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Activity Trends in Desoxy Anthrapyrazoles: The Influence of Molar Volume, Polarizability and Lipophilicity of N_2 C_5 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 N_2 and C_5 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 ($1/\log IC_{50}$). The main data set shows poor correlations between biological response and the descriptors with exception of MV of the C_5 side chain, where a moderate correlation was discerned ($R_P^2 = 0.60$, n = 18, two outliers). To extract more information regarding mechanism, the main data set was visually classified to three clusters depending on N_2 side chain. Cluster 1 containing six 5-substituted 2-[(2-hydroxyethyl) amino] ethyl anthrapyrazoles; cluster 2 contains ten 5-subsitutes 2-(diethyl amino) ethyl anthrapyrazoles and cluster 3 contains four anthrapyrazoles with miscellaneous substituents at both N_2 and C_5. For cluster 1, MV and pl of C_5 show high correlation with biological response (R^2's = 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 C_2 side chain are higher ($R_P^{2'}s = 0.66$ and 0.62 respectively) compared with MV ($R_P^2 = 0.16$). Cluster 3 shows very poor correlation with all descriptors ($R_P^{2'}s \sim 0.3$). This indicates mechanistic distinction between the three clusters. Derived descriptors which represent the difference between the descriptors of N_2 and C_5 side chains where used to explore the presence of interplay between these descriptors in affecting variability of the biological response.

Keywords

Polarizability, Molar Volume, Lipophilicity, Anthrapyrazoles, Murine Leukemia

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]. Duanorubicin 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 N_2 and C_5 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 N_2 and C_5 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 N_2 and C_5.

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

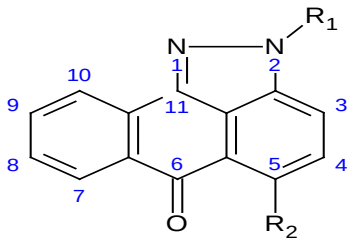

Figure 1. General structure of desoxy anthrapyrazoles.

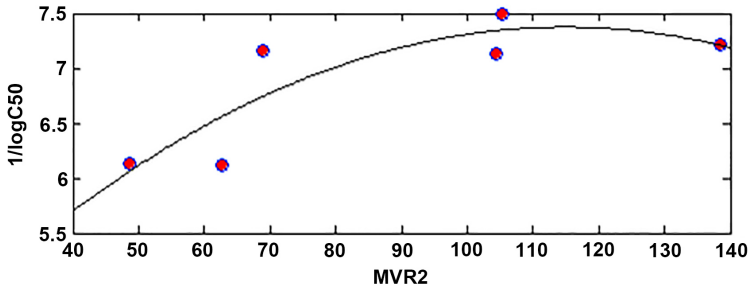

Figure 2. Plotting of $1/\log IC_{50}$ against MV_{R2} of 5-substituted 2-{2-[(2-hydroxyethyl) amino]ethyl}anthra [1,9-cd]pyrazol-6(2H)-ones.

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 squire 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).

Polarizabilty 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:

$$MV = Mw/\rho$$

where Mw is the molecular weight and ρ 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 $\Delta logP_{N2C5}$ parameters were obtained by subtracting the value of molar volume of substituent at C_5 from that of N_2 on the anthrapyrazole ring system. Parent compound from which the side chain at N_2 and C_5 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 $\Delta logP_{N2C5}$) are reported in **Table 2**.

Initially the R^2 statistic were calculated for all the sets obtained by pairing each of the calculated and the derived parameters with anticancer activity ($1/logIC_{50}$) 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 desoxy anthrapyrazoles in which $R_2 = -CH_2CH_2NHCH_2CH_2OH$ on molar volume (MV_{R2}) of the C_2 side chain was found to be parabolic as shown by the Equation (1) below

$$1/\log IC_{50} = 0.0689MV_{R2} - 0.0003(MV_{R2})^2 + 3.4201 \quad (1)$$

$n = 6$, $R^2 = 0.7535$, s ($1/logIC_{50}$) = 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 C_5 side (pl_{R2}) chain to biological activity for the same compounds

$$1/\log IC_{50} = -0.0177(pl_{R2})^2 + 0.448pl_{R2} + 4.483 \quad (2)$$

$n = 5$, $R^2 = 0.7229$, s ($logIC_{50}$) = 0.595, s (residual) = 0.313068; $F = 3.913$.

Equation (3) correlates the logarithm of octanol/water partition coefficient ($logP_{R2}$) of C_5 side chain to biological activity for same series

$$1/\log IC_{50} = 0.8945(\log P_{R2})^2 + 1.5659\log P_{R2} + 6.825 \quad (3)$$

$n = 5$, $R^2 = 0.823$, s ($logIC_{50}$) = 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-R_1	H-R_2	No	H-R_1	H-R_2
1	H-CH_2CH_2OH	$NH_2CH_2CH_2NHCH_2CH_2OH$	11	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2NH_2$
2	H-CH_2CH_2OH	$NH_2CH_2CH_2NEt_2$	12	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2NHMe$
3	H-$CH_2CH_2NH_2$	$NH_2CH_2CH_2NHCH_2CH_2OH$	13	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2NHCH_2CH_2OH$
4	$HCH_2CH_2NHCH_2CH_2OH$	NH_2CH_3	14	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2NEt_2$
5	$HCH_2CH_2NHCH_2CH_2OH$	$NH_2CH_2CH_2OH$	15	$HCH_2CH_2NEt_2$	$NH_2(CH_2)_3NEt_2$
6	$HCH_2CH_2NHCH_2CH_2OH$	$NH_2CH_2CH_2NH_2$	16	$HCH_2CH_2NEt_2$	$NH_2(CH_2)_4NEt_2$
7	$HCH_2CH_2NHCH_2CH_2OH$	$NH_2CH_2CH_2NHCH_2CH_2OH$	17	$HCH_2CH_2NEt_2$	$NH_2(CH_2)_7NEt_2$
8	$HCH_2CH_2NHCH_2CH_2OH$	$NH_2CH_2CH_2NMe_2$	18	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2$-c-$(CH_2CH_2)_2O$
9	$HCH_2CH_2NHCH_2CH_2OH$	$NH_2CH_2CH_2NEt_2$	19	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2$-c-$N(CH_2CH_2)_2NH$
10	$HCH_2CH_2NEt_2$	$NH_2(CH_2)_5CH_3$	20	$HCH_2CH_2NEt_2$	$NH_2CH_2CH_2$-c-$N(CH_2CH_2)_2NCbz$

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

No.	MV_{HR1} cm^3	MV_{HR2} cm^3	ΔMV_{N2C5} cm^3	Pl_{HR1} 10^{-24} cm^3	Pl_{HR2} 10^{-24} cm^3	ΔPl_{N2C5} 10^{-24} cm^3	$logP_{HR1}$	$logP_{HR2}$	$\Delta LogP_{N2C5}$	$1/logIC_{50}$ 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

biological activity and MV_{R2} 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 $\log P_{R2}$. This is to be expected since logP is the parameter that encodes partitioning behaviors of xenobiotics via cell membrane.

MV_{R2} gives with $1/\log IC_{50}$ a good parabolic correlation ($R^2 = 0.76$) while pl_{R2} gives a weaker correlation ($R^2 = 0.72$). This suggests slightly higher contribution MV_{R2} to the observed activity compared to pl_{R2}. It 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_{R2} 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-betweens DNA double helical structure. On the other hand, pl_{R2} 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 ($R_1 = -H_2CH_2NEt_2$) contain compounds 11 - 20. Upon similar treatment as above, the following correlations were found:

$$1/\log IC_{50} = 0.0001\left(MV_{R2}\right)^2 - 0.0377MV_{R2} + 9.8842 \quad (4)$$

$n = 10$, $R^2 = 0.7982$, s ($\log IC_{50}$) = 0.568, s (residual) = 0.266, $F = 13.827$

$$1/\log IC_{50} = 0.0066\left(pl_{R2}\right)^2 - 0.302pl_{R2} + 9.5374 \quad (5)$$

$n = 10$, $R^2 = 0.7973$, s ($\log IC_{50}$) = 0.568, s (residual) = 0.256, $F = 13.767$

$$1/\log IC_{50} = 0.12\left(\log P_{R2}\right)^2 - 0.302\log P_{R2} + 6.383 \quad (6)$$

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

For this subgroup, MV_{R2} and pl_{R2} give a better parabolic correlation (R^2's ~ 0.80) compared with those of the first subgroup (R^2's ~ 0.75 and 0.73 for MV_{R2} and pl_{R2} respectively), in contrast to $\log P_{R2}$ 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_{R2} and $1/\log IC_{50}$ 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

$$1/\log IC_{50} = -0.001\left(MV_{R1}\right)^2 + 0.238MV_{R1} - 3.597 \quad (7)$$

$n = 5$, $R^2 = 0.855$, s ($1/\log IC_{50}$) = 0.824, s (residuals) = 1.68

$$1/\log IC_{50} = -0.116\left(pl_{R1}\right)^2 + 2.087pl_{R1} - 1.560 \quad (8)$$

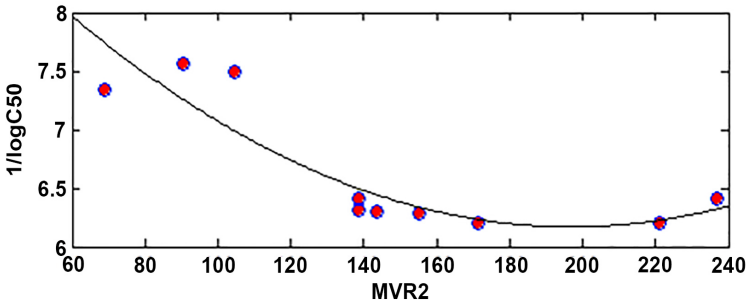

Figure 3. Plotting of $1/\log IC_{50}$ against MV_{R2} of 5-substituted 2-{2-[(2-(diethylamino)ethyl}anthra [1,9-cd]pyrazol-6(2H)-ones.

$n = 5$, $R^2 = 0.895$, $s\,(1/\log IC_{50}) = 0.824$, s (residuals) = 0.265.

$$1/\log IC_{50} = 1.527\left(\log P_{R1}\right)^2 - 2.632\log P_{R1} + 5.863 \quad (9)$$

$n = 5$, $R^2 = 0.5$, $s\,(1/\log IC_{50}) = 0.824$, s (residuals) = 0.584.

As it is apparent from Equations (7)-(9), the third subgroup shows good correlations between MV_{R1} and pl_{R1} with activity while logP gives a moderate correlation.

The side chain at C_2 gives the following equations and metrics:

$$1/\log IC_{50} = 0.001\left(MV_{R2}\right)^2 - 0.444MV_{R2} + 34.3 \quad (10)$$

$n = 5$, $R^2 = 0.334$, $s\,(1/\log IC_{50}) = 0.824$, s (residuals) = 3.00.

$$1/\log IC_{50} = 0.323\left(pl_{R2}\right)^2 - 8.643pl_{R2} + 63.33 \quad (11)$$

$n = 5$, $R^2 = 0.626$, $s\,(1/\log IC_{50}) = 0.824$, s (residuals) = 0.503.

$$1/\log IC_{50} = 0.323\left(pl_{R2}\right)^2 - 8.643pl_{R2} + 63.33 \quad (12)$$

$n = 5$, $R^2 = 0.316$, $s\,(1/\log IC_{50}) = 0.824$, s (residuals) = 0.68.

Equations (10)-(12), shows poor correlation between MV_{R2} and $logP_{R2}$ with activity while pl_{R2} gives a mild correlation. This indicates that N_2 substituent influence the activity more than C_2 substituents for this subgroup.

The present analysis shows that when N_2 side chains are held constant, the activity depends on C_2 side chains but when the N_2 substituents are varied, the activity depends on them rather C_2 side chains.

To explore the combined effect of both N_2 and C_5 substituents on biological activity, new parameters ΔMV_{N2C5}, Δpl_{N2C5}, and $\Delta logP_{N2C5}$, which represent the difference between MV, pl and log P of N_2 and C_5 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 ΔMV_{N2C5}, Significant parabolic correlation were found to $1/\log IC_{50}$ for 13 out of the 20 anthrapyrazoles (R^2 = 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 Δpl_{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. $\Delta logP_{N2C5}$ show linear correlation for 15 compounds (R^2 = 0.717). The remaining 5 compounds correlate parabolically to $1/logIC_{50}$ (R^2 = 0.846). This advocates the use of derived parameters such as ΔMV_{N2C5}, Δpl_{N2C5} and $\Delta logP_{N2C5}$ 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 N_2 determines the segregation of the compounds into three subgroups. One group contains six compounds with 2-hydroxyethylaminoethyl side chain at N_2. The second group contains 2-(diethylamino)ethyl side chain at N_2. The third group contains miscellaneous side chains at N_2. The biological response of the first and the second subgroups depends parabolically on the molar volume, polarizability and logP of C_5 side chain while the third group shows poor dependence. There is an interplay between the two side chain at N_2 and C_5 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 N_2 while the C_2 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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