Heliyon 7 (2021) e05924

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Molecular modeling and design of some β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives against chloroquine sensitive, 3D7 strain of *Plasmodium falciparum*

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ARTICLE INFO

Keywords:
Molecular modeling
Design
Antimalarial agent
β-Amino alcohol grafted 1,4,5-trisubstituted 1, 2, 3-triazoles
Molecular descriptors
First ionization potential
GFA
Plasmodium falciparum

ABSTRACT

Resistance nature of *Plasmodium falciparum* (*P. falciparum*) to the most effective antimalarial drug, Artemisinin, intimidate the global goal of total eradication of malarial. In an attempt to overcome this challenge, the research was aimed at designing derivatives of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles with improve activity against the *P. falciparum* through structural modifications of the most active compound (design template), and their activity determined using the developed theoretical predictive model. To achieve this, the geometries were optimized via density functional theory (DFT) using B3LYP/6-31G* basis set to generate molecular descriptors for model development. Analysis of the developed model and the descriptors mean effect lead to the design of derivatives with improved activity. Five (5) theoretical models were developed, where the model {pIC_{50} = 5.95067(SpMin5_Bhi) - 0.0323461(RDF45m) + 0.0203865 (RDF95e) + 0.0499285 (L1m) - 3.50822} with the highest coefficient of determination (R^2) of 0.9367, cross-validated R^2 (Q^2cv) of 0.8242, and the external validated R^2 (R^2_{pred}) of 0.9462, selected as the best model. The mean effect analysis revealed descriptor SpMin5_Bhi as the most contributive. The descriptor encodes the first ionization potentials of the compounds and are influenced by electron-withdrawing/donating substituents. Hence, structural modifications of the compound with the highest activity (a design template) using electron-withdrawing substituents such as $–NO_2$, $–SO_3H$, -Br, –I, $–CH_2CH_3$, and $–CH_3$ was done at a different positions, to obtain five (5) hypothetical novel compounds. The statistical results, shows the robustness, excellent prediction power, and validity of the selected model. Descriptor analysis revealed the first ionization potential (SpMin5_Bhi) to play a significant role in the activity of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives. The five design derivatives of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles with higher activities revealed compound 21C to have an antimalarial activity of pIC_{50} = 6.7573 higher than it co-designed compounds and even the standard drug. This claim could be verified through molecular docking to determine their interaction with the target protein.

1. Introduction

Malaria is the most deadly illness around the primitive tropical regions and its environs, and remains a major health concern globally. Children under the ages of five are mostly affected by malarial that may also result in malady in pregnant women, miscarriages, and even stillbirths (Lusakibanza et al., 2010; Manohar et al., 2014; WHO, 2016). Almost half of the world's populations are at the peril of the illness with more than 500 million clinical and over 1 million deaths estimated cases yearly (Hay et al., 2010; Guerin et al., 2002; Pink et al., 2005), with 90% of the annual deaths cases occurring in the African region (WHO, 2016). It is a virulent and infective illness induced by the protozoan, *Plasmodium* (Vaishnani, 2011) broadcasted from the blood of one infected individual to another by female Anopheles mosquito. The human *Plasmodium* grows into five specific species: *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi* (Murray and Perkins 1996) with *P. falciparum* liable for the greatest austere cases of human malaria (Newton et al., 1999).

P. falciparum survives both in the female Anopheles mosquito and the human hosts. The mosquito do not experience any destructive effect of the infection unlike in the human host where the contagion springs as the sporozoite form of the parasite penetrate the skin during nourishing and then transmit promptly via the bloodstream to the liver having a pre-symptomatic incubation period of replication in the hepatocytes

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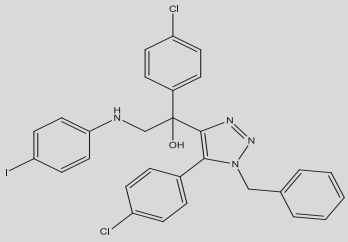
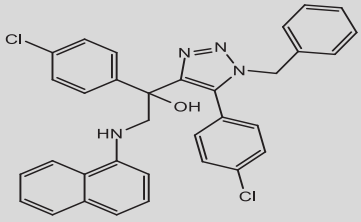
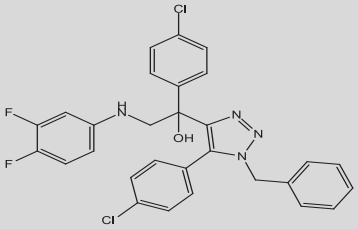
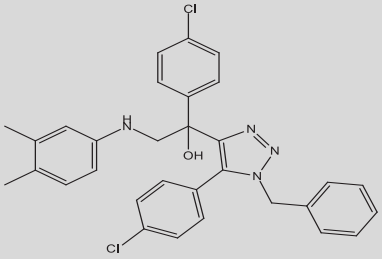
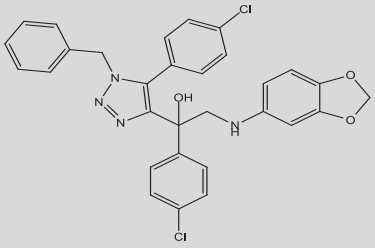
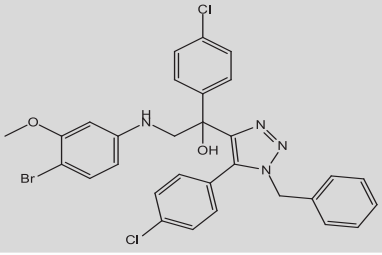
https://doi.org/10.1016/j.heliyon.2021.e05924
Received 3 August 2020; Received in revised form 13 October 2020; Accepted 6 January 2021

Table 1. Chemical structures and activities of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives against Chloroquine sensitive (3D7) strain.

Compounds	Structures	IC_{50} (μM)	pIC_{50}
1		1.48	5.8297
2		1.33	5.8761
3		2.15	5.6676
4		2.24	5.6498
5		2.73	5.5638
6		1.65	5.7825

(*continued on next page*)

Table 1 (*continued*)

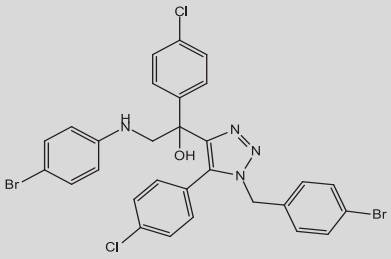
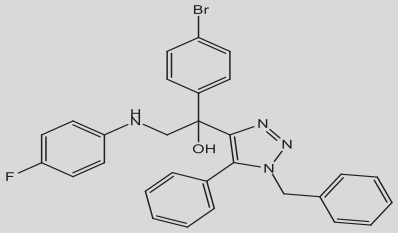
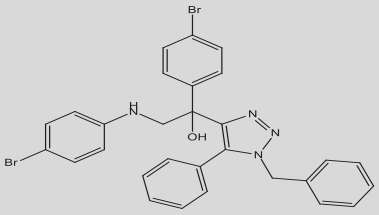
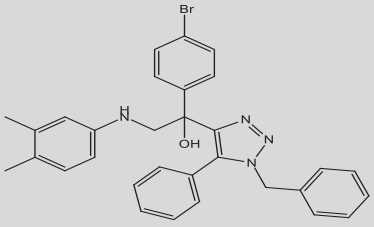
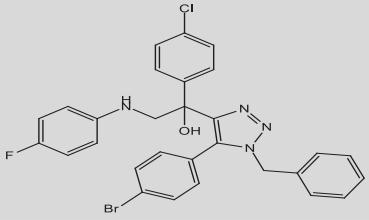
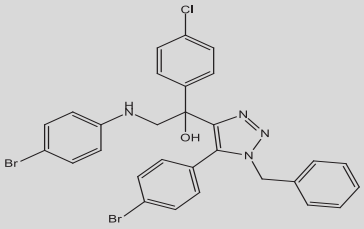
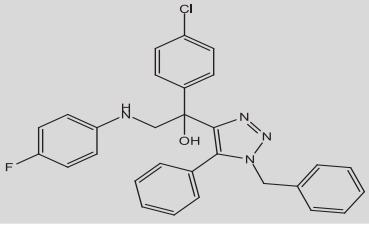
Compounds	Structures	IC_{50} (μM)	pIC_{50}
7		2.42	5.6162
8		2.71	5.5670
9		1.65	5.7825
10		2.72	5.5654
11		3.21	5.4935
12		0.87	6.0605
13		3.31	5.4802

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Table 1 (*continued*)

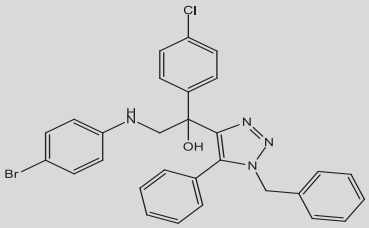
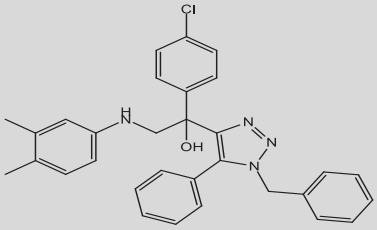
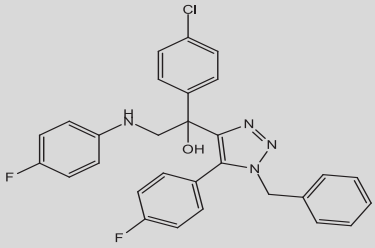
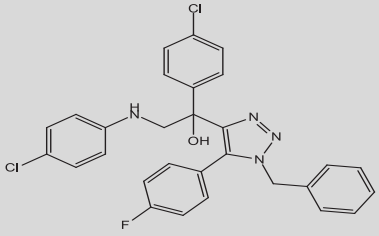
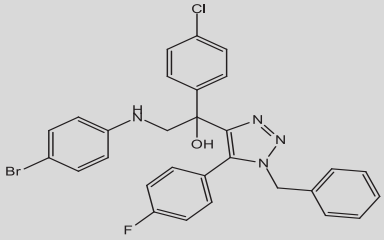
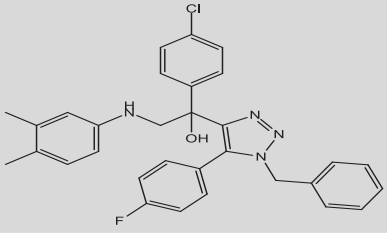
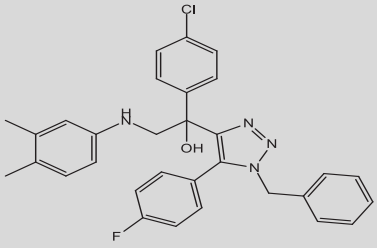
Compounds	Structures	IC_{50} (μM)	pIC_{50}
14		1.95	5.7100
15		2.58	5.5884
16		3.87	5.4123
17		2.85	5.5452
18		1.10	5.9586
19		2.67	5.5735
20		1.58	5.8013

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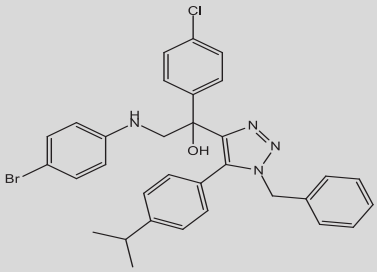
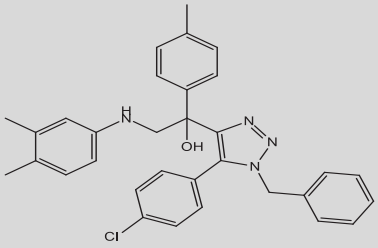
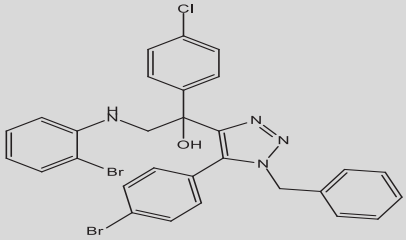
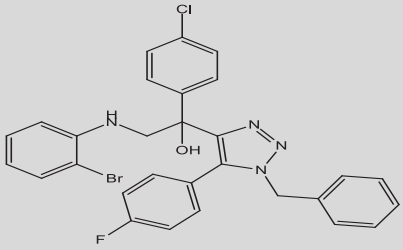
Table 1 (*continued*)

Compounds	Structures	IC_{50} (μM)	pIC_{50}
21		0.30	6.5229
22		1.78	5.7496
23		11.57	4.9367
24		9.09	5.0414

(Phillips et al., 2017). The parasite spent about a week in the liver thereafter leaves for the bloodstream to invade the red blood cells and undergo a periodic cycles of asexual replication for 2 days (White et al., 2014). These asexual blood-stage parasites causes the symptoms that indicates malarial infection (Tuteja, 2007). Few parasites will equally undergo differentiation into sexual stage gametocytes, which could be taken by another mosquito bite to endure propagation cycle, with no clinical symptoms caused by the gametocytes (Phillips et al., 2017).

The handpicked drugs for malaria therapy are artemisinin and its derivatives, on which it is considered to have a great action against

Table 2. Parameters of validating the developed models.

Parameters	Eq. (4)	Eq. (5)	Eq. (6)	Eq. (7)	Eq. (8)
Friedman LOF	0.0276	0.0314	0.0329	0.0338	0.0272
R-squared (R^2)	0.8937	0.9367	0.9337	0.9318	0.8952
Adjusted R-squared (R^2_{adj})	0.8709	0.9172	0.9134	0.9108	0.8728
Cross validated R-squared (Q^2cv)	0.8109	0.8242	0.8609	0.8387	0.8203
External Validated R^2 (R^2_{pred})	0.7953	0.9462	0.7948	0.8502	0.7612
Significant Regression	Yes	Yes	Yes	Yes	Yes
Significance-of-regression F-value	39.2229	48.1064	45.80158	44.40638	39.88006
Critical SOR F-value (95%)	3.5032	3.2266	3.226561	3.226561	3.503249
Replicate points	0	0	0	0	0
Computed experimental error	0	0	0	0	0
Lack-of-fit points	14	13	13	13	14
Min expt. error for non-significant LOF (95%)	0.0790	0.0627	0.064165	0.065098	0.078407

*The criteria for model acceptability is: $R^2 \geq 0.6$ (Alexander et al., 2015).

Table 3. Correlation matrix of the model descriptors and their VIF.

	SpMin5_Bhi	RDF45m	RDF95e	L1m	*VIF*
SpMin5_Bhi	1				1.8640
RDF45m	0.039292	1			1.0731
RDF95e	0.605871	-0.07456	1		1.7720
L1m	0.246993	0.256237	-0.10207	1	1.2577

(White, 2004). In addition to these, many other freely available and low-cost antimalarial drugs such as pyrimethamine, quinine, chloroquine, mefloquine are employed to get rid of malarial, although this is not without resistance from this protozoa (White, 2004; Zongo et al., 2005). Thus, necessitating the need to establish novel drugs for treating malaria. A five-membered ring triazole consisting of two carbon atoms and three nitrogen atoms exist as either 1,2,3-triazole and 1,2,4-triazole, having amide, carboxylic acid, ester and other heterocycles such as pyrazole isosteres acting as the framework (Bonandi et al., 2017). Triazole derivatives were reported to possess anti-tubercular (Zhang et al., 2017; Xu et al., 2017), anti-cancer (Fan et al., 2018a; Akhtar et al., 2017), antibacterial (Dheer et al., 2017; Eswaran et al., 2009), and antimalarial (Roy, 2017; Fan et al., 2018b) activities belief to be unconnected to their tendency to form non-covalent interactions capable of improving the solubility and binding ability of bimolecular targets. In addition, arylamino alcohols such as mefloquine, quinine, lumefantrine, and halofantrine are reported as antimalarial agents, although their mechanism of action is vaguely understood except for the inhibition of detoxification of heme in asexual blood stage (ABS) parasites (Müller and Hyde, 2010). Therefore, β-Amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles reported to have anticancer properties (Hamidullah et al., 2015; Ajay et al., 2012), also possessing antimalarial properties (Devender et al., 2016) could provide relief. The daunting nature of antimalarial drug discovery leads to the undertaking of a structure-activity relationship analysis to develop regression equations (Models) that connect the structural properties of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives with their activity against malarial through Genetic Function Algorithm (GFA) which laid the ways for the designing of new antimalarial derivatives with enhancing activity against *P. falciparum.*

Numerous researches were conducted on the QSAR analysis of antimalarial compounds (Hadni et al., 2018; Ibrahim et al., 2020; Tseng et al., 2016), like the 3-dimensional modeling and docking studies conducted to determine the antimalarial activity of thirty-two novel triazoles quinine derivatives using comparative-molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) (Khaldan et al., 2020), although a similar analysis is yet to be extended to β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles and its derivatives. This research was aimed at expressing the antimalarial activity of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles as a function of their structural features through model development using genetic function algorithm (GFA) to predict the activity of other derivatives, leading to the design of novel antimalarial with better activity through the help of the descriptors mean effect.

2. Materials and methods

2.1. Experimental data

Twenty-four β-amino alcohol grafted 1,4,5-trisubstituted 1, 2, 3-triazoles derivatives were used the data set. The chemical structures and their activities against *P. falciparum* were extracted from the literature

Table 4. Comparison of Experimental, predicted and residual of the data set.

S/N	Experimental pIC_{50}	Predicted pIC_{50}	Residual
1	5.8297	5.8745	-0.0448
2	5.8761	5.7121	0.1640
3	5.6676	5.5905	0.0771
4	5.6498	5.6495	0.0003
5	5.5638	5.5250	0.0388
6	5.7825	5.8204	-0.0379
7	5.6162	5.6255	-0.0093
8	5.5670	5.5742	-0.0072
9	5.7825	5.8070	-0.0245
10*	5.5654	5.7177	-0.1523
11*	5.4935	5.6162	-0.1227
12*	6.0605	5.8913	0.1692
13	5.4802	5.4449	0.0353
14	5.7100	5.7575	-0.0475
15	5.5884	5.6277	-0.0393
16	5.4123	5.4623	-0.0500
17	5.5452	5.4677	0.0775
18*	5.9586	5.7926	0.1660
19	5.5735	5.6407	-0.0672
20	5.8013	5.9514	-0.1501
21	6.5229	6.4282	0.0947
22*	5.7496	5.6820	0.0676
23*	4.9367	5.3807	-0.4440
24	5.0414	5.0514	-0.0100

NB: * Test Sets.

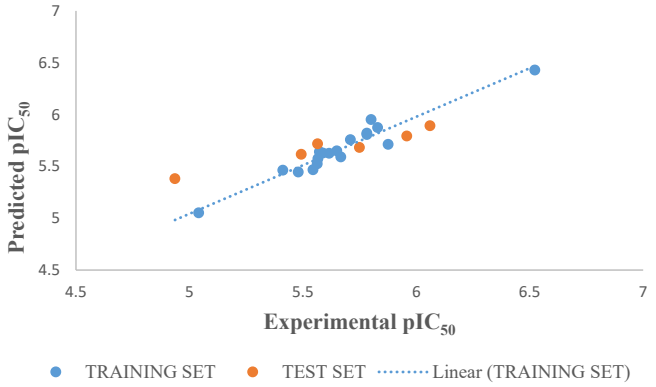


Figure 1. Experimental activity plotted against predicted activity for the entire dataset.

(Devender et al., 2016). Their activities expressed as IC_{50} (μM), were then converted to pIC_{50} by taking the negative logarithm of the IC_{50} (M) as indicated in Table 1.

2.2. Geometry optimization and descriptors calculations

The molecular geometries of the dataset were sketched on the ChemDraw Ultra 12 and thereafter imported into the spartan'14 version 1.1.2 software on which all the compounds were fully optimized using DFT by invoking B3LYP (Lee et al., 1988) and a basis set of 6-31G* to provide a precise conformer relation throughout the compounds. The energy minimized structures were ported to PaDEL-Descriptor used to compute over 1500 molecular descriptors ranging between 0-3D-classes (Yap, 2010), which were used to generate the mathematical models.

2.3. Dataset pre-treatment and division

The pre-treatment of the dataset descriptors involves; discarding descriptors with constant values, those with high correlation coefficient values, as well as columns having a less than 0.001 variance value from the pool of the descriptors. The matrix of the pre-treated data set was imported into the DatasetDivision1.2 program where it was separated into training (consisting of 18 compounds) and test set (consisting of the remaining 6 compounds) using the clustering method approach based on their activity/property (Golmohammadi et al., 2012).

2.4. Selection of variables and model development

The models were developed using Material Studio 8.0 where the outstanding blending of molecular descriptors leads to significant linear

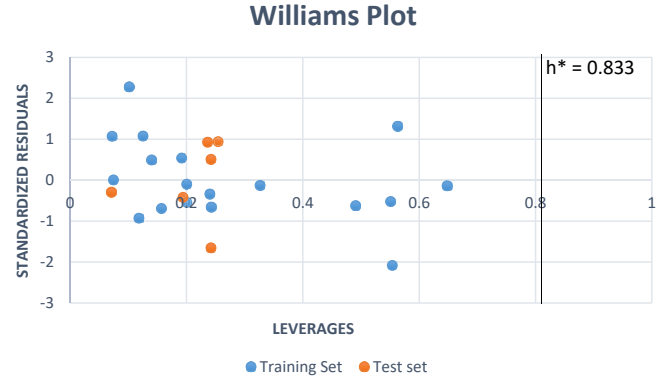


Figure 2. The plot of the standardized residuals vs. leverages (Williams plot).

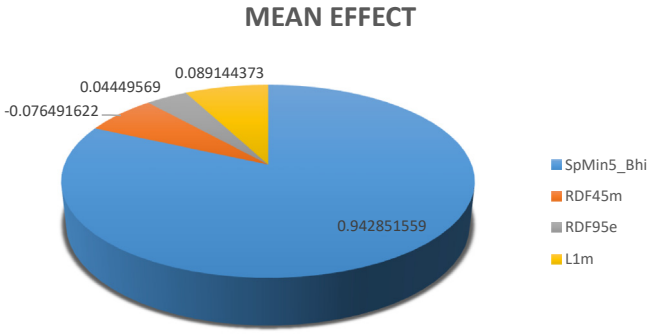


Figure 3. 3-D pie mean effect of descriptors.

QSAR models that connect the molecular structures of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives with their anti-malarial activities. This was achieved through the genetic function algorithm (GFA) component of the material studio. A genetic function algorithm searched for all the possible mixture of descriptors that give sound models plus employing a lack of fit (LOF) function to measure the fitness of each combination (Rogers and Hopfinger, 1994). The generated regression equation takes the generalized form as presented in Eq. (1).

$$Y = b_1x_1 + b_2x_2 + b_3x_3 + C \quad (1)$$

where Y denote response variable (pIC_{50}), 'b's, the coefficients of regression for, the independent variables, 'x's, model descriptors, and 'c' intercept.

2.5. QSAR model validation

The internal validation technique employed was the leave-one-out (LOO), where a training set molecule was discarded and the remaining data used to construct a model using the same descriptor combination contained in the model being validated. The new equation obtained was subjected to guessing the activity of the discarded compound. This was done for all the training set molecules and activities of the discarded compounds, in turn, predicted with the new model. The external validation involves predicting the activities of the dataset kept aside (test set) using the model. The choice of the models was based on the values of the

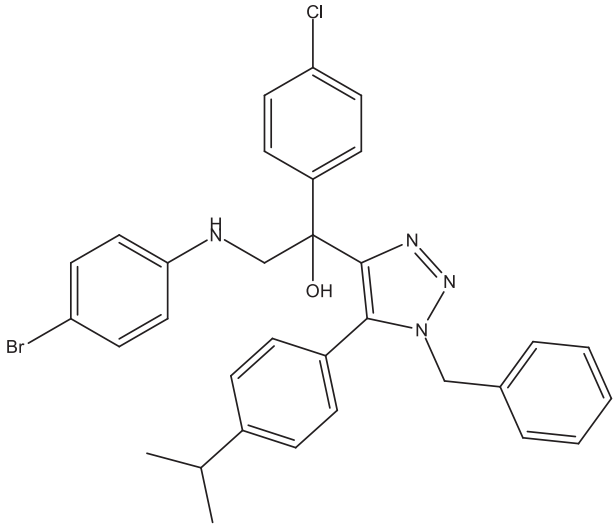
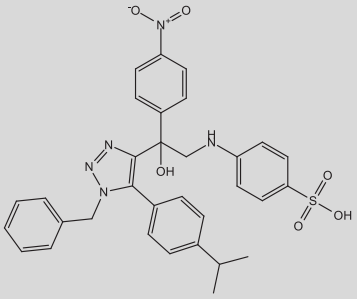
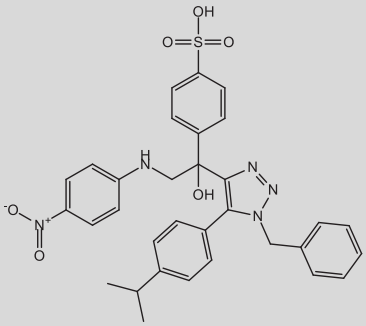
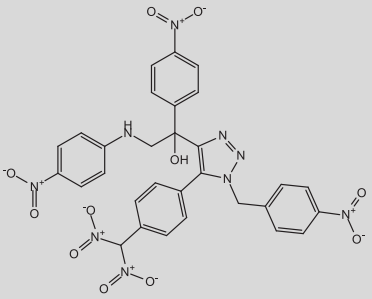
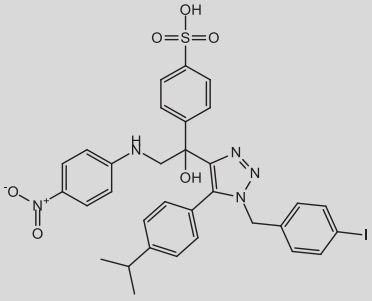
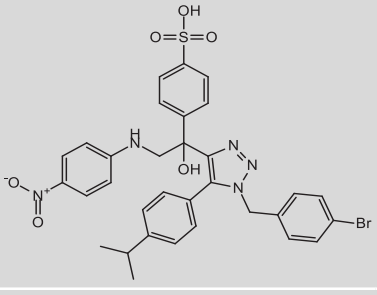


Figure 4. Designed Compound Template, 1-(1-benzyl-5-(4-isopropylphenyl)-1H-1,2,3-triazol-4-yl)-2-((4-bromophenyl)amino)-1-(4-chlorophenyl)ethanol, pIC_{50} = 6.5229.

Table 5. Molecular structures of design β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives and their hypothetical activities.

S/N	STRUCTURES	pIC_{50}
21A		6.7532
21B		6.7449
21C		6.7573
21D		6.6056
21E		6.7428
Chloroquine Standard		3.5579

coefficient of determination (R^2), cross-validated R^2 (Q^2cv), and the external validated R^2 (R^2_{pred}) (Golbraikh, and Tropsha, 2002). The model with the highest prediction on the test set (R^2_{pred}) was selected as the best model.

2.6. Descriptors variance inflation factor (VIF) determination

Inter-correlations between the selected model's descriptors (Multi-collinearity) was evaluated using the variance inflation factor (VIF)

(Myers, 1990). The VIF of regression coefficients is expressed in Eq. (2). A rule of thumb for VIF of 10 or even 4 is an indication of enormous multi-collinearity between descriptors (Belsley et al., 1980).

$$VIF = {}^{1}/_{1 - R_i^2} \tag{2}$$

where R_i denotes the coefficient produced by regressing the descriptor x_i against the other descriptors x_j ($j \neq i$).

2.7. Descriptor relevance (mean effect)

The mean effect quantifies the influence of the selected model's descriptors towards its generation. The divergent directions in the activities which may include a decrease/increase descriptor values are indicated by the signs of the mean effect which was calculated from Eq. (3).

$$Mean\ Effect = \frac{\beta_j \sum_i^n D_j}{\sum_j^m \left(\beta_j \sum_i^n D_j\right)} \tag{3}$$

where β_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 (Minovski et al., 2013).

2.8. Model applicability domain (AD)

The biological space of a model defined its limitations concerning the structural realm and capacity of response. William's plot was engaged to interpret the relevant space of the model in terms of biological territory. Compounds having their leverage values exceeding the caution leverage (h*) and determined standardized residual values greater than within plus or minus three standard deviation units were regarded as an aberration (Netzeva et al., 2005).

2.9. Molecular design

Antimalarial compounds with better activities were designed through an in-silico method of virtual template-based design. The method is often employed to filter and model compounds with improved activity by connecting the experimental activities of the compounds with their structures. Hence, the data set with the highest activity will be deployed as the template in designing hypothetical compounds with improving activities.

3. Results and discussion

3.1. Selected QSAR model

The selected models obtained through the genetic function algorithm analysis of the datasets are as presented below:

$$pIC_{50} = 0.00670571*\mathbf{SpAD\_Dzm}\text{-}0.0466513*\mathbf{RDF45m} + 0.0488028*\mathbf{L1m}\text{+}3.41559 \tag{4}$$

$$pIC_{50} = 5.95067*\mathbf{SpMin5\_Bhi}\text{-}0.0323461*\mathbf{RDF45m} + 0.0203865*\mathbf{RDF95e}\text{+}0.0499285*\mathbf{L1m}\text{-}3.50822 \tag{5}$$

$$pIC_{50} = 0.00375302*\mathbf{SpAD\_Dzp}\text{+}0.204533*\mathbf{XLogP}\text{+}0.3735*\mathbf{MOMI\text{-}XZ}\text{-} 0.0505519*\mathbf{RDF45m} + 3.38116 \tag{6}$$

$$pIC_{50} = 0.00413755*\mathbf{SpAD\_Dzm}\text{-}0.0407013*\mathbf{RDF45m} + 0.0174462*\mathbf{RDF95e}\text{+}0.0525551*\mathbf{L1m} + 3.81942 \tag{7}$$

$$pIC_{50} = 0.0071875*\mathbf{SpAD\_Dzm}\text{+}0.469588*\mathbf{MOMI\text{-}XZ}\text{-} 0.0562158*\mathbf{RDF45m} + 3.11199 \tag{8}$$

3.2. Model validation

The selected models were validated both internally and externally for their fitting, reliability, stability, and predictability with the aid of parameters as presented in Table 2, from which model 2 having the highest value of external validated R^2 (R^2_{pred}) was established to have complied with the least prerequisite for a dependable, foretelling and robust QSAR model (Veerasamy et al., 2011). Hence, it was selected the finest model in predicting and designing of unique antimalarial derivatives with its high statistical parameters of high coefficient of determination (R^2) of 0.9367, adjusted coefficient of determination (R^2_{adj}) of 0.9172, cross-validated R^2 (Q^2cv) of 0.8242, and external validated R^2 (R^2_{pred}) of 0.9462. This statistical result confirmed the validity of the molecular structures and their activities (Habib et al., 2012, 2014). These parameters, when compared to those of 3D constructed models (Khaldan et al., 2020), with their respective CoMFA and CoMSIA parameters, R^2 (0.98 and 0.95), Q^2cv (0.61 and 0.76), and R^2_{pred} (0.92 and 0.85). Hence, could predict the antimalarial activity of the novel triazoles quinine derivatives better, by virtue of the higher value of R^2_{pred} (0.9462) compared to those of the 3D model (0.92 and 0.85).

3.3. Correlation matrix and variance inflation factor (VIF) for the model descriptors

The low values of the variance in the correlation matrix shown in Table 3, indicates the non-mutual relationship among the descriptors. This claim was supported by low (less than 10) values of descriptors VIF calculated (Table 3), indicates that the descriptors are found to be orthogonal (Ibrahim et al., 2020), as such the model is statistically significant.

3.4. Comparison of the experimental with the predictive pIC_{50} of the model

The graph of experimental activities in contrast to the predicted activities of the training as well as the test sets is reflected in Figure 1 and the occurrence of the test sets scattered all around the legend line of training set speaks volumes of the accuracy of the finest model. Hence, the graph's linearity indicates the predictive strength of the model. Comparison between the Predictive pIC_{50} and the experimental pIC_{50} shows small values of the residuals for the data set as shown in Table 4, revealed a good agreement between them.

3.5. Interpretation of the best model descriptors

The descriptors SpMin5_Bhi (Smallest absolute eigenvalue of Burden modified matrix - n 5/weighted by relative first ionization potential), RDF95e (Radial distribution function - 095/weighted by relative Sanderson electronegativities), and L1m (1st component size directional WHIM index/weighted by relative mass) in the best model, contributed positively to the activity of the model, as an increase in their values, increases the value of the activity. On the contrary, the descriptor RDF45m (Radial distribution function - 045/weighted by relative mass) contributes negatively to the antimalarial activity. Increasing its values reduces the antimalarial activity of the compound and vice versa.

3.6. Applicability domain (AD) of the model

Due to the absence of a compound beyond caution leverage (h*) as reflected in Figure 2, the entire dataset was found to have good leverage values and are within the realm of the model, hence confirming the guessing strength of the model.

3.7. Descriptor relevance (mean effect)

The results of the mean effect analysis carried out revealed the contributions of the descriptors in the best model relative to one another.

Descriptors SpMin5_Bhi, RDF45m, RDF95e, and L1m have mean effect values of 0.942852, -0.07649, 0.044496, and 0.089144 respectively as revealed in Figure 3. Hence, descriptor SpMin5_Bhi which has the highest mean effect (0.942852) contributes more to the activity of the model than any other descriptor in the model, hence played a vital role in the design of better β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives.

3.8. Molecular design

Compound 21 (Figure 4) was used as the template for the design, due to its high activity ($pIC_{50} = 6.5229$). From the mean effect analysis, the descriptor SpMin5_Bhi, found to influence the model the most, was utilized in the design of several hypothetical derivatives of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles. The value of the descriptor relates to the first ionization potentials of a molecule. The first ionization potentials are lowered by electron-donating substituents while they are raised by electron-withdrawing substituents. Hence, electron-withdrawing substituents such as $–NO_2$, $–SO_3H$, -Br, –I, $–CH_2CH_3$, and $–CH_3$ were assigned at a different position on the designed template. Resulting in the design of 5 promising derivatives of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles with higher activities as can be seen in Table 5. Furthermore, the designed derivative 21C has better activities ($pIC_{50} = 6.75723$) than that of the template as well as those of its fellow designed compounds.

3.9. Conclusion

This study was conducted to explore a predictive model capable of explaining the structural requirements responsible for antimalarial activities in β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles derivatives. The selected model reveals good statistical parameters in the validation which confirm the predictive strength of the model. More so, the most contributive descriptor, SpMin5_Bhi, encodes information about the first ionization potentials of the antimalarial compound, as such is a dominant player in the design of five new potential antimalarial derivatives of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles with higher activity than even the standard drug. From which compound 21C, has better activity than its fellow designed compounds. The drug-like properties, as well as the docking analysis of these designed compounds, could be exploited to determine their interaction with their target protein.

Declarations

Author contribution statement

ZY Ibrahim and A. Uzairu: conceived and designed the experiments

ZY Ibrahim and G. Shallangwa: performed the experiments

ZY Ibrahim, A. Uzairu, S. Abechi and G. Shallangwa: analyzed and interpreted the data

A. Uzairu, S. Abechi: contributed reagents, materials, analysis tools or data.

ZY Ibrahim and G. Shallangwa: wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

Ajay, A., Gupt, M.P., Devender, N., Tripathi, R.P., 2012. Accessing a small library of pluripotent 1,4,5-trisubstituted 1H-1,2,3-triazoles via diversity-oriented synthesis. Mol. Divers. 16 (2), 335–350.

Akhtar, J., Khan, A.A., Ali, Z., Haider, R., Shahar Yar, M., 2017. Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur. J. Med. Chem. 125, 143–189.

Alexander, D.L.J., Tropsha, A., Winkler, D.A., 2015. Beware of R2: simple, unambiguous assessment of the prediction accuracy of QSAR and QSPR models. J. Chem. Inform. Model. 55 (7), 1316–1322.

Belsley, D.A., Kuh, E., Welsch, R.E., 1980. Regression Diagnostics: Identifying Influential Data and Sources of Collinearity. Wiley, New York.

Bonandi, E., Christodoulou, M.S., Fumagalli, G., Perdicchia, D., Rastelli, G., Passarella, D., 2017. The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. Drug Discov. Today 22 (10), 1572–1581.

Devender, N., Gunjan, S., Chhabra, S., Singh, K., Pasam, V.R., Shukla, S.K., Tripathi, R.P., 2016. Identification of β-Amino alcohol grafted 1,4,5 trisubstituted 1,2,3-triazoles as potent antimalarial agents. Eur. J. Med. Chem. 109, 187–198.

Dheer, D., Singh, V., Shankar, R., 2017. Medicinal attributes of 1,2,3-triazoles: current developments. Bioorg. Chem. 71, 30–54.

Eswaran, S., Adhikari, A.V., Shetty, N.S., 2009. Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. Eur. J. Med. Chem. 44 (11), 4637–4647.

Fan, Y.L., Cheng, X.W., Wu, J.B., Liu, M., Zhang, F.Z., Xu, Z., Feng, L.S., 2018. Antiplasmodial and antimalarial activities of quinolone derivatives: an overview. Eur. J. Med. Chem. 146, 1–14.

Fan, Y.-L., Ke, X., Liu, M., 2018. Coumarin-triazole hybrids and their biological activities. J. Heterocycl. Chem. 55 (4), 791–802.

Golbraikh, A., Tropsha, A., 2002. Beware of q2! J. Mol. Graph. Model. 20 (4), 269–276.

Golmohammadi, H., Dashtbozorgi, Z., Acree, W.E., 2012. Quantitative structure-activity relationship prediction of blood-to-brain partitioning behavior using support vector machine. Eur. J. Pharmaceut. Sci. 47, 421–429.

Guerin, P.J., Olliaro, P., Nosten, F., Druilhe, P., Laxminarayan, R., Binka, F., White, N.J., 2002. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. Lancet Infect. Dis. 2 (9), 564–573.

Habib, O.M.O., Hassan, H.M., Moawad, E.B., El-Mekabaty, A., 2012. Synthesis of some novel antioxidant and anticorrosive additives for Egyptian lubricating oils. Petrol. Sci. Technol. 30 (23), 2435–2449.

Habib, O.M.O., Hassan, H.M., El-Mekabaty, A., 2014. Synthesis and evaluation of some new quinazolones as antioxidant additives for Egyptian lubricating oils. Petrol. Sci. Technol. 32 (10), 1201–1212.

Hadni, H., Mazigh, M., Charif, E., Bouayad, A., Elhallaoui, M., 2018. Molecular modeling of antimalarial agents by 3D-QSAR study and molecular docking of two hybrids 4-Aminoquinoline-1,3,5-triazine and 4-Aminoquinoline-oxalamide derivatives with the receptor protein in its both wild and mutant types. Biochem. Res. Int. 1–15, 2018.

Hamidullah, Saini, K.S., Ajay, A., Devender, N., Bhattacharjee, A., Das, S., Dwivedi, S., Gupt, M.P., Bora, H.K., Mitra, K., Tripathi, R.P., Konwar, R., 2015. Triazole analog 1-(1-benzyl-5-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-2-(4-bromophenylamino)-1-(4-chlorophenyl)ethanol induces reactive oxygen species and autophagy-dependent apoptosis in both in vitro and in vivo breast cancer models. Int. J. Biochem. Cell Biol. 65, 275–287.

Hay, S.I., Okiro, E.A., Gething, P.W., Patil, A.P., Tatem, A.J., Guerra, C.A., Snow, R.W., 2010. Estimating the global clinical burden of Plasmodium falciparum malaria in 2007. PLoS Med. 7 (6), e1000290.

Ibrahim, Z.Y., Uzairu, A., Shallangwa, G., Abechi, S., 2020. Theoretical design of novel antimalarial agents against P. falciparum strain, Dd2 through the QSAR modeling of synthesized 2′-substituted triclosan derivatives. Heliyon 6 (9), e05032.

Khaldan, A., El khatabi, K., El-Mernissi, R., Ghaleb, A., Hmamouchi, R., Sbai, A., Bouachrine, M., Lakhlifi, T., 2020. 3D-QSAR Modeling and Molecular Docking Studies of novel triazoles-quinine derivatives as antimalarial agents. J. Mater. Environ. Sci. 11 (3), 429–443, 2020.

Lee, C., Yang, W., Parr, R.G., 1988. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B 37 (2), 785–789.

Lusakibanza, M., Mesia, G., Tona, G., Karemere, S., Lukuka, A., Tits, M., Frédérich, M., 2010. In vitro and in vivo antimalarial and cytotoxic activity of five plants used in Congolese traditional medicine. J. Ethnopharmacol. 129 (3), 398–402.

Manohar, S., Tripathi, M., Rawat, D.S., 2014. 4-aminoquinoline based molecular hybrids as antimalarials: an overview. Curr. Top. Med. Chem. 14 (14), 1706–1733.

Minovski, N., Župerl, S., Drgan, V., Novič, M., 2013. 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 759, 28–42.

Müller, I.B., Hyde, J.E., 2010. Antimalarial drugs: modes of action and mechanisms of parasite resistance. Future Microbiol. 5 (12), 1857–1873.

Murray, M.C., Perkins, M.E., 1996. Chapter 15. Chemotherapy of malaria. Annu. Rep. Med. Chem. 31, 141–150.
Myers, R.H., 1990. Classical and Modern Regression Application, second ed. Duxbury Press, CA.
Netzeva, T.I., Worth, A.P., Aldenberg, T., Benigni, R., Cronin, M.T., Gramatica, P., Jaworska, J.S., Kahn, S., Klopman, G., Marchant, C.A., 2005. Current status of methods for defining the applicability domain of (quantitative) structure-activity relationships. ATLA 33, 155–173.
Newton, B.M., DPhil, Mrcp, P., White, DSc, Md, Frcp, N., 1999. MALARIA: new developments in treatment and prevention. Annu. Rev. Med. 50 (1), 179–192.
Phillips, M.A., Burrows, J.N., Manyando, C., van Huijsduijnen, R.H., Van Voorhis, W.C., Wells, T.N.C., 2017. Malaria. Nature Rev. Dis. Prim. 3, 17050.
Pink, R., Hudson, A., Mouriès, M.-A., Bendig, M., 2005. Opportunities and challenges in antiparasitic drug discovery. Nat. Rev. Drug Discov. 4 (9), 727–740.
Rogers, D., Hopfinger, A.J., 1994. Application of genetic function approximation to quantitative structure-activity relationships and quantitative structure-property relationships. J. Chem. Inf. Model. 34 (4), 854–866.
Roy, K.K., 2017. Targeting the active sites of malarial proteases for antimalarial drug discovery: approaches, progress and challenges. Int. J. Antimicrob. Agents 50 (3), 287–302.
Tseng, T.-S., Lee, Y.-C., Hsiao, N.-W., Liu, Y.-R., Tsai, K.-C., 2016. Comparative study between 3D-QSAR and Docking-Based Pharmacophore models for potent Plasmodium falciparum dihydroorotate dehydrogenase inhibitors. Bioorg. Med. Chem. Lett 26 (2), 265–271.
Tuteja, R., 2007. Malaria - an overview. FEBS J. 274 (18), 4670–4679.
Vaishnani, J., 2011. Cutaneous findings in five cases of malaria. Indian J. Dermatol. Venereol. Leprol. 77 (1), 110.
Veerasamy, R., Rajak, H., Jain, A., Sivadasan, S., Varghese, C., Agrawal, R.K., 2011. Validation of QSAR models-strategies and importance. Int. J. Drug Design Discov. 2, 511–519 (2011).
White, N.J., 2004. Antimalarial drug resistance. J. Clin. Invest. 113 (8), 1084–1092.
White, N.J., Pukrittayakamee, S., Hien, T.T., Faiz, M.A., Mokuolu, O.A., Dondorp, A.M., 2014. Malaria. Lancet 383 (9918), 723–735.
World Health Organization, 2016. World Malaria Report 2015. World Health Organization, Geneva, Switzerland.
Xu, Z., Song, X.-F., Hu, Y.-Q., Qiang, M., Lv, Z.-S., 2017. Azide-alkyne cycloaddition towards 1H-1,2,3-triazole-tethered gatifloxacin and isatin conjugates: design, synthesis and in vitro anti-mycobacterial evaluation. Eur. J. Med. Chem. 138, 66–71.
Yap, C.W., 2010. PaDEL-descriptor: an open-source software to calculate molecular descriptors and fingerprints. J. Comput. Chem. 32 (7), 1466–1474.
Zhang, S., Xu, Z., Gao, C., Ren, Q.C., Chang, L., Lv, Z.S., Feng, L.S., 2017. Triazole derivatives and their anti-tubercular activity. Eur. J. Med. Chem. 138, 501–513.
Zongo, I., Dorsey, G., Rouamba, N., et al., 2005. Amodiaquine, sulfadoxine-pyrimethamine, and combination therapy for uncomplicated falciparum malaria: a randomized controlled trial from Burkina Faso. Am. J. Trop. Med. Hyg. 73, 826–832.