Review Article

Substituted O-Vanillin Schiff Base Derived Organotin (IV) Complexes: Synthesis, Characterization, Antimicrobial Evaluation and QSAR Studies

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Abstract

The synthesis and in vitro antimicrobial activity of new Schiff bases and their organotin(IV) complexes has been tested against pathogenic Gram positive bacteria (viz. Klebsiella pneumoniae, Staphylococcus aureus) Gram negative bacteria (viz. Escherichia coli, Enterobacter aerogenes) and fungi (viz. Aspergillus niger and Candida albicans). The QSAR studies of these synthesized compounds has been carried out which indicate that antimicrobial activity of target compounds is governed by topological descriptors and electronic energy of molecule.

Keywords: Schiff bases; Organotin (IV) complexes; Antimicrobial activity; QSAR

Introduction

Schiff base molecules obtained by the condensation of amine with an aldehyde or ketone have been studied widely due to their structural resemblance with natural biological substances and the presence of azomethine group (-N=CH-) which is responsible for the wide range of biological activities including anti-malarial, anti-bacterial, anti-fungal, anti-viral [1-6]. Anti tubercular and anti HIV activity. The Schiff bases are the versatile ligands, when combined with organometallic tin form compounds of high stability with varied stereochemistry [7] and having variety of biological applications [8-10].

Quantitative Structure Activity Relationship (QSAR) is one of the most important areas in computational chemistry which can extensively be used as valuable tool in drug design and medicinal chemistry. The statistically valid QSAR model is to predict the activities of the molecules and to identify the structural feature that play an important role in biological processes [11] QSAR approach is based on the assumption that the behavior of a compound expressed by any measured activities is correlated with the molecular features of the compound [12]. In the present study we have synthesized some new biologically active Schiff bases and studied their ligational behaviour towards dichloro diorganotin (IV) along with their antimicrobial evaluation and QSAR analysis.

Results and Discussion

Chemistry

The reaction of substituted o-vanillin with p-toluic hydrazide or benzhydrazide in equimolar molar ratio afforded four air and moisture stable Schiff base ligands HL₁–HL₄. These ligands were soluble in dimethyl sulfoxide and dimethyl formamide at room temperature and soluble in methanol and ethanol on heating. These bidentate ligands reacted with R₂SnCl₂ (where R = Me, Et, Bu or Ph) in methanol under dry nitrogen atmosphere to form their Sn (IV) complexes (Scheme 1). All the synthesized metal complexes were coloured and insoluble in organic solvents except DMSO. The spectral data and elemental analysis of the synthesized ligands and their metal complexes were well in agreement with their proposed structure (Table 1).

| Sr. No. | Compounds | Molecular formula | Molecular mass | Yield (%) |
|---------|-----------|-------------------|----------------|-----------|
|         |           |                   |                |           |

Analysis (%): C, H, N, Cl, Sn
The ligands HL₁ and HL₂ can coordinate through the nitrogen of azomethine and oxygen atom after the deprotonation. The ligands HL₁–HL₂ displayed band at 1615-1695 cm⁻¹ which shifted to lower frequency in the complexes, thereby suggesting the involvement of nitrogen of this group in coordination with metal. Further confirmation of the complexes was supported by appearance of some new bands in the range 447-497 cm⁻¹ [14] and 555-567 cm⁻¹ [15] which were assigned to ν(Sn-N) and ν(Sn-O) modes respectively.

Table 1: Physicochemical characterization and elemental analysis of synthesized compounds.

|   | HL₁   | C₁₁H₁₆N₂O₄ | 374.16 | 82 | 73.78(73.84) | 5.92(6.14) | 7.48(7.27) | - | - |
|---|-------|-------------|--------|----|-------------|------------|------------|---|---|
| 2 | HL₂   | C₁₁H₁₆N₂O₄ | 405.13 | 86 | 65.18(65.43) | 4.72(4.21) | 10.37(9.92) | - | - |
| 3 | HL₃   | C₁₂H₁₅N₂O₅ | 388.18 | 83 | 74.21(74.47) | 6.23(6.36) | 7.21(9.95) | - | - |
| 4 | HL₄   | C₁₂H₁₅N₂O₅ | 419.15 | 79 | 65.86(66.11) | 5.05(5.33) | 10.02(10.31) | - | - |
| 5 | Me₂Sn(L₁)Cl | C₁₁H₁₆ClN₃O₅Sn | 558.07 | 74 | 53.84(54.13) | 4.88(5.13) | 5.02(5.23) | 6.36(6.41) | 21.29(20.75) |
| 6 | Et₂Sn(L₁)Cl | C₁₁H₁₇ClN₃O₅Sn | 586.10 | 72 | 55.37(55.62) | 5.33(5.77) | 4.78(5.16) | 6.05(5.81) | 20.27(20.42) |
| 7 | Bu₂Sn(L₁)Cl | C₁₁H₁₈ClN₃O₅Sn | 642.17 | 66 | 58.01(57.86) | 6.12(6.34) | 4.36(4.63) | 5.52(5.88) | 18.50(18.11) |
| 8 | Ph₂Sn(L₁)Cl | C₁₁H₁₇ClN₃O₅Sn | 682.10 | 73 | 61.66(61.42) | 4.58(4.16) | 4.11(5.94) | 5.20(5.41) | 17.41(17.22) |
| 9 | Me₂Sn(L₂)Cl | C₁₁H₁₆ClN₃O₅Sn | 589.04 | 77 | 48.97(49.12) | 4.11(4.22) | 7.14(6.87) | 6.02(6.31) | 20.17(19.87) |
| 10 | Et₂Sn(L₂)Cl | C₁₁H₁₇ClN₃O₅Sn | 617.07 | 81 | 50.64(50.83) | 4.58(4.97) | 6.81(6.45) | 5.75(5.86) | 19.25(19.41) |
| 11 | Bu₂Sn(L₂)Cl | C₁₁H₁₇ClN₃O₅Sn | 673.14 | 75 | 53.56(53.27) | 5.39(5.58) | 6.25(6.11) | 5.27(5.15) | 17.64(17.29) |
| 12 | Ph₂Sn(L₂)Cl | C₁₁H₁₇ClN₃O₅Sn | 713.07 | 68 | 57.29(56.96) | 3.96(3.59) | 5.90(5.51) | 4.97(5.03) | 16.65(16.26) |
| 13 | Me₂Sn(L₃)Cl | C₁₁H₁₆ClN₃O₅Sn | 572.09 | 74 | 54.62(54.24) | 5.11(4.78) | 4.90(4.85) | 6.20(6.08) | 20.77(20.86) |
| 14 | Et₂Sn(L₃)Cl | C₁₁H₁₇ClN₃O₅Sn | 600.12 | 69 | 56.07(56.34) | 5.55(5.99) | 4.67(4.73) | 5.91(6.11) | 19.79(19.63) |
| 15 | Bu₂Sn(L₃)Cl | C₁₁H₁₇ClN₃O₅Sn | 656.18 | 73 | 58.60(58.89) | 6.30(6.11) | 4.27(4.55) | 5.41(5.45) | 18.10(18.27) |
| 16 | Ph₂Sn(L₃)Cl | C₁₁H₁₇ClN₃O₅Sn | 696.12 | 79 | 62.14(62.55) | 4.78(5.12) | 4.03(4.34) | 5.10(5.23) | 17.06(17.35) |
| 17 | Me₂Sn(L₄)Cl | C₁₁H₁₆ClN₃O₅Sn | 603.06 | 67 | 49.82(49.38) | 4.35(4.88) | 6.97(7.25) | 5.88(5.63) | 19.70(19.93) |
| 18 | Et₂Sn(L₄)Cl | C₁₁H₁₇ClN₃O₅Sn | 631.09 | 71 | 51.42(51.84) | 4.79(4.44) | 6.66(6.24) | 5.62(5.84) | 18.82(19.19) |
| 19 | Bu₂Sn(L₄)Cl | C₁₁H₁₇ClN₃O₅Sn | 687.15 | 68 | 54.21(54.13) | 5.58(5.76) | 6.12(6.59) | 5.16(5.34) | 17.28(17.55) |
| 20 | Ph₂Sn(L₄)Cl | C₁₁H₁₇ClN₃O₅Sn | 727.09 | 75 | 57.84(57.51) | 4.16(4.31) | 5.78(5.65) | 4.88(4.93) | 16.33(16.42) |

The electronic spectral data of the ligands and their tin complexes were recorded by dissolving these compounds in dry DMSO. The absorption spectra of HL₁–HL₂ were characterized by observing absorption bands at 387-393 nm which is attributed to transition between n-π⁺ localized on the central azomethine bond. The polarization within the >C=N- group resulting in metal-ligand interaction was shown by the blue shift in the complexes, revealed the involvement of azomethine nitrogen. The π-π⁺ transition of benzene ring of Schiff base ligands was attributed to bands of medium intensity at 243 nm, 246 nm and 262 nm, which remain unchanged in the complexes.
\[ ^1 \text{H NMR} \]

\[ ^1 \text{H NMR} \] spectra of the Schiff bases ligand and their complexes were recorded in DMSO-d\(_6\) and their chemical shifts (\(\delta\)) are given in the experimental part. The \([^1 \text{H} \text{NMR}]\) spectra of the Schiff base ligands \(\text{HL}_1-\text{HL}_4\) showed a characteristic NH proton at \(\delta\) 8.70-8.74 ppm [15] which disappeared in the spectra of the complexes after deprotonation of NH (via enolization). The azomethine proton of these ligands appeared as a sharp singlet around \(\delta\) 11.78-11.87 ppm [16]. The downfield shifting of this azomethine proton signal in the complexes was observed as a consequence of coordination through nitrogen of this group. The aromatic and aliphatic protons of ligands exhibited signals in the range \(\delta\) 7.12-7.92 ppm and \(\delta\) 2.30-5.16 ppm respectively which remain unaltered in the spectra of the complexes indicated non-participation of the atoms in bonding to which these protons are attached. The signals present at \(\delta\) 1.19-1.26 ppm, \(\delta\) 1.21-3.11 ppm, \(\delta\) 1.00-3.11 ppm and \(\delta\) 6.66-7.50 ppm were related to the methyl, ethyl, butyl and phenyl protons directly attached to tin atom. Integrated proton ratios confirmed the formation of complexes of type \(R_2\text{Sn}(L)C\).  

**Supplementary material**
$^{13}$C NMR

$^{13}$C NMR spectra of the Schiff bases ligand and their complexes were recorded in DMSO-d$_6$ and are given in the experimental part. The ligands HL$_1$–HL$_4$ displayed characteristic signal of carbon of carbonyl and azomethine (CH=N) groups at δ 163.2–163.3 ppm and δ 152.3–152.6 ppm respectively [17]. Which shifted towards lower values in the complexes, revealed the participation of carbonyl and azomethine carbon in coordination. The signals at δ 113.5-147 ppm and δ 20.8-74.7 ppm were assigned to carbons of aromatic and aliphatic regions of ligands, respectively. The signals at δ 8.5-8.6 ppm, δ 8.5-13.2 ppm and δ 8.2-28.4 ppm revealed the attachment of methyl, ethyl and n-butyl groups with the central metal atom. Similarly the signal at δ 128.1-129.2 ppm were assigned to the phenyl group attached to the tin.
**119Sn NMR**

119Sn NMR is a influential technique to find the coordination number of the central tin atom. The characteristic resonance peaks in the 119Sn NMR spectra of all of the complexes were recorded in CDCl₃ and DMSO-d₆. The 119Sn chemical shifts of organotin (IV) derivatives were in the range of -138.5 to -147.6 ppm [18] indicating penta-coordinated environment around tin atom.

**Antimicrobial activity**

The Schiff base ligands and their organotin (IV) complexes were screened for their in vitro antimicrobial activities along with conventional bactericide norfloxacin and fungicide fluconazole for comparing the activity of the compounds. The microorganisms used in the present study include *S. aureus*, *K. pneumonia*, *E. coli* *E. aerogenes*, *Fungi C. albicans* and *A. niger*.

The antimicrobial activity test results of all the tested compounds revealed their ability to act against bacterial and fungal strains appreciably and some of the compounds exhibited better activity than the standard drugs used in the assay. In the entire series, the pMIC of the compounds ranged between 0.874–2.066 μmol/mL and 0.890–2.066 μmol/mL against Gram-positive and Gram-negative bacteria, respectively. Compounds 12, 16 and 20 showed highest antibacterial activity followed by compounds 7, 8, 11, and 19 in the entire series. Similarly, antifungal data suggested that almost same results were obtained as in the antibacterial assay and compounds 11,12,15,16,19 and 20 displayed better activities than other compounds of the series and pMIC for antifungal activity of the entire series ranged from 0.890–2.066 μmol/mL.

The antimicrobial data reveals that the organotin (IV) complexes were found to be better antimicrobial agent as compared to their respective free ligands. The enhancement in the antimicrobial activity of complexes may be due to the delocalization of electron over the whole chelate ring, thereby increasing the lipophilicity of the target compound. This increased lipophilicity of the drug molecule favours its permeation through the cell membrane of microorganism [19]. The other factors which may affect the bioactivity of metal complexes include the number and the nature of the organic groups/halogen atoms directly bound to tin atom. The mode of action of metal complexes may be linked with the formation of hydrogen bond with the active centers of the cell constituents by interfering with normal cell processes.

**QSAR analysis**

Quantitative structure activity relationship (QSAR) studies between the in vitro antimicrobial activity and descriptors coding for lipophilic, electronic, steric and topological properties of four substituted o-vanillin Schiff bases and their sixteen organotin(IV) complexes were performed to find out the relationship between structural variants and antimicrobial activity using the Linear Free Energy Relationship model (LFER) described by Hansch and Fujita [20]. The dependent variable pMIC (i.e. –log MIC) used as in QSAR study was obtained by taking negative logarithm of observed antimicrobial activities (Table 2).
Table 2: Antimicrobial activity of synthesized derivatives (µM/ml).

The different independent variables (molecular descriptors) like log of octanol–water partition coefficient (log P), Molar Refractivity (MR), Kier’s molecular connectivity (χ, χ'), nuclear topological index (R), Balaban topological index (J), Wiener topological index (W), Total energy (Te), energies of Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), dipole moment (µ), Nuclear repulsion Energy (Nu.E) and Electronic Energy (Ele.E), calculated for ligands and their organotin (IV) complexes are presented in Table 3 (21-26).

### Table 3: Value of selected descriptors in the regression analysis.

| Comp. pMICsa | pMICkp | pMICec | pMICca | pMICca | pMICan |
|--------------|--------|--------|--------|--------|--------|
| 1            | 0.874  | 1.175  | 1.175  | 1.175  | 1.175  |
| 2            | 1.210  | 1.511  | 1.511  | 1.511  | 1.511  |
| 3            | 0.890  | 1.191  | 1.191  | 0.890  | 0.890  |
| 4            | 1.224  | 1.224  | 1.224  | 1.224  | 1.224  |
| 5            | 1.349  | 1.349  | 1.349  | 1.349  | 1.349  |
| 6            | 1.370  | 1.671  | 1.671  | 1.370  | 1.370  |
| 7            | 1.711  | 1.711  | 2.012  | 1.711  | 1.711  |
| 8            | 1.737  | 2.038  | 2.038  | 1.737  | 2.038  |
| 9            | 1.372  | 1.673  | 1.673  | 1.372  | 1.673  |
| 10           | 1.392  | 1.693  | 1.693  | 1.392  | 1.693  |
| 11           | 1.731  | 2.032  | 2.032  | 1.731  | 2.032  |
| 12           | 2.057  | 2.057  | 2.057  | 1.756  | 2.057  |
| 13           | 1.058  | 1.360  | 1.360  | 1.360  | 1.360  |
| 14           | 1.380  | 1.380  | 1.380  | 1.380  | 1.681  |
| 15           | 1.720  | 1.720  | 1.720  | 1.720  | 2.021  |
| 16           | 1.746  | 2.047  | 1.746  | 1.746  | 2.047  |

Norfloxacin\(^a\), Fluconazole\(^b\)

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Correlation of molecular descriptors with antimicrobial activity of synthesized derivatives.

High collinearity (r > 0.8) was observed between different parameters i.e. molecular descriptors. The high interrelationship was observed between κχ and Ele.E (r = 0.996), W and κΓ (r = 0.995), κθ and Ele.E (r = 0.995) and low interrelationship was observed between HOMO and W (r = 0.022) and HOMO and κθ (r = 0.028). The correlation matrix indicated that the antimicrobial activity of synthesized ligands and their organotin (IV) complexes are governed by topological parameters like molecular connectivity, shape indices and electronic energy.

The antifungal activity of synthesized derivatives against A. niger is governed by the second order shape attribute (Kappa shape indices), κ₂ (Eq. 1).

**QSAR model for antifungal activity against A. niger**

\[
pMIC_{an} = 0.134 \kappa_2 - 0.358 \quad \text{Eq. 1}
\]

Here and thereafter, n - number of data points, r - correlation coefficient, \( r^2 \) - squared correlation coefficient, \( q^2 \) - cross validated \( r^2 \) obtained by leave one out method, s - standard error of the estimate and F - Fischer statistics.

The QSAR model represented by Eq. 1 for antifungal activity against A. niger demonstrated the importance of second order Kappa shape indices (κ²). According to Kier, the shape of a molecule may be partitioned into attributes, each describable by the count of bonds of various path lengths [27]. The basis for devising a relative index of shape is given by the relationship of the number of path of length 1 in the molecule i, |Pi|, to some reference values based on molecules with a given number of atoms, n, in which the values of IP are maximum and minimum, IPmax and IPmin [28]. The second order shape attribute, κ₂, is given by the following expression:

\[
κ_2 = (n-1)(n-2)/|IP|^2
\]

The equation 1 highlighted the positive correlation between second order Kappa shape indices (κ₂) for the synthesized compounds and antifungal activity against A. niger which depicts that compounds having high κ₂ values (Table 3) will have high antifungal potential and the results presented in the Table 6 are in concordance with the model expressed by Eq. 1.

The linear regression model expressed by Eq. 1 was cross validated by its high \( q^2 \) values (\( q^2 = 0.898 \)) obtained with Leave One Out (LOO) method. The basic requirement for becoming a QSAR model to be valid one is that it must possess \( q^2 \) value higher than 0.5 thus supporting the fact that model expressed by Eq. 1 is valid one [29]. The comparison of observed and predicted antifungal activities is presented in (Table 6).

| Comp. | pMICan | pMICca | pMICkp | pMICcc | pMICta | pMICca | pMICca | pMICca |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Obs   | Pre    | Res    | Obs    | Pre    | Res    | Obs    | Pre    | Res    |
| 1     | 1.175  | 1.250  | -0.075 | 0.874  | 0.952  | -0.078 | 1.175  | 1.055  | 0.120  |
| 2     | 1.511  | 1.369  | 0.142  | 1.210  | 1.059  | 0.151  | 1.210  | 1.163  | 0.047  |
| 3     | 1.191  | 1.269  | -0.078 | 0.890  | 1.011  | -0.121 | 0.890  | 1.101  | -0.211 |
| 4     | 1.224  | 1.388  | -0.164 | 1.224  | 1.117  | 0.107  | 1.224  | 1.209  | 0.015  |
| 5     | 1.349  | 1.408  | -0.059 | 1.349  | 1.213  | 0.136  | 1.349  | 1.254  | 0.095  |
| 6     | 1.671  | 1.607  | 0.064  | 1.370  | 1.349  | 0.021  | 1.370  | 1.387  | -0.017 |
| 7     | 2.012  | 2.018  | -0.006 | 1.711  | 1.598  | 0.113  | 1.711  | 1.624  | 0.087  |
| 8     | 2.038  | 1.928  | 0.110  | 1.737  | 1.709  | 0.028  | 2.038  | 1.872  | 0.166  |

Table 5: Correlation of molecular descriptors with antimicrobial activity of synthesized derivatives.
The results of observed and predicted antifungal activities lie close to each other as evidenced by their low residual values (Table 6) which again supported the validity of model expressed by Eq. 1. The statistical validity of QSAR model was also cross checked by plotting the graphs of observed, predicted and residual pMIC activity values. The plot of predicted pMICan against observed pMICan (Figure 1).

**Figure 1:** Plot of observed pMICan against the predicted pMICan for the linear regression model developed by Eq. which depicted that there was no systemic error in model development [30].

QSAR models 2 – 8 were obtained by linear regression of the antibacterial and antifungal activity of synthesized derivatives against *S. aureus*, *C. albicans*, *K. pneumoniae*, *E. coli*, and *E. aerogenes* with molecular descriptors.

**QSAR model for antibacterial activity against S. aureus**

\[
\text{pMIC}_{sa} = -0.000025 \text{Ele.E} + 0.083 \quad \text{Eq. 2}
\]

\[
\begin{aligned}
&n = 20 \\
&r = 0.941 \\
&r^2 = 0.886 \\
&q^2 = 0.855 \\
&s = 0.109 \\
&F = 140.08
\end{aligned}
\]

**QSAR model for antifungal activity against C. albicans**

\[
\text{pMIC}_{ca} = 0.119 \times -0.565 \quad \text{Eq. 3}
\]

\[
\begin{aligned}
&n = 20 \\
&r = 0.936 \\
&r^2 = 0.877 \\
&q^2 = 0.830 \\
&s = 0.115 \\
&F = 127.974
\end{aligned}
\]

**QSAR model for antibacterial activity against K. pneumoniae**

\[
\text{pMIC}_{kp} = 0.112 \times -0.327 \quad \text{Eq. 5}
\]

\[
\begin{aligned}
&n = 20 \\
&r = 0.924 \\
&r^2 = 0.853 \\
&q^2 = 0.825 \\
&s = 0.120 \\
&F = 104.331
\end{aligned}
\]

**QSAR model for antibacterial activity against E. coli**

\[
\text{pMIC}_{ec} = 0.123 \times -0.239 \quad \text{Eq. 7}
\]

\[
\begin{aligned}
&n = 20 \\
&r = 0.915 \\
&r^2 = 0.837 \\
&q^2 = 0.804 \\
&s = 0.128 \\
&F = 92.54
\end{aligned}
\]
The linear regression model represented by Eq. 2 revealed that the antibacterial activity against *S. aureus* is governed by the Electronic Energy of the molecule (Ele.E). As the coefficient of electronic energy is negative, therefore the antibacterial activity against *S. aureus* will increase with decrease in Ele.E values, that can be checked from the results presented in Table 3 and 6.

Eq. 3 and 4 were obtained for the regression model describing the antifungal activity of the synthesized derivatives against *C. albicans* both of which indicated that first order molecular connectivity index ($\chi$) and Randic (R) topological parameter were equally affecting the antifungal activity against *C. albicans* as all the statistical parameters for both these equations were same. The positive coefficient of first order molecular connectivity index ($\chi$) and Randic (R) parameter in Eq. 3 and 4 demonstrated that the antifungal of the synthesized derivatives will increase with increase in value of first order molecular connectivity index ($\chi$) and Randic (R) parameter.

Similarly the regression analysis for antibacterial activity of synthesized derivatives against *K. pneumoniae* came out with two models represented by Eq. 5 and 6 thus indicating the fact that antibacterial activity against *K. pneumoniae* is governed by two parameters viz. first order molecular connectivity index ($\chi$) and Randic (R) parameter to an equal extent. Both of these models have same statistical parameters and thus indicated that the predicted antibacterial activity against *K. pneumoniae* will be same whatever the parameter we use for prediction of activity out of these two molecular descriptors. The outcome of QSAR models represented by Eq. 3 to 6 revealed the fact that *K. pneumoniae* and *C. albicans* may have similar type of binding site in their target receptor to which these molecules are binding.

QSAR model represented by Eq. 7 indicated the importance of second order Kappa shape indices ($\kappa$) in describing the antibacterial activity against *E. coli*. The positive correlation of the molecular descriptor second order Kappa shape indices ($\kappa$) with antibacterial activity revealed that increase in the value of $\kappa$ will lead to an increase in antibacterial activity against *E. coli*.

The antibacterial activity of synthesized derivatives against *E. aerogenes* was governed by first order Kappa shape indices ($\kappa$) as demonstrated by Eq. 8. The QSAR models represented by Eq. 2-8 have got high $r$, $r^2$, $q^2$ and $F$ values and low s values which indicated that that the models are valid one. The low residual values obtained after prediction of activity using these models (Table 6) confirmed the fact that models expressed by Eq. 2 – Eq. 8 were also valid ones.

| $\chi$ | $\kappa_1$ | $\kappa_2$ | R | B | W | Te | Ele.E | HOMO | pMICan |
|-------|-----------|------------|---|---|---|----|-------|------|--------|
| 1.000 | 0.939     | 0.900      | 0.774 | 0.979 | 0.671 | 0.924 | 0.970 | 0.766 |
| $\chi$ | 1.000     | 0.900      | 0.774 | 0.979 | 0.671 | 0.924 | 0.970 | 0.766 |
| $\kappa_1$ | 0.992 | 0.900 | 1.000 | 0.977 | 0.703 | 1.000 |
| $\kappa_2$ | 0.992 | 0.900 | 1.000 | 0.977 | 0.703 | 1.000 |
| R     | 0.990     | 0.900      | 1.000 | 0.976 | 0.707 | 1.000 |
| J     | -0.270    | -0.043     | -0.381 | -0.389 | -0.276 | -0.155 | -0.071 | -0.381 |
| W     | 0.986     | 0.881      | 0.995 | 0.676 | 0.975 | 0.556 | 0.966 | 0.926 |
| Te    | -0.980    | -0.894     | -0.959 | -0.956 | -0.651 | -0.978 | -0.928 | -0.959 |
| Ele.E | -0.995    | -0.948     | -0.984 | -0.960 | -0.679 | -0.996 | -0.969 | -0.984 |
| HOMO  | 0.043     | 0.302      | 0.028 | 0.374 | 0.031 | 0.399 | 0.067 | 0.083 |
| pMICan| 0.943     | 0.906      | 0.933 | 0.750 | 0.889 | 0.651 | 0.955 | 0.958 |

### Table 4: Correlation matrix for antibacterial activity of synthesized derivatives against *K. pneumoniae*

#### Experimental

#### Materials and methods

The chemicals used were of analytical grade (Aldrich) and solvents were purified according to standard procedures. The complexes were synthesized under anhydrous condition in inert atmosphere. The molar conductance was measured in dry DMSO using Systronics conductivity bridge model-306. The IR spectra were recorded using a Spectrum BX Series FT-IR spectrophotometer in the range 400-4000 cm$^{-1}$, using KBr pellets. Multinuclear magnetic resonance spectra ($^1$H, $^{13}$C, $^{119}$Sn) were recorded on a Bruker Avance II 400 MHz NMR Spectrometer and all chemical shifts were recorded using a Spectrum BX Series FT-IR spectrophotometer in the range 400-4000 cm$^{-1}$, using KBr pellets. Multinuclear magnetic resonance spectra ($^1$H, $^{13}$C, $^{119}$Sn) were recorded on a Bruker Avance II 400 MHz NMR Spectrometer and all chemical shifts...
δ were reported in ppm relative to Tetra Methyl Silane (TMS) as an internal standard in CDCl₃ and DMSO-d₆. Elemental analyses were carried out on a Perkin Elmer 2400 analyzer. Tin/chlorine was estimated gravimetrically. Bacterial and fungal strain was procured from Microbial Type Culture Collection (MTCC), IMTECH, Chandigarh.

**Synthesis of Schiff base Ligands**

Synthesis of ligands (HL₁-HL₄) were carried out in the following two steps:-

**Synthesis of 2-(4-methyl/nitro-benzyloxy)-3-methoxy-benzaldehyde (I).**

The solution of o-vanillin (10 mmol) and K₂CO₃ (20 mmol) in 26 ml of DMF was stirred and p-methyl benzyli bromide (10 mmol) was added slowly. The mixture was allowed to stir overnight. Benzylation of o-vanillin with p-methyl benzyl bromide took place through Williamson ether formation resulting in the formation of 2-(4-methyl-benzyloxy)-3-methoxy-benzaldehyde. The reaction mixture was then quenched with ice followed by the addition of 50 ml of water. The solid product obtained was filtered over the vacuum pump and dried. The same procedure was adopted for the synthesis of 2-(4-nitro-benzyloxy)-3-methoxy-benzaldehyde.

**Synthesis of Schiff base ligands (HL₁-HL₄)**

Ligands HL₁-HL₄ were synthesized by reacting substituted o-vanillin (I) with p-tollic Hydrazide or benzhydrazide (II) in equimolar ratio in dry methanol. The solid product obtained after refluxing the reaction mixture for about 3-4 hrs was filtered and recrystallized in methanol. The same procedure was adopted for the synthesis of other Schiff base ligands.

Scheme 1. Synthetic route for HL1-4 and their tin complexes

Benzoic acid [3-methoxy-2-(4-methyl-benzyloxy)-benzyledene]-hydrazide [(HL₁, C₁₃H₁₁N₂O₃)], (1)

Yield: 82 %; m.p.: 170-171 °C; IR (KBr): v = 3385 (NH), v = 1689 (C=O), v = 1550 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆, and CDCl₃), δ = 11.87 (s, 1H, -CH=N), 8.71 (s, 1H, -NH), 7.90-7.92 (d, 2H, C₁₂-H & C₁₂'-H), 7.49-7.58 (m, 4H, C₁₃'-H, C₁₄'-H, C₁₅'-H & C₁₆'-H), 7.35-7.37 (d, 2H, C₁₇'-H & C₁₈'-H), 7.16-7.18 (d, 2H, C₁₉'-H & C₂₀'-H), 7.10-7.12 (m, 2H, C₁₈'-H & C₁₉'-H), 4.97 (s, 2H, -OCH₃), 3.88 (s, 3H, -OCH₃), 2.30 (s, 3H, -CH₃) ppm; ¹³C NMR: δ = 163.3 (C=O), 152.6 (C=N), 146.4 (C-6), 143.5 (C-5), 137.2 (C-a), 133.8 (C-d), 133.4 (C-1'), 131.4 (C-4'), 128.6 (C-c & C-e), 128.4 (C-3' & C-5'), 128.2 (C-2' & C-6'), 128.1 (C-b & C-f), 127.6 (C-2), 124 (C-3), 117.2 (C-1), 113.7 (C-4), 74.7 (OCH₃), 55.3 (OCH₃), 20.8 (CH₃, at Ph ring) ppm.

4-Nitro-Benzoic acid [3-methoxy-2-(4-methyl-benzyloxy)-benzyledene]-hydrazide [(HL₂, C₂₂H₁₉N₃O₄)], (2)

Yield: 86 %; m.p.: 174-175 °C; IR (KBr): v = 3412 (NH), v = 1695 (C=O), v = 1557 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆, and CDCl₃), δ = 11.86 (s, 1H, -CH=N), 8.73 (s, 1H, -NH), 8.25-8.27 (d, 2H, C₁-H & C₂-H), 7.89-7.91 (d, 2H, C₁'-H & C₂'-H), 7.77-7.79 (d, 2H, C₃'-H & C₄'-H), 7.49-7.58 (m, 4H, C₁₂-H, C₁₃'-H, C₁₄'-H, C₁₅'-H & C₁₆'-H), 7.14-7.17 (m, 2H, C₁₈'-H & C₁₉'-H), 5.16 (s, 2H, -OCH₃), 3.87 (s, 3H, -OCH₃) ppm; ¹³C NMR: δ = 163.3 (C=O), 152.4 (C=N), 147 (C-6), 146.1 (C-5), 144.7 (C-d), 143.2 (C-a), 133.4 (C-1'), 131.5 (C-4'), 128.6 (C-3' & C-5'), 128.2 (C-b & C-f), 128.1 (C-2' & C-6'), 127.6 (C-c & C-e), 124.5 (C-5), 123.2 (C-3), 113.7 (C-1), 113.8 (C-4), 73.5 (OCH₃), 55.7 (OCH₃) ppm.

4-Methyl-Benzonic acid [3-methoxy-2-(4-methyl-benzyloxy)-benzyledene]-hydrazide [(HL₃, C₂₃H₂₁N₂O₄)], (3)

Yield: 83 %; m.p.: 164-165 °C; IR (KBr): v = 3373 (NH), v = 1687 (C=O), v = 1546 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆, and CDCl₃); δ = 11.79 (s, 1H, -CH=N), 8.70 (s, 1H, -NH), 7.82-7.84 (d, 2H, C₁'-H & C₂'-H), 7.48-7.50 (d, 1H, C₂-H), 7.35-7.37 (d, 2H, C₁'-H & C₂'-H), 7.30-7.32 (d, 2H, C₃'-H & C₄'-H), 7.16-7.18 (d, 2H, C₅'-H & C₆'-H), 7.10-7.11 (m, 2H, C₁₈'-H & C₁₉'-H), 4.97 (s, 2H, -OCH₃), 3.88 (s, 3H, -OCH₃), 2.39 (s, 3H, -CH₃, at Hydrazide ring), 2.30 (s, 3H, -CH₃, at Ph ring) ppm; ¹³C NMR: δ = 163.2 (C=O), 152.5 (C=N), 146.4 (C-6), 143.5 (C-5), 141.5 (C-4'), 137.2 (C-a), 133.8 (C-d), 130.5 (C-1'), 128.7 (C-c & C-e), 128.6 (C-3' & C-5'), 128.4 (C-2' & C-6'), 128.3 (C-b & C-f), 127.6 (C-2), 124 (C-3), 117.3 (C-1), 113.5 (C-4), 74.7 (OCH₃), 55.5 (OCH₃), 21.1 (CH₃, at Hydrazide ring), 20.8 (CH₃, at Ph ring) ppm.

4-Methyl-Benzonic acid [3-methoxy-2-(4-nitro-benzyloxy)-benzyledene]-hydrazide [(HL₄, C₂₃H₂₁N₂O₄)], (4)

Yield: 79 %; m.p.: 169-170 °C; IR (KBr); v = 3394 (NH), v = 1692 (C=O), v = 1553 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆, and CDCl₃), δ = 11.78 (s, 1H, -CH=N), 8.74 (s, 1H, -NH), 8.24-8.27 (d, 2H, C₁'-H & C₂'-H), 7.77-7.80 (d, 4H, C₁₄'-H, C₁₅'-H, C₁₆'-H & C₁₇'-H), 7.54-7.55 (d, 1H, C₃'-H), 7.28-7.30 (d, 2H, C₁₈'-H & C₁₉'-H), 7.10-7.17 (m, 2H, C₁₈'-H & C₁₉'-H), 5.16 (s, 2H, -OCH₃), 3.87 (s, 3H, -OCH₃), 2.39 (s, 3H, -CH₃, at Hydrazide ring) ppm; ¹³C NMR: δ = 163.3 (C=O), 152.4 (C=N), 146.8 (C-6), 145.2 (C-5), 144.6 (C-d), 142 (C-a),
Yield: 66 %; m.p.: 121-122 °C; IR (KBr): ν = 1554 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.81 (s, 1H, -CH=N=), 8.03-8.05 (m, 2H, C₆-H & C₅'-H), 7.76-7.78 (m, 2H, C₃'-H & C₅'-H), 7.37-7.39 (d, 2H, C₆-H & C₅'-H), 7.16-7.18 (d, 2H, C₃'-H & C₅'-H).

140.3 (C-4'), 135.2 (C-1'), 129.4 (C-3' & C-5'), 128.4 (C-b & C-f), 128.1 (C-2' & C-6'), 127.6 (C-c & C-e), 122.4 (C-2), 123.2 (C-3), 117.4 (C-1), 113.6 (C-4'), 73.5 (OCH₂), 55.6 (OCH₃), 21 (CH₃ at Hydrazide ring) ppm.

General procedure for the synthesis of organotin complexes (5-20)

The sodium salt of Schiff base ligand was prepared by reacting ligand HL¹ (4.56 g, 10 mmol) and sodium metal (0.225 g, 10 mmol) in 30 mL dry methanol followed by the slow addition of Me₂SnCl₂ (2.19 g, 10 mmol) and then the reaction mixture was refluxed for 4h. The precipitated NaCl was filtered and solvent was evaporated on rotary evaporator under reduced pressure. The final product obtained was recrystallized from dry methanol and hexane and finally dried under reduced pressure. The other tin complexes were synthesized by reacting the ligands, HL₂/HL₃ with R₂SnCl₂ in 1:1 molar ratio by the same procedure.

[(Me₂Sn(L)₂)Cl, C₆H₄ClN(O)₂Sn], (8)

Yield: 73 %; m.p.: 139-140 °C; IR (KBr): ν = 1548 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.87(s, 1H, -CH=N), 8.76-8.80 (d, 2H, C₆-H & C₆''-H), 8.11-8.51 (m, 4H, C₆'-H, C₅'-H, C₆'-H & C₅'-H), 7.85-7.95 (d, 4H, C₆-H, C₅-H, C₆'-H & C₅'-H), 6.63-7.50 (m, 10H Ph and 2H, C₂-H & C₆-H). 4.97 (s, 2H, -OCH₂), 3.87 (s, 3H, -OCH₃), 2.38 (s, 3H, -CH₃) ppm; ¹³C NMR: δ = 155.7 (C-O), 151.5 (C=N), 146.4 (C-6), 143.3 (C-5), 140.4 (C-a), 134.7 (C-d), 133.9 (C-1’), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (C-c & C-e), 128.2 (C-3' & C-5'), 127.7 (C-2' & C-6'), 127.6 (C-b & C-f), 127.2 (C-2), 124.1 (C-3), 117.1 (C-1), 113.8 (C-4), 74.7 (OCH₂), 55.7 (OCH₃), 21.1 (CH₃ at Ph ring) ppm.

[(Me₂Sn(L₂)₂)Cl, C₆H₄ClN(O)₂Sn], (9)

Yield: 77 %; m.p.: 128-129 °C; IR (KBr): ν = 1553 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.85 (s, 1H, -CH=N), 8.24-8.27 (d, 2H, C₂-H & C₆-H), 7.86-7.88 (d, 2H, C₂'-H & C₅'-H), 7.72-7.74 (d, 2H, C₃'-H & C₅'-H), 7.52-7.57 (m, 4H, C₆-H, C₅'-H, C₆'-H & C₅'-H), 7.13-7.17 (m, 2H, C₂-H & C₆-H), 5.01 (s, 2H, -OCH₂), 3.87 (s, 3H, -OCH₃), 1.23 (s, 6H, -CH₃) ppm; ¹³C NMR: δ = 155.4 (C-O), 151.4 (C=N), 146.9 (C-6), 145.9 (C-5), 144.9 (C-d), 142.9 (C-a), 133.4 (C-1’), 131.6 (C-4’), 128.8, (C-3' & C-5'), 128.1 (C-b & C-f), 127.9 (C-2' & C-6’), 127.7 (C-c & C-e), 124.5 (C-2), 123.3 (C-3), 117.5 (C-1), 113.8 (C-4), 73.6 (OCH₂), 55.7 (OCH₃), 8.6 (Me) ppm.

[(Et₂Sn(L)₂Cl, C₆H₄ClN(O)₂Sn], (10)

Yield: 81 %; m.p.: 126-127 °C; IR (KBr): ν = 1555 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.86 (s, 1H, -CH=N), 8.25-8.28 (d, 2H, C₂-H & C₆-H), 7.85-7.87 (d, 2H, C₆'-H & C₅'-H), 7.73-7.75 (d, 2H, C₆-H & C₅-H), 7.51-7.56 (m, 4H, C₆-H, C₅'-H & C₅'-H), 7.12-7.15 (m, 2H, C₂-H & C₆-H), 4.98 (s, 2H, -OCH₂), 3.85 (s, 3H, -OCH₃), 3.08-3.11 (m, 4H, -CH₂), 1.22-1.26 (t, 6H, -CH₃) ppm; ¹³C NMR: δ = 155.3 (C-O), 151.5 (C=N), 145.3 (C-6), 142.3 (C-5), 135.9 (C-d), 132.9 (C-a), 132.2 (C-1’), 131.3 (C-4’), 129.7, (C-3' & C-5'), 128.7 (C-b & C-f), 128.2 (C-2' & C-6’), 128 (C-c & C-e), 127.5 (C-2), 125 (C-3), 117.1 (C-1), 113.5 (C-4), 74.7 (OCH₂), 55.5 (OCH₃), 13.2 (Et), 8.8 (Et) ppm.
[(Bu₂Sn(μ₂-Cl), C₃₅H₃₆ClN₂O₅Sn), (11)]

Yield: 75 %; m.p.: 123-124 °C; IR (KBr): ν = 1554 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.84 (s, 1H, -CH=N), 8.23-8.26 (d, 2H, C-2 & C-6), 7.84-7.86 (d, 2H, C-1' & C-5), 7.72-7.74 (d, 2H, C-2 & C-3), 7.54-7.57 (m, 4H, C-3 & C-4), 7.17-7.19 (m, 2H, C-1 & C-3), 4.99 (s, 2H, -OCH₂), 3.88 (s, 3H, -OCH₃), 3.08-3.11 (t, 4H, -CH₂), 1.62-1.66 (m, 8H, -CH₂), 1.21-1.24 (t, 6H, -CH₃) ppm; ¹³C NMR: δ = 155.4 (C=O), 151.5 (C=N), 146.8 (C-6), 145.7 (C-5), 144.7 (C-d), 142.8 (C-a), 133.5 (C-1'), 131.5 (C-4'), 128.7, (C-3' & C-5'), 127.9 (C-b & C-f), 127.3 (C-2' & C-6'), 127.2 (C-e & C-c), 124.5 (C-2), 123.3 (C-3), 117.4 (C-1), 113.6 (C-4), 73.6 (OCH₂), 55.8 (OCH₃), 28.4 (Bu), 26.4 (Bu), 13.2 (Bu), 7.9 (Bu) ppm.

[(Ph₂Sn(μ₂-Cl), C₁₃H₁₄ClN₂O₅Sn), (12)]

Yield: 68 %; m.p.: 144-145 °C; IR (KBr): ν = 1555 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.86 (s, 1H, -CH=N), 8.26-8.29 (d, 2H, C-2 & C-6), 7.82-7.91 (d, 4H, C₁₂ & C₁₂, C₂₁ & C₂₁, C₂₂ & C₂₂, C₂₃ & C₂₃), 7.53-7.56 (m, 4H, C₁₁ & C₁₁, C₁₂ & C₁₂, C₁₇ & C₁₇, C₂₅ & C₂₅), 7.03-7.21 (m, 10H Ph and 2H, C-2 & C-3), 4.97 (s, 2H, -OCH₃), 3.86 (s, 3H, -OCH₃) ppm; ¹³C NMR: δ = 155.4 (C=O), 151.5 (C=N), 146.8 (C-6), 145.6 (C-5), 144.8 (C-d), 133.5 (C-1'), 131.5 (C-4'), 129.2 (Ph), 128.8 (Ph), 128.4 (Ph), 128.1 (Ph), 128.6 (C-3' & C-5'), 128 (C-b & C-f), 127.3 (C-2' & C-6'), 126.9 (C-c & C-e), 124.5 (C-2), 123.3 (C-3), 117.2 (C-1), 113.8 (C-4), 73.5 (OCH₂), 55.9 (OCH₃) ppm.

[(Me₂Sn(μ₂-Cl), C₁₃H₁₄ClN₂O₅Sn), (13)]

Yield: 74 %; m.p.: 127-128 °C; IR (KBr): ν = 1545 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.78 (s, 1H, -CH=N), 7.83-7.85 (d, 2H, C₁₂ & C₁₂, C₂₁ & C₂₁), 7.47-7.49 (d, 1H, C₁₇), 7.34-7.36 (d, 2H, C₂₁ & C₂₁, C₂₂ & C₂₂), 7.28-7.30 (d, 2H, C₁₁ & C₁₁), 7.18-7.20 (d, 2H, C-2 & C-3), 7.08-7.11 (m, 2H, C₂₂ & C₂₂, C₂₃ & C₂₃), 5.01 (s, 2H, -OCH₃), 3.87 (s, 3H, -OCH₃), 2.37 (s, 3H, -CH₃) ppm; ¹³C NMR: δ = 155.4 (C=O), 151.6 (C=N), 146.4 (C-6), 143.3 (C-5), 141.5 (C-4'), 137.3 (C-a), 133.8 (C-d), 129.9 (C-1'), 128.5 (C-c & C-e), 128.4 (C-3' & C-5'), 128.2 (C-2' & C-6'), 128.2 (C-b & C-f), 127.6 (C-2'), 123.9 (C-3), 113.4 (C-4), 73.6 (OCH₂), 55.4 (OCH₃), 21.2 (CH₂ at Hydrazide ring), 20.8 (CH₃ at Ph ring), 8.6 (Me) ppm.

[[Et₂Sn(μ₂-Cl), C₂₃H₂₃ClN₂O₅Sn], (14)]

Yield: 69 %; m.p.: 124-125 °C; IR (KBr): ν = 1542 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆ and CDCl₃): δ = 11.91 (s, 1H, -CH=N), 7.86-7.88 (d, 2H, C₁₂ & C₁₂, C₂₁ & C₂₁), 7.51-7.53 (d, 1H, C₁₇), 7.37-7.38 (d, 2H, C₂₁ & C₂₁, C₂₂ & C₂₂), 7.28-7.30 (d, 2H, C₁₁ & C₁₁), 7.15-7.17 (d, 2H, C₂₂ & C₂₂), 7.06-7.09 (m, 2H, C₁₂ & C₁₂), 4.9 (s, 2H, -OCH₃), 3.87 (s, 3H, -OCH₃), 2.37 (s, 3H, -CH₃) ppm; ¹³C NMR: δ = 155.3 (C=O), 151.7 (C=N), 146.8 (C-6), 145.9 (C-5), 144.6 (C-d), 143 (C-a), 141.5 (C-4'), 130.5 (C-1'), 128.7 (C-3' & C-5'), 128.5 (C-b & C-f), 128.2 (C-2' & C-6'), 127.6 (C-c & C-e), 124.5 (C-2), 123.0 (C-3), 117.3 (C-1), 113.8 (C-4), 73.3 (OCH₂), 55.7 (OCH₃), 22.9 (CH₃ at Hydrazide ring) ppm.
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A series of novel compounds was synthesized and characterized using elemental analyses, various spectroscopic techniques like UV, IR and (1H, 13C and 119Sn) NMR. The substituted o-vanillin Schiff bases and their organotin(IV) complexes were screened for antimicrobial activity against representative microorganisms and the compounds evaluated had inhibited the growth of all the tested bacterial and fungal strains. The complexes were found to be more active antimicrobial agent in comparison to the Schiff bases. The QSAR studies were carried out to find out the relationship between structural features and antimicrobial activity of synthesized deriv-

Q SAR studies

The structures of 1-20 were first pre-optimized with the Molecular Mechanics Force Field (MM) procedure included in Hyperchem 6.03 [31] And the resulting geometries were further developed by means of the semiempirical method PM3 (Parametric Method-3). A gradient norm limit of 0.01 kcal/A° was taken into consideration for the geometry optimization. The lowest energy structure was used for each individual molecule to calculate physicochemical properties using TSAR 3.3 software for Windows [32]. Further, the regression analysis was performed using the SPSS software package [33].

Conclusion

A series of novel compounds was synthesized and characterized using elemental analyses, various spectroscopic techniques like UV, IR and (1H, 13C and 119Sn) NMR. The substituted o-vanillin Schiff bases and their organotin(IV) complexes were screened for antimicrobial activity against representative microorganisms and the compounds evaluated had inhibited the growth of all the tested bacterial and fungal strains. The complexes were found to be more active antimicrobial agent in comparison to the Schiff bases. The QSAR studies were carried out to find out the relationship between structural features and antimicrobial activity of synthesized deriv-

Yield: 71%; m.p.: 127-128°C; IR (KBr): v = 1552 (C=O) cm⁻¹; 1H NMR (DMSO-d6 and CDCl3): δ = 11.75 (s, 1H, -CH=O), 8.24-8.27 (d, 2H, C-2'H & C-6'H), 7.77-7.80 (d, 4H, C-3'H, C-5'H, C-1'H & C-7'H), 7.52-7.55 (m, 1H, C-2'), 7.23-7.25 (d, 2H, C-1'H & C-7'H), 7.13-7.16 (m, 2H, C-2'H & C-6'H), 5.0 (s, 2H, -OCH3), 3.85 (s, 3H, -OCH3), 2.38 (s, 3H, -CH3 at Hydrazide ring), 3.06-3.10 (m, 4H,-CH2), 1.21-1.25 (t, 6H,-CH3 pm); 13C NMR: δ = 155.3 (C=O), 151.8 (C=N), 146.3 (C=O), 145.9 (C=O), 144.6 (C=O), 143 (C-a), 141.6 (C-b), 130.5 (C-y), 128.7 (C-z, & C-w), 128.5 (C-b & C-f), 128 (C-z', & C-w'), 127.7 (C-c & C-e), 124.3 (C-c), 123.1 (C-c), 117.3 (C-d), 113.8 (C-e), 73.4 (OCH3), 55.6 (OCH3), 23 (CH3 at Hydrazide ring), 12.9 (Et), 8.7 (Et) ppm.

[(BuSnL2)Cl, C6H3ClIN4O5Sn], (19)

Yield: 68%; m.p.: 124-125°C; IR (KBr): v = 1551 (C=N) cm⁻¹; 1H NMR (DMSO-d6 and CDCl3): δ = 11.74 (s, 1H, -CH=O), 8.21-8.25 (d, 2H, C-2'H & C-6'H), 7.76-7.80 (d, 4H, C-3'H, C-5'H, C-1'H & C-7'H), 7.51-7.55 (m, 1H, C-2'), 7.24-7.26 (d, 2H, C-1'H & C-7'H), 7.12-7.15 (m, 2H, C-2'H & C-6'H), 4.98 (s, 2H, -OCH3), 3.89 (s, 3H, -OCH3), 2.37 (s, 3H, -CH3 at Hydrazide ring), 3.07-3.11 (t, 4H,-CH2), 1.61-1.65 (m, 8H,-CH2), 1.23-1.26 (t, 6H,-CH3 ppm); 13C NMR: δ = 155.3 (C=O), 152 (C-N), 146.2 (C-O), 145.9 (C=O), 144.6 (C-d), 143.1 (C-a), 141.4 (C-e), 130.5 (C-d'), 128.7 (C-c, & C-f'), 128 (C-b', & C-f'), 128 (C-z', & C-w), 117.3 (C-d), 113.8 (C-e), 73.5 (OCH3), 55.5 (OCH3), 27.4 (Bu), 25.4 (Bu), 23.2 (CH3 at Hydrazide ring), 12.2 (Bu), 8.2 (Bu) ppm.

[(PhSnL2)Cl, C6H5ClIN4O5Sn], (20)

Yield: 75%; m.p.: 141-142°C; IR (KBr): v = 1554 (C=N) cm⁻¹; 1H NMR (DMSO-d6 and CDCl3): δ = 11.75 (s, 1H, -CH=O), 8.22-8.24 (d, 2H, C-2'H & C-6'H), 7.73-7.81 (d, 4H, C-3'H, C-5'H, C-1'H & C-7'H), 7.48-7.50 (d, 1H, C-2'), 7.27-7.29 (d, 2H, C-1'H & C-7'H), 7.12-7.24 (m, 10H, Ph & m,2H, C-1'H & C-7'H), 5.00 (s, 2H, -OCH3), 3.88 (s, 3H, -OCH3), 2.38 (s, 3H, -CH3 at Hydrazide ring) ppm; 13C NMR: δ = 155.3 (C=O), 151.5 (C=N), 145.4 (C-d), 142.4 (C-d'), 136.2 (C-d), 132.4 (C-a), 132.3 (C-d'), 131.2 (C-1'), 129.8 (C-2', & C-5'), 129 (Ph), 128.7 (Ph), 128.7 (C-b & C-f), 128.4 (Ph), 128.1 (Ph), 127.9 (C-2' & C-6'), 127.6 (C-c & C-e), 127.4 (C-c'), 123.9 (C-c'), 117.4 (C-d), 113.3 (C-4'), 74.4 (OCH3), 55.4 (OCH3), 20.4 (CH3 at Hydrazide ring) ppm.

Antimicrobial activity

Test Microorganisms

Gram positive bacteria (viz. Klebsiella pneumoniae [NCDC No. 138], Staphylococcus aureus [MTCC No. 3160] Gram-negative bacteria (viz. Escherichia coli [MTCC No. 443], Enterobacter aerogenes [NCDC No. 106] and fungus (Aspergillus niger [MTCC No. 282] and Candida albicans [MTCC No. 227] were used for antimicrobial assay. All the microbial strains were procured from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh.

Ligands and their tin complexes were screened for in-vitro antimicrobial activity using serial dilution technique to find out their Minimum Inhibitory Concentration (MIC) value. The medium was prepared by dissolving weighed amount of nutrient broth/sabouraud dextrose broth in 1L of distilled water and 1 ml of nutrient medium was transferred to each test tube. The test tubes having nutrient medium were autoclaved for 30 minutes at 120°C. The solution of test compounds was prepared by dissolving 1.0 mg of synthesized compounds in dry DMSO which was further diluted to give a stock solution of 100 µg/ml. The solution of test compounds was transferred to test tubes having sterilized nutrient medium to get a set of five dilutions of test compounds having concentrations 50, 25, 12.5, 6.25 and 3.125 µg/ml. The inoculation of test strains was done with the help of micropipette with sterilized tips as 100 µL of freshly cultured strain was transferred in to test tubes and incubated at 37°C for 24 hours for bacterial strains, 48 hours for C. albicans and 7 days at 25°C for A. niger. The DMSO was taken as negative control whereas norfloxacin and fluconazole were taken as positive control for antibacterial and antifungal activity, respectively. The experiments were performed in triplicates and the mean values were observed.

QSAR studies

The structures of 1-20 were first pre-optimized with the Molecular Mechanics Force Field (MM) procedure included in Hyperchem 6.03 [31] And the resulting geometries were further developed by means of the semiempirical method PM3 (Parametric Method-3). A gradient norm limit of 0.01 kcal/A° was taken into consideration for the geometry optimization. The lowest energy structure was used for each individual molecule to calculate physicochemical properties using TSAR 3.3 software for Windows [32]. Further, the regression analysis was performed using the SPSS software package [33].

Conclusion

A series of novel compounds was synthesized and characterized using elemental analyses, various spectroscopic techniques like UV, IR and (1H, 13C and 119Sn) NMR. The substituted o-vanillin Schiff bases and their organotin(IV) complexes were screened for antimicrobial activity against representative microorganisms and the compounds evaluated had inhibited the growth of all the tested bacterial and fungal strains. The complexes were found to be more active antimicrobial agent in comparison to the Schiff bases. The QSAR studies were carried out to find out the relationship between structural features and antimicrobial activity of synthesized deriv-
atives which revealed the fact that antimicrobial activity of these derivatives is governed by topological descriptors and electronic energy of the molecules.

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Conflict of interest

The authors declare that they have no conflict of interest.

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