A Quantitative Structure–Activity Relationship Study of 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors

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A quantitative structure–activity relationship study has been made of some 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. The HMG-CoA reductase inhibition activities of mevinolin analogs and 6-substituted 4-hydroxypyran-2 ones have been mostly found to be significantly correlated with the molecular size of substituents. In one case, however, the inhibition potency was found to be related to the hydrophobicity of molecules. These findings led us to suggest that the enzyme HMG-CoA reductase possesses an active site which is involved in dispersion interaction and another site which is involved in hydrophobic interaction with inhibitor molecules, depending upon the proper orientation of the latter towards these sites. Furthermore, the results indicate that both active sites possess limited steric bulk tolerance.

Keywords — 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor; 4-hydroxypyran-2-one; mevinolin analog; structure–activity relationship

Introduction

The enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (EC.1.1.1.34) catalyzes the conversion of HMG-CoA to mevalonic acid (Eq. 0), which is a rate limiting step in the biosynthesis of cholesterol. The hypercholesterolemia is known primary risk factor^{1,2)} for coronary heart disease (the major cause of death in Western countries). It was therefore deemed important to investigate potent inhibitors of HMG-CoA reductase.

The novel fungal metabolites compactin (ML-236B) (**1a**)^{3,4)} and mevinolin (MK-803) (**1b**)^{5,6)} were found to be potent inhibitors of HMG-CoA reductase. However, attempts were recently made to develop structurally simplified HMG-CoA reductase inhibitors.^{7–9)} Series of 5-substituted 3,5-dihydroxypentanoic acids,⁷⁾ 7-(substituted aryl)-3,5-dihydroxy-6-heptenoic acids,⁸⁾ 7-(3,5-disubstituted) [1,1'-biphen-

yl]-2-yl)-3,5-dihydroxy-6-heptenoic acids⁹⁾ and their lactone derivatives^{7–9)} were prepared and studied for their HMG-CoA reductase inhibitory activities. In order to delineate the structural features of mevinolin responsible for its HMG-CoA reductase inhibitory activity, Hoffman *et al.*¹⁰⁾ also investigated the effect of structural modifications in mevinolin. In the present communication, certain of these studies were subjected to quantitative structure activity relationships (QSAR) study so that a better picture of the structure–activity relationship might be obtained.

Materials and Method

Series of compounds that could be successfully exploited in the QSAR study are listed in Tables I–IV. All the inhibition data listed therein were those obtained by Hoffman's group.^{8,10} A simple parameter, van der Waals volume (V_w), was found to control the activity. This parameter is a measure of the molecular size of the compounds and is one of the most fundamental characteristics of drug structure controlling the biological activity. It has been successful-

ly used in many QSAR studies¹¹ and was calculated as suggested by Moriguchi *et al.*¹²

The parameter $\log P$ (P : octanol–water partition coefficient) was also used in the correlation to investigate the role of the hydrophobic character of molecules in enzyme inhibition. The values of $\log P$ were calculated according to Hansch and Leo using the fragment method.¹³

Results and Discussions

First we took mevinolin analogs (Table I)

TABLE I. Effects of Structural Modifications in Mevinolin

No.	R	$\log P$	$V_w^{a)}$ ($10^2 \text{ \AA}^3$)	$-\log IC_{50}$	
				Obsd ^{b)}	Cald ^{c)}
1		0.42	0.657	8.66	8.47
2	CH ₃	-1.55	0.245	6.57	6.31
3		-0.81	0.449	7.41	7.62
4	CH ₃ (CH ₂) ₃	0.31	0.707	8.06	8.61
5	CH ₃ (CH ₂) ₈	3.01	1.477	6.53	7.12
6	(CH ₃) ₂ CH	-0.36	0.503	8.11	7.89
7	(CH ₃) ₂ CHCH ₂	0.42	0.657	8.27	8.47
8	(CH ₃) ₂ C=CH	-0.46	0.615	7.56	8.34
9	CH ₂ =C(CH ₃)CH ₂	-0.16	0.615	8.54	8.34
10	CF ₃ CH(CH ₃)CH ₂	2.32	0.795	8.46	8.77
11		0.42	0.657	8.66	8.47
12	(CH ₃) ₃ C	0.29	0.607	8.57	8.32
13	C ₂ H ₅ C(CH ₃) ₂	1.08	0.761	9.05	8.72
14	(C ₂ H ₅) ₂ C(CH ₃)	1.86	0.815	8.85	8.80
15	(C ₂ H ₅) ₃ C	2.40	1.069	8.85	8.73
16	C ₃ H ₇ C(C ₂ H ₅) ₂	3.06	1.223	8.72	8.33
17		3.23	1.319	8.42	7.96
18	4-F-C ₆ H ₄	-0.16	0.831	7.43	7.39
19	C ₆ H ₅ CH ₂	0.24	0.939	7.72	7.43
20	C ₆ H ₅ O	-0.13	0.844	7.08	7.41

a) For R-group only. b) Ref. 10. c) Eq. 4.

and tried to correlate their inhibition parameters $-\log IC_{50}$, IC_{50} being the molar concentration of the inhibitor leading to 50% inhibition of the enzyme activity, with the value of V_w of their substituents. The correlation obtained was:

$$\begin{aligned} -\log IC_{50} &= 7.288 (\pm 4.907) V_w \\ &\quad - 4.024 (\pm 2.704) V_w^2 + 5.172 \\ n &= 20, r = 0.608, s = 0.636, \\ F_{2,17} &= 4.68 \end{aligned} \quad (1)$$

where n is the number of data points, r is the correlation coefficient, s is the standard deviation, F is the F -ratio between the variances of calculated and observed activities, and data within parentheses are 95% confidence intervals. The correlation, however, does not appear to be very significant. This is because the last three compounds (**18–20**) of this series were misfits in the correlation. These three compounds are different from others in the sense that they have aromatic substituents. If they are excluded, a better correlation is obtained (Eq. 2). The correlation of activity with $\log P$ was not found to be good. Even with the exclusion of the last three compounds, the correlation obtained with $\log P$ was poor (Eq. 3). The $\log P$ was calculated for the whole molecule in order to see the overall effect of the hydrophobicity of the compound on the activity.

$$\begin{aligned} -\log IC_{50} &= 10.298 (\pm 3.352) V_w \\ &\quad - 5.613 (\pm 1.836) V_w^2 + 4.134 \\ n &= 17, r = 0.870, s = 0.398, \\ F_{2,14} &= 21.83 \end{aligned} \quad (2)$$

$$\begin{aligned} -\log IC_{50} &= 0.750 (\pm 0.378) \log P \\ &\quad - 0.272 (\pm 0.150) (\log P)^2 \\ &\quad + 8.290 \\ n &= 17, r = 0.753, s = 0.532, \\ F_{2,14} &= 9.16 \end{aligned} \quad (3)$$

When the last three compounds were added in the correlation with a dummy parameter I , indicating the aromatic nature of substituents with a value of unity, the correlation expressed by Eq. 2 was improved (Eq. 4). The corresponding correlation with $\log P$, though improved, was still poor (Eq. 5). Along with the size of substituents, their aromatic nature also appears to be

important in governing the inhibition potency of compounds. The negative coefficient of I in Eq. 4 suggests that the aromaticity of the substituent will reduce the activity of the compound by a factor of about 27 on a molar scale. Although we have taken into consideration the aromatic nature of substituents in the calculation of $\log P$, its effect, to some extent, is exclusively accounted for by I , in Eq. 5. This effect of aromaticity was observed in the next series (Table II) also. The inhibition activity of 6-substituted 4-hydroxypyran-2-ones of Table II was first related to V_w of the substituents in the phenyl ring as:

$$\begin{aligned} -\log IC_{50} &= 10.314 (\pm 3.213) V_w \\ &\quad - 5.610 (\pm 1.759) V_w^2 \\ &\quad - 1.424 (\pm 0.552) I + 4.123 \\ n &= 20, r = 0.884, s = 0.387, \\ F_{3,16} &= 17.82 \end{aligned} \quad (4)$$

$$\begin{aligned} -\log IC_{50} &= 0.754 (\pm 0.352) \log P \\ &\quad - 0.273 (\pm 0.140) (\log P)^2 \\ &\quad - 0.859 (\pm 0.699) I + 8.291 \\ n &= 20, r = 0.793, s = 0.503, \\ F_{3,16} &= 8.46 \end{aligned} \quad (5)$$

$$\begin{aligned} -\log IC_{50} &= 2.286 (\pm 1.651) V_w(R_2) \\ &\quad + 1.083 (\pm 0.662) V_w(R_4) \\ &\quad + 2.026 (\pm 0.833) V_w(R_6) \\ &\quad - 0.310 (\pm 0.691) I_3 \\ &\quad - 0.623 (+ 1.402) I_5 + 3.777 \\ n &= 16, r = 0.921, s = 0.453, \\ F_{5,10} &= 11.21 \end{aligned} \quad (6)$$

Since, at the 3- and 5-positions of the phenyl ring, the substituents were either hydrogen or chlorine, we used two indicator parameters I_3 and I_5 with a value of unity to indicate the presence of chlorine at the two positions, respectively. But as Eq. 6 shows, these two parameters were not statistically significant. Hence, if they are dropped, there is little loss of significance of the correlation (Eq. 7). However, instead of these parameters, if the parameter I indicating the presence of an aromatic group at any position in the phenyl ring is added, a significant improvement in the correlation of Eq. 7 is obtained (Eq. 8). In Eq. 8, we find that the coefficient of

TABLE II. 6-Substituted 4-Hydroxypyran-2-ones: Effect of Substitution on Phenyl Ring

No.	R ₂	R ₃	R ₄	R ₅	R ₆	log <i>P</i>	<i>V_w</i> (10 ² Å ³)			-log IC ₅₀	
							R ₂	R ₄	R ₆	Obsd ^{a)}	Calcd ^{b)}
1	H	H	H	H	H	-1.82	0.056	0.056	0.056	3.55	3.70
2	H	H	C ₆ H ₅	H	H	-0.28	0.056	0.785	0.056	4.26	4.14
3	C ₆ H ₅	H	H	H	H	-0.28	0.785	0.056	0.056	5.52	5.47
4	Cl	H	H	H	H	-0.62	0.244	0.056	0.056	5.13	4.47
5	Cl	H	H	H	Cl	-0.40	0.244	0.056	0.244	5.10	5.03
6	Cl	H	Cl	H	H	-0.40	0.244	0.244	0.056	4.66	4.90
7	Cl	Cl	H	H	H	0.20	0.244	0.056	0.056	4.19	4.47
8	H	Cl	Cl	H	H	0.20	0.056	0.244	0.056	4.46	4.13
9	CH ₃	H	CH ₃	H	H	-0.76	0.245	0.245	0.056	4.52	4.91
10	Cl	H	C ₆ H ₅ CH ₂ O	H	Cl	1.08	0.244	0.998	0.244	6.35	5.96
11	Cl	Cl	<i>p</i> -F-C ₆ H ₄ CH ₂ O	H	H	1.88	0.244	1.044	0.056	4.77	5.50
12	Cl	H	<i>p</i> -F-C ₆ H ₄ CH ₂ O	H	Cl	1.22	0.244	1.044	0.244	6.17	6.06
13	H	Cl	H	Cl	OC ₅ H ₁₁	1.81	0.056	0.056	0.920	4.89	5.04
14	CH ₃	H	C ₆ H ₅ CH ₂ O	H	CH ₃	0.60	0.245	0.998	0.245	6.21	5.97
15	Cl	H	Cl	H	C ₆ H ₅ OCH ₂	0.82	0.244	0.244	1.020	6.41	6.54
16	Cl	H	Cl	H	4-F-C ₆ H ₄ OCH ₂	1.10	0.244	0.244	1.066	6.77	6.67

a) Ref. 8. b) Eq. 8.

each variable is statistically significant, indicating that the size and aromaticity of all R₂-, R₄- and R₆-substituents will affect the activity of the compound. In this case also, the log *P* parameter was not found to be important (Eq. 9). The aromatic nature of substituents was implicit in the calculation of log *P*.

$$\begin{aligned}
 -\log \text{IC}_{50} = & 2.758 (\pm 1.627) V_w(R_2) \\
 & + 1.193 (\pm 0.675) V_w(R_4) \\
 & + 1.880 (\pm 0.754) V_w(R_6) \\
 & + 3.542 \\
 n = 16, r = 0.890, s = 0.484, \\
 F_{3,12} = 15.30
 \end{aligned} \quad (7)$$

$$\begin{aligned}
 -\log \text{IC}_{50} = & 4.109 (\pm 1.729) V_w(R_2) \\
 & + 2.290 (\pm 1.052) V_w(R_4)
 \end{aligned}$$

$$\begin{aligned}
 & + 2.971 (\pm 1.083) V_w(R_6) \\
 & - 1.228 (\pm 1.002) I + 3.174 \\
 n = 16, r = 0.936, s = 0.392, \\
 F_{4,11} = 14.04
 \end{aligned} \quad (8)$$

$$\begin{aligned}
 -\log \text{IC}_{50} = & 0.646 (\pm 0.447) \log P \\
 & - 0.287 (\pm 0.363) (\log P)^2 \\
 & + 5.305 \\
 n = 16, r = 0.663, s = 0.764, \\
 F_{2,13} = 4.71
 \end{aligned} \quad (9)$$

The existence of significant correlations between the activity and *V_w* and no role of log *P* for compounds of Tables I and II both indicated that there might be an involvement of dispersion interaction in the inhibition of the enzyme by these series of compounds. Since, in the case of

TABLE III. 6-Substituted 4-Hydroxypyran-2-ones: Effect of Substitution on Phenyl Ring of 6-Benzyl Ether Series

No.	R	A	log <i>P</i>	<i>V_w</i> ^{a)} (10 ² Å ³)	-log IC ₅₀	
					Obsd ^{b)}	Cald ^{c)}
1	H	CH=CH	1.54	0.963	6.37	6.58
2	H	CH ₂ CH ₂	2.09	0.963	6.70	6.86
3	4-CH ₃	CH=CH	2.07	1.117	5.31	5.95
4	4-Cl	CH=CH	2.55	1.128	5.60	5.87
5	4-CN	CH=CH	0.97	1.138	5.70	5.80
6	4-CF ₃	CH ₂ CH ₂	2.97	1.255	4.89	5.25
7	4-CH ₃ O	CH=CH	1.47	1.198	5.58	5.38
8	4-F	CH=CH	1.68	1.009	6.70	6.71
9	4-F	CH ₂ CH ₂	2.23	1.009	7.12	6.98
10 ^{d)}	4-F	CH ₂ CH ₂	2.23	1.009	7.30	6.98
11	3-F	CH=CH	1.68	1.009	6.23	6.26
12	3-F	CH ₂ CH ₂	2.23	1.009	6.62	6.53
13	2-F	CH=CH	1.68	1.009	6.29	6.26
14	2-F	CH ₂ CH ₂	2.23	1.009	6.82	6.53
15	2, 4-F ₂	CH=CH	1.82	1.055	6.70	6.39
16	F ₅	CH=CH	2.43	1.193	6.15	5.42

a) For R group. b) Ref. 8. c) Eq. 12. d) Not included in correlations (see text).

mevinolin analogs (Table I), the correlation between the inhibition potency and *V_w* of R-group was parabolic (Eq. 4), the increase in the activity appeared to be limited by the size of the R-group. The optimum activity was reached when *V_w* attained an approximate value of 0.92×10^2 Å³ (Eq. 4). Beyond this value of *V_w*, the activity decreased. This showed a limited bulk tolerance of the active site of the enzyme and consequently steric hindrance was produced by a larger R-group in the inhibition mechanism.

Table III contains another series of compounds analogous to those of Table II, but with variations only in the substituent of 6-position of the phenyl ring. It is a benzyl ether series for which we found that the HMG-CoA reductase inhibition potency was a significant function of

V_w of the substituted benzyl group of ether moiety at 6-position (Eq. 10). But here, the size of the benzyl group appeared to be able to produce only a steric effect in the activity. To investigate the positional effect of R-substituents in the benzyl group, we introduced in the correlation a dummy parameter *D*₁, equal to unity for all 4-substituents and zero for others and obtained the equation:

$$-\log \text{IC}_{50} = 12.140 - 5.560 (\pm 2.398) V_w$$

$$n = 15, r = 0.812, s = 0.387,$$

$$F_{1,13} = 25.08 \quad (10)$$

$$-\log \text{IC}_{50} = 13.399 - 6.938 (\pm 3.309) V_w$$

$$+ 0.361 (\pm 0.608) D_1$$

$$n = 15, r = 0.837, s = 0.377,$$

TABLE IV. 6-Substituted 4-Hydroxypyran-2-ones: Effect of Substitution in 6-Alkyl (Aryl, Aralkyl) Ether Series

No.	R	A	log <i>P</i>	<i>V_w</i> ^{a)} (10 ² Å ³)	-log IC ₅₀	
					Obsd ^{b)}	Cald ^{c)}
1	CH ₃ SCH ₂ -	CH=CH	-0.80	0.589	6.12	5.61
2	CH ₃ O(CH ₂) ₂ OCH ₂ -	CH=CH	-1.93	0.879	4.96	4.79
3	H	CH ₂ CH ₂	-0.57	0.056	5.10	5.74
4	C ₅ H ₁₁ -	CH=CH	1.98	0.861	6.00	6.11
5	H ₂ C=CHCH ₂ -	CH=CH	-0.55	0.511	6.12	5.75
6	(CH ₃) ₃ CCH ₂ CH(CH ₃)(CH ₂) ₂ -	CH=CH	3.94	1.611	4.42	5.15
7	(CH ₂) ₂ -	CH=CH	4.49	1.627	5.52	4.69
8	-CH ₂ -	CH ₂ CH ₂	2.58	1.065	6.12	5.92
9	C ₆ H ₅ -	CH=CH	0.99	0.785	5.96	6.18
10	C ₆ H ₅ -	CH ₂ CH ₂	1.65	0.785	6.48	6.16
11	-CH ₂ -	CH=CH	3.12	1.359	5.36	5.68
12	(C ₆ H ₅) ₂ CH-	CH=CH	3.20	1.646	5.20	5.64
13	-CH ₂ -	CH=CH	1.34	0.863	6.22	6.18
14	-CH ₂ -	CH=CH	0.76	0.754	6.22	6.16
15	-CH ₂ -	CH=CH	0.72	0.896	5.43	5.45
16	-CH ₂ -	CH=CH	0.72	0.896	5.47	5.45
17	-CH ₂ -	CH=CH	0.72	0.896	5.92	5.45
18	-CH ₂ -	CH=CH	-1.86	0.969	3.93	4.15
19	-CH ₂ -	CH=CH	-1.86	0.969	3.91	4.15
20	C ₆ H ₅ CH=CHCH ₂ -	CH=CH	1.61	1.207	5.72	6.16
21	C ₆ H ₅ CH ₂ CH ₂ -	CH=CH	2.08	1.093	6.32	6.08
22	C ₆ H ₅ (CH ₂) ₃ -	CH=CH	2.84	1.247	5.84	5.82
23	4-Cl-C ₆ H ₄ (CH ₂) ₂ -	CH=CH	2.79	1.339	6.00	5.84

a) For R-group only. b) Ref. 8. c) Eq. 17.

$$F_{2,12} = 14.03 \quad (11)$$

which showed that though the coefficient of D_1 was not significant at the 95% confidence level, there was an overall improvement in the correlation, indicating an additional effect of the 4-position.

Unlike the compounds of Tables I and II, some in Table III had saturated ethenyl bridge ($A = CH_2CH_2$) between the lactone and aromatic moieties. To account for the effect of this saturation of the bridge, we introduced in the correlation another dummy parameter D_2 with a value of unity for saturated A and zero for unsaturated A. Equation 12 shows that there was some effect of saturation, as there was further improvement in the correlation. The hydrophobicity of compounds was not found to have any significant relation with activity in this case also (Eq. 13), nor had it made any improvement in the correlation when used in Eq. 12 (Eq. 14).

$$\begin{aligned} -\log IC_{50} = & 13.347 - 7.022 (\pm 3.259) V_w \\ & + 0.446 (\pm 0.616) D_1 \\ & + 0.270 (\pm 0.463) D_2 \\ n = & 15, r = 0.860, s = 0.367, \\ F_{3,11} = & 8.51 \end{aligned} \quad (12)$$

$$\begin{aligned} -\log IC_{50} = & 4.452 (\pm 3.848) \log P \\ & - 1.178 (\pm 0.967) (\log P)^2 \\ & + 2.236 \\ n = & 15, r = 0.617, s = 0.542, \\ F_{2,12} = & 3.68 \end{aligned} \quad (13)$$

$$\begin{aligned} -\log IC_{50} = & 13.348 - 7.023 (\pm 3.715) V_w \\ & + 0.446 (\pm 0.654) D_1 \\ & + 0.268 (\pm 0.666) D_2 \\ & + 0.003 (\pm 0.682) \log P \\ n = & 15, r = 0.860, s = 0.385, \\ F_{4,10} = & 5.67 \end{aligned} \quad (14)$$

In the derivation of all the equations of this series, compound **10** was not included, as it differed from **9** only in its optical activity which could not be accounted for by the parameters used.

Table IV lists a bigger ether series where the

R-group of the ether moiety at 6-position of phenyl ring is an allyl, aryl, or an aralkyl group. In this series of compounds, the hydrophobicity was found to play a significant role. A parabolic correlation obtained between $\log P$ and the inhibition potency in this case was:

$$\begin{aligned} -\log IC_{50} = & 0.417 (\pm 0.171) \log P \\ & - 0.141 (\pm 0.060) (\log P)^2 \\ & + 5.742 \\ n = & 23, r = 0.768, s = 0.483, \\ F_{2,20} = & 14.38 \end{aligned} \quad (15)$$

In this correlation, the coefficients of both $\log P$ and $(\log P)^2$ are significant at the 95% confidence level and the F -value is significant at the 99% level [$F_{2,20}(.01) = 5.85$]. On the contrary, V_w was found to have very poor correlation in this case (Eq. 16).

$$\begin{aligned} -\log IC_{50} = & 1.089 (\pm 3.016) V_w \\ & - 0.764 (\pm 1.502) V_w^2 \\ & + 5.356 \\ n = & 23, r = 0.300, s = 0.723, \\ F_{2,20} = & 0.99 \end{aligned} \quad (16)$$

The correlation between $\log P$ and the activity (Eq. 15) was further improved when a dummy parameter D with a value of unity was introduced for compounds **15–19** which distinctly contained a nitrogen atom in their R-group (Eq. 17). These compounds were misfits in the correlation expressed by Eq. 15, as they possess very low activity unaccountable by their $\log P$ values. Equation 17 shows that the presence of nitrogen in the ring will lead to a decrease in the activity by a factor of approximately 5. This decrease in the activity may be due to the basicity of the nitrogen.

$$\begin{aligned} -\log IC_{50} = & 0.343 (\pm 0.154) \log P \\ & - 0.140 (\pm 0.051) (\log P)^2 \\ & - 0.700 (\pm 0.483) D \\ & + 5.976 \\ n = & 23, r = 0.851, s = 0.408, \\ F_{3,19} = & 15.73 \end{aligned} \quad (17)$$

Now contrary to the other cases, the prime dependence of activity on $\log P$ and not on V_w

suggests in this case that the molecules have greater opportunity for hydrophobic interaction than for the dispersion interaction with the receptor. This may be due to conformational change brought out by substituents, leading to a better orientation of molecules towards the hydrophobic site than the dispersion site of the receptor. However, since the activity has a parabolic relation with $\log P$, the increase in the activity with the increase in $\log P$ would be limited. According to Eq. 17, the optimum activity would correspond to $\log P = 1.23$. This optimization in the activity may be due to a limited steric bulk tolerance at the hydrophobic site of the enzyme.

Though V_w explicitly was not found to be related to the inhibition potency in this case, there was a notable mutual correlation between $\log P$ and V_w ($r=0.69$), meaning thereby that $\log P$ accounted for, to some extent, the size effect also. Therefore, it can be assumed that it was the size effect which produced the steric hindrance leading to a decrease in the activity beyond the optimum value of $\log P$.

In preceding cases, we noted the effect of the aromatic nature of substituents and the influence of the saturation of the ethenyl bridge between the lactone and aromatic moieties. The explicit influence of these two factors cannot be observed in this case, as both factors were taken into account in the calculation of $\log P$. If one tries both dummy parameters I (Eqs. 4 and 8) and D_2 (Eq. 12), previously defined to account for the effects of these two factors, the factors were found to be completely insignificant in the correlation (Eq. 18, compare this equation with Eq. 17).

$$\begin{aligned} -\log \text{IC}_{50} = & 0.382(\pm 0.186)\log P \\ & - 0.153(\pm 0.062)(\log P)^2 \\ & - 0.603(\pm 0.579)D \\ & - 0.207(\pm 0.507)I \\ & - 0.122(\pm 0.599)D_2 \\ & + 6.121 \\ n = & 23, r = 0.858, s = 0.422, \\ F_{5,17} = & 8.36 \end{aligned} \quad (18)$$

Tables III and IV both contain ether series. Although we found that, in the case of

molecules of Table III, only the steric factor was important, in the case of those of Table IV, the hydrophobic factor was also important along with the steric factor. We can combine both series to see the combined effect of $\log P$ and V_w . Equation 19 which we obtained for the combined series expresses that while $\log P$ and $(\log P)^2$ both are statistically significant at the 95% confidence level, of V_w and V_w^2 , only the latter is marginally significant. Since the coefficient of V_w^2 is negative, the molecular size accounts for only the steric effect which is largely incorporated in $\log P$ itself. Thus we find from this study that the HMG-CoA reductase enzyme possesses an active site which can be involved in the dispersion interaction and also a site which can be involved in hydrophobic interaction with the inhibitors. However, the involvement of these sites in dispersion or hydrophobic interaction will depend upon the proper orientation of the substituent or molecule towards these sites. Both active sites are, however, shown to possess a limited steric bulk tolerance.

$$\begin{aligned} -\log \text{IC}_{50} = & 0.431(\pm 0.183)\log P \\ & - 0.090(\pm 0.073)(\log P)^2 \\ & - 0.632(\pm 0.558)D \\ & + 0.565(\pm 1.664)V_w \\ & - 0.850(\pm 0.918)V_w^2 \\ & + 6.057 \\ n = & 38, r = 0.809, s = 0.470, \\ F_{5,32} = & 11.39 \end{aligned} \quad (19)$$

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