Application of QSAR Method in the Design of Enhanced Antimalarial Derivatives of Azetidine-2-carbonitriles, their Molecular Docking, Drug-likeness, and SwissADME Properties

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Abstract

The resistance of the P. falciparum strain to some of the antimalarial drugs has been a dominant dilemma facing the treatment of this fetid disease. This necessitates the detection and development of new antimalarial agents targeting the P. falciparum. Azetidine-2-carbonitriles reported for its antimalarial activities, could provide an alternative to the customized antimalarial drugs. Leading to the use of quantitative structure-activity relationship (QSAR) studies, which relates the structures of Azetidine-2-carbonitriles with their activities to generate predictive models. The structures were optimized using density functional theory (DFT) DFT/B3LYP/6-31G* basis set to generate their molecular descriptors, where five predictive models were constructed using the generated descriptors. The models were constructed using the genetic function algorithm component of a material studio, where the model with good statistical parameters, high coefficient of determination (R^2) = 0.9465, cross-validated R^2 (Q^2cv) = 0.8981, Q^2 (LOOcv) = 0.9272, and highest external validated R^2 (R^2pred) = 0.6915 was selected as the best model. These statistical results show the robustness, excellent power of prediction, and validity of the selected model. The descriptor, SpMax2_Bhp (the maximum absolute eigenvalue of Barysz matrix for n = 2 was weighted by polarizability), was revealed to be the most influential in the model due to its highest mean effect. The descriptor played a role in the design of sixteen (16) theoretical derivatives of Azetidine-2-carbonitriles using compound 25 as the design template by increasing polarizability of the compounds through substitution of the various group with electron deactivating groups (F, I, Cl, SO_3H, CN, NO_2, etc.) at different position of the template. The designed compounds were docked with Plasmodium falciparum dihydroorotate dehydrogenase (Pf-DHODH), giving compound D9 the highest binding energy. The designed compounds were further screened for their drug-likeness, where they all pass Lipinski’s RO5. All the compounds show good skin permeability coefficient and have low Gastrointestinal absorption while few compounds D1, D2, D3, D14, and D15 inhibiting the CYP1A2.

Keywords: QSAR; design; docking; drug-likeness; Azetidine-2-carbonitriles; P. falciparum; SwissADME.

Introduction

The genus Plasmodium is the causative agent of a life-threatening infection, malarial, globally established as one of the most challenging health concerns. Malarial is transmitted within humans through a bite of infected anopheles mosquitoes (1). The global malarial index shows about 228 million malarial cases yearly with 405,000 record mortalities, where the most affected are
children below the ages of 5 years, constituting 585,000 (67%) of all cases (2).

Human malarial is transmitted by five species of Plasmodium, namely, Plasmodium ovale (P. ovale), Plasmodium falciparum (P. falciparum), Plasmodium vivax (P. vivax), Plasmodium malariae (P. malariae), and Plasmodium knowlesi (P. knowlesi) (3-4). The bulk of the fatalities are caused by P. falciparum, the most severe of all the species (5). P. falciparum altered the surface of red blood cells once present in the human body through interceding parasite proteins (6). The hemoglobin is ramshackle into amino acids and heme by enzymes cysteine and aspartic proteinases (7). The entire amino acid constituents are assembled into parasite proteins; although only a fraction of heme is incorporated into parasite hemoproteins, the parasite enzymes detoxified the remaining heme (8).

Efficacies of several drugs such as chloroquine, quinine, pyrimethamine, proguanil, artemisinin, artovaquone, and mefloquine, in treating malarial has been explored. However, the resistance of the P. falciparum strain to some of these drugs has been the major problem facing the treatment of the noxious disease (9). Hence, the detection and development of new antimalarial agents targeting P. falciparum become an extremely important task to curb the accelerated escalation of this resistance. In light of this, Azetidine-2-carbonitriles reported possessing antimalarial activities (10) could provide an alternative application to the routine antimalarial drugs.

The desire to improve drugs with better antimalarial activities leads to the adoption of quantitative structure-activity relationship (QSAR) studies, an essential process in the field of drug invention and improvement due to its time and cost-effectiveness (11). QSAR is an arithmetical relationship between the structural features (biological activities) of drugs with their physicochemical properties (molecular properties). Through this, substitutions of various groups at various positions can affect the molecular properties of the compound and hence, instrumental in the design of antimalarial compounds of novel activities against malarial agents. Various QSAR advances are employed in the studies of biological activities of antimalarial compounds as functions of their molecular properties (12-16). This research focuses on applying QSAR techniques in determining the vital structures of Azetidine-2-carbonitriles, responsible for their antimalarial activities, and utilizing the most important molecular properties in designing derivatives of derivatives Azetidine-2-carbonitriles with enhanced activity against P. falciparum. The drug-like and SwissADME studies of the designed derivatives were conducted, followed by their molecular docking to determine their binding site and energy.

Experimental

Collection of dataset and optimization

The dataset consists of thirty-four derivatives of Azetidine-2-carbonitriles, whose chemical structures and biological activities against the Dd2 strain of P. falciparum were extracted from PubChem as presented in the literature (10). Their activities, expressed as EC_{50} (μM), were then converted to pEC_{50} by taking the negative logarithm of the EC_{50} (M) as indicated in Table 1. The structures of the compounds were drawn using a ChemDraw Ultra 12, and saved in *.cdx format before exporting into the spartan’14 version 1.1.2 software and then optimized using DFT (DFT/B3LYP/6-31G*) in a vacuum, this is done using the initial molecular geometry (17).

Descriptors calculation

The thirty-four [34] optimized Spartan 14 structures saved as SDF format were then exported into PaDEL software where about 1,500 molecular descriptors ranging between 0-3D classes of descriptors were calculated (18).

Dataset pre-treatment and division

The dataset descriptors are treated by eliminating constant value descriptors, excessive values of coefficient of correlation, descriptors with less than 0.001 variance values. The treated data set was divided into 27 training compounds (consisting of 80% of the data set) and 7 test compounds (making up the remaining 20%) with the aid of the
Table 1. Chemical structures and activities of the derivatives of Azetidine-2-carbonitriles against Chloroquine resistance strain, Dd2.

| S/N | PubChem CID | STRUCTURE | $\text{EC}_{50}$ (μM) | Experimental pEC50 | Predicted pEC50 | Residuals |
|-----|-------------|-----------|------------------------|-------------------|-----------------|-----------|
| 1   | 137653939   | ![Structure 1](image1.png) | 0.3520                 | 6.4535            | 6.5741          | -0.1206   |
| 2   | 137643572   | ![Structure 2](image2.png) | 5.6400                 | 5.2487            | 5.1621          | 0.0866    |
| 3   | 137644134   | ![Structure 3](image3.png) | 1.6290                 | 5.7881            | 5.8134          | -0.0253   |
| 4*  | 137644836   | ![Structure 4](image4.png) | 0.1390                 | 6.8570            | 5.5828          | 1.2742    |
| 5   | 137645921   | ![Structure 5](image5.png) | 0.0190                 | 7.7212            | 7.8791          | -0.1579   |
| 6*  | 137646161   | ![Structure 6](image6.png) | 0.0150                 | 7.8239            | 7.7244          | 0.0995    |
| 7*  | 137650346   | ![Structure 7](image7.png) | 1.6130                 | 5.7924            | 5.5606          | 0.2318    |
| 8   | 137651551   | ![Structure 8](image8.png) | 12.6300                | 4.8986            | 5.4068          | -0.5082   |
| 9   | 137653171   | ![Structure 9](image9.png) | 0.0160                 | 7.7959            | 8.1805          | -0.3846   |
| S/N | PubChem CID | STRUCTURE | EC<sub>50</sub> (μM) | Experimental pEC<sub>50</sub> | Predicted pEC<sub>50</sub> | Residuals |
|-----|-------------|-----------|----------------------|-------------------------------|--------------------------|-----------|
| 10* | 137642840   | ![Structure Image](image1.png) | 0.0460               | 7.3372                        | 7.5196                   | -0.1824   |
| 11  | 137654044   | ![Structure Image](image2.png) | 0.0830               | 7.0809                        | 6.4812                   | 0.5997    |
| 12  | 137655290   | ![Structure Image](image3.png) | 0.3900               | 6.4089                        | 6.2552                   | 0.1537    |
| 13  | 137655453   | ![Structure Image](image4.png) | 4.3900               | 5.3575                        | 5.2809                   | 0.0766    |
| 14  | 54650710    | ![Structure Image](image5.png) | 8.3750               | 5.0770                        | 5.3577                   | -0.2807   |
| 15  | 137657208   | ![Structure Image](image6.png) | 16.2000              | 4.7905                        | 4.9780                   | -0.1875   |
| 16  | 137657282   | ![Structure Image](image7.png) | 0.0120               | 7.9208                        | 8.1037                   | -0.1829   |
| 17  | 137657611   | ![Structure Image](image8.png) | 0.0100               | 8.0000                        | 7.7291                   | 0.2709    |
| 18  | 137634425   | ![Structure Image](image9.png) | 0.0200               | 7.6990                        | 7.6427                   | 0.0563    |
Table 1. Continued.

| S/N | PubChem CID | STRUCTURE | EC₅₀ (μM) | Experimental pEC₅₀ | Predicted pEC₅₀ | Residuals |
|-----|-------------|-----------|-----------|--------------------|-----------------|-----------|
| 19  | 54650356    | ![Structure](image1) | 0.0100    | 8.0000             | 7.7300          | 0.2700    |
| 20* | 54649963    | ![Structure](image2) | 0.0190    | 7.7212             | 7.0403          | 0.6809    |
| 21  | 54650362    | ![Structure](image3) | 0.0150    | 7.8239             | 7.9583          | -0.1344   |
| 22  | 137631863   | ![Structure](image4) | 5.5410    | 5.2564             | 5.4263          | -0.1699   |
| 23  | 137632547   | ![Structure](image5) | 4.4400    | 5.3526             | 5.4498          | -0.0972   |
| 24  | 134962527   | ![Structure](image6) | 0.2490    | 6.6038             | 6.3440          | 0.2598    |
| 25  | 137632930   | ![Structure](image7) | 0.0050    | 8.3010             | 8.1214          | 0.1796    |
| 26* | 54650719    | ![Structure](image8) | 0.0130    | 7.8861             | 7.1942          | 0.6919    |
| 27  | 137635190   | ![Structure](image9) | 0.3070    | 6.5129             | 6.5881          | -0.0752   |
Table 1. Continued.

| S/N | PubChem CID | STRUCTURE | EC₅₀ (μM) | Experimental pEC₅₀ | Predicted pEC₅₀ | Residuals |
|-----|-------------|-----------|-----------|-------------------|----------------|-----------|
| 28  | 121596187   | ![Image](image1.png) | 0.0160    | 7.7959            | 7.5877         | 0.2082    |
| 29  | 137637648   | ![Image](image2.png) | 0.4270    | 6.3696            | 5.9310         | 0.4386    |
| 30  | 137638588   | ![Image](image3.png) | 0.0350    | 7.4559            | 7.7675         | -0.3116   |
| 31  | 137640699   | ![Image](image4.png) | 0.0970    | 7.0132            | 6.9392         | 0.0740    |
| 32  | 137641113   | ![Image](image5.png) | 0.0160    | 7.7959            | 8.0999         | -0.3040   |
| 33* | 137641836   | ![Image](image6.png) | 0.1020    | 6.9914            | 6.7894         | 0.2020    |
| 34  | 137642074   | ![Image](image7.png) | 0.1060    | 6.9747            | 6.7087         | 0.2660    |

NB: *Test Set.

Dataset

DatasetDivision1.2 program by employing the Kennard-Stone’s algorithm method (19).

Selection of variables and model development

Material Studio 8.0 software was employed for the development of a model connecting the biological activities of the Azetidine-2-carbonitriles to their molecular structures. The genetic function algorithm (GFA) component of the material studio was elected to carry out the model development. All possible mixtures...
of molecular descriptors were searched by the algorithm to produce a good model together with the use of a lack of fit function in measuring the fitness of all individual combinations (20).

Model Validation
The models were subjected to both internal and external validations, where both the leave-one-out (LOO) and leave-many-out (LMO) internal validation techniques were employed. The LOO involves casting away a molecule of the training set before developing a model with the remnant data, and the activity of the discarded compound was in turn predicted by the model, and this was performed across other compounds in the training set. The LMO involves a selection of the group of compounds to validate the developed model. The external validation entails predicting the biological activities of some dataset separated from the training set (test set) applying the model. The best predictive models were chosen based on the values of the coefficient of determination ($R^2$), cross-validated $R^2$ ($Q_{cv}^2$), and the external validated $R^2$ ($R_{pred}^2$) (21). The model with the highest test set ($R_{pred}^2$) prediction was picked as the best model.

Descriptors variance inflation factor (VIF)
The multicollinearity of the model descriptors was investigated employing the variance inflation factor (VIF) (22). The rule of thumb for descriptors VIF (Equation 1) values was set for not greater than 10 as an omen of huge multicollinearity between descriptors (23). The VIF is obtainable by utilizing Equation 1.

$$VIF = \frac{1}{1 - R_i^2}$$

Where $R_i$ denotes the coefficient produced by regressing the descriptor $x_i$ against the other descriptors $x_j$ (j ≠ i).

Descriptors Mean effect
The mean effect refers to the measures of the descriptor’s relevancies in a generated model; it reveals the respective contributions of molecular descriptors to the selected model. The sign of the mean effect indicates the variations of its contribution as a function of descriptor values. The mean effect could be estimated with the aid of Equation 2.

$$\text{Mean Effect} = \frac{\beta_j \sum D_j}{\sum (\beta_j \sum D_j)}$$

where $\beta_j$ Conforms with the descriptor j’s coefficient, $D_j$ conforms with each value of matrix descriptor in the training set, and m conforms with the tally of model descriptors present, and n stands for the tally of molecules used as training set (24).

Model Applicability Domain (AD)
The model limitations are defined by its biological space, which relates to the structural realm and response capacity. Interpretation of the relevant space of the model was performed using Williams’s plot. Higher leverage compounds with values exceeding the caution leverage ($h^*$) in addition to determining standardized residual values beyond plus or minus three standard deviation units were regarded as an impairment (25).

Molecular design
The ligand-based design method was employed to design compounds possessing improved antimalarial activities. Compounds with enhanced activity are usually refined and modeled through this means by linking the empirical activities of the compounds with their molecular structures. Antimalarial derivatives possessing the highest activity will be utilized as a guide (Template) in designing theoretical compounds with elaborating activities.

Molecular docking studies
The molecular docking studies between the ligands and their protein target were carried out with the Molegro Virtual Docker (MVD). The 3D structure of the target protein was extracted from Protein Data Bank (PDB) (www.rcsb.org) and saved in PDB file format. The designed derivatives of Azetidine-2-carbonitriles were docked to a high resolution 2.4 Å crystal structure of Plasmodium falciparum dihydroorotate dehydrogenase (Pf-DHODH) (PDB ID: ITV5).

Ligand and Protein Preparation
The ligands and protein structure saved in
PDB format may be lost components such as hydrogen atoms, its charges, etc. The ligands and the protein were imported into the MVD, and were prepared using the preparation wizard (capable of fixing the missing hydrogens and charges) of the MVD. The binding pocket for the interaction of the ligands and the protein target was calculated within the in-built cavity algorithm executed by the MVD software. The MVD cavity detects the algorithm and then performs the molecular docking to predict the ligand’s binding mode and the target protein in the form of a scoring function.

Docking Protocol Validation
The docking protocol was validated through the re-docking of the crystallized ligand unto the binding site of the protein receptor. The initial crystalized ligand was superimposed on the docked pose to produce the value of the root mean square deviation (RMSD). The permitted range of the RMSD value within ≤ 2.0Å validates the docking protocols and confirms its usage in docking (26).

In-silico ADME prediction
An excellent medication is not necessarily the one with the best binding interactions with the target. Hence, the need to evaluate the ligand’s pharmacokinetic properties, ADME (absorption, distribution, metabolism, and excretion), for their activity within the human system. The compounds that are likely to be taken as oral medication, should be fast and absorb completely from the gastrointestinal tract, distribute in the direction of its target, metabolize slowly, and properly dispense harmlessly. Drug failure has been associated with poor ADME properties (27). The SwissADME, an online ADME prediction tool was deployed in the present studies to predict the drug-like and the pharmacokinetic properties of the sixteen [16] designed derivatives of Azetidine-2-carbonitriles. The predictive absorption for molar refractivity (MR), skin permeability coefficients (log Kp), total polar surface area (TPSA), number of rotatable bonds (nRotB), Gastrointestinal (GI) absorption, and CYP1A2 inhibitor were evaluated besides the Lipinski’s Rule of 5 (RO5), which predicts drug-likeness of the design derivatives were also considered. Lipinski’s RO5 states that compound in excess of 5 H-bond donors, 10 H-bond acceptors, molecular weight more than 500 Da, and the calculated Log P (MLogP) greater than 5 likely had poor absorption or permeation of the molecular entities. Hence, molecules will unlikely to become orally bioavailable as a drug if they pose properties greater than the desired number (28).

Results and Discussion

QSAR model
Several QSAR models were generated with a large value of the coefficient of determination; however, a model that is robust, efficient, and more reliable model was chosen as the best model based on the significance of its parameters since it has the largest value of 

\[ R^2 = 0.9465, R^2_{\text{Adj}} = 0.9304, Q^2 = 0.8981, 
Q^2_{(L4O)} = 0.9272, \text{ and } R^2_{\text{ext}} = 0.6915. \]

The robustness and the predictive capacity of the QSAR model were predicted through the statistical parameters. The chosen model is presented below with the names, definitions, and coefficients of the descriptors listed in Table 2.

\[
pEC_{50} = 5.79415 \times (ATSC_{5c}) - 9.38708 \times (MATS_{5e}) + 12.85927 \times (GATS_{8i}) - 10.11181 \times (SpMax2_{Bhp}) + 18.90418 \times (PetitjeanNumber) + 1.54996 \times (XLogP) + 18.22399
\]

\[ N = 27, R^2 = 0.9465, R^2_{\text{Adj}} = 0.9304, Q^2 = 0.8981, Q^2_{(L4O)} = 0.9272, \text{ LOF} = 0.4280, R^2_{\text{ext}} = 0.6915, N_{\text{ext}} = 7 \]

Model Validation
The high value of $Q^2$ (0.8981), and that of $Q^2_{(L4O)}$ = 0.9272 are indicators of good internal validations; the model was utilized externally to predict the activity of an external set which is reflected in the squared regression coefficient of the test set, $R^2_{\text{ext}}$ (0.6915). These results are a strong indication of the exclusive (internal and external) validation of a model. The plot of predicted activity against the experimental activity revealed a cluster of data points around the legend line, as shown in Figure 1, indicating the robustness and strength of the selected model. The small difference between the
Design, Docking and ADME Properties of Antimalarial Derivatives

Experimental and predicted activity (Table 1) emphasizes the accuracy of the model. Also, the Y-randomization test carried out shows the values of $R^2$ and $Q^2$ obtained after 15 repetitions are far smaller than their values in the model, confirming that the model does not occur by chance.

Descriptors correlation matrix and Variance inflation factor (VIF)

The low variance in the correlation matrix (Table 3) between the model’s descriptors reveals a non-mutual relationship among the descriptors, which was supported by low values of calculated descriptors VIF ($< 10$) as

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**Table 2.** Names, definitions, and coefficients of descriptors appearing in the selected model.

| Descriptor name                                                                 | Type                  | Notation  | Coefficient |
|--------------------------------------------------------------------------------|-----------------------|-----------|-------------|
| Centered Broto-Moreau autocorrelation - lag 5/weighted by charges               | 2D-Autocorrelation    | ATSC5c    | 5.79        |
| Moran autocorrelation - lag 5/weighted by Sanderson electronegativities          | 2D-Autocorrelation    | MATS5e    | -9.39       |
| Geary autocorrelation - lag 8/weighted by first ionization potential            | 2D-Autocorrelation    | GATS8i    | 12.86       |
| Largest absolute eigenvalue of Barysz matrix - n 2/weighted by relative polarizabilities | Barysz matrix | SpMax2_Bhp | -10.11      |
| Petitjean number                                                               | Petitjean number      | PetitjeanNumber | 18.90       |
| XLogP                                                                         | XLogP                 | XLogP     | 1.55        |

**Table 3.** Descriptors correlation matrix, VIF, and their Mean effect.

| pEC50 | ATSC5c | MATS5e | GATS8i | SpMax2_Bhp | PetitjeanNumber | XLogP | VIF | MF |
|-------|--------|--------|--------|------------|-----------------|-------|-----|----|
| pEC50 | 1      |        |        |            |                 |       |     |    |
| ATSC5c| 0.0516 | 1      |        |            |                 |       | 2.3640 | -0.3262 |
| MATS5e| 0.0729 | 0.5890 | 1      |            |                 | 3.0033 | 0.0717 |
| GATS8i| 0.2138 | -0.1170| 0.3532 | 1          |                 | 2.6423 | -1.0598 |
| SpMax2_Bhp| 0.2163 | -0.0471| -0.1380| 0.2733     | 1               | 1.8832 | 3.3244 |
| PetitjeanNumber| 0.3992 | 0.0425 | 0.0150 | 0.2741     | 0.1633         | 1.1472 | -0.7846 |
| XLogP | 0.7071 | -0.0473| -0.0205| -0.2401    | 0.3923          | -0.0038 | 1   | 1.7121 | -0.2254 |

![Figure 1. Experimental pEC50 plotted against predicted pEC50 for the dataset.](image-url)
found in Table 3. Indicating that the descriptors are found to be orthogonal (22), as such the model is statistically significant.

**Applicability Domain (AD) of the model**

The model application limit defined by the applicability domain reflects the presence of the data sets within space, with no data point located outside the domain, as reflected in Figure 2. The threshold ($h^*$) leverage is estimated for 0.778, beyond which the applicability of the models fails. Therefore, the whole dataset was found to possess decent leverage values and is within the model's space, affirming the model's predictive strength.

**Interpretation and contribution of descriptors**

The activity of the model, $pEC_{50} = 5.79415(\text{ATSC}5c)-9.38708(\text{MATS}5e)+12.85927(\text{GATS}8i)-10.11181(\text{SpMax}2_\text{Bhp})+18.90418(\text{PetitjeanNumber})+1.54996(\text{XLogP})+18.22399$, is determined by the constituent descriptors ATSC5c, MATS5e, GATS8i, SpMax2_Bhp, PetitjeanNumber, and XLogP.

The first descriptor, ATSC5c, which is defined as centered Broto–Moreau autocorrelation—lag 5/weighted by charges. The descriptor is related to the polarization of the molecules caused by highly electronegative elements present in a compound. The descriptor has a mean effect of $MF = -0.3262$ (Table 3) which indicates the activity increases with a decrease in the numeric values of the descriptors. The second descriptor, MATS5e belongs to the autocorrelation, and it describes the dependence of the compound on electronegativity (29). The autocorrelation descriptors check out the dependence of properties in one special molecule with the neighbor molecule and detect the conformity of the molecules (30). The mean effect (MF) analysis revealed the descriptor to have made $MF = 0.0717$ contribution. The positive sign of the MF indicates a positive contribution to the antimalarial activity. Hence, an increase in the value of the descriptor increases the antimalarial activity. The descriptor, GATS8i is a Geary autocorrelation of lag 8 weighted by first ionization potential. The 2D autocorrelation descriptors explained how the values of certain functions (topological distance) at intervals equal to the lag (atomic properties) were correlated. The analysis of the descriptors contribution yields the $MF = -1.0598$. The negative sign of the mean effect ensures the increase of activity with decrease descriptor values. SpMax2_Bhp is a Barysz matrix type descriptor in which the maximum absolute eigenvalue of Barysz matrix for $n = 2$ was weighted by polarizability (18). Analysis of the mean effect confirms SpMax2_Bhp to be the most contributive descriptor with $MF = 3.3244$, whose increase in numerical value increases the activity of compounds due to the positive MF. The value of shape parameter PetitjeanNumber increases when the substituents are changed from F, Cl to CF$_3$, -OCH$_3$ at a ring and hence increases the activity (31). The negative mean effect (MF = -0.7846) implies decreasing the descriptor.
values to increase the activity of the compound. The last descriptor, XlogP signifies the ratio of solute concentration in octanol & water and generally termed as octanol-water partition coefficient. The negative mean effect (MF = -0.2254) indicates decreasing the descriptor values to increase the compound activity.

**Molecular design**

The compound with the highest activity (pEC\textsubscript{50} = 8.301), compound 25 presented in Figure 3, was adopted as the design template. The descriptor, SpMax2_Bhp (a descriptor in which the maximum absolute eigenvalue of Barysz matrix for n = 2 was weighted by polarizability), was established as the most influential descriptor, was employed in the design of many speculative derivatives of Azetidine-2-carbonitriles. The descriptor relates to the polarizability of a molecule, and since it has a positive mean effect, increasing the polarizability of the compounds should be able to increase the antimalarial activity. Hence, polarizability can increase through the substitution of various electron deactivating groups (F, I, Cl, SO\textsubscript{3}H, CN, NO\textsubscript{2}, etc) at different positions of the template. This lead to the design of sixteen [16] speculative derivatives of the template as depicted in Table 4. Ten of the design derivatives (D3-4, D8-13, and D15-16) have better activity than the template. The compound D13 {2S,3S,4S}-

![Figure 3](image3.png)

**Figure 3.** Design template, Compound 25, (2S,3S,4S)-2-cyano-4-(hydroxymethyl)-3-(4'-phenoxy-[1,1'-biphenyl]-4-yl)-N-propylazetidine-1-carboxamide, with pEC\textsubscript{50} = 8.301.

| Compound | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | R\textsubscript{4} | R\textsubscript{5} | EC\textsubscript{50} (μM) | pEC\textsubscript{50} |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| D1       | Cl              | H               | H               | H               | H               | 0.00266         | 8.5759         |
| D2       | H               | H               | H               | H               | Cl              | 0.01178         | 7.9288         |
| D3       | H               | H               | H               | H               | Cl              | 0.00210         | 8.6776         |
| D4       | NO\textsubscript{2} | H             | H               | H               | H               | 0.00180         | 8.7437         |
| D5       | H               | NO\textsubscript{2} | H             | H               | H               | 0.00531         | 8.2747         |
| D6       | H               | H               | NO\textsubscript{2} | H             | H               | 0.00365         | 8.4381         |
| D7       | H               | H               | H               | H               | NO\textsubscript{2} | 0.03227         | 7.4912         |
| D8       | H               | Cl              | H               | NO\textsubscript{2} | H             | 0.00191         | 8.7196         |
| D9       | H               | NO\textsubscript{2} | Cl             | H               | H               | 0.00019         | 9.7283         |
| D10      | Cl              | H               | H               | NO\textsubscript{2} | H             | 0.00081         | 9.0893         |
| D11      | H               | H               | H               | NO\textsubscript{2} | Cl             | 0.00042         | 9.3819         |
| D12      | H               | H               | Cl              | NO\textsubscript{2} | H             | 0.00115         | 8.9411         |
| D13      | F               | H               | H               | H               | H               | 0.00014         | 9.8641         |
| D14      | I               | H               | H               | H               | H               | 0.00343         | 8.4647         |
| D15      | H               | Br              | H               | H               | H               | 0.00081         | 9.0932         |
| D16      | H               | Br              | H               | NO\textsubscript{2} | H             | 0.00014         | 9.8493         |
| Template | H               | H               | H               | H               | H               | 0.00500         | 8.3010         |
| Chloroquine |                |                |                |                |                | 0.94585         | 6.0242         |

**Table 4.** Structures of the template, designed derivatives of Azetidine-2-carbonitriles and Chloroquine standard along with their respective activities.
2-cyano-3-(2'-fluoro-4'-phenoxy-[1,1'-biphenyl]-4-yl)-4-(hydroxymethyl)-N-propylazetidine-1-carboxamide}, was found to have better antimalarial activity, (pEC\textsubscript{50} = 9.8641) than those of the design template (pIC\textsubscript{50} = 8.301), co-designed compounds as well as the chloroquine standard (pEC\textsubscript{50} = 6.0242) as reflected in Table 4.

**Docking Protocol Validation**

The validation of the docking protocols was conducted to ascertain the docking method through the determination of the deviation of the re-docking output from the original docking pose. The deviation expressed as the root mean square deviation (RMSD) value produces the RMSD value of 1.895Å. This, therefore, validate the protocols employed in the docking and can be deployed in docking the designed ligands.

**Docking Analysis**

The binding conformation of the design derivatives to the binding site of the target protein is discussed in the docking analysis. The structure of Plasmodium falciparum dihydrolorotate dehydrogenase (Pf-DHODH) with the target site is reflected in Figure 4. Moreover, the docking result of the designed derivatives, template, and standard drug was shown in Table 5. The interactions of the ligand and the protein residues are analyzed, where hydrogen attached to either the hydroxyl or the Azetidine ring in most ligands showed H-bond interaction with Asp204 or Asp200 active site of the residues. The oxygen of the nitro in all the ligands shows H-bond interaction with either Lys305, Lys239, Lys559, Thr201, Ile206, Met536, Gly35, Asp216, or Asn195 active site residue, except in ligands D2, D3, D12, D13, D14, and D15. H-bond interaction could also be observed between the protein active site Lys239, Lys305, or Leu302 and Oxygen of N-propylacetamide of the ligands. Almost all compounds bar D1, D4, D11, D14, and D16, show H-bond interaction between the Asp200, Asp204, Ser202, Ser477, Ile218, Lys239, and Leu238 active site with methylene hydrogen of hydroxymethyl group of the compounds. Likewise, the oxygen of the hydroxyl group of the D2, D3, D14, and D15 ligands results in H-bond formation with Lys543, Lys239, Asn203, and Gly241 active sites of the protein residue. Seven of the designed derivatives, D2 (-150.8650 kcal/mol), D7 (-140.8770 kcal/mol), D9 (-177.0910 kcal/mol), D10 (-164.6990 kcal/mol), D12 (-150.2670 kcal/mol), D13 (-146.0110 kcal/mol), and D15 (-158.7300 kcal/mol), were found to possess higher binding affinity than the design template (-120.2690 kcal/mol) and the chloroquine standard (-140.3940 kcal/mol). Compound D9 was found to have the highest binding affinity (-177.0910 kcal/mol), as shown in Table 5. Hence, form better interaction than other designed derivatives as well as the standard chloroquine drug. Four H-bond in addition to several hydrophobic

![Figure 4](image_url). Ribbon diagram showing the indolyl-3-ethanone-α-thioethers binding site on PfDHODH. Indolyl-3-ethanone-α-thioethers is displayed as IEαT, FMN, and L-orotate.
Table 5. Docking parameters of designed derivatives of Azetidine-2-carbonitriles, template, and chloroquine standard in the active site of PfDHODH protein.

| Compound No. | MolDock Score (kcal/mol) | No. of H-Bonds | Amino acid involved | Atom of ligands | H-Bond length (Å) |
|--------------|---------------------------|----------------|---------------------|-----------------|-------------------|
| D1           | -128.8790                 | 2              | Lys305              | O of NO₂        | 2.48              |
|              |                           |                | Asp204              | H of OH         | 2.14              |
| D2           | -150.8650                 | 11             | Lys543              | O of OH         | 2.75              |
|              |                           |                | Lys543              | O of OH         | 2.76              |
|              |                           |                | Ser202              | H of OH         | 2.14              |
|              |                           |                | Leu302              | H of Amide      | 2.49              |
| D3           | -128.8700                 | 3              | Asp200              | H of OH         | 1.74              |
|              |                           |                | Lys239              | O of OH         | 2.84              |
| D4           | -133.4450                 | 3              | Lys305              | O of N-propylacetamide | 2.54 |
|              |                           |                | Asp204              | H of OH         | 2.13              |
| D5           | -122.6040                 | 5              | Lys305              | O of N-propylacetamide | 2.33 |
|              |                           |                | Asp204              | H of OH         | 2.17              |
| D6           | -139.4120                 | 4              | Leu238              | H of OH         | 2.46              |
|              |                           |                | Ile206              | O of NO₂        | 2.67              |
| D7           | -140.8770                 | 3              | Asp200              | H of OH         | 2.38              |
|              |                           |                | Lys239              | O of NO₂        | 2.46              |
|              |                           |                | Lys305              | O of N-propylacetamide | 2.69 |
| D8           | -124.5920                 | 6              | Lys239              | O of NO₂        | 2.46              |
|              |                           |                | Leu238              | H of OH         | 2.10              |
| D9           | -177.0910                 | 4              | Met536              | O of NO₂        | 2.28              |
|              |                           |                | Ser477              | H of the CH₂ of hydroxymethyl | 1.76 |
| D10          | -164.6990                 | 7              | Lys559              | O of NO₂        | 2.36              |
|              |                           |                | Leu238              | H of OH         | 2.10              |
| D11          | -125.9140                 | 4              | Asn195              | O of NO₂        | 2.44              |
|              |                           |                | Lys239              | O of NO₂        | 1.97              |
| D12          | -150.2670                 | 6              | Lys305              | O of hydroxymethyl | 2.20 |
| D13          | -146.0110                 | 4              | Asp200              | H of OH         | 2.08              |
| D14          | -137.2260                 | 7              | Thr201              | H of OH         | 1.97              |
interactions were observed between D9 and the protein residue, two of which are conventional, between the oxygen of the nitro group of the ligand with Met536 protein residue, bond distance 2.28Å also, the interaction between the hydrogen of the methylene bridge bonded to a hydroxyl group of the ligand and Ser477 active site with bond distance 1.76Å. The other two interactions are carbon-hydrogen bonding between the oxygen of the ligand nitro group, hydrogen of N-propylacetamide with Gly535 bond distance 2.70Å, and Ala225, bond distance 2.60Å, respectively. Lastly, an unfavorable bump exists between the Asn274 residues with methylene hydrogen, which could add to the observer binding affinity. The binding modes for the best compound, D9, are presented in Figure 5. These interactions show the binding role of oxygen, hydrogen, and carbon atoms as well as their strength of inhibition.

**Drug-likeness ADME predictions**

The results of Lipinski’s parameters, drug-likeness as well as the in-silico ADMET screening predicted for the designed derivatives of Azetidine-2-carbonitriles were depicted in Table 6. The results show that all the designed derivatives obeyed Lipinski’s rule of five, hence possess excellent drug-like properties (32),

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**Table 5. Continued.**

| Compound No. | MolDock Score (kcal/mol) | No. of H-Bonds | Amino acid involved | Atom of ligands | H-bond length (Å) |
|--------------|--------------------------|----------------|---------------------|----------------|------------------|
| D15          | -158.7300                | 6              | Asn203              | O of OH        | 2.91             |
|              |                          |                | H of CH₂ of hydroxymethyl | O of N-propylacetamide | 2.62             |
|              |                          |                | Ser202              | H of Azetidine ring | 2.88             |
|              |                          |                | Leu302              | O of N-propylacetamide | 2.85             |
|              |                          |                | Asp204              | H of a delocalized benzene ring | 2.99             |
| D16          | -134.3030                | 3              | Lys239              | O of NO₂       | 1.89             |
|              |                          |                | Lys305              | O of N-propylacetamide | 2.48             |
|              |                          |                | Asp204              | H of OH        | 2.13             |
| Template     | -120.2690                | 3              | Lys305              | O of N-propylacetamide | 2.56             |
|              |                          |                | Asp204              | H of OH        | 2.17             |
| Cholorquine  | -140.3940                | 2              | His185              | N of Quinoline ring | 1.54             |
|              |                          |                | Val532              | H of amine     | 2.67             |

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**Figure 5.** 3- and 2-Dimensional docking pose of the interactions between D9 and the active site of the amino acid residues.
Design, Docking and ADME Properties of Antimalarial Derivatives

Other parameters like molar refractivity (MR), and the number of rotatable bonds (nRotB) were determined in addition to Lipinski’s parameters. Molar refractivity measures both the ease of polarization and volume of a compound; it ranges between 40 - 130 (33). The rule is deployed to assess the drug-likeness of a drug candidate (34). The nRotB measures the molecular flexibility of the molecule, which should be ≤ 10. The violation of more than one rule of five by a drug candidate is a pointer to the poor oral absorption of the candidate. The great combination of membrane permeability and oral bioavailability are functions of the Log of octanol/water partition coefficient (LogP), Molecular weight (MW), and Total polar surface area (TPSA) values. In addition to the role played by hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) in determining the hydrophobicity, membrane permeability, and the bioavailability of drug candidates. The results in Table 6 indicate that all compounds are within the parameter range of MW ≤ 500 Da, LogP < 5, nHBD ≤ 5, nHBA ≤ 10, and TPSA < 140 Å². This shows that the design derivatives are not only bioavailable, they are also membrane-permeable besides their hydrophobicity nature. The predicted ADME values (Table 6) have the skin permeability (log Kp) for the design compounds to be within -6.31 to -5.69 cm/s, lying between the acceptance range -8.0 to -1.0 cm/s (35). With the values of the nRotB ≤ 10, those of the MR were slightly outside the range. While most compounds showed low gastrointestinal absorption with only compounds D1-3, D13-15 that have high absorption, only a few compounds, D1, D2, D3, D14, and D15, show inhibition to CYP1A2.

Conclusion

In this research, the ligand-base method was adopted to design sixteen (16) derivatives of Azetidine-2-carbonitriles. Ten of the designed derivatives (D3-4, D8-13, and D15-16) have better activity than the template. Molecular docking studies of the derivatives show the various interactions and the binding sites of the compounds. The compound with the highest binding energy (D9) shows its

### Table 6. Lipinski properties of the derivatives of Azetidine-2-carbonitriles analyzed with SwissADME.

| S/N | MW (≤500 Da) | LogP (<5) | nHBD (≤5) | nHBA (≤10) | TPSA (<140 Å²) | Lipinski Violation | MR log Kp (cm/s) | nRotB (≤10) | GI absorption | CYP1A2 inhibitor |
|-----|--------------|-----------|------------|------------|----------------|------------------|-----------------|--------------|--------------|----------------|
| D1  | 475.97       | 3.42      | 2          | 4          | 85.59          | 0                | 135.82          | -5.69        | 9            | High Yes       |
| D2  | 475.97       | 3.42      | 2          | 4          | 85.59          | 0                | 135.82          | -5.69        | 9            | High Yes       |
| D3  | 475.97       | 3.42      | 2          | 4          | 85.59          | 0                | 135.82          | -5.69        | 9            | High Yes       |
| D4  | 486.52       | 2.07      | 2          | 6          | 131.41         | 0                | 139.64          | -6.31        | 10           | Low No         |
| D5  | 486.52       | 2.07      | 2          | 6          | 131.41         | 0                | 139.64          | -6.31        | 10           | Low No         |
| D6  | 486.52       | 2.07      | 2          | 6          | 131.41         | 0                | 139.64          | -6.31        | 10           | Low No         |
| D7  | 486.52       | 2.07      | 2          | 6          | 131.41         | 0                | 139.64          | -6.31        | 10           | Low No         |
| D8  | 486.52       | 2.07      | 2          | 6          | 131.41         | 0                | 139.64          | -6.31        | 10           | Low No         |
| D9  | 520.96       | 2.53      | 2          | 6          | 131.41         | 1                | 144.65          | -6.08        | 10           | Low No         |
| D10 | 520.96       | 2.53      | 2          | 6          | 131.41         | 1                | 144.65          | -6.08        | 10           | Low No         |
| D11 | 520.96       | 2.53      | 2          | 6          | 131.41         | 1                | 144.65          | -6.08        | 10           | Low No         |
| D12 | 520.96       | 2.53      | 2          | 6          | 131.41         | 1                | 144.65          | -6.08        | 10           | Low No         |
| D13 | 459.51       | 3.32      | 2          | 5          | 85.59          | 0                | 130.77          | -5.96        | 9            | High No        |
| D14 | 567.42       | 3.61      | 2          | 4          | 85.59          | 1                | 143.53          | -6.23        | 9            | High Yes       |
| D15 | 520.42       | 3.51      | 2          | 4          | 85.59          | 1                | 138.51          | -5.91        | 9            | High Yes       |
| D16 | 565.42       | 2.63      | 2          | 6          | 131.41         | 1                | 147.34          | -6.31        | 10           | Low No         |

MW: Molecular weight; LogP: Log of octanol/water partition coefficient; GI (Gastrointestinal) absorption; nHBA: Number of hydrogen bond acceptor(s); nHBD: Number of hydrogen bond donor(s); CYP1A2: Cytochrome P450 family 1 subfamily A member 2; MR-Molar refractivity, nRotB: Number of rotatable bonds; TPSA: Total polar surface area; log Kp: Log of skin permeability.
interaction with Met536, Ser477, Gly535, and Asn274 amino acid residues, which may be responsible for the high antimalarial activities. The designed compounds were found to pass all Lipinski’s RO5. The compounds were found to have their skin permeability coefficient within limits, with most of them having low gastrointestinal absorption, while compounds D1, D2, D3, D14, and D15 show inhibition to CYP1A2.

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Authors’ contributions

This research involves the combined efforts of all the authors. ZY. Ibrahim and A. Uzairu, Conceived and designed the research, ZY. Ibrahim and G. Shallangwa, Performed the experiments, ZY. Ibrahim, A. Uzairu, and S. Abechi Analyzed and interpreted the data, ZY. Ibrahim, G. Shallangwa, and S. Abechi Contributed materials, analysis tools, or data, ZY. Ibrahim and S. Abechi. Wrote the manuscript. All authors read and approved the final manuscript.

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This research does not require ethical approval.

Consent for publication

On behalf of the authors, I hereby granted the right of this entire article content to this journal.

Declaration of Conflicting Interests

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References

1. Pinheiro JC, Kiralj R, Ferreira MMC and Romero OAS. Artemisinin derivatives with antimalarial activity against Plasmodium falciparum designed with the aid of quantum chemical and partial least squares methods. QSAR Comb. Sci. (2003) 22: 830–42.
2. World Health Organization, 2019. World Malaria Report. Available from URL: http://apps.who.int/malaria/ media/world-malaria-report-2019. Accessed 20/05/2020.
3. Murray MC and Perkins ME. Chapter 15. Chemotherapy of malaria. Annu. Rep. Med. Chem. (1996) 31: 141–50.
4. Singh B, Sung LK, Matusop A, Radhakrishnan A, Shamsul SS, Cox-Singh J, Thomas A and Conway DJ. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet. (2004) 363: 1017–24.
5. Sondo P, Derra K, Lefevre T, Diallo-Nakanabo S, Tarnagda Z, Zampa O, Kazienaga A, Valea I, Sorgho H, Ouédraogo JB, Guiguemde TR and Tinto H. Genetically diverse Plasmodium falciparum infections, within-host competition and symptomatic malaria in humans. Sci. Rep. (2019) 9: 1-9.
6. Bowman S, Lawson D, Basham D, Brown D, Chillingworth T, Churcher CM and Barrett BG. The complete nucleotide sequence of chromosome 3 of Plasmodium falciparum. Nature. (1999) 400: 532–8.
7. Pandey AV, Tekwani BL, Singh RL and Chauhan VS. Artemisinin, an endoperoxide antimalarial, disrupts the hemoglobin catabolism and heme detoxification systems in malarial parasite. J. Biol. Chem. (1999) 274: 19383–8.
8. Kamchonwongpaisan S, Samoff E and Meshnick SR. Identification of hemoglobin degradation products in Plasmodium falciparum. Mol. Biochem. Parasitol. (1997) 86: 179–86.
9. Calderón F, Wilson DM and Gamo FJ. Antimalarial Drug Discovery. Prog. Med. Chem. (2013) 97–151.
10. Maetani M, Kato N, Jabor V, Calil FA, Nonato MC, Scherer CA and Schreiber SL. Discovery of antimalarial azetidine-2-carbonitriles that inhibit P. falciparum dihydroorotate dehydrogenase. ACS Med. Chem. Lett. (2017) 8: 438–42.
11. Ekins S, Mestres J and Testa B. In-silico pharmacology for drug discovery: applications to
targets and beyond. Br. J. Pharmacol. (2007) 152: 21–37.
(12) Paliwal S, Sharma J and Paliwal S. Quantitative structure activity relationship analysis of bisbenzo furan cations as antimalarial agents employing multivariate statistical approach. Indian J. Chem. (2012) 51: 617–30.
(13) Santos CB, Vieira JB, Lobato CC, Hage-Melini LI, Souto RN, Lima CS, Costa EV, Brasil DS, Macêdo WJ and Carvalho JC. A SAR and QSAR study of new artemisinin compounds with antimalarial activity. Molecules. (2013) 19: 367–99.
(14) Liu H, Qu L, Gao H, Wang J, Han L and Xiang B. Study on the quantitative structure-activity relationship of C-10 substituted artemisinin (QHS) ’s derivatives using rough set theory. Sci. China. B Chem. (2008) 51: 937–45.
(15) Najafi A, Sobhanardakani S and Marjani M. Exploring QSAR for antimalarial activities and drug distribution within blood of a series of 4-aminoquinoline drugs using genetic-MLR. J. Chem. (2013) 2013: 1–12.
(16) Hadanu R, Mastjeh S, Mustofa M, Sholikhah EN, Wijayanti MA and Tahir I. Quantitative structure-activity relationship analysis (QSAR) of antimalarial 1,10-phenanthroline derivatives compounds. Indo. J. Chem. (2007) 7: 72–7.
(17) Adedirin O, Uzairu A, Shallangwa GA and Abechi SE. Optimization of the anticonvulsant activity of 2-acetamido-N-benzyl-2-(5-methylfuran-2-yl) acetamide using QSAR modeling and molecular docking techniques. J. Basic Appl. Sci. (2018) 7: 430–40.
(18) Yap CW. PaDEL-descriptor: An open-source software to calculate molecular descriptors and fingerprints. J. Comput. Chem. (2010) 32: 1466–74.
(19) Abdullahi M, Uzairu A, Shallangwa GA, Mamza P, Arthur DE and Ibrahim MT. In-silico modelling studies on some C14-urea-tetrandrine derivatives as potent anti-cancer agents against prostate (PC3) cell line. J. King Saud Univ. Sci. (2020) 32: 770-9.
(20) Rogers D and Hopfinger AJ. Application of genetic function approximation to quantitative structure-activity relationships and quantitative structure-property relationships. J. Chem. Inf. Model. (1994) 34: 854–66.
(21) Golbraikh A and Tropsha A. Beware of q2! J. Mol. Graph. Model. (2002) 20: 269–76.
(22) Myers RH. Classical and modern regression application. 2nd ed. Duxbury Press, California (1990) 2: 488.
(23) Belsley DA, Kuh E and Welsch RE. Regression diagnostics: identifying influential data and sources of collinearity. John Wiley & Sons, New York (1980).
(24) Minovski N, Župrl S, Dragan V and Novič M. Assessment of applicability domain for multivariate counter-propagation artificial neural network predictive models by minimum Euclidean distance space analysis: A case study. Anal. Chim. Acta. (2013) 759: 28–42.
(25) Netzeva TI, Worth AP, Aldenberg T, Benigni R, Cronin MT, Gramatica P, Jaworska JS, Kahn S, Klopmann G and Marchant CA. Current status of methods for defining the applicability domain of (quantitative) structure-activity relationships. ATLA (2005) 33: 155–73.
(26) Kontoyianni M, McClellan LM and Sokol GS. Evaluation of docking performance: comparative data on docking algorithms. J. Med. Chem. (2004) 47: 558–65.
(27) Hodgson J. “ADMET—turning chemicals into drugs.” Nat. biotechnol. (2001) 19: 722–6.
(28) Ibrahim ZY, Uzairu A, Shallangwa G and Abechi S. Molecular docking studies, drug-likeness and in-silico ADMET prediction of some novel β-Amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives as elevators of p53 protein levels. Sci. Afr. (2020) 10: e00570.
(29) Lee A, Mercader AG, Duchowicz PR, Castro EA and Pomilio AB. QSAR study of the DPPH radical scavenging activity of di(hetero)arylamines derivatives of benzo[b]thiophenes, halophenols and caffeic acid analogues. Chemom. Intell. Lab. Sys. (2012) 116: 33–40.
(30) Fernández M and Caballero J. QSAR modeling of matrix met-alloproteinase inhibition by N-hydroxy-a-phenylsulfonylacetamide-mide derivatives. Bioorg. Med. Chem. (2007) 15: 6298–310.
(31) Amin SA and Gayen S. Modelling the cytotoxic activity of pyrazolo-triazole hybrids using descriptors calculated from the open source tool “PaDEL-descriptor.” J. Taibah Univ. Sci. (2016) 10: 896–905.
(32) Kalita J, Chetia D and Rudrapal M. Molecular Docking, Drug-likeness Studies and ADMET Prediction of Quinoline Imines for Antimalarial Activity. J. Med. Chem. Drug Des. (2019) 2: 1-7.
(33) Mishra S and Dahima R. In vitro adme studies of tug-891, a gpr-120 inhibitor using swiss adme data on docking algorithms. J. Drug Deliv. Ther. (2019) 9: 366-9.
(34) Rudrapal M, Washmin Banu Z and Chetia D. Newer series of trioxane derivatives as potent antimalarial agents. Med. Chem. Res. (2017) 27: 653–68.
(35) Gaur R, Thakur JP, Yadav DK, Kapkoti DS, Verma RK, Gupta N, Khan F, Suikia D and Bhakuni RS. Synthesis, antitubercular activity, and molecular modeling studies of analogues of isoliquiritigenin and liquiritigenin, bioactive components from Glycyrrhiza glabra. Med. Chem. Res. (2015) 24: 3494–503.

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