[Chem. Pharm. Bull. 31(1) 144—148 (1983)]

Studies on Quantitative Structure–Activity Relationships. V. QSAR Investigations of Rifamycin B Amides and Hydrazides by Utilization of the Substituent Entropy Constant $\sigma_S°$

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(Received May 20, 1982)

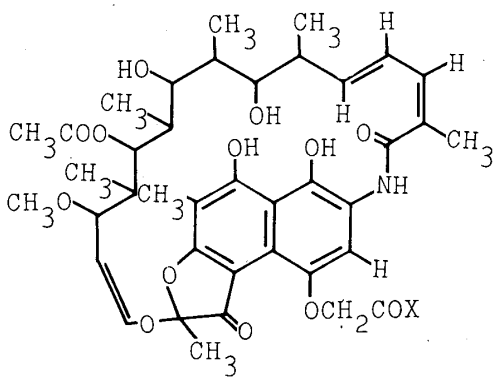
QSAR analyses of rifamycin B amides and hydrazides were carried out, and the following equations containing the substituent entropy constant, $\sigma_S°$, were obtained (the subscripts 1, 2 and 3 denote the substituent groups on the nitrogen atom).

$$\log (1/C) = -6.69(\pm 4.89)(\Sigma\sigma_S°)^2_{1,2} + 9.33(\pm 3.37)(\Sigma\sigma_S°)_{1,2} + 5.54$$
where $n=23$, $r=0.929$, $F=62.6$,** SD=0.34.

$$\log (1/C) = -6.00(\pm 1.70)(\Sigma\sigma_S°)^2_{1,2,3} + 6.71(\pm 1.47)(\Sigma\sigma_S°)_{1,2,3} + 6.93$$
where $n=17$, $r=0.950$, $F=64.4$,** SD=0.16.

Keywords——substituent entropy constant $\sigma_S°$; substituent constant; QSAR analysis; regression analysis; rifamycin B amide; rifamycin B hydrazide

The biological activities of 44 rifamycin B amide congeners (I) and 26 hydrazide congeners (II) against five kinds of gram-positive bacteria were reported by Sensi *et al.*[1] and by Quinn *et al.*[2] The results of QSAR analyses of (I) for activity against *M. aureus* could be expressed by a linear combination of three kinds of descriptors, namely, a quadratic term of the partition coefficient in the *n*-octanol/H_2O system, log *P* and a dummy parameter *D* of the substituent groups R_1 and R_2, and gave a correlation coefficient $r=0.920$ and standard deviation SD=0.324 for 42 congeners.



I: $X=N\begin{matrix}R_1\\R_2\end{matrix}$

II: $X=N(R_1)-N\begin{matrix}R_2\\R_3\end{matrix}$

For (II), by using the aliphatic substituent constant σ^*,[3] $r=0.937$ and SD=0.189 were obtained for 24 congeners. However, in these cases, the constant terms were not in agreement with the values for reference compounds.

In addition, for 44 congeners of rifamycin B amides, a component PR_p given by the successful principal component analysis of Lukovits *et al.*[4] does not appear to have an explicit chemical meaning.

Our QSAR analyses were carried out by using the Hammett type substituent constant σ_i and σ_π,[5] representing an enthalpy term, in addition to the novel substituent entropy constant $\sigma_S°$[6] defined by $\sigma_S° = \log (S_R°/S_H°)$, where S° denotes the standard entropy of the 3rd law of

thermodynamics, and the subscripts R and H mean the substituted compound and the reference, CH_4. Thermodynamically, the necessary and sufficient conditions are fulfilled when the biological responses are expressed by a linear combination of the enthalpy and entropy parameters (*cf.* Eq.1),

$$BR = a(\sigma_S{}^\circ)^2 + b\,\sigma_S{}^\circ + c\,\sigma_i + d\,\sigma_\pi + e \qquad (1)$$

where the combination of (σ_i, σ_π) or ($|\sigma_i|$, $|\sigma_\pi|$) represents strong or weak drug-site interaction, respectively.

Methods

Reported biological activities of the rifamycin B amides and hydrazides[2] are summarized in Tables I and II.

Numerical Treatment———QSAR analyses were carried out by using an ACOS 900 system computer at Osaka University Computer Center and a PC-8001 personal computer utilizing a library program, NEC TSS Library TSS/LIB-6, and our original program written in BASIC. The standard deviation SD is given by $SD=[S_{se}/(n-k-1)]^{1/2}$, where n and k denote the number of observations and variables, and S_{se} denotes the sum of squares of the residuals. ** and * (F test) denote 99 and 95% confidence limits of the statistical hypothesis.

TABLE I. Biological Activities of Rifamycin B Amides

R_1	R_2	log (1/C) 1	2	3	$\Sigma\sigma_S{}^{\circ a)}$	$\Sigma\sigma_i{}^{b)}$
H	H	5.70	4.91	4.78	0	0
H	Me	6.68	5.89	5.09	0.091	−0.033
H	Et	6.99	6.20	5.40	0.161	−0.033
H	*n*-Pr	6.50	5.82	5.41	0.222	−0.033
H	iso-Pr	6.70	5.90	5.41	0.199	−0.039
H	*tert*-Bu	6.73	5.83	5.42	0.216	−0.044
H	Ph	6.92	6.04	5.43	0.236	0.081
Me	Me	7.12	6.02	5.72	0.182	−0.067
Et	Et	7.91	7.01	6.03	0.322	−0.067
n-Pr	*n*-Pr	8.15	7.15	6.53	0.444	−0.067
n-Bu	*n*-Bu	8.46	7.46	7.16	0.544	−0.067
iso-Bu	iso-Bu	8.86	7.86	7.28	0.532	−0.067
n-C_5H_{11}	*n*-C_5H_{11}	8.65	7.65	7.05	0.638	−0.067
Bzl	Bzl	8.49	7.49	6.89	0.574	−0.067
Me	Et	7.95	7.06	6.03	0.252	−0.067
Me	*n*-Pr	7.91	7.31	6.65	0.313	−0.067
Me	*n*-Bu	8.44	7.22	6.35	0.363	−0.067
Et	*n*-Pr	8.01	7.22	6.35	0.383	−0.067
Et	*n*-Bu	8.62	7.62	7.27	0.433	−0.067
Me	*cyclo*-C_5H_9	8.14	7.22	6.36	0.352	−0.073
Me	*cyclo*-C_6H_{11}	8.15	7.53	6.68	0.357	−0.073
Me	Bzl	8.24	7.09	6.37	0.378	−0.067
Et	Ph	8.46	7.33	6.37	0.397	0.048

1, *M. aureus.* 2, *S. faecalis.* 3, *B. subtilis.*
a) and *b*) are estimated as the simple sum of those of the substituents R_1 and R_2. The latter is converted to the aliphatic from the aromatic value by multiplication by a factor of 0.74.

TABLE II. Biological Activities of Rifamycin B Hydrazides

R_1	R_2	R_3	log(1/C) 1	2	3	$\Sigma\sigma_S^\circ$	$\Sigma\sigma_i$
H	H	H	6.98	6.04	5.40	0	0
Me	Me	Me	8.13	7.21	6.65	0.273	−0.100
Me	Et	Et	8.62	7.62	6.96	0.413	−0.100
Me	*n*-Pr	*n*-Pr	8.94	7.76	6.98	0.535	−0.100
Me	*n*-Bu	*n*-Bu	8.87	7.95	7.30	0.635	−0.100
Et	Me	Me	8.62	7.44	6.62	0.343	−0.100
Et	Et	Et	8.93	7.63	7.63	0.483	−0.100
Et	*n*-Pr	*n*-Pr	8.87	7.77	7.29	0.605	−0.100
Et	*n*-Bu	*n*-Bu	8.80	7.96	7.31	0.705	−0.100
n-Pr	Me	Me	8.43	7.60	6.65	0.404	−0.100
n-Pr	Et	Et	8.94	7.63	7.64	0.544	−0.100
n-Pr	*n*-Pr	*n*-Pr	8.48	7.65	7.17	0.666	−0.100
n-Pr	*n*-Bu	*n*-Bu	8.49	7.66	7.49	0.766	−0.100
n-Bu	Me	Me	8.93	7.68	7.28	0.454	−0.100
n-Bu	Et	Et	8.64	7.94	7.64	0.594	−0.100
n-Bu	*n*-Pr	*n*-Pr	8.66	7.66	7.31	0.716	−0.100
n-C_5H_{11}	Me	Me	8.64	7.94	7.28	0.501	−0.100

1, *M. aureus.* 2, *S. faecalis.* 3, *B. subtilis.*

Results and Discussion

In our previous communication,[7] the result of the cluster analysis of 18 current QSAR parameters showed that σ_i and $|\sigma_i|$ belong to the same cluster, whereas σ_π and $|\sigma_\pi|$ are classified into different ones.

As the sign of σ_S° is always positive, we distinguished in the previous report[8] between the real and absolute combinations, namely (σ_i, σ_π) and ($|\sigma_i|$, $|\sigma_\pi|$), for the evaluation of an enthalpy term, where the former represents a strong drug-site interaction and the latter a weak one.

In this work, for the polysubstituted compounds summarized in Tables I and II, the values of σ_S° and those of σ_i are estimated tentatively as the simple sum of those for the groups R_1 and R_2.

As shown in Table I, values of log(1/*C*) of rifamycin B amides increase in the order $NH_2 < NHR_1 < NR_1R_2$; for the NR_1R_2 group, the congeners having OH, CN, Cl, NEt_2, CO_2Et groups on the side chain and rifamycin morpholides are excluded from the regression analyses, because they are active against both gram-positive and -negative bacteria. As the descriptor representing the contribution of the enthalpy term due to the alkyl groups R_1 or R_2, the substituent constant σ_i is employed. For a set of substituents, $\Sigma\sigma_S^\circ$ and $\Sigma\sigma_i$ are used, where the latter is converted to the aliphatic system from the aromatic one by multiplication by a factor of 0.74.[9] It was found that $|\Sigma\sigma_i|$ gives a better result than $\Sigma\sigma_i$ (*cf.* Table III).

This can probably be ascribed to a weak drug-site interaction. For rifamycin B hydrazides, a quadratic equation of σ_S° gives the best result (*cf.* Table IV), in contrast with the Quinn's result using σ^*.

Two factors must be taken into account.

1) In this work, the value of $\Sigma\sigma_i$ of alkyl groups takes a dummy-like 0 or −0.1 value. Under these conditions, the correlations of both σ^* *vs.* σ_i and σ^* *vs.* *D* (0 when R=H and 1 when R=alkyl) gave the same coefficient of $r=0.958$, SD=0.15.

TABLE III. Regression Equations for Activity of Rifamycin B Amides (n=23) against to *M. aureus*

	$a(\Sigma\sigma_S^\circ)^2$	$b\Sigma\sigma_S^\circ$	$c\Sigma\sigma_i$	e	r	F	SD
1	−5.04 (±6.57)	+7.81 (±5.24)	+5.41 (±14.11)	+5.51	0.931	41.5**	0.34
	−6.69 (±4.89)	+9.33 (±3.37)		+5.54	0.929	62.6**	0.34
			+34.09 (±13.68)	+5.76	0.749	26.9**	0.59
2	−6.51 (±4.89)	+9.02 (±3.42)	−2.04 (±4.06)	+5.52	0.933	42.7**	0.33
	−6.69 (±4.89)	+9.33 (±3.37)		+5.54	0.929	62.6**	0.34
			−9.51 (±8.86)	+7.29	0.438	5.0*	0.80

1, $|\sigma_i|$. 2, σ_i.

TABLE IV. Regression Equations for Activity of Rifamycin B Hydrazides (n=17) against *M. aureus*

$a(\Sigma\sigma_S^\circ)^2$	$b\Sigma\sigma_S^\circ$	$c\lvert\Sigma\sigma_i\rvert$	e	r	F	SD
−8.23 (±4.24)	+9.16 (±4.52)	− 6.89 (±12.01)	+6.98	0.955	45.1**	0.16
−6.00 (±1.70)	+6.71 (±1.47)		+6.93	0.950	64.4**	0.16
		+17.07 (±5.07)	+6.98	0.880	51.6**	0.23
	+1.76 (±0.96)		+7.69	0.709	15.2**	0.34
+1.39 (±1.38)			+8.18	0.485	4.6*	0.43

TABLE V. QSAR Analyses of Biological Activities of Rifamycin B Amides (n=23)

	$a(\Sigma\sigma_S^\circ)^2$	$b\Sigma\sigma_S^\circ$	$c\lvert\Sigma\sigma_i\rvert$	e	r	F	SD
1	−5.04 (±6.57)	+7.81 (±5.24)	5.41 (±14.11)	+5.51	0.931	41.5**	0.34
	−6.69 (±4.89)	+9.33 (±3.37)		+5.54	0.929	62.6**	0.34
2	−5.29 (±6.37)	+7.61 (±5.09)	+4.58 (±13.69)	+4.75	0.924	37.1**	0.33
	−6.70 (±4.70)	+8.90 (±3.24)		+4.77	0.922	56.8**	0.32
3	−1.69 (±5.48)	+5.13 (±4.37)	+3.26 (±11.77)	+4.52	0.933	42.8**	0.28
	−2.69 (±4.03)	+6.05 (±2.78)		+4.54	0.932	66.2**	0.28
		+4.27 (±0.79)		+4.77	0.925	124.8**	0.28

1, *M. aureus*. 2, *S. faecalis*. 3, *B. subtilis*.

TABLE VI. QSAR Analyses of Biological Activities of Rifamycin B Hydrazides (n=17)

	$a(\Sigma\sigma_S^\circ)^2$	$b\Sigma\sigma_S^\circ$	$c\lvert\Sigma\sigma_i\rvert$	e	r	F	SD
1	−8.23 (±4.24)	+9.16 (±4.52)	−6.89 (±12.01)	+6.98	0.955	45.1**	0.16
	−6.00 (±1.70)	+6.71 (±1.47)		+6.93	0.950	64.4**	0.16
2	−5.43 (±3.21)	+6.62 (±3.42)	−2.35 (± 9.08)	+6.04	0.972	72.9**	0.12
	−4.67 (±1.23)	+5.78 (±1.07)		+6.02	0.971	114.8**	0.11
3	−6.26 (±6.66)	+8.20 (±7.10)	−6.84 (±18.86)	+5.40	0.917	22.9**	0.24
	−4.05 (±2.59)	+5.76 (±2.24)		+5.35	0.913	35.0**	0.24

1, *M. aureus*. 2, *S. faecalis*. 3, *B. subtilis*.

2) Among alkyl substituent groups, the correlation of σ_i against $(\sigma_S^\circ)^2+\sigma_S^\circ$ is excellent, namely, $r=0.979$, SD=0.06.

Thus, from the statistical viewpoint, Quinn's result and ours are comparable.

The values of $\log(1/C)$ of rifamycin B hydrazides can be expressed by a quadratic equation of $\Sigma\sigma_S^\circ$ (*cf.* Table IV); this equation gives $\log(1/C)_{max}$ at $\Sigma\sigma_S^\circ=0.56$ for *M. aureus*, and reproduces the biological responses summarized in Table II. Consequently, the QSAR equation with the quadratic term of $\Sigma\sigma_S^\circ$ is preferable to that with σ^*. As shown in Table V, regression analyses of the $\log(1/C)$ values of rifamycin B amides for *M. aureus, S. faecalis* and *B. subtilis* with three kinds of parameters ---$(\Sigma\sigma_S^\circ)^2$, $\Sigma\sigma_S^\circ$, and $\Sigma\sigma_i$--- can be reduced to a linear combination of $(\Sigma\sigma_S^\circ)^2$ and $\Sigma\sigma_S^\circ$.

The $\log(1/C)_{max}$ of rifamycin B amides are expected at $\Sigma\sigma_S^\circ=0.70$, 0.66, but for *B. subtilis,* the observed values are distributed in a narrow range, and a linear equation in $\Sigma\sigma_S^\circ$ is obtained.

As summarized in Table VI, the values of $\log(1/C)_{max}$ of rifamycin B hydrazides for three kinds of bacteria can be expressed by a quadratic equation in $\Sigma\sigma_S^\circ$, which leads to $\Sigma\sigma_S^\circ=0.56$, 0.62 and 0.71 (*cf.* Table II).

In their principal component analysis of rifamycin B amides, Lukovits *et al.* could not assign an explicit chemical meaning to PR_p. A comparison of their result and ours suggests that PR_p corresponds to the contribution of the entropy term.

In conclusion, our approach is superior in the following respects to that reported by Quinn *et al.*[2] or by Lukovits *et al.*[4]

1. The chemical meaning of the QSAR parameters is explicit.
2. A linear combination of the four kinds of QSAR parameters ---$(\sigma_S^\circ)^2$, σ_S°, σ_i and σ_π--- satisfies the necessary and sufficient conditions thermodynamically.

References

1) P. Sensi, N. Naggi, R. Ballotta, S. Furesz, R. Pallanza and V. Arioli, *J. Med. Chem.*, **7**, 596 (1964).
2) F.R. Quinn, J.S. Driscoll and C. Hansch, *J. Med. Chem.*, **18**, 332 (1975).
3) R.W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M.S. Newmann, John Wiley, New York, 1956, p. 556.
4) I. Lukovits and A. Lopata, *J. Med. Chem.*, **23**, 449 (1980).
5) *a*) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi,* **86**, 873 (1965); *b*) M. Sawada, M. Ichihara, Y. Yukawa, T. Nakachi and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **29**, 2055 (1980).
6) Y. Sasaki, T. Takagi, Y. Yamazato, A. Iwata and H. Kawaki, *Chem. Pharm. Bull.*, **29**, 3073 (1981).
7) T. Takagi, A. Iwata, Y. Sasaki and H. Kawaki, *Chem. Pharm. Bull.*, **30**, 1091 (1982).
8) Y. Sasaki, T. Takagi, A. Iwata and H. Kawaki, *Chem. Pharm. Bull.*, **30**, 3069 (1982).
9) Y. Tsuno, M. Fujio, M. Sawada and Y. Yukawa, *Tetrahedron Lett.*, **23**, 213 (1982).