Activity Trends in Desoxy Anthrapyrazoles: The Influence of Molar Volume, Polarizability and Lipophilicity of N₂ C₅ Side Chains on Their Anticancer Response

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Abstract

QSAR methodology was used to assess the effects of lipophilicity (logP), molar volume (MV) and polarizability (pl) of the side chains at N₂ and C₅ of 20 known desoxy anthrapyrazoles on their in vitro anticancer activity expressed as the negative logarithm of the inhibitory concentration of 50% of L1210 murine leukemia cell line (1/logIC₅₀). The main data set shows poor correlations between biological response and the descriptors with exception of MV of the C₅ side chain, where a moderate correlation was discerned ($R^2 = 0.60$, $n = 18$, two outliers). To extract more information regarding mechanism, the main data set was visually classified to three clusters depending on N₂ side chain. Cluster 1 containing six 5-substituted 2-[(2-hydroxyethyl) amino]ethyl anthrapyrazoles; cluster 2 contains ten 5-substitutes 2-(diethyl amino)ethyl anthrapyrazoles and cluster 3 contains four anthrapyrazoles with miscellaneous substituents at both N₂ and C₅. For cluster 1, MV and pl of C₅ show high correlation with biological response ($R^2 = 0.75$ and 0.72 respectively) while logP gives a weak correlation ($R^2 = 0.44$). For cluster 2, the correlations of logP and pl of C₂ side chain are higher ($R^2 = 0.66$ and 0.62 respectively) compared with MV ($R^2 = 0.16$). Cluster 3 shows very poor correlation with all descriptors ($R^2 ≤ 0.3$). This indicates mechanistic distinction between the three clusters. Derived descriptors which represent the difference between the descriptors of N₂ and C₅ side chains where used to explore the presence of interplay between these descriptors in affecting variability of the biological response.
1. Introduction

Anthrapyrazoles (Figure 1) are totally synthetic anti cancer agents that exhibit a good efficacy in the treatment of breast cancer [1] [2].

They relate to the anthracene-9, 10-dione based family of anticancer agents which include anthracyclines, e.g., Daunorubicin and doxorubicin [3]. Duano-rubicin and doxorubicin, in addition to alkylaminoalkyl anthracene-9, 10-diones such as ametantrne and mitoxantrone [4].

Different mechanisms had been suggested to account for anticancer activity of anthracenediones-based anticancer chemotherapeutic agent like DNA intercalation [5], Topoisomerase II inhibition [6], generation of reactive oxygen species (ROS) among others. ROS generation is associated with all quinone containing anticancer agent and is an outcome of flavoenzyme-assisted redox cycling inside biological systems [7]. This redox cycling plays an important role in cytotoxicity of these compounds [8]. Regardless of the mechanism by which a given class of quinonoid drugs exerts its activity, substituents do indeed modify this activity either by enhancing, retarding or even banning it altogether. This is evident from the fact that from the multitude known anthrapyrazoles, only piroxantrone and losoxantrone has surfaced as potent clinical agents [9].

Similar argument could be assumed for anthracyclines and indeed for all other drugs. We reason that some kind of interplay may exist between substituents restricted in N2 and C5 positions of the basic nucleus which lead eventually to the observed alteration of activity profile of individual compound relative the parent anthrapyrazole. Shwalter et al. [1] found that basic side chains with two to three carbon spacers between the nitrogens, at positions N2 and C5 of the anthrapyrazole ring structure, enhanced in vivo antitumor activity against P388 murine leukemia. DNA binding and intercalation were also influenced by the side chains at N2 and C5.

Quantitative structure activity relationships is a field of science inaugurated in 1964 by seminal two papers by Hansch and Fujita [10], on one hand, and Free and Wilson [11] in the other. Since then tremendous strides were made in

![Figure 1. General structure of desoxy anthrapyrazoles.](image-url)
Figure 2. Plotting of $1/\log IC_{50}$ against MVR2 of 5-substituted 2-[2-[(2-hydroxyethyl) amino]ethyl]anthra [1,9-cd]pyrazol-6(2H)-ones.

This field and indeed, in all *in silico* methods. Now QSAR methodology is a fully mature area of science which endeavor to correlate molecular descriptor or physicochemical parameters with biological response. The correlation is formulated in the form of a mathematical equation with statistical validation metrics. The formulated equation could be linear or non linear. Various algorithms had been devised to follow up relations between molecular and biological parameters. These include linear regression, partial least square regression, neural networks among others [12]. The algorithm used in present study is non linear regression. The physicochemical descriptors used in the present study are two geometrical parameters polarizability (pol) and molar volume (MV), in addition to lipophilicity parameter (logP).

Polarizability is a measure of the ease with which the electrons of a molecule are distorted. It is the basis for evaluating the nonspecific attraction forces (London dispersion forces) that arise when two molecules approach each other. Each molecule distorts the electron cloud of the other and thereby induces an instantaneous dipole. The induced dipoles then attract each other [13]. Polarizability has been shown to play an important role in chemical-biological interactions. The first attempt to apply molecular refractivity in terms of the Polarizability was made by Pauling and Pressman [14]. Many empirical quantum mechanical methods of differing accuracy have been proposed for calculating molecular polarizabilities [15]-[20] and [21]. Molecular polarizability influences several other physical properties, including electronegativity [22] [23] [24] and [25], dipole moment [26] and ionization potential [27].

Molar volume (MV) is the geometrical-polarizability descriptor obtained from chemical structure according to the following formula:

$$\text{MV} = \frac{M_w}{\rho}$$

where $M_w$ is the molecular weight and $\rho$ is density. This parameter is closely related to the other two polarizability descriptors: molar refractivity and parachor but while the latters are additive, molar volume is strictly not. It is typically the volume enclosed within molecular surface area which is the area of outer surface of the volume from which water molecules are excluded [28].

logP is the calculated logarithm of octanol/water partition coefficient. It is the mostly used physicochemical parameters in QSAR studies [29]. It mimics the
partitioning happening for xenobiotic between aqueous and lipid environments inside the body. The pharmokinetic stage in drug journey through various barriers inside the organism is monitored by this descriptor.

This paper is a continuation of our customary interest in mechanistic aspect of quionoid anticancer drugs [30] [31].

2. Material and Methods

The biological data were taken from literature [1]. Molar volumes (MV), polarizabilities (pl) and lipophilicities (logP) were calculated using ACD lab chemsketch 15 freeware, Advanced Chemistry Development Toronto Canada (http://www.acdlabs.com/). ΔMV_{N2C5}, Δpl_{N2C5}, and ΔlogP_{N2C5} parameters were obtained by subtracting the value of molar volume of substituent at C5 from that of N2 on the anthrapyrazole ring system. Parent compound from which the side chain at N2 and C5 were derived, were used for calculating the molar volume. General chemical structure of anthrapyrazoles used in this analysis is illustrated in Figure 1 and their individual chemical structures are illustrated in Table 1. The calculated parameters (MV, pl and logP) and the derived parameters (ΔMV_{N2C5}, Δpl_{N2C5} and ΔlogP_{N2C5}) are reported in Table 2.

Initially the R² statistic were calculated for all the sets obtained by pairing each of the calculated and the derived parameters with anticancer activity (1/logIC50) to specify if any correlation exists between them. Then regression analysis was carried out.

3. Results and Discussion

The dependence of biological activity of the 6 deoxy anthrapyrazoles in which R₂ = -CH₂CH₂NHCH₂CH₂OH on molar volume (MV_{R₂}) of the C₅ side chain was found to be parabolic as shown by the Equation (1) below

\[
\frac{1}{\log IC_{50}} = 0.0689MV_{R₂} - 0.0003(MV_{R₂})^2 + 3.4201
\]

n = 6, R² = 0.7535, s (1/logIC₅₀) = 0.595, s (residual) = 0.295; F = 4.585.

The data set used to derive the above equation comprize compounds 4 - 9 (Table 1). Equation (2) correlates polarizability of C₅ side (pl_{R₂}) chain to biological activity for the same series

\[
\frac{1}{\log IC_{50}} = -0.0177(pl_{R₂})^2 + 0.448pl_{R₂} + 4.483
\]

n = 5, R² = 0.7229, s (logIC₅₀) = 0.595, s (residual) = 0.313068; F = 3.913.

Equation (3) correlates the logarithm of octanol/water partition coefficient (logP_{R₂}) of C₅ side chain to biological activity for same series

\[
\frac{1}{\log IC_{50}} = 0.8945(logP_{R₂})^2 + 1.5659logP_{R₂} + 6.825
\]

n = 5, R² = 0.823, s (logIC₅₀) = 0.572, s (residual) = 0.240768, F = 4.65.

Compound 8 is considered to be an outlier.

All the above 3 equations show reasonable statistics. For instant in Equation (1), F-test indicate that the probability that there is no relationship between
Table 1. Individual structure of used Anthrapyrazole compounds.

| No | H-R1          | H-R2          | No | H-R1          | H-R2          |
|----|---------------|---------------|----|---------------|---------------|
| 1  | H-CH₂CH₂OH    | NH₂CH₂CH₂NHCH₂CH₂OH | 11 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂NH₂  |
| 2  | H-CH₂CH₂OH    | NH₂CH₂CH₂NEt₂  | 12 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂NHMe |
| 3  | H-CH₂CH₂NH₂   | NH₂CH₂CH₂NHCH₂CH₂OH | 13 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂NHCH₂CH₂OH |
| 4  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂       | 14 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂NEt₂ |
| 5  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂CH₂OH   | 15 | HCH₂CH₂NEt₂    | NH₂(CH₂)₂NEt₂ |
| 6  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂CH₂NH₂  | 16 | HCH₂CH₂NEt₂    | NH₂(CH₂)₃NEt₂ |
| 7  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂CH₂NHCH₂CH₂OH | 17 | HCH₂CH₂NEt₂    | NH₂(CH₂)₄NEt₂ |
| 8  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂CH₂NEt₂ | 18 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂-c-(CH₂CH₂)₂O |
| 9  | HCH₂CH₂NHCH₂CH₂OH | NH₂CH₂CH₂NH₂  | 19 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂-c-N(CH₂CH₂)₂NH |
| 10 | HCH₂CH₂NEt₂   | NH₂(CH₂)₂CH₂   | 20 | HCH₂CH₂NEt₂    | NH₂CH₂CH₂-c-N(CH₂CH₂)₂Ncbz |

Table 2. Parameters and biological activity for compounds 1 - 20.

| No | MV₁RH₁ cm⁻³ | MV₁RH₂ cm⁻³ | ΔMV₁N₂C₅ cm⁻³ | PL₁RH₁ 10⁻⁻¹⁴ cm⁻³ | PL₁RH₂ 10⁻⁻¹⁴ cm⁻³ | ΔPL₁N₂C₅ 10⁻⁻¹⁴ cm⁻³ | logP₁RH₁ | logP₁RH₂ | ΔLogP₁N₂C₅ | 1/logIC₅₀ μM |
|----|--------------|--------------|---------------|---------------------|---------------------|----------------------|----------|----------|------------|-------------|
| 1  | 59.0         | 104.5        | −45.5         | 5.09                | 11.59               | −6.5                 | −0.19    | −1.69    | 1.5        | 5.7447      |
| 2  | 59.0         | 138.5        | −79.5         | 5.09                | 14.7                | −9.61                | −0.19    | 0.21     | −0.4       | 6.05552     |
| 3  | 65.2         | 104.5        | −39.3         | 5.88                | 11.59               | −5.71                | −0.13    | −1.69    | 1.56       | 7.09691     |
| 4  | 100.8        | 48.7         | 52.1          | 10.19               | 4.05                | 6.14                 | −0.44    | −0.66    | 0.22       | 6.13077     |
| 5  | 100.8        | 62.7         | 38.1          | 10.19               | 6.49                | 3.7                  | −0.44    | −1.31    | 0.87       | 6.12494     |
| 6  | 100.8        | 68.9         | 31.9          | 10.19               | 7.28                | 2.91                 | −0.44    | −2.04    | 1.6        | 7.16115     |
| 7  | 100.8        | 104.5        | −3.7          | 10.19               | 11.59               | −1.4                 | −0.69    | −1.69    | 1          | 7.13077     |
| 8  | 100.8        | 105.4        | −4.6          | 10.19               | 11.03               | −0.84                | −0.44    | −0.85    | 0.41       | 7.4948      |
| 9  | 100.8        | 138.5        | −37.7         | 10.19               | 14.7                | −4.51                | −0.44    | 0.21     | −0.65      | 7.22185     |
| 10 | 134.8        | 131.2        | 3.6           | 13.3                | 13.23               | 0.07                 | 1.66     | 1.99     | −0.33      | 5.69897     |
| 11 | 134.8        | 68.9         | 65.9          | 13.3                | 7.28                | 6.02                 | 1.66     | −2.04    | 3.7        | 7.33724     |
| 12 | 134.8        | 90.5         | 44.3          | 13.3                | 9.14                | 4.16                 | 1.66     | −1.15    | 2.81       | 7.56864     |
| 13 | 134.8        | 104.5        | 30.3          | 13.3                | 11.59               | 1.71                 | 1.66     | −1.69    | 3.35       | 7.49485     |
| 14 | 134.8        | 138.5        | −3.7          | 13.3                | 14.7                | −1.4                 | 1.66     | 0.21     | 1.45       | 6.40894     |
| 15 | 134.8        | 155          | −20.2         | 13.3                | 16.54               | −3.24                | 1.66     | 0.77     | 0.89       | 6.284       |
| 16 | 134.8        | 171.5        | −36.7         | 13.3                | 18.38               | −5.08                | 1.66     | 1.07     | 0.59       | 6.20761     |
| 17 | 134.8        | 221          | −86.2         | 13.3                | 23.89               | −10.59               | 1.66     | 2.36     | −0.7       | 6.20066     |
| 18 | 134.8        | 138.7        | −3.9          | 13.3                | 14.87               | −1.57                | 1.66     | −1.01    | 2.67       | 6.31875     |
| 19 | 134.8        | 143.7        | −8.9          | 13.3                | 15.56               | −2.26                | 1.66     | −0.86    | 2.52       | 6.301       |
| 20 | 134.8        | 237          | −102.2        | 13.3                | 29.7                | −16.4                | 1.66     | 2.12     | −0.46      | 6.4089      |

The correlation is depicted graphically in Figure 2.

Biological activity and MV₂ is less than 5%. The standard deviation of the residuals calculated from the model (0.295) is smaller than the standard deviation of the original data (0.595). The correlation is depicted graphically in Figure 2.
It is apparent from Equation (3) that anticancer activity of this particular series of anthrapyrazoles show excellent dependence on log PR$_2$. This is to be expected since log P is the parameter that encodes partitioning behaviors of xenobiotics via cell membrane.

MV$_{R_2}$ gives with 1/logIC$_{50}$ a good parabolic correlation ($R^2 = 0.76$) while pl$_{R_2}$ gives a weaker correlation ($R^2 = 0.72$). This suggests slightly higher contribution MV$_{R_2}$ to the observed activity compared to pl$_{R_2}$. It is well known that biological activity of anthrapyrazole is due to their capability to bind and to intercalate to DNA. The former is due largely to the effect of substituents at N$_2$ and C$_5$ and the latter is enhanced by certain features of the rigid chromophore, e.g., presence of hydroxyl group at Ring A. It may be suggested that MV$_{R_2}$ contributes to the capability of anthrapyrazoles to intercalate into DNA possibly by adding to the overall molar volume and modifying the orientation of the intercalator in-between DNA double helical structure. On the other hand, pl$_{R_2}$ contributes to DNA binding ability of anthrapyrazole since it is the basis for evaluating the nonspecific attraction forces (London dispersion forces) that may arise between the molecule and DNA.

The second subset where side chain at N$_2$ is fixed as 2-(diethylamino) ethyl (R$_1$ = −H$_2$CH$_2$NEt$_2$) contain compounds 11-20. Upon similar treatment as above, the following correlations were found:

\[
\frac{1}{\log IC_{50}} = 0.0001(MV_{R_2})^2 + 0.0377MV_{R_2} + 9.8842
\]

\(n = 10, \ R^2 = 0.7982, \ s(\log IC_{50}) = 0.568, \ s(\text{residual}) = 0.266, \ F = 13.827\)  
\[
\frac{1}{\log IC_{50}} = 0.0066(pl_{R_2})^2 - 0.302pl_{R_2} + 9.5374
\]

\(n = 10, \ R^2 = 0.7973, \ s(\log IC_{50}) = 0.568, \ s(\text{residual}) = 0.256, \ F = 13.767\)  
\[
\frac{1}{\log IC_{50}} = 0.12(\log P_{R_2})^2 - 0.302\log P_{R_2} + 6.383
\]

\(n = 10, \ R^2 = 0.646, \ s(\log IC_{50}) = 0.568, \ s(\text{residual}) = 0.337, \ F = 14.64\).

For this subgroup, MV$_{R_2}$ and pl$_{R_2}$ give a better parabolic correlation ($R^2s \sim 0.80$) compared with those of the first subgroup ($R^2s \sim 0.75$ and 0.73 for MV$_{R_2}$ and pl$_{R_2}$ respectively), in contrast to log P$_{R_2}$ which gives a poorer correlation ($R^2 = 0.65$) compared to that of the first subgroup($R^2 = 0.82$). This indicates a modified mechanistic profile in which steric and polarizability effects have a greater influence on the activity while lipophilicity has a lesser influence as compared to first subgroup. The correlation between MV$_{R_2}$ and 1/logIC$_{50}$ for compounds 11-20 is shown graphically in Figure 3.

Third group of compounds contains compounds 1, 2 and 3 in addition to compounds 8 and 10 which were removed as outliers from the first and the second subgroups. The following equations were obtained for the substituents at N$_2$

\[
\frac{1}{\log IC_{50}} = -0.001(MV_{R_1})^2 + 0.238MV_{R_1} - 3.597
\]

\(n = 5, \ R^2 = 0.855, \ s(1/\log IC_{50}) = 0.824, \ s(\text{residuals}) = 1.68\)  
\[
\frac{1}{\log IC_{50}} = -0.116(pl_{R_1})^2 + 2.087pl_{R_1} - 1.560
\]
Figure 3. Plotting of 1/logIC₅₀ against MVR₂ of 5-substituted 2-[2-[(2-(diethylamino)ethyl]anthra [1,9-cd]pyrazol-6(2H)-ones.

\[ n = 5, R^2 = 0.895, s(\frac{1}{\log IC_{50}}) = 0.824, s(\text{residuals}) = 0.265. \]

\[ \frac{1}{\log IC_{50}} = 1.527(\log P_{R1})^2 - 2.632\log P_{R1} + 5.863 \] (9)

\[ n = 5, R^2 = 0.5, s(\frac{1}{\log IC_{50}}) = 0.824, s(\text{residuals}) = 0.584. \]

As it is apparent from Equations (7)-(9), the third subgroup shows good correlations between MVR₁ and plR₁ with activity while logP gives a moderate correlation.

The side chain at C₂ gives the following equations and metrics:

\[ \frac{1}{\log IC_{50}} = 0.001(MVR_{R2})^2 - 0.444MVR_{R2} + 34.3 \] (10)

\[ n = 5, R^2 = 0.334, s(\frac{1}{\log IC_{50}}) = 0.824, s(\text{residuals}) = 3.00. \]

\[ \frac{1}{\log IC_{50}} = 0.323(pl_{R2})^2 - 8.643pl_{R2} + 63.33 \] (11)

\[ n = 5, R^2 = 0.626, s(\frac{1}{\log IC_{50}}) = 0.824, s(\text{residuals}) = 0.503. \]

\[ \frac{1}{\log IC_{50}} = 0.323(pl_{R2})^2 - 8.643pl_{R2} + 63.33 \] (12)

\[ n = 5, R^2 = 0.316, s(\frac{1}{\log IC_{50}}) = 0.824, s(\text{residuals}) = 0.68. \]

Equations (10)-(12), shows poor correlation between MVR₂ and logP₂ with activity while pl₂ gives a mild correlation. This indicates that N₂ substituents influence the activity more than C₂ substituents for this subgroup.

The present analysis shows that when N₂ side chains are held constant, the activity depends on C₂ side chains but when the N₂ substituents are varied, the activity depends on them rather C₂ side chains.

To explore the combined effect of both N₂ and C₅ substituents on biological activity, new parameters ΔMV䓬C₅, ΔplₙC₅, and ΔlogPₙC₅ which represent the difference between MV, pl and log P of N₂ and C₅ side chains respectively, were introduced. Visual clustering yields poor results with these derived descriptors, in contrast to regression clustering which separates the original data set into 2 clusters for each descriptor, with expelling of a few data points as outliers. This indicates a kind of interplay between the two side chains in affecting the variability of the biological response.

For ΔMVₙC₅ Significant parabolic correlation were found to 1/logIC₅₀ for 13 out of the 20 anthrapyrazoles (R² = 0.816). Six of the remaining seven compounds which do not fit into above mentioned correlation give a parabolic cor-
relation \( R^2 = 0.88 \) while one compound was considered to be as an outlier. For \( \Delta \rho \text{N2C5} \) a parabolic correlation were discerned for 12 of them \( R^2 = 0.778 \). Six of the remaining compound shows a different parabolic correlation \( R^2 = 0.84 \) and two were considered as outliers. \( \Delta \log \text{P}\text{N2C5} \) show linear correlation for 15 compounds \( R^2 = 0.717 \). The remaining 5 compounds correlate parabolically to \( 1/\log IC_{50} \) \( R^2 = 0.846 \). This advocates the use of derived parameters such as \( \Delta MV \text{N2C5}, \Delta \rho \text{N2C5} \) and \( \Delta \log \text{P}\text{N2C5} \) to explore the interplay of local molecular descriptors on the global activity of different molecular entity.

4. Conclusion

For the desoxy anthrapyrazoles studied in the present paper, the side chain at N2 determines the segregation of the compounds into three subgroups. One group contains six compounds with 2-hydroxyethylaminoethyl side chain at N2. The second group contains 2-(diethylamino)ethyl side chain at N2. The third group contains miscellaneous side chains at N2. The biological response of the first and the second subgroups depends parabolically on the molar volume, polarizability and logP of C5 side chain while the third group shows poor dependence. There is an interplay between the two side chain at N2 and C5 through derived descriptor obtained by subtracting the MV’s, pl’s and logP’s of the two side chains. The third subgroup shows strong dependence of descriptor/response correlation on the miscellaneous side chain at N2 while the C5 side chain has poor dependence. Such findings indicate mechanistic intricacies between the members of this group of desoxy anthrapyrazoles.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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