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 congenic 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 substitutes 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 balanab 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 sterric 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 *In silico* 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.

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.

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

$R^2_{\text{pred.}}$ 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 Ym indicates mean activity value of the training set [31].

The multi-collinearity between the descriptors used in the

![Figure 1. QSAR methodology flowchart. Source: Ameji et al. [30]](image-url)
model was detected by calculating their variance inflation factors (VIF), which can be calculated as using equation 2.

\[
VIF = \frac{1}{1 - R^2}
\]

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.

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

| Cpd. | Structure | pMIC | Cpd. | Structure | pMIC |
|------|-----------|------|------|-----------|------|
| C1   | ![Structure Image](image1) | 0.97 | C2   | ![Structure Image](image2) | 1.41 |
| C3   | ![Structure Image](image3) | 1.26 | C4   | ![Structure Image](image4) | 2.41 |
| C5   | ![Structure Image](image5) | 1.70 | C6   | ![Structure Image](image6) | 1.70 |
| C7   | ![Structure Image](image7) | 1.70 | C8   | ![Structure Image](image8) | 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.

\[
pMIC = 1.518\text{WD}.\text{volume} + 1.888\text{Weta3.polar} + 0.104\text{nT6Ring} - 0.071\text{Kier3} + 0.122\text{nHBAcc2} - 0.121\text{nHBAcc3} + 0.122
\]
| Cpd. | Structure | pMIC | Cpd. | Structure | pMIC |
|------|-----------|------|------|-----------|------|
| C9   | ![C9 structure](C9_structure.png) | 1.49 | C10  | ![C10 structure](C10_structure.png) | 1.38 |
| C11  | ![C11 structure](C11_structure.png) | 1.48 | C12  | ![C12 structure](C12_structure.png) | 2.00 |
| C13  | ![C13 structure](C13_structure.png) | 1.11 | C14  | ![C14 structure](C14_structure.png) | 1.30 |
| C15  | ![C15 structure](C15_structure.png) | 1.81 | C16  | ![C16 structure](C16_structure.png) | 1.51 |
| C17  | ![C17 structure](C17_structure.png) | 2.11 | C18  | ![C18 structure](C18_structure.png) | 2.51 |
| C19  | ![C19 structure](C19_structure.png) | 2.68 | C20  | ![C20 structure](C20_structure.png) | 1.30 |
| C21  | ![C21 structure](C21_structure.png) | 1.28 | C22  | ![C22 structure](C22_structure.png) | 1.32 |
| C23  | ![C23 structure](C23_structure.png) | 1.51 | C24  | ![C24 structure](C24_structure.png) | 3.00 |
| Cpd. | Structure | pMIC | Cpd. | Structure | pMIC |
|------|-----------|------|------|-----------|------|
| C25  | ![Structure](image1.png) | 2.70 | C26  | ![Structure](image2.png) | 2.00 |
| C27  | ![Structure](image3.png) | 1.70 | C28  | ![Structure](image4.png) | 1.81 |
| C29  | ![Structure](image5.png) | 1.86 | C30  | ![Structure](image6.png) | 1.85 |
| C31  | ![Structure](image7.png) | 1.51 | C32  | ![Structure](image8.png) | 2.11 |
| C33  | ![Structure](image9.png) | 0.90 | C34  | ![Structure](image10.png) | 1.88 |
| C35  | ![Structure](image11.png) | 1.70 | Cc36 | ![Structure](image12.png) | 2.11 |
| Cc37 | ![Structure](image13.png) | 0.90 | Cc38 | ![Structure](image14.png) | 2.11 |
| Cpd. | Structure | pMIC | Cpd. | Structure | pMIC |
|------|-----------|------|------|-----------|------|
| Cc39 | ![Cc39](image) | 0.72 | Cc40 | ![Cc40](image) | 1.19 |
| Cc41 | ![Cc41](image) | 1.20 | Cc42 | ![Cc42](image) | 2.41 |
| Cc43 | ![Cc43](image) | 1.70 | Cc44 | ![Cc44](image) | 1.70 |
| Cc45 | ![Cc45](image) | 1.70 | Cc46 | ![Cc46](image) | 1.08 |
| Cc47 | ![Cc47](image) | 2.70 | Cc48 | ![Cc48](image) | 1.45 |
| Cc49 | ![Cc49](image) | 1.38 | Cc50 | ![Cc50](image) | 2.00 |
| Cc51 | ![Cc51](image) | 1.04 | Cc52 | ![Cc52](image) | 1.30 |
| Cc53 | ![Cc53](image) | 1.70 | Cc54 | ![Cc54](image) | 1.72 |
Table 1: Insilico Predictive Model for Anti-Microbial Properties of Ni (II)-Schiff Bases' Complexes Against Staphylococcus aureus and Candida albicans

| Cpd | Structure | pMIC | Cpd | Structure | pMIC |
|-----|-----------|------|-----|-----------|------|
| Cc55 | ![Image](image1.png) | 1.51 | Cc56 | ![Image](image2.png) | 2.62 |
| Cc57 | ![Image](image3.png) | 2.70 | Cc58 | ![Image](image4.png) | 1.97 |
| Cc59 | ![Image](image5.png) | 1.78 | Cc60 | ![Image](image6.png) | 2.70 |
| Cc61 | ![Image](image7.png) | 2.70 | Cc62 | ![Image](image8.png) | 2.00 |
| Cc63 | ![Image](image9.png) | 2.00 | Cc64 | ![Image](image10.png) | 2.00 |
| Cc65 | ![Image](image11.png) | 1.70 | Cc66 | ![Image](image12.png) | 2.11 |

Key to Table 1:
C: anti- *Staphylococcus aureus* complex
Cc: anti- *Candida albicans* complexe

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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         | 1.11398000     | -0.14398000 |
| 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  |

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 permeation 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.

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