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in-vitro Antimicrobial activity of Pd(II) And Ni(II) Chiral Schiff Base Ligand Complexes

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ABSTRACT: Chiral Schiff base ligands (CSBLs) are synthesized in water as a green approach. Bis [(R,R/S,S)-2-(E)-(2-hydroxy-1-phenylalkylimino)methyl}phenoxide- κ^2 -N,O]Palladium(II)/Nickel(II) complexes (**PdL1-L4** and **NiL1-L4**) are prepared from these enantiopure CSBLs. Metal complexes of nickel(II) and Palladium(II) ions are characterized for their probable structures by spectroscopic techniques. All complexes are screened for their antimicrobial activity against some selected pathogenic bacteria (*Staphylococcus aureus*, *Escherichia coli*) and fungi (*Candida albicans*, *Aspergillus nigers*). Amongst the 8 complexes, **PdL1-PdL4** exhibited both antibacterial, antifungal activity and **NiL1-NiL4** exhibited moderate to good antifungal activity. **PdL2** and **PdL3** displayed excellent antibacterial and antifungal activities respectively.

KEYWORDS: Chiral Schiff base ligands, chiral complexes of nickel and palladium, Antimicrobial activity, enantiopure

I. INTRODUCTION

It is well established fact that Schiff bases had gained far attention since their premier introduction [1]. These are synthesised as multifunctional compounds and possess a wide range of biological activities [2, 3]. Poly dentate Schiff bases have preparative accessibilities, structural variety, different coordination number and crystalline architectures [4, 5]. These are condensed products of primary amines and carbonyl compounds. Structural variation is feasible both in carbonyl and amine group containing organic moieties.

High selectivity of chiral molecules is paramount in entire biological features. Chirality determines the precise role in the fields of pharmaceutical, flavours, agrochemicals and fragrances [6]. Chirality can be incorporated conveniently into these molecules via amine component of condensing species, which preferentially include α -amino acids or β -amino alcohols, since they are found in optically pure form in the nature. The role of Schiff bases as a chelating agents in coordination chemistry is extensively studied due to formation of air stable transition metal complexes by them. These complexes exhibit biological, catalytic activities [7], and made noteworthy contribution to the field of magnetism and material sciences [8].

Although transition metal complexes of chiral Schiff base ligands (CSBLs) concisely fascinated in asymmetric organic transformations, recently there is emerging curiosity in the field of biochemical responses of inorganic metal complexes. As a result many research groups have focused their attention towards the bio-manifestations of chiral metal complexes [9-13].

Metal complexes of CSBLs are always superior to their corresponding ligands towards biological activity [14, 15]. This trend in biological activity of metal complexes enforces the urgent need to synthesize the metal complexes of CSBLs, which may coordinate through mixed donor (N, O) atoms. Coordination compounds of Co, Ni, Cu, Zn, Pd and Pt are extensively studied for their broad spectrum biological activities. Moderate to good antibacterial [16-18] and antifungal [14] activities are noticeable for Co, Ni, Cu, Zn and Pd complexes. Since after successful administration of cisplatin as a choice of drug in the treatment of cancer in humans, many researchers have screened Pd complexes for anticancer [19-21] and antitumor [22, 23] activities with more or less success. Along

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Vol. 5, Issue 1, January 2016

with Pd, salen type Zn complexes also had a potential to be an anticancer agent [24]. Chiral complexes of Cu shows better selectivity against certain phenotypes of all human cancer cells and DNA binding ability [25]. Nontoxic metal ions could be effective to deliver a chelating agent to target area due their coordination tendency and variable oxidation states [26]. The enhanced biological activity of metal complexes compared to isolated chelating agents is a new trend in bioinorganic chemistry. Structural variation, coordinating patterns, enantioselectivity of ligands and oxidation states of metal ions are utmost important parameters, which influence the biological activities of coordination compounds. Combined effect of these parameters on the antimicrobial activity of Pd (II) and Ni (II) complexes of CSBLs is studied in this report.

II. MATERIALS AND METHODS

2.1 General

All commercially available products were used without further purification unless otherwise specified. CSBLs were prepared by known procedure [27]. NMR spectra were recorded on 400MHz spectrometer in DMSO- d_6 with $(Me)_4Si$ as internal standard and chemical shifts recorded in δ units. Infrared spectra were recorded on FT-IR 8400 Shimadzu model as KBr discs. Elemental analysis was performed on Thermo flash microanalyzer with K factors calibration method. UV-VIS spectra were plotted on Shimadzu uv-1800 model.

2.2 Test microorganisms

Two bacterial species viz. *Staphylococcus aureus*, (Gram-positive) and *Escherichia coli* (Gram-negative) and two fungi, *Aspergillus niger*-mold and *Candida albicans*-yeast, the ear pathogens procured from Dept of Microbiology Haribhai V. Desai College, Pune,(India).

2.2.1 In-vitro antibacterial activity

The antibacterial activity of all chiral nickel (II) and palladium (II) complexes was evaluated by the agar well diffusion method [28], [29]. All the cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5×10^8 cfu /mL. The 20mL of Mueller Hinton agar medium was poured into each Petri plate and the agar plates were swabbed with 100 μ L inocula of each test bacterium and kept for 15 min for adsorption. Using sterile cork borer of 8mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 μ L volume with concentration of 5.0 mg/mL of each compound reconstituted in the methanol. All the plates were incubated at 37°C for 48 hrs. Antibacterial activity, indicated by an inhibition zone surrounding the well containing the compounds, was recorded if the zone of inhibition was greater than 8 mm. The experiments were performed in triplicate. Methanol was used as a negative control whereas streptomycin (100 μ g/mL) was used as a positive control.

2.2.2 In-vitro antifungal activity

Antifungal activity of Ni L1-Ni L4, PdL1-PdL4 was evaluated by the agar well diffusion method [28], [29]. All the cultures were adjusted to approximately 1.5×10^8 spores/mL. The 20mL of Sabouraud's dextrose agar (SDA) was poured into each Petri plate and the agar plates were swabbed with 100 μ L inocula of each test fungus and kept for 15 min for adsorption. Using sterile cork borer of 8mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 μ L volume with concentration of 5.0 mg/mL of each compound reconstituted in the methanol. All the plates were incubated at 25°C for 7 days. Antifungal activity, indicated by an inhibition zone surrounding the well containing the compounds, was recorded if the zone of inhibition was greater than 8 mm. The experiments were performed in triplicate. Methanol was used as a negative control whereas mycostatin (1000 μ g/mL) was used as a positive control.

III. EXPERIMENTAL WORK

3.1 General procedure for synthesis of Pd(II) and Ni(II) complexes

The Schiff base ligand, e.g. (R)-2-[(E)-(2-hydroxy-1-phenylethylimino)methylphenol((R)-HL1) (120mg, 0.5mmol) was dissolved in MeOH (20mL) and solid $(NiOAc)_2 \cdot 4H_2O$ (45mg, 0.25mmol) added to it with constant stirring at room temperature. A solution of $NaHCO_3$ (41mg, 0.5mmol) in MeOH (5mL) was poured into the reaction mixture and stirring continued for 24h. Colour of solution changed from yellowish green to dark green as reaction proceeds. Progress of the reaction was monitored by TLC. After completion of reaction solvent was removed by evaporation at reduced pressure and solid product washed with water and then with cold methanol. Solid was purified by

International Journal of Innovative Research in Science, Engineering and Technology

(A High Impact Factor, Monthly Peer Reviewed Journal)

Vol. 5, Issue 1, January 2016

crystallization in methanol-DMF. The same procedure was used to prepare all other complexes except for palladium complexes where acetonitrile was used as solvent due to less solubility of Pd(OAc)₂ in methanol.

3.1.1 Bis [(R,R)-2-((E)-(2-hydroxy-1-phenylethylimino)methyl)phenoxy-κ²N,O]nickel(II) (NiL1)

Yield 89mg (67%). UV-VIS (0.5x10⁻⁵M/L, MeOH), 369,266,258nm. IR, (KBr, cm⁻¹); 3024brs, 2359, 1629s, 1444, 1190, 752,516(w), 457(m). ¹H NMR (400Mz in DMSO-d₆), δ =8.6 (s, 2H), 6.90-7.50 (m, 18H), 4.44(m, 4H), 3.7(m, 2H), 2.5(s, 2H). Required for C₃₀H₂₈N₂NiO₄;C, 66.82; H, 5.23; N, 5.19; Ni, 10.88; O, 11.87, Observed - C, 66.77; H, 5.20; N 5.18.

3.1.2 Bis [(S, S)-2-((E)-(2-hydroxy-1-phenylethylimino)methyl)phenoxy-κ²N,O]nickel(II) (NiL2)

Yield 87mg (65%). UV-VIS (0.5x10⁻⁵M/L, MeOH), 369,271,267,258nm. IR, (KBr, cm⁻¹); 3024brs, 1629(s), 1444, 1192, 758,516(w), 457(m). ¹H NMR (400Mz in DMSO-d₆), δ =8.5 (s, 2H), 6.89-7.47 (m, 18H), 4.50(m, 4H), 4.40(m, 2H), 2.47(s, 2H). Required for C₃₀H₂₈N₂NiO₄;C, 66.82; H, 5.23; N, 5.19; Ni, 10.88; O, 11.87, Observed - C, 66.80;H, 5.18; N, 5.21.

3.1.3 Bis[(R,R)-2-((E)-(1-hydroxy-3-phenylpropan-2-ylimino)methyl)phenoxy-κ²N,O]nickel(II) (NiL3)

Yield 101mg (72%). UV-VIS (0.5x10⁻⁵M/L, MeOH), 369,270,266,258nm. IR, (KBr, cm⁻¹); 3020brs, 2619, 1635(s), 1456, 1192, 748, 464(m). ¹H NMR (400Mz in DMSO-d₆), δ =8.03 (s, 2H), 6.42-7.42 (m, 18H), 3.80(m, 4H), 3.5(m, 2H), 2.90(m, 4H), 1.3(s, 2H). Required for C₃₂H₃₂N₂NiO₄;C, 67.75; H, 5.69; N,4.94; Ni, 10.35; O, 11.28 Observed C, 67.74; H, 5.67; N, 4.92.

3.1.4 Bis[(S,S)-2-((E)-(1-hydroxy-3-methylbutan-2-ylimino)methyl)phenoxy-κ²N,O]nickel(II) (NiL4)

Yield 76mg (65%). UV-VIS (0.5x10⁻⁵M/L, MeOH), 367,272,267,258nm. IR, (KBr, cm⁻¹); 2960brs, 1633(s), 1442, 1145, 748, 455(m). ¹H NMR (400Mz in DMSO-d₆), δ =8.45(s, 2H), 6.80-7.44 (m, 8H), 4.47(m, 4H), 3.95(m, 2H), 2.50(s, 2H), 1.94(m, 2H), 0.86(d, 12H). Required for C₂₄H₃₂N₂NiO₄;C, 61.17; H, 6.84; N, 5.94; Ni, 12.46; O, 13.58 Observed C, 61.14; H, 6.87; N, 5.92.

3.1.5 Bis[(R,R)-2-((E)-(2-hydroxy-1-phenylethylimino)methyl)phenoxy-κ²N,O]palladium(II) (PdL1)

Yield 107mg (70%). UV-VIS (0.5x10⁻⁵M/L, CH₂Cl₂), 389,279,260,255nm. IR, (KBr, cm⁻¹); 3254brs, 3039, 1620(s), 1450, 1049, 754,461(m). ¹H NMR (400Mz in DMSO-d₆), δ =7.86 (s, 2H), 6.53-7.54 (m, 18H), 4.77(m, 4H), 3.7(m, 2H), 2.59(s, 2H). Required for C₃₀H₂₈N₂O₄Pd; C, 61.39; H, 4.81; N, 4.77; O, 10.90; Pd,18.13. Observed C, 61.35; H, 4.76; N, 4.74.

3.1.6 Bis[(S,S)-2-((E)-(2-hydroxy-1-phenylethylimino)methyl)phenoxy-κ²N,O]palladium(II) (PdL2)

Yield 104mg (68%). UV-VIS. (0.5x10⁻⁵M/L, CH₂Cl₂MeOH), 390,260,254nm. IR, (KBr, cm⁻¹); 3250brs, 3029, 1614(s), 1450, 1055, 756, 461(m). ¹H NMR (400Mz in DMSO-d₆), δ =7.92 (s, 2H), 6.55-7.45 (m, 18H), 4.39(m, 4H), 3.70(m, 2H), 2.49(s, 2H). Required for C₃₀H₂₈N₂O₄Pd; C, 61.39; H, 4.81; N, 4.77; O, 10.90; Pd, 18.13. Observed C, 61.40; H, 4.74; N, 4.71.

3.1.7 Bis[(R, R)-2-((E)-(1-hydroxy-3-phenylpropan-2-ylimino)methyl)phenoxy-κ²N,O]palladium(II) (PdL3)

Yield 114mg (75%). UV-VIS (0.5x10⁻⁵M/L, CH₂Cl₂), 390,261,256nm. IR, (KBr, cm⁻¹); 3358brs, 3022, 1620(s), 1448, 1026, 752, 455(m). ¹H NMR (400Mz in MSO-d₆), δ =7.85 (s, 2H), 6.56-7.38(m, 18H), 4.50(m, 4H), 3.60(m, 2H), 3.16(m, 4H), 2.40(s, 2H). Required for C₃₂H₃₂N₂O₄Pd; C, 62.49; H, 5.24; N, 4.55; O, 10.41; Pd, 17.30. Observed C, 62.47; H, 5.21; N, 5.41.

3.1.8 Bis[(S,S)-2-((E)-(1-hydroxy-3-methylbutan-2-ylimino)methyl)phenoxy-κ²N,O]palladium(II) (PdL4)

Yield 81mg (63%). UV-VIS (0.5x10⁻⁵M/L, CH₂Cl₂), 391,280,258,354nm. IR, (KBr, cm⁻¹); 3298brs, 2960, 1620(s), 1448, 1047, 756, 461(m). ¹H NMR (400Mz in DMSO-d₆), δ =7.83(s, 2H), 6.55-7.40 (m, 8H), 3.98(dd, 4H), 3.6(m, 2H), 2.48(s, 2H), 2.31(m, 2H), 0.99(d, 12H). Required for C₂₄H₃₂N₂O₄Pd; C, 55.55; H, 6.22; N, 5.40; O, 12.33; Pd, 20.51. Observed C, 55.47; H, 6.21; N, 5.41.

International Journal of Innovative Research in Science, Engineering and Technology

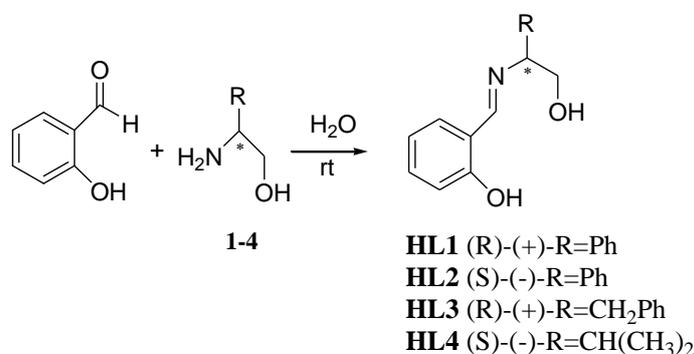
(A High Impact Factor, Monthly Peer Reviewed Journal)

Vol. 5, Issue 1, January 2016

IV. RESULTS AND DISCUSSION

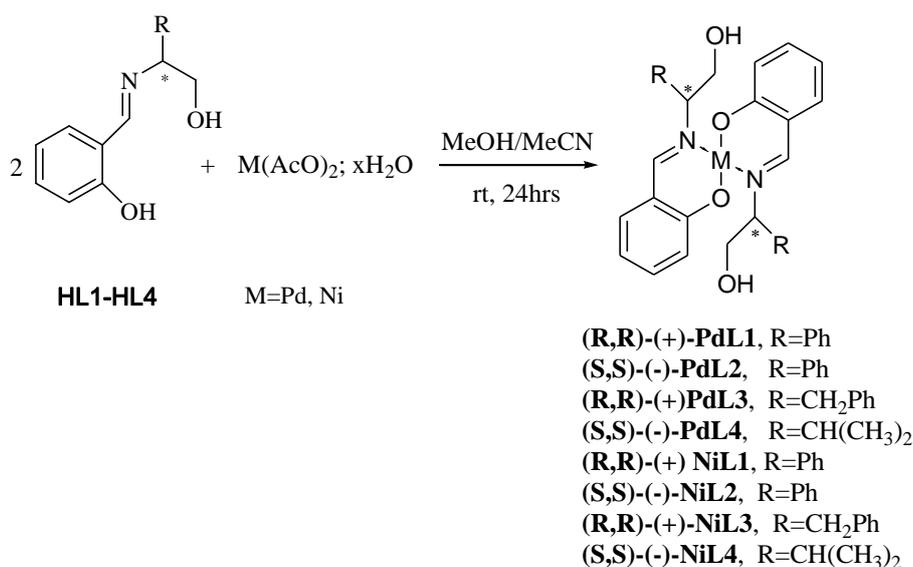
4.1 Chemistry

More simplicity in the synthesis of Schiff bases leads to wide range of such compounds. Recently we synthesized a series of CSBLs (imines and diimines) by condensation of enantiopure β -aminoalcohols and aromatic aldehydes in water as a green approach [27]. CSBLs (**HL1-HL4**) are categorically selected for complexation with Pd (II) and Ni (II) metal ions by reason of their easy preparation, high optical purity, quantitative yields and simple purification method (Scheme-1). All the CSBLs are well characterised before coordinating with metal ions.



Scheme 1: Synthesis of CSBLs in water

Enantiopure (R or S)CSBLs (**HL1-HL4**) reacts with palladium(II) and nickel(II) acetates in presence of sodium carbonate to give optically pure Bis[(R,R/S,S)-2-[(E)-(2-hydroxy-1-phenylalkylimino)methyl]phenoxy-N,O]Palladium(II)/Nickel(II) complexes(**R,R/S,S-Pd-L1-L4/Ni-L1-L4**) in CH₃CN and methanol solvents respectively(Scheme-2).



Scheme 2: Synthesis of Palladium(II) and Nickel(II) complexes

Structures of metal complexes prepared are conveniently supported by spectroscopic techniques and data available in literature [30, 31]. Electronic spectra of **HL1-HL4** are dominated by two absorption peaks at 254-256nm and 314-

International Journal of Innovative Research in Science, Engineering and Technology

(A High Impact Factor, Monthly Peer Reviewed Journal)

Vol. 5, Issue 1, January 2016

316nm for $n-\pi^*$ and $\pi-\pi^*$ transitions in azomethine group. These absorption maxima shows bathochromism in both peaks (258-266, 367-369nm for **NiL1-L4** and 260-279,389-391nm for **PdL1-L4** complexes due to metal→ligand charge transfer and d-d transitions (Fig.1).

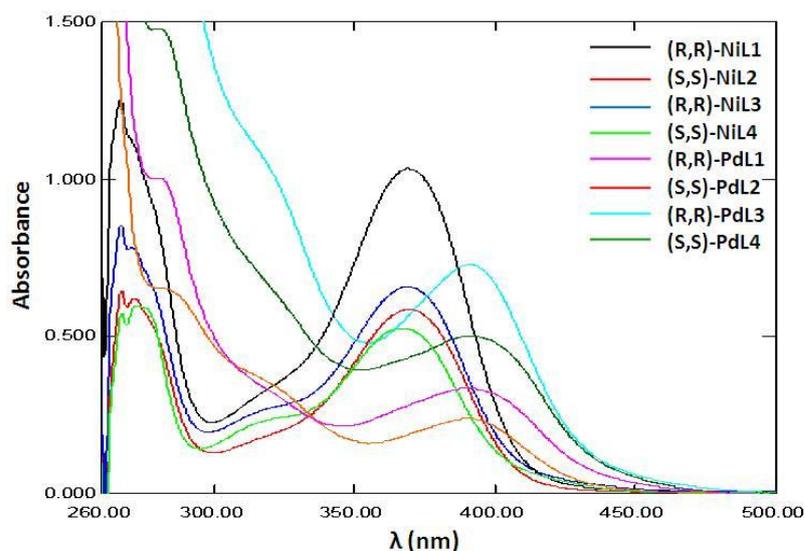


Fig. 1: Electronic absorption spectra of metal complexes **NiL1-4**, **PdL1-4**

The enhancement in the red shift is more for palladium complexes compared to nickel complexes. FT Infrared spectrums of CSBLs arises with absorption bands in lower region $462-466\text{cm}^{-1}$ for M-O bond which is not seen in parent CSBLs.

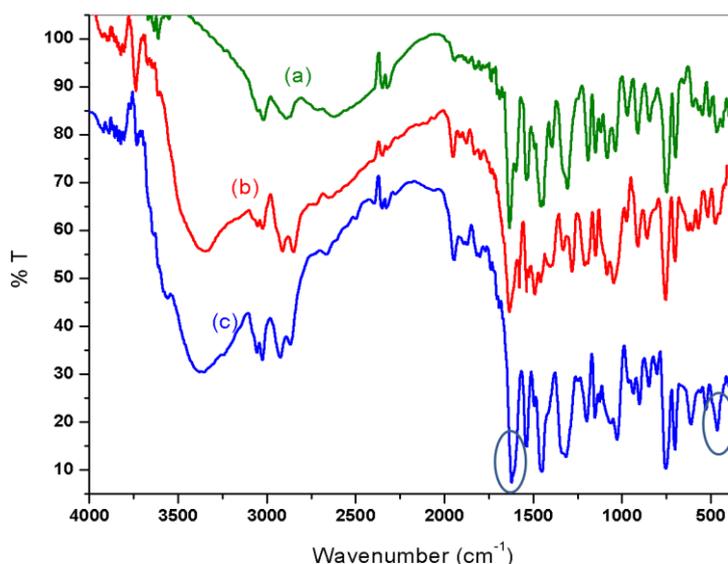


Fig. 2: IR spectra of (a) (R)-(+)-**HL3** (b) **NiL3** (c) **PdL3**

Azomethine vibrational frequency for (R,R/S,S)**PdL1-L4** is considerably shifted to lower value (1622cm^{-1}) as compared to CSBLs but Ni(II) complexes has noticed minor shift in this frequency. A representative vibrational spectrums of ligand and metal complexes are shown in Fig.2.

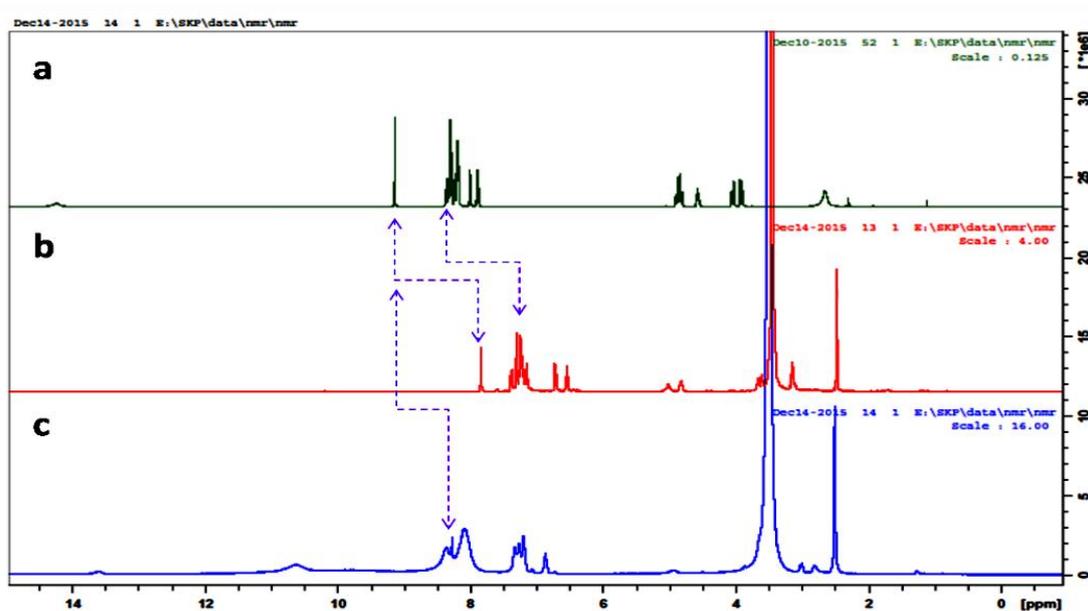


Fig. 3: ^1H NMR Spectra (a) CSBL (R)-(+)-HL3 (b) PdL3 (c) NiL3

Similar pattern is witnessed in ^1H NMR spectroscopy. Azomethine proton generally appeared at $8.35\text{-}8.40\delta$ in CSBLs which shifted to much lower value in the shielded region ($7.83\text{-}7.92\delta$) and same effect is noticed in case of other remaining protons due to coordination of metal with ligands (Fig.3). Phenolic OH generally appears beyond 10δ value, which disappeared in Fig.3 b and c but alcoholic OH maintained its position in the ^1H NMR spectra of metal complexes. Elemental analysis data is also in good agreement with theoretical values with proposed structural formulae.

4.2 Antibacterial activity

Antimicrobial study of CSBL complexes of nickel (II) and palladium (II) revealed that, complex (S, S)-**PdL2** showed highest antibacterial activity (inhibition zone 15mm) against *Staphylococcus aureus*, (Gram-positive) bacterial strains and comparable activity (13mm) by (S, S)-**PdL4** (Table 1). This is evident that stereo chemical control is prominent in case of gram-positive bacteria since *Escherichia coli* (Gram-negative) are resistant to both (**PdL2** and **PdL4**) complexes. Complexes **NiL1** and **PdL1** showed moderate activity towards *Staphylococcus aureus*. Antibacterial activity of all the complexes against *Escherichia coli* (Gram-negative) bacteria is negligible and remained resistant to methanol solution of these complexes.

International Journal of Innovative Research in Science, Engineering and Technology

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Vol. 5, Issue 1, January 2016

Table 1: Antimicrobial activity of complexes

Complex	Zone of inhibition (mm)			
	Antibacterial activity		Antifungal activity	
	<i>E. coli</i>	<i>S. aureus</i>	<i>Candida albicans</i>	<i>Aspergillus niger</i>
NiL1	----	10	10	8
NiL2	----	----	8	7
NiL3	----	8	8	8
NiL4	8	7	8	8
PdL1	7	9	10	----
PdL2	7	15	7	10
PdL3	----	7	20	10
PdL4	----	13	10	13
Standard antimicrobial control				
Streptomycin (Antibacterial)	8	13	----	----
Mycostatin (Antifungal)	----	----	Nil	Nil
Solvent control (Methanol)	7	2	Nil	Nil

4.3 Antifungal activity

Two fungi, *Aspergillus niger*-mold and *Candida albicans*-yeast were tested to evaluate the antifungal activity of the complexes synthesized. Unlike antibacterial activity almost all the complexes **NiL1-NiL4** and **PdL1-PdL4** exhibited antifungal activity against both fungal strains. Complex **PdL3** confirmed excellent activity against the *Candida albicans* while **PdL4** towards *Aspergillus niger* (Table 1). Antifungal activity of complexes **NiL1**, **PdL1** and **PdL3** is also good as compared to mycostatin antifungal (Standard antimicrobial control). Stereo chemical control aspect is less operative in the antifungal tests.

International Journal of Innovative Research in Science, Engineering and Technology

(A High Impact Factor, Monthly Peer Reviewed Journal)

Vol. 5, Issue 1, January 2016

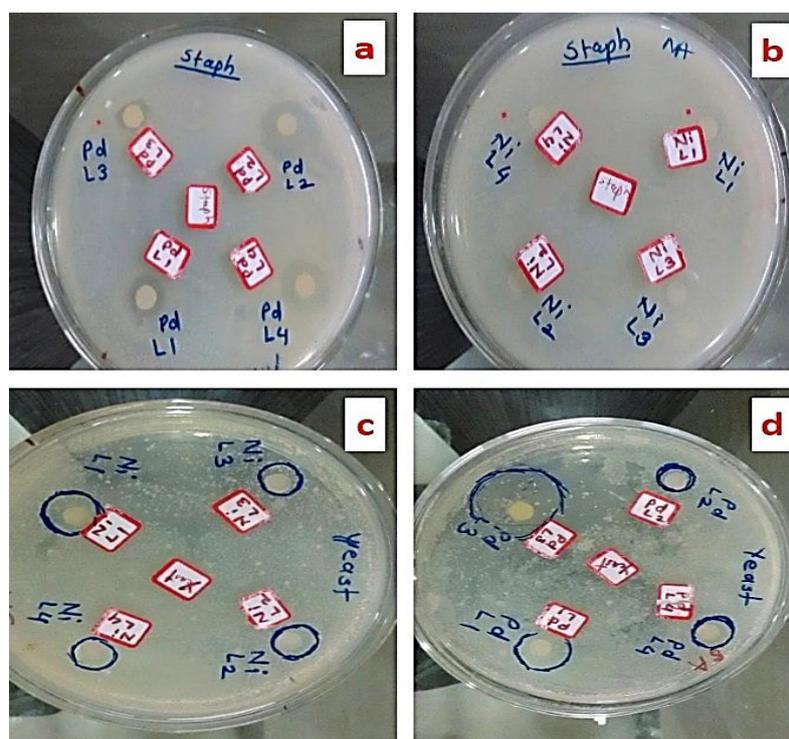


Fig. 4: Images of inhibition zones of antimicrobial activities of (a) Antibacterial activity of PdL1-PdL4 (b) Antibacterial Activity of NiL1-NiL4 (c) Antifungal activity of NiL1-NiL4 (d) Antifungal activity of PdL1-PdL4

In general palladium complexes are better antimicrobial agents than the nickel complexes. The images of inhibition zones observed for antibacterial and antifungal activities are shown in Fig.4

V. CONCLUSION

Enantiopure CSBLs are synthesized in bulk quantities with green concept. Coordination compounds are prepared by reaction of these mixed donor atoms (N, O) ligands with palladium and nickel salts and characterised by spectroscopic techniques. Among the complexes evaluated for antimicrobial activity, palladium complexes remained most active to both antibacterial and antifungal activities. Stereo chemical control is visible in case of antibacterial activity of gram-positive and gram-negative strains. Amongst the 8 complexes **PdL1-PdL4** exhibited both antibacterial, antifungal activity and **NiL1-NiL4** moderate to good antifungal activity. **PdL2** displayed excellent antibacterial and **PdL3** antifungal activities respectively.

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International Journal of Innovative Research in Science, Engineering and Technology

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Vol. 5, Issue 1, January 2016

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