QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP ANALYSIS AND LIGAND BASE DRUG DESIGN OF NEW POTENT COMPLEXES FOR ANTIMALARIA

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Abstract

This investigation necessitates the modelling of the biological activity of antimalarial complexes on plasmodium falciparum; where 40 compounds that frames the data set were divided into training and test set to be used for developing and validating the model correspondingly. The internal and external validation parameter R^2 for the training and test set given as 0.7683 and 0.5217separately rationalises the robustness of the model ability to predict antimalarial activity of the compounds. The contributions made by shadow length LX, rotatable bonds and CIC chemical information were significant and hence were used as a guide for the ligand base design of more potent antimalarial complexes.

Keywords: QSAR, Antimalarial, Complexes, Molecular descriptors, Genetic algorithm

Introduction

The issue that is gone up against by a large portion of the developing and under developed countries which are in tropical and sub-Saharan Africa is malaria, influencing just about 250 million individuals and causing more than 800,000 deaths every year. The vast majority of the cases watched are in children under five years and the event is more in pregnant ladies (Dondorp et al., 2009; Dondorp et al., 2010). Most of the time demise is caused because of disease from Plasmodium falciparum. In developed country, for example, United States, the instances of malaria is less normal influencing just 1300-1500 individuals for every year. 10% of these cases which experience the ill effects of perilous end-organ harm is dealt with by IV quinidine gluconate, which has indicated better adequacy yet its standard utilize has demonstrated symptoms (Aregawi, Cibulskis, Otten, & Williams, 2009; Kortepeter, Bausch, & Bray, 2011) The three types of malarial parasite- P.falciparum, P.vivax and P.malariae have indicated signs of immunity from antimalarial drugs. (World Health Organization. Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000–2010) Resistance to chloroquine (CQ) was first revealed in under twenty years from its presentation in twentieth century for treatment against P.falciparum. At that point antifolate blend treatment was utilized which used sulfadoxine and pyrimethamine (SP) mixtures however soon resistance was produced to this mixture treatment as well (Bunnag & Harinasuta, 1987; Chawira, Warhurst, Robinson, & Peters, 1987; Peters, Robinson, & Ellis, 1987; Roper et al., 2004; White et al., 1982) P. falciparum immunity from the old medication treatment has prompted the disclosure of new medications called artemisinin-based combination treatments (ACTs) for intestinal sickness control (Enserink, 2007). The essential explanation behind utilization of ACTs is to join any long half-life medication, for example, mefloquine, amodiaquine, piperaquine, pyrimethamine/sulfadoxine or lumefantrine with quick acting medication artemisinin, which brings about accomplishing successful and fast destruction of malarial parasite (World Health Organization, Roll Back Malaria Department, Guidelines for the Treatment of Malaria, 2006.) However, resistance from ACTs is likewise developing since parasites began indicating signs of immunity towards the long half-life drugs utilized as a part of the mix.

For decades now, Quantitative Structure-Activity Relationships (QSAR) (Bajot, 2010), have been applied in many areas enabling to prevent time consuming and cost during the analysis of biological activities of interest. The primary speculation associated with any QSAR is the supposition that the variety of the conduct of chemical substance, as communicated by any tentatively estimated organic or physicochemical property, can be connected with numerical elements identified with some part of the compound structure named molecular descriptors (Todeschini, Consonni, & Pavan, 2007; Toropov & Benfenati, 2008; Tropsha, 2010). These descriptors can thus, be utilized as a part of enhancing the action of a lead compound by modifying a portion of the substance data observed to be to a great extent in charge of the bio-activity of the medication.

Hence, this research aims to design new antimalarial drugs with the Desired and Essential Characteristics, such as antimalarial, which are active against all known malaria parasites that

infect humans (P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi) (Baird, 2005, 2013; Bunnag & Harinasuta, 1987; Bunnag et al., 1994), antimalarial drugs which are specific towards Plasmodium species while showing zero poisonous quality in people. Drugs that can target Plasmodium species via only parasite-specific modes of action involving molecular targets and organelles found exclusively in these protozoans (Schrader, Barho, Steiner, Ortmann, & Schlitzer, 2012; Schrader et al., 2013). Lastly, antimalarial drugs that could be dynamic against blood phases of different Plasmodium species and block transmission of gametocytes of Plasmodium species from people to vector female Anopheles spp. mosquitoes during blood meal event.

Experimental Section:

The Data set, which comprises of the chemical structures and the bioactivity used for developing the QSAR model were collected from two sources Hubin (Hubin et al., 2014) and Bahl research (Bahl et al., 2010) separately.

The hardware and software used in this work for descriptors generation, model building, molecular mechanics and quantum mechanical calculations includes: Computer (HP pavilion Intel(R) core i5-4200U with 1.63Hz and 2.3Hz processor and windows 8.1 operating system), Spartan 14 (Hehre & Huang, 1995), ChemBio Ultra 12.0 (Evans, 2014; Li, Wan, Shi, & Ouyang, 2004), Dragon 5 (Talete, 2007), MS Excel (Denton, 2001).

Generation of molecular descriptors

Descriptors were computed from the 3D structure of the compounds. The 2D structure of each of the compounds was generated by using the sketch option on Spartan 14 graphic user interface (GUI) and was subsequently converted into 3D structure by using the view option on Spartan 14. From the build option on Spartan 14 the structures were clean by checking minimize using molecular mechanic force field (MM+). From the set up calculation option on Spartan 14, the calculation was set to equilibrium geometry at the ground state using density functional theory at B3LYP (Becke88 three-parameter hybrid exchange potentials with Lee-Yang-Parr correlation potential) level of theory and 6-311G (d) basis set for the geometrical optimization of the cleansed structures i.e. B3LYP/6-311G (d) level of theory. After optimization, Spartan molecular descriptors were obtained from the display-output and display-properties option on Spartan 14 GUI. The fully optimized 3D structure without symmetry restrictions, were saved as SD file through the file option on the Spartan 14 GUI. The fully optimized 3D structure in SD file were then imported into the Dragon program and molecular descriptors consisting of constitutional descriptors, topological descriptors, RDF descriptors, WHIM, functional group, charge, 3D-Morse, GATEWAY, molecular properties descriptors etc were then calculated after which the values of the descriptors calculated were subjected to a pair correlation descriptor exclusion where descriptor values with pair correlation of 0.9 and above were excluded, before the processed result was finally saved as readable text file.

Splitting of data-set into modelling sets and evaluation test sets

The data set were divided into modelling set and external evaluation set. The modelling sets are used in the building of the model and consist of about eighty percent of the entire data set. The evaluation set which constitute about fifteen to twenty percent of the entire data set were not involved in the construction of the model but used to ascertain the predictive ability of the model (Tropsha, 2010).

Table 1. Chemical structure of the data set and their corresponding experimental and predicted pIC_{50} values

	Chemical Structure	Experimental IC_{50} µM	Actual pIC50	Predicted pIC50	Residual
1		4.589	5.34	5.18	0.16
2		1.3±0.5	5.89	5.92	-0.03
3		2.3 ± 0.3	5.64	5.88	-0.24

4		3.1 ± 0.2	5.51	5.78	-0.27
5		2.6 ± 0.3	5.59	5.73	-0.14
6		0.22 ± 0.02	6.66	6.26	0.40
7		1.7 ± 0.3	5.77	5.51	0.26
8		1.56 ± 0.04	5.81	5.87	-0.06

9		0.9 ± 0.2	5.86*	6.05	-0.19
10		2.2 ± 0.4	5.90*	5.66	0.24
11		0.6 ± 0.2	5.74*	6.22	-0.49
12		2.3 ± 0.3	5.64	5.45	0.19
13		2.3 ± 0.2	5.64	5.52	0.12

14		1.8 ± 0.3	5.75	5.78	-0.03
15		1.5 ± 0.1	5.87*	5.82	0.05
16		2.2 ± 0.8	5.66	5.73	-0.07
17		0.89 ± 0.01	5.80*	6.09	-0.29
18		1.0± 0.2	6.00	5.84	0.17

19		1.7 ± 0.3	5.77	5.81	-0.04
20		1.0 ± 0.1	5.75*	6.00	-0.25
21		2.1 ± 0.6	5.68	5.59	0.09
22		2.4 ± 0.2	5.62	5.84	-0.22
23		1.1 ± 0.5	5.98*	5.96	0.02

24		0.30	6.51	6.37	0.13
25		0.41	6.38*	6.39	-0.01
26		0.71	6.40	6.15	0.25
27		0.52	6.24*	6.28	-0.05
28		0.63	6.20	6.24	-0.03

29		1.7 ± 0.2	5.72*	5.77	-0.05
30		0.809	6.09	6.09	0.00
31		0.959	6.02	6.02	0.00
32		1.326	5.88	6.06	-0.18
33		0.593	6.23	6.17	0.05

34		0.814	5.80*	6.09	-0.29
35		0.312	6.66*	6.52	0.14
36		1.538	5.80	5.87	-0.06
37		2.139	5.67	6.04	-0.37

38		0.545	6.26	6.41	-0.14
39		0.426	6.37	6.31	0.06
40		0.127	6.90	6.62	0.27

Where the symbol * stands for the compounds selected as test set.

Scaling of activities and descriptors data

The response variable (biological activities) and the explanatory variable (molecular descriptors) and were scaled using auto-scaling and range scaling procedure. According to Golbraith et al. (Golbraikh et al., 2003), the modelling set and the evaluation set were scaled separately. Auto-scaling consists of mean centering and variance scaling. s

Model development

MLR is a strategy, utilized for displaying direct relationship between a dependent variable Y and independent variable X (atomic descriptors). The model is fit such that sum-of-squares difference between the experimental and predicted values of set biological activity is minimized. In regression analysis, contingent mean of dependant variable Y relies on (descriptors) X. MLR examination extends this thought to incorporate more than one autonomous variable, regression equation takes the form.

$$Y = b_1 x_1 + b_2 x_2 + b_3 x_3$$

where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept.

Validation of the QSAR model

The capability of the QSAR equation to predict bioactivity of new compounds was determined using the leave-one-out cross-validation method. The cross-validation regression coefficient (Q_{cv}^2) was calculated with the following equation:

$$q_{CV}^2 = 1 - {PRESS}/{TOTAL} = 1 - \frac{\sum_{i=1}^{n}(y_{exp} - y_{pred})^2}{\sum_{i=1}^{n}(y_{exp} - \bar{y})^2}$$

Where y_{pred}, y_{exp}, and $\tilde{y}$ are the predicted, experimental, and mean values of experimental activity, respectively.

Evaluation of the applicability domain of the model

Assessment of the applicability domain of the QSAR model is viewed as an important step in establishing that the model is equipped to make predictions within the chemical space for which it was produced (Tropsha et al., 2003). The leverage approach was utilized in describing the applicability domain of the QSAR models (Gramatica, Giani, & Papa, 2007).

Results and Discussion

Table 1 shows the test set and the remaining compounds as the training set. Genetic approximation-multiple linear regression (GA-MLR) technique is the regular means for multivariate data examination. It estimates the values of the regression coefficients by applying least squares curve fitting method. For getting reliable results, dataset having typically 5 times as many data points (molecules) as independent variables (descriptors) is required.

According to the statistical calculation, it was obtained the strong correlation between the topological, geometrical and functional group descriptors to the antimalaria activity of the substituted analogue. The QSAR models have shown good correlation between their corresponding descriptors and biological activity. The higher the F value is, the more significant the data would be. Data would be significant if $F_{calc}/F_{table} > 1$. According to the F_{calc}/F_{table} value, it indicated that the models fits in all cases was not a chance occurrence and all models were statistically significant. Based on the R^2 criteria ($R^2 > 0.6$), the model was passed to validation step. To validate the selected prediction function, a cross-validation and an external test were carried out. Cross-validation is a practical and reliable method for testing the significance.

The developed QSAR model was validated using the following statistical measures: Q^2 (coefficient of determination). A QSAR model is considered to be predictive, if the following conditions are satisfied: $Q^2 > 0.6$. The Q^2 values were used as deciding factors in selecting the optimal models.

Table 2: Model statistics

Friedman LOF	0.1992
R-squared	0.7683
Adjusted R-squared	0.6988
Cross validated R-squared	0.7683
Predicted R-squared	0.5217
Significant Regression	Yes
Significance-of-regression F-value	11.0546
Critical SOR F-value (95%)	2.6102
Replicate points	0
Computed experimental error	0.0000
Lack-of-fit points	20
Min expt. error for non-significant LOF (95%)	0.1633

The developed model and definition of the independent variables X1, X2, X3, X4, X5 and X6 are given as:

$$\boldsymbol{pIC_{50}} = -2.3346\,(\boldsymbol{X1}) + 0.9287\,(\boldsymbol{X2}) - 0.2723\,(\boldsymbol{X3}) + 0.4620\,(\boldsymbol{X4}) + 1.6047\,(\boldsymbol{X5}) - 0.4808\,(\boldsymbol{X6}) + 5.5657$$

X1 = Rotatable bonds (Fast Descriptors)

X2 = Complementary information content (CIC) (Fast Descriptors)

X3 = E-state keys (sums): S_sNH2 (Fast Descriptors)

X4 = Shadow area: ZX plane (Spatial Descriptors)

X5 = Shadow length: LX (Spatial Descriptors)

X6 = E LUMO (kJ/mol)

The predicted anti-malaria activity by the above model was shown in Table 1, while the model statistics is presented in Table 2. The result of evaluation antimalaria activity that is the predicted pIC50 and correlation with antimalaria activity (actual pIC50) for the model by using density functional theory (DFT) level using Becke's three-parameter Lee-Yang-Parr hybrid functional (B3LYP) in combination with the 6-31G* basis set of test set and training set can be seen at Figure 1. From the Table 1 it is evident that the predicted activities of all

the compounds in the test set are in good agreement with their corresponding experimental activities and optimal fit is obtained generated by the QSARs utilizing different set of topological, geometrical and functional group descriptors. The statistically best significant model obtained by GA-MLR method with R^2 = 0.7683 was considered, as the model showed good internal predictive power (Q^2 = 0.7683) of over 76% and predicatively for the external test set (R^2_{test} = 0.5217) of about 52% consequently.

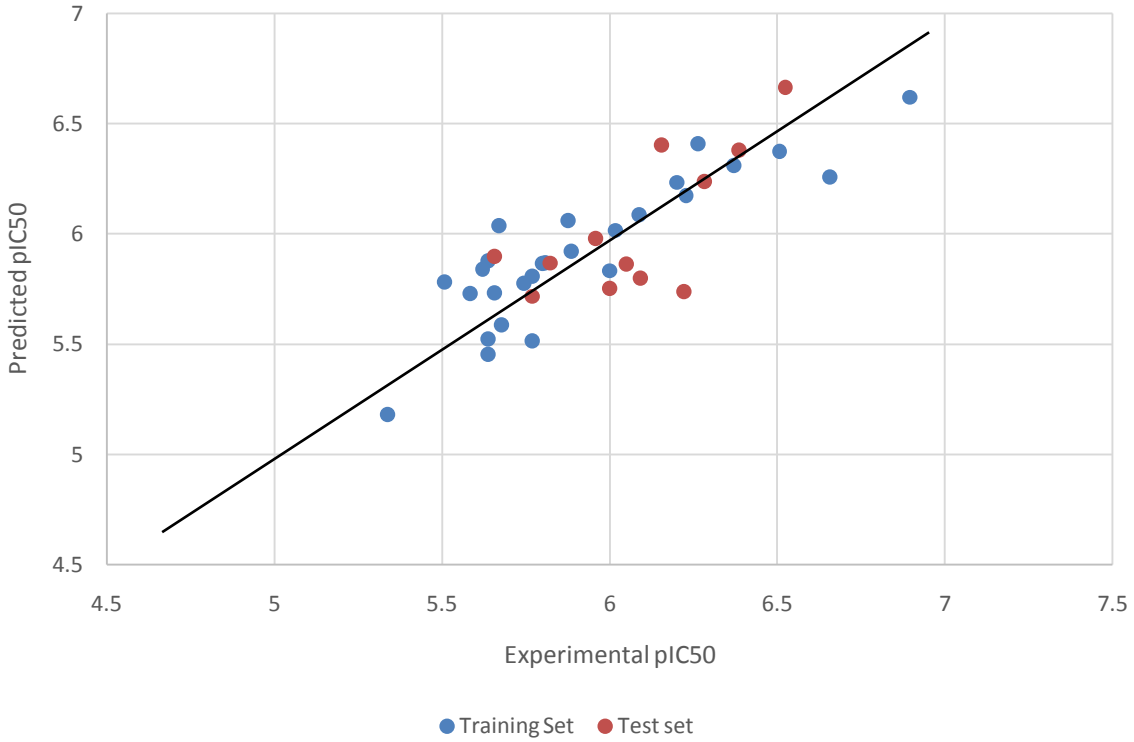

Fig. 1: A plot of Predicted pIC50 against Experimental pIC50 of the antimalarial drugs

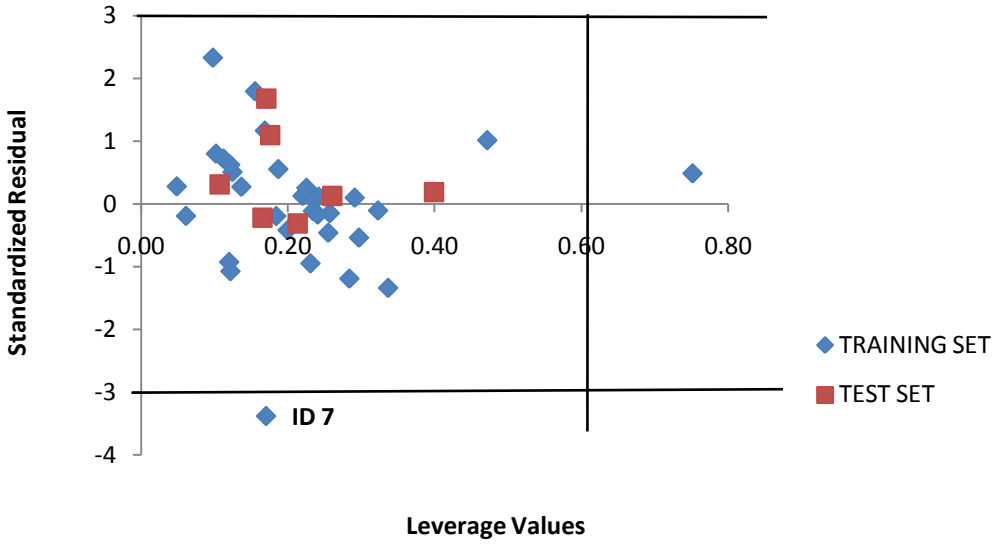

Fig.2: A Williams plot showing the plot of standardized residual against the leverage vales of the drugs

The William plots in figure 2, shows that more than 95% of the data set were found within the chemical space of the model. This applicability domain identifies one outlier and one influential molecule, which were both members of the training set. The plot shows that the model could not predict the bioactivity of compound ID7; we suspect that this is as a result of errors from the experimental data which was indicative in the large difference in the standardized residual with its predicted value.

Interpretation of descriptors

Rotatable bonds is one of the descriptors included in our model, it is defined as the number of rotatable bond counts in the molecule structure, with exception of the terminal bonds. This descriptor has the highest contribution and can be seen from the significant value of its coefficient when compared with the rest. The activity is inversely proportional to the number of rotatable bonds in this chemical specie, it was noticed that as we increase the number of rotatable bonds on the compound we inherently affects its ability to lie firmly at the point of attachment or at the target site where its function is primary.

Complementary information content index, is a 2D information content descriptor, which was created by Todeschini, R. and Consonni, V. (2009), the descriptor is defined as follows:

$$^{k}CIC = \log_2 n - {}^{k}IC$$

$$^{k}IC = -\sum_{i=1}^{k} \frac{n_i}{n} \log_2 \frac{n_i}{n}$$

n_i - number of atoms in the *i*th class

n - the total number of atoms in the molecule

k - number of atomic layers in the coordination sphere around a given atom that are accounted for (Basak, Harriss, & Magnuson, 1984).

The cic descriptors contributes about 10-15% of the overall effect on the activities of the dataset, the coefficient which was positive (+0.9287) passively influences the activity of the drugs, the number of atoms within the same class greatly influences the activity since a significant number means a higher overall value for cic.

The E-state keys (sums): S_sNH2 (Fast Descriptors), Shadow length: LX (Spatial Descriptors) and Shadow area: ZX plane (Spatial Descriptors) are also included in the model. Shadow indices are a set of 3D geometrical descriptors similar to a moore shape indices, which are related shape and size of molecules. They are calculated by projecting the molecular surface of three mutually perpendicular planes XY, XZ and YZ, assuming van der Waals radii for atoms (R. Rohrbaugh & P. C. Jurs, 1987; R. H. Rohrbaugh & P. C. Jurs, 1987)

Shadow areas of a molecule is defined

Ligand base design

With the information extracted from the descriptors contained in the model, 20 new complexes was then designed, the bioactivity of complexes were then calculated using the developed model. The result and their structures are presented in table 3.

Table 3.

NAME	Rotatable bonds (Fast Descriptors)	Complementary information content (CIC) (Fast Descriptors)	E-state keys (sums): S_sNH2 (Fast Descriptors)	Shadow area: ZX plane (Spatial Descriptors)	Shadow length: LX (Spatial Descriptors)	E LUMO (kJ/mol)	P(IC50)	IC50
1a	0.333	0.024	0	0.622	0.613	0.379	5.899375	1.26074
2a	0.111	0.241	0	0.639	0.597	0.517	6.535034	0.29172
3a	0.333	0.185	0	0.332	0.146	0.45	5.131411	7.389064
4a	0.444	0.255	0	0.63	0.643	0.446	5.874393	1.335386
5a	0.222	0.185	0.338	0.447	0.373	0.517	5.683669	2.071721
6a	0.444	0.171	0	0.528	0.431	0.448	5.408105	3.907468
7a	0.444	0.187	0	0.632	0.611	0.452	5.757929	1.746109
8a	0.556	0.213	0	0.706	0.749	0.453	5.775747	1.675919
10a	0.778	0.311	0	0.999	1	0.517	5.855837	1.393681
9a	0.889	0.432	0	0.617	0.62	0.52	4.921376	11.98462
11a	0.222	0.369	0	0.657	0.471	0.514	6.202336	0.627572
12a	0.667	0.099	0	0.565	0.503	0.509	4.923913	11.9148
13a	0.333	0.345	0	0.896	0.482	0.508	6.051849	0.887464
14a	0.444	0.167	0	0.749	0.452	0.517	5.507011	3.111639
15a	0.444	0.36	0	0.952	0.837	0.456	6.427166	0.373967
16a	0.444	0.316	0	0.364	0.28	0.51	5.194894	6.384188
17a	0.667	0.204	0	0.708	0.584	0.523	5.210741	6.155432
18a	0.333	0.283	0.681	0.776	0.715	0.518	6.122423	0.754357
19a	0.444	0.103	0	0.496	0.348	0.498	5.17294	6.715212
20a	1	0.386	0	0.886	0.941	0.528	5.255035	5.558599

Conclusion

The pIC_{50} for the malaria (plasmodium falciparum) was confidently modelled for a series of antimalarial complexes collected from the literature. This was achieved by using less inter-correlated descriptors computed through the Dragon 5.5 program, the statistical parameters of the model satisfy the criteria proposed by Tropsha, Roy and Grammatica for validating QSAR models. A small number of descriptors such as CIC, number of rotatable bonds, E-state S_sNH2, E LUMO and shadow length LX respectively, were found to be responsible for the antimalarial activity of the of the complexes used in the data set.

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