Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(21):10-16
(http://www.derpharmachemica.com/archive.html)

Synthesis, Characterization and Antimicrobial Evaluation of Organotin (IV) Complexes Derived from Schiff Bases of Thiophene-2-carboxylic Acid Hydrazide

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ABSTRACT

The endeavour of the present work is to synthesize some biologically active Schiff bases and their organotin (IV) complexes derived from substituted o-vanillin and thiophene-2- carboxylic acid hydrazide. Organotin (IV) complexes were synthesized by reacting R_2SnCl_2 (Where, R=Ph, Bu, Et and Me) with ligands in 1:1 ratio in methanol as solvent. The biological activity of Schiff base ligands enhanced on complexation under similar experimental conditions. The newly synthesized compounds were characterized by elemental analyses, UV-Vis, IR and NMR (^1H, ^{13}C and ^{119}Sn) spectral techniques.

Keywords: Schiff bases, o-vanillin, Hydrazide, Organotin, Spectral techniques

INTRODUCTION

Schiff bases containing azomethine group (–RCH=N–) are obtained by the condensation of carbonyl group with primary amines. Schiff bases of aliphatic aldehyde groups are less stable and easily pollymerizable [1,2] as compared to one with aromatic aldehydes because of conjugation system in aromatic aldehydes [3-6]. Many Schiff base ligands of varied structural type have been synthesized owing to the enormous synthetic flexibility, due to easily tunable electronic and steric effect [7,8]. Schiff base ligands with bidentate and tetradentate binding ability containing both hard and soft donor groups have been used extensively in coordination and organometallic chemistry [9]. Schiff base ligands coordinate with metals through imine nitrogen and another group usually linked to aldehyde to form coordination compounds with varied stereochemistry. The coordination compounds have active sites for metalloenzymes, so possess pronounced biological activities [10]. Organotin compounds are used as pharmaceuticals, antimicrobial (antibacterial, antifungal and antiviral), anti-inflammatory, anti-HIV agents, antifeedant, acaricides and antituberculosis agent [11-15]. One of the major applications of organotin complexes is as antitumor agents aiming toward the discovery of an effective and safe therapeutic regimen for the treatment of cancers.

The objectives of the present work are to evaluate structural features and *in vitro* antimicrobial activities of novel Schiff base complexes derived from substituted o-vanillin with thiophene-2-carboxylic acid hydrazide.

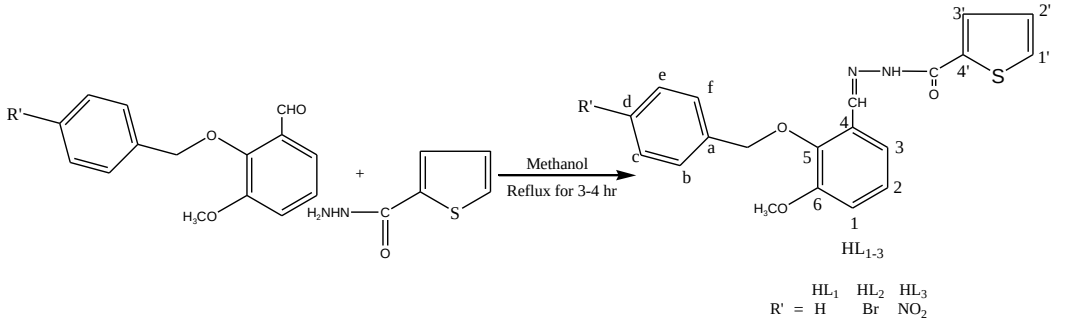
MATERIALS AND METHODS

All the experimental work was carried out under the dry nitrogen using vacuum line. All chemicals were procured from Aldrich and used as received without further purification. Solvents were purified according to the standard procedures. Anhydrous conditions were maintained throughout during the synthesis of the complexes, since the dichlorodiorganotin and their product complexes are highly moisture-sensitive. Molar conductance was measured in dry Dimethyl Sulfoxide (DMSO) with a conductivity bridge model-306 Systronics. Tin was estimated gravimetrically as SnO_2. IR spectra were recorded using Spectrum BX Series FTIR spectrophotometer using KBr pellets in the range 4000-400 cm^{-1}. ^1H, ^{13}C and ^{119}Sn-NMR were recorded on Bruker Avance II 400 MHz NMR Spectrometer and all chemical shifts (δ) are reported in part per million (ppm) relative to Tetramethylsilane (TMS) as an internal standard in $CDCl_3$ and DMSO.

Synthesis of Schiff base ligands (HL_1-HL_3) were carried out in the following steps

Synthesis of 2-Benzyloxy-3-methoxy-benzaldehyde and 2-(4-Bromo/Nitro-benzyloxy)-3-methoxy-benzaldehyde: Mixture of hydroxy benzaldehyde (10 mmol), alkyl halide (benzyl bromide and bromo/nitro benzyl bromide) 10 mmol and K_2CO_3 (20 mmol) were taken in 25 ml of Dimethyl Formamide (DMF) and the reaction mixture was stirred overnight. The reaction mixture was then quenched with ice followed by the addition of water. The solid product obtained was filtered over the vacuum pump and dried. The progress of reaction was checked through Thin Layer Chromatography and the visualization was accomplished with UV light.

Synthesis of Schiff base ligands (HL_1-HL_3): Schiff base ligand Thiophene-2-carboxylic acid (2-benzyloxy-3-methoxy-benzaldehyde) hydrazide [HL_1] was synthesized by dissolving 2-benzyloxy-3-methoxy-benzaldehyde (substituted o-vanillin) and thiophene-2-carboxylic acid hydrazide in 1:1 molar ratio in methanol. The reaction mixture was refluxed for 3-4 h and the progress of reaction was checked by thin layer chromatography. After the completion of reaction, the solid product precipitated out was filtered and recrystallized in hot methanol. The similar procedure was adopted to synthesize HL_2 and HL_3 Schiff base ligand (Scheme 1).



Scheme 1: Synthetic route for HL_{1-3}

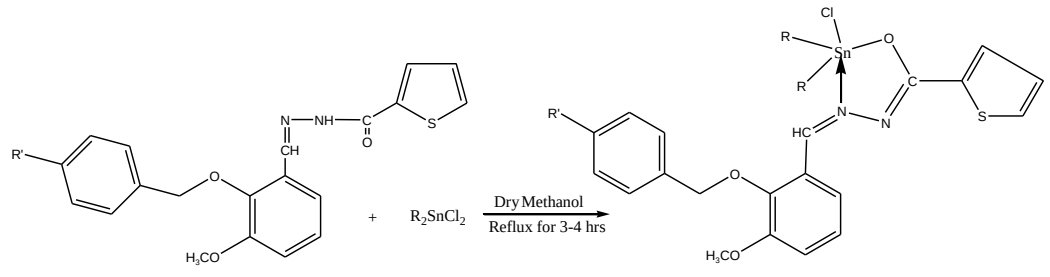
Thiophene-2-carboxylic acid (2-benzyloxy-3-methoxy-benzaldehyde)-hydrazide: (1, HL_1, $C_{20}H_{18}N_2O_3S$); Yield: 81%; IR (KBr): ν=3380 (NH), ν=1680 (C=O), ν=1565 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.15 (s, 1H, -CH=N), 9.01 (s, 1H, -NH), 8.65-8.72 (d, 1H, $C_{1'}$-H), 8.17-8.19 (d, 1H, $C_{3'}$-H), 7.62-7.66 (m, 1H, $C_{2'}$-H), 7.24-7.37 (m, 5H, Aromatic), 7.05-7.07 (d, 1H, C_3-H), 6.95-6.99 (m, 2H, C_1-H & C_2-H), 4.96 (s, 2H, -OCH_2), 3.87 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=165.54 (C=O), 158.32 (C=N), 152.89 (C-5), 149.16 (C-6), 145.29 (C-4'), 143.61 (C-a), 142.16 (C-d), 138.52 (C-3'), 135.75 (C-1'), 133.08 (C-2'), 131.18 (C-c & C-e), 129.23 (C-b & C-f), 127.58 (C-3), 123.78 (C-2), 117.42 (C-4), 114.07 (C-1), 75.51 (OCH_2), 54.78 (OCH_3) ppm.

Thiophene-2-carboxylic acid [2-(4-bromo-benzyloxy)-3-methoxy-benzylidene]-hydrazide (2, HL_2, $C_{20}H_{17}BrN_2O_3S$): Yield: 84%; IR (KBr): ν=3384 (NH), ν=1685 (C=O), ν=1569 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=12.01 (s, 1H, -CH=N), 9.27 (s, 1H, -NH), 8.91-8.92 (d, 1H, $C_{1'}$-H), 8.73-8.75 (d, 1H, $C_{3'}$-H), 8.24-8.27 (m, 1H, $C_{2'}$-H), 7.76-7.81 (m, 4H, Aromatic), 7.51-7.52 (d, 1H, C_3-H), 7.15-7.18 (m, 2H, C_1-H & C_2-H), 5.17 (s, 2H, -OCH_2), 3.88 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=163.20 (C=O), 152.32 (C=N), 146.99 (C-5), 146.03 (C-6), 144.70 (C-4'), 142.92 (C-a), 141.60 (C-d), 130.41 (C-3'), 128.70 (C-1'), 128.45 (C-2'), 128.13 (C-c & C-e), 127.55 (C-b & C-f), 124.43 (C-3), 123.18 (C-2), 117.36 (C-4), 113.64 (C-1), 73.42 (OCH_2), 55.60 (OCH_3) ppm.

Thiophene-2-carboxylic acid [2-(4-nitro-benzyloxy)-3-methoxy-benzylidene]-hydrazide (3, HL_3, $C_{20}H_{17}N_3O_5S$): Yield: 78%; IR (KBr): ν=3390 (NH), ν=1689 (C=O), ν=1573 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.97 (s, 1H, -CH=N), 9.30 (s, 1H, -NH), 9.18-9.20 (d, 1H, $C_{1'}$-H), 9.03-9.05 (d, 1H, $C_{3'}$-H), 8.72-8.75 (m, 1H, $C_{2'}$-H), 8.23-8.27 (m, 4H, Aromatic), 7.76-7.78 (d, 1H, C_3-H), 7.52-7.55 (m, 2H, C_1-H & C_2-H), 5.17 (s, 2H, -OCH_2), 3.88 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=162.28 (C=O), 155.17 (C=N), 151.46 (C-5), 148.22 (C-6), 146.34 (C-4'), 145.06 (C-a), 143.42 (C-d), 139.83 (C-3'), 136.64 (C-1'), 135.46 (C-2'), 133.24 (C-c & C-e), 130.14 (C-b & C-f), 128.80 (C-3), 125.63 (C-2), 117.08 (C-4), 113.68 (C-1), 74.68 (OCH_2), 55.63 (OCH_3) ppm.

Synthesis of complexes

All the organotin (IV) complexes were synthesized in inert atmosphere under dry nitrogen. The Schiff base ligand and triethylamine was dissolved in dry methanol in 1:1 molar ratio and refluxed for 4 h. Then the weighed amount of dichlorodiorganotin was dissolved in dry methanol and slowly added drop wise in 1:1 ratio. The resulting mixture was refluxed for 4 h after which the Et_3NHCl formed during the reaction was removed by filtration and the excess solvent was evaporated under vacuum. The compound was repetitively washed with dry hexane and the solid obtained was recrystallized with a mixture of dry methanol and dry hexane to make sure the purity of compound. The compound was finally dried under reduced pressure. The entire series of organotin (IV) complexes with Schiff base ligands were synthesized by using the same procedure (Scheme 2).



Scheme 2: Synthetic route for compounds 4-15

(4, $Me_2Sn(L_1)Cl$, $C_{22}H_{23}ClN_2O_3SSn$): Yield: 85%; IR (KBr): ν=1568 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.50 (s, 1H, -CH=N), 8.83-8.84 (d, 1H, $C_{1'}$-H), 8.59-8.60 (d, 1H, $C_{3'}$-H), 7.75-7.79 (m, 1H, $C_{2'}$-H), 7.40-7.46 (m, 4H, Aromatic), 7.14-7.16 (d, 1H, C_3-H), 7.03-7.07 (m, 2H, C_1-H & C_2-H), 5.11 (s, 2H, -OCH_2), 3.94 (s, 3H, -OCH_3), 1.69 (s, 6H, -CH_3) ppm; ^{13}C-NMR: δ=155.58 (C=O), 152.39 (C=N), 148.61 (C-5), 147.17 (C-6), 145.94 (C-4'), 141.58 (C-a), 138.84 (C-d), 136.31 (C-3'), 132.44 (C-1'), 128.35 (C-2'), 126.67 (C-c & C-e), 125.03 (C-b & C-f), 127.26 (C-3), 123.39 (C-2), 117.62 (C-4), 114.19 (C-1)77.50 (OCH_2), 56.06 (OCH_3), 8.58 (Me) ppm.

(5, $Et_2Sn(L_1)Cl$, $C_{24}H_{27}ClN_2O_3SSn$): Yield: 85%; IR (KBr): ν=1568 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.92 (s, 1H, -CH=N), 8.77-8.78 (d, 1H, $C_{1'}$-H), 8.21-8.22 (d, 1H, $C_{3'}$-H), 7.74-7.77 (m, 1H, $C_{2'}$-H), 7.28-7.39 (m, 5H, Aromatic), 7.05-7.07 (d, 1H, C_3-H), 6.85-6.88 (m, 2H, C_1-H & C_2-H), 5.00 (s, 2H, -OCH_2), 3.78(s, 3H, -OCH_3), 3.07-3.12 (m, 4H, -CH_2), 1.18-1.22 (t, 6H, -CH_3) ppm; ^{13}C-NMR: δ=156.32 (C=O), 154.78 (C=N), 153.11 (C-5), 149.07 (C-6), 147.63 (C-4'), 145.30 (C-a), 143.19 (C-d), 139.22 (C-3'), 135.36 (C-1'), 133.41 (C-2'), 131.83 (C-c & C-e), 128.26 (C-b & C-f), 125.08 (C-3), 123.14 (C-2), 117.32 (C-4), 114.03 (C-1), 78.03 (OCH_2), 55.42 (OCH_3), 13.26 (Et), 8.55 (Et) ppm.

(6, $Bu_2Sn(L_1)Cl$, $C_{28}H_{35}ClN_2O_3SSn$): Yield: 84%; IR (KBr): ν=1571 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.78 (s, 1H, -CH=N), 8.82-8.83 (d, 1H, $C_{1'}$-H), 8.19-8.21 (d, 1H, $C_{3'}$-H), 7.73-7.76 (m, 1H, $C_{2'}$-H), 7.27-7.39 (m, 5H, Aromatic), 7.03-7.06 (d, 1H, C_3-H), 6.87-6.90 (m, 2H, C_1-H & C_2-H), 4.97 (s, 2H, -OCH_2), 3.85 (s, 3H, -OCH_3), 3.08-3.11 (t, 4H, -CH_2), 1.20-1.23 (m, 8H, -CH_2), 1.05-1.11(t, 6H, -CH_3) ppm; ^{13}C-NMR: δ=155.27 (C=O), 152.14 (C=N), 149.26 (C-5), 148.45 (C-6), 145.24 (C-4'), 141.19 (C-a), 139.06 (C-d), 137.32 (C-3'), 133.40 (C-1'), 131.16 (C-2'), 129.72 (C-c & C-e), 128.14 (C-b & C-f), 125.39 (C-3), 124.09 (C-2), 117.51 (C-4), 113.68 (C-1), 77.51 (OCH_2), 58.61 (OCH_3), 28.13 (Bu), 24.43 (Bu), 14.28 (Bu), 8.22 (Bu) ppm.

(7, $Ph_2Sn(L_1)Cl$, $C_{32}H_{27}ClN_2O_3SSn$): Yield: 87%; IR (KBr): ν=1571 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.81 (s, 1H, -CH=N), 8.85-8.86 (d, 1H, $C_{1'}$-H), 8.16-8.17 (d, 1H, $C_{3'}$-H), 7.72-7.75 (m, 1H, $C_{2'}$-H), 7.24-7.37 (m, 5H, Aromatic), 7.03-7.27 (m, 10H Ph and 3H, C_1-H, C_2-H & C_3-H), 4.98 (s, 2H, -OCH_2), 3.88 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=156.11 (C=O), 153.27 (C=N), 148.26 (C-5), 146.29 (C-6), 143.16 (C-4'), 141.23 (C-a), 138.37 (C-d), 135.92 (C-3'), 132.66 (C-1'), 131.73 (C-2'), 129.89 (C-c & C-e), 128.81 (Ph), 128.65 (Ph), 128.56 (Ph), 128.50 (Ph), 128.08 (C-b & C-f), 125.41 (C-3), 123.15 (C-2), 117.14 (C-4), 113.88 (C-1), 75.53 (OCH_2), 56.42 (OCH_3) ppm.

(8, $Me_2Sn(L_2)Cl$, $C_{22}H_{22}BrClN_2O_3SSn$): Yield: 86%; IR (KBr): ν=1566 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.87 (s, 1H, -CH=N), 8.75-8.76 (d, 1H, $C_{1'}$-H), 8.18-8.20 (d, 1H, $C_{3'}$-H), 7.75-7.78 (m, 1H, $C_{2'}$-H), 7.26-7.38 (m, 5H, Aromatic), 7.03-7.07 (d, 1H, C_3-H), 6.94-6.97 (m, 2H, C_1-H & C_2-H), 4.99 (s, 2H, -OCH_2), 3.84 (s, 3H, -OCH_3), 1.68 (s, 6H, -CH_3) ppm; ^{13}C-NMR: δ=157.28 (C=O), 155.28 (C=N), 149.92 (C-5), 147.25 (C-6), 145.18 (C-4'), 144.24 (C-a), 141.25 (C-d), 139.27 (C-3'), 136.33 (C-1'), 135.01 (C-2'), 132.26 (C-c & C-e), 129.38 (C-b & C-f), 127.62 (C-3), 124.28 (C-2), 117.28 (C-4), 113.66 (C-1), 75.35 (OCH_2), 54.66 (OCH_3), 8.64 (Me) ppm.

(9, $Et_2Sn(L_2)Cl$, $C_{24}H_{26}BrClN_2O_3SSn$): Yield: 74%; IR (KBr): ν=1565 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=12.02 (s, 1H, -CH=N), 9.05-9.08 (d, 1H, $C_{1'}$-H), 8.72-8.74 (d, 1H, $C_{3'}$-H), 8.24-8.27 (m, 1H, $C_{2'}$-H), 7.49-7.55 (m, 4H, Aromatic), 7.41-7.42 (d, 1H, C_3-H), 7.11-7.14 (m, 2H, C_1-H & C_2-H), 4.98 (s, 2H, -OCH_2), 3.88 (s,3H, -OCH_3), 3.05-3.11 (m, 4H,-CH_2), 1.20-1.24 (t, 6H, -CH_3) ppm; ^{13}C-NMR: δ=155.62 (C=O), 151.54 (C=N), 146.39 (C-5), 143.28 (C-6), 141.57 (C-4'), 137.19 (C-a), 133.89 (C-d), 130.51 (C-3'), 128.77 (C-1'), 128.66 (C-2'), 128.48 (C-c & C-e), 128.38 (C-b & C-f), 127.66 (C-3), 124.09 (C-2), 117.17 (C-4), 113.74 (C-1), 74.70 (OCH_2), 55.65 (OCH_3), 12.28 (Et), 8.47 (Et) ppm.

(10, $Bu_2Sn(L_2)Cl$, $C_{28}H_{34}BrClN_2O_3SSn$): Yield: 86%; IR (KBr): ν=1569 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.55 (s, 1H, -CH=N), 8.78-8.79 (d, 1H, $C_{1'}$-H), 8.62-8.63 (d, 1H, $C_{3'}$-H), 7.78-7.82 (m, 1H, $C_{2'}$-H), 7.37-7.45 (m, 4H, Aromatic), 7.16-7.18 (d, 1H, C_3-H), 7.05-7.09 (m, 2H, C_1-H & C_2-H), 4.98 (s, 2H, -OCH_2), 3.97 (s, 3H, -OCH_3), 3.10-3.13 (t, 4H, -CH_2), 1.16-1.19 (m, 8H, -CH_2), 1.03-1.10 (t, 6H, -CH_3) ppm; ^{13}C-NMR: δ=156.04 (C=O), 152.35 (C=N), 147.45 (C-5), 142.38 (C-6), 138.64 (C-4'), 136.27 (C-a), 132.81 (C-d), 129.91 (C-3'), 128.68 (C-1'), 125.05 (C-2'), 123.89 (C-c & C-e), 123.32 (C-b & C-f), 122.17 (C-3), 120.98 (C-2), 117.42 (C-4), 113.94 (C-1), 73.34 (OCH_2), 55.01 (OCH_3), 27.88 (Bu), 25.16 (Bu), 15.08 (Bu), 8.31 (Bu) ppm.

(11, $Ph_2Sn(L_2)Cl$, $C_{32}H_{26}BrClN_2O_3SSn$): Yield: 77%; IR (KBr): ν=1570 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=10.72 (s, 1H, -CH=N), 8.86-8.87 (d, 1H, $C_{1'}$-H), 8.78-8.79 (d, 1H, $C_{3'}$-H), 7.76-7.80 (m, 1H, $C_{2'}$-H), 7.37-7.45 (m, 4H, Aromatic), 7.01-7.25 (m, 10H Ph and 3H, C_1-H, C_2-H & C_3-H), 4.98 (s, 2H, -OCH_2), 3.97 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=155.55 (C=O), 151.65 (C=N), 147.18 (C-5), 146.42 (C-6), 145.14 (C-4'), 141.79 (C-a), 139.25 (C-d), 136.31 (C-3'), 135.28 (C-1'), 129.94 (C-2'), 128.85 (Ph), 128.71 (Ph), 128.64 (Ph), 128.48 (Ph), 127.87 (C-c & C-e), 125.15 (C-b & C-f), 123.46 (C-3), 123.05 (C-2), 116.92 (C-4), 114.06 (C-1), 78.63 (OCH_2), 58.42 (OCH_3) ppm.

(12, $Me_2Sn(L_3)Cl$, $C_{22}H_{22}ClN_3O_5SSn$): Yield: 89%; IR (KBr): ν=1567 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.85 (s, 1H, -CH=N), 8.88-8.90 (d, 1H, $C_{1'}$-H), 8.73-8.74 (d, 1H, $C_{3'}$-H), 8.69-8.71 (m, 1H, $C_{2'}$-H), 8.26-8.30 (m, 4H, Aromatic), 7.82-7.83 (d, 1H, C_3-H), 7.53-7.56 (m, 2H, C_1-H & C_2-H), 5.03 (s, 2H, -OCH_2), 3.89 (s, 3H, -OCH_3), 1.73(s, 6H, -CH_3) ppm; ^{13}C-NMR: δ=157.19 (C=O), 153.75 (C=N), 146.24 (C-5), 144.39 (C-6), 141.46 (C-4'), 138.35 (C-a), 135.33 (C-d), 132.12 (C-3'), 129.63 (C-1'), 124.86 (C-2'), 123.05 (C-c & C-e), 122.78 (C-b & C-f), 122.15 (C-3), 121.80 (C-2), 117.15 (C-4), 114.07 (C-1), 75.38 (OCH_2), 54.24 (OCH_3), 8.63 (Me) ppm.

(13, $Et_2Sn(L_3)Cl$, $C_{24}H_{26}ClN_3O_5SSn$): Yield:78 %; IR (KBr): ν=1572 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.82 (s, 1H, -CH=N), 8.87-8.88 (d, 1H, $C_{1'}$-H), 8.74-8.75 (d, 1H, $C_{3'}$-H), 8.67-8.70 (m, 1H, $C_{2'}$-H), 8.25-8.29 (m, 4H, Aromatic), 7.77-7.78 (d, 1H, C_3-H), 7.55-7.58 (m, 2H, C_1-H & C_2-H), 5.01 (s, 2H, -OCH_2), 3.87 (s, 3H, -OCH_3), 3.06-3.10 (m, 4H,-CH_2), 1.23-1.26 (t, 6H,-CH_3) ppm; ^{13}C-NMR: δ=155.25 (C=O), 152.31 (C=N), 148.33 (C-5), 145.29 (C-6), 141.57 (C-4'), 139.08 (C-a), 134.78 (C-d), 132.64 (C-3'), 128.61 (C-1'), 125.42 (C-2'), 123.16 (C-c & C-e), 122.83 (C-b & C-f), 122.02 (C-3), 121.85 (C-2), 117.53 (C-4), 113.87 (C-1), 76.44 (OCH_2), 54.61 (OCH_3), 12.61 (Et), 8.54 (Et) ppm.

(14, $Bu_2Sn(L_3)Cl$, $C_{28}H_{34}ClN_3O_5SSn$): Yield: 82%; IR (KBr): ν=1568 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.78 (s, 1H, -CH=N), 8.85-8.86 (d, 1H, $C_{1'}$-H), 8.77-8.78 (d, 1H, $C_{3'}$-H), 8.65-8.69 (m, 1H, $C_{2'}$-H), 8.28-8.32 (m, 4H, Aromatic), 7.82-7.83 (d, 1H, C_3-H), 7.54-7.57 (m, 2H, C_1-H & C_2-H), 4.97 (s, 2H, -OCH_2), 3.88 (s, 3H, -OCH_3), 3.08-3.11 (t,4H, -CH_2), 1.21-1.24 (m, 8H, -CH_2), 1.07-1.11 (t, 6H, -CH_3) ppm; ^{13}C-NMR: δ=155.03 (C=O), 153.33 (C=N), 146.67 (C-5), 144.35 (C-6), 142.59 (C-4'), 138.46 (C-a), 136.52 (C-d), 134.48 (C-3'), 129.95 (C-1'), 127.11 (C-2'), 125.06 (C-c & C-e), 123.91 (C-b & C-f), 123.13 (C-3), 121.74 (C-2), 117.31 (C-4), 114.07 (C-1), 75.39 (OCH_2), 56.38 (OCH_3), 26.65 (Bu), 25.13 (Bu), 16.22 (Bu), 8.48 (Bu) ppm.

(15, $Ph_2Sn(L_3)Cl$, $C_{32}H_{26}ClN_3O_5SSn$): Yield: 89%; IR (KBr): ν=1572 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=11.85 (s,1H, -CH=N), 8.88-8.89 (d, 1H, $C_{1'}$-H), 8.80-8.81 (d, 1H, $C_{3'}$-H), 8.67-8.69 (m, 1H, $C_{2'}$-H), 8.25-8.29 (m, 4H, Aromatic), 7.84-7.85 (d, 1H, C_3-H), 7.52-7.55 (m, 2H, C_1-H & C_2-H), 7.03-7.27 (m, 10H, Ph), 5.03 (s, 2H, -OCH_2), 3.89 (s, 3H, -OCH_3) ppm; ^{13}C-NMR: δ=156.42 (C=O), 152.26 (C=N), 147.46 (C-5), 143.41 (C-6), 140.78 (C-4'), 138.57 (C-a), 136.66 (C-d), 135.45 (C-3'), 133.12 (C-1'), 131.20 (C-2'), 128.96 (C-c & C-e), 128.78 (Ph), 128.70 (Ph), 128.64 (Ph), 128.56 (Ph), 125.31 (C-b & C-f), 122.91 (C-3), 122.04 (C-2), 117.37 (C-4), 113.59 (C-1), 77.50 (OCH_2), 54.93 (OCH_3) ppm.

Biological activity

Microbial strains

Gram-positive bacteria (*viz. K. pneumoniae* NCDC No. 138, *S. aureus* MTCC No. 3160, Gram-negative bacteria (*viz. E. coli* MTCC No. 443, *E. aerogenes* NCDC No. 106) and fungi (*A. niger* MTCC No.282, *C. albicans* MTCC No. 227) were used for antimicrobial assay.

In vitro antimicrobial assay

The synthesized ligands and their corresponding complexes were evaluated for *in vitro* antimicrobial activity against bacterial and fungal strains by using serial dilution technique and MIC were calculated to determine the inhibitory effect of tested compounds. Stock solution was prepared by dissolving 1.0 mg of synthesized compounds in dry DMSO and was further diluted to give a stock solution of 100 µg/ml concentration. Set of five dilutions with test compounds having concentrations 50, 25, 12.5, 6.25 and 3.125 µg/ml were obtained. Medium was prepared by dissolving nutrient agar in 1 L of distilled water. The mixture was autoclaved for 15 min at 120°C. Target microorganism cultures were prepared separately in 15 ml of nutrient broth for activation. Inoculation was done with the help of micropipette with sterilized tips, 100 µl of activated strain was placed in tubes and then 100 µl of sterilized stock solution was poured in the tube and incubated at 37°C for 24 h for antibacterial, 48 h for *C. albicans* and 7 days at 25°C for *A. niger*. The inhibitory effect of all the compounds against the tested microbes was compared with standard drugs norfloxacin and fluconazole for antibacterial and antifungal activity, respectively. Each sample was assayed in triplicate and the concordant values were reported.

RESULTS AND DISCUSSION

Chemistry

The ligands (1-3) were prepared by the condensation of substituted o-vanilin and Thiophene-2-carboxylic acid hydrazide. Dichlorodiorganotin was reacted with the synthesized salt of Schiff base in dry methanol in 1:1 molar ratio. The homogeneity of the compounds was regularly monitored through TLC. The elemental analyses data of the synthesized compounds are in good agreement with the corresponding molecular formulae (Table 1).

Molar conductance

The molar conductance values of all the complexes (4-15) were observed at room temperature in DMSO and their results were recorded in $ohm^{-1}.cm^2.mol^{-1}$. Molar conductance values of the complexes were found to be in the range 7-12 $ohm^{-1}.cm^2.mol^{-1}$ suggesting their non-electrolytic nature [16].

Electronic spectra

The electronic spectra of Schiff base ligands and their complexes were recorded in DMSO. Electronic spectra give information about the environment around tin atom. Schiff base ligands HL_{1-3} exhibited a maxima at 388-391 nm, respectively, which may be assigned to the n-π* transition of the >C=N– group. In the complexes these bands showed blue shift because of the interaction among metal and ligand, which indicate the involvement of azomethine nitrogen. Some medium intensity bands at 240 nm, 247 nm and 260 nm due to π-π* transition of benzene ring of Schiff base ligands, which remained unchanged in the electronic spectra of organotin complexes [17].

Table 1: Physicochemical characterization and elemental analysis of organotin (IV) complexes with substituted o-vanillin and thiophene-2-carboxylic acid hydrazide Schiff bases

Compound No.	Compounds	Molecular formula	m/z	Yield (%)	Analysis (%), Found (Calcd.)			
					C	H	N	Sn
1	HL_1	$C_{20}H_{18}N_2O_3S$	366.10	81	65.55(65.07)	4.95(5.11)	7.64(7.82)	-
2	HL_2	$C_{20}H_{17}BrN_2O_3S$	444.01	84	53.94(53.23)	3.85 (4.15)	6.29(6.02)	-
3	HL_3	$C_{20}H_{17}N_3O_5S$	411.09	78	58.38(58.46)	4.16(4.21)	10.21(10.53)	-
4	$Me_2Sn(L_1)Cl$	$C_{22}H_{23}ClN_2O_3SSn$	550.01	86	48.07(45.88)	4.22(4.08)	5.10(4.88)	21.60(20.87)
5	$Et_2Sn(L_1)Cl$	$C_{24}H_{27}ClN_2O_3SSn$	577.71	85	49.90(49.21)	4.71(4.34)	4.85(5.03)	20.55(19.97)
6	$Bu_2Sn(L_1)Cl$	$C_{28}H_{35}ClN_2O_3SSn$	634.11	84	53.06(55.84)	5.57(5.64)	4.42(4.61)	18.73(18.26)
7	$Ph_2Sn(L_1)Cl$	$C_{32}H_{27}ClN_2O_3SSn$	674.05	87	57.04(56.78)	4.04(4.16)	4.16(3.92)	17.62(17.85)
8	$Me_2Sn(L_2)Cl$	$C_{22}H_{22}BrClN_2O_3SSn$	627.92	85	42.04(42.61)	4.44(4.61)	4.96(5.03)	20.18(20.81)
9	$Et_2Sn(L_2)Cl$	$C_{24}H_{26}BrClN_2O_3SSn$	655.96	74	43.90(43.13)	4.99(5.03)	4.27(4.56)	20.38(20.84)
10	$Bu_2Sn(L_2)Cl$	$C_{28}H_{34}BrClN_2O_3SSn$	712.71	86	47.19(47.31)	5.61(5.38)	4.93(4.55)	18.66(18.59)
11	$Ph_2Sn(L_2)Cl$	$C_{32}H_{26}BrClN_2O_3SSn$	751.96	77	51.06(51.42)	3.48(3.41)	3.72(3.23)	15.77(15.31)
12	$Me_2Sn(L_3)Cl$	$C_{22}H_{22}ClN_3O_5SSn$	595.00	89	44.44(44.27)	3.73(3.32)	7.07(6.96)	19.96(20.01)
13	$Et_2Sn(L_3)Cl$	$C_{24}H_{26}ClN_3O_5SSn$	623.03	78	46.29(46.38)	4.21(3.99)	6.75(6.52)	19.06(18.88)
14	$Bu_2Sn(L_3)Cl$	$C_{28}H_{34}ClN_3O_5SSn$	679.09	82	49.54(49.22)	5.05(5.11)	6.19(6.34)	17.49(17.62)
15	$Ph_2Sn(L_3)Cl$	$C_{32}H_{26}ClN_3O_5SSn$	719.03	89	53.47(53.61)	3.65(3.45)	5.85(6.05)	16.52(16.38)

IR spectra

The infrared spectra of the complexes were compared with that of the Schiff base ligands to determine the coordination sites of the ligand. The changes in the electronic environment of the ligands after the formation of Sn-N and Sn-O bonds was determined on the basis of shifts in the frequency of various groups and the absence of certain bands. In the spectra of the ligands, a strong band at 1680-1689 cm^{-1} [18] and 3380-3390 cm^{-1} were due to *ν* (C=O) and *ν* (N-H) bands, respectively indicating the ketonic nature of ligand in free state and disappearance of these bands in the spectra of complexes suggested enolization of the ligand after deprotonation on coordination with tin metal. A sharp band at 1565-1573 cm^{-1} assigned to azomethine *ν* (C=N) group in Schiff base ligands was shifted to lower frequency in the complexes, indicating the donation of the lone pair of electrons from azomethine nitrogen to tin metal. The appearance of some new bands in the range 455-467 and 538-566 were due to *ν*(Sn-N) and *ν*(Sn-O) modes respectively, further confirmed the involvement of oxygen and nitrogen atom in the bond formation with tin metal. The IR bands are given in the experimental part.

^{1}H-NMR spectra

The coordinating modes of the Schiff base ligands were also confirmed by recording ^{1}H-NMR spectra of the ligands and their organotin (IV) complexes in $CDCl_3$ and DMSO-d_6. ^{1}H-NMR signals were assigned on the basis of chemical shift values and intensity pattern. In the spectra of the free ligands the signals at 9.01-9.30 ppm were exhibited by NH proton, which disappeared in spectra of the complexes indicating deprotonation of NH (Via enolization). The azomethine proton showed a sharp singlet at 11.97-12.01 ppm and shifted to lower value in the complexes suggested the participation of azomethine proton in bond formation [19]. Aromatic and aliphatic protons of ligands appeared in the range 7.24-8.27 ppm and 3.87-5.17 ppm respectively and the position of these signals remained same in the spectra of complexes, suggested

non-involvement of these protons in bond formation. Further formation of complexes was supported by appearance of new signals at 1.68-1.73 ppm, 1.18-3.12 ppm, 1.03-3.13 ppm and 7.01-7.27 ppm due to methyl, ethyl, butyl and phenyl protons directly attached to tin atom. The data is given in the experimental part.

^{13}C-NMR spectra

In the ^{13}C-NMR spectra of the ligands, carbon of carbonyl and azomethine group appeared at 162.28-165.54 ppm and 152.32-158.32 ppm respectively, which shifted towards lower values in the complexes, indicated participation of carbonyl and azomethine carbon in bond formation [20]. Signals due to aromatic carbons of ligands observed in the range 113.64-152.89 ppm and aliphatic carbons appeared at 54.78-75.51 ppm. The signal due to the carbons of the methyl, ethyl and n-butyl groups attached to the tin atom appeared in the range of 8.58-8.63 ppm, 8.47-13.26 ppm and 8.28-28.13 ppm. The peaks due to the carbons of phenyl ring attached to the tin atom appeared in the range 128.48-128.85 ppm. The ^{13}C shifts are given in the experimental part.

^{119}Sn-NMR spectra

The ^{119}Sn chemical shift values for all the organotin (IV) complexes were found to be in the range -142.63 to -162.14 with respect to TMS, indicated penta-coordinated geometry around the tin atom (Figure 1) [21].

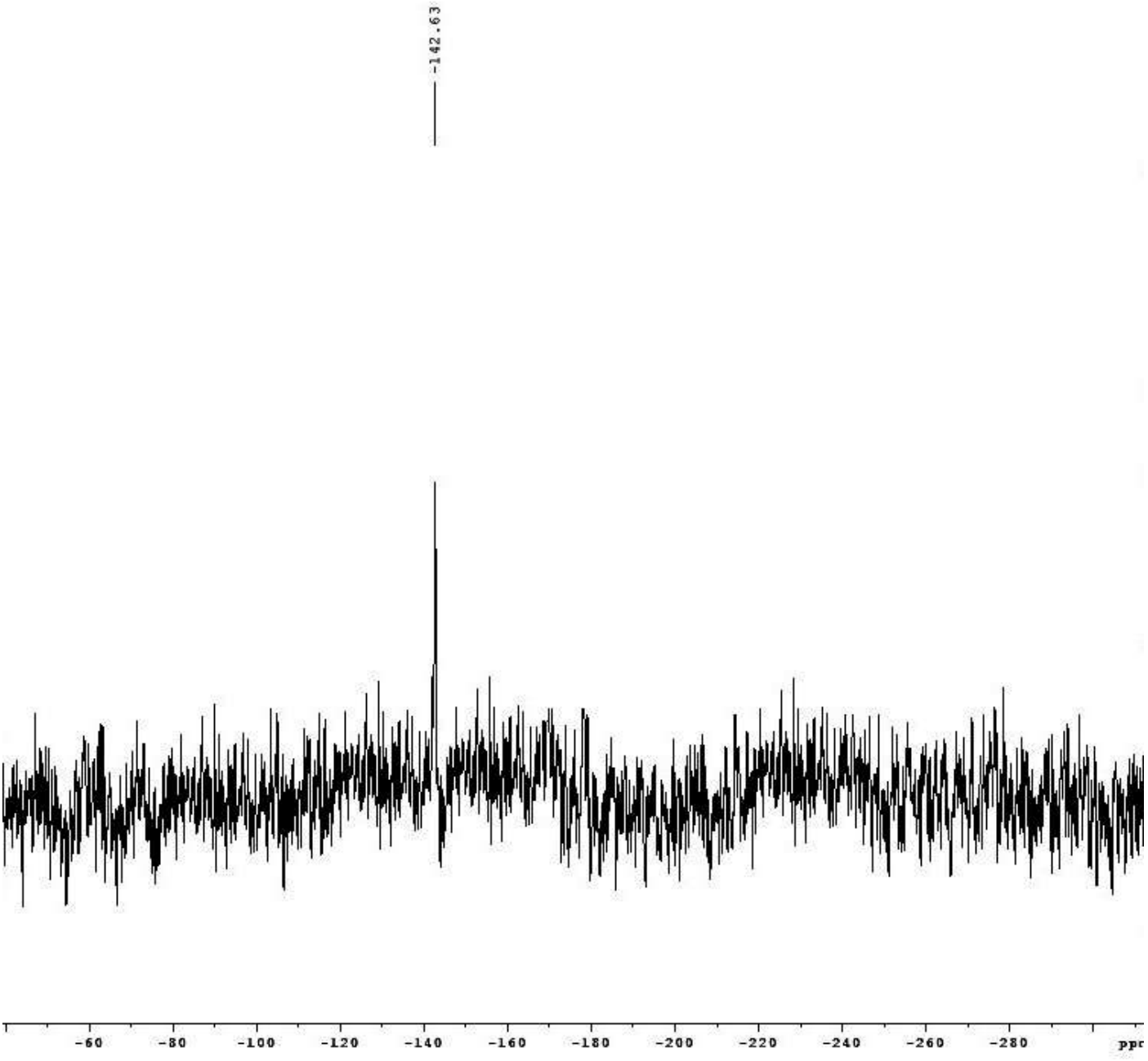


Figure 1: ^{119}Sn-NMR of Bu_2SnClL_2

Antimicrobial evaluation

The ligands and their organotin (IV) complexes were tested for *in vitro* antimicrobial activity against two Gram-positive bacteria *viz. Klebsiella pneumoniae* and *Staphylococcus aureus*, two Gram-negative bacteria *viz. Escherichia coli* and *Enterobacter aerogenes* and two fungal strains

Aspergillus niger and Candida albicans. The antimicrobial activity of the synthesized compounds was evaluated by serial dilution method and MICs were determined in terms of µg/ml (Table 2). The graphical representation for antimicrobial activity is given in Figure 2. DMSO was used as negative control and produced no visible inhibitory effect on growth, whereas norfloxacin and fluconazole were used as positive controls for antibacterial and antifungal activity, respectively.

The obtained antimicrobial results suggested that:

- Most of the compounds exhibited moderate to good activity against all the tested bacterial and fungal strains. The biological activity of these compounds might be due to the presence of azomethine group, which conveyed some transformation reaction in the biological system.
- The activity of complexes got increased as compared to their respective ligands under the similar experimental conditions. The enhancement in the biological activity of complexes was explained on the basis of Overtone's concept of cell permeability and chelation theory [22-24].
- Among the synthesized compounds phenyl derivatives were found to be more active with lowest MIC as compared to other derivatives against all the microbial strains [25-28]. This difference in the activity may be due to the bulkiness of substituent R, which increases the lipophilicity coupled with the polarity of metal carbon bond, which increase the activity of these complexes. In addition, phenyl group exhibited π–π interaction, which plays an important role in increasing the bioactivity. Hence the trend of biological activity in the entire series was Ph > Bu > Et > Me.
- On the basis of these results the compound 7, 10, 11, 14 and 15 exhibited highest activity in the series and compound 15 was found to be the highly active with lowest minimum MIC (6.25 µg/ml) for all the strains in the biological assay.

Table 2: Antimicrobial activity (MIC in µg/ml) of organotin (IV) complexes with substituted o-vanillin and thiophene-2-carboxylic acid hydrazide Schiff bases

Compound No.	Compounds	MIC (µg/ml)					
		Gram-positive bacteria		Gram-negative bacteria		Fungus	
		Staphylococcus aureus	*Klebsiella pneumonia*	*Escheriea coli*	*Enterobacter aerogenes*	*Candida albicans*	*Aspergillus niger*
1	HL_1	50	25	25	50	50	25
2	HL_2	50	25	25	50	25	25
3	HL_3	25	25	25	25	25	25
4	$Me_2Sn(L_1)Cl$	25	25	25	50	25	25
5	$Et_2Sn(L_1)Cl$	25	12.5	25	25	25	12.5
6	$Bu_2Sn(L_1)Cl$	12.5	12.5	12.5	25	12.5	6.25
7	$Ph_2Sn(L_1)Cl$	12.5	6.25	6.25	12.5	12.5	6.25
8	$Me_2Sn(L_2)Cl$	25	25	25	25	25	12.5
9	$Et_2Sn(L_2)Cl$	12.5	12.5	12.5	25	25	12.5
10	$Bu_2Sn(L_2)Cl$	12.5	6.25	6.25	12.5	12.5	6.25
11	$Ph_2Sn(L_2)Cl$	6.25	6.25	6.25	12.5	12.5	6.25
12	$Me_2Sn(L_3)Cl$	25	12.5	25	25	25	12.5
13	$Et_2Sn(L_3)Cl$	12.5	12.5	12.5	12.5	25	12.5
14	$Bu_2Sn(L_3)Cl$	6.25	6.25	6.25	12.5	12.5	6.25
15	$Ph_2Sn(L_3)Cl$	6.25	6.25	6.25	6.25	12.5	6.25
16	Fluconazole	-	-	-	-	12.5	3.12
17	Norfloxacin	12.5	12.5	12.5	25	-	-

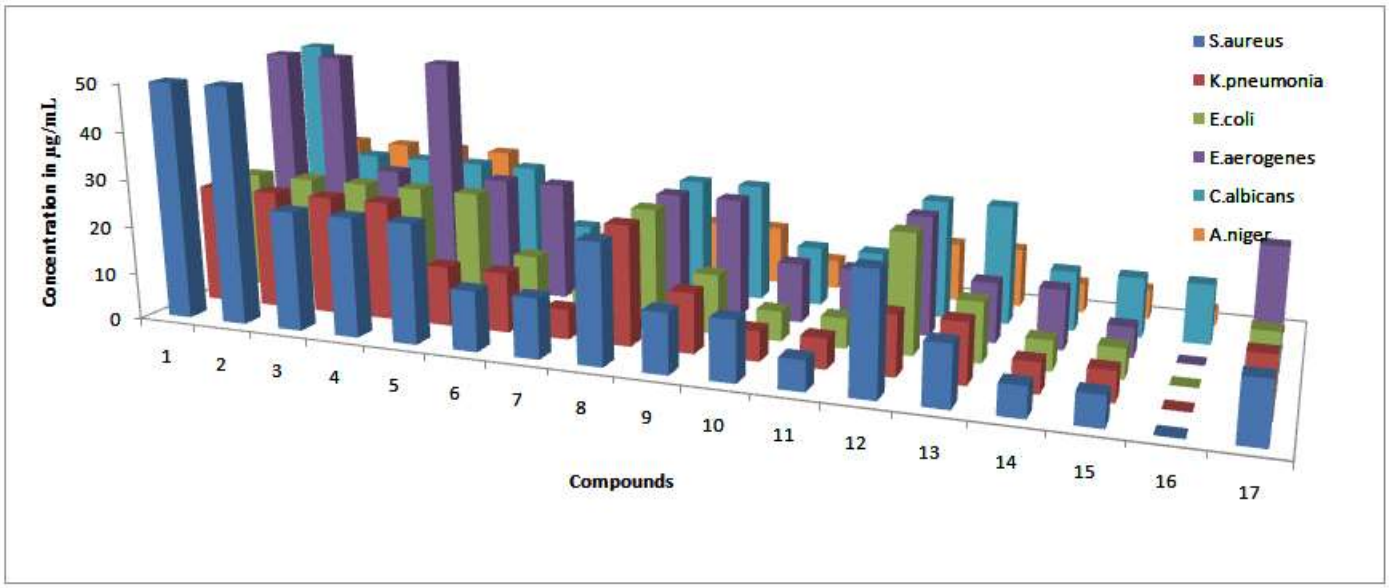


Figure 2: Graphical representation for antimicrobial activity of synthesized compounds

CONCLUSIONS

In present study, 15 new compounds were synthesized successfully and characterized using various spectral techniques (UV-Vis, IR, ^{1}H, ^{13}C and ^{119}Sn-NMR). The spectral studies revealed pentacoordinated geometry around tin metal in all the complexes where Schiff base coordinates through oxygen and nitrogen with metal. The synthesized compounds were tested against the microbial strains. Almost all the compounds exhibited good antimicrobial activity but compound 7, 10, 11, 14 and 15 were found to be most potent antimicrobial agent against the tested strains.

ACKNOWLEDGEMENT

Ankit Ravesh is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for the financial support to the research.

Ethical statement

The authors declare that they have no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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