



Insilico Predictive Model for Anti-Microbial Properties of Ni (II)-Schiff Bases' Complexes Against *Staphylococcus aureus* and *Candida albicans*

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Abstract: The emergence of multi-drug resistant strain of *Staphylococcus aureus* and *Candida albicans* has necessitated the exploration and development of newer structural moiety of Nickel-Schiff bases' complexes as potential drug candidates against the aforementioned pathogens owing to their enormous inhibitory activity against these microbes. In this study, a Quantitative Structure Activity Relationship analysis was performed on some selected complexes by correlating their experimentally validated bioactivities against the pathogenic microbes with the OD, 1D, 2D and 3D descriptors of the molecules through linear regression resulting in the generation of three statistically significant models from which a hexa-parametric model was selected as the most robust model with $R^2 = 0.909$, $R^2_{adj} = 0.890$, $Q^2 = 0.844$, $R^2_{ext} = 0.609$. The optimization model hinted the predominance of the size descriptors (WD, volume and nT6Ring), descriptors of hydrogen bond acceptor ability of the complexes (nHBAcc2 and nHBAcc3) and a descriptor of molecular polarity (Weta 3, polar) in influencing the observed anti-microbial activities of the complexes. The wealth of information in this study could provide a blueprint in the design of novel bioactive complexes that could curb the alarming trend of multi-drug resistant strain of *Staphylococcus aureus* and *Candida albicans*.

Keywords: *Staphylococcus aureus*, *Candida albicans*, Descriptors, QSAR, Drug

1. Introduction

The abuse of the conventional antibiotics in the treatment of microbial infections has resulted to increased incidence of resistance to the available drugs. Though large number of antibiotics are available for clinical use, the occurrence of antibiotic resistance in recent years against bacterial and fungal strains has necessitated an urgent need for the discovery of new class of antimicrobial agents [1-2].

Staphylococcus aureus and *Candida albicans* constitute a major causative agent of nosocomial infections. The most frequent infections are those of surgical wound, blood,

urinary and gastro-intestinal tract infections [3]. Nosocomial infections divert financial resources that otherwise could be used for improving health and threatens the success of global efforts to combat major infectious diseases, poverty and ignorance [4]. These organisms do not have fastidious growth requirements and can grow at various temperatures and pH conditions prevalent in the hospital environment. These features combined with their ability to exploit varieties of carbon and energy sources afford them the opportunity to survive for a reasonable time in either dry or moist conditions

in the hospital environment thereby causing diseases [3]. Their intrinsic resistance to many anti-microbial agents also contributes to the organism's fitness and enable them to spread in hospital environment [5].

Schiff bases and their complexes with nickel (II) ion are considered to be among the most important stereo - chemical model in the future design of potential antibiotics that could curb the menace of anti-microbial resistance to the existing antibiotics due to their preparative accessibility, structural varieties and high activities against disease causing bacteria and fungi species [6]. Abundant literature exists for biological activity of Ni - Schiff base complexes against *Candida albicans* and *Staphylococcus aureus* [7-17]. These complexes have been reported to possess higher anti-microbial activities compared to their organic ligands. This is significant in the light of increasing bacterial and fungal resistance to the existing antibiotics.

The increased activity of the metal chelates can be explained on the basis of Overtone's concept and chelation theory. According to Overtone's concept of cell permeability the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials [18]. On chelation, the polarity of metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups [18]. Further, it increases the delocalization of π -electrons over the whole chelate ring and enhances the lipophilicity of the complex. The increased lipophilicities of complexes permit easy penetration into lipid membranes of organisms and facilitates as blockage of metal binding sites in enzymes [18].

The fundamental principle underlying Quantitative structure activity relationship (QSAR) is that the difference in structural properties is responsible for the variations in biological activities of the compounds. It assumes that the potency of a certain biological activity exerted by a series of congeneric compounds is a function of various physicochemical parameters of the compounds. Once statistical analysis shows that certain physico-chemical properties are favourable to the concerned activity, the concerned activity can be optimized by choosing such substituents which would enhance such physicochemical properties [19]. By multi-target QSAR modelling, it means that effort is geared toward building models that could connect the structure of drugs with their biological activity against different targets [20].

The aim of the present study is to build robust and rational Genetic function approximation (GFA) based two-target QSAR model for predicting the anti-microbial activity of nickel-schiff base complexes against *S. aureus* and *C. albicans* by exploring the correlations between the experimental MIC of the complexes and their calculated molecular descriptors.

Substantial progress has been made in recent years on the application of computational methods to predict *Candida albicans* and *S. aureus* inhibition activities of some chemicals.

Preeti *et al.* 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 [21].

The MLR-mt QSAR studies carried out by Pradeep *et al.* 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 [22].

Sumit *et al.* 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 [23].

The result of the QSAR models built by Milan *et al.* 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 [24].

Vikramjeet *et al.* carried out a semi-empirical (PM3) multi-target QSAR studies on anti-microbial activity of 15 isonicotinic acid hydrazide derivatives. The result indicated the importance of nuclear repulsion energy in explaining the antimicrobial activity of isoniazid derivatives. The result of the statistical analysis includes; $n=15$, $R^2=0.887$, $Q^2=0.835$, $S=0.061$ [25].

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-*staphylococcus aureus* and anti-*C. albicans* 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 minimum inhibitory concentration of compounds against *S. aureus* and *C. albicans*, this study focused on complexes since research has shown that the biological activities of compounds increase on complexation due to chelation [26]. 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 minimum inhibitory concentration of compounds against *S. aureus* and *C. albicans* are performed predominantly using the semi-empirical method even though research in QSAR studies [15, 27-28] have shown the choice of DFT instead of semi-empirical (AM1 and PM3) 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.

2. Method

In this work, QSAR studies were performed using Hansch's approach [29]. In Hansch's approach, structural properties of compounds are calculated in terms of different physicochemical parameters and these parameters are correlated with biological activity through equation using regression analysis. Figure 1 gives the flow chart of all the *Insilico* techniques deployed in this study. The chemical structures and experimental minimum inhibitory concentration (MIC) values of anti-*Candida albicans* and *Staphylococcus aureus* complexes were taken from literature [7-17]. The experimentally determined MIC values of the complexes were converted to log MIC (pMIC). This operation was performed in order to reduce the dispersion of data

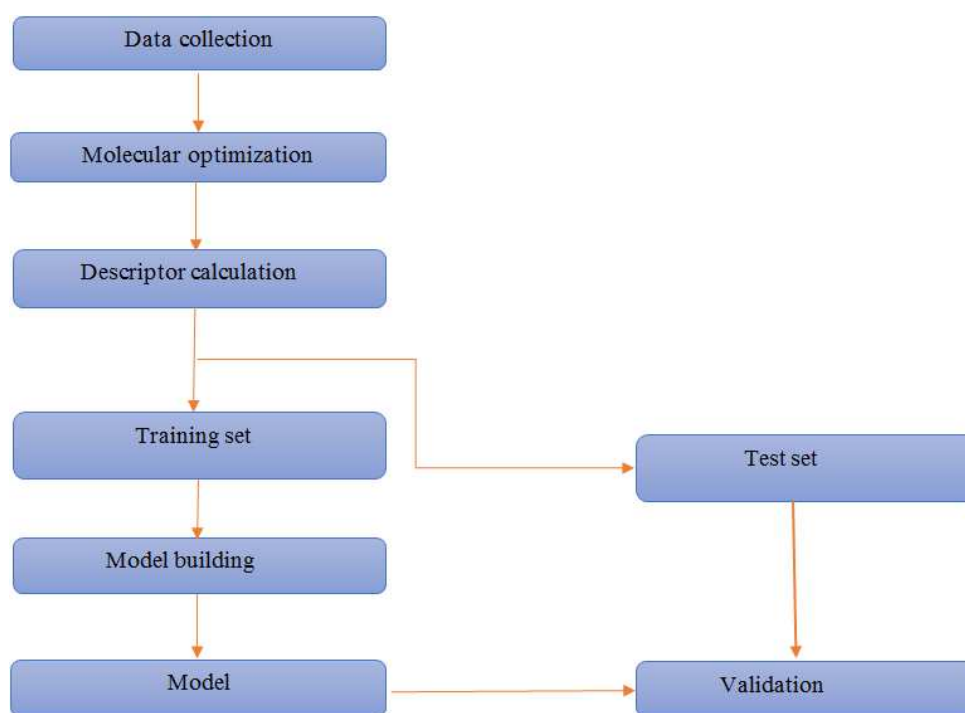


Figure 1. QSAR methodology flowchart. Source: Ameji et al. [30]

The molecular structure of each molecule was optimized using the molecular modeling program, Spartan'14 V1.1.0 on H. P 650 computer system (Intel Pentium), 2.43GHz processor, 4GB ram size on Microsoft windows 7 Ultimate operating system using Density Functional Theory (the B3LYP version and 6-31G* basis set). The chemical descriptors of the molecules were calculated using the Spartan'14 V1.1.0 quantum chemistry package and Padel descriptor tool kit. The data set of the molecules were split into 70% Training set for model development and 30% Test set for external validation of the models. Subsequently, the QSAR models were built by means of Genetic Function Approximation (GFA) techniques embedded in Material Studio, a modelling and simulation software using the experimentally obtained biological activities as dependent variable and the computed molecular descriptors as

independent variables. Five QSAR models were generated but the best was selected based on the model with the least Lack of Fit (LOF) score.

The external predictive ability and extrapolation of the best model was evaluated using the test set molecules with the aid of equation 1.

$$R^2_{\text{pred}} = 1 - \frac{\sum(\text{pred.Yte} - \text{Act.Yte})^2}{\sum(\text{Act.Yte} - Y_m)^2} \quad (1)$$

R^2_{pred} is termed the predictive R^2 of a development model and is an important parameter that is used to test the external predictive ability of a QSAR model, Pred. Yte and Act. Yte indicate predicted and observed activity values respectively of the test set compounds and Y_m indicates mean activity value of the training set [31].

The multi-collinearity between the descriptors used in the

model was detected by calculating their variance inflation factors (VIF), which can be calculated as using equation 2.

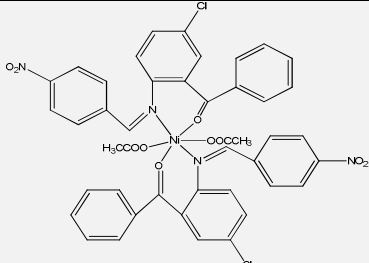
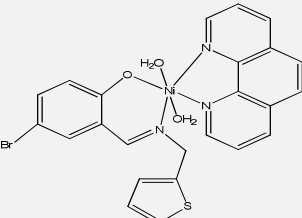
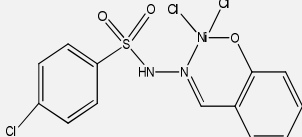
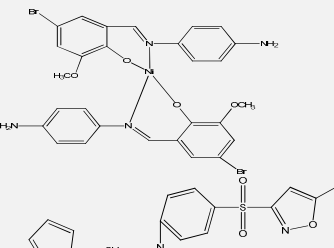
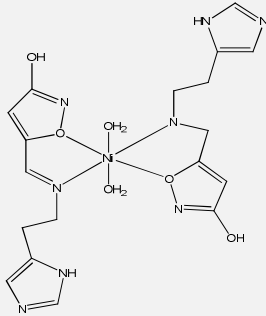
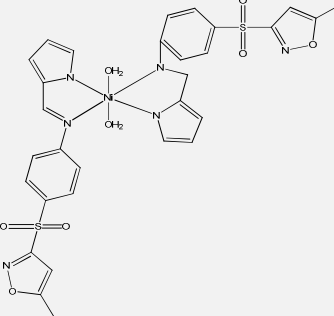
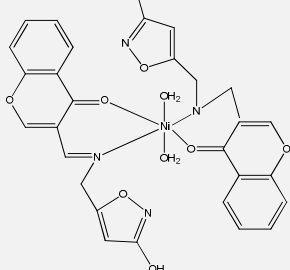
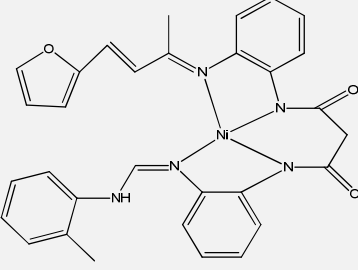
$$\text{VIF} = 1 / (1 - R^2) \quad (2)$$

Where R^2 is the correlation coefficient of the multiple regression between the variables within the model. If VIF equals to 1, then no inter-correlation exists for each variable; if VIF falls within the range of 1–5, the related model is acceptable; and if VIF is larger than 10, the related model is unstable and a recheck is necessary [32].

The notation, structure and pMIC values for each member of the data set are presented in Table 1

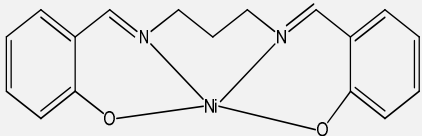
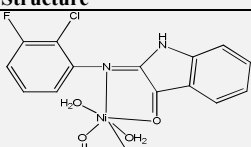
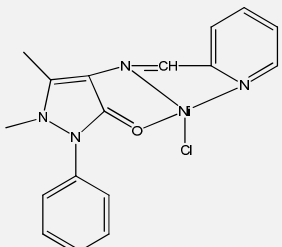
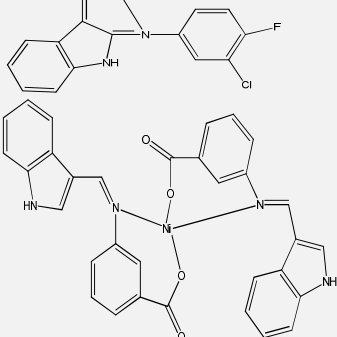
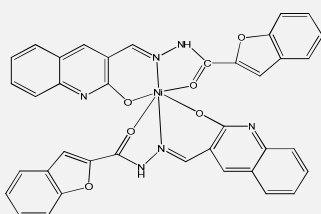
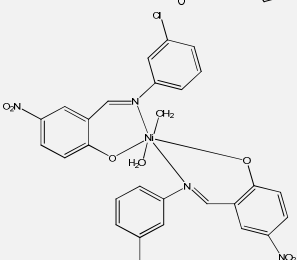
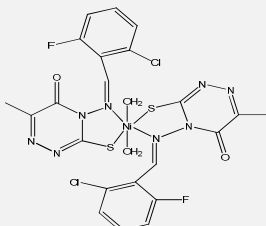
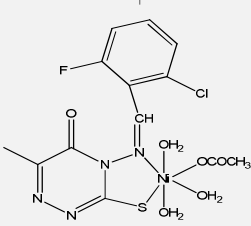
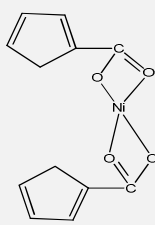
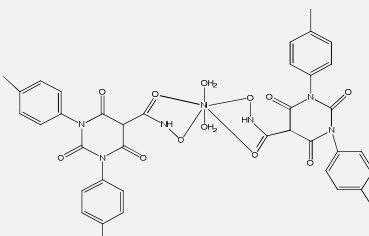
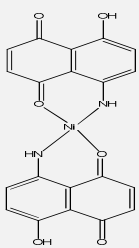
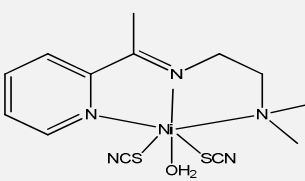
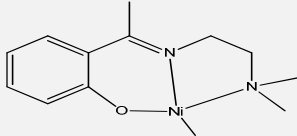
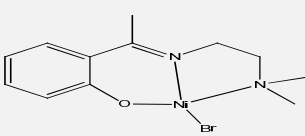
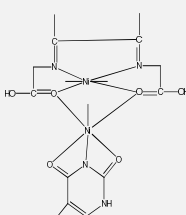
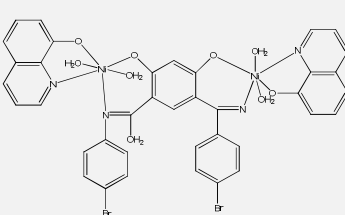
$$\text{pMIC} = 1.518\text{WD.volume} + 1.888\text{Weta3.polar} + 0.104\text{nT6Ring} - 0.071\text{Kier3} + 0.122\text{nHBacc2} - 0.121\text{nHBacc3} + 0.122 \quad (3)$$

Table 1. The notation, structure and pMIC values for each member of the data set.

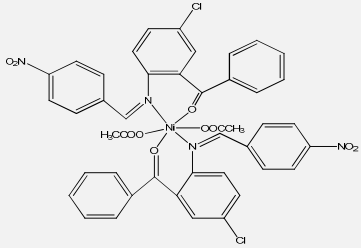
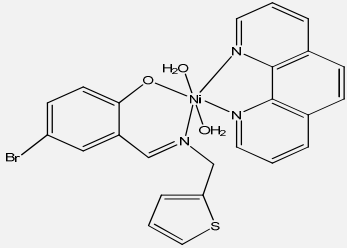
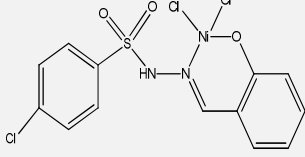

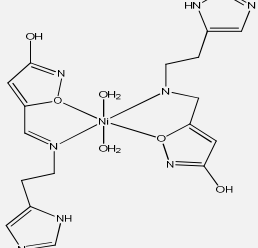
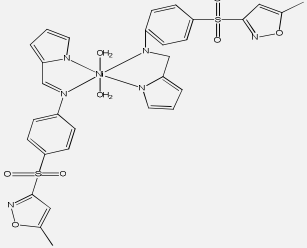
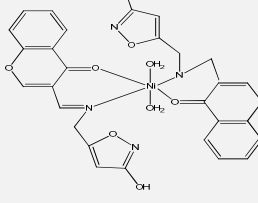
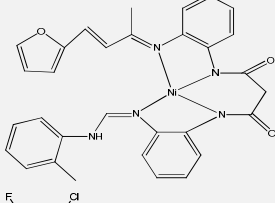
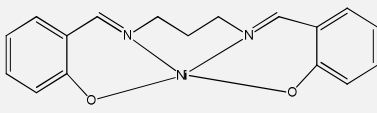
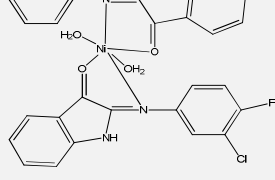
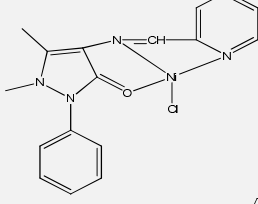
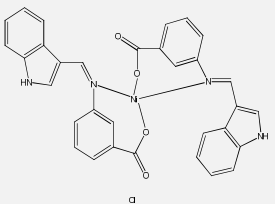
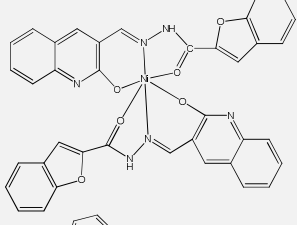
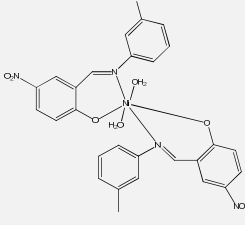
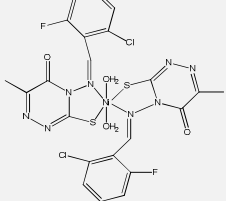
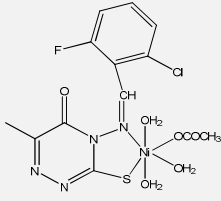
Cpd.	Structure	pMIC	Cpd	Structure	pMIC
C1		0.97	C2		1.41
C3		1.26	C4		2.41
C5		1.70	C6		1.70
C7		1.70	C8		1.29

3. Result

The best GFA derived two-target QSAR models for the anti-microbial activity of the complexes is represented by equation 3. The validation parameters for the QSAR model is presented in Table 2 and the detailed definition of the descriptors in the model are presented in Table 3. Table 4 and Table 5 give the VIF Statistics table and the Comparison of observed pMIC and predicted pMIC of the model, respectively. The plot of actual pMIC verses predicted pMIC is depicted by Figure 2 while Figure 3 gives the residual plot of the model.

Cpd.	Structure	pMIC	Cpd	Structure	pMIC
C9		1.49	C10		1.38
C11		1.48	C12		2.00
C13		1.11	C14		1.30
C15		1.81	C16		1.51
C17		2.11	C18		2.51
C19		2.68	C20		1.30
C21		1.28	C22		1.32
C23		1.51	C24		3.00

Cpd.	Structure	pMIC	Cpd	Structure	pMIC
C25		2.70	C26		2.00
C27		1.70	C28		1.81
C29		1.86	C30		1.85
C31		1.51	C32		2.11
C33		0.90	C34		1.88
C35		1.70	Cc36		2.11
Cc37		0.90	Cc38		2.11

Cpd.	Structure	pMIC	Cpd	Structure	pMIC
Cc39		0.72	Cc40		1.19
Cc41		1.20	Cc42		2.41
Cc43		1.70	Cc44		1.70
Cc45		1.70	Cc46		1.08
Cc47		2.70	Cc48		1.45
Cc49		1.38	Cc50		2.00
Cc51		1.04	Cc52		1.30
Cc53		1.70	Cc54		1.72

Cpd.	Structure	pMIC	Cpd	Structure	pMIC
Cc55		1.51	Cc56		2.62
Cc57		2.70	Cc58		1.97
Cc59		1.78	Cc60		2.70
Cc61		2.70	Cc62		2.00
Cc63		2.00	Cc64		2.00
Cc65		1.70	Cc66		2.11

Key to Table 1:

C: anti- *Staphylococcus aureus* complexCc: anti-*Candida albicans* complex**Table 2.** Validation Metrics for the Best QSAR Model.

S/n	Parameter	Computed Value	Recommended Value
1	R-squared (R^2)	0.909472	≥ 0.6
2	Adjusted R^2 (R^2_{adj})	0.890073	Should be very close to R^2
3	Cross validated R-squared (Q^2)	0.843522	< 0.5
4	Friedman LOF	0.094522	Very low
5	External validation R^2 (R^2_{ext})	0.6085	≥ 0.6

Table 3. Definition of descriptors in the best QSAR model.

S/n	Descriptor	Definition
1	nHBAcc2	Number of hydrogen bond acceptors
2	nHBAcc3	Number of hydrogen bond acceptors
3	WD. volume	Non-directional WHIM, weighted by van der Waals volumes
4	Weta3.polar	Directional WHIM, weighted by atomic polarizabilities
5	nT6Ring	Number of 6-membered rings (includes counts from fused rings)
6	Kier 3	Third kappa shape index

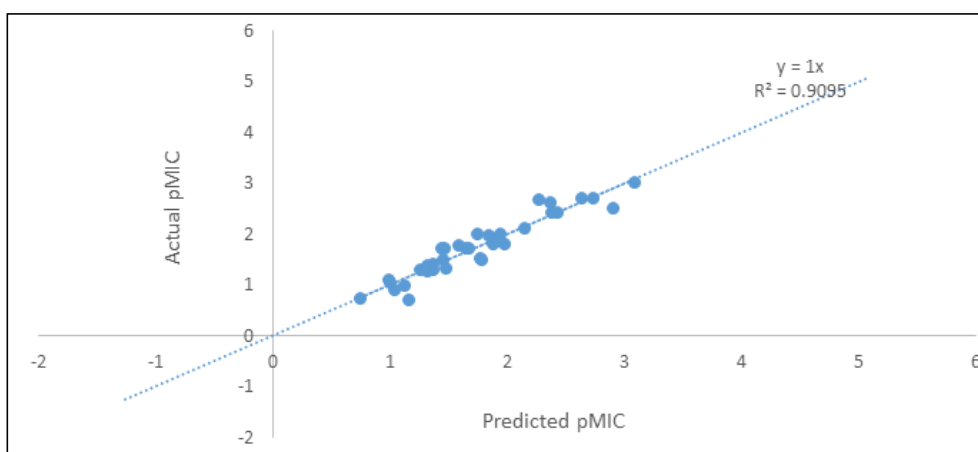
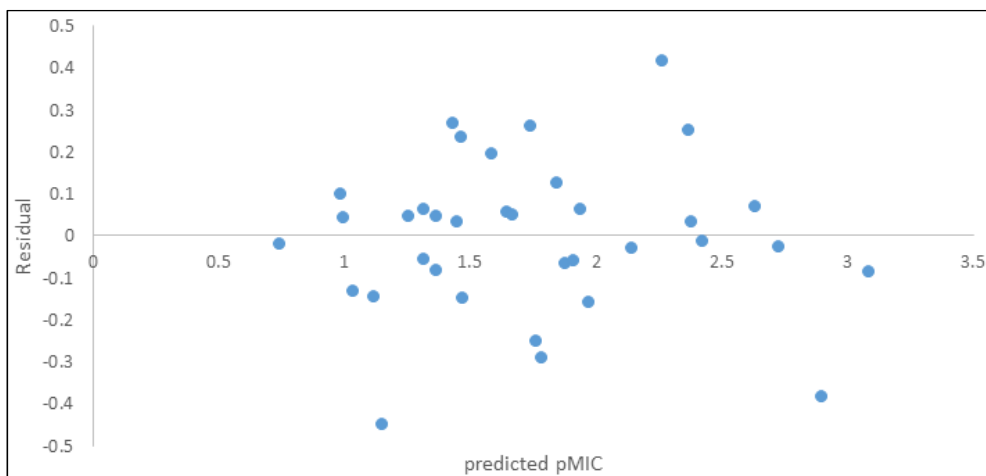
Table 4. Variance Inflation Factor (VIF) Statistic for the Descriptors in the Model.

S/n	Dependent Variable	R ²	VIF
1	WD. volume	0.068	1.073
2	nT6Ring	0.106	1.119
3	Wta3.po	0.298	1.425
4	Kier3	0.330	1.493
5	HBAcc2	0.895	9.524
6	HBAcc3	0.896	9.615

Table 5. Comparison of observed pMIC and predicted pMIC of the model.

Compound	Observed pMIC	Predicted pMIC	residual
C1	0.970	1.11349800	-0.14349800
C11	1.48000000	1.44668300	0.03331700
C12	2.00000000	1.93740900	0.06259100
C14	1.30000000	1.25152500	0.04847500
C15	1.81000000	1.96624100	-0.15624100
C16	1.51000000	1.76105100	-0.25105100
C18	2.51000000	2.89314700	-0.38314700
C19	2.68000000	2.26206100	0.41793900
C2	1.41000000	1.36397300	0.04602700
C21	1.28000000	1.36025300	-0.08025300
C22	1.32000000	1.46597800	-0.14597800
C24	3.00000000	3.08451000	-0.08451000
C25	2.70000000	2.63050300	0.06949700
C26	2.00000000	1.73661900	0.26338100

Compound	Observed pMIC	Predicted pMIC	residual
C28	1.81000000	1.87403100	-0.06403100
C3	1.26000000	1.31385800	-0.05385800
C30	1.85000000	1.90937800	-0.05937800
C32	2.11000000	2.13746400	-0.02746400
C33	0.90000000	1.03035200	-0.13035200
C34	2.41000000	2.42335500	-0.01335500
C4	2.41000000	2.37448000	0.03552000
C5	1.70000000	1.46385000	0.23615000
C7	1.70000000	1.64317300	0.05682700
C9	1.49000000	1.78004100	-0.29004100
C36	1.70000000	1.43149400	0.26850600
CC4	0.72000000	0.73927600	-0.01927600
CC11	1.08000000	0.98091800	0.09908200
CC12	2.70000000	2.72539500	-0.02539500
CC14	1.38000000	1.31489400	0.06510600
CC16	1.04000000	0.99462700	0.04537300
CC19	1.72000000	1.66765200	0.05234800
CC21	2.62000000	2.36670200	0.25329800
CC23	1.97000000	1.84158000	0.12842000
CC24	1.78000000	1.58536800	0.19463200
CC31	0.70000000	1.14866100	-0.44866100

**Figure 2.** Plot of actual pMIC verses predicted pMIC of the Model.**Figure 3.** Residual plot of the model.

4. Discussion

The statistical parameters of the Genetic Function Algorithm derived QSAR model is in compliance with the standard shown in Table 2. The high predictability of the model is evidenced by the low residual values observed in Table 5 which gives the comparison of observed and predicted antibacterial activities of the complexes. Also, the high linearity of the plot of predicted *pMIC* against observed *pMIC* (R^2 value of 0.9095) shown in Figure 2 confirms the robustness of the model. Furthermore, the plot of observed *pMIC* versus residual *pMIC* (Figure 3) indicates that there was no systemic error in model development as the propagation of residuals was observed on both sides of zero [33].

The multi-collinearity between the descriptors used in the model was detected by calculating their VIF. The corresponding VIF values of the six descriptors used in the optimization model are presented in Table 4. From this table, all the variables have VIF values of less than 10 indicating that the obtained model has statistical significance, and the descriptors were found to be reasonably orthogonal.

The result of the QSAR modelling revealed that Wta3.po, a descriptor of molecular polarity predominantly influences the observed anti-microbial activities of the studied complexes against the aforementioned organisms as this descriptor contributes to the model by 49.37%. The percentage contribution of other descriptors to the model include: WD. volume (39.7%), nT6Ring (2.72%), Kier3 (1.86%), nHBAcc2 (3.19%), nHBAcc3 (3.14%). The positive coefficient of the descriptor indicated that the magnitude of the MIC of these complexes against these organisms increases with increase in the value of this descriptor. However, since the activity of drug varies inversely with its minimum inhibitory concentration (MIC), the lower the value of this descriptor in a molecule, the more the activity of the molecule against *S. aureus* / *C. albicans* and vice versa. This can be rationalized thus: 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 [34]. Wta3.po is a descriptor of molecular polarity, the decrease in the anti-*S. aureus* and *C. albicans* 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. Thus, for an enhanced inhibitory activity of the studied class of complex against the organisms, the polarity of the complex should be slightly low.

5. Conclusion

QSAR analysis on a set of biologically active Nickel-

Schiff base complexes against *S. aureus* and *C. albicans* was carried out using the GFA technique. The robustness and applicability of QSAR equation has been established by internal and external validation techniques.

The best QSAR model hinted that the minimum inhibitory concentration of the studied complexes were predominantly influenced by descriptors of molecular polarity (Weta3.polar) and molecular size (WD. volume). The minimum inhibitory concentration of these complexes against *S. aureus* and *C. albicans* could be enhanced by reducing their molecular polarities and sizes considerably.

It is envisioned that the QSAR results identified in this study will offer important structural insight in the future design of novel anti-*S. aureus* and *C. albicans* drugs from nickel-schiff base complexes.

References

- [1] Perez, K. K.; Olsen, R. J.; Musick, W. L.; Cernoch, P. L.; Davis J. R.; Peterson, L. E.; Musser J. M. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic resistant Gramnegative bacteremia. *J. Infect.*, 2014; 69: 216-225.
- [2] Narasimhan, B.; Judge, V.; Narang, R.; Ohlan, S.; Ohlan, R. Quantitative structure activity relationship studies for prediction of antimicrobial activity of synthesized 2,4-hexadienoic acid derivatives. *Bioorg Med Chem Lett*, 2007; 21: 5836-5845.
- [3] El-Mahmood, A. M.; De, N.; Alo, A. B. Susceptibility of nosocomial *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* to some antimicrobial drugs routinely used in Adamawa State Hospitals, Nigeria. *Journal of Clinical Medicine and Research*, 2010; 2(8): 125-134.
- [4] Amita, S.; Chowdhury, R.; Thungapathia, M.; Ramamuthy, T.; Nair, G. B.; Ghosh, A. Class1 Integrins and SXT Elements in EL Tor Strains isolated before and after 1992 *Vibrio cholerae* 0139 outbreak, Calcutta, India. *Emerg. Infect. Dis.* 2003; 9(4): 500-502.
- [5] Beaudin, B. A.; Brosnikoff, C. A.; Grimsrud, K. M.; Heffner, T. M.; Rennie, R. P.; Talbot, J. A. Susceptibility of human isolates of *Salmonella typhimurium* DT104 to antimicrobial agents used in human and veterinary medicine. *Diagn. Microbiol. Infect. Dis.*, 2004; 42: 7-20.
- [6] Keypour, H.; Rezaeivala, M.; Valencia, L.; Perez- Lourido, P.; Raza Khavasi, H. *Polyhedron*. 2009; 28: 3755
- [7] Aurora, R.; Mariana, Carmen Chifiriuc; Emilia, Amzoiu; Cezar, Ionuu Spînu. Transition Metal (II) Complexes with Cefotaxime-Derived Schiff Base: Synthesis, Characterization, and Antimicrobial Studies. *Hindawi Publishing Corporation Bioinorganic Chemistry and Applications*. 2014; Article ID 926287, 17 pages.
- [8] Hitendra, Kumar Lautre; Snigdha, Das; Kishor, Patil; Hafid, Yousseouffi; Taibi, Ben Hadda; Ajai, Kumar Pillai. Evaluation of antimicrobial and diuretic activity of Schiff base metal complexes, part-i. *World journal of pharmacy and pharmaceutical sciences*. 2014; 3(6): 1267-1281.

- [9] Joshi, K. R.; Rojivadiya, A. J.; Pandya, J. H. Synthesis, spectroscopic and antimicrobial studies of Schiff base metal complexes derived from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde. *International Journal of Inorganic Chemistry*. 2014; Article ID 817412, 8 pages.
- [10] Abhay, Nanda Srivastava; Netra, Pal Singh; Chandra, Kiran Shrivastaw. In vitro antibacterial and antifungal activities of binuclear transition metal complexes of ONNO Schiff base and 5-methyl-2,6-pyrimidine-dione and their spectroscopic validation, 2014; 30;30.
- [11] Bhawani, Shankar; Rashmi, Tomar; Rakesh, Kumar; Madhu, Godhara; Vijay, Kumar Sharma. Antimicrobial activity of newly synthesized hydroxamic acid of pyrimidine-5-carboxylic acid and its complexes with Cu (II), Ni(II), Co(II) and Zn(II) metal ions. *Journal of Chemical and Pharmaceutical Research*, 2014; 6(5): 925-930.
- [12] Halli, M. B.; Mallikarjun, K.; Suryakanth, S. S.; Vithal, Reddy P. Synthesis, characterization and biological studies of some metal complexes derived from benzofuran Schiff's base. *World journal of pharmacy and pharmaceutical sciences*. 2014; 3(7), 1499-1512.
- [13] Rayees, Ahmad Shiekh; Ismail, Ab Rahma; Maqsood, Ahmad Malik; Norhayati, Luddi; Sam'an, Malik Masud; Shaeel, Ahmed Al-Thabaiti. Transition Metal Complexes with Mixed Nitrogen-Sulphur (N-S) Donor Macrocyclic Schiff Base Ligand: Synthesis, Spectral, Electrochemical and Antimicrobial Studies. *Int. J. Electrochem. Sci.*, 2013; 8: 6972 – 6987
- [14] Mesut, Gomleksiz; Cihan, Alkan; Belgin, Erdem. Synthesis, characterization and antibacterial activity of 2-*p*-tolyl-1*h*-imidazo [4, 5 *f*] [1, 10] phenanthroline and its co(ii), ni(ii) and cu(ii) complexes. *Bull. Chem. Soc. Ethiop.* 2013; 27(2): 213-220.
- [15] Singh, P. P.; Srivastava, H. K.; Pasha, F. A (2004). DFT-based QSAR study of testosterone and its derivatives, *Bioorg Med Chem.* 12(1): 171-7
- [16] Dipti, Lakhe; Kiran, V. Mangaonkar. Synthesis, Characterization and Antimicrobial activity of Mixed Ligand Complexes of Ni (II), Cu(II) and Fe(III) ions with [phenol-2-[(3-methylphenyl)imino]methyl-4-nitro-] and [phenol-2-[(3-chlorophenyl)imino]methyl-4-nitro-]. *International Journal of ChemTech Research*. 2013; 5 (1): 293-298.
- [17] Madhavan, Sivasankaran Nair; Dasan, Arish; Raphael, Selwin Joseyphus. Synthesis, characterization, antifungal, antibacterial and DNA cleavage studies of some heterocyclic Schiff base metal complexes. *Journal of Saudi Chemical Society*. 2012; 16: 83–88.
- [18] Richa, Gupta; Nisha, Agrawal; Gupta, K. C. Synthesis, IR Spectral Studies and Biological Activities of some Rare Earth Metal Complexes with Biochemically relevant Ligand. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 2012; 3(5): 50.
- [19] Jhanwar, Bharat; Vandana, Sharma; Rajeev, K. Singla; Birendra, Shrivastava. QSAR - Hansch Analysis and Related Approaches in Drug Design. *Pharmacologyonline 1*. 2011; 306-344.
- [20] Prado-Prado, F. J.; de la Vega, O. M.; Uriarte, E.; Ubeira, F. M.; Chou, K. C.; Gonzalez-Diaz H. *Bioorg. Med. Chem.* 2009; 17: 569.
- [21] Preeti, Arora; Rakesh, Narang; Sonam, Bhatia; Surendra, Kumar Nayak; Sachin, Kumar Singh; Balasubramanian, Narasimhan. Synthesis, molecular docking and QSAR studies of 2, 4-disubstituted thiazoles as antimicrobial agents. *Journal of Applied Pharmaceutical Science*, 2015; 5 (02): 028-042.
- [22] Pradeep, Kumar; Balasubramanian, Narasimhan; Kalavathy, Ramasamy; Vasudevan, Mani; Rakesh, Kumar Mishra; Abu Bakar, Abdul Majeed. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of 2/3-bromo-N0-(substituted benzylidene/3 phenylallylidene) benzohydrazides. *Arabian Journal of Chemistry*. 2014; 30: 30.
- [23] Sumit, Tahlan; Pradeep, Kumar; Kalavathy, Ramasamy; Vasudevan, Mani; Rakesh, Kumar Mishra; Abu Bakar, Abdul Majeed; Balasubramanian, Narasimhan. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of *N'*-substituted benzylidene/2-hydroxynaphthalen-1-ylmethylene/3-phenylallylidene/5-oxopentylidene-4-(2-oxo-2-(4*H*-1,2,4-triazol-4-yl) methylamino) benzohydrazides. *Arabian journal of chemistry*, 2013; 10: 10-16.
- [24] Milan, Mladenović; Nenad, Vuković; Slobodan, Sukdolak; Slavica, Solujić. Design of Novel 4-Hydroxy-chromene-2-one Derivatives as Antimicrobial Agents. *Molecules*, 2010; 15: 4294-4308.
- [25] Vikramjeet, Judge; Balasubramanian, Narasimhan; Munish, Ahuja; Dharmarajan, Sriram; Perumal, Yogeeswari; Erik, De Clercq; Christophe, Pannecouque; Jan, Balzarini. Isonicotinic acid hydrazide derivatives: synthesis, antimicrobial activity, and QSAR studies. *Med Chem Res.* 2012; 21: 1451–1470
- [26] Chaudhary, A.; Swaroop, R.; Singh, R. *Buletin dela Sociead Chilena de Quimica*, 2002; 47; 203.
- [27] Trohalaki, S.; Giffort, E.; Pachter, R. Improved QSARs for predictive toxicology of halogenated hydrocarbons. *Computers and Chemistry*, 2000; 24: 421.
- [28] Zhang, L.; Wan, J.; Yang, G (2004). A DFT-based QSARs study of protoporphyrinogen oxidase inhibitors: phenyl triazolinones. *Bioorg Med Chem.* 12(23): 6183-91.
- [29] Hansch, C.; Fujita, T. P. Analysis: A Method for the correlation of biological activity and chemical structure. *J Am Chem Soc.* 1964; 86: 1616-1626.
- [30] Ameji J. P., A. Uzairu and S. O. Idris (2015). Quantitative structure activity relationship study of nickel schiff base complexes as potent anti-candida albicans agents. *Journal of Computational Methods in Molecular Design*, 5 (3): 120-134.
- [31] Ravichandran, Veerasamy; Harish, Rajak; Abhishek, Jain; Shalini, Sivadasan; Christopher, P. Varghese; Ram, Kishore Agrawal (2011). Validation of QSAR Models - Strategies and Importance: *International Journal of Drug Design and Discovery*, 2011; 2: 511-519.
- [32] Shapiro, S.; Guggenheim, B. Inhibition of oral bacteria by phenolic compounds. Part 1. QSAR analysis using molecular connectivity. *Quant. Struct. -Act. Relat.*, 1998; 17: 327–337.
- [33] Heravi, M. J.; Kyani, A. Use of computer-assisted methods for the modeling of the retention time of a variety of volatile organic compounds: a PCA-MLR-ANN approach *J. Chem. Inf. Comput. Sci.*, 2004; 44: 1328–1335.
- [34] Raj Kaushal, Sheetal Thakur (2013). Syntheses and Biological screening of Schiff base complexes of Titanium (IV), *Chemical Engineering Transactions*, 32: 1801-1806.