EFFECT OF MOLECULAR SIZE ON THE ACTIVITY OF ADRIAMYCIN ANALOGUES: A QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDY

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The in vitro anti-tumor activity (inhibition of human lymphoblastic leukemia cells) of some adriamycin analogues is found to be significantly correlated with the van Waals volume ($V_w$) of the substituents. Activity is also found to be well correlated with first-order valence molecular connectivity index ($\chi^v$) but no correlation is found to exist between it and the hydrophobic parameter, log $P$ ($P$: octanol–water partition coefficient). On the basis of these findings, it is suggested that the activity would be affected by the steric influence and to some extent by the electronic character of the substituents. From the correlating equations, it is observed that the size of C-7 glycoside ring and that of NHR$_2$ group at its third position would greatly affect the activity. The size of C-14-R$_1$ however, is not found to have much effect on the activity.

Keywords — adriamycin analogue; anti-tumor activity; structure-activity relationship study; van der Waals volume; molecular connectivity

INTRODUCTION

Adriamycin and daunorubicin (Ia and Ib) are clinically important antitumor agents due to their effectiveness against a wide variety of solid tumors normally refractory to drug treatment.\(^1\)\(^-\)\(^3\) These anthracycline antibiotics are known to bind with deoxyribonucleic acid (DNA). The binding of these drugs with DNA was therefore suggested as a possible mechanism for their antitumor activity.\(^4\) However, recent studies have shown that there exists no general correlation between the antitumor activity and the DNA binding affinity of this class of drugs.\(^5\)\(^-\)\(^9\) Israel and coworkers\(^6\)\(^-\)\(^9\) synthesized a number of analogues of adriamycin and studied their structure-activity relationship in order to find a drug superior to adriamycin, as the latter is found to produce some side effects such as myelosuppression, cardiac toxicity, local tissue ulceration and necrosis and gastrointestinal toxicity. The present communication aims at analyzing the structure-activity relationships quantitatively. A quantitative structure-activity relationship (QSAR) study provides a better rationale to drug-design.

Many a drug activity has been found to depend upon the molecular size.\(^10\) It is one of the most fundamental characteristics of drug-structure controlling biological activity. The molecular size can be easily accounted for by van der Waals volume. The van der Waals volume ($V_w$) is related to various physicochemical properties of molecules.\(^11\)\(^-\)\(^12\) The biological activities of adriamycin analogues are,
therefore, analyzed in relation to this parameter. Significant correlations are found to exist between the activities of adriamycin analogues and $V_w$. The results are discussed in the following sections.

**METHOD**

**Materials** — The adriamycin analogues synthesized by Israel and Coworkers$^{6-9}$ are listed in Tables I and II along with their in vitro antitumor activity and DNA binding affinity. The in vitro antitumor activity is reported as ID$_{50}$, the minimum dose (mol/l) of the drug leading to 50% inhibition of human lymphoblastic leukemia cells (CCRF-CEM), and the DNA binding affinity as the absorbance ratio $A/A_0$, where $A$ is the absorbance of drug DNA mixture and $A_0$ the drug absorbance in the absence of DNA.

**Calculation of $V_w$** — The $V_w$ is calculated by assuming a spherical shape for all atoms in accordance with Bondi$^{13}$ 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.$^{11}$ 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.$^{11}$ Least squares method was applied to find the quantitative correlations between the activities and $V_w$ and other parameters used.

**RESULTS AND DISCUSSION**

In the first attempt, compounds 1–23 were considered in which the varying groups are C-14-R$_1$ and -NHR$_2$ present at the third position of the C-7 glycoside ring. For these compounds (excluding those for which activity data were uncertain) the in vitro antitumor activity (CCRF-CEM cell inhibition activity) is found to be correlated with $V_w$ of substituents as,

$$n = 18, r = 0.792, s = 0.384, \quad F_{2,15} = 12.64 \quad (1)$$

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 the 95% confidence intervals. Equation 1 represents a moderately significant correlation, the $F$-value being significant at the 99% level ($F_{2,12} (0.01) = 6.36$). The correlation is, however, significantly improved if an indicator variable, $I_1$, indicating whether R$_1$ is H, OH, or OR group or any SR or SeR group (R being alkyl or aryl moiety) with its value zero or unity correspondingly, is also introduced in the correlation (Eq. 2). In Eq. 2, however, the coefficient of $V_w \cdot R_1$ is not significant at the 95% confidence level. Hence the role of this variable on the activity may not be considered very significant. The correlation remains significant even if this parameter is excluded (Eq. 3). Equations 2 and 3, therefore, lead to the suggestion that the cell inhibition activity of adriamycin analogues largely depends upon the size of the NHR$_2$ group of the glycoside ring and little upon the size of R$_1$ group.

$$- \log \text{ID}_{50} = 7.732 - 1.692(\pm 0.413)$$
$$V_w \cdot \text{NHR}_2 - 0.229(\pm 0.305)$$
$$V_w \cdot I_1 - 0.949(\pm 0.365) \quad I_1$$

$$n = 18, r = 0.941, s = 0.221,$$
$$F_{3,14} = 35.78$$
$$F_{3,14}(0.01) = 5.56 \quad (2)$$

$$- \log \text{ID}_{50} = 7.663 - 1.693(\pm 0.432)$$
$$V_w \cdot \text{NHR}_2 - 1.137(\pm 0.278) \quad I_1$$

$$n = 18, r = 0.929, s = 0.233,$$
$$F_{2,15} = 47.33$$
$$F_{2,15}(0.01) = 6.36 \quad (3)$$

If one compares Eq. 3 with Eq. 1, one finds that the indicator variable is a better descriptor of the activity than $V_w \cdot R_1$. It is therefore apparent that, irrespective of its size, R$_1$ will lead to a drastic decrease in the activity if it contains S or Se.
<table>
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<th>Compd. No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>( V_W \cdot R_1 ) (10&lt;sup&gt;5&lt;/sup&gt;A&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>( V_W \cdot NHR_2 ) (10&lt;sup&gt;5&lt;/sup&gt;A&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>( V_W \cdot \text{gly} ) (10&lt;sup&gt;5&lt;/sup&gt;A&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>( \chi^V \cdot R_1 )</th>
<th>( \chi^V \cdot NHR_1 )</th>
<th>( \chi^V \cdot \text{gly} )</th>
<th>log P</th>
<th>( -\log ID_{50} ) (CCRF-CEM)</th>
<th>DNA binding affinity ( A/A_0 )</th>
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\(^{a)}\) Taken from refs. 6, 7 and 9. \(^{b)}\) Not included in correlation. \(^{c)}\) Could not be calculated. \(^{*}\) In place of six membered ring.
atom. This may be due to the change in the electronic character of the groups because of the presence of S or Se atom. Because of non-availability of specific values of electronic parameters of R_1-substituents, it has not been possible to ascertain the role of the electronic character of the groups.

To widen the scope of investigation, four more compounds (24–27) whose glycoside rings are five membered but have NHR_2 at 3-position were added in the analysis with a new indicator variable I_2. The indicator I_2 is defined to account for the variations in C-7 glycoside ring. It will take a value of zero when C-7 glycoside is a naturally occurring 3-amino sugar, daunessamine, or its derivative, and unity otherwise. The correlation for compounds 1–27 then becomes;

\[
-\log ID_{50} = 7.621 - 1.632(\pm 0.369) V_w \cdot NHR_2 - 1.115(\pm 0.251) I_1 - 0.632(\pm 0.293) I_2
\]

\[
 n=22, \ r=0.930, \ s=0.218, \ F_{3.18}=38.32 \ F_{3.18}(0.01)=5.09
\]

(4)

which shows that any substituent, other than a naturally occurring glycoside ring at C-7, will lead to a decrease in the activity.

Compounds considered thus far had NHR_2 group at 3-position of their glycoside ring. At one time DiMarco and Arcamone suggested that a 3-amino group of C-7 glycoside is required for complexation with DNA and for antitumor activity. This was challenged by the synthesis and evaluation of compounds 28 and 29 wherein the glycoside is a 2-amino sugar, β-D-glucosamine or its derivative. These two compounds are insufficient to draw any conclusion based on statistics. Here we made an attempt to show that these compounds can also be included along with other compounds. To consider these 2-amino sugar derivatives in regression the total volume of glycoside ring, \( V_w \cdot \text{gly} \), was considered. The correlating equation with additional parameters \( I_1 \) and \( I_2 \) is;

\[
-\log ID_{50} = 9.147 - 1.532(\pm 0.420) V_w \cdot \text{gly} - 1.080(\pm 0.301) I_1 - 0.913(\pm 0.324) I_2
\]

\[
 n=24, \ r=0.892, \ s=0.258, \ F_{3.20}=26.01 \ F_{3.20}(0.01)=4.76
\]

(5)

Equation 5 represents a significant correlation and the activity values reproduced from this equation are in good agreement with the observed ones. Hence NHR_2 group need not be necessarily at 3-position of glycoside ring for the activity of the compounds.

In contrast to the adriamycin analogues of Table I, the 9,10-anhydro and 9-deoxy compounds of this class (Table II, 30–40 and 41–43 respectively) do not show any linear relationship with \( V_w \) (Eq. 6).

\[
-\log ID_{50} = 6.192 + 0.333(\pm 0.730) V_w \cdot R_1 - 1.014(\pm 0.955) V_w \cdot NHR_2
\]

\[
 n=12, \ r=0.625, \ s=0.434, \ F_{2.9}=2.88
\]

(6)

Our attempts to improve Eq. 6 by considering higher order terms of \( V_w \) were not successful. A significant but parabolic correlation, however, could be obtained when \( V_w \cdot R_1 \) and \( V_w \cdot NHR_2 \) were combined and were used as \( \Sigma V_w \) (Eq. 7).

\[
-\log ID_{50} = 6.822 - 2.667(\pm 1.499) \Sigma V_w + 1.087(\pm 0.647)(\Sigma V_w)^2
\]

\[
 n=12, \ r=0.804, \ s=0.331, \ F_{2.9}=8.24 \ F_{2.9}(0.01)=8.02
\]

(7)

An attempt was made to distinguish 9,10-anhydro compounds from 9-deoxy compounds with the use of indicator variable \( I_3 \) taking values 0 and 1 for 9,10-anhydro and 9-deoxy compounds respectively. The resulting equation is

\[
-\log ID_{50} = 6.805 - 2.661(\pm 1.620) \Sigma V_w + 1.026(\pm 0.698)(\Sigma V_w)^2 + 0.042(\pm 0.546) I_3
\]
In Eq. 8, the coefficient of $I_3$ is not significant; there is no improvement in $r$ and the significance of F-value went down to the 95% level ($F_{3,8} \ (0.05) = 4.07$). In deriving all these equations, compound 32 was not included because it deviated greatly from the rest of the compounds in the preliminary plots (activity vs. $\Sigma V_w$). Its inclusion made Eq. 7 insignificant. No reason could be assigned to the behaviour of this compound. Compound 33 was not included because of its uncertain activity. However, the different nature of the dependence of activity on $V_w$ for the rest of the compounds of Table II from that for compounds of Table I may be due to variations in structure, caused by the elimination of 9-hydroxy group and/or the formation of 9,10-double bond. All these studies, however, suggest that the size of the substituents, in general, is a determining factor in the activity of adriamycin analogues. Discussion of the actual mechanism of drug-receptor interaction will follow.

In case of nonavailability of the values of electronic parameters such as $\sigma$, $\sigma^+$, $E_R$, etc. that describe the electronic character of groups explicitly, the molecular connectivity indices ($\chi$) have often been used \textsuperscript{14} to account for the electronic effect in the activity of drugs. We therefore calculated $\chi^V$ (first-order valence molecular connectivity) of the substituents, but unfortunately it had high collinear correlation with $V_w$ in each case ($r = 0.8 - 0.99$). Because of this, it could not be used with $V_w$ in the correlation, and alone, it did not produce any better correlation with activity than $V_w$, particularly in case of compounds of Table I (compare Eqs. 9, 10 and 11 with Eqs. 3, 4 and 5, respectively).

$$-\log ID_{50} = 7.284 - 2.579(\pm 0.848) \chi^v \cdot R_2 - 1.008(\pm 0.323) I_1 \quad n = 18, \ r = 0.893, \ s = 0.284, \ F_{2,15} = 29.41$$

(9)

**TABLE II. $V_w$ and Other Parameters with CCRF-CEM Cell Growth Inhibitory Activity of 9,10-Anhydro and 9-Deoxy Adriamycin Analogues**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$V_w \cdot R_1$</th>
<th>$V_w \cdot NHR_2$</th>
<th>$\chi^v \cdot R_1$</th>
<th>$\chi^v \cdot NHR_2$</th>
<th>$-\log ID_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>($10^2$ A$^2$)</td>
<td>($10^2$ A$^2$)</td>
<td></td>
<td></td>
<td>Obsd$^a)$</td>
</tr>
<tr>
<td>30</td>
<td>H</td>
<td>H</td>
<td>0.056</td>
<td>0.177</td>
<td>0</td>
<td>0</td>
<td>3.76</td>
</tr>
<tr>
<td>31</td>
<td>H</td>
<td>COCF$_3$</td>
<td>0.056</td>
<td>0.652</td>
<td>0</td>
<td>0.369</td>
<td>4.89</td>
</tr>
<tr>
<td>32</td>
<td>H</td>
<td>COCF$_2$CH$_3$</td>
<td>0.056</td>
<td>0.898</td>
<td>0</td>
<td>0.980</td>
<td>5.30</td>
</tr>
<tr>
<td>33</td>
<td>H</td>
<td>CO(CF$_2$)$_2$CF$_3$</td>
<td>0.056</td>
<td>1.144</td>
<td>0</td>
<td>0.421</td>
<td>5.54</td>
</tr>
<tr>
<td>34</td>
<td>OH</td>
<td>H</td>
<td>0.137</td>
<td>0.177</td>
<td>0.316</td>
<td>0</td>
<td>3.03</td>
</tr>
<tr>
<td>35</td>
<td>OH</td>
<td>COCF$_3$</td>
<td>0.137</td>
<td>0.652</td>
<td>0.316</td>
<td>0.369</td>
<td>4.16</td>
</tr>
<tr>
<td>36</td>
<td>OH</td>
<td>COCF$_2$CF$_3$</td>
<td>0.137</td>
<td>0.898</td>
<td>0.316</td>
<td>0.395</td>
<td>4.57</td>
</tr>
<tr>
<td>37</td>
<td>OH</td>
<td>CO(CF$_2$)$_2$CF$_3$</td>
<td>0.137</td>
<td>1.144</td>
<td>0.316</td>
<td>0.421</td>
<td>4.81</td>
</tr>
<tr>
<td>38</td>
<td>O-Valerate</td>
<td>COCF$_3$</td>
<td>1.001</td>
<td>0.652</td>
<td>3.335</td>
<td>0.369</td>
<td>6.85</td>
</tr>
<tr>
<td>39</td>
<td>O-Valerate</td>
<td>COCF$_2$CF$_3$</td>
<td>1.001</td>
<td>0.898</td>
<td>3.335</td>
<td>0.395</td>
<td>7.26</td>
</tr>
<tr>
<td>40</td>
<td>O-Valerate</td>
<td>CO(CF$_2$)$_2$CF$_3$</td>
<td>1.001</td>
<td>1.144</td>
<td>3.335</td>
<td>0.421</td>
<td>7.50</td>
</tr>
<tr>
<td>41</td>
<td>H</td>
<td>H</td>
<td>0.056</td>
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<tr>
<td>42</td>
<td>H</td>
<td>COCF$_3$</td>
<td>0.056</td>
<td>0.652</td>
<td>0</td>
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<tr>
<td>43</td>
<td>O-Valerate</td>
<td>COCF$_3$</td>
<td>1.001</td>
<td>0.652</td>
<td>3.335</td>
<td>0.369</td>
<td>7.01</td>
</tr>
</tbody>
</table>

$a)$ Taken from refs. 7 and 8.  
$b)$ Not included in correlations, see text.
\[- \log ID_{50} = 6.958 - 1.774(\pm 0.852) \chi^v \cdot R_2 \\
\quad - 0.698(\pm 0.323) I_1 \\
\quad + 0.031(\pm 0.410) I_2 \\
n = 22, r = 0.805, s = 0.352, \\
F_{3,18} = 11.04 \tag{10}\]

\[- \log ID_{50} = 15.840 - 2.598(\pm 0.918) \chi^v \cdot \text{gly} \\
\quad - 0.876(\pm 0.358) I_1 \\
\quad - 1.631(\pm 0.698) I_2 \\
n = 24, r = 0.823, s = 0.336, \\
F_{3,20} = 14.05 \tag{11}\]

In case of compounds of Table II, the correlations obtained between \(\chi^v\) and activity were, however, better than those obtained between \(V_w\) and the activity (compare Eqs. 12, 13 and 14 with Eqs. 6, 7 and 8, respectively).

\[- \log ID_{50} = 6.204 + 0.117(\pm 0.179) \chi^v \cdot R_1 \\
\quad - 2.361(\pm 1.597) \chi^v \cdot R_2 \\
n = 12, r = 0.744, s = 0.372, \\
F_{2,9} = 5.59 \tag{12}\]

\[- \log ID_{50} = 6.426 - 2.298(\pm 0.850) \Sigma \chi^v \\
\quad + 0.564(\pm 0.209)(\Sigma \chi^v)^2 \\
n = 12, r = 0.898, s = 0.245, \\
F_{2,9} = 18.71 \tag{13}\]

\[- \log ID_{50} = 6.564 - 2.506(\pm 0.841) \Sigma \chi^v \\
\quad + 0.614(\pm 0.206)(\Sigma \chi^v)^2 \\
\quad - 0.266(\pm 0.365) I_3 \\
n = 12, r = 0.926, s = 0.223, \\
F_{3,8} = 15.94 \tag{14}\]

But as the coefficient of \(V_w \cdot R_1\) is not significant at 95% confidence level in Eq. 6, so is the coefficient of \(\chi^v \cdot R_1\) in Eq. 12. The coefficient of \(I_3\) is neither significant in Eq. 8 nor in Eq. 14 at the 95% confidence level. Hence one can say that it would scarcely matter whether there is a double bond or a single bond between the 9 and 10 positions. However, the unsaturation in the substituents appears to have some effect on the activity. This is indicated by \(\chi^v\) term. Eq. 13 shows that up to a particular value of \(\Sigma \chi^v\) (\(\Sigma \chi^v = 2.037\)), the activity decreases and then starts increasing. Now for given \(R_1\) and \(R_2\) substituents for whose \(\Sigma \chi^v \geq 2.037\), the activity of compounds can be increased by making the groups unsaturated or replacing a few atoms by more electronegative atoms as these two factors will lead to the decrease in the value of \(\chi^v\).\(^{14}\)

Thus unsaturation and/or the presence of more electronegative atoms in smaller substituents will make them more effective.

However, the hydrophobicity was not found to play any role in the anti-tumor activity of adriamycin analogues. In neither case (Table I or II) was the activity found to have any significant correlation with \(\log P\) (Eqs. 15 and 16).

\[- \log ID_{50} = 6.450 + 0.109(\pm 0.441) \log P \\
\quad - 0.017(\pm 0.038)(\log P)^2 \\
\quad - 0.403(\pm 0.695) I_1 \\
\quad - 0.453(\pm 0.598) I_2 \\
n = 21, r = 0.537, s = 0.532, \\
F_{4,16} = 1.62 \tag{15}\]

\[- \log ID_{50} = 9.535 - 1.501(\pm 2.113) \log P \\
\quad + 0.134(\pm 0.193)(\log P)^2 \\
n = 12, r = 0.475, s = 0.490, \\
F_{2,9} = 1.31 \tag{16}\]

In deriving Eq. 15, compounds 17, 23 and 29 were further excluded in addition to those already excluded in Eq. 5. The reason for excluding these additional compounds was the difficulty in calculating the \(\log P\) values for these compounds. The \(\log P\) values were calculated by the fragments method as described by Hansch and Leo.\(^{15}\)

Equation 16 was obtained corresponding to Eq. 7. \(I_3\) parameter was not included in this correlation as it was considered in the calculation of \(\log P\).

In spite of the fact that \(\log P\) was found to have significant correlation \((r > 0.95)\) with \(V_w \cdot R_2\) and \(V_w \cdot R_1\) taken together in each case, it was not found to have any significant correlation with the activity. It indicates, therefore, that the dependence of the anti-tumor activity of adriamycin analogues on \(V_w\) and \(\chi^v\) may be due to
the steric hindrance that the substituents may provide and to the unsaturation and/or the electronegativity of the atoms present in them.

As regards the correlation of DNA binding affinity of these drugs with $V_w$, $\chi^*$, or $\log P$, no conclusive correlation can be obtained as there is not much variation among the data points. All compounds appear to have almost equal capability of interacting with DNA, though they have widely different antitumor activity. This leads to the suggestion that antitumor activity and the interaction of the molecules with DNA involve quite different mechanisms.

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**REFERENCES**


