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Use of van der Waals Volume in Structure-Activity Studies[1]

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Several structure-activity data which had been analysed using molar attraction constant, partition coefficient, connectivity index, and molar refraction as a parameter for drug structure were reexamined by the use of van der Waals volume (V_W). These data included antibacterial activity of penicillins, tadpole narcosis with miscellaneous compounds, inhibition of neuraminidase by dihydroisoquinolines, fungus toxicity with miscellaneous molecules, inhibition of xanthine oxidase by phenylguanines, and tuberculostatic activity of isoniazid derivatives. In all the cases, very significant correlations were found by regression analysis. These findings supported the generality of the use of V_W to analyse and predict biological activity relating to molecular structure.

Keywords——van der Waals volume; structure-activity relationship; drug design; multiple regression analysis; tadpole narcosis; inhibition of neuraminidase; inhibition of xanthine oxidase; tuberculostatic activity

The van der Waals volume is one of the most fundamental characteristics of the drug structure controlling biological activity. The molecular size and shape, which are very important in the aspect of drug-receptor interactions, are generally determined by the van der Waals volume of molecules or some specific substructures. Furthermore, the preceding paper[1b] showed that the hydrophobic behavior of drug molecules was significantly correlated with geometrically calculated van der Waals volume (V_W).

A number of parameters probably relating to the volume of molecules have been used in the analysis of structure-activity data; these parameters include molar attraction constant,[3] partition coefficient,[4] connectivity index,[5] and molar refraction.[6] In this report, for comparative purposes, some typical structure-activity data which had been analysed using these parameters were reexamined by the use of V_W to seek more meaningful relationships. The following data were studied: antibacterial activity of penicillins,[3] tadpole narcosis with miscellaneous compounds,[7] inhibition of neuraminidase by dihydroisoquinolines,[8] fungus toxicity with miscellaneous molecules,[9] inhibition of xanthine oxidase by phenylguanines,[10] and tuberculostatic activity of isoniazid derivatives.[11] The resultant correlations were very significant.

Method

Calculation of van der Waals Volume (V_W)——The values of V_W were calculated as described in the previous paper[1b] except with the following modification. For van der Waals radii of Cl, Br, and I atoms,

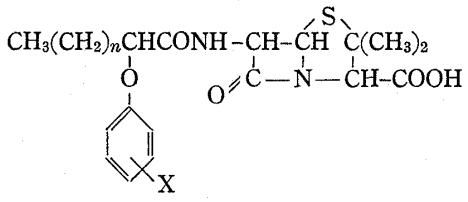
1) *a*) This forms Part III of "Quantitative Structure-Activity Studies" by I. Moriguchi; *b*) Part II: I. Moriguchi, Y. Kanada, and K. Komatsu, *Chem. Pharm. Bull.* (Tokyo), **24**, 1799 (1976).
2) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
3) J.A. Ostrenga, *J. Med. Chem.*, **12**, 349 (1969).
4) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
5) L.B. Kier, L.H. Hall, W.J. Murray, and M. Randic, *J. Pharm. Sci.*, **64**, 1971 (1975).
6) D. Agin, L. Hersh, and D. Holtzman, *Proc. Natl. Acad. Sci. U.S.*, **53**, 952 (1965).
7) A. Leo, C. Hansch, and C. Church, *J. Med. Chem.*, **12**, 766 (1969).
8) M.S. Tute, *J. Med. Chem.*, **13**, 48 (1970).
9) L.B. Kier, W.J. Murray, and L.H. Hall, *J. Med. Chem.*, **18**, 1272 (1975).
10) C. Silipo and C. Hansch, *J. Med. Chem.*, **19**, 62 (1976).
11) J.K. Seydel, K. Schaper, E. Wempe, and H.P. Cordes, *J. Med. Chem.*, **19**, 483 (1976).

1.8, 1.9, and 2.1 Å were used respectively, regardless whether the atoms were aliphatic or aromatic.[12] Owing to this simplification, the correction for the effect of branching was modified to be -0.06 (10^2 Å^3). Aromatic iso-propyl and *t*-butyl substituents were excluded in the application of the correction for branching.[13] The correction for intramolecular hydrophobic bonding[1b] as well as that for branching was included in the value of V_W as a matter of convenience. The value of V_W was given in a unit of 10^2 Å^3 throughout this report. Example[14].

V_W for 1,3-dichloro-2-propanol ($C_3H_6OCl_2$) $= 0.206 \times 3$ (for 3C) $+ 0.056 \times 6$ (for 6H) $+ 0.115$ (for O) $+ 0.244 \times 2$ (for 2Cl) $- 0.078 \times 2$ (for 2C–C) $- 0.043 \times 5$ (for 5C–H) $- 0.066 \times 2$ (for 2C–Cl) $- 0.056$ (for C–O) $- 0.034$ (for O–H) $- 0.06$ (for branching) $= 0.904$ (10^2 Å^3)

Regression Analysis——Correlations and regression equations were calculated with a JEOL digital computer, model JEC-7E.

TABLE I. Variables for Structure-Activity Correlation for Antibacterial Activity of Penicillin Derivatives:



No.	X	*n*	log (1/*C*)[a]		V_W[d]
			Obsd.[b]	Calcd.[c]	
1	H	0	5.86	5.82	0.056
2	4-Cl	0	5.79	5.50	0.244
3	4-OCH_3	0	5.69	5.40	0.304
4	H	1	5.54	5.50	0.245
5	4-NO_2	0	5.53	5.46	0.265
6	2-Cl	0	5.40	5.50	0.244
7	2,5-Cl_2	0	5.24	5.18	0.432
8	H	2	5.03	5.20	0.419
9	3,5-$(CH_3)_2$	0	5.03	5.20	0.419
10	H	3	5.01	4.94	0.573
11	2,4-Cl_2	0	4.97	5.18	0.432
12	2,4-Br_2	0	4.87	5.03	0.518
13	2,3,6-Cl_3	0	4.72	4.86	0.620
14	4-cyclohexyl	0	4.70	4.47	0.851
15	4-*t*-Bu	0	4.67	4.71	0.707
16	3,4,5-$(CH_3)_3$	0	4.65	4.94	0.573
17	4-*t*-Amyl	1	4.57	4.40	0.895
18	Cl_5	0	4.25	4.23	0.996

a) activity against *Staphylococcus aureus* in mice *b*) ref. 3 *c*) calculated using Eq. 1 *d*) for substituents

Results and Discussion

Antibacterial Activity of Penicillins

The activity data of 18 penicillin derivatives against *Staphylococcus aureus* in mice were compiled by Ostrenga.[3] The correlation of log (1/*C*) (*C* is the effective concentration of penicillins) with V_W of the substituents has been formulated from the data in Table I.

$$\log(1/C) = -1.692(\pm 0.364)\,V_W(9.86) + 5.911(\pm 0.199) \qquad (1)$$
$$n = 18 \quad r = 0.927 \quad s = 0.180$$

12) This simplification did not significantly affect the correlations previously reported.[1b]
13) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
14) The reader is referred to Table I and II in ref. 1*b* for the figures used in the calculation.

TABLE II. Variables for Structure-Activity Correlation for Tadpole Narcosis with Miscellaneous Compounds

No.	Compound	log (1/C)[a]		V_W	V_H[d]
		Obsd.[b]	Calcd.[c]		
1	methanol	0.24	0.26	0.326	0.54
2	ethanol	0.54	0.71	0.480	0.54
3	propanol	0.96	1.16	0.634	0.54
4	butanol	1.42	1.61	0.788	0.54
5	octanol	3.40	3.43	1.404	0.54
6	2-propanol	0.89	0.99	0.574	0.54
7	isobutyl alcohol	1.35	1.44	0.728	0.54
8	*t*-butyl alcohol	0.89	1.26	0.668	0.54
9	isoamyl alcohol	1.64	1.89	0.882	0.54
10	*t*-amyl alcohol	1.24	1.71	0.822	0.54
11	1,3-dichloro-2-propanol	1.92	1.96	0.904	0.54
12	thymol	4.26	4.10	1.482	0.32
13	1,3-$(CH_3O)_2C_6H_4$	3.35	2.94	1.268	0.58
14	1,4-$(CH_3O)_2C_6H_4$	3.05	2.94	1.268	0.58
15	acetone	0.54	0.80	0.587	0.65
16	2-butanone	1.04	1.25	0.741	0.65
17	3-pentanone	1.54	1.71	0.895	0.65
18	2-pentanone	1.72	1.71	0.895	0.65
19	acetophenone	3.03	2.57	1.127	0.56
20	acetal	1.98	1.46	0.548	0.27[e]
21	ethyl ether	1.57	1.77	0.801	0.48
22	anisole	2.82	2.84	1.033	0.29
23	methyl acetate	1.10	1.22	0.668	0.56
24	ethyl formate	1.15	1.22	0.668	0.56
25	ethyl acetate	1.52	1.67	0.822	0.56
26	ethyl propionate	1.96	2.13	0.976	0.56
27	propyl acetate	1.96	2.13	0.976	0.56
28	ethyl butyrate	2.37	2.58	1.130	0.56
29	ethyl isobutyrate	2.24	2.43	1.080	0.56
30	butyl acetate	2.30	2.58	1.130	0.56
31	isobutyl acetate	2.24	2.40	1.070	0.56
32	ethyl valerate	2.72	3.03	1.284	0.56
33	pentyl acetate	2.72	3.03	1.284	0.56
34	butyl valerate	3.60	3.94	1.592	0.56
35	diethyl tartrate	1.21	0.87	1.676	2.20
36	methyl carbamate	0.57	0.43	0.613	0.87
37	ethyl carbamate	1.39	0.89	0.767	0.87
38	phenyl carbamate	3.19	2.45	1.153	0.66
39	pentane	2.55	2.96	0.874	0.00
40	pentene	2.64	2.84	0.832	0.00
41	benzene	2.68	2.74	0.798	0.00
42	xylene	3.42	3.64	1.106	0.00
43	naphthalene	4.19	3.97	1.218	0.00
44	phenanthrene	5.43	5.21	1.638	0.00
45	ethyl chloride	2.35	2.09	0.577	0.00
46	ethyl bromide	2.57	2.21	0.618	0.00
47	ethyl iodide	2.96	2.49	0.715	0.00
48	ethylene chloride	2.64	2.57	0.742	0.00
49	chloroform	2.85	2.43	0.693	0.00
50	nitromethane	1.09	0.61	0.445	0.54
51	acetonitrile	0.44	0.46	0.435	0.60
52	azobenzene	4.74	4.67	1.661	0.30
53	acetaldoxime	0.92	0.71	0.550	0.64

a) narcotic activity in tadpole *b*) ref. 7 *c*) calculated using Eq. 3 *d*) ref. 1*b*, unless otherwise noted
e) evaluated from the log P value (0.86) according to the definition of V_H described in ref. 1*b*

In this and subsequent equations, the figures in parenthes after regression coefficients and after parameters are the 95% confidence intervals and t-values, respectively, n is the number of data points used in deriving the equation, r the correlation coefficient, and s the standard deviation. The correlation is highly significant. The negative coefficient with the V_W term indicates that bulky groups reduce effectiveness.

Ostrenga[3] obtained the following equation using molar attraction constant (F) for the substituents.

$$\log(1/C) = -1.78\times10^{-3}F + 7.64 \quad n = 18 \quad r = 0.892 \quad s = 0.204 \qquad (2)$$

However, there is a high linearity between the F and V_W values with 18 penicillins (r=0.973). Probably V_W is more fundamental than F in the relationship to the activity.

Tadpole Narcosis with Miscellaneous Compounds

The classical data of tadpole narcosis with miscellaneous compounds were compiled by Leo, *et al.*[7] The structure-activity correlation has been formulated from the data in Table II

$$\log(1/C) = 2.940(\pm0.243)V_W(24.29) - 2.022(\pm0.235)V_H(17.21) + 0.390(\pm0.246) \quad n = 53 \quad r = 0.969 \quad s = 0.290 \qquad (3)$$

In this equation, log $(1/C)$ is the narcotic activity, and V_H is the parameter for hydrophilic effect.[1b] The squared correlation coefficient (r^2) between V_W and V_H was 0.03. This shows that the degree of collinearity between them is very low. Equation 3 shows hydrophobic factor controlling the biological responce.

Leo, *et al.*[7] statistically analysed the same data using the following parameters and compared the resultant squared correlations (r^2) with the activity: octanol-water partition coefficient (r^2=0.913), molar refraction (r^2=0.683), molecular weight (r^2=0.567), molar attraction constant (r^2=0.758), parachor (r^2=0.556), and adjusted parachor (r^2=0.861). In the present work, Eq. 3 leads to r^2=0.939.

Inhibition of Neuraminidase by Dihydroisoquinolines

Inhibition of viral neuraminidase by a series of 1-(*para* and *meta*-substituted phenoxymethyl)-3,4-dihydroisoquinolines was studied by Tute.[8] From the data in Table III, a statistical analysis yields the following results:

TABLE III. Variables for Structure-Activity Correlation for Inhibition of Viral Neuraminidase by 1-(*para* and *meta*-Substituted phenoxymethyl)-3,4-dihydroisoquinolines

No.	Function	log $(1/C)^{a)}$		$V_W^{d)}$	$R^{e)}$	$V_H^{f)}$
		Obsd.[b)]	Calcd.[c)]			
1	*p*-NO_2	2.903	2.856	0.265	0.155	0.31
2	*p*-Br	2.767	2.764	0.287	−0.176	0.00
3	*p*-CN	2.839	2.842	0.268	0.184	0.44
4	*p*-Cl	2.807	2.739	0.244	−0.161	0.00
5	*p*-F	2.635	2.538	0.115	−0.336	0.00
6	H	2.577	2.683	0.056	0.000	0.00
7	*p*-CH_3	2.682	2.751	0.245	−0.141	0.00
8	*p*-OCH_3	2.620	2.520	0.304	−0.500	0.29
9	*p*-OH	2.244	2.300	0.137	−0.643	0.32
10	*p*-OC_2H_5	2.650	2.672	0.458	−0.444	0.29
11	*p*-OC_3H_7	2.791	2.785	0.612	−0.457	0.29
12	*p*-OBu	2.785	2.852	0.766	−0.551	0.29
13	*p*-*t*-Bu	3.149	3.114	0.707	−0.138	0.00
14	*m*-CH_3	2.783	2.809	0.245	−0.038	0.00
15	*m*-F	2.666	2.677	0.115	−0.091	0.00
16	*m*-Cl	2.818	2.806	0.244	−0.043	0.00

a) 40% inhibitory activity *b*) ref. 8 *c*) calculated using Eq. 4 *d*) for substituents *e*) See text *f*) ref. 1*b*

$$\log(1/C) = 0.783(\pm 0.193)V_W(8.86) + 0.568(\pm 0.161)R(7.65) - 0.254(\pm 0.238)V_H(2.32) + 2.639(\pm 0.069) \quad (4)$$
$$n = 16 \quad r = 0.950 \quad s = 0.066$$

$$\log(1/C) = 0.737(\pm 0.215)V_W(7.39) + 0.601(\pm 0.182)R(7.13) + 2.625(\pm 0.077) \quad (5)$$
$$n = 16 \quad r = 0.926 \quad s = 0.076$$

where R is the parameter for resonance effect evaluated using the resonance constant ($\mathscr{R}$) as $0.72\mathscr{R}$ and $1.00\mathscr{R}$ for *meta*- and *para*-substituents, respectively.[15] Table IV shows the squared correlation matrix for degree of collinearity between the variables used in Eq. 4 and 5. These equations suggest that bulky and π-electron-attracting groups enhance the inhibitory activity, but that the contribution of hydrophobic factor is minor.

TABLE IV. Squared Correlation Matrix for Independent Variables in Eq. 4 and 5

	V_W	R	V_H
V_W	1.00		
R	0.12	1.00	
V_H	0.09	0.08	1.00

For comparison, Eq. 6 is shown which Tute[8] proposed as the most significant relationship.

$$\log(1/C) = 0.271\pi + 0.062\mu_V + 0.030\mu_V^2 + 2.552 \quad (6)$$
$$n = 16 \quad r = 0.937 \quad s = 0.074$$

In this equation, π is the lipophilic constant, and μ_V is the group dipole moment along the vertical axis through 1′ and 4′ position of the phenoxy moiety. Tute speculated the interaction of a dipole on the drug with an anion on the receptor along the vertical axis because the sign of the coefficient in μ_V was positive. However, Cammarata, *et al.*[16] indicated the insignificance of the μ_V-term, and stated that the following representation was more appropriate.

$$\log(1/C) = 0.265(\pm 0.032)\pi(8.11) + 0.014(\pm 0.003)\mu_V^2(3.67) + 2.548 \quad (7)$$
$$n = 16 \quad r = 0.916 \quad s = 0.081$$

Fungus Toxicity with Miscellaneous Molecules

The data of nonspecific toxicity on the Madison 517 fungus with miscellaneous molecules were compiled by Kier, *et al.*[9] The correlation of log $(1/C)$ (C is the minimum toxic dose) with V_W has been formulated from the data in Table V, showing that V_W controls effectiveness.

$$\log(1/C) = 2.645(\pm 0.158)V_W(33.80) - 1.236(\pm 0.181) \quad (8)$$
$$n = 45 \quad r = 0.982 \quad s = 0.191$$

Equation 9 obtained by Kier, *et al.*[9] from the same data using the connectivity index (χ) is shown for the purpose of comparison.

$$\log(1/C) = 0.775(\pm 0.032)\chi - 1.077(\pm 0.119) \quad (9)$$
$$n = 45 \quad r = 0.965 \quad s = 0.263$$

Inhibition of Xanthine Oxidase by Phenylguanines

Baker's data concerning xanthine oxidase inhibition by 9-phenylguanines were compiled by Silipo and Hansch.[10] The structure-activity correlation has been formulated from the data in Table VI.

15) C.G. Swain and E.C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968).
16) A. Cammarata, R.C. Allen, J.K. Seydel, and E. Wempe, *J. Pharm. Sci.*, **59**, 1496 (1970).

TABLE V. Variables for Structure-Activity Correlation for Fungus Toxicity with Miscellaneous Molecules

No.	Compound	V_W	log $(1/C)^{a)}$	
			Obsd.[b)]	Calcd.[c)]
1	methanol	0.326	−0.24	−0.37
2	ethanol	0.480	−0.04	0.03
3	proanol	0.634	0.44	0.44
4	butanol	0.788	0.87	0.85
5	pentanol	0.942	1.38	1.26
6	hexanol	1.096	1.83	1.66
7	heptanol	1.250	2.32	2.07
8	octanol	1.404	2.86	2.48
9	nonanol	1.558	3.18	2.89
10	decanol	1.712	3.57	3.29
11	2-propanol	0.574	0.24	0.28
12	*sec*-butyl alcohol	0.728	0.60	0.69
13	*t*-butyl alcohol	0.668	0.46	0.53
14	*sec*-amyl alcohol	0.882	1.08	1.10
15	2-methylbutanol	0.882	1.19	1.10
16	3-methylbutanol	0.882	1.25	1.10
17	3-pentanol	0.882	1.01	1.10
18	*t*-amyl alcohol	0.822	1.44	0.94
19	2-ethylbutanol	1.036	1.73	1.50
20	1-methylheptanol	1.344	2.49	2.32
21	2-ethylhexanol	1.344	2.55	2.32
22	diphenylmethanol	1.514	2.57	2.77
23	phenylethanol	1.174	1.57	1.87
24	3-phenylpropanol	1.188	2.00	1.91
25	ethyl ether	0.801	0.55	0.88
26	propyl ether	1.109	1.55	1.70
27	isopropyl ether	0.989	1.13	1.38
28	butyl ether	1.417	2.54	2.51
29	acetone	0.587	0.15	0.32
30	methyl acetate	0.668	0.59	0.53
31	ethyl acetate	0.822	0.80	0.94
32	propyl acetate	0.976	1.23	1.35
33	butyl acetate	1.130	1.69	1.75
34	pentyl acetate	1.284	2.15	2.16
35	heptyl acetate	1.592	2.60	2.98
36	ethyl propionate	0.976	1.20	1.35
37	ethyl butyrate	1.130	1.63	1.75
38	ethyl caproate	1.438	2.59	2.57
39	ethyl caprylate	1.746	3.39	3.38
40	pentyl butyrate	1.592	2.85	2.98
41	2-ethylbutyl acetate	1.378	2.36	2.41
42	1-methylisoamyl acetate	1.318	2.14	2.25
43	pentyl *t*-amylacetate	1.934	3.60	3.88
44	isobutyl alcohol	0.728	0.77	0.69
45	2-heptanone	1.203	1.94	1.95

a) minimum toxic effect on Madison 517 fungus
b) ref. 9
c) calculated using Eq. 8

TABLE VI. Variables for Structure-Activity Correlation for Inhibition of Xanthine Oxidase by 9-(Substituted Phenyl) guanines

No.	Substituent	log (1/C)[a] Obsd.[b]	log (1/C)[a] Calcd,[c]	V_{W-2}	V_{W-3}	E_{s-4}[b]	D_1[d]	D_2[e]
1	2-Cl	5.09	5.36	0.244	0.056	1.24	0	0
2	2-Br	5.11	5.13	0.287	0.056	1.24	0	0
3	3-NHCONHPh-3′-SO_2F, 4-OMe	5.25	5.36	0.056	1.505	0.69	1	0
4	3-NHCOPh-3′-SO_2F, 4-OMe	5.31	5.29	0.056	1.398	0.69	1	0
5	3-NHCONHPh-4′-SO_2F, 4-OMe	5.35	5.36	0.056	1.505	0.69	1	0
6	2,3-CH=CHCH=CH	5.38	5.19	0.309	0.309	1.24	0	0
7	3-NHCOPh-4′-SO_2F, 4-OMe	5.39	5.29	0.056	1.398	0.69	1	0
8	4-NH_2	5.43	6.27	0.056	0.056	0.63	0	0
9	4-$NHSO_2$Ph-4′-SO_2F	5.60	5.95	0.056	0.056	−1.25	0	0
10	4-NMe_2	5.68	6.08	0.056	0.056	−0.47	0	0
11	4-$NHCOCH_2Br$	5.72	5.91	0.056	0.056	−1.47	0	0
12[f]	3-NHCONHPh-3′-SO_2F	5.74	7.39	0.056	1.505	1.24	0	0
13	4-Cl	5.74	6.21	0.056	0.056	0.27	0	0
14	4-CMe_3	5.74	5.90	0.056	0.056	−1.54	0	0
15	4-Me	5.80	6.16	0.056	0.056	0.00	0	0
16	4-CF_3	5.89	5.96	0.056	0.056	−1.16	0	0
17[f]	3-$NHSO_2$Ph-3′-SO_2F	5.89	7.40	0.056	1.521	1.24	0	0
18	3,4-Cl_2	5.96	6.34	0.056	0.244	0.27	0	0
19	4-$O(CH_2)_3NHCOPh$-4′-SO_2F	6.00	6.28	0.056	0.056	0.69	0	0
20	4-$NHSO_2$Ph-3′-SO_2F	6.02	5.95	0.056	0.056	−1.25	0	0
21[f]	3-$NHSO_2$Ph-4′-SO_2F	6.14	7.40	0.056	1.521	1.24	0	0
22	3,4-$(OMe)_2$	6.14	6.45	0.056	0.304	0.69	0	0
23	4-NHCOPh-4′-SO_2F	6.15	5.91	0.056	0.056	−1.47	0	0
24	4-$O(CH_2)_2NHCOPh$-4′-SO_2F	6.16	6.28	0.056	0.056	0.69	0	0
25	4-$O(CH_2)_3NHCONHPh$-4′-SO_2F	6.16	6.28	0.056	0.056	0.69	0	0
26	4-C_2H_5	6.17	6.15	0.056	0.056	−0.07	0	0
27	4-$O(CH_2)_3NHCOPh$-3′-SO_2F	6.20	6.28	0.056	0.056	0.69	0	0
28	2-F	6.21	6.06	0.115	0.056	1.24	0	0
29	4-$(CH_2)_3CH_3$	6.21	6.09	0.056	0.056	−0.39	0	0
30	3-NH_2	6.22	6.46	0.056	0.177	1.24	0	0
31	4-$O(CH_2)_2NHCOPh$-3′-SO_2F	6.28	6.28	0.056	0.056	0.69	0	0
32	4-OMe	6.30	6.28	0.056	0.056	0.69	0	0
33	4-$O(CH_2)_2NHCOPh$-4′-Me, 3′-SO_2F	6.31	6.28	0.056	0.056	0.69	0	0
34	4-$CONH_2$	6.38	6.21	0.056	0.056	0.28	0	0
35	3,4-CH=CHCH=CH	6.39	6.40	0.056	0.309	0.36	0	0
36	H	6.39	6.37	0.056	0.056	1.24	0	0
37	4-$O(CH_2)_3NHCONHPh$-3′-SO_2F	6.40	6.28	0.056	0.056	0.69	0	0
38	4-$O(CH_2)_2NHCONHPh$-4′-SO_2F	6.48	6.87	0.056	0.056	0.69	0	1
39	4-NHCOPh-3′-SO_2F	6.55	5.91	0.056	0.056	−1.47	0	0
40	3-Cl	6.57	6.50	0.056	0.244	1.24	0	0
41	4-$CHMe_2$	6.60	6.08	0.056	0.056	−0.47	0	0
42	4-Ph	6.60	6.21	0.056	0.056	0.28	0	0
43	3-Me	6.62	6.51	0.056	0.245	1.24	0	0
44	3-NHCHO	6.64	6.59	0.056	0.360	1.24	0	0
45	3-OMe	6.66	6.55	0.056	0.304	1.24	0	0
46	4-OH	6.68	6.28	0.056	0.056	0.69	0	0
47	4-$O(CH_2)_2NHCONHPh$-3′-SO_2F	6.74	6.87	0.056	0.056	0.69	0	1
48	3-CF_3	6.82	6.52	0.056	0.263	1.24	0	0
49	4-$O(CH_2)_2NHCONHPh$-4′-Me,3′-SO_2F	6.92	6.87	0.056	0.056	0.69	0	1
50	3-NHCOPh-3′-SO_2F	6.96	7.32	0.056	1.398	1.24	0	0
51	4-OEt	6.96	6.28	0.056	0.056	0.69	0	0
52	3-$NHCOCH_2OPh$-4′-SO_2F	7.00	7.48	0.056	1.633	1.24	0	0
53	4-$O(CH_2)_2NHCONHPh$-2′-Cl,5′-SO_2F	7.04	6.87	0.056	0.056	0.69	0	1
54	3-NHCOPh-4′-Me,3′-SO_2F	7.04	7.43	0.056	1.552	1.24	0	0
55[f]	4-$O(CH_2)_3Ph$	7.08	6.28	0.056	0.056	0.69	0	0

No.	Substituent	log (1/C)[a] Obsd.[b]	Calcd.[c]	V_{W-2}	V_{W-3}	E_{S-4}[b]	D_1[d]	D_2[e]
56	3-Ph	7.09	6.89	0.056	0.785	1.24	0	0
57	3-NHCOPh	7.14	7.07	0.056	1.054	1.24	0	0
58	3-NHCOCH$_2$Br	7.15	6.84	0.056	0.720	1.24	0	0
59	3-NHCOPh-2′-Cl,5′-SO$_2$F	7.15	7.43	0.056	1.563	1.24	0	0
60	4-O(CH$_2$)$_2$NHCONHPh-2′-OMe, 5′-SO$_2$F	7.16	6.87	0.056	0.056	0.69	0	1
61	3-NHCONHPh-2′-Cl, 5′-SO$_2$F	7.28	7.51	0.056	1.670	1.24	0	0
62	3-NHCOPh-4′-SO$_2$F	7.29	7.32	0.056	1.398	1.24	0	0
63	3-NHCONHPh-3′-Cl,4′-SO$_2$F	7.48	7.51	0.056	1.670	1.24	0	0
64	3-NHCO(CH$_2$)$_2$Ph-4′-SO$_2$F	7.58	7.53	0.056	1.706	1.24	0	0
65	3-NHCONHPh-4′-SO$_2$F	7.62	7.39	0.056	1.505	1.24	0	0
66	3-NHCONHPh-4′-Me,3′-SO$_2$F	7.74	7.50	0.056	1.659	1.24	0	0
67	3-NHCONHPh-2′-OMe,5′-SO$_2$F	7.80	7.56	0.056	1.740	1.24	0	0
68	3-NHCOCH$_2$Ph-4′-SO$_2$F	7.82	7.43	0.056	1.552	1.24	0	0
69	3-NHCO(CH$_2$)$_4$Ph-4′-SO$_2$F	8.00	7.75	0.056	2.014	1.24	0	0

a) C is the 50% inhibitory concentration *b*) ref. 10 *c*) calculated using Eq. 10 *d*) dummy parameter which accounts for the presence of both 3-substituent bearing SO_2F and 4-OMe *e*) dummy parameter which accounts for the presence of 4-$OCH_2CH_2NHCONHPh$-SO_2F *f*) these points not used in deriving Eq. 10

$$\log(1/C) = -5.367(\pm 1.636)V_{W-2}(6.56) + 0.704(\pm 0.147)_{W-3}(9.59) + 0.172(\pm 0.109)E_{S-4}(3.13) - 1.935(\pm 0.331)D_1(11.68) + 0.590(\pm 0.287)D_2(4.11) + 6.421(\pm 0.153) \quad (10)$$
$$n = 65 \quad r = 0.920 \quad s = 0.295$$

In this equation, C is the 50% inhibitory concentration, E_S is the Taft steric constant, D_1 is the dummy parameter which accounts for the presence of both 3-substituent bearing SO_2F and 4-OCH_3, and D_2 accounts for the presence of 4-$OCH_2CH_2NHCONHPhSO_2F$. The interrelationship of the variables is shown in Table VII. Equation 10 suggests that bulky groups

Table VII. Squared Correlation Matrix for Independent Variables in Eq. 10

	V_{W-2}	V_{W-3}	E_{S-4}	D_1	D_2
V_{W-2}	1.00				
V_{W-3}	0.02	1.00			
E_{S-4}	0.04	0.22	1.00		
D_1	0.00	0.13	0.00	1.00	
D_2	0.00	0.04	0.00	0.01	1.00

in the 2 position reduce effectiveness whereas those in the 3 position enhance the activity. The steric hindrance by 4-substituents lowers the inhibitory action. The dummy parameters are also significantly related to the activity.

For comparative purposes, Eq. 11 formulated by Silipo and Hansch[10] is shown here.

$$\log(1/C) = 0.267(\pm 0.06)MR_3 - 0.647(\pm 0.12)MR_3 \cdot MR_4 + 1.291(\pm 0.39)E_{S-2} + 0.101(\pm 0.04)MR_4 + 0.252(\pm 0.11)E_{S-4} + 4.552(\pm 0.45) \quad (11)$$
$$n = 65 \quad r = 0.910 \quad s = 0.308$$

In this equation, MR is the molar refraction. The use of cross product term $MR_3 \cdot MR_4$ is characteristic.

Tuberculostatic Activity of Isoniazid Derivatives

Tuberculostatic activity of 2-substituted isoniazid derivatives was studied by Seydel, *et al.*[11] From the data in Table VIII, Eq. 12 has been derived,

TABLE VIII. Variables for Structure-Activity Correlation for Tuberculostatic Activity of 2-Substituted Isoniazid Derivatives

No.	Substituent	log (1/C)[a] Obsd.[b]	log (1/C)[a] Calcd.[c]	V_{W-2}	$\mathscr{F}$[d]	$\mathscr{R}$[d]	D[e]
1	H	−0.041	−0.243	0.056	0.00	0.00	0
2	CH_3	−0.716	−0.773	0.245	−0.04	−0.13	0
3	C_2H_5	−1.324	−1.123	0.399	−0.05	−0.10	0
4	n-C_3H_7	−1.742	−1.486	0.553	−0.06	−0.08	0
5	iso-C_4H_9	−2.653	−2.525	0.647	−0.06	−0.11	1
6	OCH_3	−2.185	−2.360	0.304	0.26	−0.51	0
7	OC_2H_5	−2.655	−2.565	0.458	0.22	−0.44	0
8	NH_2	−1.161	−1.417	0.177	0.02	−0.68	0
9	$NHCOCH_3$	−3.332	−3.459	0.514	0.28	−0.26	1
10	$CH_2NHCOCH_3$	−2.386	−2.385	0.681	0.10	−0.10	0
11	$N(C_2H_5)_2$	−2.856	−2.688	0.749	0.07	−0.29	0
12	F	−2.415	−2.213	0.115	0.43	−0.34	0
13	Cl	−2.593	−2.280	0.244	0.41	−0.15	0
14	Br	−2.790	−2.519	0.287	0.44	−0.17	0
15	I	−2.404	−2.684	0.388	0.40	−0.19	0
16	NO_2	−2.569	−2.841	0.265	0.67	0.16	0
17[f]	C_6H_5	−1.699	−2.578	0.785	0.08	−0.08	0
18	$CH_2C_6H_5$	−1.585	−2.007	0.799[g]	−0.08	−0.01	0
19	$CH{=}CH_2$	−1.544	−1.383	0.357	0.07	−0.08	0

a) C is the minimum inhibitory concentration. *b*) ref. 11 *c*) calculated using Eq. 13 *d*) C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, and E.J. Lien, *J. Med. Chem.*, **16**, 1207 (1973) *e*) dummy parameter accounting for the presence of methyl branch attached to the β-carbon *f*) not used in deriving Eq. 13 *g*) corrected for intramolecular hydrophobic bonding

$$\log(1/C) = -2.321(\pm 0.826)V_{W-2}(6.03) - 3.246(\pm 0.817)\mathscr{F}(8.51) + 1.188(\pm 0.858)\mathscr{R}(2.97) - 0.868(\pm 0.538)D(3.46) - 0.200(\pm 0.502) \qquad n = 19 \quad r = 0.938 \quad s = 0.325 \qquad (12)$$

where C is the minimum inhibitory concentration of the drugs, $\mathscr{F}$ and $\mathscr{R}$ are the field and resonance constants for 2-substituents, respectively, and D is the dummy parameter which accounts for the presence of methyl branch attached to the β-carbon of 2-substituents. This kind of branch seems to cause a large steric hindrance.[17] Moreover, Eq. 12 suggests that bulky groups having strong field effect reduce effectiveness whereas π-electron attracting groups enhance the tuberculostatic activity. The interrelationship of the variables is shown in Table IX.

TABLE IX. Squared Correlation Matrix for Independent Variables in Eq. 13

	V_{W-2}	$\mathscr{F}$	$\mathscr{R}$	D
V_{W-2}	1.00			
$\mathscr{F}$	0.15	1.00		
$\mathscr{R}$	0.03	0.00	1.00	
D	0.09	0.01	0.00	1.00

Compound 17, with a phenyl substituent, is poorly fit for Eq. 12 probably owing to the perpendicular conformation of phenyl ring.[11] When compound 17 is deleted from the set of data, the resultant regression equation becomes

17) In the Taft steric constant (E_s) for aliphatic series, the difference between n-C_4H_9 (−0.39) and iso-C_4H_9 (−0.93) is much greater compared with those between n-C_3H_7 (−0.36) and iso-C_3H_7 (−0.47), and between n-C_5H_{11} (−0.40) and iso-C_5H_{11} (−0.35): R.W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M.S. Newman, John Wiley and Sons, New York, 1956, p. 598.

$$\log(1/C) = -2.715(\pm 0.726)V_{W-2}(8.08) - 3.304(\pm 0.662)\mathscr{F}(10.79) + 1.146(\pm 0.693)\mathscr{R}(3.57) - 0.750(\pm 0.443)D(3.66) - 0.091(\pm 0.413) \quad n = 18 \quad r = 0.963 \quad s = 0.261 \quad (13)$$

There is no substantial difference in the physical meaning between Eq. 12 and 13, although the statistics for the correlation are much improved.

For comparison, Eq. 14 and 15 derived by Seydel, *et al.*[11] are shown here.

$$\log(1/C) = 0.232\mathrm{p}K_a(5.79) - 1.073\pi(6.57) - 1.454 \quad (14)$$
$$n = 19 \quad r = 0.883 \quad s = 0.41$$

In this equation, $\mathrm{p}K_a$ is the value for 2-substituted pyridine, and π is the "steric π value."[18] When the observed π values instead of the steric π values were used, the correlation became insignificant in the π term.

$$\log(1/C) = 0.152\mathrm{p}K_a(2.20) - 0.304\pi(1.34) - 2.289 \quad (15)$$
$$n = 19 \quad r = 0.518 \quad s = 0.75$$

Conclusions

The generality of the use of van der Waals volume V_W to analyse and predict biological activity relating to molecular structure is supported by these findings. The great appeal of V_W lies both in the simplicity of its evaluation without any experiment or troublesome computation, and in its fundamental relationship to molecular structure.

18) π values corrected using the van der Waals volume given by Bondi or using the Taft E_s constant. For details see Ref. 11.