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Quantitative structure activity relationship study of nickel schiff base complexes as potent anti-candida albicans agents

J. P. Ameji, A. Uzairu and S. O. Idris

Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria
E-mail: philo4real55@gmail.com

ABSTRACT

A dataset of Nickel-Schiff base complexes displaying potent activity against *Candida albicans* has been investigated utilizing 0D,1D,2D, and 3D Quantitative Structure-Activity Relationship (QSAR) techniques. Genetic Function Approximation method was used to produce QSAR models that correlated the Minimum Inhibitory Concentration (MIC) values against *Candida albicans* with the molecular structures of the active complexes. A training set of 21 active complexes was used to develop the models; the optimum model was then evaluated by a series of internal and external cross-validation techniques. A test set of 10 complexes was used for the external validation. The optimum model has squared correlation coefficient R^2 value of 0.934, adjusted squared correlation coefficient R^2_{adj} value of 0.918, Leave one out (LOO) cross validation coefficient (Q^2) value of 0.9059, F value of 56.70, Friedman's Lack of Fit (LOF) of 0.124. The external set used for confirming the predictive power of the model has its $R^2_{pred} = 0.830$. Our work may offer a pathway to the design of novel and biologically active Nickel-Schiff base complexes that will arrest the growing trend of *C. albicans* resistance.

Keywords: QSAR, MIC, GFA, nickel-schiff base complexes, *Candida albicans*

INTRODUCTION

The global incidence of infections caused by pathogenic microorganisms has increased over the years, resulting in significant morbidity and mortality in many countries of the world. More worrisome is the increasing pace of resistance to existing antibiotics by these organisms posing a great threat to humanity. *Candida albicans* is the most common human fungal pathogen, and mortality from *C. albicans* infection is still unacceptably high [1]. It is an opportunistic and often deadly pathogen that attacks host tissues, undergoes a dimorphic shift, and then grows as a fungal mass in the kidney, heart or brain. It is the fourth leading cause of hospital-acquired infection in the United States and over 95% of AIDS patients suffer from infections by *C. albicans*. It is the predominant organism associated with candidiasis [1]. *C. albicans* is the fourth most common cause of nosocomial bloodstream infection in the United States and one of the major species of candida responsible for Vulvovaginal candidiasis (VVC), a fungal infection of the female lower genital tract-the vulva and the vagina [2] VVC is a commonly reported gynecological condition and it has been reported that 75% of women experience this infection in their life time [3].

Despite this increasing problem of antibiotic resistance, the number of different antibiotics available is dwindling and there are only a handful of new antibiotics in the drug development pipeline, this situation pushed researchers to

discuss if humanity have reached the Post-Antibiotic era [4]. Therefore, there is an urgent need for new anti-microbial (anti-*Candida albicans*) drugs preferably with new modes of action to potentially avoid cross-resistance [5].

Schiff bases and their nickel complexes have been known to possess enormous biological activity against candida albicans [6-18].

These complexes have been reported to possess higher anti-fungal 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 [19-21]. Harnessing the structure-activity relationship of this class of complexes which show considerable biological activity against *Candida albicans* via QSAR may represent an interesting approach for designing new anti- *Candida albicans* drugs.

Novel medicines are typically developed using a trial and error approach, which is time consuming and costly. The application of quantitative structure activity relationship (QSAR) methodologies to this problem has potential to decrease substantially the time and effort required to discover new medicines or to improve current ones in terms of their efficacy. QSAR establishes the mathematical relationship between physical, chemical, biological or environmental activities of interest and measurable or computable parameters such as topological, physicochemical, stereo chemical or electronic indices [22] called molecular descriptors. As against the recent QSAR works on anti-candidal activities of molecules [23-26], this study focused on complexes since research has shown that the biological activities of compounds increases on complexation due to chelation [19; 20; 21; 27]. Also, the QASR model generated was validated externally in addition to internal validation. 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 *C. albicans*.

The aim of this research is to quantitatively harness the dominant structural features controlling the anti-candida albicans inhibitory activity of nickel-schiff base complexes and to mathematically describe the relationship between the biological activity of the complexes and their harnessed structural features.

MATERIALS AND METHODS

The methodology used in this work is presented in the chart.

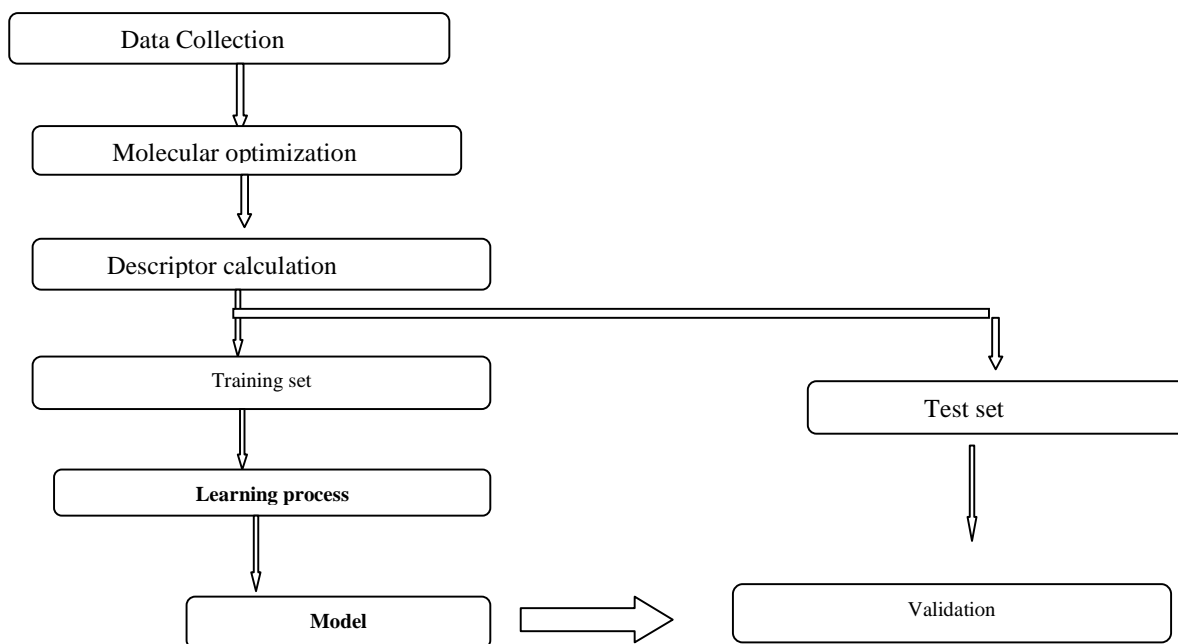
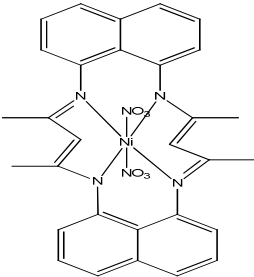
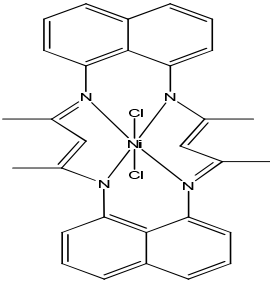
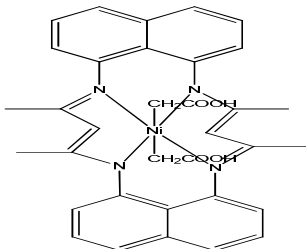
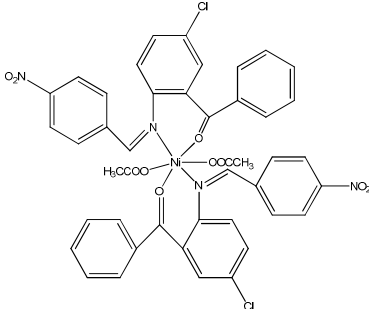


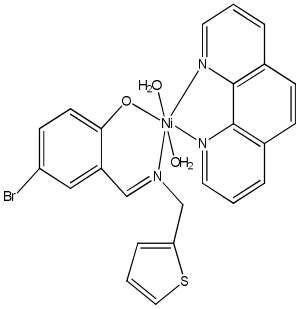
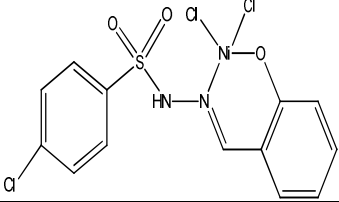
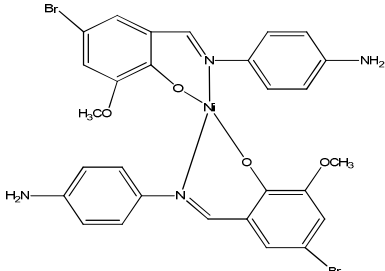
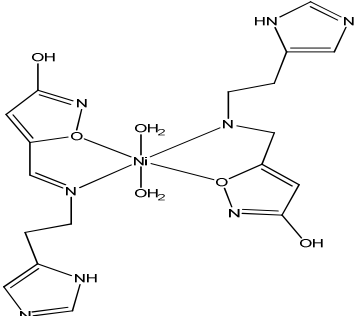
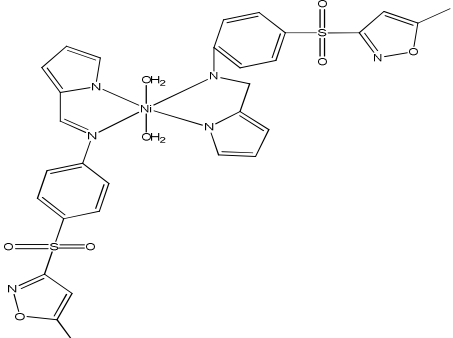
Figure 1: QSAR methodology flowchart

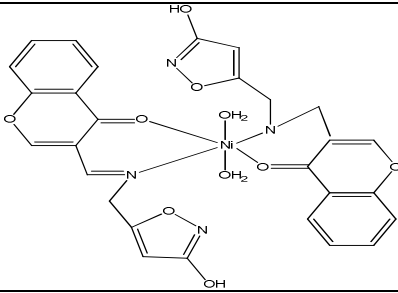
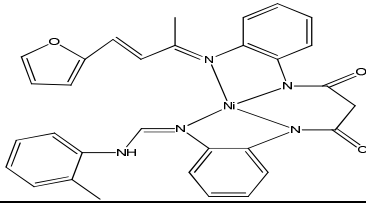
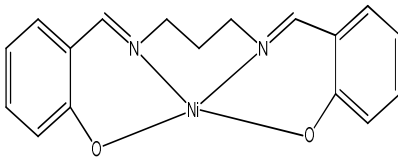
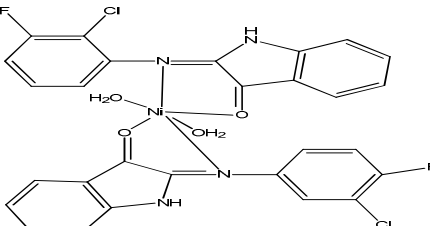
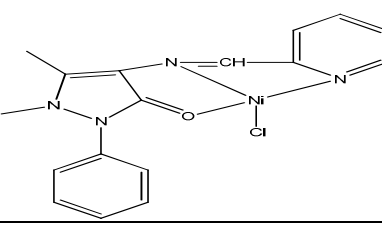
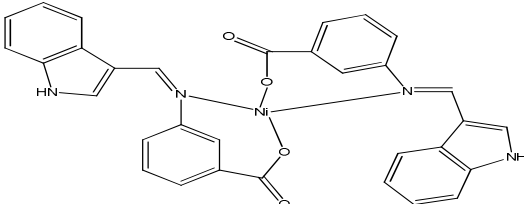
2.1 Data collection

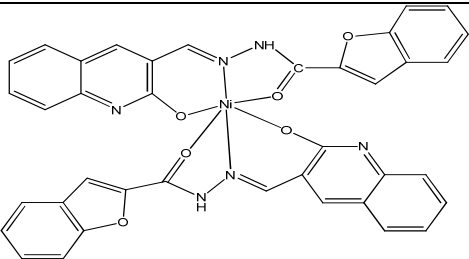
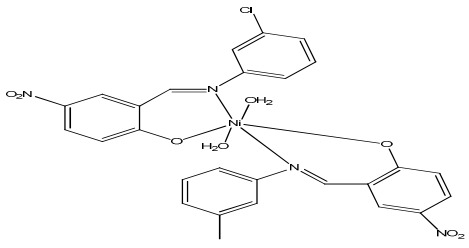
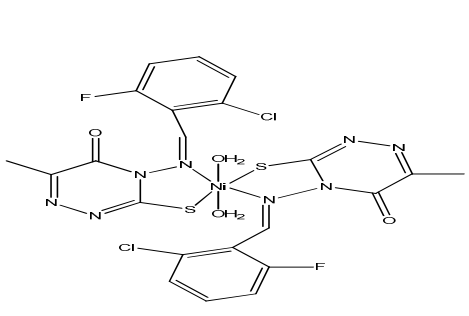
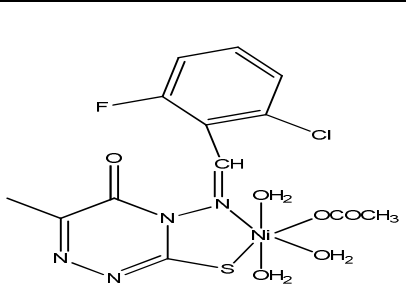
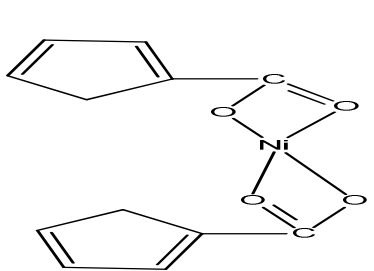
The chemical structures and experimental minimum inhibitory concentration (*MIC*) values in $\mu\text{g/ml}$ of anti-*Candida albicans* complexes were taken from literature [6-18]. The *MIC* values of the compounds were converted to logarithmic scale [$\text{pMIC} = \log\text{MIC} (\mu\text{g/ml})$] in order to reduce the dispersion of data set and to get linear response and well data fitting. The notation, structure, *MIC* and *pMIC* values for each member of the training set are presented in Table 1.

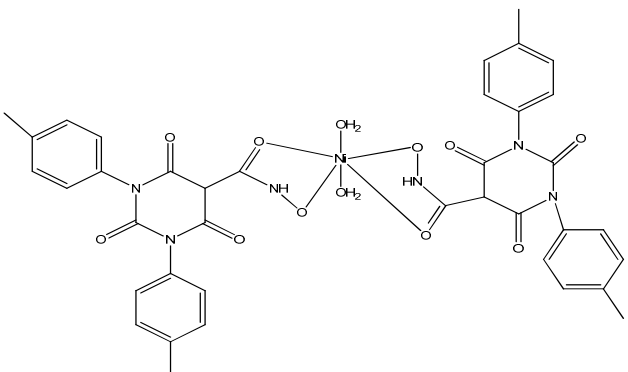
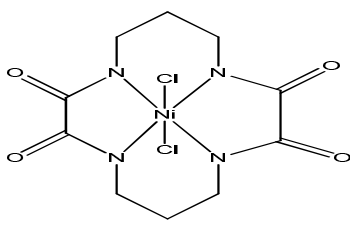
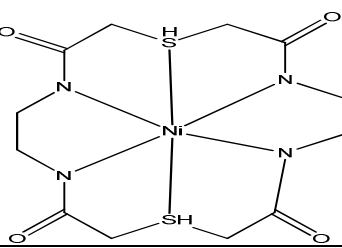
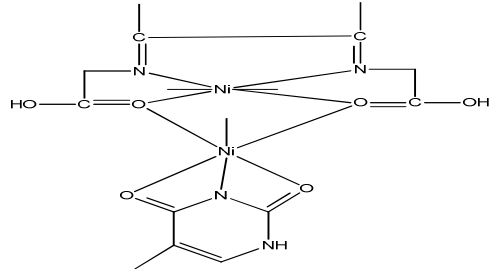
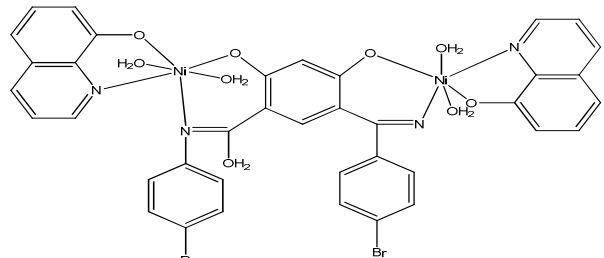
TABLE 1: Experimental *MIC* values of anti-*Candida albicans* molecules

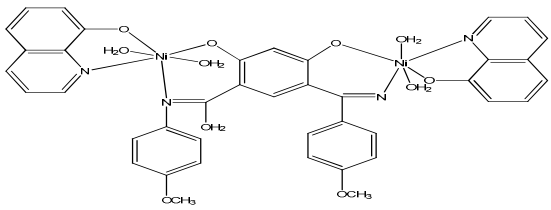
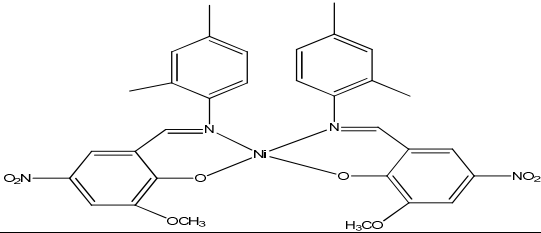
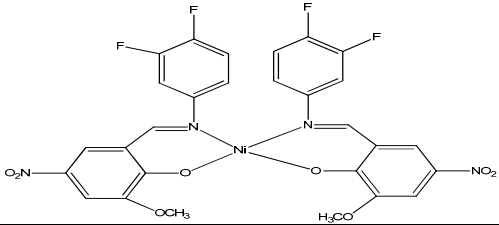
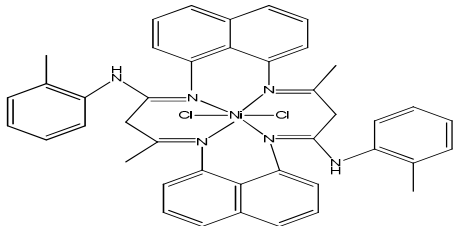
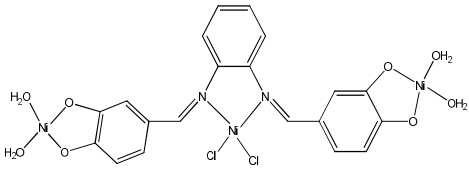
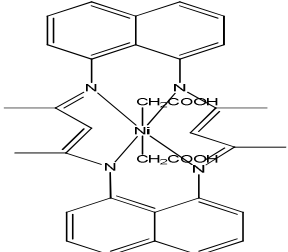
Cpd.	Compound	MIC VALUE ($\mu\text{g/ml}$)	pMIC
C1		128	2.11
C2		8	0.90
C3		128	2.11
C4		5.2	0.72

C5		15.63	1.19
C6		15.8	1.20
C7		256	2.41
C8		50	1.70
C9		50	1.70

C10		50	1.70
C11		12	1.08
C12		500	2.70
C13		28	1.45
C14		24	1.38
C15		100	2.00
C16		11	1.04

			
C17		20	1.30
C18		50	1.70
C19		53	1.72
C20		32	1.51

C21		413	2.62
C22		500	2.70
C23		93	1.97
C24		59.6	1.78
C25		500	2.70

C26		500	2.70
C27		100	2.00
C29		100	2.00
C30		100	2.00
C31		5	0.70
C32		128	2.11

2.3 Molecular optimization

Optimization is the process of finding the equilibrium or lowest energy geometry of molecules. The chemical structure of each compound in the data set was drawn with Chemdraw ultra V12.0 and saved as *.cdx file. The molecules were first pre-optimized with the molecular mechanics (MMFF) procedure included in Spartan'14 V1.1.0

soft ware 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 (molecular descriptor).

2.4 Descriptor calculation

Molecular descriptors are numerical values that characterize properties of molecules. The quantum chemical descriptors were calculated using the Spartan'14 V.1.1.0 quantum chemistry package while the 1D,2D and 3D descriptors were calculated using *Padel descriptor* tool kit.

2.5 Training and Test set

The training set comprises of molecules used in model development while the test set is made up of molecules not used in building the model, they are used in the external validation of the model. 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 [28]. Consequently, the data set of 31 complexes was split into 21 training set and 10 test set. The training set was used to generate the model while the test set was used to evaluate its prediction abilities.

2.6 Learning process

During this process, the correlation between minimum inhibitory concentration (*MIC*) values of the complexes against *C. albicans* and the calculated descriptors was obtained via correlation analysis using the Microsoft excel package in Microsoft office 2007. Pearson's correlation matrix was used as a qualitative model, in order to select the suitable descriptors for regression analysis. The selected descriptors were subjected to regression analysis with the experimentally determined minimum inhibitory concentration (*MIC*) on logarithmic scale as the dependent variable and the selected descriptors as the independent variables using Genetic function approximation (GFA) method in Material studio software. To develop the optimization model, we included 21 samples in the training set. The number of descriptors in the regression equation was 3, and Population and Generation were set to 1,000 and 5,000, respectively. The number of top equations returned was 3. Mutation probability was 0.1, and the smoothing parameter was 0.5. The models were scored based on Friedman's LOF.

In GFA algorithm, an individual or model was represented as one-dimensional string of bits. It was a distinctive characteristic of GFA that it could create a population of models rather than a single model. GFA algorithm, selecting the basis functions genetically, developed better models than those made using stepwise regression methods. And then, the models were estimated using the "lack of fit" (LOF), which was measured using a slight variation of the original Friedman formula, so that best model received the best fitness score [29].

In Materials Studio, LOF is measured using a slight variation of the original Friedman formula [30]. The revised formula is:

$$\text{LOF} = \text{SSE} / \left(1 - \frac{c+dp}{M}\right)^2 \dots\dots\dots (1)$$

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).The significant regression is given by F-test, and the higher the value, the better the model [31].

2.8 Model Validation

The fitting ability, stability, reliability and predictive ability of the developed models were evaluated by internal and external validation parameters. The validation parameters were compared with the minimum recommended value for a generally acceptable QSAR model proposed by Ravinchandran et al. [32] shown in Table 2.

Table 2: Minimum recommended value of Validation Parameters for a generally acceptable QSAR model
(Source: Ravinchandran et al., 2011)

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

2.8.1 Internal validation parameters

R² (the square of the correlation coefficient) describes the fraction of the total variation attributed to the model. The closer the value of R² is to 1.0, the better the regression equation explains the Y variable. R² is the most commonly used internal validation indicator and is expressed as follows:

$$R^2 = 1 - \frac{\sum(Y_{obs} - Y_{pred})^2}{\sum(Y_{obs} - Y_{training})^2} \dots\dots\dots (1)$$

Where, Y_{obs}; Y_{pred}; Y_{training} are the experimental property, the predicted property and the mean experimental property of the samples in the training set, respectively (Wu et al., 2015).

Adjusted R² (R²_{adj}): R² value varies directly with the increase in number of regressors i.e. descriptors, thus, R² cannot be a useful measure for the goodness of model fit. Therefore, R² is adjusted for the number of explanatory variables in the model. The adjusted R² is defined as:

$$R^2_{adj} = 1 - (1 - R^2) \frac{n-1}{n-p-1} = \frac{(n-1)R^2 - p}{n-p-1} \dots\dots\dots (2)$$

Where p = number of independent variables in the model.[33].

Q² (Leave one out cross validation coefficient): The LOO cross validated coefficient (Q²) is given by;

$$Q^2 = 1 - \frac{\sum(Y_p - Y)^2}{\sum(Y - Y_m)^2} \dots\dots\dots (3)$$

Where Y_p and Y represent the predicted and observed activity respectively of the training set and Y_m the mean activity value of the training set [33].

2.8.2 External validation parameters

Internal validation is an essential step in QSPR model development. The desired internal validation results show that the model exhibits higher stability and prediction ability. However, no real prediction ability is shown for external samples. Therefore, the external predictive ability and extrapolation of the models should be evaluated [29].

R²_{pred}: R²_{pred} is termed the predictive R² of a development model and is an important parameter that is used to test the external predictive ability of a QSAR model. The predicted R² value is calculated as follows;

$$R^2_{pred} = 1 - \frac{\sum[Y_{pred}(te) - Y(te)]^2}{\sum[Y(te) - Y_m(tr)]^2} \dots\dots\dots (4)$$

Y_{pred}(test) and Y(test) indicate predicted and observed activity values respectively of the test set compounds and Y_m(tr) indicates mean activity value of the training set [32].

4.0 QSAR study results and discussion

Model 1, 2, 3 represent the three QSAR models built using GFA algorithm vis-a-viz their statistical parameters. The name and symbol of the descriptors used in the QSAR optimization model and Pearson's correlation matrix for descriptors used in the model are shown in the Tables 3 and 4 respectively. Likewise, Table 5 gives the *P*-values at 95% confidence level of the four descriptors in the model.

Table 3: The name and symbols of descriptors used in the models

S/N	Descriptor symbol	Definition.
1.	apol	Sum of the atomic polarizabilities (including implicit hydrogens)
2.	TopoPSA	Topological polar surface area
3.	Wld1.mass	Directional WHIM, weighted by atomic masses
4.	WD.volume	Non-directional WHIM, weighted by van der Waals volumes

Table 4: Pearson's correlation matrix for descriptors used in QSAR model for the MIC of anti-*Candida albicans* molecules.

	<i>logmic</i>	<i>Wld1.mas</i>	<i>WD.volume</i>	<i>apol</i>	<i>TopoPSA</i>
<i>logmic</i>	1				
<i>Wld1.mas</i>	-0.53937	1			
<i>WD.volume</i>	0.706073	-0.06591	1		
<i>apol</i>	0.289578	0.146252	0.128009	1	
<i>TopoPSA</i>	0.338211	-0.13403	-0.11346	0.031185	1

Table 5: Contributions of the individual descriptors in the model

	<i>Coefficients</i>	<i>Standard Error</i>	<i>P-value</i>
Intercept	-0.71577	0.244114	0.009767
<i>Wld1.mas</i>	-0.04544	0.006143	1.51E-06
<i>WD.volume</i>	1.747704	0.168658	1.67E-08
<i>apol</i>	0.006748	0.001683	0.001014
<i>TopoPSA</i>	0.005245	0.001004	8.37E-05

Model 1:

$$pMIC = -0.045435177 \text{ Wld1.mas} + 1.747704284 \text{ WD.volume} + 0.006748001 \text{ apol} + 0.005244524 \text{ TopoPSA} - 0.715769312$$

$n = 21$, Friedman LOF = 0.11406900, $R^2 = 0.93410200$, $R^2_{adj.} = 0.91762700$, $Q^2 = 0.90586900$, Min. expt.error for non-significant LOF (95) = 0.12381300, F value = 56.70

Model 2:

$$pMIC = -0.04137 \text{ Wld1.mass} + 1.84721 \text{ WD.volume} + 0.00552 \text{ TopoPSA} - 0.28292$$

$n = 21$, Friedman LOF = 0.1238, $R^2 = 0.8679$, $R^2_{adj.} = 0.8446$, $Q^2 = 0.8125$, Min. expt.error for non-significant LOF (95) = 0.1711, F value = 37.24

Model 3:

$$pMIC = -0.046149879 \text{ Wld1.mas} + 1.733352599 \text{ WD.volume} + 0.321184632$$

$n = 21$, Friedman LOF = 0.1511, $R^2 = 0.7425$, $R^2_{adj.} = 0.7139$, $Q^2 = 0.6295$, Min. expt.error for non-significant LOF (95) = 0.2336, F value = 25.95

Model 1 gives the best QSAR model among the three models generated based on statistical significance as it has the highest R^2 , $R^2_{adj.}$, Q^2 and F value. Also, it has the lowest LOF value and error. Based on this analysis, Model 1 was selected as the optimization model.

4.1 Effect of model 1

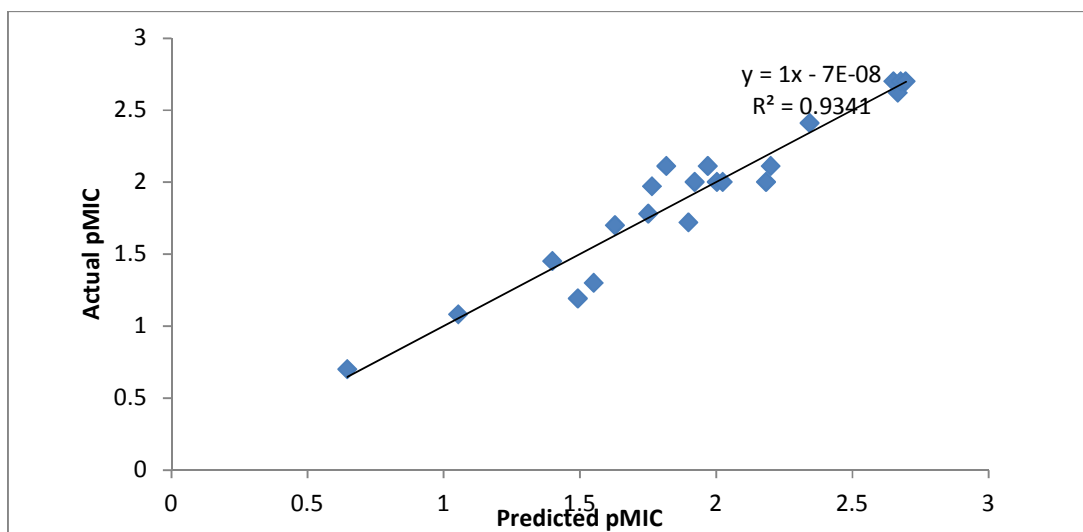


Figure 2

4.2: Residual plot of model 1.

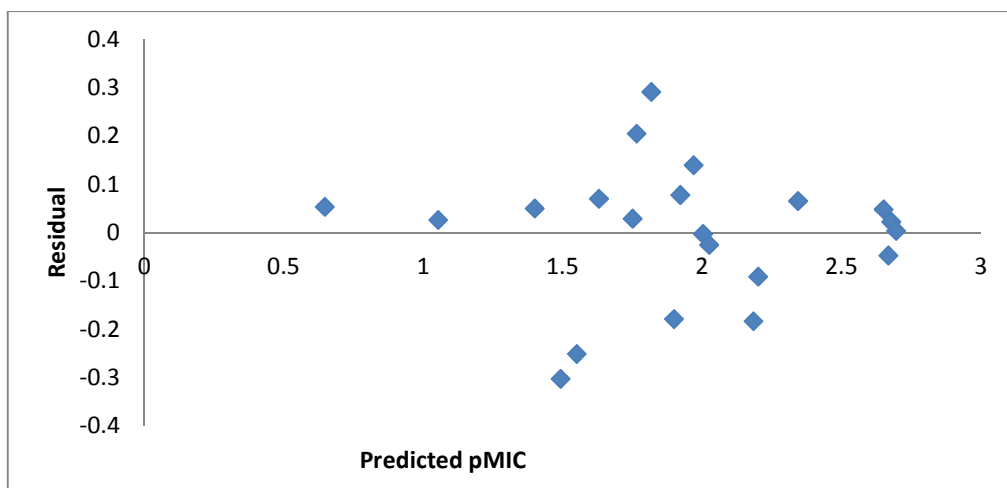


Figure 3

Table 6: Comparison of observed pMIC and predicted pMIC of model 1

Compound	Observed pMIC	Predicted pMIC	Residual
C1	2.11	1.96987100	0.14012900
C3	2.11	2.20146800	-0.09146800
C5	1.19	1.49311100	-0.30311100
C7	2.41	2.34436900	0.06563100
C9	1.70	1.62964400	0.07035600
C11	1.08	1.05363200	0.02636800
C13	1.45	1.39981800	0.05018200
C15	2.00	2.00300600	-0.00300600
C17	1.30	1.55135900	-0.25135900
C19	1.72	1.89896700	-0.17896700
C21	2.62	2.66745700	-0.04745700
C22	2.70	2.65155200	0.04844800
C23	1.97	1.76484400	0.20515600
C24	1.78	1.75111600	0.02888400
C25	2.70	2.67752500	0.02247500
C26	2.70	2.69626400	0.00373600
C27	2.00	2.18374800	-0.18374800
C29	2.00	1.92184300	0.07815700
C30	2.00	2.02539700	-0.02539700
C31	0.70	0.64675400	0.05324600
C32	2.11	1.81825400	0.29174600

Table 7a: External validation of Model-1a

Test cpd	Actual Logmic	Wld1.mass	WD.vol	TopoPSA	apol	pred.logmic	residual
C2	0.9	2.233436	0.660583	6.48	85.69662	0.949523	-0.04952
C4	0.72	11.8023	0.202596	131.04	122.3574	0.614979	0.105021
C6	1.2	2.651635	0.720546	81.24	44.36952	1.148525	0.051475
C8	1.7	3.750844	1.015376	117.2	68.76182	1.96705	-0.26705
C10	1.7	1.593184	1.17922	105.34	89.597	2.429831	-0.72983
C12	2.7	0.686853	1.575287	18.46	51.19269	2.448421	0.251579
C14	1.38	5.865006	0.964273	6.48	54.77069	1.106594	0.273406
C16	1.04	2.714917	0.501346	85.7	101.095	1.168727	-0.12873
C18	1.7	6.608577	0.858463	140.66	80.80427	1.76727	-0.06727
C20	1.51	3.295557	1.085973	18.46	37.79593	1.384317	0.125683

Table 7b: External validation of Model-1a

Test cpd	Ym(tr)	Y(te)	Ypre(te)	[Ypred.(te) - Y(te)] ²	[Y(te) - Ym(tr)] ²
C2	1.8852	0.9	0.968392	0.002453	0.970619
C4	1.8852	0.72	0.65757	0.011029	1.357691
C6	1.8852	1.2	1.168117	0.00265	0.469499
C8	1.8852	1.7	1.980755	0.071316	0.034299
C10	1.8852	1.7	2.438889	0.532653	0.034299
C12	1.8852	2.7	2.437098	0.063292	0.663899
C14	1.8852	1.38	1.11363	0.074751	0.255227
C16	1.8852	1.04	1.198694	0.016571	0.714363
C18	1.8852	1.7	1.787858	0.004525	0.034299
C20	1.8852	1.51	1.387632	0.015796	0.140775
				$\Sigma = 0.795035$	$\Sigma = 4.67497$

$$\text{But Pred-R}^2 = 1 - \frac{\Sigma[Y_{\text{pred}}(te) - Y(te)]^2}{\Sigma[Y(te) - Y_m(tr)]^2}$$

$$\text{Thus, pred-r}^2 = 1 - (0.795035/4.67497) = 0.8299379$$

From the correlation matrix shown in Table 4 above, it is clear that the correlation coefficients between each pair of descriptors is very low, thus, it can be inferred that there exist no significant inter-correlation among the descriptors used in building the model. Also, in order to avoid the effect of multi-collinearity on the regression model, the probability (p) values of each coefficient were used. It is generally accepted if the p-value is less than 0.05 [34]. Table 5 shows that all the P-values of five descriptors in Model 1 are very low ($P \leq 0.005$), showing that multi-collinearity could not affect the correlation here.

Comparison of the validation parameters of model 1 with the optimum standard proposed by Ravinchandra et al. in Table 2 shows that the parameters are in conformity with the standard as $R^2 = 0.9341$, $R^2_{adj} = 0.9176$, $P\text{-value} = < 0.05$, $Q^2 = 0.9059$, $R^2_{pred.} = 0.830$. This confirms the robustness of the model. Likewise, the comparison of observed and predicted anti-candidal activities is presented in Table 6; the high predictability of model 1 is evidenced by the low residual values observed in the Table. Also, Figure 2 gives the plot of predicted pMIC against observed pMIC on Microsoft excel package, the R^2 value of 0.934 is in agreement with GFA derived R^2 value, this further confirms the reliability of the model. Furthermore, the plot of observed pMIC versus residual pMIC (Fig. 3) indicated that there was no systemic error in model development as the propagation of residuals was observed on both sides of zero [35].

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. The P -values of all the descriptors in the model at 95% confidence level shown in Table 5 are less than 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 Minimum inhibitory concentration (MIC) of a molecule is inversely proportional to its biological activity. As shown in model 1 above, the pMIC of the complexes increases with increase in the values of the descriptors; TopoPSA (topological surface area), apol (sum of atomic polarizabilities), and W.D vol. (non-directional WHIM, weighted by van der waals volumes), this is evidenced by their positive correlation with the dependent variable. It implies that the inhibitory activity (MIC) of the complexes against the fungi species is inversely proportional to these descriptors in the molecules. Also, it can be inferred that the MIC of the complexes increases with the increase in Wld1.mass (Directional WHIM, weighted by atomic masses) descriptor in the molecules due to its negative correlation with pMIC as shown in model 1. These results can be clearly rationalized thus;

WD. Vol. describes the size of the molecules; its positive correlation with pMIC as shown in model-1 indicates that the anti-candidal activity of the complexes decreases with increase in size of the complexes. This may be due to the possibility of the molecule been largely confined to the plasma compartment because of their excessively large size [36] affecting its distribution via out the body.

TopoPSA and apol describe the polarity of a molecule. It can be inferred that their positive correlation with pMIC as shown in model-1 indicates that, the anti-candidal activity of the complexes decreases with the increase in polarity of the complexes. This may be due to decrease in lipophilicity orchestrated by increase in polarity since 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 [37]. 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.

Wld1.mass describes the molecular weight of the molecule. Though, drugs with high molecular weights or drugs that are extremely hydrophilic tend to stay within the circulatory system and organs with a rich blood supply, and have a smaller apparent volume of distribution [38], increasing molecular weight likely facilitate porin-mediated permeation through the outer membrane of the fungus thereby increasing its activity.

CONCLUSION

This work addresses the Quantitative structure activity relationship (QSAR) between a set Ni-schiff base complexes and their minimum inhibitory concentration (MIC) against *C.albicans*. Our study developed three GFA derived models out of which the optimal model was selected on the basis of its superior statistical significance. Results from the optimal model showed that the MIC of the studied complexes against *C.albicans* were affected by WHIM descriptors weighted by atomic masses and van der Waals volume as well as topological polar surface area and sum of atomic polarisabilities. The robustness and applicability of QSAR equation has been established by internal and external validation techniques. This study provides an effective approach for the design and synthesis of new bioactive nickel-schiff base complex that will curb the emerging trend of multi-drug resistant strain of the fungus, *Candida albicans*.

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