QSAR Studies of Potent Inhibitors of Malaria Parasite Dihydroorurate Dehydrogenase By Comparative Analysis

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ABSTRACT

Three-dimensional quantitative structure–activity relationship (3D-QSAR) analyses were carried out on derivatives as Dihydroorurate dehydrogenase inhibitors in order to elucidate their antimalarial activities. The most significant values of model 1 generated are internal predictivity 77.039% (q2 = 0.77039) and external predictivity 89.00% (pred_r2 = 0.89) variance in antimalarial activity. The comparative studies had performed with different software. By studying the QSAR model one can select the suitable parameter for designing active compound with maximum potency and relation of the physiochemical property with biological activity can be easily understood. It is hoped that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable parameter for designing active compound for antimalarial activity with maximum potency. By the help of the QSAR we can generate a most active compound which is helpful in the future designing of the new compound. The parameter which contribute maximum in the biological activity are molecular weight (MW), Principal Moment of Inertia – Z (PMIZ) and Non-1,4 Van der waal Energy N1,4 VDWE. Valstat software generates the biological equation and the correlation matrix which is beneficial in understanding the potency of the compound.

KEY WORD: Dihydroorurate dehydrogenase inhibitors, antimalarial, external predictivity, potency, structure

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INTRODUCTION

Plasmodium falciparum DHODH activity can be destroyed by using inhibitor or lowering the expression level of plasmodium falciparum Dihydroorotate dehydrogenase (DHODH), which inhibits parasite growth. So plasmodium DHODH is a good target for drug development.\(^1\) Pyrimidines are a key component of nucleic acids as well as phospholipids and glycoproteins. Humans can acquire pyrimidines via the salvage pathway as well as de novo biosynthesis of pyrimidines via the conserved pathway. However, P. falciparum lacks a salvage pathway for pyrimidines and is therefore totally reliant on the de novo biosynthetic pathway. Therefore, de novo pyrimidine biosynthesis represents an attractive and selective target for the development of new therapeutics against P. falciparum.\(^6\)\(^-\)\(^8\) The anti-malarial drug atovaquone occupies the quinol oxidase (Qo) site of mitochondrial cyt b, inhibiting electron flux through the cyt bc1 complex (ubiquinol:cytochrome c oxidoreductase or complex III) and collapsing mitochondrial membrane potential with a potency 1000-fold greater in Plasmodium than mammalian cells.\(^9\)\(^,\)\(^10\) Unfortunately, high rates of recrudescent infection and treatment failure were seen after antimalarial use of atovaquone alone\(^11\), and treatment failures after The de novo pyrimidine pathway appears to be important for several cellular functions. Pyrimidines are needed notonly for RNA and DNA synthesis but also for protein glycosylation, membrane lipid biosynthesis, and strand breakrepair. Recent efforts for the development of antipyrimidine drugs with an antiinflamatory, immunosupressive, antiproliferative, or antiparasitic efficacy profile have focused on dihydroorotate dehydrogenase (DHODH), the fourth sequential step in the de novo pyrimidine nucleotide synthesis pathway, as a promising target enzyme to depress the intracellular level of pyrimidine nucleotides.\(^12\)\(^-\)\(^14\) Dihydroorotate dehydrogenase catalyses the oxidation of dihydroorotate to orotate, the first aromatic intermediate in this biosynthetic pathway, with the aid of a flavin cofactor and an electron receptor.\(^15\) On the basis of sequence similarity, the DHODHs can be divided in two major families, i.e., family 1 (A and B) and family 2.\(^16\) This division correlates with subcellular location of the proteins as well as their preferences for electron acceptors. Enzymes of family 1, found in Gram-positive bacteria and in the anaerobic yeast Saccharomyces cerevisiae, are located in the cytosol of the cell. They have less than 20% sequence identity with the membrane-bound enzymes of family 2, found in eukaryotes and in some prokaryotes such as the Gram-negative bacteria related to Escherichia coli. The cytoplasmic enzymes utilize fumarate or NAD\(^+\) to oxidase FMNH\(^2\), whereas the membrane-bound enzymes, which are mitochondrial in eukaryotes, require quinones as their physiological oxidant.\(^17\) Several additional classes of compounds have been found to inhibit this complex in Plasmodium falciparum, leading to
additional potential drugs in early stages of development. Inhibitors of another essential mitochondrial enzyme, dihydroorotate dehydrogenase (DHODH), are also advancing toward drug development. 18,19

MATERIAL AND METHOD
The antimalarial activity data of derivatives as were taken from the reported work of Heikkila et al. 20 (Table 1). The biological activity data (IC₅₀) was converted to negative logarithmic mole dose (pIC₅₀) for quantitative structure activity relationship (QSAR) analysis. The molecular modeling study was performed using CS Chem Office version 8 while the regression analysis was carried out with VALSTAT and SPSS software.

The VALSTAT is interactive program, when initiated, asks for declaration in the format of (y/n). If user enters ‘n’, then program is terminated automatically. The main options that appear on the screen based on the user’s interest are, (i) have you entered data in specific files (y/n), (ii) do you want test and training set (y/n), (iii) do you want intercorrelation matrix (y/n), (iv) are you going for simple Linear Regression Analysis (y/n), (v) are you going for Stepwise Linear Regression Analysis (y/n), (vi) enter correlation limit within the parameters (0-0.99), (viii) are you going for nonlinear Stepwise Regression Analysis(y/n), (ix) enter number of independent variables for Multiple Linear Regression Analysis (1-24), (x) do you want correlation matrix for Multiple Linear Regression parameter (y/n) and (xi) are you going for validation of model (y/n). Here it asks for training/test set (y/n). If answer is ‘n’, then program progresses to next step automatically. Now question appears on screen for correlation matrix (y/n), if reply is ‘y’ then program starts for finding of inter correlation within the independent parameters and the result of inter-correlation gets stored in the RESULT.TXT file in matrix form.

QSAR models were built using the regression analysis module of SPSS version 17. The correlation matrix was used to correlate the biological activity with the various predictor variables. The QSAR models were evaluated by using the statistical parameters viz., correlation coefficient (r) or coefficient of determination (r²), adjusted r² (r² Adj), Standard error of estimate and Fischer F-value. The latter is used to assess the significance of the individual regression terms. The figures within the parentheses following the coefficient terms are the standard error of the regression terms and the constants. Durbin–Watson (DW) test was employed to check the serial correlation in residuals. Since the DW values in all our derived models are greater than 2.0, there is probably not any serious auto correlation in the residuals.
Table 1: General structure of the compounds of derivatives and their biological activities (data set of 11 molecules)

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Structure</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µm)</th>
<th>pIC&lt;sub&gt;50&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>1.</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>190.1</td>
<td>3.721018</td>
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<td>4.</td>
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<td>5.</td>
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<td>4.556268</td>
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<tr>
<td>7.</td>
<td><img src="image7.png" alt="Structure 7" /></td>
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<td>8.</td>
<td><img src="image8.png" alt="Structure 8" /></td>
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</table>
RESULT AND DISCUSSION

The result of valstat model is as:

**Model 1** is a monoparametric equation developed for available antimalarial activity data. The most significant values of model generated are internal predictivity 77.039\% (q^2 = 0.77039) and external predictivity 89.00 % (pred_r^2 = 0.89) variance in antimalarial activity.

Model: 1 \[ BA = [1.94151(\pm 1.45976)] +PMIZ [0.000620399(\pm 0.000248639)] +N1,4VDWE [-0.52281(\pm 0.247224)] \]

Contribution of parameters to model is PMIZ:N1,4VDWE::5.52713:1

n=11, r=0.946203, r^2=0.895301, variance=0.214732, std=0.463392, F=34.2047, FIT=456.063, q^2 = 0.770396, Spress=0.686226, SDEP=0.585216

**Table 2: correlation matrix of model 1**

<table>
<thead>
<tr>
<th></th>
<th>PMIZ</th>
<th>N1,4VDWE</th>
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<tr>
<td>PMIZ</td>
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<tr>
<td>N1,4VDWE</td>
<td>0.126656</td>
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**Model 2** is a monoparametric equation developed for available antimalarial activity data. The most significant values of model generated are internal predictivity 74.0\% (q^2 = 0.74) and external predictivity 87.31 % (pred_r^2 = 0.8731) variance in antimalarial activity.

Model: 2 \[ BA = [2.62926(\pm 1.34973)] +PMIY [0.000579024(\pm 0.000261937)] +N1,4VDWE [-0.502971(\pm 0.273597)] \]

Contribution of parameters to model is PMIY:N1,4VDWE::4.53782:1

n=11, r=0.934399, r^2=0.873101, variance=0.260263, std=0.51016, F=27.5211, FIT=366.948, q^2 = 0.740636, Spress=0.729343, SDEP=0.621986

**Table 3: Correlation matrix of model 2**

<table>
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<th>N1,4VDWE</th>
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<tr>
<td>PMIY</td>
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<tr>
<td>N1,4VDWE</td>
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</table>
Model 3 is a monoparametric equation developed for available antimalarial activity data. The most significant values of model generated are internal predictivity 67.01% (q^2 = 0.6701) and external predictivity 84.01% (pred_r^2 = 0.8401) variance in antimalarial activity.

Model: 3 \[ BA = [-2.51614(\pm 4.31312)] + MW [0.0253119(\pm 0.0136511)] + N1,4VDWE [-0.569884(\pm 0.30799)] \]

Contribution of parameters to model is MW:N1,4VDWE::11.834:1

n=11, \( r = 0.913973 \), \( r^2 = 0.835346 \), variance=0.337697, std=0.581117, F=20.2934, FIT=270.578, \( q^2 = 0.671932 \), Spress=0.820275, SDEP=0.699533

<table>
<thead>
<tr>
<th></th>
<th>MW</th>
<th>N1,4VDWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
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<tr>
<td>N1,4VDWE</td>
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</tr>
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</table>

Table 4: Correlation matrix of model 3

The result of SPSS model is as:

Model 1 The most significant values of model generated external predictivity 84.01% (pred_r^2 = 0.873) variance in antimalarial activity.

Model 1 \[ 2.629 \pm 0.571 + PMIY[0.001(\pm 0.000)] + NVWDE[(-0.503) \pm (0.116)] \]

n=11, \( r = 0.934 \), \( r^2 = 0.873 \), Adj \( r^2 = 0.841 \), F=27.521, Durbin Watson constant= 2.040, Standard error of estimate=0.5101

Finally, it is hoped that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable parameter for designing active compound for antimalarial activity with maximum potency.

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REFERENCE


