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Synthesis, Characterization And Evaluation Of Biological Activities Of Pd(II) Complexes Of Schiff Base Incorporating Sulpha Drugs

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Abstract
In this study, synthesis and spectral characterization and antimicrobial activities of four sulpha drugs-based Schiff base ligands and their Pd(II) complexes were reported. The ligands were synthesized by the condensation reaction of amino substituted sulpha drugs and carbonyl compounds and then Pd complex synthesized by refluxing ligands with palladium chloride. The structure of the ligands ***(L^1H-L^4H)*** *& their complexes* ***(C^1-C^4)*** *were characterized by IR, (^1H & ^{13}C) NMR and Mass spectrometry studies. All the compounds have been screened for antibacterial and antifungal activity against bacterial strains E. coli, P. aeruginosa, S. aureus, S. pyogenus and fungal strains C. albicans, A. niger, A. clavatus by using broth micro dilution method. Best antibacterial activity exhibit by complex* ***C^3*** *(MIC= 60 µg/mL) against E. coli. Results indicated that the coordinated compounds of palladium have exhibited better inhibition potential compared with the ligands.*
Keywords: *Sulphadrug Schiff base, Pd(II) complex, antibacterial activity, antifungal activity*

INTRODUCTION

In 1864 Hugo Schiff first described coordination properties and preparation of Schiff bases[1]. These compounds can be prepared when a primary amine reacts with carbonyl compounds under mild acidic conditions. These compounds have received considerable attention because of their numerous profits such as easy synthesis, friendly processing, better solubility, structural diversity, high stability of their coordination compounds[2]. The presence of a lone pair on N_2-atom and the electron donating character of double bond impart these compounds with immense potential in the field of coordination chemistry[3]. The presence of nitrogen and oxygen donor atoms in these complexes makes them efficient and effective catalysts for many chemical transformations, analytical reagents, and medicinally important[4].

Schiff bases are also reported to possess diverse biological activities like anti-inflammatory[5], antiviral[6], anti-tuberculosis[7-8], carcinogenic[9-12], antifungal[13-16], antibacterial[13-16], antinociceptive[17], HIV protease inhibitors[17] and antitumor activities[18]. They are also used in optical and electrochemical sensors as well as in various chromatographic methods to enable enhanced selectivity and sensitivity at the time of compound detection[19].

The metal complexes chemistry with Schiff bases has also drawn much attention, mainly due to their structural variability, preparative accessibility and diverse range of applications in catalysis[20]. Moreover, these complexes reported to posses antibacterial, antifungal, antimalarial, anticancer and antineoplastic activities[21]. Here in, we explain preparation, spectral characterization and biological evaluation of 4 sulpha drugs based Schiff base ligands & their Pd(II) complexes.

EXPERIMENTAL

MATERIALS AND METHODS

Anhydrous palladium chloride and sulphadiazine were collected from Alfa-Aesar. Sulphacetamide, sulphamethazine, sulphamerazine and anisaldehyde were purchased from Sigma-Aldrich, India. Anhydrous medium were used for all the reactions. Purity of all ligands & compounds were confirmed by TLC. Using Myra apparatus melting of all synthesized compounds were checked. ^1H & C^{13} NMR spectra were recorded using (BRUKER AVANCE NEO 500 MHz NMR spectrometer) and Mass spectrum recorded from Sophisticated Analytical Instrument Facilities, Chandigarh, India, using (SYNAPT-XSDBATOF-MS ES+ mass spectrometer). Infra-red spectrum was recorded (Bruker alpha-T Frontier Transform-IR spectrometer) from chemistry department, MLSU, Udaipur (Rajasthan), India. An antibacterial, antifungal activity of the all newly synthesized Pd-compounds & ligands was done from Surat (Gujarat), India, at the MicroCare Laboratory & TRC.

Method of synthesis of ligands

To obtain the sulpha-drug based Schiff base ligands, ethanolic solution of aldehyde (anisaldehyde) (5 mL) (0.01 mol, 1.22 mL) was allowed to mix with hot absolute ethanolic solution of sulpha drugs (5 mL) such as sulphacetamide, sulphadiazine, sulphamethazine, sulphamerazine (0.01 mol, 1.24 g), (0.01 mol, 2.50 g), (0.01 mol, 2.7 g), (0.01 mol, 2.64 g) taken in molar ratio 1:1 in 250 mL clean round bottom flasks. Some drops of CH_3COOH were added to this solution, which served as catalyst. Upon addition, the reaction mixtures were refluxed for about 20-24 h in an oil bath at 60-80°C. Thin layer chromatography (TLC) was done after repeated intervals to check the progress and completion of the reaction. Finally, the obtained products were cooled in the refrigerator. The products, so obtained were repeatedly washed using cold ethanol and purified by recrystallization using the same solvent.

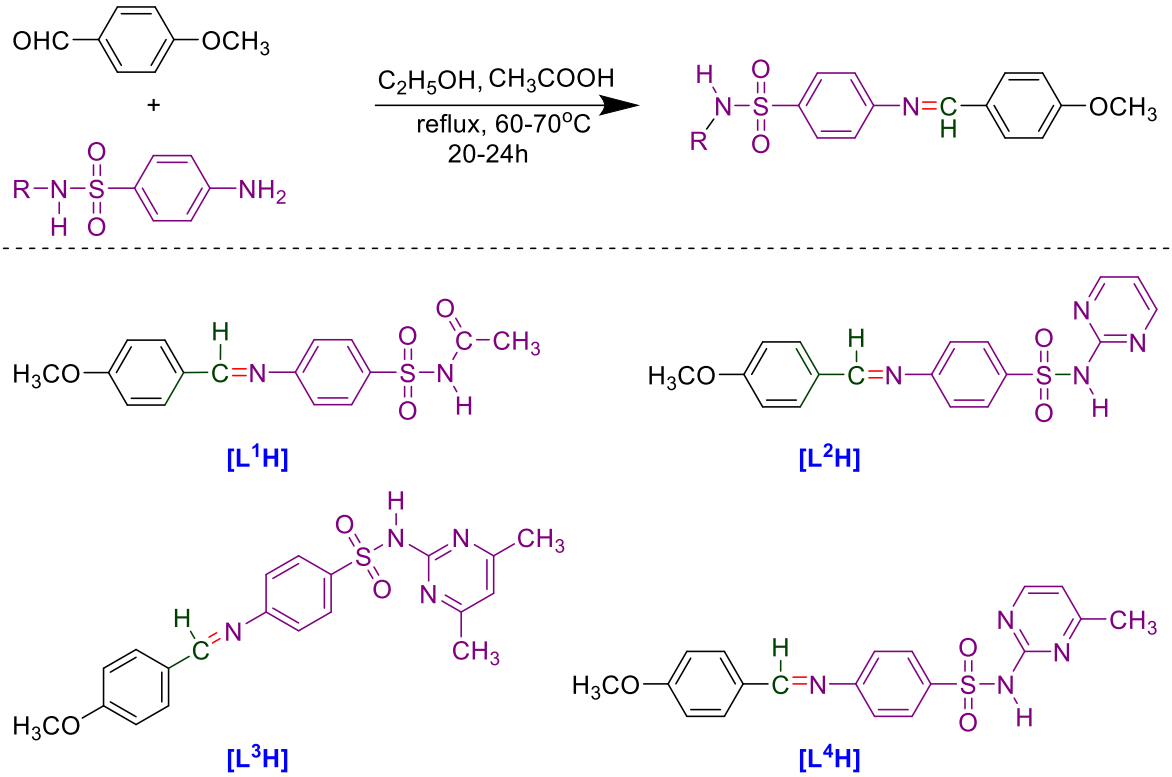

Fig. 1. Synthesis of sulphadrug based Schiff base ligands [L^1H-L^4H]

Sulphacetamide-anisaldehyde ligand [L^1H]:
$C_{16}H_{16}N_2O_4S$; Light yellow; yield, 68.40%; m.pt. 210°C; FT-IR (KBr): ν >C=N— (1610 cm^{-1}), ν OCH_3 (2920 cm^{-1}), ν NH (3260 cm^{-1}), ν $COCH_3$ (1700-1720 cm^{-1}), ν SO_2 1315 & 1150 cm^{-1} (Asym. & Symm.). ^{1}H NMR: (δ in ppm) = 8.55 (S, 1H, —CH=N—), 1.87 (S, 3H, CH_3), 11.67 (1H, S, NH), 3.85 (S, 3H, OCH_3), 6.62-7.87 (m, Ar-H). ^{13}C-NMR: (δ in ppm) = 23.07 (CH_3), 55.49 (OCH_3), 191.21 (C=O), 135.47 (C_1), 121.19 (C_2, C_6), 123.73 (C_3, C_5), 142.00 (C_4), 128.32 (C_7), 130.92 (C_8, C_{12}), 114.42 (C_9, C_{11}), 164.12 (C_{10}) (Ar-C), 162.38 (–CH=N).. Mass (m/z): 332.62(M)$^+$[$C_{16}H_{16}N_2O_4S$]$^+$ (Base peak), 333.67 (M+1) [$C_{16}H_{17}N_2O_4S$]$^+$, 107.95 [SO_2COCH_3]$^+$.

Sulphadiazine-anisaldehyde ligand [L^2H]:
$C_{18}H_{16}N_4O_3S$; Red; yield, 50%; m.pt. 240°C; FT-IR (KBr): ν SO_2 (1320 & 1200 cm^{-1}), ν NH (3270 cm^{-1}), ν CH=N (1620 cm^{-1}). ^{1}H-NMR: (δ in ppm) = 8.5 (S, 1H, CH=N), 3.65 (S, 3H, –OCH_3), 11.60 (S, 1H, NH), 6.67-8.52 (m, Ar-H). ^{13}C-NMR: (δ in ppm) = 55.93 (OCH_3), 115.59 (C_1), 122.40 (C_2, C_4), 161.06 (C_3), 142.99 (C_5), 131.46 (C_6, C_{10}), 130.19 (C_7, C_9), 150.99 (C_8), 128.40 (C_{11}), 130.20 (C_{12}, C_{16}), 114.40 (C_{13}, C_{15}), 162.90 (C_{14}) (Ar-C), 158.14 (CH=N). Mass (m/z): 368.60 (M)$^+$ [$C_{18}H_{16}N_4O_3S$]$^+$, 370.56 (M+2), 372.56 (M+4).

Sulphamethazine-anisaldehyde ligand [L^3H]:
$C_{20}H_{20}N_4O_3S$; Orange; yield, 79%; m.pt. 191°C; FT-IR (KBr): ν CH=N (1576 cm^{-1}), ν NH (3300 cm^{-1}), ν CH_3 (2855 cm^{-1}), ν OCH_3 (2950 cm^{-1}), ν SO_2 (1350 and 1247 cm^{-1}). ^{1}H NMR: (δ in ppm) = 10.50 (S, 1H, NH), 8.52 (S, 1H, CH=N), 3.71 (S, 3H, OCH_3), 6.56-7.86 (m, Ar-H). ^{13}C-NMR: (δ in ppm) = 55.30 (OCH_3), 22.90 (CH_3), 111.65 (C_1), 167.17 (C_2, C_4), 171.90 (C_3), 134.03 (C_5), 129.80 (C_6, C_{10}), 129.30 (C_7, C_9), 150.90 (C_8), 131.70 (C_{11}), 130.19 (C_{12}, C_{16}), 114.40 (C_{13}, C_{15}), 158.02 (C_{14}) (Ar-C), 160.22 (CH=N). Mass (m/z): 396.74 (M)$^+$[$C_{20}H_{20}N_4O_3S$]$^+$, 397.77 (M+1) [$C_{20}H_{21}N_4O_3S$]$^+$ (Base peak), 398.78 (M+2), 400.81 (M+4), 363.68 [$C_{19}H_{16}N_4O_2S$]$^+$.

Sulphamerazine-anisaldehyde ligand [L^4H]:
$C_{19}H_{18}N_4O_3S$; Dark brown; yield, 64%; m.pt. 215°C; FT-IR (KBr): ν CH=N (1575 cm^{-1}), ν NH (3220 cm^{-1}), ν CH_3 (2850 cm^{-1}), ν OCH_3 (2945 cm^{-1}), ν SO_2 (1347 & 1243 cm^{-1}). ^{1}H NMR: (δ in ppm) = 10.31 (S, 1H, NH), 8.53 (S, 1H, CH=N), 3.86 (S, 3H, OCH_3), 6.95-8.31 (m, Ar-H). ^{13}C-NMR: (δ in ppm) = 55.57 (OCH_3), 23.22 (CH_3), 160.00 (CH=N), 111.91 (C_1), 152.84 (C_2), 168.90 (C_3), 191.18 (C_4), 131.68 (C_5), 129.36 (C_6, C_{10}), 124.82 (C_7, C_9), 156.80 (C_8), 129.91 (C_{11}), 130.78 (C_{12}, C_{16}), 114.44 (C_{13}, C_{15}), 164.10 (C_{14}) (Ar-C). Mass (m/z): Base peak, 248.64 $[C_{11}H_{10}N_3SO_2]^+$, 382.53 $(M)^+[C_{19}H_{18}N_4O_3S]^+$, 383.82 (M+1), 384.82 (M+2), 367.89$[C_{18}H_{15}N_4O_3S]^+$.

Method of synthesis of Pd(II) Complexes

Palladium complexes were synthesized using palladium chloride and sulpha drugs based Schiff bases (**L^1H** to **L^4H**) in 1:2 molar ratio, respectively. Triethyl amine (2-3 drops) were added into the reaction mixture to adjust slight basic pH. The solution was refluxed for 6 hours on magnetic stirrer with hot plate. After completion of reaction, products were dried at room temperature and recrystallized in ethanol followed by drying at 60°C for 4-5h.

$[C_{33}H_{34}Cl_2N_4O_8S_2Pd]$($C^1$): Yellow; m.p. 224 °C; FT-IR (KBr): ν CH=N (1600 cm^{-1}), ν C-O-C (1070 cm^{-1}), ν SO_2 (1315-1325 cm^{-1}, 1145-1150 cm^{-1}) (Asy. & Sym.), ν Pd-N (405), ν Pd-Cl (287). ^{1}H NMR: (δ in ppm) = 8.53 (S, 2H, >CH=N—), 3.51 (S, 6H, OCH_3), 1.05 (S, 6H, CH_3), 6.77-7.84 (M, Ar-H). ^{13}C-NMR: (δ in ppm) = 200 (>C=O), 160.0 (>CH=N—), 55 ($COCH_3$), 18.52 (CH_3), 136.7 (C_1), 115.3 (C_2, C_6), 125.00 (C_3, C_5), 129.09 (C_4), 120.12 (C_7), 120.86 (C_8, C_{12}), 110.35 (C_9, C_{11}), 160.7 (C_{10}) (Ar-C). LC-MS (m/z): 840 $(M)^+$, 842.04 (M+2), 844.10 (M+4), cal. 840.11; found 840.00.

$[C_{36}H_{32}Cl_2N_8O_6S_2Pd]$($C^2$): Orange; m.p. 247°C; FT-IR (KBr): ν NH (1030 cm^{-1}), ν >CH=N— (1620 cm^{-1}), ν Pd-N (412), ν Pd-Cl (301). ^{1}H NMR: (δ in ppm) = 8.00 (S, 2H, >CH=N—), 11.85 (S, 2H, NH), 3.60 (S, 6H, OCH_3), 6.00-7.77 (m, Aryl, 16H), 8.00 (d, 4H, $H_{diazine}$), 6 (t, 2H, $H_{diazine}$). ^{13}C-NMR: (δ in ppm) =170 (>CH=N—), 50.70 (OCH_3), 170.3 (C_1), 160.9 (C_2, C4), 111.3 (C_3), 140.7 (C_5), 125.3 (C_6, C_{10}), 125.7 (C_7, C_9), 148.1 (C_8), 120.7 (C_{11}), 123.0 (C_{12}, C_{16}), 113.3 (C_{13}, C_{15}), 150.6 (C_{14}) (Ar-C). LC-MS (m/z): cal. 912.05; found 912.46.

$[C_{42}H_{44}Cl_2N_8O_6S_2Pd]$($C^3$): Dark brown; m.p. 308°C; FT-IR (KBr): ν NH (1050 cm^{-1}), ν CH=N (1500 cm^{-1}), ν Pd-N (407), ν Pd-Cl (350). ^{1}H NMR: (δ in ppm)= 8.11 (S, 2H, >CH=N—), 10.60 (S, 2H, NH), 3.00 (S, 6H, OCH_3), 2.69 (d, 12H, $CH_{3diazine}$, J= 1.5 Hz), 6.66 (m, 2H, $H_{diazine}$), 7.12 (d, J= 8.7 Hz, 4H), 6.00 (d, J= 8.7 Hz, 4H), 6.00-8.00 (m, 8H, Ar-H). ^{13}C-NMR: (δ in ppm) = 21.00 (CH_3), 160.3 (C_1), 114.8 (C_2, C_6), 124.6 (C_3, C_5), 122.9 (C_4), 144.10 (C_7), 122.7 (C_8, C_{12}), 129.3 (C_9, C_{11}), 169.0 (C_{13}), 165.6 (C_{14}, C_{16}), 110.88 (C_{15}), 125.19 (C_{10}) (Ar-C), 87.26 (CH=N). LC-MS (m/z): 968.11 $(M)^+$, 970.10 [M+2], 972.14 [M+4], Cal. 968.14; found 968.11.

$[C_{38}H_{36}Cl_2N_8O_6S_2Pd]$($C^4$): Green; m.p. 220°C; FT-IR (KBr): ν NH (1020 cm^{-1}), ν CH=N (1565 cm^{-1}), ν Pd-N (418), ν Pd-Cl (359). ^{1}H NMR: (δ in ppm) = 11.68 (S, 2H, NH), 8.00 (S, 2H, CH=N), 3.00 (S, 6H, OCH_3), 2.50 (t, 6H, CH_3), 6.00-8.20 (m, aryl, 16H), 8.00 (q, 4H, $H_{diazine}$). ^{13}C-NMR: δ(ppm) = 54.8 (OCH_3), 23.90 (CH_3), 167.1 (C_1), 115.1 (C_2,C_4), 166.9 (C_3), 137.1 (C_5), 114.0 (C_6, C_{10}), 120.3 (C_7, C_9), 138.7 (C_8), 115.7 (C_{11}), 137.3 (C_{12}, C_{16}), 110.3 (C_{13}, C_{15}), 155.6 (C_{14}) (Ar-C), 169.9 (CH=N). LC-MS (m/z): Cal. 940.08; found 940.

Antimicrobial Activity

Antibacterial activity of Pd(II) complexes (**C^1-C^4**) and (**L^1H-L^4H**) ligands have studied by Broth dilution method[22-23]. Following bacterial strains *E. coli*, *P.* aureginosa, *S. aureus* and *S. pyogenus* were used. DMSO was used to dilute the synthesized compounds and stock solution of 2000 µg/mL was made. An initial screening was performed by preparing a working standard (1000, 500, 250 µg/mL) from the above prepared stock solution of the synthesized compounds. Further, the concentrations which were found better in the preliminary screening selected for the secondary screening by preparing a series of dilutions (200, 100, 50, 25, 12.5, 6.25) microgram per mL of all tested compounds. One mL of prepared concentration of each compound was added to 6 different test tubes containing sterile broth (MHB for bacteria and SDA for fungi) in such a way that test tube no.1 contained highest concentration *i.e.* 200 µg/mL and test tube 6 contain the lowest concentration of complex *i.e.* 6.25 µg/mL (v/v). Then 100 µL of mircoorganism suspension of the selected isolates were inoculated in the labelled test tubes (containing MHB medium and complex concentrations). After incubation for a period of 24 hours at 37 °C, the turbidity (bacterial growth) was evaluated. The control tubes were inoculated with only bacterial suspension and MIC were determined.

Furthermore, to determine the MIC of the all newly synthesized compounds against test fungi (*C. albicans*, *A. niger*, *A. clavatus*), hundred micro liter spore suspension (10^6 spores/mL) of all test fungi were inoculated in the labelled test tubes (containing SDB media along with complex concentrations) and were incubated for seven days at room temperature (25± 2°C). For the control experiment, control tubes containing SDB media were taken following inoculation with only the test fungal suspension. The lowest concentration which was capable of inhibition of microbial growth was perceived as the MIC.

RESULTS AND DISCUSSION

Characterization of Pd(II) complexes

The fourier transform-IR spectra of all the complex depicted azomethine peak appeared at 1575-1620 cm^{-1}. Owing to bonding of azomethine nitrogen with palladium, this particular peak goes to the lower frequency in Pd-complexes. IR spectra of ligands demonstrated stretching vibrations frequency of SO_2 group at 1315-1350 cm^{-1} (asy.) & 1150-1247 cm^{-1} (symm.). These peaks didn't undergo any change on complexation indicating lack of coordination between the group (SO_2) with the metal. Furthermore, two new bands appeared around 405-418 cm^{-1} and 287-359 cm^{-1} attributed to Pd-N & Pd-Cl bonds, respectively. These bands further proved the existence of metal-ligand bonding.

Proton Nuclear Magnetic Resonance spectra of all synthesized ligands & their respective palladium complexes divulged some interesting findings. The shifting of azomethine proton signal (–C**H**=N–) from δ 8.52-8.55 in ligands to 8-8.53 ppm in their palladium complexes, could be due to sharing of lone pair at N-atom to the metal ion. Another upfield shifting of –N**H** peak, from (11.31-11.67 to 10.95-11.68 ppm) also confirms the formation of palladium complex. Moreover, all the aromatic protons exhibited a downfield shifting on complexation with the palladium metal.

In ^{13}C-Nuclear Magnetic Resonance spectra of complexes, azomethine carbons signal shifted towards downfield region could be due to sharing of lone pair of the N-atom towards palladium metal ion. Moreover, all aryl ring carbons signal shifted towards downfield zone.

Mass Spectrometry of Schiff base ligands (**L^1H-L^4H**) and their complexes (**C^1-C^4**) were recorded. In the mass spectra of **L^3H** and its palladium complex **C^3**, (M+) peak appear at m/e 396.74 and 968.11 assign to the ligand & its complex, respectively. **C^3** showed peaks at m/e 968.11, 970.10, 972.14 corresponding to (M^+) peak, (M+2) and (M+4) peak, respectively which confirm that complex contain two Cl-atoms. The tentative structure of typical complexes is shown in fig.2.

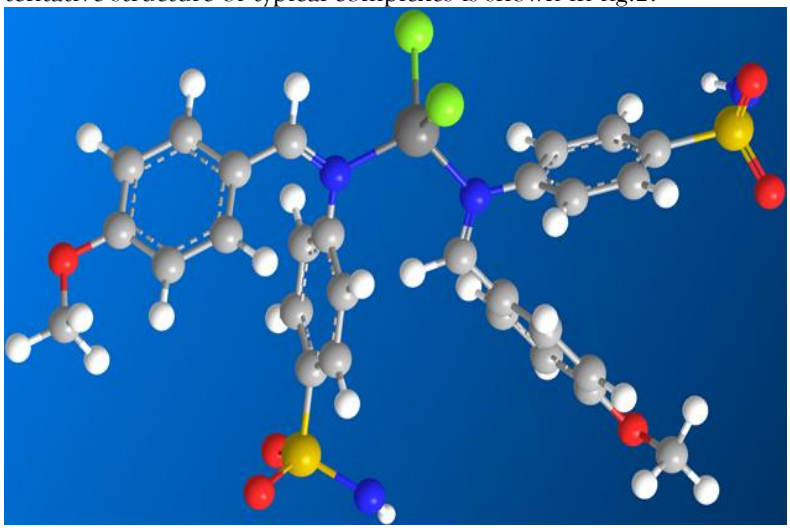

Fig. 2: Tentative typical structure of palladium complex

Results of antimicrobial Activities

Antibacterial activity data's showed **C^3** exhibit best activity against *E. coli* (MIC= 60 µg/mL) and showed moderate activity (MIC= 125 µg/mL) against *P. aeruginosa*. **C^1** & **C^3** showed good activity against *S. aureus*. **L^2H** showed better activity (MIC= 62.5 µg/mL) against *E. coli*. Ciprofloxin was used as standard drug. Thus, these result tells Pd-complexes are much better than the ligands when compaired their activities.

Using (*C. albicans*, *A niger* & *A. clavatus*) fungal strains antifungal activities of four (**L^1H-L^4H**) Schiff base ligands & their complexes (**C^1-C^4**) have been tested. **C^2** showed better results (MIC= 500 µg/mL) against pathogen *C. albicans*. **C^3** complex was exhibited good activity (MIC= 250 µg/mL) against *A. Niger*. **C^3** & **C^4** were found with good, moderate activities (MIC= 500, 250 µg/mL) against *A. clavatus*, respectively. We have used Greseofulvin as the standard drug against the fungi.

Further, **L^1H**, **L^3H** and **L^4H** were found with good activity against *C. albicans, Aspergillus Niger* & A. clavatus (MIC= 500 microgram per mL). The results indicate that the Pd-complexes find good activity compare to ligands.

Table 1: Result of antimicrobial activities of (L^1H-L^4H) Schiff base ligands and (C^1 to C^4) complexes

Sr. No.	Ligands / complexes	MIC (microgram per ml)						
		Antibacterial activity				Antifungal activity		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
1	L^1H	125	100	250	125	500	1000	1000
2	L^2H	62.5	100	100	125	>1000	>1000	>1000
3	L^3H	100	250	250	125	1000	500	500
4	L^4H	100	125	50	62.5	500	1000	>1000
5	$[PdCl_2(L^1H)_2]$ (C^1)	100	100	100	200	1000	>1000	>1000
6	$[PdCl_2(L^2H)_2]$ (C^2)	100	125	200	125	500	500	500
7	$[PdCl_2(L^3H)_2]$ (C^3)	60.0	125	100	250	1000	250	250
8	$[PdCl_2(L^4H)_2]$ (C^4)	200	125	250	125	500	1000	>1000
Standard drugs		25	25	50	50	500	100	100

CONCLUSION

In this study, Pd(II) complexes and sulphadrugs were prepared by heating process and characterization done by various spectral techniques. All the Pd-complexes and ligands were screened for antibacterial & antifungal biological activities. Those complexes whose having sulphadiazene moiety showed good antibacterial as well as antifungal activity. This study suggests that Pd(II) complexes and sulpha drugs-based Schiff bases can be good antimicrobial agents, if explored further.

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Conflicts of Interest: The authors are declaring no conflict of interest.

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