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QSAR Study of Nickel-Schiff Base Complexes as Anti-bacterial Agents against *Staphylococcus aureus*

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JPA and AU designed the study and wrote the protocol. Author JPA did the literature search and performed the statistical analysis. Authors JPA, AU and SOI wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To develop good and rational Quantitative Structure Activity Relationship (QSAR) mathematical models that can predict to a significant accuracy the anti-*Staphylococcus aureus* Minimum inhibitory concentration (MIC) of Ni-Schiff base complexes.
Place and Duration of Study: Department of Chemistry (Physical Chemistry unit), Ahmadu Bello University, Zaria, Nigeria, between January and June 2015.
Methodology: A set of 36 nickel-Schiff base complexes with their antibacterial activities in terms of minimum inhibitory concentration (MIC) against the gram-positive bacteria, *Staphylococcus aureus* were selected for 0D, 1D, 2D and 3D quantitative structure activity relationship (QSAR) analysis by means of Density Functional Theory (DFT) using the Becke's three-parameter hybrid functional (B3LYP) and 6-31G* basis set. The computed descriptors were correlated with their experimental MIC. Genetic function approximation (GFA) method and Multi-linear regression analysis (MLR) was used to derive the most statistically significant QSAR model.

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Results: Among the obtained QSAR models, the most statistically significant one was a tri-parametric linear equation with the squared correlation coefficient R^2 value of 0.9399, adjusted squared correlation coefficient R^2_{adj} value of 0.9313 and Leave one out (LOO) cross validation coefficient (Q^2) value of 0.9074. An external set was used for confirming the predictive power of the model, its R^2_{pred} = 0.9725.
Conclusion: The QSAR results reveal that molecular size and polarity predominantly influence the anti-*Staphylococcus aureus* activity of the complexes. The wealth of information in this study will provide an insight to designing novel bioactive nickel-schiff base complexes that will curb the emerging trend of multi-drug resistant strain of *Staphylococcus aureus*.

Keywords: QSAR; Staphylococcus aureus; GFA; MLR; Ni-schiff base complexes; MIC.

1. INTRODUCTION

The discovery and development of antibiotics are among the most powerful and successful achievement of modern science and technology for the control of infectious diseases. After the discovery of penicillin by Alexander Fleming, antibiotics were regarded as wonder drugs for curing virtually all infections. However, the careless use and overconsumption of antibiotics in both human and veterinary medicine have led to the emergence of antibiotic-resistant bacterial and fungal strains [1].

Of major concern is the development of antibiotic resistance in *Staphylococcus aureus.* Infections with multi-drug resistant *S. aureus* have become responsible for huge healthcare costs and are projected to be responsible for more deaths at present in the United States than HIV/AIDS [6]. *S. aureus* can be both a commensal and a dangerous pathogen causing severe infections—skin abscesses, endocarditis, pneumonia, osteomyelitis—even leading to toxic shock syndrome. *S. aureus* infection is a major cause of skin, soft tissue, respiratory, bone, joint, and endovascular disorders [2]. It is also an important etiological agent of food-borne diseases. This bacterium produces heat-resistant enterotoxins when growing in food leading to staphylococcal food poisoning [3]. In fact, *S. aureus* is a pathogenic bacterium considered as a major threat to food safety and food-borne disease worldwide [4-6].

Schiff base and its complexes with nickel (ii) ion are considered to be among the most important stereo - chemical models due to their preparative accessibility, structural varieties and high anti-microbial activities against disease causing bacteria and fungi species [7].

There is abundant literature concerning the biological activity of Ni – Schiff base complexes against *Staphylococcus aureus*. These complexes have been reported to possess higher anti-microbial activities compared to their organic ligands. The increase in activity of the complexes has been explained on the basis of the overtone concept and chelation theory [8-10].

Quantitative structure activity relationship (QSAR) study provides medicinal chemists valuable information that is useful for drug design and prediction of drug activity. QSAR models are mathematical equations which construct a relationship between chemical structures and their biological activities as a linear regression model in the form Y = Xb + e. This equation may be used to describe a set of predictor variables (X) with a predicted variable (y) by means of a regression vector (b) [11].

In recent years, substantial progress has been made in the application of *in silico* computational methods to predict *S. aureus* inhibition activities of some chemicals.

Preeti et al. [12] performed a multi-target QSAR studies on a data set of 12 thiazole derivatives. The structures of the compounds were pre-optimized with molecular mechanics forcefield (MMFF) and the resulting geometries were further refined by means of semi-empirical (PM3) method. The mt-QSAR model (n=12, r=0.986, r^2 = 0.972, Q^2 = 0.963, S=0.055, F=119.646) indicated that molecular connectivity index and kier's shape index are the key parameters for anti-microbial activity of the compounds studied.

The MLR-mt QSAR studies carried out by Pradeep et al. [13] on 22 benzohydrazide derivatives (n=13, r=0.808, Q^2 = 0.515, S=0.0198, F=9.43) indicated that the anti-microbial activities of the compounds were governed by balaban index and valence molecular connectivity. The structures of compounds were pre-optimized with molecular

mechanics force field (MM^+) and the resulting geometries were further refined by means of semi-empirical (PM3) method.

Sumit et al. [14] also performed a QSAR studies on anti-microbial activity of 17 triazole derivatives against *C. albicans* and *S. aureus*. The structures of compounds were pre-optimized with molecular mechanics force field (MM^+) and the resulting geometries were further refined by means of semi-empirical (PM3) method. The QSAR model (n=13, r=0.842, Q^2=0.530, S=0.058, F=12.17) indicated the importance of topological and electronic parameter in describing the anti-microbial activities of the compounds.

The result of the QSAR models built by Milan et al. [15] on 15 coumarin derivatives using both semi-empirical and DFT based calculations indicated that number of thiazole atom played dominant influence on the activity the compounds against S.aureus (n =15, r = 0.997, s = 0.03, Q^2 = 0.995, F = 104.2987). The equation (n = 15, r = 0.991, s = 0.068, F = 42.6548, Q^2 = 0.983) explaining the anti-fungal activity of the compounds against *C. albicans* identified the influence of solubility, electronic and sterric parameter on the activity of the compounds.

However, external validation of QSAR model reflects the predictive capability of the model on new data set. This validation technique is conspicuously lacking in recent QSAR studies on anti-staphylococcal activities of compounds as reviewed above. In this study, the statistically significant model selected has been subjected to external validation in addition to internal validation in order to confirm its predictive power and robustness.

As against the recent QSAR works on anti-*Staphylococcus aureus* activities of molecules, this study focused on complexes since research has shown that the biological activities of compounds increases on complexation due to chelation [16]. QSAR works on Complexes are expected to provide a better option to man in his desperate search for potent anti-microbial drug to curb the emerging trend of multi-drug resistance in *Staphylococcus aureus*.

Likewise, literature search (as evidenced in the review above) has shown that molecular optimization in recent QSAR studies on anti-Staphylococcal activities of compounds are performed predominantly using the semi-empirical method even though research in QSAR studies [17-19] have shown that DFT method gives better result compared to the semi-empirical (AM1 and PM3) as the former gives better correlation between calculated results and experimental data. Therefore, the DFT method because of its accuracy over the semi-empirical methods is expected to lead to a more reliable and accurate results. This necessitated the preference of DFT/B3LYP method in this work over PM3 or AM1 semi-empirical method.

The aim of this study is to develop good and rational QSAR mathematical models that can predict to a significant accuracy the anti-Staphylococcal inhibitory activities (in form of MIC) of Ni-Schiff base complexes.

Harnessing the structure-activity relationship of this class of complexes which show considerable biological activity against *Staphylococcus aureus* may represent an interesting approach for designing new anti-staphylococcal aureus drugs. This may be due to the dual possibility of both ligands plus metal ion interacting with different steps of the pathogen life cycle.

2. MATERIALS AND METHODS

2.1 Materials

The materials use in this study include; H.P 650 computer system (Intel Pentium), 2.43GHz processor, 4GB ram size on Microsoft windows 7 Ultimate operating system, Spartan 14 V.1.1.0, Chm 3D Pro 12.0.1V, Padel descriptor tool kit and Microsoft office Excel 2013 version + *Analyze it*$^@$ Statistical software, Material Studio (modeling and simulation software) version 7.0, Printers.

2.2 Computational Methodology

Chemdraw ultra software was used to draw the structure of the compounds in the data set and each structure was saved as *MDL* file. The Spartan 14 V.1.1.0 software was used for the optimization of the molecules. The molecules were first pre-optimized with the Semi-empirical (AM1) procedure included in Spartan'14 V1.1.0 software and the resulting geometries were further refined by means of Density functional theory (DFT) using the B3LYP version and 6-31G* basis set. The lowest energy structure was used for each molecule to calculate their physicochemical properties. The quantum chemical descriptors were calculated using the

Spartan'14 V.1.1.0 quantum chemistry package. *Padel descriptor* tool kit was used to calculate 1D, 2D and 3D descriptors as well.

2.3 QSAR Methodology

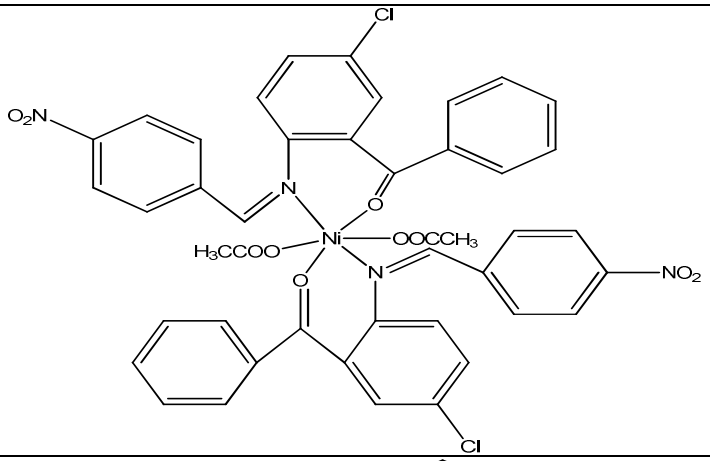
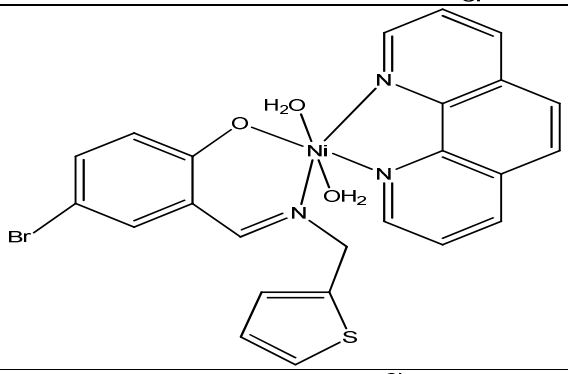
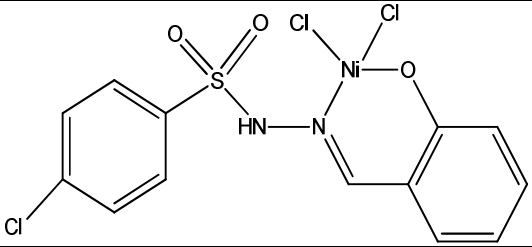
2.3.1 Data collection

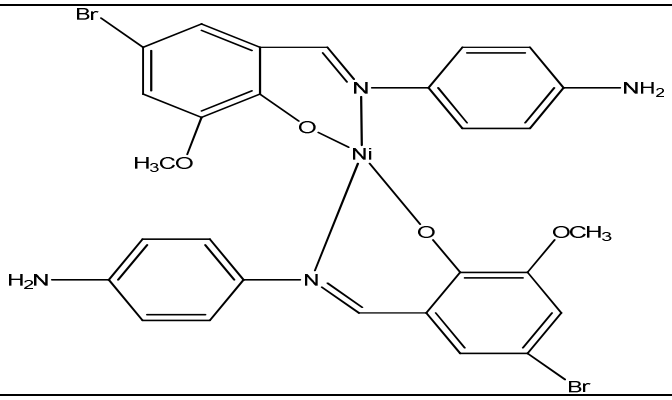
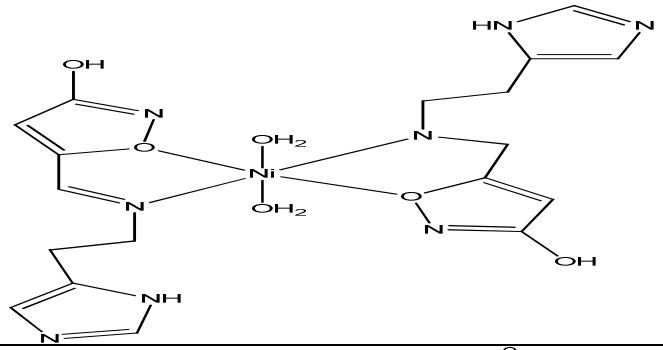
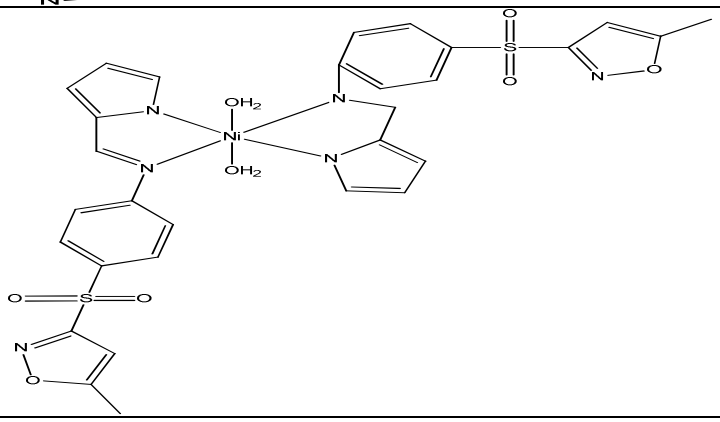
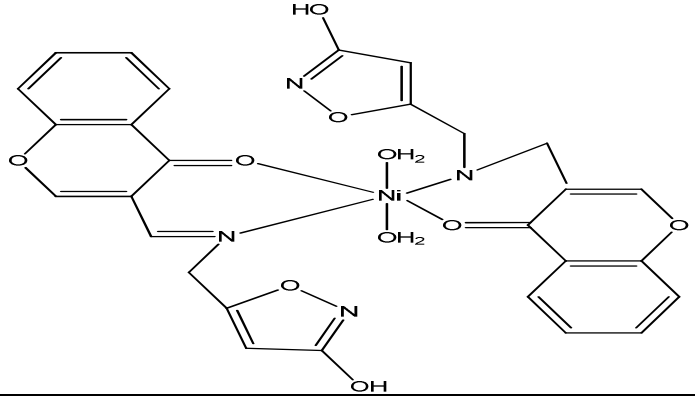
The chemical structures and experimental minimum inhibitory concentration (*MIC)* values in µg/ml of anti- *Staphylococcus aureus* were taken from literature [20-36]. The *MIC* values of the compounds were converted to logarithmic scale [p*MIC* = log*MIC* (µg/mL)]. The notation, structure, MIC and pMIC values for each member of the training set are presented in Table 1.

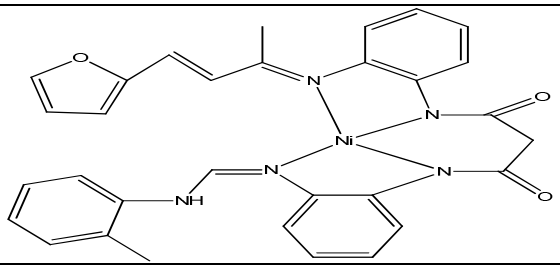
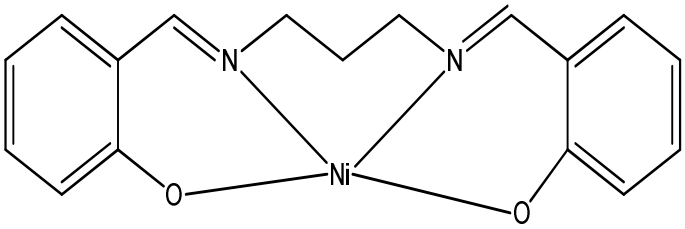
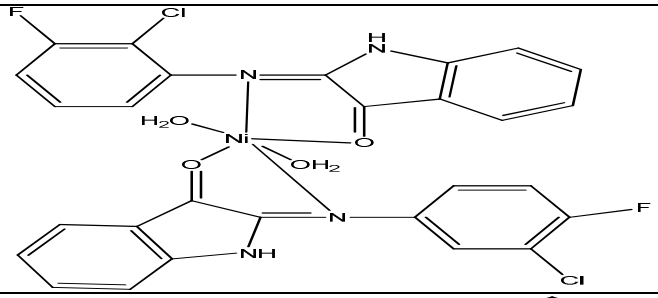
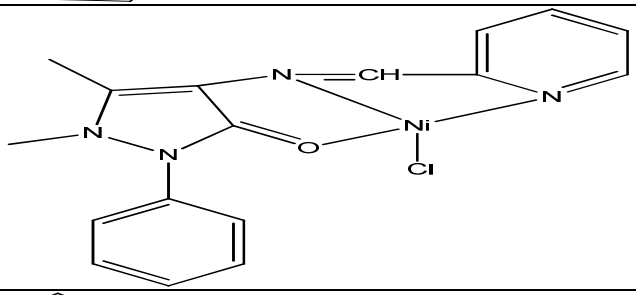
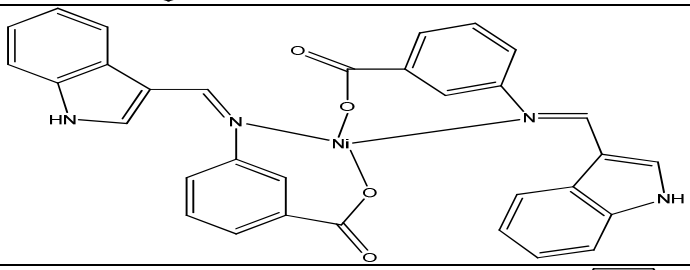
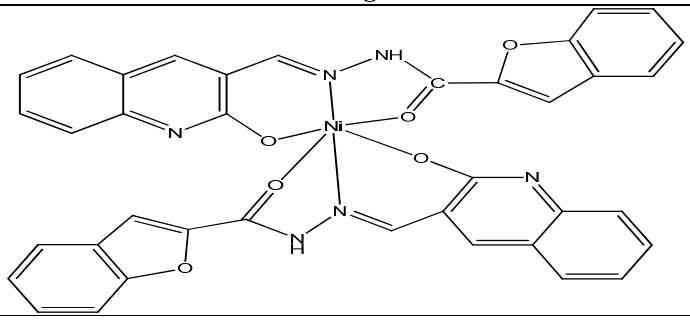
2.3.2 Descriptor selection

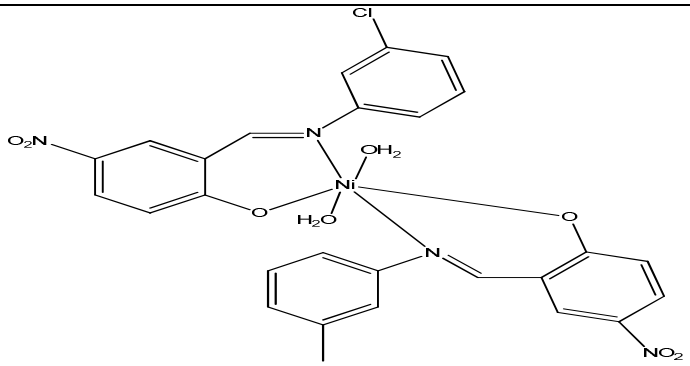
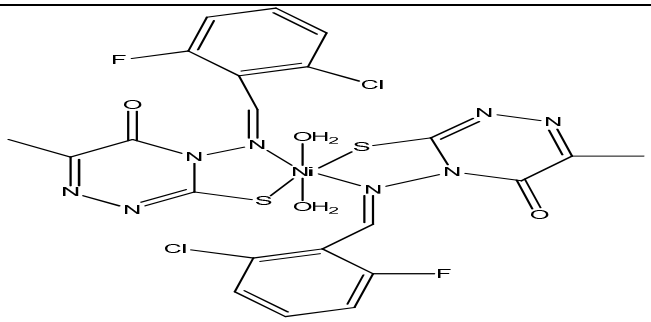
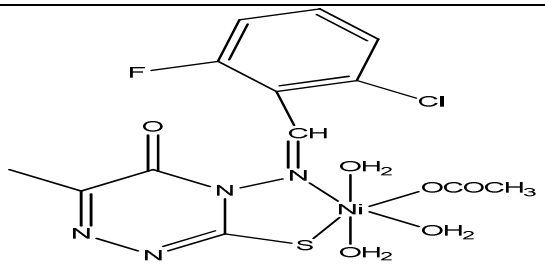
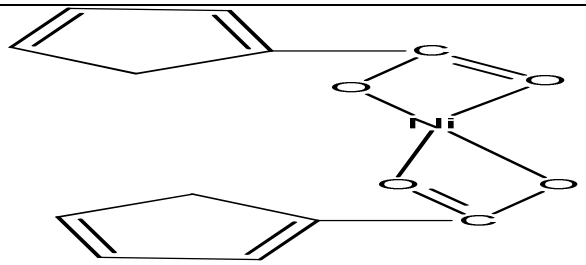
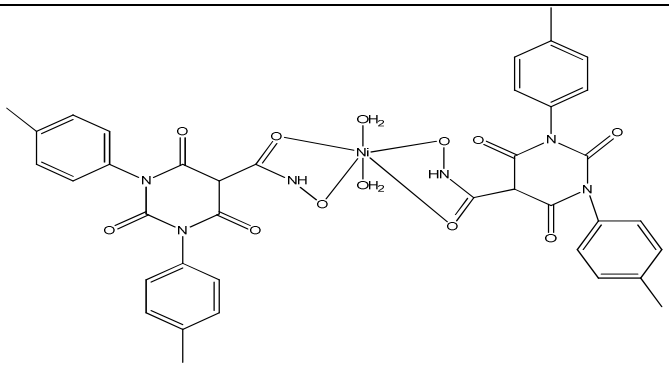
Over 1000 descriptors comprising of 0D, 1D, 2D, and 3D types were generated for each molecule. The descriptors were correlated with the biological activities of the molecules using Pearson's correlation matrix. Pearson's correlation matrix was used to select the suitable descriptors for Genetic Function Approximation (GFA) and multi-linear regression (MLR) analysis based on the correlation coefficients.

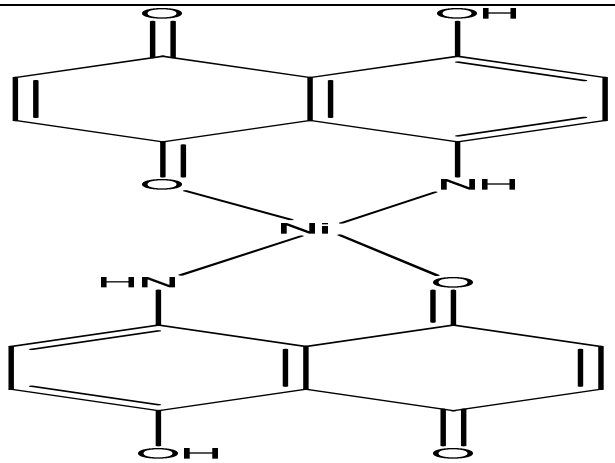
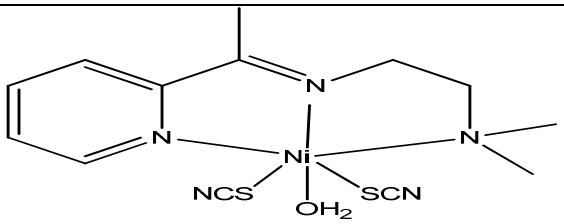
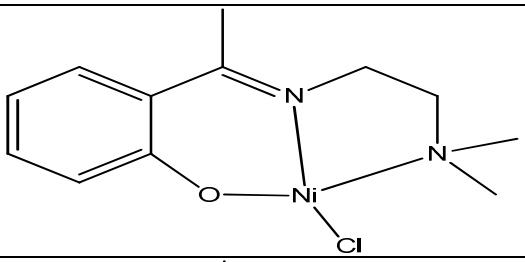
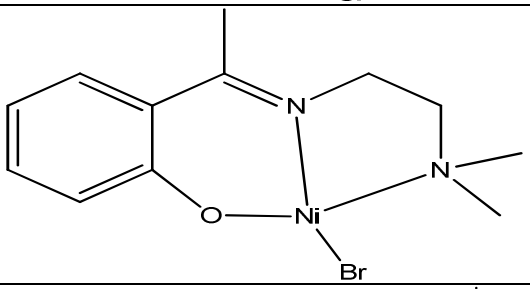
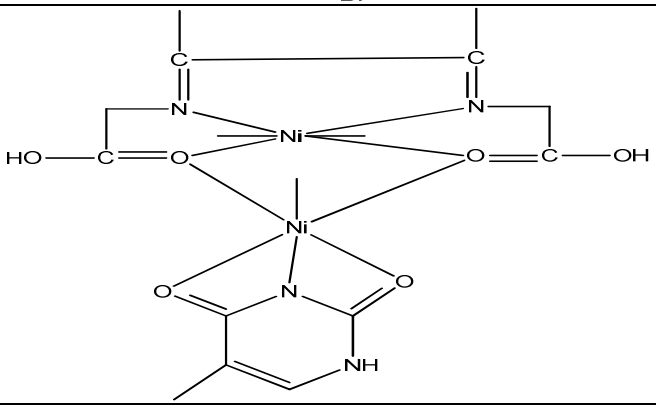
Table 1. Experimental *MIC* values of the complexes against *Staphyloccocus aureus*

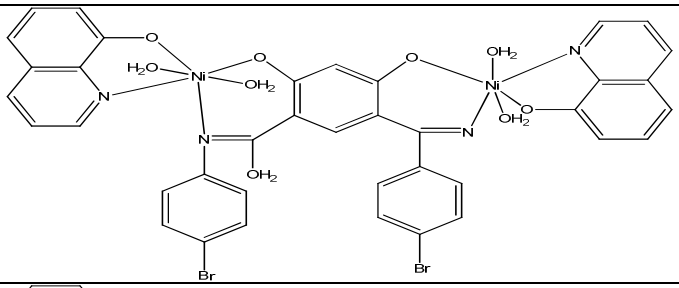
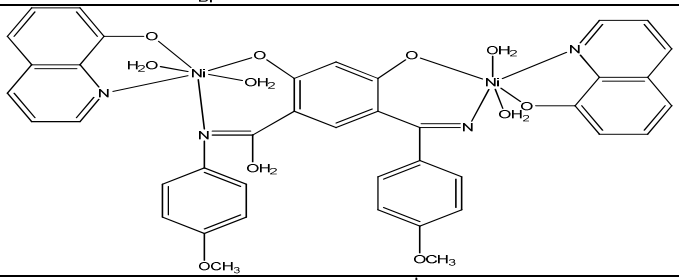
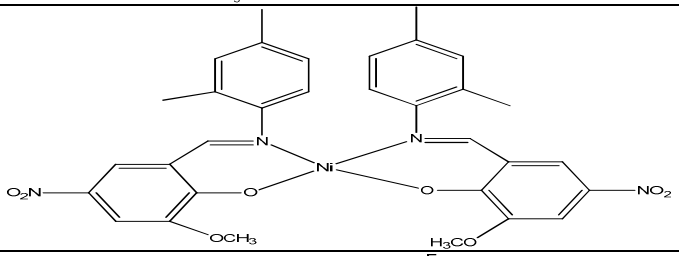
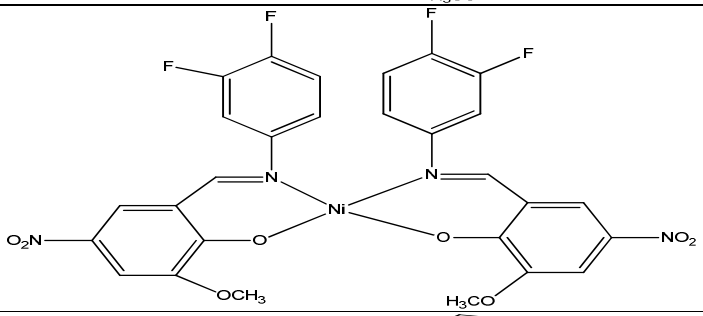
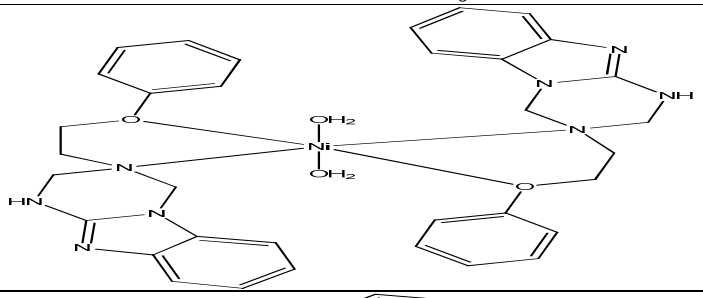
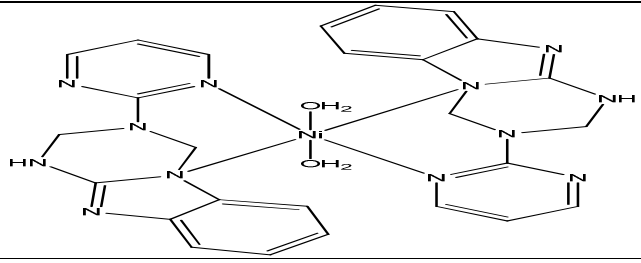
Cpd.	Structure	MIC value (µg/ML)	pMIC
C1		9.3	0.97
C2		26	1.41
C3		18.3	1.26

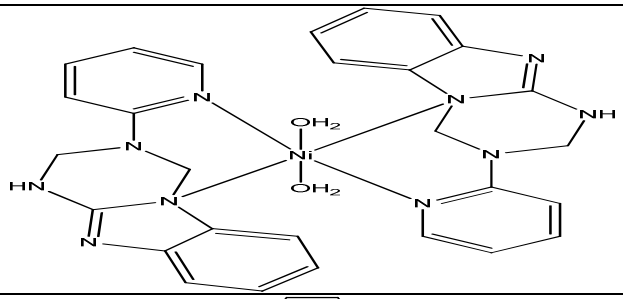
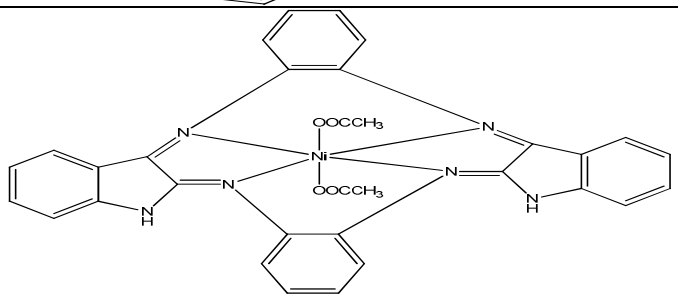
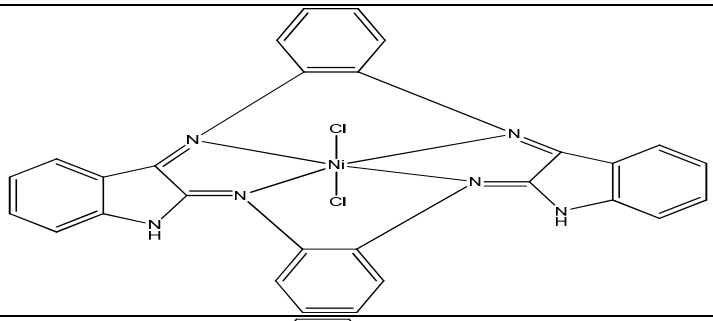
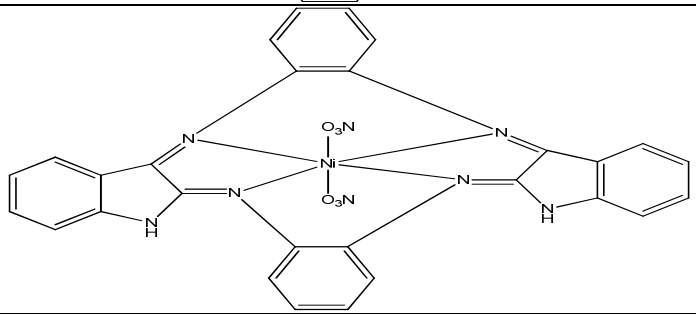
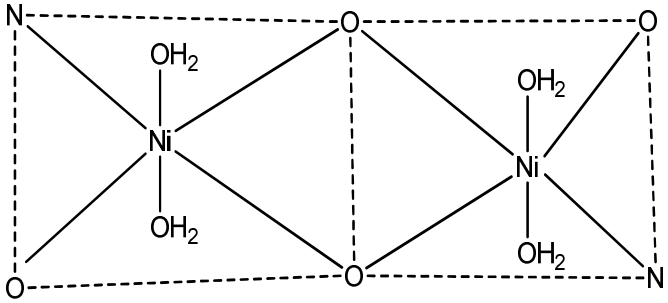
C4		256	2.41
C5		50	1.70
C6		50	1.70
C7		50	1.70

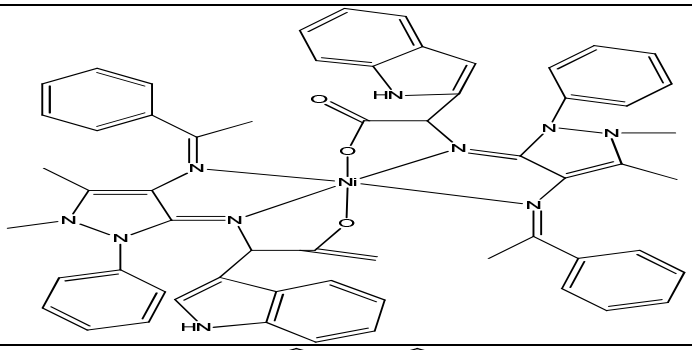
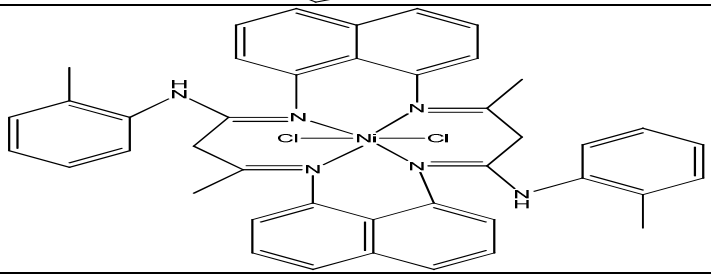
C8		26	1.41
C9		31.25	1.49
C10		24	1.38
C11		50	1.48
C12		100.5	2.00
C13		13	1.11

C14		20	1.30
C15		64	1.81
C16		32	1.51
C17		128	2.11
C18		325	2.51

C19		475	2.68
C20		20	1.30
C21		19	1.28
C22		21	1.32
C23		32	1.51

C24		1000	3.00
C25		500	2.70
C26		100	2.00
C27		50	1.70
C28		64	1.81
C29		73	1.86

C30		70	1.85
C31		32	1.51
C32		128	2.11
C33		8	0.90
C34		256	2.41

C35		75	1.88
C36		50	1.70

2.3.3 Training set and data set

The data set for the biological activity was split into training set and test set. At least 70% of the data set was used as training set and the rest as test set in line with the optimum splitting pattern of data set in QSAR study [37]. Consequently, the data set of 36 complexes was split into 25 training set and 11 test set. The training set was used to generate the model while the test set was used to evaluate their prediction abilities.

2.3.4 Regression analysis

Different possible combinations of descriptors were subjected to Genetic Function Approximation (GFA) and multiple linear regressions (MLR) analysis with the experimentally determined biological activity on logarithmic scale (pMIC) as dependent variable and the descriptors as independent variable. Out of the three statistically significant generated GFA models, the best (model-1a) was selected based on the one with the smallest LOF score. The MLR equation was generated in stepwise manner by forward selection method starting with best single variable and adding further significant variable according to their contribution to the model that leads to the smallest P-value at 95 percent confidence level, until there is no other variable outside the equation that satisfies the selection criteria [38]. The P-values of the model was provided by the *Analyze it*® statistical software at 95% confidence level. The p-value is a probability that measures the evidence against the null hypothesis. Lower probabilities provide stronger evidence against the null hypothesis. The null hypothesis implies that there is no association between the descriptors and the pMic of the molecules. Model (1a and 1b) gives the best QSAR equations using GFA and MLR analysis respectively.

Use of the Friedman lack-of-fit (LOF) measure has several advantages over the regular least square error measure. In Materials Studio, LOF is measured using a slight variation of the original Friedman formula [39]. The revised formula is:

$$LOF = SSE / (1 - \frac{C+dp}{M})^2 \quad (1)$$

Where SSE is the sum of squares of errors, c is the number of terms in the model, other than the constant term, d is a user-defined smoothing parameter, p is the total number of descriptors contained in all model terms (ignoring the constant term) and M is the number of samples in the training set. Unlike the commonly used least squares measure, the LOF measure cannot always be reduced by adding more terms to the regression model. While the new term may reduce the SSE, it also increases the values of c and p, which tends to increase the LOF score. Thus, adding a new term may reduce the SSE, but actually increases the LOF score. By limiting the tendency to simply add more terms, the LOF measure resists over fitting better than the SSE measure (Materials Studio 5.0 Manual).

2.3.5 Model validation

Validation is a crucial aspect of any QSAR modeling. It is the process by which the reliability and relevance of a procedure are established for a specific purpose [40]. It is the process of establishing the reliability and predictivity of a QSAR model. Both external and internal validations were carried out on the model. The minimum recommended value for a generally acceptable QSAR model proposed by Ravinchandran et al. [41] is shown in Table 2.

2.3.6 Model validation

Validation is a crucial aspect of any QSAR modeling. It is the process by which the reliability and relevance of a procedure are established for a specific purpose [40]. It is the process of establishing the reliability and predictivity of a QSAR model. Both external and internal validations were carried out on the model.

2.3.6.1 Internal validation

This is the validation done using the data that created the model. The QSAR models were internally validated using the methods of least squares fit (R^2), cross validation coefficient (Q^2), adjusted R^2 (R^2adj), difference between R^2 and Q^2 (R^2 - Q^2) and its confidence interval of all regression coefficient at 95% significant level (α value). The values of these parameters were compared with the minimum criterion for robust QSAR models proposed by Ravichandran et al. [41] in Table 2.

R^2 value is interpreted as the proportion of variation in Y that is explained by the model. It is given by the formula:

$$R^2 = \frac{SSR}{SST} = \frac{SST-SSE}{SSE} \quad (2)$$

Where SST = total sum of squares, SSR = regression sum of squares, and SSE = minimum sum of squared residuals of any linear model.

R^2 value varies directly with the increase in number of regressors i.e. descriptors, thus, R^2 cannot be a useful measure for the goodness of model fit. Therefore, R^2 is adjusted for the number of explanatory variables in the model. The adjusted R^2 is defined as:

$$R^2_{adj} = 1 - (1 - R^2)\frac{n-1}{n-p-1} = \frac{(n-1)R^2-P}{n-p+1} \quad (3)$$

Where p = number of independent variables in the model [42].

The LOO cross validated coefficient (Q^2) is given by;

$$Q^2 = 1 - \frac{\sum(Yp-Y)^2}{\sum(Y-Ym)^2} \quad (4)$$

Where Yp and Y represent the predicted and observed activity respectively of the training set and Y_m the mean activity value of the training set.

The predicted r^2 value is calculated as follows;

$$\text{Pred-}R^2 = 1 - \frac{\sum[Ypred(te)-Y(te)]^2}{\sum[Y(te)-Ym(tr)^2} \quad (5)$$

Ypred.(test) and Y(test) indicate predicted and observed activity values respectively of the test set compounds and Ym(tr) indicates mean activity value of the training set.

2.3.6.2 External validation

The real predictive ability of any *QSAR* model cannot be judged solely by using internal validation, it has to be validated on the basis of predictions of activities of molecules not used in the models [41]. Prior to the development of the models, each data set was split into training and test set. QSAR models were built using the training set while the tests set were used for externally validating the models. The predicted R^2 was computed in each case using the formula in equation (5).

Table 2. Minimum recommended value of validation parameters for a generally acceptable QSAR model

S/n.	Validation parameter		Value
	Symbol	Name	
1.	R^2	Coefficient of determination	≥ 0.6
2.	$P_{(95\%)}$	Confidence interval at 95% confidence level.	< 0.05
3.	Q^2	Cross validation coefficient	< 0.5
4.	$R^2_{ext.}$	Coefficient of determination for external test set	≥ 0.6
5.	R^2 - Q^2	Difference between R^2 and Q^2	≤ 0.3
6.	$N_{ext.\ test\ set}$	Minimum number of external test set	≥ 5

(Source: Ravinchandran et al. [41])

3. QSAR STUDY RESULTS AND DISCUSSION

The best performing QSAR model for the pMIC of the complexes against *S. aureus* using GFA and MLR is represented by model 1a and 1b respectively. The name and symbol of the descriptors used in the QSAR model and Pearson's correlation matrix for descriptors used in the model are shown in the Tables 3 and 4 respectively.

3.1 Model –1a: GFA Derived Model for Anti-staphylococcal Activity of the Complexes

pMIC = 1.314686782 WD.polar + 0.094735041 nT6Ring + 2.031680337 Wta3.po - 0.716922788

n = 25, Friedman LOF = 0.09036500, R^2 = 0.93993300, R^2adj. = 0.93135200, Q^2=0.90741600

F-value = 109.5362400, Min. expt. error for non-significant LOF (95) = 0.11706500

3.1.1 Effect of model

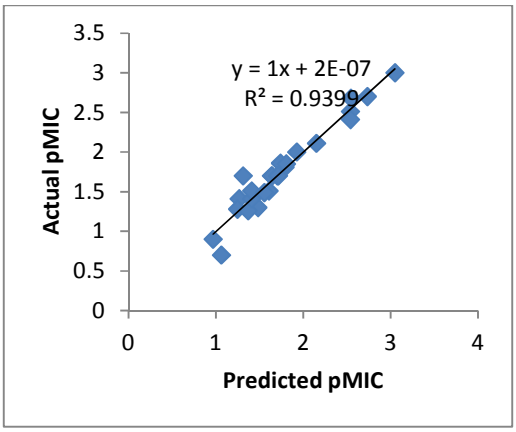


Fig. 1. Plot of actual verses predicted pMIC of the complexes

3.1.2 Residual plot of model -1a

Pred-R^2 =1-(0.05397395/1.9621) = 0.9725 i.e. using the formula in equation 5.

3.1.3 Model – 1b: MLR derived model for anti-staphylococcal activity of the complexes

pMIC =-0.7169 + 1.315 WD.polar + 0.09474 nT6Ring + 2.032 Wta3.po

n = 25, R^2 = 0.940, R^2_{adj} = 0.931, SE (RMSE) = 0.1462, P-value at 95% C.L < 0.0001.

The result of the GFA QSAR model is in conformity with the standard shown in Table 2 as R^2 = 0.9399, R^2_{adj} = 0.9313, Q^2 = 0.9074, R^2_{pred}. = 0.9725. This confirms the robustness of the model.

The comparison of observed and predicted antibacterial activities of the complexes is presented in Table 5. The predictability of model-1 is evidenced by the low residual values observed in Table 5 as well by the plot of predicted pMIC against observed pMIC (Fig. 1). Further, the plot of observed pMIC versus residual pMIC (Fig. 2) indicated that there was no systemic error in model development as the propagation of residuals was observed on both sides of zero [43].

The P-value of the model at 95% confidence level shown in model-1b is < 0.05. This reveals that the alternative hypothesis that there is an association between the descriptors used in the model and the pMic of the complexes takes preference over the null hypothesis.

The effect of terms shown in section Table 7 reveals that at 95% confidence level, all the descriptors in the model contribute significantly as their P-values are < 0.05, a requirement at this confidence limit.

Table 3. Pearson's correlation matrix for descriptors used in QSAR model for the pMIC of anti-*Staphylococcus aureus* molecules

	log Mic	WD.polar	nT6Ring	Wta3.po
log Mic	1			
WD.polar	0.67652	1		
nT6Ring	0.634432	0.304345	1	
Wta3.po	0.775394	0.345518	0.207828	1

Table 4. The symbol and definition of the descriptors used in the models

S/N	Descriptor symbol	Definition
1	Weta3.polar	Directional WHIM, weighted by atomic polarizabilities
2	WD.polar	Non-directional WHIM, weighted by atomic polarizabilities
3	nT6Ring	Number of 6-membered rings (includes counts from fused rings)

Table 5. Comparison of observed pMIC and predicted pMIC of model 1a

Cpd.	Observed Pmic	Predicted Pmic	Residuals
C15	1.81	1.792307	0.017693
C18	2.51	2.537564	-0.02756
C19	2.68	2.546037	0.133963
C2	1.41	1.265634	0.144366
C20	1.30	1.482121	-0.18212
C21	1.28	1.247022	0.032978
C23	1.51	1.608446	-0.09845
C24	3.00	3.048398	-0.0484
C25	2.70	2.732927	-0.03293
C26	2.00	1.924718	0.075282
C27	1.70	1.635391	0.064609
C29	1.86	1.738337	0.121663
C3	1.26	1.368422	-0.10842
C30	1.85	1.806446	0.043554
C8	1.41	1.408819	0.001181
C32	2.11	2.150687	-0.04069
C33	0.90	0.968175	-0.06818
C31	1.51	1.408819	0.101181
C4	2.41	2.540626	-0.13063
C5	1.70	1.31214	0.38786
C6	1.70	1.642009	0.057991
C7	1.70	1.704352	-0.00435
C9	1.49	1.55428	-0.06428
C36	1.70	1.713982	-0.01398
C37	0.70	1.062339	-0.36234

The closeness of the values of R^2, R^2_{adj}, Q^2 of model obtained from GFA to that obtained through MLR, further reveals the reliability and robustness of the GFA model.

Model-1 was developed to predict the antibacterial activity of the complexes against *S. aureus*. The positive coefficient of the descriptors; directional WHIM weighted by atomic polarizabilities (Wta3.po), non-directional WHIM weighted by atomic polarizabilities (WD.polar), and number of 6-membered ring (nT6Ring) indicated that the magnitude of the pMIC of these complexes increases with increase in the values of these descriptors. Since the activity of drug varies inversely with its minimum inhibitory concentration (MIC), the lower the values of these descriptors in a molecule, the more the activity of the molecule against *S. aureus.*

Increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of the organism, disturbing the respiratory process of its cell and blocking the synthesis of proteins thereby restricting further growth of the organism [44]. Wta3.po and WD.polar are WHIM descriptors which describe the polarity of a molecule. The decrease in the anti-*Staphylococcus aureus* activity with increasing polarity of the complexes as shown in the model may be due to decrease in lipophilicity orchestrated by increase in polarity. Since biological membranes are lipophilic, highly polar complexes may not be able to penetrate these membranes to bring about their inhibitory role on the growth of this pathogen, thus, reducing their activities.

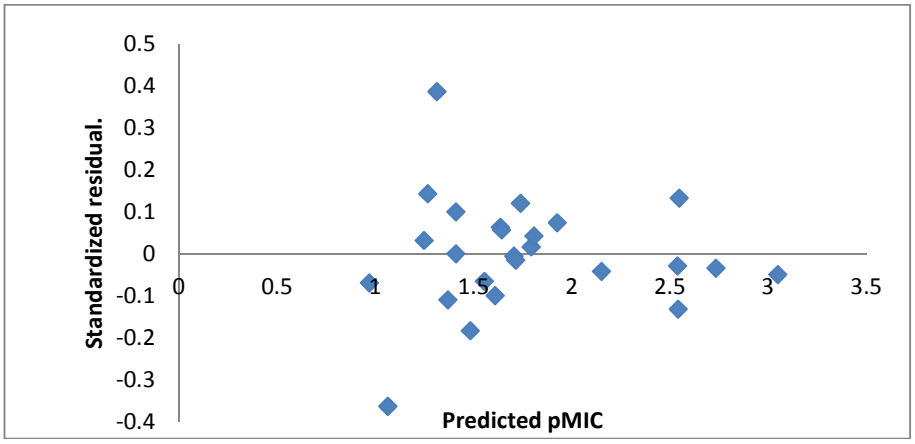


Fig. 2. Plot of standardized residual against predicted pMIC of the complexes

Table 6a. External validation of model – 1a

Test set	WD.polar	Weta3.polar	nT6Ring	Actual pMIC	Pred.pMIC	Residual
C1	0.525646	0.117027	8	0.97	0.969779	0.000221
C10	1.026511	0.189124	4	1.38	1.395797	-0.0158
C11	1.073042	0.292321	2	1.48	1.477164	0.002836
C12	1.14945	0.40593	4	2	1.997904	0.002096
C13	0.825646	0.101061	8	1.11	1.331747	-0.22175
C14	0.903492	0.133213	6	1.3	1.309943	-0.00994
C16	0.99044	0.382282	2	1.51	1.55134	-0.04134
C17	1.653996	0.303764	0	2.11	2.074715	0.035285
C22	0.870735	0.363509	2	1.32	1.355825	-0.03583
C28	0.989987	0.329866	6	1.81	1.823193	-0.01319
C34	1.366777	0.191048	10	2.41	2.41546	-0.00546

Table 6b. External validation of model – 1a

cpd	Yte	Ym(tr)	$[Yte - Ym(tr)]^2$	Ypred(te)	$(YpTe-Yte)^2$
C1	0.97	1.768	0.636804	0.969779	4.8841E-08
C10	1.38	1.768	0.150544	1.395797	0.00024955
C11	1.48	1.768	0.082944	1.477164	8.0429E-06
C12	2	1.768	0.053824	1.997904	4.3932E-06
C13	1.11	1.768	0.432964	1.331747	0.04917173
C14	1.3	1.768	0.219024	1.309943	9.8863E-05
C16	1.51	1.768	0.066564	1.55134	0.001709
C17	2.11	1.768	0.116964	2.074715	0.00124503
C22	1.32	1.768	0.200704	1.355825	0.00128343
C28	1.81	1.768	0.001764	1.823193	0.00017406
C34	2.41	1.768	0.412164	2.41546	2.9812E-05
			∑ = 1.9621		∑ = 0.05397395

Table 7. Effect of terms at 95% confidence level

Term	SS	DF	MS	F	p-value
WD.polar	0.781	1	0.781	36.56	<0.0001
nT6Ring	1.113	1	1.113	52.13	<0.0001
Wta3.po	2.090	1	2.090	97.84	<0.0001

The decrease in activity of the complexes with increasing number of fused 6-membered ring as depicted in the model may be attributed to the possibility of excessive increment of the molecular size of the complexes due to the increasing ring size, making the molecule to be largely confined to the plasma compartment because of their large size [45] affecting its distribution via out the body.

4. RECOMMENDATION

In the future design of novel Ni-Schiff base complexes as anti-*Staphylococcus aureus* drug, it is recommended based on this research that the complexes should be made less polar as possible. Also, number of fused 6-membered ring/bulkier ligands in the moieties should be reduced or completely substituted with a less bulky ligand or ring system.

5. CONCLUSION

The generated QSAR models, performed to explore the structural requirements controlling the observed antibacterial properties, hinted that the biological activities were affected by WHIM descriptors weighted by atomic polarizabilities as well as number of fused 6-membered ring. The robustness and applicability of QSAR equation has been established by internal and external validation techniques. It is envisaged that the wealth of information in this QSAR model will provide an insight to designing a novel bioactive nickel-schiff base complex that will curb the emerging trend of multi-drug resistant strain of *Staphylococcus aureus*.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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