

Original Research Article

In Silico Prediction of Anti-Candidal Activity of Nickel-schiff Base Complexes through Quantitative Structure Activity Relationship (QSAR) Modelling.

ABSTRACT

Aim: To develop good and rational QSAR mathematical models that can predict to a significant accuracy the anti-candidal inhibitory activities (in form of 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: Quantitative Structure Activity Relationship (QSAR) analysis was applied for 33 nickel-schiff base complexes using a combination of 0D, 1D, 2D and 3D molecular descriptors obtained by Density Functional Theory (DFT) method by employing Becke's three-parameter hybrid functional (B3LYP) and 6-31G(d) basis set. The computed descriptors were correlated with the log of their experimental minimum inhibitory concentration (pMIC) against *C. albicans*. Genetic function approximation (GFA) and Multi-linear regression analysis (MLR) was used to derive the most statistically significant QSAR model as a calibration model for predicting the inhibitory activity (pMIC) of this class of molecules.

Results: Among the obtained QSAR models, the most statistically significant one was a four parameter linear equation with the squared correlation coefficient R^2 value of 0.939, adjusted squared correlation coefficient R^2_{adj} value of 0.926 and Leave one out (LOO) cross validation coefficient (Q^2) value of 0.939. An external set was used for confirming the predictive power of the model, its $R^2_{pred} = 0.82$

Conclusion: The QSAR results reveal that molecular size and polarity predominantly influence the anti-candidal activity of the complexes. The wealth of information in this study 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 the fungus, *Candida albicans*.

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

1.0 INTRODUCTION

The occurrence of morbidity and mortality orchestrated by bacterial and fungal infections has increased globally mostly in developing countries due to the emerging incidence of resistance to a number of antimicrobial agents such as β -lactam antibiotics, macrolides, quinolones and vancomycin [20]. The increase in the number of immuno-compromised patients orchestrated by

cancer chemotherapy, organ transplantation, and HIV infections are major factors contributing to this increase [5].

Candida albicans 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 [32]. *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 [3]. VVC is a commonly reported gynecological condition and it has been reported that 75% of women experience this infection in their life time [33].

Successful treatment of infectious diseases requires the availability of more effective new antimicrobial compounds. Because pathogenic organisms constantly undergo mutation in their bid to develop new resistance mechanisms, there is an urgent need to develop a steady stream of new antimicrobial agents to which existing bacteria and fungi have not developed resistance.

There is abundant literature concerning the biological activity of Ni – Schiff base complexes against *candida albicans* [1;2;4;6;7;10;12;13;15;18;19;26;30].

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 [11; 17; 27].

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 [28] called molecular descriptors.

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

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

Preeti et al., (2015) 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., (2014) 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., (2013) 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., (2010) 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 steric parameter on the activity of the compounds.

81 2.0 MATERIALS and METHODS

82 2.1 Materials

83 The materials use in this study include; H.P 650 computer system (Intel Pentium), 2.43GHz
84 processor, 4GB ram size on Microsoft windows 7 Ultimate operating system, Spartan 14
85 V.1.1.0, Chm 3D Pro 12.0.1V, Padel descriptor tool kit and Microsoft office Excel 2013 version +
86 *Analyze it*[®] Statistical software, Printers.

87 2.2 Computational Methodology

88 Chemdraw ultra software was used to draw the structure of the compounds in the data set and
89 each structure was saved as *MDL* file. The Spartan 14 V.1.1.0 soft ware was used for the
90 optimization of the molecules. The molecules were first pre-optimized with the Semi-empirical
91 (AM1) procedure included in Spartan'14 V1.1.0 soft ware and the resulting geometries were
92 further refined by means of Density functional theory (DFT) using the B3LYP version and 6-
93 31G^{*} basis set. The lowest energy structure was used for each molecule to calculate their
94 physicochemical properties. The quantum chemical descriptors were calculated using the
95 Spartan'14 V.1.1.0 quantum chemistry package. *Padel descriptor* tool kit was used to calculate
96 1D, 2D and 3D descriptors as well.

97 2.3 QSAR methodology

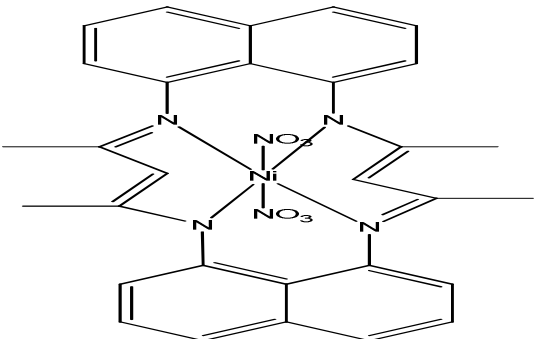
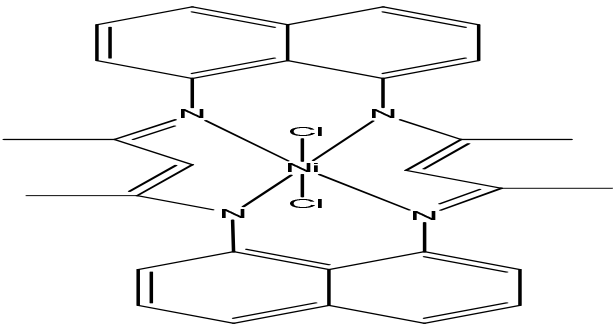
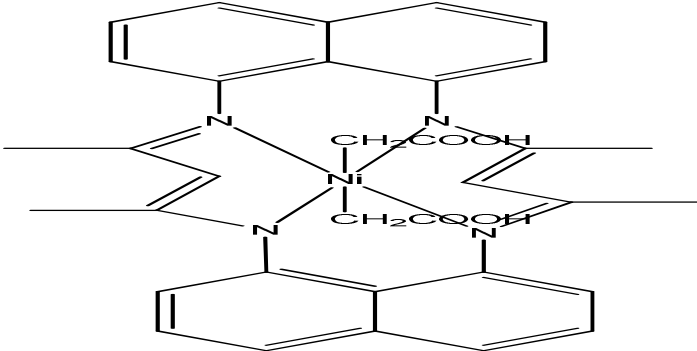
98 In the present study, the QSAR studies was performed by Hansch's analysis using the linear
99 free energy relationship (LFER) model described by Hansch and Fujita (1964). In Hansch's
100 approach, structural properties of compounds are calculated in terms of different
101 physicochemical parameters and these parameters are correlated with biological activity
102 through equation using regression analysis. Before using the biological activity data for QSAR
103 study experimentally determined MIC values changed to log MIC or pMIC (in µg/ml) to get
104 normal distribution of errors and to get linear free energy relationship of these data with
105 physicochemical parameters (Preeti et al., 2015).

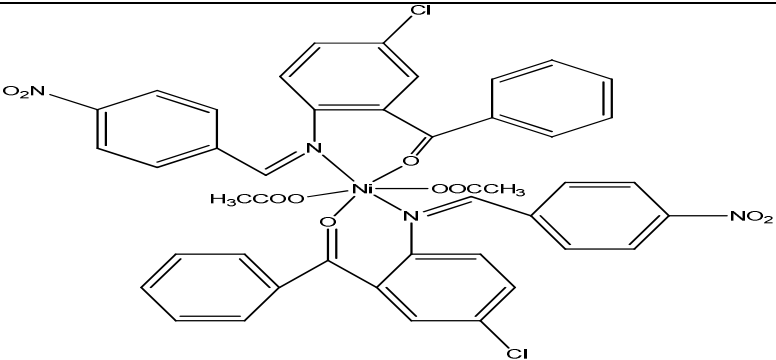
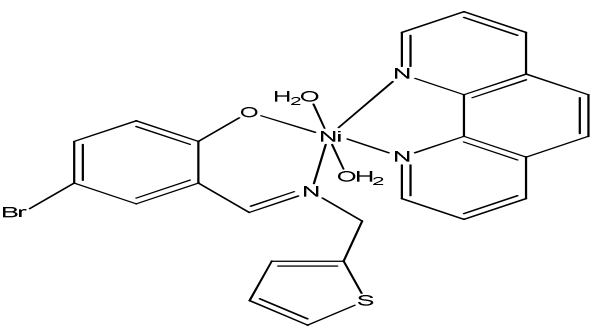
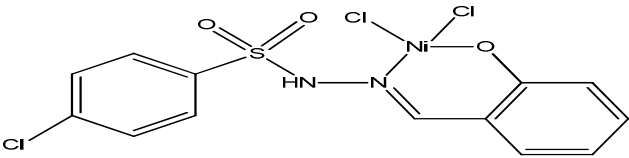
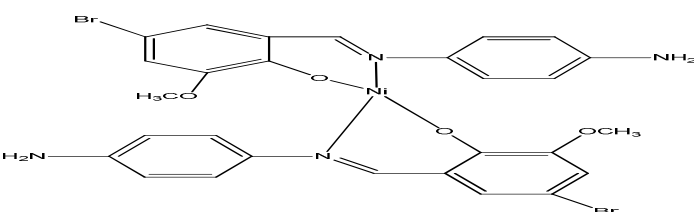
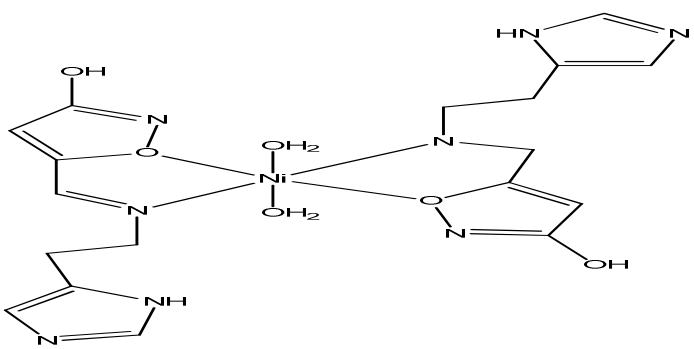
106 2.3.1 Data collection

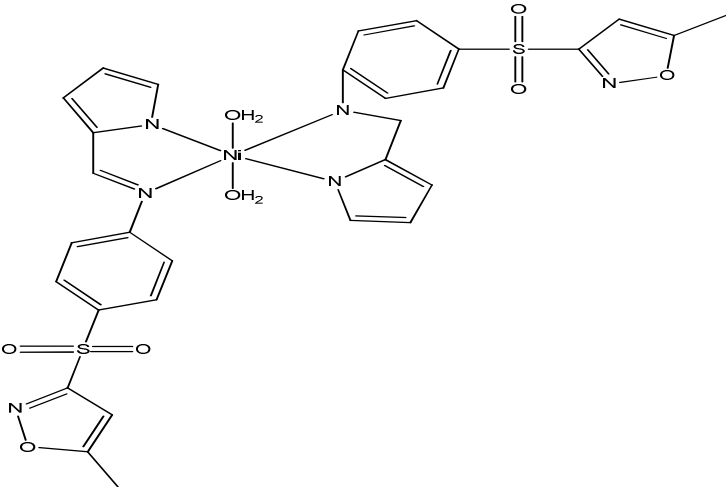
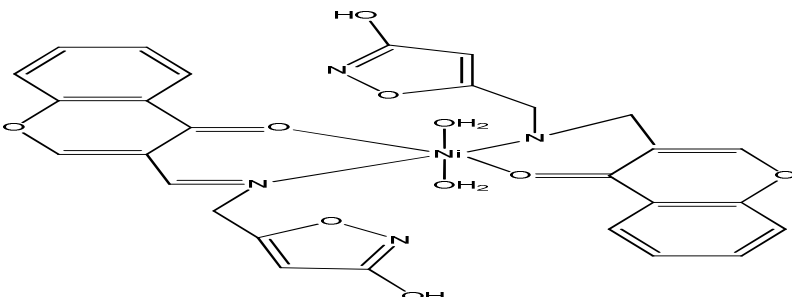
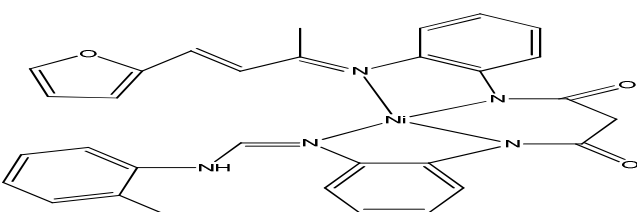
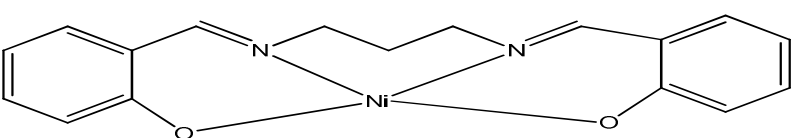
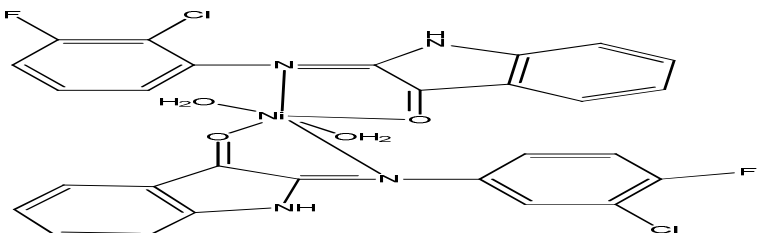
107 The chemical structures and experimental minimum inhibitory concentration (*MIC*) values in
108 µg/ml of anti- *Candida albicans* were taken from literature [1;2;4;6;7;10;12;13;15;18;19;26;30].
109 The *MIC* values of the compounds were converted to logarithmic scale [*pMIC* = log*MIC* (µg/ml)].

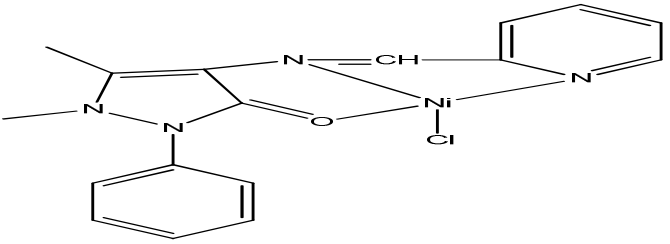
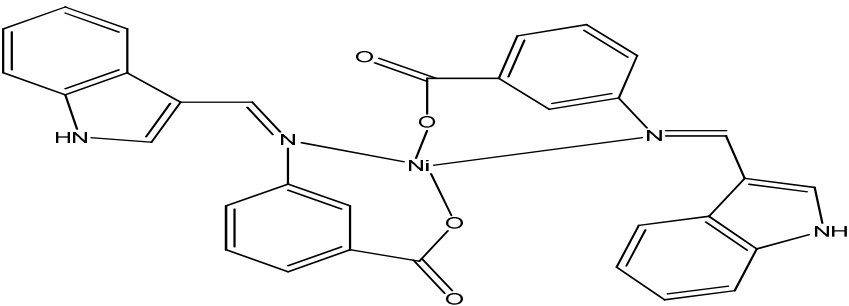
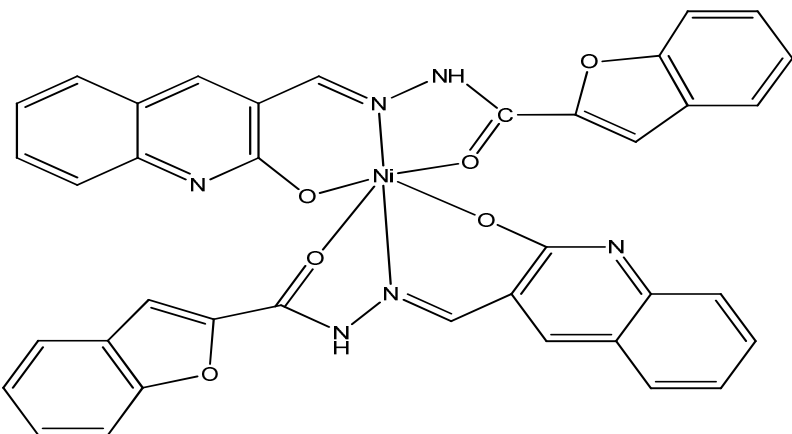
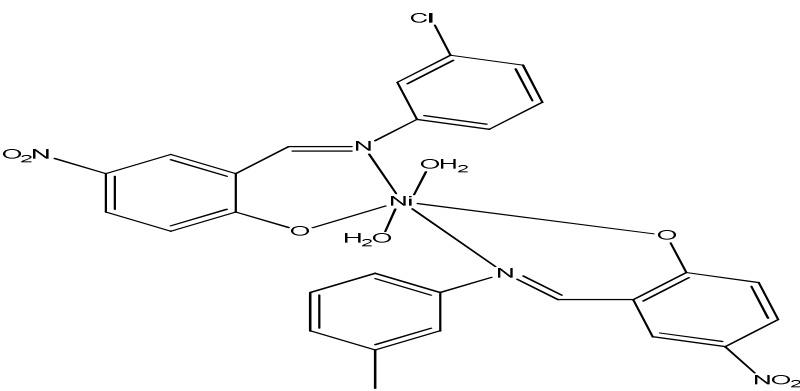
110 The notation, structure, MIC and pMIC values for each member of the training set are presented
 111 in Table 1.

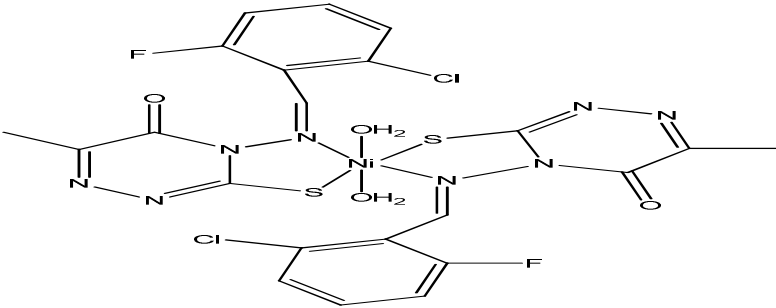
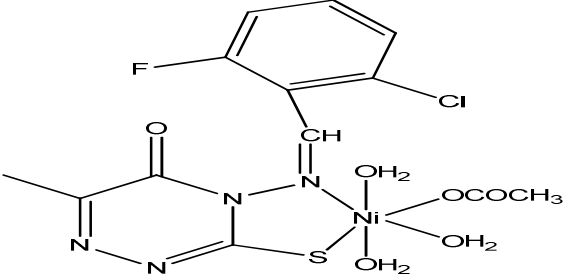
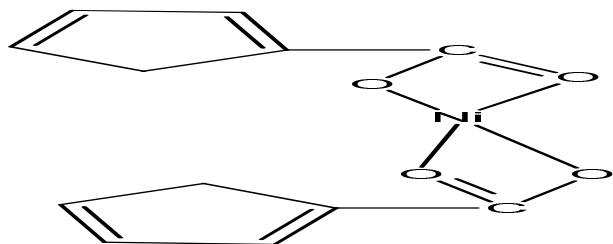
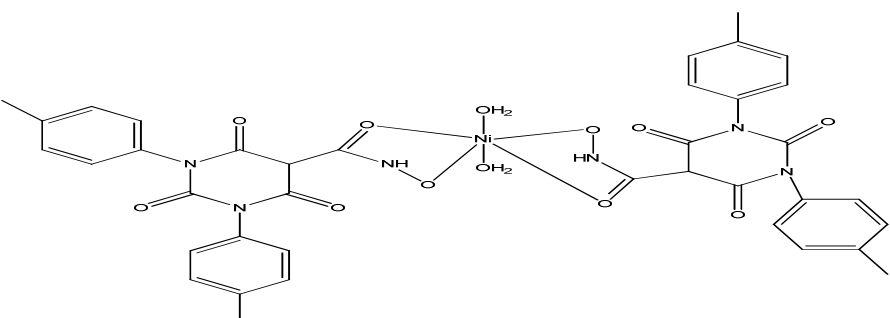
112 TABLE 1: Experimental MIC values of anti-*Candida albicans* molecules.

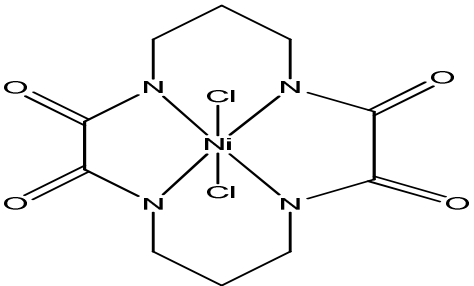
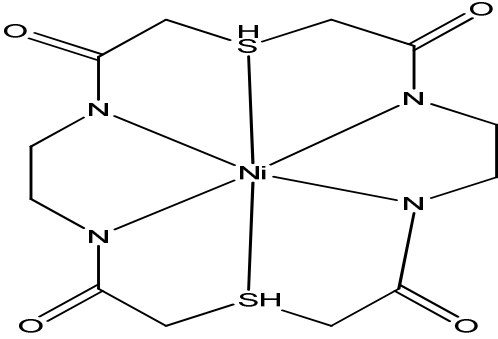
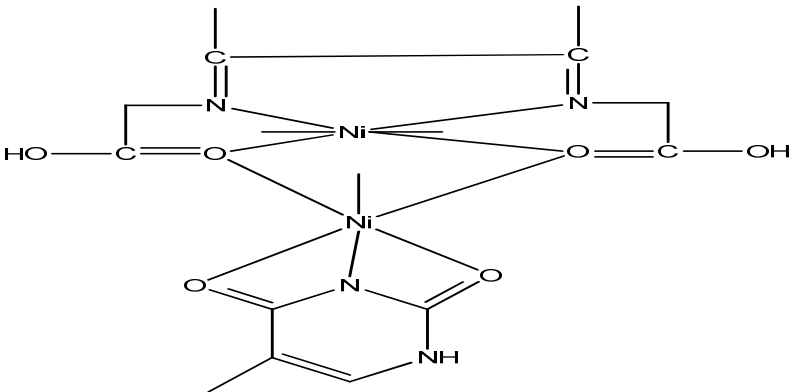
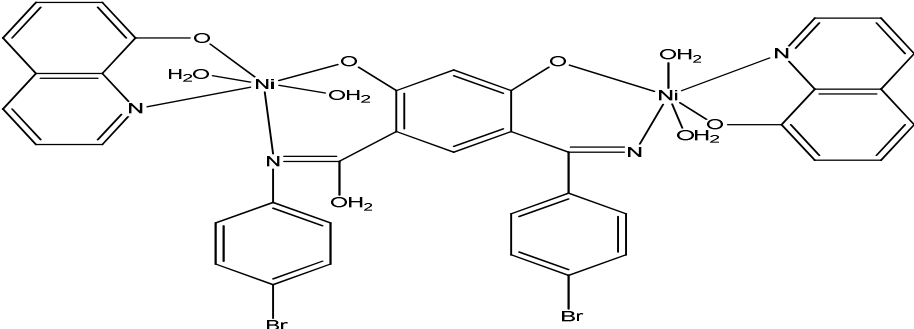
Cpd.	Compound	MIC VALUE ($\mu\text{g/ml}$)	pMIC
C1		128	2.11
C2		8	0.90
C3		128	2.11

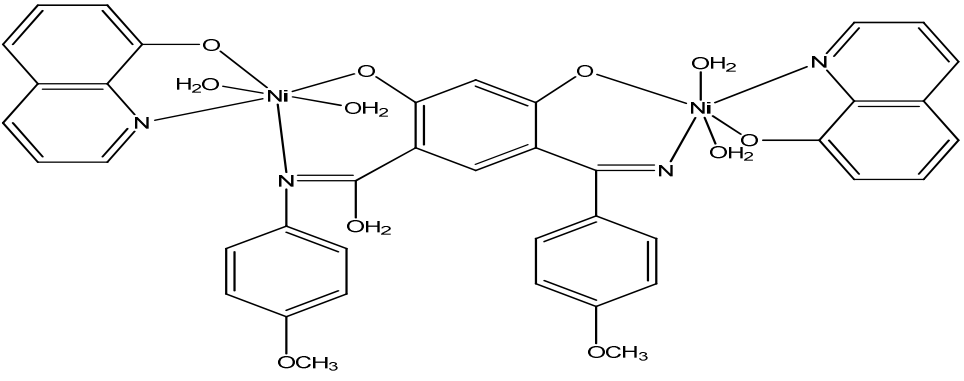
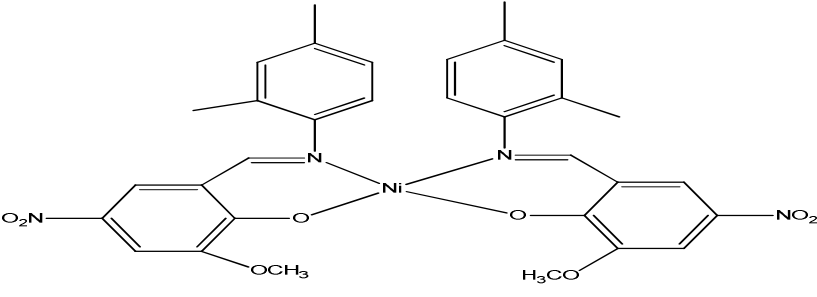
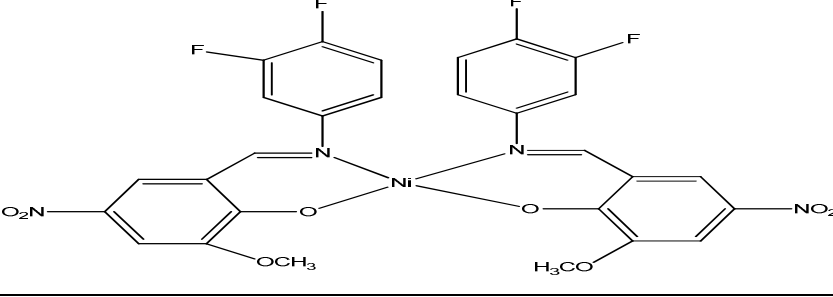
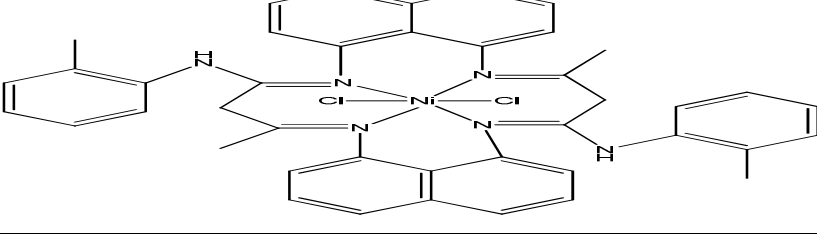
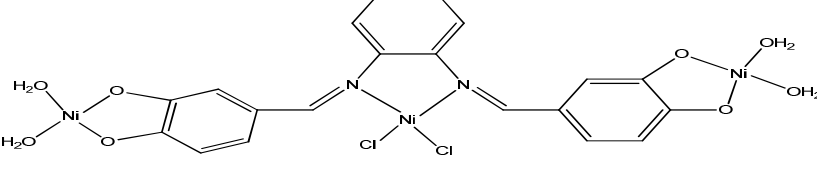
C4		5.2	0.72
C5		15.63	1.19
C6		15.8	1.20
C7		256	2.41
C8		50	1.70

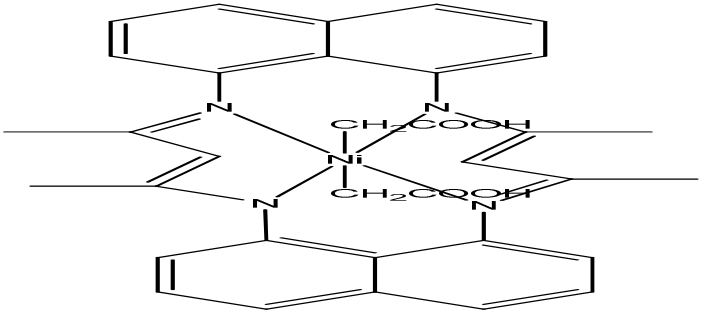
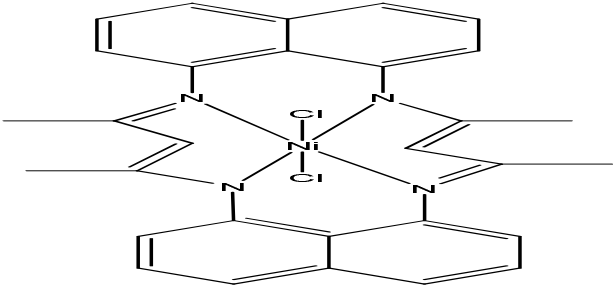
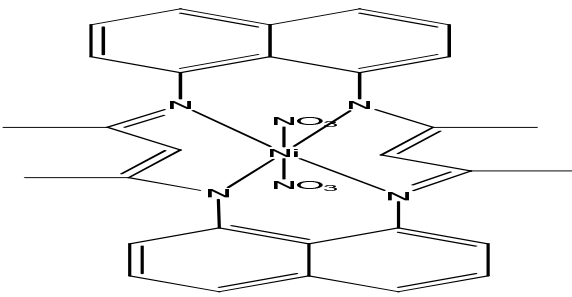
C9		50	1.70
C10		50	1.70
C11		12	1.08
C12		500	2.70
C13		28	1.45

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
C33		8	0.90
C34		128	2.11

113

114 **2.3.2 Descriptor selection**

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

120

121 **2.3.3 Training set and test set.**

122

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 [21]. Consequently, the data set of 33 complexes was split into 23 training set and 10 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 [34]. 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 (Friedman, 1990). The revised formula is:

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

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 (Khaled and Abdel-Shafi, 2011).

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 [8]. 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., is 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.	$R^2_{\text{ext.}}$	Coefficient of determination for external test set	≥ 0.6
5.	$R^2 - Q^2$	Difference between R^2 and Q^2	≤ 0.3
6.	$N_{\text{ext. test set}}$	Minimum number of external test set	≥ 5

2.3.5.1 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^2_{adj}), 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.* 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 formulae:

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

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:

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

Where p = number of independent variables in the model.
(Brandon and Aline, 2015).

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

$$Q^2 = 1 - \frac{\sum(Y_p - Y)^2}{\sum(Y - Y_m)^2} \dots\dots\dots (4)$$

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.

The predicted r^2 value is calculated as follows;

$$\text{Pred-}R^2 = 1 - \frac{\sum[Y_{pred}(te) - Y(te)]^2}{\sum[Y(te) - Y_m(tr)]^2} \dots\dots\dots (5)$$

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

3.3.5.2 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 [29]. Prior to the development of the models, each data set was split into training

201 and test set. The QSAR model was built using the training set while the test set was used for
 202 externally validating the model. The predicted R^2 was computed using the formulae in equation
 203 (5).

204 4.0 QSAR study results and discussion

205 The best performing QSAR model for the pMIC of the complexes against *Candida albicans*
 206 using GFA and MLR is represented by model 1a and 1b respectively. The name and symbol of
 207 the descriptors used in the QSAR model and Pearson's correlation matrix for descriptors used
 208 in the model are shown in the Table 3 and 4 respectively.

209 **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

210 **Table 4: Pearson's correlation matrix for descriptors used in QSAR model for the**
 211 **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				

Wld1.mas	-0.50199	1			
WD.volume	0.733758	-0.06287	1		
apol	0.274696	0.145962	0.124259	1	
TopoPSA	0.446864	-0.12502	0.036857	0.036676	1

212

213 4.1 Model-1a: Best GFA Derived Model for pMIC of Anti-Candidal Complexes.

214 $pMIC = -0.045554457 \text{ Wld1.mas} + 1.715671092 \text{ WD.volume} + 0.005310437 \text{ TopoPSA} +$

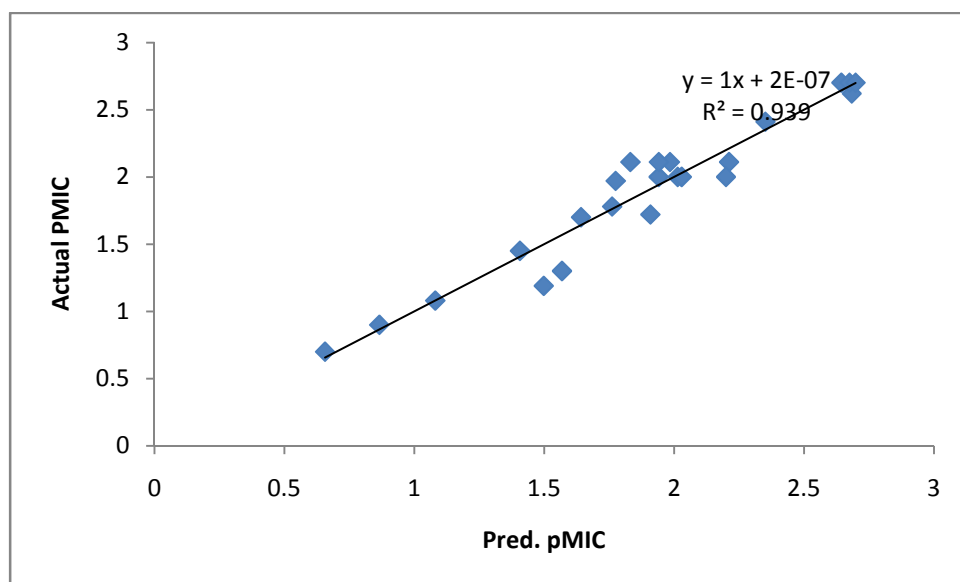
215 $0.006802068 \text{ apol} - 0.680533985$

216 $n = 23$, Friedman LOF = 0.05571900, $R^2 = 0.93914900$, $R^2_{adj.} = 0.92562600$, $Q^2 = 0.91722700$

217 F-value = 69.45099900, Min. expt.error for non-significant LOF (95) = 0.12289400

218

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220

221

222 **Figure 1: Effect of model-1a.**

223

224 **Table 6: Comparison of observed pMIC and predicted pMIC of model 1a.**

225

Observed pMIC	Predicted pMIC	Residuals
2.11	1.983986	0.126014
2.11	2.211145	-0.10115

1.19	1.497804	-0.3078
2.41	2.351284	0.058716
1.70	1.641202	0.058798
1.08	1.080053	-5.30E-05
1.45	1.40638	0.04362
2.00	2.013466	-0.01347
1.30	1.568026	-0.26803
1.72	1.908342	-0.18834
2.62	2.683626	-0.06363
2.70	2.643594	0.056406
1.97	1.774775	0.195225
1.78	1.761216	0.018784
2.70	2.674821	0.025179
2.70	2.698223	0.001777
2.00	2.199462	-0.19946
2.00	1.940436	0.059564
2.00	2.028909	-0.02891
0.70	0.655888	0.044112
2.11	1.831449	0.278551
0.90	0.864779	0.035221
2.11	1.941135	0.168865

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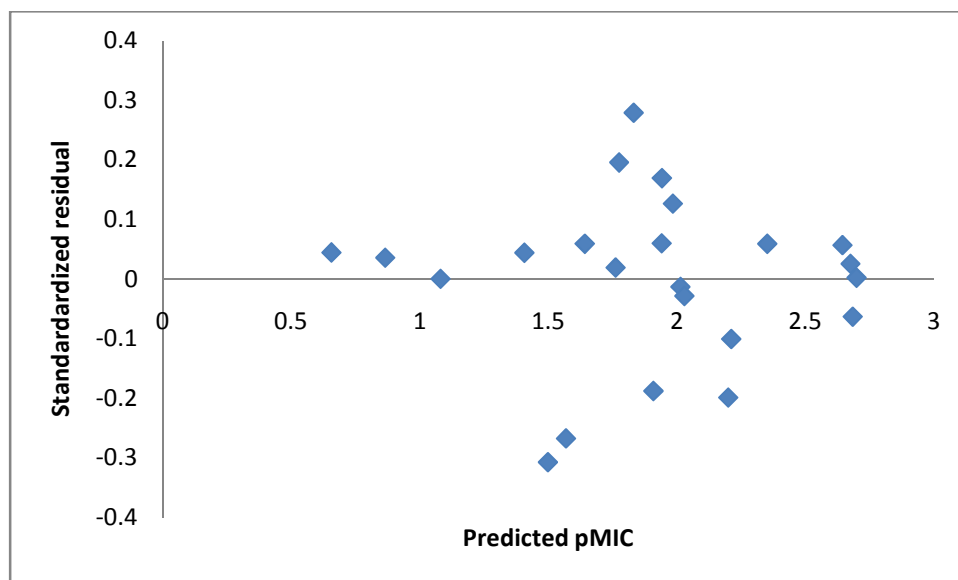


Figure 2: Residual plot of model-1a.

4.3.3 Model – 1b: MLR Derived Model for pMIC of Anti-Candidal Complexes.

$$\text{pMIC} = -0.6805 - 0.04555 \text{ Wld1.mas} + 1.716 \text{ WD.volume} + 0.00531 \text{ TopoPSA} + 0.006802 \text{ apol}$$

$n = 23$, $R^2 = 0.939$, $R^2_{\text{adj}} = 0.926$, $\text{SE (RMSE)} = 0.1558$, $P\text{-value at } 95\% \text{ C.L} < 0.0001$

Table 7: Effect of terms at 95% confidence level.

Term	SS	DF	MS	F	P-Value
Wld1.mas	1.399	1	1.399	57.64	<0.0001
WD. Volume	3.073	1	3.073	126.60	<0.0001
TopoPSA	0.898	1	0.898	36.98	<0.0001
apol	0.414	1	0.414	17.05	0.0006

Table 8a: External validation of Model-3a

Test cpd	Actual Logmic	Wld1.mass	WD.vol	TopoPSA	apol	pred.logmic	residual
C2	0.9	2.233436	0.660583	6.48	85.69662	0.968392	-0.06839
C4	0.72	11.8023	0.202596	131.04	122.3574	0.65757	0.06243

C6	1.2	2.651635	0.720546	81.24	44.36952	1.168117	0.031883
C8	1.7	3.750844	1.015376	117.2	68.76182	1.980755	-0.28076
C10	1.7	1.593184	1.17922	105.34	89.597	2.438889	-0.73889
C12	2.7	0.686853	1.575287	18.46	51.19269	2.437098	0.262902
C14	1.38	5.865006	0.964273	6.48	54.77069	1.11363	0.26637
C16	1.04	2.714917	0.501346	85.7	101.095	1.198694	-0.15869
C18	1.7	6.608577	0.858463	140.66	80.80427	1.787858	-0.08786
C20	1.51	3.295557	1.085973	18.46	37.79593	1.387632	0.122368

Table 8b: External validation of Model-3a.

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	0.004677	0.970619
C4	1.8852	0.72	0.65757	0.003898	1.357691
C6	1.8852	1.2	1.168117	0.001017	0.469499
C8	1.8852	1.7	1.980755	0.078824	0.034299
C10	1.8852	1.7	2.438889	0.545957	0.034299
C12	1.8852	2.7	2.437098	0.069117	0.663899
C14	1.8852	1.38	1.11363	0.070953	0.255227
C16	1.8852	1.04	1.198694	0.025184	0.714363
C18	1.8852	1.7	1.787858	0.007719	0.034299
C20	1.8852	1.51	1.387632	0.014974	0.140775
				$\Sigma = 0.82232$	$\Sigma = 4.67497$

But $Pred-R^2 = 1 - \frac{\Sigma[Ypred(te) - Y(te)]^2}{\Sigma[Y(te) - Ym(tr)]^2}$

Thus, $pred-r^2 = 1 - (0.82232/4.67497) = 0.8241$

The result of the GFA QSAR model (model 1a) is in conformity with the standard depicted in Table 2 as $R^2 = 0.9391$, $R^2_{adj} = 0.9256$, $P\text{-value} = < 0.05$, $Q^2 = 0.9172$, $R^2_{pred.} = 0.82$. This confirms the robustness of the model. The comparison of observed and predicted anti-fungal

activities is presented in Table 6. The predictability of model-1a is evidenced by the low residual values observed in Table 6. The plot of predicted pMIC against observed pMIC shown in Fig. 1 also confirms the robustness of the model. 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 [9].

The *P*-value of the model at 95% confidence level shown in MLR model (model 1b) is < 0.001 . 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 less than 0.05, a requirement at this confidence limit. This further reveals the reliability and robustness of the MLR model.

Model-1a was developed to predict the anti-fungal activity of the complexes against *Candida albicans*. A positive correlation of anti-bacterial activity against *C. albicans* with TopoPSA (topological surface area), apol (sum of atomic polarizabilities), and W.D vol. (non-directional WHIM, weighted by van der waals volumes) indicated that the magnitude of the pMIC of these complexes is directly proportional to 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 and vice versa. Also, pMIC of the complexes is negatively correlated to their Wld1.mass. It implies that the higher the value of this descriptor, the higher the antifungal activity of the complexes against *C. albicans* and vice versa. 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 too large size [22] 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 [27]. However, 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 [23], increasing molecular weight likely facilitate porin-mediated permeation through the outer membrane of the fungus thereby increasing its activity.

5.0 Conclusion

The generated QSAR models, performed to explore the structural requirements controlling the observed anti-*candida albicans* activities of the studied complexes hinted that the biological activities 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. 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 the fungus, *Candida albicans*.

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