Synthesis, Characterization and Biological Evaluation of Schiff Base (*N*-4-(thiophene-2-yl-methyleneamino)-2,6-dimethylpyrimidine-4-yl)benzenesulfonamide and its Complexes with Cu(II), Ni(II), Co(II), Fe(II), Mn(II), Zn(II) Ions

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Two step synthesis of Schiff base ligand and its transition metal complexes was done by condensation reaction. In first step, the drug and aldehyde in equimolar ratio were refluxed for one hour at pH 8-9 in order to get Schiff base ligand. In second step, ligand and metal salts were refluxed for 2 hour. The ligand and Cu(II), Ni(II), Co(II), Fe(II), Mn(II), Zn(II) complexes were characterized by using different instruments like FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass, Atomic absorption spectrometer, Elemental analyzer, UV-visible spectrophotometer, Evans balance, Conductivitymeter and Thermogravimeter. In vitro antibacterial, antifungal and anti-inflammatory activities were also studied. The synthesized ligand and transition metal complexes were tested against Escherichia coli, Enterobacter aerogenes, Staphylococcus aureus, Bacillus pumilus, Klebsiella oxytoca, Clostridium butyrium, Mucor and Aspergillus niger. These studies demonstrated the enhanced activity of metal complexes against reported bacterial and fungal strains when compared with free Schiff base ligand. The Cu(II) complex recognized as anti-inflammatory agent while the parent drug showed no activity.

Keywords: Schiff base, metal complex, sulfisomidine, thiophene-2-carboxaldehyde, bacteria, fungi

The Schiff base metal complexes have been known since the mid 19th century and even before the report of general arrangement of the Schiff base ligands. The interest in organic chelating ligands and their metal complexes are increasing day by day. Their importance is expanding scholarly, commercially and biochemically, therefore, they have brought development, in the fields of organometallic chemistry, homogenous catalysis and bio-inorganic science. Among the chelating ligands, Schiff bases have attracted scientists because of the simple synthesis and complex formation. Schiff bases have the azomethine unit as a functional group and are generally shaped by the buildup of primary amine with a dynamic carbonyl compound [1, 2]. Many drugs have improved pharmacological properties when forms Schiff base metal complexes. The Schiff base metal chelates have gained attention in fields like medicine and pharmaceutical because of wide spectrum of biological activities such as anti-inflammatory drugs, antimicrobial, antifungal, antispasmodic, tuberculosis, anticancer, anthelmintic, antioxidant and so forth [3-10].

Mumtaz et al. synthesized a series of copper(II), cobalt(II), zinc(II), nickel(II), manganese(II), iron(II) complexes of a novel Schiff base prepared by the condensation of sulphadizine and pyridoxal hydrochloride. Schiff base and its metal complexes were characterized by thermogravimetric examination and spectroscopy. The integrated ligand and transition metal complexes were screened against various bacteria and fungus. The studies demonstrated the enhanced activity of metal complexes against reported microbes compared to free ligand [11].

Schiff bases include have a wide variety of applications in organic and inorganic chemistry. Aside from biological activities, Schiff bases are additionally utilized as catalysts [12-14], dyes and pigments, polymers and corrosion inhibitors [15-21]. Schiff bases assumed an impact part in the improvement of coordination science and were included as key point in the advancement of inorganic biochemistry and optical materials [22].

In this context, the new derivatives of sulfisomidine were synthesized in order to obtained potential antimicrobial agents with higher activities. The drug molecule used to study recognized very suitable for the formation of chelate compound as it have amino group (-NH_2). Therefore, Schiff base ligand and its Cu(II), Ni(II), Co(II), Fe(II), Mn(II), Zn(II) complexes were prepared by reacting sulfisomidine and thiophene-2-carboxaldehyde at specific conditions;

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then characterization was done with different techniques. Schiff base ligand and its transition metal complexes were screened for their antibacterial, antifungal and anti-inflammatory activities.

Experimental part

Material and methods

Pure chemicals and solvents were used throughout the studies. Sulfisomidine and thiophene-2-carboxaldehyde were taken from BDH while other chemicals and solvents were purchased from Alfa Aesar. Microanalysis was performed utilizing normal strategies. Metals in the complexes were assessed by atomic absorption spectroscopy. Basic investigations were resolved on a CE-440 Elemental analyzer, FT-IR spectra were recorded with a Perkin Elmer Spectrum-100 spectrometer utilizing KBr plates. ^{1}H-NMR, ^{13}C-NMR spectra were measured on a Jeol ECS 400 spectrometer. Mass spectra were measured with the assistance of Thermo Scientific Exactive TM PlusOrbitrap spectrometer. Thermogravimetric analyzes for the molecules were completed on a SDT-Q600 instrument. Magnetic moments were estimated using Evans balance with anhydrous calcium chloride. Electronic absorption spectra of all the complexes were recorded on a Shimadzu-1800 spectrophotometer. Jenway-4510 conductivitymeter was used for conductance measurement of the complexes by using DMSO (10^{-3} mol.L^{-1}) as a solvent.

Step - I: Preparation of Schiff base ligand

1.0 mmole of sulfisomidine was dissolved in 2.0 ml (1N) sodium hydroxide. To this, ethanolic solution of thiophene-2-carboxaldehyde (1.0 mmole) was added and refluxed for one hour (Fig. 1). The Schiff base ligand was formed as a crystalline product; It was filtered. The crystalline product was washed with absolute alcohol, dried under vacuum and kept in a desiccator for further"use.

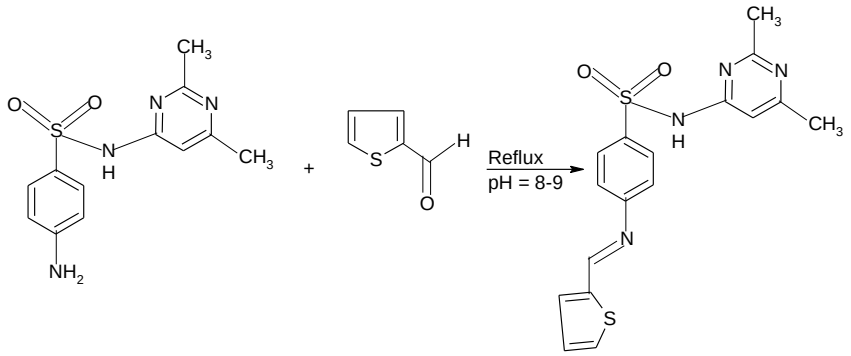

Fig. 1. Preparation of Schiff base ligand

Step - II: Preparation of Schiff base metal complexes

Preparation of Cu(II), Ni(II), Co(II), Fe(II), Mn(II), Zn(II) complexes was done by using the same protocol as described in literature. The metal(II) salts and ligand were dissolved in ethanol separately and mixed with 1:2 ratio (Fig. 2). The reaction mixture was then refluxed for 2 hour. After preparation, the colored precipitates of Schiff base metal complexes were filtered off, washed with water and ethyl alcohol respectively and dried under reduced pressure at room temperature.

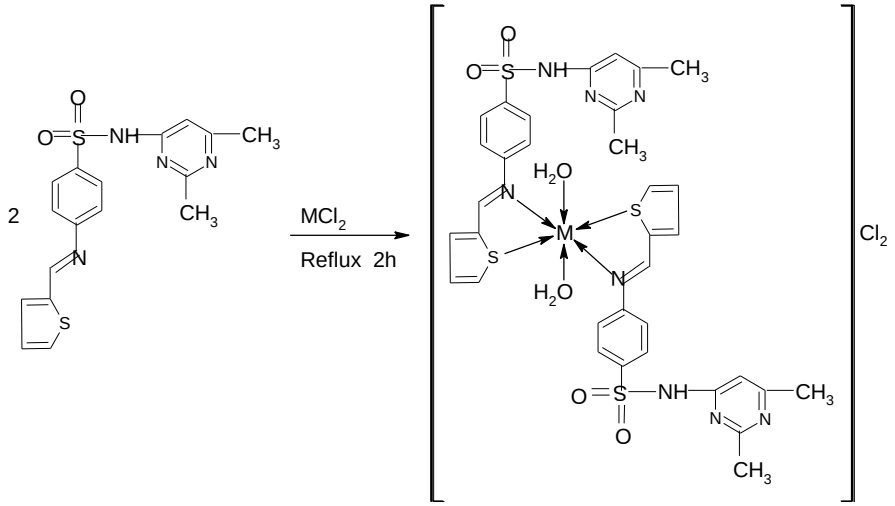

Fig. 2. Preparation of Schiff base metal complexes

M = Cu(II), Ni(II), Co(II), Fe(II), Mn(II), Zn(II)

Biological assay

In vitro antimicrobial and antifungal tests were estimated by agar well diffusion method [23]. The antimicrobial and antifungal activities of synthesized compounds were investigated against *Escherichia coli, Enterobacter aerogenes, Staphylococcus aureus, Bacillus pumilus, Klebsiella oxytoca, Clostridium butyrium. Mucor, Aspergillus niger.* In vitro anti-inflammatory activity was determined by Oxidative Burst Assay using chemiluminescence technique [24].

Results and discussions

The synthesis of ligand was accomplished by refluxing the sulfisomidine and thiophene-2- carboxaldehyde in a molar ratio 1:1 in ethanol. The metal complexes of ligand were prepared using metal(II) chloride and ligand in a 1:2 molar ratio. The structure elucidation of Schiff base and complexes was done with Elemental analyzer, FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, Thermogravimetric analysis and Microanalytical data. All the metal complexes are amorphous solids and have decomposition point; they are insoluble in water, organic solvents, partially soluble in acetone and completely soluble in DMF and DMSO. Molar conductance values (75-144 $\mu S.cm^{-1}$) point out the electrolytic nature of metal complexes. The structures of synthesized Schiff base ligand along with metal complexes were investigated by different techniques.

Synthesis of (N-4-(thiophene-2-yl-methyleneamino)-2,6-dimethylpyrimidine-4-yl)benzene-sulfonamide (Schiff base ligand)

Yield: 70 % (Pale Yellow); m.p. 170-173^{o}C; IR (KBr, cm^{-1}): 3266 (OH), 1611 (HC=N azomethine), 1590 (C=N-pyrimidine), 1141 (O=S=O), 1080 (C-N);

Anal.: Calcd. for $C_{15}H_{16}N_4O_2S_2$ (372.477); Calcd.: C, 54.76; H, 4.29; N, 15.03 %;

Found: C, 54.69; H, 4.35; N, 15.03 %;

^{1}H-NMR (DMSO-d_6, δ ppm): 10.21 (NH), 8.75 (-CH=N), 8.11-7.22 (phenyl), 2.14-2.04 (-CH_3);

^{13}C-NMR (DMSO-d_6, δ ppm): 163.1 (-CH=N), 121.1-135.6 (-C- thiophene), 122.1-149.2 (phenyl), 22.4-22.9 (-CH_3); MS (EI): m/z (%) = 373.0680 [M^+].

Cu(II) complex

Yield: 71 % (Blue); d.p. 210-214^{o}C; IR (KBr, cm^{-1}): 3376 (OH), 1620 (HC=N azomethine), 1590 (C=N-pyrimidine), 1195(O=S=O), 417(M-N), 351(M-O); UV-Vis (DMSO), λ_{max}(cm^{-1}): 15350, 24332; B.M. (1.83 μ_{eff}); molar conductance (131 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Cu$ (920.46); Calcd.: C, 52.17; H, 3.91; N, 13.26; Cu, 6.90 %; Found: C, 52.50; H, 3.87; N, 13.36; Cu, 7.10 %.

Co(II) complex

Yield: 70 % (Pink); d.p. 229-231^{o}C; IR (KBr, cm^{-1}): 3263 (OH), 1615 (HC=N azomethine), 1596 (C=N-pyrimidine), 1181(O=S=O), 436(M-N), 353(M-O); UV-Vis (DMSO), λ_{max}(cm^{-1}): 14792, 16286; B.M. (4.75 μ_{eff}); molar conductance (137 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Co$ (915.85); Calcd.: C, 52.41; H, 3.93; N, 13.33; Co, 6.43 %; Found: C, 52.62; H, 3.88; N, 13.38; Co, 6.72 %.

Zn(II) complex

Yield: 72 % (Pale yellow); d.p. 228-230^{o}C; IR (KBr, cm^{-1}): 3333 (OH), 1616 (HC=N azomethine), 1589 (C=N-pyrimidine), 1188 (O=S=O), 470 (M-N), 340 (M-O); UV-Vis (DMSO), λ_{max}(cm^{-1}): 28328; Diamagnetic; molar conductance (100 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Zn$ (922.30); Calcd.: C, 52.03; H, 3.90; N, 13.23; Zn, 7.08 %; Found: C, 52.39; H, 3.70; N, 13.29; Zn, 7.19 %.

Ni(II) complex

Yield: 71 % (Green); d.p. 219-222^{o}C; IR (KBr, cm^{-1}): 3371 (OH), 1613 (HC=N azomethine), 1589 (C=N-pyrimidine), 1188(O=S=O), 470(M-N), 340(M-O); UV-Vis (DMSO), λ_{max}(cm^{-1}): 16230, 25248; B.M (3.17 μ_{eff}); molar conductance (139 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Ni$ (915.61); Calcd.: C, 52.42; H, 3.93; N, 13.33; Ni, 6.02 %;

Found: C, 52.39; H, 4.01; N, 13.41; Ni, 6.35 %.

Mn(II) complex

Yield: 72 % (Light brown); d.p. 210-214ºC; IR (KBr, cm^{-1}): 3371 (OH), 1613 (HC=N azomethine), 1597 (C=N-pyrimidine), 1155 (O=S=O), 470 (M-N), 341 (M-O); UV-Vis (DMSO), $\lambda_{max}(cm^{-1})$: 18507, 28461; B.M. (5.01 μ_{eff}); molar conductance (75 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Mn$ (911.86); Calcd.: C, 52.63; H, 3.9; N, 13.39; Mn, 6.02 %;

Found: C, 52.63; H, 3.91; N, 13.38; Mn, 5.99 %.

Fe(II) complex

Yield: 75 % (Brown); d..p. 219-223ºC; IR (KBr, cm^{-1}): 3440 (OH), 1619 (HC=N azomethine), 1593 (C=N-pyrimidine), 1181 (O=S=O), 466 (M-N), 350 (M-O); UV-Vis (DMSO), $\lambda_{max}(cm^{-1})$: 19230, 34722; B.M. (5.54 μ_{eff}); molar conductance (144 $\mu S.cm^{-1}$);

Anal.: Calcd. for $C_{34}H_{32}N_8O_4S_4Fe$ (912.76); Calcd.: C, 52.58; H, 3.94; N, 13.38; Fe, 6.11 %;

Found: C, 52.33; H, 3.81; N, 13.42; Fe, 6.30 %.

NMR spectra

^{1}H-NMR and ^{13}C-NMR spectra were taken in DMSO-d_6. The peaks of all the proton and carbon atoms were fixed in their expected region. The NMR spectrum of Schiff base ligand confirmed the absence of aldehyde peak at δ 9-10 ppm and presence of azomethine at δ 8.75 ppm. Phenyl protons appeared at δ 8.11-7.22 ppm while the methyl protons showed values at δ 2.14-2.04 ppm. ^{13}C-NMR spectra also verify azomethine peak at δ 163.1 ppm. The peaks of other groups in ligand showed values δ 121.1-135.6 ppm (thiophene carbon), δ 122.1-149.2 ppm (phenyl) and δ 22.4-22.9 ppm (-CH_3) respectively.

The diamagnetic Zn(II) complex showed a slight change in spectra because of increased conjugation and coordination to metal ion.

FT-IR spectra

The metal-ligand bond was verified by comparing the IR spectrum of the Schiff base ligand with metal(II) complexes. The FT-IR spectra predicted all the absorption bands of the Schiff base ligand and some new bands at specific frequency confirmed the modes of absorption and the coordination of the ligand with the metal ions through nitrogen and sulfur. The azomethine group of ligand 1611 cm^{-1} was shifted to value 1613-1620 cm^{-1} in all the complexes thus suggested the coordination of metal to ligand bond through azomethine (HC=N). Absorption bands of the sulfonamides moiety in the synthesized ligand and in metal complexes have same frequency. Further definitive proof of the coordination of the Schiff base with the metal ions was confirmed by the appearance new bands at 417-470 cm^{-1} and 340-353 cm^{-1} designate to the metal-nitrogen ν(M-N) and metal-sulfur ν(M-S) extending vibrations, individually [25, 26]. These bands were not present in the spectrum of the free ligand, therefore affirming the presence of S and N in the coordination.

Moreover, the C=N stretching vibrations of pyrimidine ring were observed in ligand at 1590 cm^{-1} shifted slightly in all the metal complexes, indicating that these groups are not involved in coordination. The water-containing complexes present a broad diffuse band of medium intensity in the 3263–3440 cm^{-1} region which may be assigned to the OH stretching vibration for the coordinated water [27].

Electronic spectra and magnetic susceptibility

The geometry of metal complexes was also confirmed on the basis of data collected through electronic absorption spectra and magnetic moment. The values of transition metal(II) complexes were obtained in DMSO (10^{-3} M solutions of each complex) at room temperature. The electronic absorption spectra and magnetic moment values suggested their octahedral geometry as shown in (table 1) [28, 29].

Table 1

UV-VIS. ASSIGNMENT AND MAGNETIC MOMENT OF TRANSITION METAL COMPLEXES

S. No.	Metal complexes	$\lambda_{max}(cm^{-1})$	Tentative assignment	B.M. (μ_{eff})
1.	$[Cu(LH)_2(H_2O)_2]Cl_2$	15350	$^2E_g \rightarrow {}^2T_{2g}$	1.83
2.	$[Co(LH)_2(H_2O)_2]Cl_2$	14792, 16286	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	4.57
3.	$[Zn(LH)_2(H_2O)_2]Cl_2$	28328	Ligand → metal	Diamagnetic

4.	$[Ni(LH)_2(H_2O)_2]Cl_2$	16230, 25248	$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$	3.17
5.	$[Mn(LH)_2(H_2O)_2]Cl_2$	18507, 28461	$^6A_{1g} \rightarrow {}^4A_{1g}(G)$ $^6A_{1g} \rightarrow {}^4A_{1g}, {}^4E_g$	5.01
6.	$[Fe(LH)_2(H_2O)_2]Cl_2$	19230	$^5T_{2g} \rightarrow {}^5E_g$	5.54

Thermal studies

Thermogravimetric analyzes (TGA) for the transition metal complexes were done from room temperature to 1000˚C. The decomposition steps are same in all metal complexes as calculated and found mass losses have little difference in values.

First step of decomposition was due to the loss of two coordinated water molecules in the complexes.

In second step of thermolysis curve a sharp decrease in weight indicated a loss of part of Schiff base ligand(2-iminopyrimidine) and loss of $2SO_2$ from the complexes (table 2) [30, 31].

Table 2
THERMAL ANALYSIS DATA OF THE METAL(II) COMPLEXES

S. No.	Metal complexes	Temperature range (ºC)	Mass loss (%) Found (Calculated)	Assignment
1.	$[Cu(LH)_2(H_2O)_2]Cl_2$	118-227 227-374	4.33(4.26) 34.11(34.12)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$
2.	$[Co(LH)_2(H_2O)_2]Cl_2$	122-251 251-370	4.31(4.28) 33.99(34.31)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$
3.	$[Zn(LH)_2(H_2O)_2]Cl_2$	120-230 230-355	4.41(4.25) 34.22(34.04)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$
4.	$[Ni(LH)_2(H_2O)_2]Cl_2$	125-250 250-365	4.39(4.28) 33.95(34.12)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$
5.	$[Mn(LH)_2(H_2O)_2]Cl_2$	120-235 235-375	4.25(4.30) 34.29(34.47)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$
6.	$[Fe(LH)_2(H_2O)_2]Cl_2$	125-245 245-365	4.48(4.30) 34.15(34.43)	Loss of $2H_2O$ Loss of (2-iminopyrimidine) + Loss of $2SO_2$

Biological activity

Antimicrobial and Antifungal activities

Antimicrobial and antifungal activities of all the synthesized transition metal complexes and Schiff base ligand were tested against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Bacillus pumilus*, *Klebsiella oxytoca*, *Clostridium butyrium* and *Mucor*, *Aspergillus niger* by using Agar well method. The results showed enhanced activity when coordinated with transition metals (Table 3). It was reported previously that metal complexes suppressed the microorganism growth and involved in blocking the proteins.

Presently, various bacteria (*E.coli*, *E.aerogenes*, *S.aureus*, *B.pumilus*, *K.oxytoca*, *C.butyrium*) and fungal strains (*Mucor* and *A. niger*) were used to investigate the inhibitory effects of newly synthesized Schiff base metal complexes.

All compounds were found to be significantly active against bacterial and fungal strains when compared with ligand and reference drug. No significant different was found between reference drug and ligand for their antimicrobial activities.

Both fungal strains including *Mucor* and *A. niger* were found to be resistance against reference drug and ligand. Metal complexes easily penetrate into the lipid membrane and block the enzymes in the microorganism. Metal complexes convert the super coiled DNA to open chain and cleave the DNA in the presence H_2O_2 [32, 33].

Table 3
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SCHIFF BASE LIGAND AND ITS METAL COMPLEXES (zone of inhibition - mm; 350 μg.mL^{-1})

Compounds	E. coli (mm)	E. aerogenes (mm)	S. aureus (mm)	B. pumilus (mm)	K. oxytoca (mm)	C. butyrium (mm)	A. niger (mm)	Mucor (mm)
$[Cu(LH)_2(H_2O)_2]Cl_2$	17±0.29	15±0.14	19±0.31	16±0.18	11±0.29	13±0.22	12±0.09	17±0.22
$[Co(LH)_2(H_2O)_2]Cl_2$	12±0.21	12±0.23	12±0.14	13±0.20	-	10±0.26	10±0.12	12±0.15
$[Zn(LH)_2(H_2O)_2]Cl_2$	18±0.19	17±0.16	15±0.22	19±0.14	12±0.14	17±0.25	12±0.15	18±0.09
$[Ni(LH)_2(H_2O)_2]Cl_2$	16±0.25	16±0.22	20±0.21	15±0.23	12±0.15	140±0.22	11±0.18	14±0.17
$[Mn(LH)_2(H_2O)_2]Cl_2$	11±0.12	12±0.23	15±0.19	13±0.18	11±0.22	15±0.19	12±0.22	13±0.19
$[Fe(LH)_2(H_2O)_2]Cl_2$	15±0.17	14±0.21	13±0.16	12±0.22	10±0.17	10±0.18	10±0.25	13±0.24
Ligand (LH)	9±0.18	10±0.21	11±0.22	10±0.14	9±0.20	9±0.23	-	-
Drug	8±0.21	7±0.19	10±0.16	8±0.28	7±0.28	9±0.25	-	-

Anti-inflammatory activity

Anti-inflammatory activity of all the synthesized transition metal complexes and Schiff base ligand was done by Oxidative Burst Assay using Chemiluminescence Technique.

The Co(II), Zn(II), Ni(II), Mn(II) and Fe(II) complexes showed no activity.

In case of anti-inflammatory effect, the Cu(II) complex exhibited good anti-inflammatory activity (IC_{50}: 14.3 ± 0.9) compared with ibuprofen (11.2 ± 1.9).

Conclusions

The main objectives of this research work were to synthesize new Schiff base ligands and their corresponding transition metal complexes, their spectroscopic characterization and their use as potent anti-inflammatory, antimicrobial & antifungal agents. The results obtained after investigation demonstrated that the derivatives of drugs showed enhanced activities against chosen strains of microbes. The parent drugs having no inflammatory activity become active on complexation with Cu(II). The metal complexes additionally demonstrate action against *Mucor* and *Aspergillus niger* though parent drug and ligand showed no antifungal activity. These observations, in accordance with different studies, prescribe that metal based drugs have potential as therapeutics.

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