CORRELATION OF BIOLOGICAL ACTIVITIES OF MESOIONIC AND BENZ-FUSED MESOIONIC XANTHINE ANALOGS WITH VAN DER WAALS VOLUME AND MOLECULAR CONNECTIVITY

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The adenosine cyclic 3',5'-monophosphate (c-AMP) phosphodiesterase (PDE) inhibitory activity of a series of mesoionic 1,3,4-thiadiazolopyrimidines and of a group of benz-fused mesoionic xanthine analogs are found to be significantly correlated with the van der Waals volume (V_w) of the substituents or the first order valence connectivity index ($^1\chi^v$) of the molecule. From the correlating equations it is observed that the size of the substituents at certain positions, of pyrimidine ring particularly, in the molecule are determinative to the activity. Further based on these equations it may be suggested that PDE inhibition by this class of drugs involves either hydrophobic interaction or van der Waals type of interaction. In certain cases steric and electronic factors are also indicated to affect the inhibition.

Keywords — mesoionic xanthine analog; cyclic AMP phosphodiesterase inhibitor; structure-activity relationship; van der Waals volume; molecular connectivity

INTRODUCTION

Recently the derivatives of mesoionic 1,3,4-thiadiazolopyrimidine (Table I) and some benz-fused mesoionic xanthine analogs (Table II) have been reported to possess theophylline like activity, and therefore to act as inhibitors of adenosine cyclic 3',5'-monophosphate (c-AMP) phosphodiesterase (PDE).^{1,2)} The c-AMP PDE is an enzyme which converts c-AMP to adenosine 5'-monophosphate and is responsible, in part, for regulation of intracellular levels of this cyclic nucleotide, and hence the inhibitors of this enzyme may produce hypotensive activity. The mesoionic xanthine derivatives were found to display weak hypotensive effects *in vivo*.¹⁾ In their studies, Glennon *et al.*^{1,2)} presented a qualitative picture of their structure-activity relationship, but to provide a better rationale to design potent inhibitors, a quantitative structure-activity relationship (QSAR) study would be more useful. The present communication therefore aims at analyzing the activities of these inhibitors in relation to simple parameters, such as van der Waals volume (V_w) and the molecular connectivity

index (χ). V_w and χ both are theoretically accessible and simple in calculation, and provide quite vivid picture of structural influence on the activity. Both parameters have been therefore extensively used in QSAR studies.^{3,4)}

Calculation of V_w

The V_w is calculated by assuming spherical shapes for all atoms in accordance to Bondi⁵⁾ due to the absence of generally accepted pear shapes. We used the values of van der Waals radii and atomic volumes as listed by Moriguchi *et al.*⁶⁾ Since van der Waals radii are greater than covalent radii, a correction for sphere overlapping due to the covalent bonding between atoms was needed for the calculation of V_w for polyatomic molecules or groups. Such correction factors and a correction for branching were taken from the paper of Moriguchi *et al.*⁶⁾

Calculation of χ

The molecular connectivity index χ is calculated from the hydrogen suppressed graph of the molecule and the first-order valence connectivity index ($^1\chi^v$) which has been used in the present study is defined as,⁴⁾

$${}^1\chi^v = \Sigma(\delta_i^v \delta_j^v)^{-1/2} \quad (1)$$

where δ_i^v and δ_j^v are atom connectivity terms reflecting the number of non-hydrogenic atoms adjacent or connected to atoms i and j which are formally bonded, and the summation extends to all connections or edges in the hydrogen suppressed graph. The δ^v for any atom can be calculated by using the equation

$$\delta^v = Z^v - N_H \quad (2)$$

where Z^v is the number of valence electrons of the atom and N_H is the number of hydrogen

atoms attached to it. Their values have also been tabulated,⁴⁾ but for halogens which have identical Z^v values, Eq. 2 leads to identical value of δ^v , hence for them δ^v is calculated by,^{7,8)}

$$\delta^v = (Z^v - N_H)/(Z - Z^v) \quad (3)$$

where Z is the atomic number of the atom.

MATERIALS AND METHOD

The PDE inhibition activities of mesoionic and benz-fused mesoionic xanthine analogs listed in Tables I and II respectively are those

TABLE I. Derivatives of Mesoionic 1,3,4-Thiadiazolopyrimidine and Their *c*-AMP PDE Inhibition Activity and V_w and ${}^1\chi^v$ Values

Compd. No.	R_2	R_6	$V_w \cdot R_6$ ($10^2 \text{ \AA}^3$)	${}^1\chi^v$	pI_{50}		
					Obsd ^{a)}	Cald Eq. 6	Cald Eq. 7
1	H	H	0.056	4.599	3.11	2.78	2.86
2	H	Me	0.245	5.022	2.94	3.12	3.10
3	H	Et	0.399	5.583	3.26	3.40	3.41
4	H	<i>n</i> -Pr	0.553	6.083	3.60	3.68	3.70
5	H	iso-Pr	0.503	5.965	3.60	3.59	3.63
6	H	<i>sec</i> -Bu	0.657	6.503	3.63	3.87	3.93
7	H	<i>tert</i> -Bu	0.657	6.438	3.81	3.87	3.90
8	H	Amyl	0.861	7.083	3.81	4.24	4.26
9	H	Bzl	0.939	7.140	4.28	4.38	4.29
10	H	<i>p</i> -MeO-Bzl	1.174	7.663	^{b)}	4.80	4.58
11	H	<i>p</i> -Cl-Bzl	1.104	7.648	5.02	4.67	4.58
12	H	Ph	0.785	6.683	4.62	4.10	4.03
13	Me	Me	0.245	5.387	2.61	2.54	2.36
14	Me	Et	0.399	5.948	2.77	2.81	2.68
15	Et	Me	0.245	5.948	2.62	2.54	2.68
16	Et	Et	0.399	6.509	2.70	2.81	2.99

a) See ref. 1. b) Not reported.

evaluated by Glennon *et al.*^{1,2)} against the enzyme extracted from bovine heart. The V_w values listed in these Tables are only for the different substituents, while $^1\chi^v$ was evaluated for the whole molecule. The least square method was applied to find the correlation of inhibition activity with V_w and $^1\chi^v$.

($pI_{50} = -\log I_{50}$, I_{50} being the inhibitor's concentration leading to 50% enzyme inhibition) is found to have a linear significant correlation with $V_w \cdot R_6$ as shown by,

$$pI_{50} = 1.835 (\pm 0.696) V_w \cdot R_6 + 2.661 (\pm 0.474) \\ n=11, r=0.893, s=0.30, F_{1,9}=35.61 \quad (4)$$

RESULTS AND DISCUSSIONS

It should be noted that in Table I compounds 1–12 have the substituent at only 6-position. For such compounds the inhibition activity

where n is the number of data points, r is the correlation coefficient, s is the standard deviation and F is the F -ratio between the variances of calculated and observed activities. The data

TABLE II. *Benz-Fused Mesoionic Xanthine Analogs and Their c-AMP PDE Inhibition Activity and V_w and $^1\chi^v$ Values*

Compd. No.	R_1	R_3	R	V_w ($10^2 \text{ \AA}^3$)			$^1\chi^v$	pI_{50}		
				R_1	R_3	R		Obsd ^{a)}	Cald Eq. 11	Cald Eq. 17
1	CH ₃	H	H	0.245	0.056	0.056	6.090	3.49	3.64	3.62
2	CH ₃	CH ₃	H	0.245	0.245	0.056	6.513	3.57	3.64	3.57
3	CH ₃	C ₂ H ₅	H	0.245	0.399	0.056	7.073	3.82	3.64	3.57
4	iso-C ₃ H ₇	H	H	0.503	0.056	0.056	6.946	3.60	3.65	3.56
5	iso-C ₃ H ₇	CH ₃	H	0.503	0.245	0.056	7.369	3.54	3.65	3.59
6	iso-C ₃ H ₇	C ₂ H ₅	H	0.503	0.399	0.056	7.929	3.59	3.65	3.69
7	iso-C ₃ H ₇	<i>n</i> -C ₃ H ₇	H	0.503	0.553	0.056	8.429	3.64	3.65	3.83
8	iso-C ₃ H ₇	iso-C ₃ H ₇	H	0.503	0.503	0.056	8.312	3.72	3.65	3.79
9	cyclo-C ₃ H ₅	H	H	0.449	0.056	0.056	7.108	3.64	3.65	3.57
10	cyclo-C ₃ H ₅	C ₂ H ₅	H	0.449	0.399	0.056	8.091	3.79	3.62	3.73
11	cyclo-C ₃ H ₅	iso-C ₃ H ₇	H	0.449	0.503	0.056	8.474	^{b)}	3.62	3.85
12	cyclo-C ₃ H ₅	C ₂ H ₅	8-OCH ₃	0.449	0.399	0.304	8.407	3.96	3.95	3.82
13	cyclo-C ₃ H ₅	C ₂ H ₅	8-OC ₂ H ₅	0.449	0.399	0.458	8.994	4.16	4.16	4.05
14	cyclo-C ₃ H ₅	C ₂ H ₅	7,8-(CH ₃) ₂	0.449	0.399	0.490	8.711	^{b)}	4.21	3.93
15	cyclo-C ₄ H ₇	C ₂ H ₅	H	0.603	0.399	0.056	8.591	3.78	3.76	3.89
16	cyclo-C ₅ H ₉	C ₂ H ₅	H	0.757	0.399	0.056	9.091	3.99	4.03	4.10
17	cyclo-C ₆ H ₁₁	C ₂ H ₅	H	0.911	0.399	0.056	9.591	4.47	4.45	4.36
18	cyclo-C ₆ H ₁₁	C ₂ H ₅	8-OC ₂ H ₅	0.911	0.399	0.458	10.491	^{b)}	5.00	4.97

a) See ref. 2. b) Not reported.

within parentheses are 95% confidence intervals. In deriving Eq. 4 compound 10 was not included, as its activity was not reported.

The corresponding equation showing the correlation of the activity with $^1\chi^v$ for the same set of data is as follows.

$$pI_{50} = 0.599(\pm 0.252)^1\chi^v + 0.045(\pm 1.590) \\ n=11, r=0.873, s=0.33, F_{1,9}=28.93 \quad (5)$$

Now Eq. 4 accounts for about 80% of the variance in the activity and Eq. 5 for about 76% (r^2 ca. 0.80 and 0.76 respectively), and F -values in both the equations are significant at 99% level [$F_{1,9}(.01)=10.56$].

The remaining four compounds of Table I, in which 2-position is also substituted and the substituted group is either a methyl group or an ethyl group, can also be included in the regression analysis with an indicator variable I , taking $I=0$ for no substituent at 2-position, and $I=1$ for methyl or ethyl group at that position. The regression analysis then reveals the following equations correlating the activity with V_w and $^1\chi^v$.

$$pI_{50} = 1.810(\pm 0.583) V_w \cdot R_6 - 0.585(\pm 0.377) I \\ + 2.677(\pm 0.398) \\ n=15, r=0.944, s=0.26, F_{2,12}=48.97 \quad (6)$$

$$pI_{50} = 0.563(\pm 0.220)^1\chi^v - 0.944(\pm 0.394) I \\ + 0.268(\pm 1.391) \\ n=15, r=0.924, s=0.31, F_{2,12}=35.01 \quad (7)$$

Eqs. 6 and 7 express more significant correlation than Eqs. 4 and 5, and explicitly exhibit a decrease in the activity by the presence of methyl or ethyl group at 2-position.

In case of benz-fused analogs (Table II), there are three substituents: R_1 , R_3 and R . But in most of the cases $R=H$, so that if one takes only those compounds in which $R=H$, excluding of course those for which activity data are not reported, the regression analysis is found to reveal the fol-

lowing equation showing the effect of $V_w \cdot R_1$ and $V_w \cdot R_3$ on the activity.

$$pI_{50} = 0.965(\pm 0.621) V_w \cdot R_1 + 0.230 \\ (\pm 0.713) V_w \cdot R_3 + 3.194(\pm 0.340) \\ n=13, r=0.777, s=0.18, F_{2,10}=7.62 \quad (8)$$

Eq. 8 is not so highly significant but exhibits that there is positive effect on activity by an increase in the size of R_1 and R_3 both and that $V_w \cdot R_1$ produces a greater effect than $V_w \cdot R_3$. In fact the equation shows that $V_w \cdot R_3$ is not significant at 95% confidence level, hence if this term is excluded the correlation obtained (Eq. 9) is found to be almost equally significant with rather a smaller value of standard deviation.

$$pI_{50} = 1.024(\pm 0.574) V_w \cdot R_1 + 3.236(\pm 0.303) \\ n=13, r=0.764, s=0.17, F_{1,11}=15.42 \quad (9)$$

This leads to suggest that the size of R_3 substituent has in fact a negligible effect on the activity. Now the correlation expressed by Eq. 9 is significantly improved if square term of $V_w \cdot R_1$ is also included (Eq. 10). Thus Eq. 10 shows that there exists a parabolic correlation between the

$$pI_{50} = 3.977(\pm 0.426) - 2.085(\pm 1.635) V_w \cdot R_1 \\ + 2.856(\pm 1.466) (V_w \cdot R_1)^2 \\ n=13, r=0.925, s=0.11, F_{2,10}=29.62 \quad (10)$$

c-AMP PDE inhibition activity of the compounds and the size of their R_1 substituent, and that the activity will first decrease and then increase as the $V_w \cdot R_1$ increases. Further it reveals that the lowest activity will correspond to a value of $0.365 \times 10^2 \text{Å}^3$ of $V_w \cdot R_1$. This value of $V_w \cdot R_1$ approaches to the V_w of C_2H_5 group ($0.399 \times 10^2 \text{Å}^3$). Thus the substitution of a linear alkyl group upto $CH_2-C_2H_5$ i.e. C_3H_7 at nitrogen will lead to decrease the activity. However further substitution is either of a branched chain alkyl group or a cyclic group which are bigger in size than C_2H_5 group (Table II). It may

be therefore said that the increase in the activity after $R_1 = C_2H_5$ may not be due to only the bigger size of the substituent but due to the conformational requirements also. The linear chain may have more conformational flexibility than the branched chain or cyclic group. Probably the ability of the group to lie in the plane of the molecule will produce a positive effect on the activity. It may be therefore that a bigger linear chain due to its conformational flexibility may not lead to an increase in the activity but a further decrease in it.

If all those compounds for which R is something other than hydrogen and for which activity data are reported (there are only two such compounds 12 and 13) are also included in the regression analysis, the correlation obtained with square term in $V_w.R_1$ is as shown by,

$$pI_{50} = 3.901(\pm 0.399) - 2.083(\pm 1.539) V_w.R_1 + 2.854(\pm 1.379)(V_w.R_1)^2 + 1.356(\pm 0.524) V_w.R$$

$$n=15, r=0.940, s=0.10, F_{3,11}=27.93 \quad (11)$$

which shows that R will also produce a positive effect on the activity. Eq. 11 also leads to the same value of $V_w.R_1$ as Eq. 10 for the lowest activity of the compounds.

The inclusion of $V_w.R_3$ term was though found to improve the correlations expressed by Eqs. 10 and 11 slightly, its coefficient was found in neither case to be significant at 95% confidence level (Eqs. 12 and 13)

$$pI_{50} = 3.952(\pm 0.394) - 2.291(\pm 1.536) V_w.R_1 + 2.957(\pm 1.362)(V_w.R_1)^2 + 0.312(\pm 0.405) V_w.R_3$$

$$n=13, r=0.945, s=0.10, F_{3,9}=24.83 \quad (12)$$

$$pI_{50} = 3.881(\pm 0.365) - 2.292(\pm 1.435) V_w.R_1 + 2.957(\pm 1.270)(V_w.R_1)^2 + 0.312(\pm 0.377) V_w.R_3 + 1.277(\pm 0.490) V_w.R$$

$$n=15, r=0.956, s=0.09, F_{4,10}=26.37 \quad (13)$$

Now it may be noted that while substitution of methyl or ethyl group at 2-position in mesoionic 1,3,4-thiadiazolopyrimidine (Table I) is found to reduce the activity (Eq. 6 and 7), the substitution of methoxy or ethoxy group in the benzene nucleus of benz-fused mesoionic xanthine analogs (Table II) at 8-position is found to enhance the activity (Eq. 11). From this observation it appears that in the former case the alkyl groups might be producing some steric effects, while in the latter case the alkoxy groups might be affecting the activity by some of their electronic properties. It has been pointed out by Glennon *et al.*^{1,2)} that the benz-fusion of mesoionic thiazolopyrimidine (the molecule which has CH group in place of N-3 in thiadiazolopyrimidine) at its 2-3-bond region enhances the inhibition activity many-fold. This therefore suggests that conformational rigidity or the planarity of the molecule which the fused benzene ring may provide might be one of essential factors for the activity of the compounds and the alkoxy groups may simply add to this property of the molecules by participating in their electronic delocalization.

In order to reduce the number of variables in correlation in case of benz-fused xanthine analogs, if one uses ΣV_w (the sum of V_w of all substituents in a molecule) the significant correlations are again shown only by quadratic equations (Eqs. 14 and 15) which give $(V_w)_L$, the value of ΣV_w corresponding to the lowest activity as 0.567 and $0.619 \times 10^2 \text{ \AA}^3$, respectively.

$$pI_{50} = 3.982(\pm 0.702) - 1.509(\pm 1.868) \Sigma V_w + 1.330(\pm 1.146)(\Sigma V_w)^2$$

$$n=13, r=0.844, s=0.15, F_{2,10}=12.37 \quad (14)$$

$$pI_{50} = 4.059(\pm 0.704) - 1.624(\pm 1.712) \Sigma V_w + 1.312(\pm 0.965)(\Sigma V_w)^2$$

$$n=15, r=0.876, s=0.14, F_{2,12}=19.81 \quad (15)$$

Eq. 14 corresponds to Eq. 12 and Eq. 15 to 13. The corresponding equations showing the corre-

lation between the activity and $^1\chi^v$ are

$$\begin{aligned} pI_{50} &= 8.771(\pm 4.810) - 1.503(\pm 1.242) ^1\chi^v \\ &\quad + 0.108(\pm 0.079) (^1\chi^v)^2 \\ n &= 13, r = 0.886, s = 0.13, F_{2,10} = 18.32, \\ (^1\chi^v)_L &= 6.958 \end{aligned} \quad (16)$$

$$\begin{aligned} pI_{50} &= 8.457(\pm 4.652) - 1.434(\pm 1.203) ^1\chi^v \\ &\quad + 0.105(\pm 0.076) (^1\chi^v)^2 \\ n &= 15, r = 0.889, s = 0.13, F_{2,12} = 22.54, \\ (^1\chi^v)_L &= 6.829 \end{aligned} \quad (17)$$

Equally significant correlations of activity with V_w and with $^1\chi^v$ in each case is due to the existence of very high correlation between the two parameters (Eqs. 18 and 19). However from all these correlations we find that c-AMP PDE

$$\begin{aligned} ^1\chi^v &= 2.983(\pm 0.196) V_w R_6 + 4.417(\pm 0.133) \\ n &= 11, r = 0.996, s = 0.084, F_{1,9} = 1187 \end{aligned} \quad (18)$$

$$\begin{aligned} ^1\chi^v &= 3.259(\pm 0.386) \Sigma V_w + 4.923(\pm 0.371) \\ n &= 15, r = 0.981, s = 0.204, F_{1,13} = 332 \end{aligned} \quad (19)$$

inhibitory activity of mesoionic xanthine analogs is very much a function of the size of the substituents and of the degree of branching in them. Since both V_w and $^1\chi^v$ have been shown to be related with hydrophobic parameter of molecules in many cases,^{4,5)} the hydrophobic binding may be supposed to be most likely involved in the drug-receptor interaction in this case; otherwise the van der Waals interaction may be another possibility.^{3,f)} However, on the basis of only these studies it is difficult to say what are the exact mechanism and site of interaction of these molecules with phosphodiesterase enzyme.

The correlating equations obtained are however of high predictive value and can be used to predict the activity of any prospective congener in the series. The activity values reproduced by

these equations are found to be in good agreement with the observed ones (see Tables I and II).

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