



Research article

QSAR and molecular docking studies of 1,3-dioxoisindoline-4-aminoquinolines as potent antiplasmodium hybrid compounds

Aliyu Wappah Mahmud^{a,*}, Gideon Adamu Shallangwa^b, Adamu Uzairu^b^a Department of Applied Chemistry, Kaduna Polytechnic, Kaduna, Nigeria^b Chemistry Department, Ahmadu Bello University, Zaria, Nigeria

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ABSTRACT

Quantitative structure–activity relationships (QSAR) provides a model that link biological activities of compounds to their chemical structures and molecular docking study reveals the interaction between drug and its target enzyme. These studies were conducted on 1,3-dioxoisindoline-4-aminoquinolines with the aim of producing a model that could be used to design highly potent antiplasmodium. The compounds were first optimized using Density Functional Theory (DFT) with basis set B3LYP/6-31G* then their descriptors calculated. Genetic Function Algorithm (GFA) was used to select descriptors and build the model. One of the four models generated was found to be the best having internal and external squared correlation coefficient (R^2) of 0.9459 and 0.7015 respectively, adjusted squared correlation coefficient (R_{adj}) of 0.9278, leave-one-out (LOO) cross-validation coefficient (Q^2_{cv}) of 0.8882. The model shows that antiplasmodial activities of 1,3-dioxoisindoline-4-aminoquinolines depend on ATSC5i, GATSP, minHBint3, minHBint5, MLFER_A and topoShape descriptors. The model was validated to be predictive, robust and reliable. Hence, it can predict the antiplasmodium activities of new 1,3-dioxoisindoline-4-aminoquinolines. The docking result indicates strong binding between 1,3-dioxoisindoline-4-aminoquinolines and *Plasmodium falciparum* lactate dehydrogenase (*p*fLDH), and revealed the important of the morpholinyl substituent and amide linker in inhibiting *p*fLDH. These results could serve as a model for designing novel 1,3-dioxoisindoline-4-aminoquinolines as inhibitors of *p*fLDH with higher antiplasmodial activities.

1. Introduction

Malaria is an infection with high morbidity and mortality burden all over world which is endemic in African region. Data from the World Health Organization malaria report 2019 revealed the occurrence of an estimate of 228 million cases and 405 000 deaths from the infection worldwide in 2018. Nigeria has 25% and 19% of the global cases and deaths respectively, follow by Democratic Republic of Congo with 11% each of the global cases and deaths. The most vulnerable are children below 5 years of age responsible for 67% (585 000) of the global malaria deaths in 2018 (WHO, 2019). *Plasmodium falciparum* is the most deadly of the five species of malaria parasite known to infect human (Cohen et al., 2012; WHO, 2019).

Quinoline present in several antimalarial drugs such as Chloroquine, Amodiaquine, Mefloquine, Primaquine, Ferroquine, etc. has been considered as the most important moiety that impact antimalarial action out of many heterocycle pharmacophores known for treatment of malaria (Kumar et al., 2016; Ilhami et al., 2010). Chloroquine has been the most

effective antimalaria for decades, but the wide spread of its resistance led to the development of Artemisinin-based Combination Therapy (ACTs), the WHO recommended drug for treatment of uncomplicated malaria (Beteck et al., 2014). ACTs are drug combinations containing artemisinin derivatives and other antimalarials such as quinoline compounds. Resistance to ACTs was reported in some part of the world which jeopardized their future effectiveness hence, the need for promising antimalaria that will meet the challenge of eradicating the disease (Burrows et al., 2011; Aguiar et al., 2012). Alternative to ACTs are hybrid compounds which have advantage of hitting two or more molecular targets (Oliveira et al., 2015). Earlier this year, Rania and coworkers reported the synthesis of 1,3-dioxoisindoline-4-aminoquinolines (Figure 1) as potent and noncytotoxic hybrid compounds having excellent antiplasmodial activities against W2 strain of *P. falciparum* (Rania et al., 2019).

Conventional drug discovery methods are expensive and time-consuming, hence, the need for more effective methods in terms of time and resources (Jitender et al., 2010). Discovery of novel drug

* Corresponding author.

E-mail address: aliyumahmudwappah@yahoo.com (A.W. Mahmud).

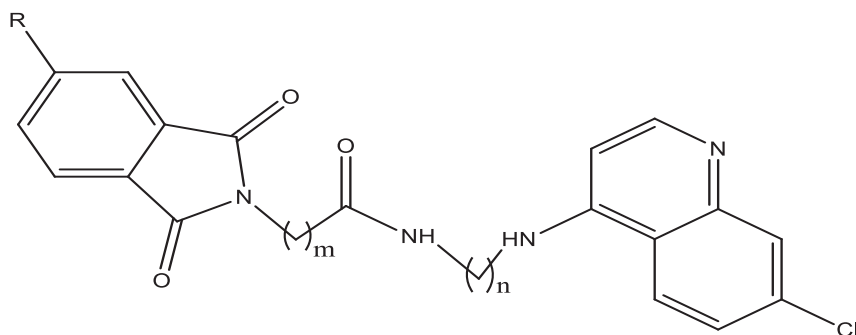


Figure 1. 1,3-dioxisoindoline-4-aminoquinolines.

candidates require efficient and vigorous methods that can screen chemical databases against molecules with known biological activities (Tropsha, 2010). QSAR and molecular docking studies have been successfully deployed in the discovery and design of many drugs for their time and cost effectiveness (Talele et al., 2010). This work aim at applying these techniques to reveal the connection between chemical structures of 1,3-dioxisoindoline-4-aminoquinolines and their antiplasmodial activities so as to come up with a model that could be used to design highly potent antimalaria.

2. Materials and method

2.1. Data collection

36 compounds of 1,3-dioxisoindoline-4-aminoquinolines (Figure 1) and their antiplasmodial activities against W2 strain of *Plasmodium falciparum* were obtained from the work of Rania and co-workers (Rania et al., 2019) and used in this research. The antiplasmodial activities of the compounds were gotten as IC_{50} (nM) and converted to pIC_{50} ($pIC_{50} = -\log IC_{50}$ (M)) for the purpose of this work. The compounds with their respective activities were presented in Table 1.

2.2. Geometric optimization

The 2D structures of the molecules shown in Table 1 were drawn using Chemdraw version 12.0.2 software (Li et al., 2004), converted to 3D and optimized using Spartan 14 Version 1.1.4 software (using B3LYP functional and 6-31G basis set) (Becke, 1993) (see Supplementary file Table 1 for 2D and 3D structures).

2.3. Molecular descriptors calculation

A total of 1875 molecular descriptors of the optimized molecules of 1,3-dioxisoindoline-4-aminoquinolines derivatives were computed with PaDEL-Descriptor software version 2.20 (Yap, 2011).

2.4. Normalization and data pretreatment

Using Eq. (1), the computed descriptors were normalized so that each variable will have equal opportunity in construction of the model (Singh, 2013).

$$X = \frac{X_i - X_{min}}{X_{max} - X_{min}} \quad (1)$$

where X is the normalized descriptors, X_i is the descriptor's value for each molecule, X_{min} and X_{max} are minimum and maximum values for each descriptor. Data Pretreatment software of Drug Theoretical and Cheminformatics Laboratory (DTC Lab) was used to eliminate redundancy in the normalized data.

2.5. Data Division

Kennard-Stone's algorithm was employed to divide the data into training set and test set (Kenard and Stone, 1969) using Data Division software of DTC Lab. Training set (70%) was used in building the model while test set (30%) in validating the model.

Table 1. Compounds of Figure 1 with their antiplasmodial activities.

Compounds	R	m	N	IC_{50} (nM)
1	H	1	2	5.65
2	H	1	4	3.66
3	H	1	6	3.35
4	H	1	8	0.24
5	H	2	2	0.30
6	H	2	4	0.41
7	H	2	6	0.29
8	H	2	8	0.15
9	H	3	2	0.28
10	H	3	4	0.84
11	H	3	6	1.57
12	H	3	8	0.58
13	F	1	2	1.99
14	F	1	4	1.05
15	F	1	6	1.49
16	F	2	2	0.36
17	F	2	4	0.22
18	F	2	6	0.66
19	Morpholinyl	1	2	3.21
20	Morpholinyl	1	4	1.28
21	Morpholinyl	1	6	1.78
22	Morpholinyl	2	2	0.13
23	Morpholinyl	2	4	0.22
24	Morpholinyl	2	6	0.64
25	Diethylamino	1	2	1.14
26	Diethylamino	1	4	1.17
27	diethylamino	1	6	1.22
28	diethylamino	2	2	0.097
29	diethylamino	2	4	0.26
30	diethylamino	2	6	0.53
31	2-(piperazin-1-yl)ethan-1-ol	1	2	1.04
32	2-(piperazin-1-yl)ethan-1-ol	1	4	0.86
33	2-(piperazin-1-yl)ethan-1-ol	1	6	0.46
34	2-(piperazin-1-yl)ethan-1-ol	2	2	0.28
35	2-(piperazin-1-yl)ethan-1-ol	2	4	0.14
36	2-(piperazin-1-yl)ethan-1-ol	2	6	0.18

2.6. Model generation

Regression analysis of the training set was carried out using Genetic Function Approximation (GFA) technique in Material Studio software to generate the model. Activities in pIC₅₀ were taken as the dependent variable and the descriptors independent variables.

2.7. Internal validation of the model generated

The model generated was assessed using Friedman formula (Friedman, 1991) defined as;

$$LOF = \frac{SEE}{\left(1 - \frac{c+dp}{M}\right)^2} \quad (2)$$

LOF is the Friedman's Lack of fit which is a measure of fitness of a model, SEE is the standard error of estimation, p is the total number of descriptors in the model, d is the user-defined smoothing parameter, c is the number of terms in the model and M is the number of compounds in the training set.

SEE is defined as;

$$SEE = \sqrt{\frac{(Y_{exp} - Y_{prd})^2}{N - P - 1}} \quad (3)$$

which is the same as the standard deviation of the model and its value has to be low for a model to be good.

Correlation coefficient, R² of a built model is another parameter considered and the closer it is to 1.0, the better the model built. R² is expressed as;

$$R^2 = 1 - \frac{\sum (Y_{exp} - Y_{prd})^2}{\sum (Y_{exp} - Y_{mtrn})^2} \quad (4)$$

where Y_{prd}, Y_{exp} and Y_{mtrn} are the predicted, experimental and mean experimental activities in the training set, respectively.

The stability of a model is not reliable on the value of R² as it is directly proportional to the number of descriptors in the model. Thus, for a reliable and stable model, R² is adjusted according to the expression:

$$R_{adj}^2 = \frac{(n-1)(R^2-p)}{n-p-1} \quad (5)$$

where p is the number of descriptors in the model and n number of compounds used in training set.

The cross-validation coefficient, Q²_{cv} expressed as:

$$Q_{cv}^2 = 1 - \frac{\sum (Y_{prd} - Y_{exp})^2}{\sum (Y_{exp} - Y_{mtrn})^2} \quad (6)$$

where Y_{prd}, Y_{exp} and Y_{mtrn} are the predicted, experimental and average experimental activity in the training set, respectively.

2.8. External validation of the model generated

Test set was used in validating the generated model externally by assessing the value of R²_{pred} expressed as;

$$R_{pred}^2 = 1 - \frac{\sum (Y_{prd} - Y_{exp})^2}{\sum (Y_{exp} - Y_{mtrn})^2} \quad (7)$$

where Y_{prd} and Y_{exp} are respectively the predicted and experimental activities of the test set and Y_{mtrn} the mean experimental activity of the training set. The closer the value is to 1.0, the better the model generated (Tropsha et al., 2003).

Table 3. Experimental and predicted pIC₅₀ of 1,3-dioxoisindoline-4-aminoquinolines with their residuals.

Compounds	Experimental pIC ₅₀	Predicted pIC ₅₀	Residual
1	5.248	5.331	-0.083
2 ^a	5.437	5.523	-0.087
3	5.475	5.523	-0.048
4 ^a	6.62	6.355	0.2644
5	6.523	6.716	-0.193
6 ^a	6.387	6.777	-0.39
7	6.538	6.434	0.1035
8	6.824	6.914	-0.09
9	6.553	6.518	0.0352
10 ^a	6.076	5.909	0.1669
11	5.804	5.746	0.0581
12 ^a	6.237	6.236	0.0007
13	5.701	5.655	0.0459
14	5.979	5.8	0.179
15	5.827	6.006	-0.179
16	6.444	6.447	-0.003
17 ^a	6.658	6.526	0.1317
18	6.18	6.204	-0.024
19	5.493	5.57	-0.077
20 ^a	5.893	5.53	0.363
21 ^a	5.75	5.796	-0.046
22	6.886	6.793	0.0932
23	6.658	6.634	0.0238
24	6.194	6.342	-0.148
25	5.943	5.998	-0.055
26 ^a	5.932	5.912	0.0194
27 ^a	5.914	6.147	-0.233
28	7.013	6.726	0.287
29	6.585	6.566	0.0193
30	6.276	6.286	-0.011
31	5.983	5.867	0.1161
32 ^a	6.066	5.858	0.2075
33	6.337	6.202	0.1356
34	6.553	6.644	-0.091
35	6.854	6.942	-0.088
36	6.745	6.751	-0.006

^a Test set.

Table 2. Validation parameters for the selected model.

S/N	Parameter	Value
1	Friedman LOF	0.083
2	R ² _{train}	0.946
3	Adjusted R-squared	0.928
4	Cross-validated R-squared (Q ² _{cv})	0.888
5	Significant regression	Yes
6	Significance-of-regression F-value	48.26
7	Critical SOR F-value (95%)	2.672
8	Replicate points	0
9	Computed experimental error	0
10	Lack-of-fit points	18
11	Min expt. error for nonsignificant LOF (95%)	0.103
12	R ² _{test}	0.702

Table 4. Pearson's correlation, Variance Inflation Factor (VIF) and Mean Effect (MF) of descriptors used in the selected model.

Descriptor	Inter-correlation						VIF	MF
	ATSC5i	GATS8p	minHBint3	minHBint5	MLFER_A	topoShape		
ATSC5i	1						1.391	-0.005
GATS8p	-0.1181	1					2.994	0.983
minHBint3	-0.3422	0.3350	1				1.500	-0.010
minHBint5	-0.4024	0.6021	0.3330	1			5.148	-0.020
MLFER_A	0.1375	0.1420	0.1317	-0.5053	1		2.704	-0.110
topoShape	-0.0275	-0.0451	0.2254	-0.2468	0.2461	1	1.221	0.166

2.9. Y-Randomization test

Random Multi-Linear regression models are generated (using training set) in Y-randomization test whose R^2 and Q^2 values have to be low for the QSAR model to be robust (Tropsha et al., 2003). Coefficient of determination, cR_p^2 , whose value has to be greater than 0.5 for passing this test is also calculated in the Y-randomization test and is expressed as;

$$cR_p^2 = R_x(R^2 - R_r^2)^2 \quad (8)$$

where R is the correlation coefficient for Y-randomization and R_r^2 is the average 'R' of the random models.

2.10. Applicability domain of the generated model

Leverage (h_i) method was used in describing the applicability domain of the QSAR models (Veerasingam et al., 2011) and for a chemical compound is expressed as;

$$h_i = X_i(X^T X)^{-1} X_i^T \quad (9)$$

where X_i is training compounds matrix of i. X is the $n \times k$ descriptor matrix of the training set compound and X^T is the transpose matrix of X used to generate the model. The warning leverage, h^* is the maximum value for X and is expressed as;

$$h^* = \frac{3(p+1)}{n} \quad (10)$$

where n is the number of training compounds and p is the number of descriptors in the model.

2.11. Descriptors analyses

Correlation analysis was carried out to check the presence of correlation among the descriptors in the built model. This was further evaluated by computing the variance inflation factor (VIF) for each descriptor using the equation below (see supplementary file Table 2 for the values of descriptors used in the model):

$$VIF_i = \frac{1}{1 - R_{ij}^2} \quad (11)$$

VIF_i is the variance inflation factor for a given descriptor i in the model R_{ij}^2 is the correlation coefficient of the multiple regression between the descriptor i and the remaining j descriptors in the model (Beheshti et al., 2016).

The relative significance and influence of every descriptor in the model was estimated by its mean effect (MF) value. The MF_j for a given descriptor j in a model is given as;

$$MF_j = \frac{\beta_j \sum_{i=1}^n d_{ij}}{\sum_j \beta_j \sum_i d_{ij}} \quad (12)$$

where b_j is the coefficient of descriptor j in the model, d_{ij} is the value of the descriptor j in the descriptor matrix for each molecule in the training set, m is the number of descriptors that appear in the model, and n is the number of molecule that made up the training set (Habibi-Yangjeh and Danandeh-Jenagharad, 2009).

2.12. Docking study

Plasmodium falciparum lactate dehydrogenase (PfLDH) enzyme is regarded as a potential molecular target for antimalarials because of the parasite's reliance on glycolysis to produce energy (Penna-Coutinho et al., 2011). Therefore, molecular docking study was conducted between PfLDH and 1,3-dioxoisindoline-4-aminoquinolines to investigate their interaction. Crystal structure of PfLDH was obtained from protein data bank (PDB ID: 1CET). Ten compounds with best activities were prepared as the ligands for this study. PfLDH was prepared as the receptor with the aid of Discovery Studio software. The prepared receptor and ligands were docked using Autodock Vina in Pyrx software (Trott and Olson, 2010). Discovery Studio Visualizer was used to analyze the results.

3. Result and discussion

Four QSAR models were built using GFA in material studio software to study how the biological activities of 1,3-dioxoisindoline-4-aminoquinolines as potent antiplasmodium relate with their chemical structures. One of the QSAR models generated was selected for its statistical significance and reported herein as follow:

Table 5. Y-Randomization test result.

Model	R	R^2	Q^2
Original	0.9726	0.9459	0.8883
Random 1	0.4172	0.1741	-0.7131
Random 2	0.4080	0.1665	-0.6273
Random 3	0.6915	0.4782	0.0379
Random 4	0.4669	0.2180	-0.4743
Random 5	0.6025	0.3631	-0.2769
Random 6	0.3653	0.1335	-0.6688
Random 7	0.4835	0.2338	-0.6283
Random 8	0.5267	0.2774	-0.4792
Random 9	0.2620	0.0686	-0.8088
Random 10	0.6430	0.4135	-0.3519
Random Models Parameters			
Average r:			0.4867
Average r2:			0.2526
Average Q2:			-0.4990
cRp2:			0.8189

$$\begin{aligned}
 \text{pIC}_{50} = & -0.013998081 * \text{ATSC5i} \\
 & -13.821502296 * \text{GATS8p} \\
 & +0.328734328 * \text{minHBint3} \\
 & +0.138391673 * \text{minHBint5} \\
 & +3.211439246 * \text{MLFER_A} \\
 & -2.474169940 * \text{topoShape} \\
 & +20.552944618
 \end{aligned}$$

Table 2 presents the validation parameters of the model which passed the thresholds required for a QSAR model to be accepted (Veerasamy et al., 2011; Tropsha, 2010).

The model contained 2D Autocorrelation descriptors ATSC5i and GATS8p which described how the considered properties (first ionization potential and atomic polarizabilities) are distributed along the topological structures of the molecules. ATSC5i is defined as centered Broto-Moreau autocorrelation of lag 5 weighted by first ionization potential and it present in the model related the first ionization potential of pairs atoms that are separated by five bonds (lag 5) with the antiplasmodial activities of 1,3-dioxoisindoline-4-aminoquinolines, while GATS8p is defined as Geary autocorrelation of lag 8 weighted by atomic polarizabilities and it present in the model associated the presence of polarizable pairs of atoms eight bonds apart on the antiplasmodial activities the compounds. The model also contained 2D atom type electro-topological state descriptors minHBint3 and minHBint5 which are defined as Minimum E-State descriptors of strength for potential Hydrogen Bonds of path length 3 (minHBint3) and of path length 5 (minHBint5). These descriptors indicated the importance of hydrogen bonds of path length 3 and 5 (Arthur et al., 2016). Other descriptors in the model were Overall or summation solute hydrogen bond acidity, MLFER_A which is related with molecular linear free energy relations (Platts et al., 1999) and Petitjean topological shape index, topoShape.

Table 3 shows the residual values between the experimental and predicted activities of 1,3-dioxoisindoline-4-aminoquinolines as potent *Plasmodium falciparum* inhibitors. The low residual values were indicative of the high predictability of the model.

Table 4 presents the result of statistical analysis of the descriptors. The low values of the inter-correlation between any pair of descriptors as shown by the Pearson's correlation matrix suggest no significant inter-correlation among the descriptors used in building the model. This was confirmed by the low value of the Variance Inflation Factor which was less than 10 for every descriptor. Hence, the descriptors used in building the model were good. The mean effects of the descriptors gave the relative influences of the descriptors on the antiplasmodial activities of the compounds where the signs and the magnitudes indicated the directions and extent of the influences respectively. The MF values suggested that the descriptors ATSC5i, minHBint3, minHBint5 and MLFER_A decrease the antimalarial activities of 1,3-dioxoisindoline-4-aminoquinolines with increase in their values while the descriptors GATS8p and topoShape increase the antimalarial activities of 1,3-dioxoisindoline-4-aminoquinolines with increase in their values. The magnitude of the MF values shows that the descriptor GATS8p has greatest influence on the antiplasmodial activities of the compounds and should be highly considered when designing more potent 1,3-dioxoisindoline-4-aminoquinolines. The descriptor ATSC5i had the least influence on the antiplasmodial activities of the compounds as shown by the magnitude of its MF.

The reliability, robustness and stability of the built QSAR model were confirmed by Y-Randomization test. This was true for the low R^2 and Q^2 values for several trials in the result presented in Table 5. The cr^2_p value which was greater than 0.5 also shows the model is good and not gotten by chance.

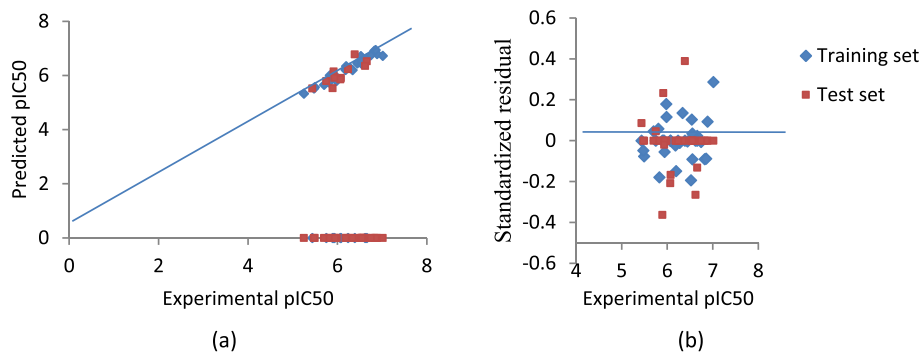


Figure 2. (a) Plot of predicted activities against experimental activities (b) Plot of Standardized residuals against experimental activities of the compounds.

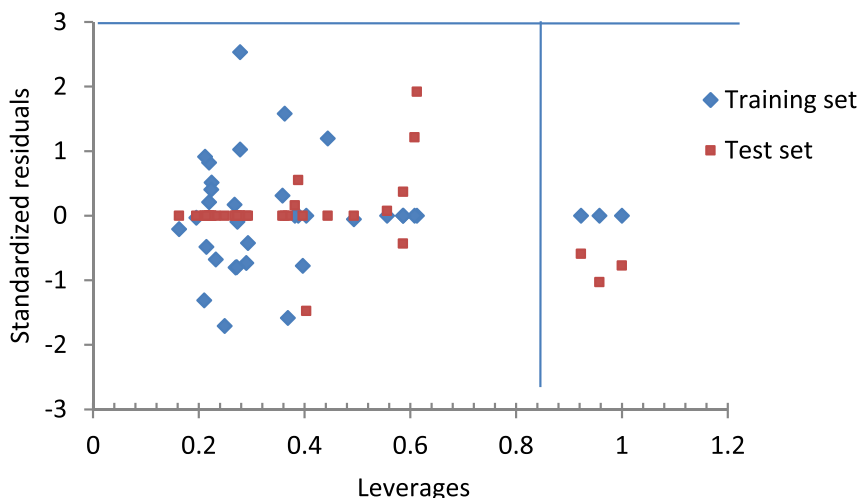


Figure 3. Plot of the standardized residuals against the leverages (Williams plot).

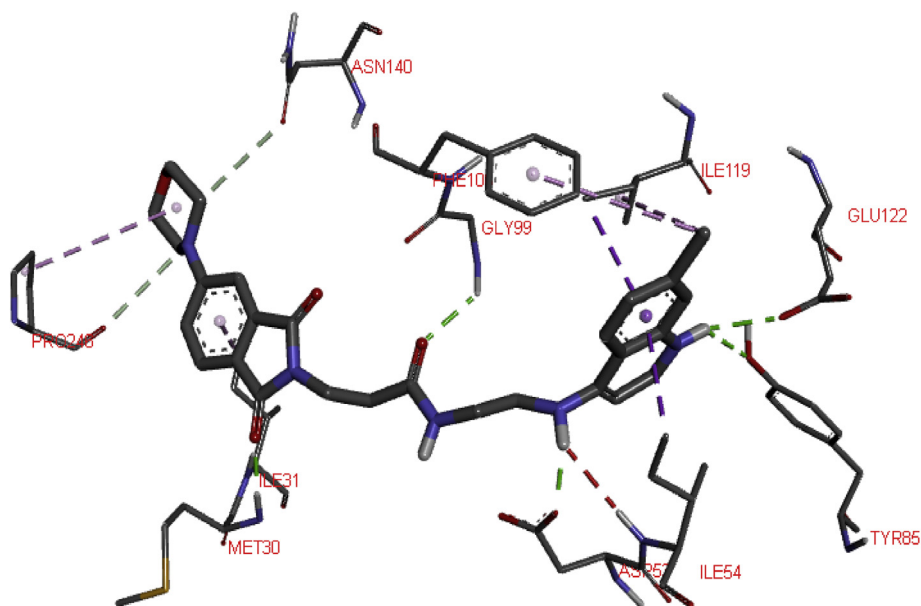


Figure 4. 3D interaction between Ligand 22 and *pflDH*.

The linearity of the plot of predicted activities against experimental activities of the compounds (Figure 2a) shows the strength of the model in predicting antiplasmodial activities of the 1,3-dioxoisindoline-4-aminoquinolines. The dispersal of standardized residuals of both training and test set on both sides of zero (Figure 2b) suggested no systematic error in the generated model (Jalali-Heravi and Kyani, 2004).

The Williams plot presented by Figure 3 shows no outliers in the compounds but three influential compounds because their leverages were greater than the warning leverage ($h^* = 0.84$) which might arise from their structural feature. All the compounds were within the applicability domain except the influential compounds which were all from test set (compound 4, 10 and 32). These compounds should not be considered when designing novel 1,3-dioxoisindoline-4-aminoquinolines.

The result of the molecular docking study conducted between *Plasmodium falciparum* lactate dehydrogenase, *PflDH* (receptor) and ten 1,3-dioxoisindoline-4-aminoquinolines with highest activities (ligands) is presented in Table 3 of the supplementary file. All the docked ligands interacted strongly with the active sites of the receptor with binding affinity ranging from -6.7 to -9.2 kcal/mol. They all exhibited significant hydrogen bonding and hydrophobic interaction with the amino acids of the protein. Figures 4 and 5 presented respectively the 3D and 2D *pflDH* interactions which had the best binding affinity (-9.2 kcal/mol). Five conventional hydrogen bonds were formed between one of the C=O of the 1,3-dioxoisindoline moiety and residue MET30, NH of the quinoline moiety and residue GLU122 and TYR85, C=O of the amide linker and residue GLY99 and NH of the amino group and residue ASP53. Two Carbon hydrogen bonds type were formed between two carbons of the

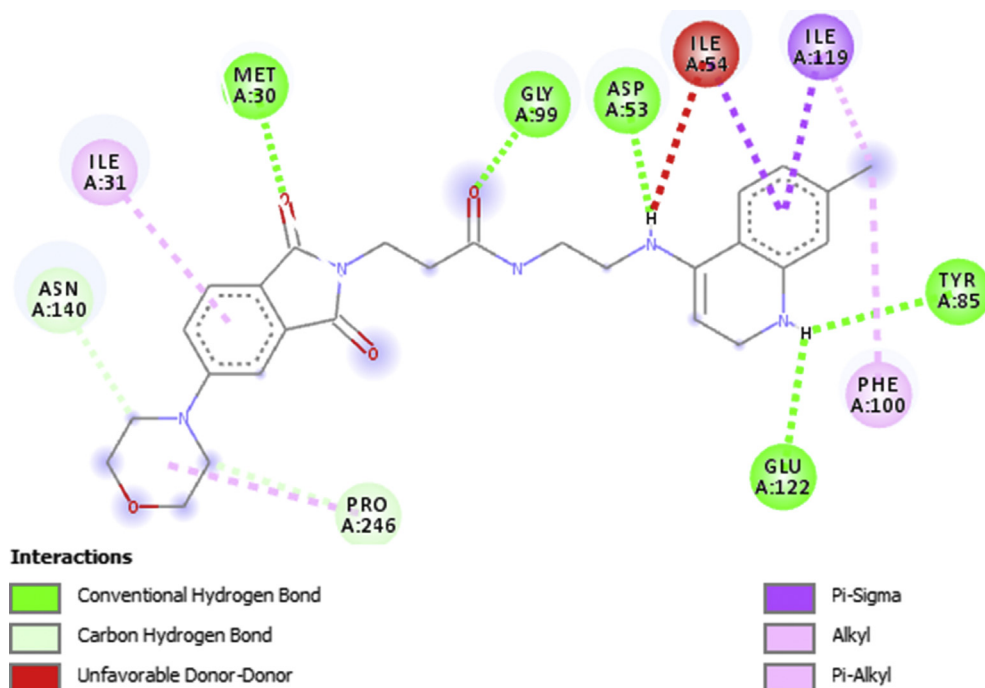


Figure 5. 2D interaction between Ligand 22 and *pflDH*.

morpholinyl substituent on the 1,3-dioxoisindoline moiety and C=O of PRO246 and ASN140 of the target. The ligand also formed Hydrophobic interactions with the receptor via Pi-Sigma type with ILE54 and ILE119, Alkyl-Alkyl type with PRO246 and ILE119 and Pi-Alkyl type with PHE100 and ILE31 of the target. Unfavorable donor-donor interaction was also observed between the H of the amino group of the ligand H of the ILE54 of the receptor. The docked compounds have better binding affinity and interactions than chloroquine (a well known inhibitor of pflDH).

4. Conclusion

QSAR and molecular docking techniques were successfully applied on 1,3-dioxoisindoline-4-aminoquinolines as potent antiplasmodial in order to produce a model that relates the chemical structures of the molecules and their antiplasmodial activities. A predictable, reliable and robust model was generated using Genetic Function Approximation (GFA) technique in Material Studio software. The model has internal and external validation R^2 values of 0.9459 and 0.701544 respectively. The model revealed that the antiplasmodial activities of 1,3-dioxoisindoline-4-aminoquinolines is influence by ATSC5i, GATS8p, minHBint3, minHBint5, MLFER_A and topoShape descriptors with greatest and least effect from GATS8p and ATSC5i respectively. The docking study revealed the important of some strategic point on the structural features of the molecules in inhibiting *Plasmodium falciparum* lactate dehydrogenase (PflDH). This information could be used together with the built model to design novel 1,3-dioxoisindoline-4-aminoquinolines inhibitors of PflDH with higher antiplasmodial activities.

Declarations

Author contribution statement

Aliyu Wappah Mahmud: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gideon Adamu Shallangwa: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Adamu Uzairu: Conceived and designed the experiments; Performed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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References

- Aguiar, A.C.C., Rocha, E.M., Souza, N.B., França, T.C., Krettli, A.U., 2012. New approaches in antimalarial drug discovery and development: a review. *Mem. Inst. Oswaldo Cruz* 107, 831–845.
- Arthur, D.E., Uzairu, A., Mamza, P., Abechi, S., 2016. Quantitative structure–activity relationship study on potent anticancer compounds against MOLT-4 and P388 leukemia cell lines. *J. Adv. Res.* 7, 823–837.
- Becke, A.D., 1993. Becke's three parameter hybrid method using the LYP correlation functional. *J. Chem. Phys.* 98, 5648–5652.
- Beheshti, A., Pourbasheer, E., Nekoei, M., Vahdani, S., 2016. QSAR modeling of antimalarial activity of urea derivatives using genetic algorithm–multiple linear regressions. *J. Saudi Chem. Soc.* 20, 282–290.
- Beteck, R.M., Smit, F.J., Haynes, R.K., N'Da, D.D., 2014. Recent progress in the development of anti-malarial quinolones. *Malar. J.* 13, 339.
- Burrows, J.N., Leroy, D., Lotharius, J., Waterson, D., 2011. Challenges in antimalarial drug discovery. *Future Med. Chem.* 3, 1401–1412.
- Cohen, J.M., Smith, D.L., Cotter, C., Ward, A., Yamey, G., Sabot, O.J., Moonen, B., 2012. Malaria resurgence: a systematic review and assessment of its causes. *Malar. J.* 11, 122.
- Friedman, J.H., 1991. Multivariate adaptive regression splines. *Ann. Stat.* 1–67.
- Habibi-Yangjeh, A., Danandeh-Jenagharad, M., 2009. Application of a genetic algorithm and an artificial neural network for global prediction of the toxicity of phenols to *Tetrahymena pyriformis*. *Monatsh. Chem.-Chem. Mon.* 140, 1279–1288.
- Ihhami, G., Riad, E., Akcahan, G., Aun, C., Fevzi, T., 2010. Antioxidant activity of bisbenzylisoquinoline alkaloids from *Stephania rotunda*: cepharanthine and fangchinoline. *J. Enzym. Inhib. Med. Chem.* 25 (1), 44–53.
- Jalali-Heravi, M., Kyani, A., 2004. Use of computer-assisted methods for the modeling of the retention time of a variety of volatile organic compounds: a PCA-MLR-ANN approach. *J. Chem. Inf. Comput. Sci.* 44, 1328–1335.
- Jitender, V., Vijay, M.K., Evans, C.C., 2010. 3D-QSAR in drug design: a review. *Curr. Top. Med. Chem.* 10, 95–115.
- Kenard, R.W., Stone, L.A., 1969. Computer aided design of experiments. *Technometrics* 11 (1), 137–148.
- Kumar, S., Singh, R.K., Patial, B., Goyal, S., Bhardwaj, T.R., 2016. Recent advances in novel heterocyclic scaffolds for treatment of drug-resistant malaria. *J. Enzym. Inhib. Med. Chem.* 31, 173.
- Li, Z., Wan, H., Shi, Y., Ouyang, P., 2004. Personal experience with four kinds of chemical structure drawing software: review on ChemDraw, ChemWindow, ISIS/Draw, and ChemSketch. *J. Chem. Inf. Comput. Sci.* 44, 1886–1890.
- Oliveira, R., Miranda, D., Magalhaes, J., Capela, R., Perry, M.J., O'Neill, P.M., Moreira, R., Lopes, F., 2015. From hybrid compounds to targeted drug delivery in antimalarial therapy. *Bioorg. Med. Chem.* 23.
- Penna-Coutinho, J., Cortopassi, W.A., Oliveira, A.A., Franc, a, T.C.C., Krettli, A.U., 2011. Antimalarial activity of potential inhibitors of plasmodium falciparum lactate dehydrogenase enzyme selected by docking studies. *PLoS One* 6 (7), e21237.
- Platts, J.A., Butina, D., Abraham, M.H., Hersey, A., 1999. Estimation of molecular linear free energy relation descriptors using a group contribution approach. *J. Chem. Inf. Comput. Sci.* 39 (5), 835–845.
- Rania, A., Legach, J., Rosenthal, P.J., Kumara, V., 2019. Substituted 1,3-dioxoisindoline-4-aminoquinolines coupled via amide linkers: synthesis, antiplasmodial and cytotoxic evaluation. *Bioorg. Chem.* 88, 102–912.
- Singh, P., 2013. Quantitative structure-activity relationship study of substituted-[1, 2, 4] oxadiazoles as S1P1 agonists. *J. Curr. Chem. Pharm. Sci* 3.
- Talele, T.T., Santosh, A.K., Alan, C.R., 2010. Successful applications of computer aided drug discovery: moving drugs from concept to the clinic. *Curr. Top. Med. Chem.* 10, 127–141.
- Tropsha, A., 2010. Best practices for qsar model development, validation, and exploitation. *Mol. Inf.* 29, 476–488.
- Tropsha, A., Gramatica, P., Gombar, V.K., 2003. The importance of being earnest: validation is the absolute essential for successful application and interpretation of QSPR models. *Mol. Inform.* 22, 69–77.
- Trott, O., Olson, A.J., 2010. Autodock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *J. Comput. Chem.* 22, 455–461.
- Veerasamy, R., Rajak, H., Jain, A., Sivadasan, S., Varghese, C.P., Agrawal, R.K., 2011. Validation of QSAR models-strategies and importance. *Int. J. Drug Des. Discov.* 3, 511–519.
- World Health Organization, 2019. World Malaria Report. <http://apps.who.int/malaria/media/world-malaria-report-2019>.
- Yap, C.W., 2011. PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. *J. Comput. Chem.* 32, 1466–1474.