Synthesis, Characterization and Evaluation of Biological Activities of Sn(II) Complexes of Schiff base Incorporating Sulpha Drugs

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ABSTRACT

In this study, we report synthesis, characterization and biological activities of four sulphur drug based Schiff base ligands and their Sn(II) complexes. The Schiff bases and their Sn(II) complexes have been synthesized by traditional methods and characterized by the spectral techniques IR, NMR (¹H and ¹³C), mass and TGA-DTA. Newly synthesized Schiff bases (L¹-L⁴) and their Sn(II) complexes (C-1 to C-4) have been screened for antibacterial activity against bacterial strains S. aureus, S. pyogenus, E. coli, P. aeruginosa and antifungal activity against fungal strains C. albicans, A. niger, A. clavatus using broth micro dilution method. Best antimicrobial activity was shown by C-3 complex against E. coli (MIC, 50.0 µg/mL) and A. niger (MIC, 100 µg/mL). Moreover, antimalarial activity against Plasmodium falciparum was also studied. Complex C-3 was found to be more active against parasite P. falciparum (IC₅₀, 0.04 µg/mL). Results showed that dichloride tin complexes are more active with respect to their corresponding Schiff base ligands.

Keywords: Sulpha drug Schiff base, Sn(II) complexes, Antibacterial, Antifungal and Antimalarial activities.

INTRODUCTION

Hugo Schiff in 1864 first reported preparation and coordination properties of Schiff bases. Schiff bases which have azomethine linkage (–CH = N–) can be synthesized by condensation of active carbonyl compounds with primary amines under acidic or basic conditions¹-². The azomethine linkage is responsible for coordination properties and biological activities such as antimalarial³, anticancer⁴, antibacterial⁵, antifungal⁶, antitubercular⁷, anti-inflammatory⁸, antitumor⁹, insecticidal⁹, catalytic activity¹⁰ and other applications¹¹. Bacterial and fungal infectious diseases increased mortality in living organism. Mainly following bacterial strains E. coli, P. aeruginosa, S. aureus, S. pyogenus are responsible for many diseases like food borne diseases and food poisoning etc. With the time microbes may have developed resistance to antibiotics that causes many difficulties in treatment of such diseases and it has
created global concern to human health. Thus, it is urgent necessity to the exploration and development of new more effective antibacterial and antifungal drugs. Schiff base and their complexes has potential to be good antibacterial and antifungal agents\textsuperscript{12-13}.

Malaria is one of the most destructive infectious diseases and causing serious health problems. \( P. \text{falciparum, P. ovale, P. vivax and P. malariae} \) species of plasmodium are responsible for malaria in humans. Among these species \( P. \text{falciparum} \) parasite is most dangerous and which is vectored by female anopheles mosquito. For the treatment of malaria, first discovered antimalarial drug was quinine, isolated from the bark of cinchona plant\textsuperscript{15}. Currently, chloroquine is used to treat malaria because it is less toxic, cheaper and effective drug\textsuperscript{16}.

**EXPERIMENTAL**

**MATERIALS AND METHODS**

Anisaldehyde, sulphacetamide, sulphamethazine and sulphamerazine were bought from Sigma-Aldrich, India. Sulphadiazine and Anhydrous metal salt (tin chloride) were purchased from Alfa-Aesar. Standard method\textsuperscript{32} was used for drying the solvents. All the reactions were carried out under anhydrous conditions. Purification of all the compounds has been checked by aluminium silica plate. Melting points of were measured by the Myra melting point apparatus. IR spectrum was recorded using (Bruker alpha-T FT-IR spectrometer) from Department of Chemistry, MLSU, Udaipur (Raj.), India. Spectrum of \( ^1\text{H & } ^{13}\text{C-NMR} \) were recorded (BRUKER AVANCE NEO 500 MHz NMR SPECTROMETER) using DMSO-\text{d}_6 solution from SAIF, Panjab University Chandigarh, India. Mass spectrum was obtained (SYNAPT-XSDBATO-MS ES+ mass spectrometer) from SAIF, Chandigarh, India. Thermogravimetric analysis was recorded (DTA-TGA Perkin Elmer 6000) from MNIT Jaipur, India. Antimicrobial activities of the synthesized compounds have been performed at Micro Care Laboratory, Surat (Gujarat), India.

**Synthesis of ligands**

Sulpha drug based Schiff base ligands have been synthesized as per reported method\textsuperscript{33-34}. In this method, we have used a 100 mL neat and clean round bottom flask, 5 mL of alcoholic solution of anisaldehyde (1.22 mL, 0.01 mol) was mixed with hot absolute ethanol-acetone (THF) solution of sulphacetamide (1.24 g, 0.01 mol / sulphadiazine (2.50 g, 0.01 mol) / sulphamethazine (2.7 g, 0.01 mol) / sulphamerazine (2.64 g, 0.01 mol) in 1:1 molar ratio. To this solution we have added 4-5 drops of catalyst (glacial acetic acid) and refluxed for about 24 h on oil bath at 60-70°C temperature. Completion of the reaction has been checked by TLC and then it was allowed to cool in refrigerator. The obtained precipitates were filtered off, washed several times with the cold ethanol and purification was done by recrystallization from absolute ethanol. The scheme of the reaction is shown in Figure 2.
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Fig. 2. Synthesis of sulphadrug based Schiff base ligands [L1-L4]

**N-((4-(4-methoxybenzylidene) amino) phenyl) sulfonyl]acetamide [L1]**

C$_6$H$_5$N$_2$O$_4$S; Yellow colored; yield, 68.42%; m.p. 190°C; FT-IR (KBr, cm$^{-1}$): v C=N (1635 cm$^{-1}$), v NH (2920 cm$^{-1}$), v CO (1700-1720 cm$^{-1}$), v SO$_2$ (1315 & 1150 cm$^{-1}$ (Asy.& Sym.), v C=H (3050 cm$^{-1}$). 1H-NMR: δ (ppm)= 8.55 (S, 1H, CH=N), 11.67 (S, 1H, NH), 1.87 (S, 3H, CH$_3$), 3.85 (S, 3H, OCH$_3$), 7.10 (d, 2H, J= 1.8 Hz), 7.87 (dd, 2H, J= 2.0 Hz), 7.38 (d, 2H, J=1.75 Hz), 6.61 (d, 2H, J= 1.75 Hz). 13C-NMR: δ (ppm) = 162.38 (–CH=N–), 23.07 (CH$_3$), 55.49 (OCH$_3$), 191.21 (C=O), 121.19 (C$_2$, C$_5$), 123.73 (C$_3$, C$_4$), 142.00 (C$_1$), 128.32 (C$_6$), 130.92 (C$_7$, C$_8$, C$_9$, C$_12$), 114.42 (C$_{10}$, C$_{11}$) (Ar-C). Mass (m/z): Base peak = 332.62 (M)+[C$_6$H$_5$N$_2$O$_4$S]+, 333.67 (M+1) [C$_6$H$_5$N$_2$O$_4$S]$^+$, 107.95 [SO$_2$COCH$_3$]$^+$, cal. 332.08; found 332.62.

**N-((4,6-dimethylpyrimidin-2-yl)-4-(4-methoxy benzylidene) amino) benzenesulfonamide [L2]**

C$_6$H$_5$N$_2$O$_4$S; Orange colored; yield, 79%; m.p. 190°C; FT-IR (KBr, cm$^{-1}$): v C=N (1626 cm$^{-1}$), v NH (3350 cm$^{-1}$), v CO (2950 cm$^{-1}$), v SO$_2$ (1350 & 1247 cm$^{-1}$). 1H-NMR: δ (ppm)= 8.52 (S, 1H, CH=N), 11.50 (S, 1H, NH), 3.81 (S, 3H, OCH$_3$), 7.07 (d, 2H, J= 2.7 Hz), 7.02 (dd, 2H, J= 5 Hz), 6.78 (d, 2H, J= 8.5 Hz), 7.87 (dd, 2H, J= 8.5 Hz), 6.56 (m, 6H, Hdiazine), 2.25 (d, 1H, J= 5 Hz, CH$_3$). 13C-NMR: δ (ppm) = 160.22 (–CH=N–), 157.17 (C$_2$, C$_5$), 171.90 (C$_3$), 134.03 (C$_4$), 129.80 (C$_6$, C$_9$), 129.30 (C$_7$, C$_8$, C$_9$), 131.70 (C$_{10}$, C$_{11}$), 130.19 (C$_{12}$, C$_{13}$), 114.40 (C$_{14}$, C$_{15}$), 158.02 (C$_{16}$) (Ar-C). Mass (m/z): 396.74 (M)+[C$_6$H$_5$N$_2$O$_4$S]+, Base peak = 397.77 (M+1) [C$_6$H$_5$N$_2$O$_4$S]$^+$, 398.78 (M+2), 400.81 (M+4), 363.68 [C$_6$H$_5$N$_2$O$_3$]$^+$, cal. 396.13; found 396.74.

**4-(4-methoxybenzylidene) amino)-N-(pyrimidin-2-yl) benzenesulfonamide [L3]**

C$_6$H$_5$N$_2$O$_4$S; Dark red colored; yield, 50%; m.p. 210°C; FT-IR (KBr, cm$^{-1}$): v C=N (1626 cm$^{-1}$), v NH (3350 cm$^{-1}$), v CO (2950 cm$^{-1}$), v SO$_2$ (1350 & 1247 cm$^{-1}$). 1H-NMR: δ (ppm)= 8.52 (S, 1H, CH=N), 11.50 (S, 1H, NH), 3.81 (S, 3H, OCH$_3$), 7.07 (d, 2H, J= 2.7 Hz), 7.02 (dd, 2H, J= 5 Hz), 6.78 (d, 2H, J= 8.5 Hz), 7.87 (dd, 2H, J= 8.5 Hz), 6.56 (m, 6H, Hdiazine), 2.25 (d, 1H, J= 5 Hz, CH$_3$). 13C-NMR: δ (ppm) = 160.22 (CH=N), 55.30 (OCH$_3$), 22.90 (CH$_3$), 111.65 (C$_1$), 167.17 (C$_2$, C$_5$), 171.90 (C$_3$), 134.03 (C$_4$), 129.80 (C$_6$, C$_9$), 129.30 (C$_7$, C$_8$, C$_9$), 131.70 (C$_{10}$, C$_{11}$), 130.19 (C$_{12}$, C$_{13}$), 114.40 (C$_{14}$, C$_{15}$), 158.02 (C$_{16}$) (Ar-C). Mass (m/z): 396.74 (M)+[C$_6$H$_5$N$_2$O$_4$S]+, Base peak = 397.77 (M+1) [C$_6$H$_5$N$_2$O$_4$S]$^+$, 398.78 (M+2), 400.81 (M+4), 363.68 [C$_6$H$_5$N$_2$O$_3$]$^+$, cal. 396.13; found 396.74.
4-((4-methoxybenzylidene)amino)-N-(4-methyl pyrimidin-2-yl)benzenesulfonamide [L4]

\[ \text{C}_{19}\text{H}_{18}\text{N}_{4}\text{O}_{3}\text{S}; \text{Brown colored}; \text{yield, 64.92\%}; \text{m.p. 204–215°C}; \text{FT-IR (KBr, } \nu \text{ cm}^{-1}) : \nu \text{ CH} = \text{N (1590 cm}^{-1}), \nu \text{ NH (3320 cm}^{-1}), \nu \text{ CH}_{2} (2850 \text{ cm}^{-1}), \nu \text{ OCH}_{3} (2945 \text{ cm}^{-1}), \nu \text{ SO}_{2} (1347 \& 1243 \text{ cm}^{-1}) . \]  

\[ ^{1}H\text{-NMR: } \delta (\text{ppm}) = 8.53 (\text{S, 1H, CH} = \text{N}), 11.31 (\text{S, 1H, NH}), 3.86 (\text{S, 3H, OCH}_{3}), 7.08 (\text{d, 2H, } J = 8.7 \text{ Hz, 8.31 (dd, 2H, } J = 1.5 \text{ Hz}), 7.63 (\text{d, 2H, } J = 8.75 \text{ Hz, 8.00 (d, 2H, } J = 8.5 \text{ Hz, 7.86 (d, 1H, } J = 1.95 \text{ Hz, 6.95 (m, 1H), 2.32 (d, 3H, } J = 10 \text{ Hz, CH}_{3}). \]  

\[ ^{13}C\text{-NMR: } \delta (\text{ppm}) = 160.00 (\text{CH} = \text{N}), 55.57 (\text{OCH}_{3}), 23.22 (\text{CH}_{2}), 111.91 (\text{C}), 152.84 (\text{C}), 168.90 (\text{C}), 191.18 (\text{C}), 131.18 (\text{C}), 129.36 (\text{C}), 124.62 (\text{C}), 114.44 (\text{C}), 164.10 (\text{C}) \text{(Ar-C). Mass (m/z): 382.53 (M)+, 383.82 (M+1), 384.82 (M+2), Base peak = 248.64[C}_{11}\text{H}_{10}\text{N}_{3}\text{SO}_{2}+, 367.89[C}_{18}\text{H}_{15}\text{N}_{4}\text{O}_{3}\text{S}+, \text{cal. 382.11; found 382.44.} \]

**Synthesis of Sn(II) Complexes**

Tin(II) complexes under investigation were prepared through the reaction of anhydrous tin(II) chloride (0.001 mol, 0.18 g) with sulpha drug based Schiff base ligands (L1, 0.66 g, 0.002 mol; L2, 0.73 g, 0.002 mol; L3, 0.79 g, 0.002 mol; L4, 0.76 g, 0.002 mol) in MeTHF as reaction medium in 1:2 molar ratio in a 100 mL neat and clean round bottom flask and refluxed on oil bath at 50-65°C for about 4-5 hours. In reaction mixture to adjust pH 5-6 we have added 2-3 drops of glacial acetic acid. The obtained precipitates were filtered off and washed with cold absolute ethanol 2-3 times and kept in refrigerator for 2-3 days for drying.

Purification of the obtained solid compounds was done by recrystallization using absolute ethanol. Purity of each complex was checked by TLC by using silica gel-G as an adsorbent. Structures of synthesized complexes have been shown in Figure 3.

![Image of synthesized complexes](image-url)

**Fig. 3. The proposed structure of tin complexes (C-1 to C-4)**

\[ [\text{C}_{33}\text{H}_{34}\text{Cl}_{2}\text{N}_{4}\text{O}_{8}\text{S}_{2}\text{Sn}] (C-1): \text{Dark brown colour; yield, 73.77\%; m.p. 223°C; FT-IR (KBr, } \nu \text{ cm}^{-1}): \nu \text{ CH} = \text{N (1612-1623 cm}^{-1}), \nu \text{ C-O-Cl (1090 cm}^{-1}), \nu \text{ SO}_{2} (1315-1325 \text{ cm}^{-1} \text{ (Sym.)}. \]  

\[ ^{1}H\text{-NMR: } \delta (\text{ppm}) = 8.49 (\text{S, 2H, CH} = \text{N}), 1.05 (\text{S, 2H, CH}_{2}), 3.71 (\text{S, 6H, OCH}_{3}), 6.87 (\text{d, 4H, } J = 3.5 \text{ Hz, 7.48 (dd, 4H, } J = 5 \text{ Hz, 7.66 (d, 4H, } J = 8.5 \text{ Hz, 6.58 (d, 4H, } J = 8.5 \text{ Hz).} \]  

\[ ^{13}C\text{-NMR: } \delta (\text{ppm}) = 169.3 (\text{CH} = \text{N}), 206.42 (\text{C=O}), 55.92 (\text{COCH}_{3}), 18.43 (\text{CH}_{3}), 137.7 (\text{Cl1}), 116.3 (\text{Cl2}), 127.30 (\text{Cl1}, \text{Cl2}), 130.09 (\text{C}), 122.12 (\text{C}), 123.86 (\text{C}), 114.35 (\text{C}), 168.7 (\text{C}), (\text{Ar-C). Mass (m/z): 868.42(M)+, 870.34 (M+2), 872.80 (M+4), 851.85 [C}_{33}\text{H}_{33}\text{Cl}_{2}\text{N}_{4}\text{O}_{7}\text{S}_{2}\text{Sn}]^{*}, 904.22 [C}_{33}\text{H}_{38}\text{Cl}_{2}\text{N}_{4}\text{O}_{10}\text{S}_{2}\text{Sn}^{*}, 905.75 [C}_{33}\text{H}_{39}\text{Cl}_{2}\text{N}_{4}\text{O}_{10}\text{S}_{2}\text{Sn}, \text{cal. 868.04; found 868.42.} \]
\[
[C_4_{2}H_{5}Cl_2N_8O_6S_2Sn]^{+}\text{(C-2): Red colour; yield, 52\%; m.p. 252°C; FT-IR (KBr, v cm\textsuperscript{-1}): v (CH=N) (1605 cm\textsuperscript{-1}), v NH (1070 cm\textsuperscript{-1}). ^1H-NMR: \delta (ppm) = 8.00 (S, 2H, CH=N), 11.66 (S, 2H, NH), 3.81 (S, 6H, OCH\textsubscript{3}), 6.90-8.00 (m, 16H, Aryl), 8.48 (d, 4H, H\textsubscript{diazine}), 7.02 (t, 2H, H\textsubscript{diazine}). ^13C-NMR: \delta (ppm) = 174.2 (CH=N), 55.8 (OCH\textsubscript{3}), 23.90 (CH\textsubscript{3}), 170.1 (C\textsubscript{1}), 110.1 (C\textsubscript{2}, C\textsubscript{3}), 168.9 (C\textsubscript{4}), 147.1 (C\textsubscript{5}), 124.0 (C\textsubscript{6}, C\textsubscript{10}), 127.3 (C\textsubscript{7}, C\textsubscript{8}), 139.7 (C\textsubscript{9}), 122.7 (C\textsubscript{i}), 114.3 (C\textsubscript{13}, C\textsubscript{15}), 160.6 (C\textsubscript{14}) (Ar-C). Mass (m/z): cal. 926.05; found 926.46.}
\]

\[
[C_4_{3}H_{41}Cl_2N_8O_6S_2Sn]^{+}\text{(C-3): Orange colour; yield, 79.80%; m.p. 309°C; FT-IR (KBr, v cm\textsuperscript{-1}): v CH=N (1598 cm\textsuperscript{-1}), v NH (1066 cm\textsuperscript{-1}). ^1H-NMR: \delta (ppm) = 8.50 (S, 2H, CH=N), 10.95 (S, 2H, NH), 3.81 (S, 6H, OCH\textsubscript{3}), 2.49 (d, 12H, J=1.5 Hz, CH\textsubscript{3}diazine), 7.01 (d, 4H, J= 8.7 Hz), 6.56 (d, 4H, J=8.7 Hz), 6.55-6.93 (m, 8H, Aryl). ^13C-NMR: \delta (ppm) = 81.26 (CH=N), 23.02 (CH\textsubscript{3}), 170.1 (C\textsubscript{1}), 157.9 (C\textsubscript{2}, C\textsubscript{4}), 127.6 (C\textsubscript{6}, C\textsubscript{10}), 125.7 (C\textsubscript{7}, C\textsubscript{9}), 127.3 (C\textsubscript{8}), 147.1 (C\textsubscript{14}) (Ar-C). Mass (m/z): cal. 954.08; found 954.52.}
\]

\[
[C_4_{4}H_{45}Cl_2N_8O_6S_2Sn]^{+}\text{(C-4): Mud colour; yield, 65.50%; m.p. 310°C; FT-IR (KBr, v cm\textsuperscript{-1}): v CH=N (1585 cm\textsuperscript{-1}), v NH (1066 cm\textsuperscript{-1}). ^1H-NMR: \delta (ppm) = 8.00 (S, 2H, CH=N), 11.68 (S, 2H, NH), 3.81 (S, 6H, OCH\textsubscript{3}), 2.50 (t, 6H, CH\textsubscript{3}), 6.93-9.20 (m, 16H, aryl), 8.11 (q, 4H, H\textsubscript{diazine}). ^13C-NMR: \delta (ppm) = 168.9 (CH=N), 55.8 (OCH\textsubscript{3}), 23.90 (CH\textsubscript{3}), 170.1 (C\textsubscript{1}), 110.1 (C\textsubscript{2}, C\textsubscript{3}), 168.9 (C\textsubscript{4}), 147.1 (C\textsubscript{5}), 124.0 (C\textsubscript{6}, C\textsubscript{10}), 127.3 (C\textsubscript{7}, C\textsubscript{8}), 139.7 (C\textsubscript{9}), 122.7 (C\textsubscript{i}), 114.3 (C\textsubscript{13}, C\textsubscript{15}), 160.6 (C\textsubscript{14}) (Ar-C). Mass (m/z): cal. 1010.14; found 1010.96.}
\]

**Antibacterial and Antifungal Activity**

Antibacterial activity of ligands \( \text{L}^1-\text{L}^3 \) as well as their Sn(II) complexes \( \text{C-1 to C-4} \) have studied by Broth dilution method\(^{35,36} \) and MIC values were calculated. Following bacterial strains viz. \( S. aureus, S. pyogenus \) (Gram-positive) and \( E. coli, P. aeruginosa \) (Gram-negative) were used. These strains were procured from institute of microbial technology, Chandigarh, India. Dimethyl sulfoxide solvent was used for serial dilution to receive the appropriate concentration of drugs.

In this method, stock solution of concentration 2000 µg/mL was prepared. In primary screening, the stock solution was diluted to give 1000, 500, 250 µg/mL concentration and screened for their activity and active drug then screened in secondary screening with 200, 100, 50, 25, 12.5, 6.2 µg/mL concentration. After serial dilution the control tube with lowest concentration was taken. The control tubes without antibiotic were immediately subcultured by uniform spreading over a quarter of plate of medium with the help of loop for growth of the test organism and control tubes incubated overnight at 37°C temperature. After incubation, turbidity was measured and microbial growth in the control tubes was compared. The control tubes before incubation represented the original inoculums. The effect of concentration of drug was checked after incubation and the control tube with lowest concentration of drug (lack of turbidity), was shown better inhibition in growth of bacteria. Inoculums size was adjusted to 10\(^{6}\) CFU/mL for bacterial test strain by comparing the turbidity in the tubes.

The antifungal activities of the synthesized compounds were tested against fungal strains \( \text{C. albicans, A. niger, A. clavatus} \) and MIC values were determined. SDB (Sabourand dextrose broth) medium was used for the fungal nutrition, which contains 10 g peptone (from casein), 40 g dextrose (glucose), 1L of distilled water, pH adjusted to 5.6 at 25°C\(^{37} \). Essential amount of the compounds was added into this medium in DMSO. Serial dilutions were prepared for primary and secondary screening as discussed in previous section. The control tubes were kept for incubation for 72 h at 22°C and MIC were recorded. Standard drug Greseofulvin was used.

**Antimalarial Activity**

\( \text{In vitro} \) antimalarial activities of all ligands and their Sn(II) complexes were evaluated against \( P. falciparum \) strain. In antimalarial activity we have used 96 well microtitre plates. The cultures of \( P. falciparum \) strain were maintained in the medium RPMI 1640 supplemented with 1% D-glucose, 25 Mm HEPS, NaHCO\(_3\) 0.23% and 10% heat inactivated human serum. In this method, prepared...
a stock solution of (5 µg/mL) of all test samples using DMSO.

Serial dilutions were prepared with culture medium in same solvent. 20 µL of the samples were diluted at five fold to give 0.4 µg/mL to 100 µg/mL concentration which were kept in the culture plates for incubation at 37°C for 36-40 h into a candle jar. Thin blood smears were prepared after incubation from each well then stained it with JSB stain. To record maturation of ring stage parasites into trophozoites and schizonts, slides were microscopically examined38-43 and percent inhibition in maturation, average rings of trophozoites and schizontes were recorded per 100 parasites from the duplicate wells. Results were expressed as IC50 value as depicted in Table 1.

RESULTS AND DISCUSSION

Preparation & Characterization of Sn(II) complexes

[Sn(L) 2Cl 2] type of complexes were prepared through the reaction of anhydrous tin dichloride with bi-dentate sulpha drug ligands in 1:2 molar ratio using three different solvents ethanol, MeTHF and THF were used and MeTHF solvent was found with best results. The reaction found to be quite facile and could be completed in 4-5 h of refluxing on oil bath. All newly synthesized complexes were obtained in the form of colored solid and the color of the complexes are associated with the presence of chromophoric azomethine group (>C=N–).

FT-IR gives the information about functional group attached to metal atom44. In FT-IR spectrum of all the complexes azomethine peak shifted towards lower frequency in Sn(II) complexes that represent bonding of azomethine nitrogen with metal ion. In the IR spectrum of ligands, stretching vibrations of >C=O group appeared at 1700-1720 cm⁻¹ and SO₂ group appeared at 1315-1350 cm⁻¹ (asymmetric) & 1150-1247 cm⁻¹ (symmetric) are not changed on complexation which indicates both groups (>C=O & SO₂) are not involved in coordination with metal. Two new bands appeared around at 519-555 cm⁻¹ and 410 cm⁻¹ due to ν M-N and ν M-Cl bonds confirm metal-ligand bonding, respectively.

Thermogravimetric Analysis (TGA)

The thermal decomposition analysis of synthesized complex C-3 was carried out under an inert nitrogen atmosphere (Fig. 4). A weight loss of 8% was observed between 100-230°C due to loss of two chlorine atoms. Another thermal decomposition occurs between 230-882°C with weight loss of 52% due to loss of remaining organic part. Total 60% weight loss was observed between 100-882°C. Heating rate was suitably controlled at 30°C minute⁻¹.

Thus TGA curve indicates presence of two chlorine atoms in the tin complex and tetrahedral geometry has been suggested having 1:2 stoichiometric ratio of Sn(II) and ligand, respectively.

Differential Thermal Analysis (DTA)

In DTA curve of C-3 complex two downward peaks around 250-290°C and 450-470°C were observed which indicate reaction is endothermic in nature.

Fig. 4.(a) TGA curve (b) DTA curve for C-3 complex
1H-NMR of azomethine nitrogen (–CH=N–) showed upfield shifting from δ 8.52-8.55 to 8.00-8.50 ppm in their tin complexes. This upfield shifting in complex indicate discharging of lone pair of nitrogen atom towards the metal ion. Methoxy proton appeared at δ 3.86-3.65 ppm as singlet, this indicates methoxy group is not involved in coordination with metal ion.

All aromatic protons shifted towards downfield region on complexation with the Sn metal ion. In C-1 and C-3 complexes ortho protons of aryl shifted towards downfield region at δ 7.38 to 7.66 ppm and δ 6.78 to 7.01 ppm, respectively due to complexation with metal.

The proposed structures (Fig. 3.) of tin(II) complexes (C-1 to C-4) is in good agreement with the spectral data presented and reported literature45-46. In13C-NMR spectra of C-3 complex, a downfield shifting was observed in the azomethine carbons from δ 158.14-162.39 ppm (free ligands) to δ 169.3-174.2 ppm (tin complexes) may be due to shifting of lone pair of nitrogen towards metal ion. Similarly all phenyl ring carbons shifted towards downfield region by 0.1-0.40 ppm.

Mass fragmentation pattern of all Schiff base ligands (L1-L4) and their complexes (C-1 to C-4) were recorded. LC-MS of Schiff base L3 and its tin complex C-3 were explained here. The molecular ion peaks at m/e 396.74 and 1010.96 attributed to the ligand & its complex, respectively. Mass spectra of the complex C-3 showed peaks at m/e 1010.96, 1012.25, 1014.58, 1031.30 and 1016.85 corresponding to (M+), (M+2), (M+4), [C61H41Cl2N8O6S2Sn]+ and [C41H42Cl2N8O5S2Sn]+, respectively and confirms that complex contains two chlorine atoms.

**Antibacterial Activity**

Results of antibacterial activity indicate that the C-3 complex was found most active (MIC, 55.6 µg/mL) against E. coli. Further C-2 was found more active and C-3, C-4 was found with good activity against Gram-negative P. aeruginosa. C-1, C-2 and C-3 complexes were found with good activity against S. aureus bacteria. Complex C-1 was found with better activity against S. pyogenus bacteria. L3 was found with better activity (MIC, 52 µg/mL) against the pathogen E. coli. Thus these results indicate that complexes exhibit better activity than the ligands.

**Antifungal Activity**

The antifungal activity of four Schiff base ligands (L1-L4) and their complexes (C-1 to C-4) were tested against fungal strains C. albicans, A. niger and A. clavatus. Complex C-3 exhibit better activity (MIC, 250 µg/mL) and complex C-1 was found with good activity (MIC, 500 µg/mL) against C. albicans. C-3 complex was found with better activity (MIC, 100 µg/mL) and C-1, C-2, C-4 complexes showed good activity against A. Niger. C-4 complex was found with good activity (MIC, 250 µg/mL) against A. clavatus bacteria. Greseofulvin drug was used against the bacteria. L3 and L4 showed with good activity against A. niger and C. albicans (MIC, 250 µg/mL). These results indicate that the complexes show good activity than the ligands.

**Antimalarial Activities**

In vitro antimalarial activities of ligands (L1-L4) and their complexes (C-1 to C-4) were evaluated against parasite P. falciparum strain. Results of antimalarial activity were expressed as IC50 value (Table 1). The smaller IC50 value indicates higher the antimalarial activity. Chloroquine was used as control drug in this study. Complex C-3 was found more active against chloroquine (IC50, 0.04 µg/mL) and complex C-1 was found with good activity (IC50, 0.07 µg/mL) than other complexes. L3 showed with good activity against chloroquine (IC50, 0.10 µg/mL) than other complexes. These results indicate that complexes are more significant than the ligands.

**Table 1: Result of antibacterial, antifungal and antimalarial activities of Schiff base ligands (L1-L4) and complexes (C-1 to C-4)**

| S. No. | Compound | Antibacterial activity (MIC, µg/mL) | Antifungal activity (MIC, µg/mL) | Antimalarial activity (MIC, µg/mL) |
|--------|----------|----------------------------------|-------------------------------|----------------------------------|
|        |          | E. coli (MTCC 443) | P. aeruginosa (MTCC 441) | S. aureus (MTCC 96) | S. pyogenus (MTCC 442) | C. albicans (MTCC 227) | A. niger (MTCC 282) | A. clavatus (MTCC 1323) | P. falciparum |
| 1      | L1       | 62.5          | 100          | 100          | 100          | 500          | 1000          | 0.14 µg/mL |
| 2      | L2       | 100           | 125          | 125          | 125          | 500          | 250           | 1.36 µg/mL |
| 3      | L3       | 52            | 125          | 61.3         | 100          | 500          | 250           | 0.10 µg/mL |
| 4      | L4       | 125           | 250          | 100          | 125          | 250          | 250           | 0.19 µg/mL |
| 5      | C-1      | 55.6          | 100          | 65.6         | 125          | 500          | 250           | 0.07 µg/mL |
| 6      | C-2      | 100           | 62.5         | 100          | 125          | 500          | 250           | 0.90 µg/mL |
| 7      | C-3      | 50            | 100          | 51.5         | 100          | 250          | 500           | 0.04 µg/mL |
| 8      | C-4      | 250           | 125          | 100          | 250          | 250          | 200           | 0.40 µg/mL |
|        | Standard drugs | 25          | 25          | 50          | 50          | 50          | 100           | 0.020 µg/mL |
Structure Activity Relationship (SAR) studies

To look at the structure activity relationship (SAR) of sulpha drug Schiff base ligands, the variations were determined on one end of sulphonamide moiety with six membered two heteroatoms with alkyl groups. On the other hand azomethine linkage was responsible for biological activity. Among the four complexes (C-1 to C-4), complex C-3 was found to be best antibacterial, antifungal and antimalarial agent due to sulphadiazine moiety and two methyl substituents.

Moreover, comparative study of biological activities of all the tested Schiff bases and their complexes revealed that Sn(II) complexes are more active as compared to respective ligands.

CONCLUSION

In our present studies, sulpha drugs based Schiffbases and their Sn(II) complexes (C-1 to C-4) were prepared in MeTHF by conventional method and characterized by various techniques. Thus Schiff bases can bind with metal ion through N-atom and tetrahedral geometry is proposed. All the Schiff base ligands and their complexes were screened for antibacterial, antifungal and antimalarial activities. Complex having sulphadiazene moiety has presented good antibacterial, antifungal and antimalarial activity. It was concluded that Sn(II) complexes are more active as compare to respective ligands.

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Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. Abbas, S.A.; Munir, M.; Fatima, A.; Naheed, S.; Ilyas, Z.; Electronic J. of Life Science., 2010, 1, 37-40.
2. El-Mossalamy, E.H.; Al-Thabati, S.A.; Al-Nowalser, F.M.; Al-Sulami, Q.A.; Communications Faculty of Sciences University of Ankara Series B., 2005, 51, 21-30.
3. Li, Y.; Yang, Z.S.; Zhang, H.; Cao, B.J.; Wang, F.D.; Bioorg.&Med. Chem., 2003, 11, 4363-4368.
4. Villar, R.; Encio, I.; Migliaccio, M.; Gil, M.G.; Martinez-Merino, V.; Bioorg. & Med. Chem., 2004, 12, 963-968.
5. Panneerselvam, P.; Nair, R.R.; Vijayalakshmi, G.; Subramanian, E.H.; Sridhar, S.K.; Eur. J. Med. Chem., 2005, 40(2), 225-229.
6. Bhat, M.A.; Imran, M.; Khan, S.A.; Siddiqui, N.J.; Pharm. Sci., 2005, 67, 151-159.
7. Wang, L.; Feng, Y.; Xue, J.; Li, Y. J.; Serbian Chem. Soc., 2008, 73, 1-6.
8. Wadhner, S.J.; Puranik, M.P.; Karande, N.A.; Yeole, P.G.; Int. J. Pharm. Tech. Res., 2009, 1, 22-33.
9. Matela, G.; Anti-cancer agents in medicinal chemistry., 2020, 20, 1908-1917.
10. Zoubi, W.A.; Int. J. of Org. Chem., 2013, 3, 73-95.
11. Prakash, A.; Adhikari, D. J.; Pharm. Tech. Res., 2011, 3-4, 1891-1896.
12. Mostafa, A.A.; Al-Askar, A.A.; Almaary, K.S.; Dawoud, T.M.; Sholkamy, E.N.; Bakri, M.M.; Saudi J. of Biological Sciences., 2018, 25, 361-366.
13. Balouiri, M.; Sadiki, M.; Ibsnsouda, S.K.; J. of pharma. Analysis., 2016, 6, 71-79.
14. Silva, C.M.; Silva, D.L.; Modolo, L.V.; Alves, R.B.; Reuse, M.A.; Martins, C.V.B.; Fatima, A.D.; J. of Adv. Res., 2011, 2, 1-8.
15. Chukwujekwu, J.C.; Staden, J.V.; Smith, P.; South African. J. of Botany., 2005, 71, 316-325.
16. Rudrapal, M.; Chetia, D.; Prakash, A.; Med. Chem. Res., 2013, 22, 3703-3711.
17. Chauhan, L.K.; Nimodia, K.; Ranawat, P.S.; Goswami, A.K.; Baroliya, P.K.; Orient. J. Chem., 2020, 36(5), 855-862.
18. Regar, M.; Baroliya, PK.; Patidar, A.; Dashora, R.; Mehta, A.; Chauhan, R.S.; Goswami, A.K.; Pharmaceutical Chemistry journal., 2016, 50, 5.
19. Dayma, V.; Chopra, J.; Sharma, P.; Dwivedi, A.; Tripathi, I.P.; Bhargava, A.; Murugesan, V.; Goswami, A.K.; Baroliya, P.K.; Heliyon., 2020, 6, 4787.
20. Patil, U.; Khan, A.; Nagarsekhar, A.; Mandewale, M.; Yamgar, R.; Orient. J. Chem., 2018, 34(6), 2796-2805.
21. (a) Supuran, C.T.; Casini, A.; Scozzafava, A.; Med. Res. Rev., 2003, 5, 535. (b) Scozzafava, A.; Owa, T.; Mastrolirenzo, A.; Supuran, C.T.; Curr. Med. Chem., 2003, 10, 925.

22. Kelemann, A.; Engel, J.; Kutscher, B.; Reichert, D.; Eds. Pharmaceutical Substances, Syntheses, Patents, Applications., (Thieme, Stuttgart., 1999).

23. Domagk, G. Chemotherapy of bacterial infections. Dtsch. Med. Wochensch., 1935, 61, 250-253.

24. Domagk G. A new class of disinfectants. Dtsch. Med. Wochensch., 1935, 61, 829-832.

25. Mahmood-ul, H.; J. Enzyme Inhibition & Med. Chem., 2004, 19, 263-267.

26. Singh, V.; Kaushik, N.K.; Singh, R.; Asian J. Research Chem., 2011, 4(3), 339-347.

27. Downes, F.P.; Ito, K. Compendium of Methods for the Microbiological Examination of Food 4th ed, APHA, Washington., 2001.

28. Singh, J. J. S. B. Stain.; A review. Indian J. Malaria., 1956, 10, 117-129.

29. Abu-Khadra, A.S.; Afify, A.S.; Mohamed, A.; Farag, R.S.; Aboul-Enein, H.Y.; The Open Bioactive Compounds Journal, 2018, 6, 1-10.

30. Bhatra, P.; Sharma, J.; Sharma, R.A.; Singh, Y.; Appl. Org. Chem., 2017, 31, 3639.