electrostatically important. These results support the DNA gyrase inhibition mechanism proposed by Shen *et al.*[22] According to the mechanism, R_1 is needed for self-association and R_7 is the binding site with DNA gyrase. So, R_1 plays a key role in steric interaction and R_7 in electrostatic interaction with gyrase.

On the ground of this mechanism, our results may be interpreted as follows: the binding process with gyrase is the most important to determine activity for quinolone, and the transferability and self-association process of the drug are for naphthyridine.

In conclusion, for Gram-negative bacteria, the activities of quinolones and naphthyridines can be described by the selected theoretical descriptors within the reliable confidence limit. The results show that the QSAR of quinolone and naphthyridine are substantially different: to describe the activity, the electrostatic effect is the most important for quinolone, and the steric effect and transferability for naphthyridine.

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