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COPPER (II) COMPLEXES OF SCHIFF BASE TRIDENTATE LIGANDS: SYNTHESIS AND THEIR ANTI-MICROBIAL ACTIVITIES

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ABSTRACT

Two new Schiff base tridentate ligands (*E*)-2-(3-hydroxy-4-methoxybenzalidene)-N^4-methylhydrazinecarbothioamide (**L^4**) and (*E*)-2-(3,4-dihydroxybenzalidene)-hydrazinecarboamide (**L^5**) derived from simple condensation of 3-hydroxy-4-methoxybenzaldehyde and 3,4-dihydroxybenzaldehyde with N^4-methylthiosemicarbazide and semicarbazide hydrochloride respectively. Schiff base Copper (II) complexes (**4a-b, 5a-b**) derived from Schiff base bidentate ligand L^4 and L^5 with $CuCl_2.2H_2O$ (4a and 5a) and $CuBr_2$ (4b and 5b) respectively. The synthesized Schiff bases have been characterized by microanalysis, FT-IR, ^{1}H NMR and ^{13}C NMR. The copper (II) complexes have been characterized by microanalysis and FT-IR. All Schiff bases and copper (II) complexes showed good activity against the Gram- positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis)*, Gram-negative bacteria (*Escherichia coli* and *Salmonella paratyphi)* and fungi (*Aspergillus niger and Candida albicans*). The antimicrobial results also indicate that the copper (II) complexes are better antimicrobial agents as compared to the Schiff bases.

KEYWORDS: Schiff base, Copper complex, Anti-bacterial activity, Anti-fungal activity.

INTRODUCTION

The synthesis of new compounds that are used for the treatment of infections with less secondary effects is a biomedical problem.[1,2] Recently research has focused increasingly on the synthesis of transition metal complexes with Schiff-type ligands, due to the biological properties that they present. Many compounds derived from Schiff bases exhibit antibacterial, antifungal, antitumor and anti-HIV activities.[3–14] Schiff bases derived from salicylaldehyde represent an important class of ligands due to their ability to be used in various fields.[15–19]

Having a high capacity chelating and redox potential the positive Cu^{2+} ion is biologically active, and participates in many processes in the body.[20–22] Copper complexes are also among the most potent antiviral, antitumor and anti-inflammatory agents.[23] In addition, it was found that most of benzocaine-containing compounds are biologically active. Recent research has demonstrated that, these derivatives exhibit antimicrobial activity against different species.[24–26]

In our previous work, we synthesized and screened an *in-vitro* anti-bacterial and anti-fungal activities of three new Schiff base ligands (**L^1-L^3**) and their copper (II) and Zinc (II) complexes (**1a-c, 2a-c, 3a-c**) of L^1-L^3 (**Fig.1).** Complexes **1a** and **1b** were found to be very active against bacteria and fungi compared to all other ligands and complexes.[27]

Previous work

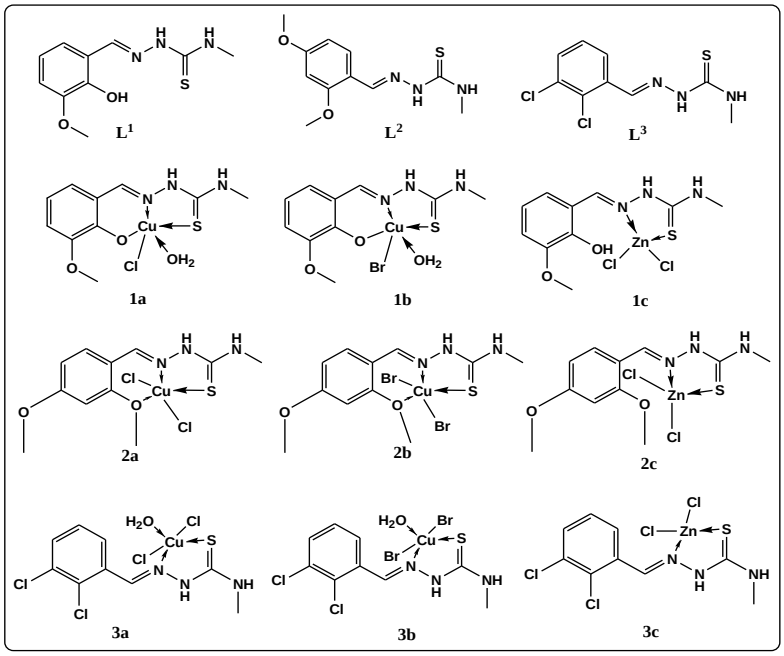


Fig. 1: Structures of Schiff base ligand L^1-L^3 and their complexes 1a-c, 2a-c, 3a-c

In the present work, we report the four copper (II) complexes (**4a-b, 5a-b**) obtained from copper (II) halides with Schiff base tridentate ligands of (*E*)-2-(3-hydroxy-4-methoxybenzalidene)-N^4-methylhydrazinecarbothioamide (**L^4**) derived from the condensation reaction of N^4-methyl-3-thiosemicarbazide with 3-hydroxy-4-methoxybenzaldehyde and (*E*)-2-(3,4-dihydroxybenzalidene)-hydrazinecarboamide (**L^5**) derived from semicarbazide hydrochloride with 3,4-dihydroxybenzaldehyde respectively. The **L^4, L^5, 4a-b, 5a-b** were tested for their *in vitro* antibacterial activity against

Staphylococcus aureus and *Bacillus subtilis* (Gram-positive), *Escherichia coli* and *Salmonella paratyphi* (Gram-negative) and antifungal activity against *Aspergillus niger*, *Candida albicans.*

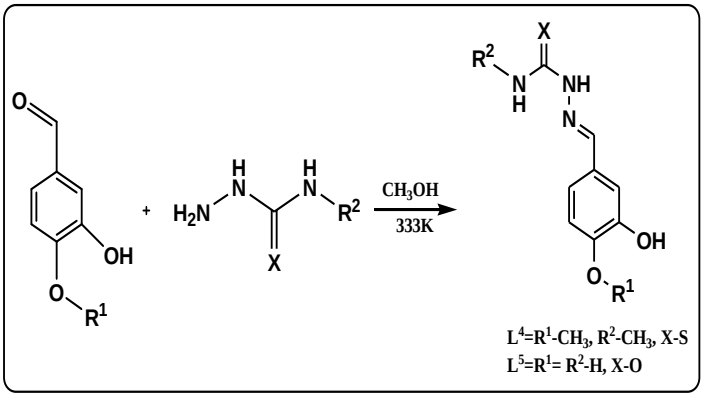
MATERIALS AND METHODS

Chemicals: All chemicals and solvents were of reagent grade and were used as commercially purchased without further purification.

Methods: The elemental analyses were determined using a Perkin Elmer EA 2400 Series Elemental Analyzer. Infrared spectra of the compounds were recorded on KBr pellets using a Perkin Elmer RX1-FTIR Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz) at 298 K. Chemical shifts δ in ppm were referenced to the solvent residual peak as an internal standard. ^{13}C NMR was recorded on a Bruker Avance spectrometer (400 MHz) and spectra was referenced to the solvent residual peak.

Synthesis of Schiff base ligand L^4, L^5 and their complexes of 4a-b and 5a-b

Synthesis of **L^4, L^5, 4a-b, 5a-b** were done by the methods of our previous work as described earlier (**Scheme 1**).[27]



Scheme 1: Synthesis of Schiff base ligand L^4 and L^5

The color, yield (%), m.p. (ºC), R_f value, elemental analysis, IR (KBr, cm^{-1}), ^{1}H-NMR (DMSO-d6) and ^{13}C-NMR (DMSO-d6) data of L^4 and L^5 are given as follows:

L^4: brown crystals, yield (2.3000g, 96%), 143–145ºC, 0.84, Anal. calc. for $C_{10}H_{13}N_3O_2S$ (239.61 g mol^{-1}): C, 50.19; H, 5.48; N, 17.56; S, 13.40, found: C, 50.12; H, 5.54; N, 17.59; S, 13.36%. IR (cm^{-1}): υ(OH) 3311, υ(NH) 3384,1343, 635, υ(N-N) 944, υ(C=N) 1555, 1508, 470, υ(C=S) 829. ^{1}H NMR (δ in ppm): 11.28, 9.78, 9.56 (s, 1H, C**H**=N^{1}), 9.02 (s, 1H, O**H**), 8.37, 8.36 (d, 1H, Ar-**H**), 7.42-7.10 (m, 2H, Ar-**H**), 7.92, (s, 1H, N**H)**, 6.96, 6.94 (s, 1H, N**H)**,

3.88, 3.82 (s, 3H, OC**H$_3$**), 3.01 (s, 3H, N^4–C**H$_3$**). ^{13}C NMR (δ in ppm): 149.46 (**C**=S), 146.64 (**C**H=N), 142.20 (Ar**C$_4$**–OCH$_3$), 127.17(Ar**C$_3$**–OH), 119.99 (Ar**C$_1$**), 113.54 (Ar**C$_6$**), 113.19 (Ar**C$_2$**), 111.70 (Ar**C$_5$**), 55.66 (ArC$_4$–O**C**H$_3$), 30.74 (N^4–**C**H$_3$).

L^5: pale yellow powder, yield (1.8795g, 96%), 155–157ºC, 0.67, Anal. calc. for $C_8H_9N_3O_3$ (195.29 g mol^{-1}): C, 49.23; H, 4.65; N, 21.53; O, 24.59, found: C, 49.28; H, 4.60; N, 21.49; O, 24.63%. IR (cm^{-1}): υ(OH) 3329, υ(NH) 3425,1372, 620, υ(N-N) 951, υ(C=N) 1588, 1528, 495, υ(C=O) 1666, 1281. ^{1}H NMR (δ in ppm): 10.09 (s, 1H, C**H**=N^1), 9.71 (s, 1H, O**H**), 9.29 (s, 1H, O**H**), 7.68 (s, 1H, Ar-**H**), 7.29, 7.27 (m, 1H, Ar-**H**), 6.94, 6.92, (s, 1H, N**H)**, 6.75, 6.73 (d, 1H, Ar-**H**), 6.30 (s, 1H, N**H)**. ^{13}C NMR (δ in ppm): 156.79 (**C**=O), 146.88 (**C**H=N), 145.43 (Ar**C$_4$**-OH), 140.16(Ar**C$_3$**–OH), 128.85, 126.27 (Ar**C$_1$**), 124.44 (Ar**C$_6$**), 119.07 (Ar**C$_2$**), 115.47, 113.12 (Ar**C$_5$**).

The color, yield (g, %), m.p. (ºC), R_f value, elemental analysis and IR (KBr, cm^{-1}) data of the complexes are given as follows:

4a: dark brown powder, yield (0.1458g g, 41%), >200ºC, 0.78, Anal. Calc. for $C_{10}H_{14}N_3O_3SCuCl$ (355.46 g mol^{-1}): C, 33.80; H, 3.97; N, 11.83; S, 9.02, Cu, 17.89; found: C, 33.86; H, 3.94; N, 11.88; S, 8.98, Cu, 17.95. IR (cm^{-1}): υ(NH) 3418, 1353, 641, υ(N-N) 1018, υ(C=N) 1584, 1504, 466, υ(C=S) 873.

4b: dark brown powder, yield (0.1298g, 32%), >200ºC, 0.76, Anal. Calc. for $C_{10}H_{14}N_3O_3SCuBr$ (399.69 g mol^{-1}): C, 30.05; H, 3.53; N, 10.51; S, 8.02; Cu, 15.90; found: C, 30.10; H, 3.50; N, 10.56; S, 7.98; Cu, 15.95. IR(cm^{-1}): υ(NH) 3382, 1353, 641, υ(N-N) 1021, υ(C=N) 1585, 1505, 464, υ(C=S) 873.

5a: dark brown powder, yield (0.1654g, 53%), >200ºC, 0.79, Anal. Calc. for $C_8H_{10}N_3O_4CuCl$ (311.27 g mol^{-1}): C 30.88; H, 3.24; N, 13.50; O, 20.57, Cu, 20.42; found: C 30.94; H, 3.21; N, 13.54; O, 20.56, Cu, 20.47. IR (cm^{-1}): υ(NH) 3420, 1367, υ(N-N) 974, υ(C=N) 1556, 1538, υ(C=O) 1603.

5b: dark brown powder, yield (0.1255g, 35%), >200ºC, 0.91, Anal. Calc. for $C_8H_{10}N_3O_4CuBr$ (335.63g mol^{-1}): C, 27.02; H, 2.83; N, 11.82; O, 18.00, Cu, 17.87; found: C, 27.08; H, 2.80; N, 11.85; O, 18.05, Cu, 17.92. IR(cm^{-1}): υ(OH) 3311, υ(NH) 3417, 1394, 676, υ(N-N) 972, υ(C=N) 1556, 1538, υ(C=O) 1614.

RESULTS AND DISCUSSION

The synthesized **L^4, L^5, 4a-b, 5a-b** were checked by comparing the TLC with the starting materials, which resulted in a single spot different from the starting materials. The synthesis achieved high yields**.** The structure of synthesized compounds (**Fig. 2**) was confirmed on the basis of elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectral data.

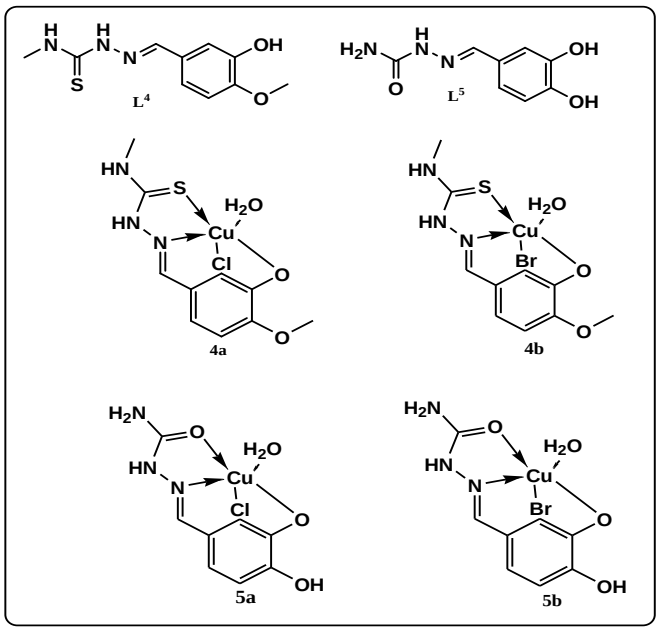


Fig. 2: Structures of Schiff bases and their copper (II) complexes

Infrared Spectra and Coordination Mode

The IR data of the spectra of complexes were compared with those of the free ligands **L^4, L^5** in order to determine the coordination sites that may be involved in chelation. There were some guide peaks in the spectra of the ligands, which were helpful in achieving this goal. The position and/or the intensities of these peaks are expected to change upon chelation. New peaks are also guide peaks, as is water, in chelation. Upon comparison, it was determined that the υ(C=N) stretching vibration is found in the free ligands at 1555 and 1588 cm^{-1} for the L^4 and L^5 ligands, respectively. This band was shifted to higher or lower wavenumbers in the complexes, indicating the participation of the azomethine nitrogen in coordination Cu←N=C).[28]

The phenolic υ(C–O) stretching vibrations in the free **L^4** and **L^5** is observed at 1120 and 1123 cm^{-1}, respectively, which is shifted by 6–8 cm^{-1} towards higher or lower wave numbers in the complexes. The phenolic υ(O-H) at 3311 and 3329 cm^{-1} in free **L^4** and **L^5** respectively, Which disappeared in copper complexes, indicating coordination of the phenolic oxygen to the Cu^{2+} ion. The complexes **5a** and **5b** exhibited in the region at 3420 and 3311cm^{-1}

respectively, which indicated the presence of one non-chelated phenolic hydroxyl group. The band appeared in the region 829 cm^{-1} and 1666 cm^{-1} in the ligands spectra, were assigned to stretching vibration modes υC=S and υC=O, respectively. This band was shifted to higher and lower wavenumbers in the complexes **4a-b** and **5a-b**, indicating the participation of the thiocarbonyl sulfur atom (C=S) and carbonyl oxygen atom (C=O) in coordination (M←X, X=S, O) respectively.

^{1}H-NMR and ^{13}C-NMR spectra

A review of the literature revealed that NMR spectroscopy has been proven to be useful in establishing the nature and structure of many Schiff bases, as well as their complexes in solutions. The NMR spectra of Schiff bases were recorded in d6-dimethylsulfoxide (DMSO-d6) solution, using tetramethylsilane (TMS) as internal standard. The ^{1}H-NMR spectra of **L^4** and **L^5** showed a low field one proton singlet at 11.28 and 10.09 ppm (1H) due to the –**CH**=N respectively. The O–H proton signal is observed at 9.17 ppm (1H) in **L^4**, 9.71 (1H) and 9.29 (1H) ppm in **L^5**. The methyl protons signal are observed as a doublet at 3.01 ppm (3H) and singlet at 3.88, 3.82 (3H) due to N-CH_3 and O-CH_3 protons in **L^4** respectively.

The ^{13}C-NMR spectra of **L^4** and **L^5** showed a singlet at 149.46 and 156.79 ppm due to the C=S in **L^4** and C=O in **L^5** respectively. The –**CH**=N peak observed at 146.64 ppm in **L^4** and 146.88 ppm in **L^5**. The two singlets observed at 55.66 and 30.74 ppm due to N-CH_3 and O-CH_3 protons in **L^4** respectively.

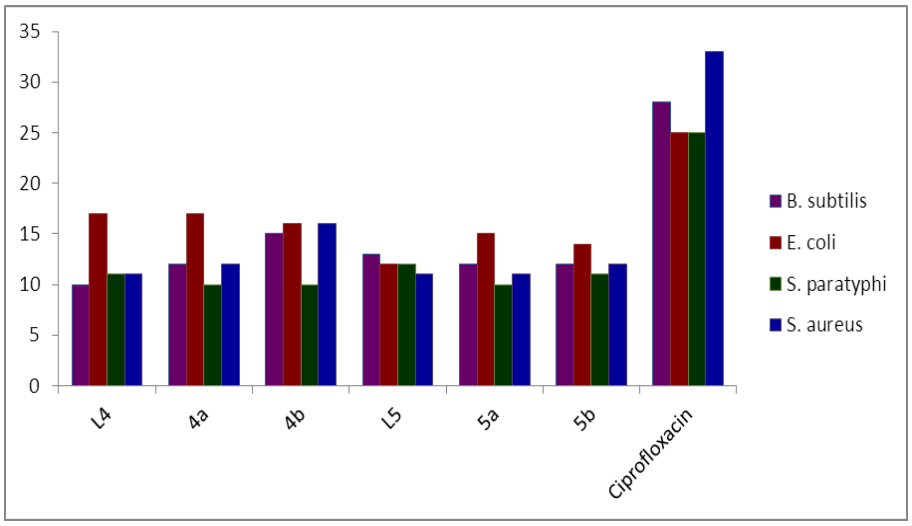
Anti-microbial Screening

The anti-bacterial and anti-fungal activity of **L^4**, **L^5** and their copper (II) complexes (**4a-b, 5a-b**) were tested and the zone of inhibition calculated (**Table 1**) as described earlier.[27]

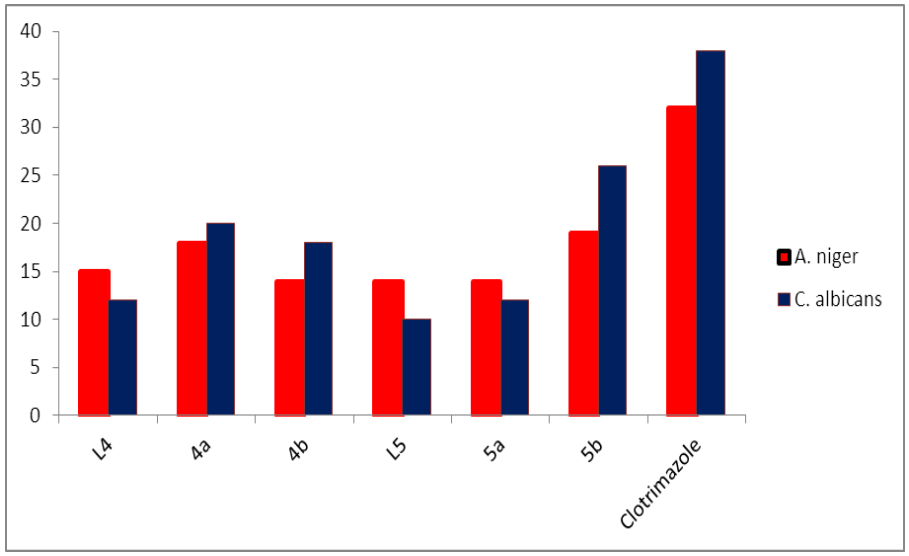
Table 1: Anti-microbial activity of L^4, L^5 and their copper (II) complexes

Ligand/ Complex	Inhibition zone (mm)					
	Antibacterial activity				Antifungal activity	
	B. subtilis	*E. coli*	*S. paratyphi*	*S. aureus*	*A. niger*	*C. albicans*
L^4	10	17	11	11	15	12
4a	12	17	10	12	18	20
4b	15	16	10	16	14	18
L^5	13	12	12	11	14	10
5a	12	15	10	11	14	12
5b	12	14	11	12	19	26
Ciprofloxacin	28	25	25	33	-	-
Clotrimazole	-	-	-	-	32	38

All the new copper (II) complexes showed a remarkable biological activity against bacteria and fungus. From the results it is clear that the copper (II) complexes are found to have good biological activity than the parent ligands (**Graph 1 and Graph 2**).



Graph 1: Antibacterial activity of Schiff bases and their copper (II) complexes



Graph 2: Antifungal activity of Schiff bases and their copper (II) complexes

CONCLUSION

The approach of the present study was to synthesize two Schiff base tridentate ligands, their copper (II) complexes and evaluate the anti-bacterial and anti-fungal activities. The results generated in this study lead to the following conclusions. (i) Tested complex 4b was found to possess good anti-bacterial activity against *Bacillus subtilis* and *Staphylococcus aureus.* While the complex 5a and 5b were found to possess good anti-bacterial activity against *Escherichia coli*. (ii) Tested complex 4a and 5b were found to possess good anti-fungal

activity against *Aspergillus niger*. While the complex 4a, 4b and 5b were found to possess very good anti-bacterial activity against *Candida albicans*.

As the copper (II) complexes possess wide spectrum of activities, the synthesized compounds lead to a promising tool for extrapolating the biological activities.

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REFERENCES

1. Rawal, R.K.; Tripathi, R.; Kati, S.B.; Pannecouque, C.; de Clercq, E. Design, synthesis, and evaluation of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones as anti-HIV agents. Bioorg. Med. Chem. 2007; 15: 1725–1731.
2. Giovine, A.; Muraglia, M.; Florio, M.A.; Rosato, A.; Corbo, F.; Franchini, C.; Musio,B.; Degennaro, L.; Luisi, R. Synthesis of functionalized arylaziridines as potential antimicrobial agents. Molecules., 2014; 19: 11505–11519.
3. Wang, P.H.; Keck, J.G.; Lien, E.J.; Lai, M.M.C. Design, synthesis, testing and quantitative structure-activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus. J. Med. Chem.1990; 33: 608–614.
4. Jarrahpour, A.; Motamedifar, M.; Pakshir, K.; Hadi, N.; Zarei, M. Synthesis of novel azo Schiff bases and their antibacterial and antifungal activities. Molecules, 2004; 9: 815–824.
5. Omar, M.M.; Mohamed, G.G.; Ibrahim, A.A. Spectroscopic characterization of metal complexes of novel Schiff base: Synthesis, thermal and biological activity studies. Spectrochim. Acta- A. 2009; 73: 358–369.
6. Ceyhana, G.; Urus, S.; Demirtas, I.; Elmastas, M.; Tumera, M. Antioxidant, electrochemical, thermal, antimicrobial and alkane oxidation properties of tridentate Schiff base ligands and their metal complexes. Spectrochim. Acta- A, 2011; 81: 184–198.
7. Mladenova, R.; Ignatova, M.; Manolova, N.; Petrova, T.; Rashkov, I. Preparation, characterization and biological activity of Schiff base compounds derived from 8-

hydroxyquinoline-2-carboxaldehyde and Jeffamines ED. Eur. Polym. J. 2002; 38: 989–999.

8. Huang, G.S.; Liang, Y.M.; Wu, X.L.; Liu, W.M.; Ma, Y.X. Some ferrocenyl Schiff bases with nonlinear optical properties. Organomet. Chem. 2003; 17: 706–710.
9. Walsh, O.M.; Meegan, M.J.; Prendergast, R.M.; Nakib, T.A. Synthesis of 3-acetoxyazetidin-2-ones and 3-hydroxyazetidin-2-ones with antifugal and antifungal and antibacterial activity. Eur. J.Med. Chem. 1996; 31: 989–1000.
10. Liu, Y.; Yang, Z. Synthesis, crystal structure, antioxidation and DNA binding properties of binuclear Ho(III) complexes of Schiff-base ligands derived from 8-hydroxyquinoline-2-carboxyaldehyde and four aroylhydrazines. J. Organomet. Chem. 2009; 694: 3091–3101.
11. Santra, B.K.; Reddy, P.A.N.; Neelakanta, G.; Mahadevan, S.; Nethaji, M.; Chakravarty, A.R. Oxidative cleavage of DNA by a dipyridoquinoxaline copper(II) complex in the presence of ascorbic acid. J. Inorg. Biochem. 2002; 89: 191–196.
12. Aslantaş, M.; Kendi, E.; Demir, N.; Şabik, A.E.; Tümer, M.; Kertmen, M. Synthesis, spectroscopic, structural characterization, electrochemical and antimicrobial activity studies of the Schiff base ligand and its transition metal complexes. Spectrochim. Acta-A, 2009; 74: 617–624.
13. Chandra, S.; Kumar, A. Electronic, EPR and magnetic studies of Co(II), Ni(II) and Cu(II) complexes with thiosemicarbazone (L1) and semicarbazone (L2) derived from pyrole-2-carboxyaldehyde. Spectrochim. Acta A, 2007; 67: 697–701.
14. Das, A.; Trousdale, M.D.; Ren, S.; Lien, E.J. Inhibition of herpes simplex virus type 1 and adenovirus type 5 by heterocyclic Schiff bases of aminohydroxyguanidine tosylate. Antivir. Res. 1999; 44: 201–208.
15. Shanker, K.; Rohini, R.; Reddy, P.M.; Ho, Y.P.; Ravinder, V. Ru(II) complexes of N4 and N2O2 macrocyclic Schiff base ligands: Their antibacterial and antifungal studies. Spectrochim. Acta A, 2009; 73: 205–211.
16. Kureshy, R.I.; Khan, N.H.; Abdi, S.H.R.; Patel, S.T.; Iyer, P. Chiral Ru(II) Schiff base complexes catalysed enantioselective eposidation of styrene derivatives using iodosyl benzene as oxidant II J. Mol. Catal. 1999; 150: 175–183.
17. Aoyama, Y.; Kujisawa, J.T.; Walanawe, T.; Toi, A.; Ogashi, H. Catalytic reactions of metalloporphyrins. 1. Catalytic modification of borane reduction of ketone with rhodium (III) porphyrin as catalyst. J. Am. Chem. Soc. 1986; 108: 943–947.

18. Kelly, T.R.; Whiting, A.; Chandrakumar, N.S. A rationally designed chiral Lewis acid for the asymmetric induction of some Diels-Alder reactions. J. Am. Chem. Soc. 1986; 108: 3510–3512.
19. Sengupta, P.; Ghosh, S.; Mak, T.C.W. A new route for the synthesis of bis(pyridine dicarboxylato)bis(triphenylphosphine) complexes of ruthenium(II) and X-ray structural characterisation of the biologically active trans-[Ru(PPh3)2(L1H)2] (L1H2=pyridine 2,3-dicarboxylic acid). Polyhedron, 2001; 20: 975–980.
20. Ibrahim, O.B.; Mohamed, M.A.; Refat, M.S. Nano Sized Schiff Base Complexes with Mn(II), Co(II), Cu(II), Ni(II) and Zn(II) Metals: Synthesis, Spectroscopic and Medicinal Studies. Can. Chem. Trans. 2014; 2: 108–121.
21. Green, D.R.; Reed, J.C. Mitochondria and apoptosis. Science, 1998; 281: 1309–1312.
22. Easmon, J.; Pürstinger, G.; Heinisch, G.; Roth, T.; Fiebig, H.H.; Holzer, W.; Jäger, W.; Jenny, M.; Hofmann, J. Synthesis, cytotoxicity, and antitumor activity of copper(II) and iron(II) complexes of (4)N-azabicyclo[3.2.2]nonane thiosemicarbazones derived from acyl diazines. J. Med. Chem. 2001; 44: 2164–2171.
23. Kumar, S.; Dhar, D.N.; Saxena, P.N. Applications of metal complexes of Schiff bases—A review. J. Sci. Ind. Res. 2009; 68: 181–187.
24. Morrow, M.E.; Berry, C.W. Antimicrobial properties of topical anesthetic liquids containing lidocaine or benzocaine. Anesth. Prog. 1988; 35: 9–13.
25. Pongratz, Z. Über neue pharmakologisch wirksame Amide und Ester der Nicotinsäure. Monatsh.Chem. 1957; 88: 330–335.
26. Perrin, D.D.; Armarego, W.L.; Perrin, D.R. Purification of Laboratory Chemicals, 2nd ed.; Pergamon: New York, NY, USA, 1990; 140–142.
27. D. Satheesh and K. Jayanthi, An in vitro antibacterial and antifungal activities of copper (II) and zinc (II) complexes of N^4-methyl-3-thiosemicarbazones, Int. J. Chem. and Pharm. Anal., In Editing.
28. A. A. Soliman and W. Linert, Investigations on new transition metal chelates of the 3-methoxy-salicylidene-2-aminothiophenol Schiff base, Thermochimica Acta, 1999; 338 (s 1-2): 67-75.