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Synthesis and antimicrobial activities of new Schiff's base and metal complexes derived from imidazole

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ABSTRACT

Schiff base ligand ***(BCIMED)*** *was synthesized by reacting 2-n-butyl-5-chloroimidazol-4-carbaldehyde and ethylenediamine with metal complexes* $[Mg(C_{18}H_{26}Cl_2N_6;]Cl_2$, $[Ni(C_{18}H_{26}Cl_2N_6;]Cl_2$, $[Zn(C_{18}H_{26}Cl_2N_6;]Cl_2$ *and* $[Pb(C_{18}H_{26}Cl_2N_6;]Cl_2$ *in 2:1 ratio in methanol solution. The Schiff base ligand and their metal complexes have been characterized with the help of elemental analysis, and their structure configuration has been determined by various spectroscopic methods such as IR,* ^1H *NMR,* ^{13}C *NMR, and Mass techniques etc., Electronic spectra of the complexes indicate that the geometry of the metal center was square pyramidal. These metal complexes were also tested for their antimicrobial activities to assess their inhibiting potential.*

Key words: Schiff base, imidazole, ethylenediamine, metal salts, antimicrobial activity.

INTRODUCTION

The search of novel Schiff's base heterocyclic compounds has led to the discovery of many molecules having tremendous potentiality, These heterocyclic compounds have been proven to be backbone for the discovery of several biologically active compounds. Schiff base metal complexes have been widely studied because their industrial, antifungal, antibacterial, anticancer, antiviral and herbicidal applications [1-6]. They serve as models for biologically important species and find many applications in biomimetic catalytic reactions. Chelating ligands containing N, S and O donor atoms show broad biological activity and are of special interest because of the variety of ways in which they are bonded to metal ions. It is known that the existence of metal ions bonded to biologically active compounds may enhance their activities [7-9]. Schiff base metal complexes have been known since the mid nineteenth century [10] and even before the general preparation of the Schiff bases ligands themselves. Schiff base metal complexes has a major role in the development of coordination chemistry after the work of Jorgensen and Werner [11].

Imidazole and its derivatives are of great significance due to their important roles in biological systems, particularly in enzymes, as proton donors and/or acceptors, coordination system ligands and the base of charge–transfer processes. Unlike pyrrole (a proton donor) and pyridine (a proton acceptor), 1*H*-imidazole has both proton donor and acceptor properties [12,13]. Substituted imidazoles are reported to possess anti-fungal activity [14-16] along with anti-mycobacterial activity [17] .Schiff's bases of various heterocyclic scaffolds exhibits varieties of biological activities like anti-HIV [18], anti-cancer [19] , anti-bacterial[20] , fungicidal [21] and anti- inflammatory [22] .

In view of these facts, a project was undertaken to synthesize a new series of Schiff base ligand containing 2-n-butyl-5-chloroimidazol-4-carbaldehyde (BCI) **1** and ethylene diamine 2 (2:1 ratio), a series of their metal salts and to evaluate the new compounds for their biological activity.

MATERIALS AND METHODS

Experimental:
Elemental analysis for C, H and N was performed using Perkin Elmer CHN analyzer. The IR spectra (4000- 400 cm^{-1}) in KBr discs were recorded on TENSOR 2 Spectrophotometer. The ^1H NMR (400 MHz) spectrophotometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. 2-n-butyl-5-chloroimidazol-4-carbaldehyde, ethylene diamine, nickel chloride, magnesium chloride, nickel chloride, palladium chloride and solvents used were procured from Merck. The chemicals and solvents used were of commercial grade and used without further purification.

General Procedure:
Synthesis of ligand-(N^1E, N^2E)-N^1, N^2-bis(2-butyl-5-chloro-*1H*-imidazol-4-yl) methylene) ethane-1,2-diamine (BCIMED):
2-n-butyl-5-chloroimidazol-4-carbaldehyde **(1)** (2 mmol) in ethanol (20 mL) was added to a solution of ethylenediamine **(2)** (1 mmol) in ethanol (30 mL). The reaction mixture was refluxed for 4 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure by rotavapour until a solid product was formed that was washed with cold ethanol and dried under vacuum.

Yield 85% ; M.P:170^oC; ^1H NMR (400MHz, DMSO-d_6): δ = 0.90 (t,2x3H,-CH_3), 1.23-(sex,2x2H,-CH_2), 1.59 (quint, 2x2H, -CH_2), 2.62 (t, 2x2H,-CH_2), 3.80 (s, 2H,2xCH_2), 8.02(s,2x1H,CH=N), 12.6-12.8 (br, s, 2xNH, imidazole-NH) ^{13}C NMR (100MHz, DMSO-d_6), 14.00, 21.99, 27.88, 30.19, 39.53, 40.57, 61.26, 123.34, 149.50 (C=N). IR (KBr): ν(NH) 3245, ν(C=N) 1678, ν(N–N) 1115 cm^{-1}. Mass (m/z): 398 (M+1): Elemental analysis for $C_{18}H_{26}Cl_2N_6$; Calcd. C 54.41, H 6.60, N 21.15; found C 54.34, H 6.52, N 21.12.

Synthesis of the metal complexes 5(a-d):
The metal complexes of the ligand **(BCIMED) (5a-d)** were prepared by mixing a hot methanolic solution of the metal salts with required amount of a hot ethanolic solution of the ligand to form metal/ligand complexes.

Synthesis of the metal complex (5a-d):
A solution of metal chlorides in methanol (10 ml) was added to a hot solution of **BCIMED (1)** in ethanol (20 mL), and the reaction mixture was refluxed for 5-6h. The solution was concentrated under vacuum. The precipitate was filtered off, washed with methanol and dried under vacuum over anhydrous $CaCl_2$ to form corresponding metal complexes.

Synthesis of Mg(BCIMED)Cl_2 (5a):
Yield: 76%; m.pt: 262-264 ^0C; IR (KBr): ν(H2O) 3345, ν(N2H) 3275, ν(C=N) 1656, ν(N–N) 1123, ν(M–Cl) 298, ν(M–N) 424 cm^{-1}. Mass (m/z): 493(M+1): Elemental analysis for $C_{18}H_{26}Cl_4N_6$;Mg: calcd. C 43.89, H 5.32, N 17.06; found C 43.78, H 5.29, N 17.01.

Synthesis of Ni(BCIMED)Cl_2 (5b):
Yield: 67%; m.pt: 243-244 ^0C; IR (KBr): ν(H2O) 3348, ν(N2H) 3272, ν(C=N) 1650, ν(N–N) 1123, ν(M–Cl) 293, ν(M–N) 424 cm^{-1}. Mass (m/z): 527(M+1): Elemental analysis for $C_{18}H_{26}Cl_4N_6Ni$; Calcd. C 41.03, H 4.97, N 15.95; found C 40.97, H 4.91, N 15.89.

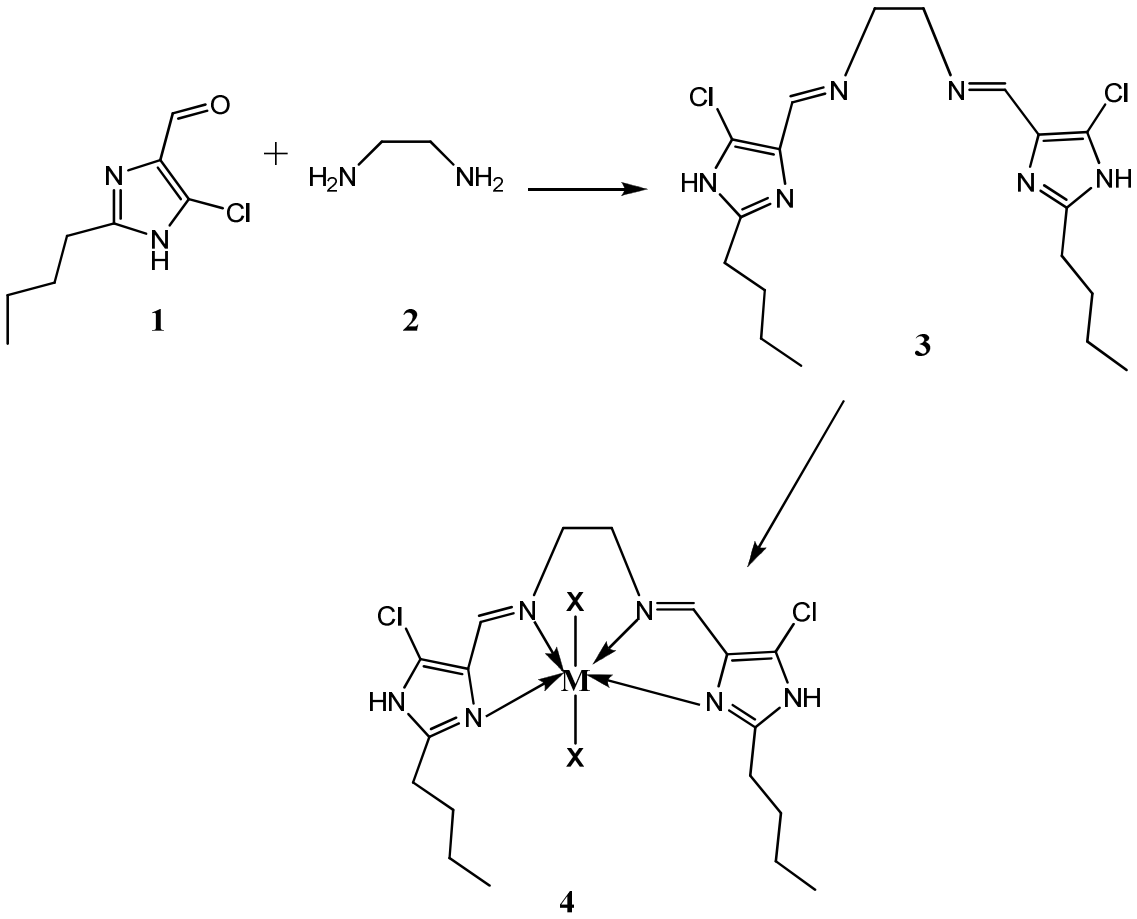
Synthesis of Zn(BCIMED)Cl_2 (5c):
Yield: 62%; m.pt: >300 ^0C; IR (KBr): ν(H2O) 3354, ν(N2H) 3248, ν(C=N) 1652, ν(N–N) 1123, ν(M–Cl) 293, ν(M–N) 424 cm^{-1}. Mass (m/z): 534(M+1): Elemental analysis for $C_{18}H_{26}Cl_4N_6Zn$; Calcd. C 40.51, H 4.91, N 15.75; found C 40.45, H 4.87, N 15.69.

Synthesis of Pd(BCIMED)Cl_2 (5d):
Yield: 72%; m.pt: 278-280 ^{0}C; IR (KBr): ν(H2O) 3352, ν(N2H) 3254, ν(C=N) 1657, ν(N–N) 1123, ν(M–Cl) 294, ν(M–N) 424 cm^{-1}. Mass (m/z): 575(M+1): Elemental analysis for $C_{18}H_{26}Cl_4N_6Pd$; Calcd. C 37.62, H 4.56, N 14.62; found C 37.57, H 4.49, N 14.57.

RESULTS AND DISCUSSION

The designated compounds were synthesized according to **Scheme 1**. Reaction of 2-n-butyl-5-chloroimidazol-4-carbaldehyde (BCI) **1** and ethylene diamine 2 (2:1 ratio) afforded (N^1E, N^2E)-N^1, N^2-bis(2-butyl-5-chloro-*1H*-imidazol-4-yl)methylene)ethane-1,2-diamine **(BCIMED)**.

Scheme-1:



Where, M= Mg (II) Ni(II), Zn(II), Pd(II); X=Cl

A survey of literature reveals that the NMR spectroscopy has been proved useful in establishing the structure and nature of many Schiff base ligand and their complexes. The ^{1}H NMR spectra of Schiff base ligand **(BCIMED)** was recorded in DMSO-d_6 solution using TMS as internal standard. The ^{1}H NMR spectra of the ligand shows broad signal at 12.6- 12.8 ppm due to the –NH of imidazole ring. The singlet in the region 3.80 ppm may be assigned to –CH_2 protons indicated the formation of bis ligand. ^{13}C NMR of the Schiff base ligand, the signal appeared in the region of 1.49.50 ppm are due to -C=NH.

The mass spectra of Schiff base ligand **(BCIMED)** and metal complexes have been recorded. The molecular ion *(M^{+1})* peaks obtained from various complexes are as follows: m/z = 398, m/z=493 [Mg(BCIMED)Cl_2]Cl_2, (complex 1), m/z = 527 [Ni(BCIMED)Cl_2]Cl_2 (complex 2), m/z = 534 [Zn((BCIMED)Cl_2]Cl_2 (complex 3), m/z = 575 [Pd((BCIMED)Cl_2]Cl_2 (complex 4), This data is in good agreement with the proposed molecular formula for these complexes. In addition to the peaks due to the molecular ion, the spectra exhibit peaks assignable to various

fragments arising from the thermal cleavage of the complexes. The peak intensity gives an idea of the stability of the fragments.

Antimicrobial activity:

The agar disc-diffusion method [20] was used for the screening of *in vitro* antimicrobial activity. The anti-microbial activity of the synthesized ligand **(BCIMED)** and corresponding metal (II) complexes were screened for their antibacterial activity against Gram +ve *Staphylococcus aureus* and Gram –ve *Escherichia Coli* using nutrient agar medium , whereas antifungal activity of these compounds was tested against *Candia albicans* and *Aspergillus niger* using Sabouraded dextrose agar medium. The minimum inhibitory concentration (MIC) was carried out using micro dilution susceptibility method [21] . Ciprofloxacin was used as a standard antibacterial drug and Flucanazole was used as a standard antifungal drug. The observed data on the antimicrobial activity of compounds and control drugs are given in **Table 1.**

Table-1: Minimum inhibitory concentration (MIC, µg/ml) of synthesized ligand (BCIMED) and their metal complexes

	Bacterial strains	(+ Ve and –Ve)	Fungal strains	
Compound	***S. aureus***	***E. coli***	***C. albicans***	***A. niger***
BCIMED	50	65	50	75
Mg(II)	11.5	11.5	11.5	25
Ni(II)	6..25	6.25	12.5	25
Zn(II)	25	12.5	6.25	6.25
Pd(II)	8.25	8.25	6.2.5	6.25
Ciprofloxacin	6.25	6.25		
Flucanazole			6.25	6.25

From **Table 1**, it can be seen that the more antibacterial activity of Ni(II) complex against the bacterium S. aureus (6.25 µg/ml) and *E-Coli* (6.25 µg/ml). On the other hand, Zn (II) and Pd (II) complexes showed the best activity towards fungi against *C. albicans and A. niger* (6.25 µg/ml). There was a marked increase in the bacteria and fungi activities of the other metal complexes respectively, as compared with the free ligand.

Biological Protocol:

Preliminary antimicrobial activities of ligand **(BCIMED)** and their metal complexes were tested by Agar disc diffusion method. Sterile filter paper discs (6 mm diameter) monitored with the test compound solution in DMSO of specific concentration 100 and 200 µg/ disc were carefully placed on the agar culture plates that had been previously incubated separately with the micro organisms. The plates were incubated at 37 ^{0}C and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of fungi. The MICs of the compound assays were carried out using micro dilution susceptibility method. Ciprofloxacin was used as reference for antibacterial activity agent. Flucanazole was used as reference for anti fungal agent. The test compounds, Ciprofloxacin and Flucanazole were dissolved in DMSO at concentration of 400 µg/ml and two fold serial dilution of the solution was prepared (200, 100,.6.25 µg/ml). The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 37^{0}C for 24 h and 48 h for bacteria and fungi respectively. The minimum inhibitory concentration (MIC µg /ml) of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes without turbidity (i.e. no growth) of inoculated bacteria / fungi.

CONCLUSION

The analytical data showed a single metal ion mononuclear square pyramidal geometry of the metal (II) complexes. This study reports the successful synthesis of new Schiff base **(BCIMED)** and their metal complexes with Mg (II), Ni (II), Zn (II) and Pd (II) ions. The structures of the ligand and metal complexes were confirmed by the elemental analysis, FT-IR, ^{1}H-NMR and mass spectral studies. All the newly synthesized compounds were screened for their *in vitro* antimicrobial activity. Among the screened samples the more antibacterial activity of Ni(II) complex against S.aureus and *E-Coli* (6.25 µg/ml) bacteria. On the other hand, Zn (II) and Pd(II) complexes showed the best activity towards fungi. There was a marked increase in the bacteria and fungi activities of the other metal complexes respectively, as compared with the free ligand.

REFERENCES

[1] K Singh, M S Barwa, P Tyagi, *Eur. J. Med. Chem*, **2007**, 42, 394-402.

[2] P G Cozzi, *Chem. Soc. Rev*. **2004**, 33, 410-421.
[3] S Chandra, J Sangeetika, *J. Ind Chem. Soc*, **2004**, 81, 203-206.
[4] M B Ferrari, S Capacchi, G Pelosi, G Reffo, P Tarasconi, R Albertini, S Pinelli, P Lunghi, *Inorg. Chim. Acta*, **1999**, 286, 134-141.
[5] E Canpolat, M Kaya, *J. Coord. Chem.***2004**, 57(14), 1217-2223.
[6] M Yildiz, B Dulger, SY Koyuncu, BM Yapici, *J. Indian Chem. Soc.* **2004**, 81, 7-12.
[7] M B Ferrari, S Capacchi, G Pelosi, G Reffo, P Tarasconi, R Albertini, S Pinelli, P Lunghi, *Inorg. Chim. Acta*, **1999,** 286,134-141.
[8] E Canpolat, M Kaya, *J. Coord. Chem.* **2004**, 57, 1217-2223.
[9] M Yildiz, B Dulger, SY Koyuncu, B M Yapici, *J. Indian Chem. Soc.* **2004,** 81,7-12.
[10] H Schiff, *Ann. Chem. Pharm.* **1869**,150, 193.
[11] C K Jorgensen, *Acta Chem. Scand.* **1957**, 11, 73-85.
[12] E J Foster, C Lavigueur, Y C KE, V E Williams, *J .Mater. Chem.* **2005**, 37, 4062-4068.
[13] L Brunsveld, H Zong, M E W Glasbeek, E W Meijer, *J. Am. Chem. Soc.* **2000**, 122, 6175-6182.
[14]O Dorota Z Justyna L Victor, L Roman, K Aleksandra, F. Andrzej, Z Lucjusz, *Eur. J Med. Chem.* **2009,** 44, 645-652.
[15] K Hori, A Csakaguchi, M Kudoh, K Ishida, Y Aoyama, Y Yoshida, *Chem. Pharm. Bull*, **2000,** 48**(**1), 60-64.
[16] V T Andriole, *J. Antimicrob. Chemother*, **1999,** 44, 151–162.
[17] Z Daniele, G M Maria, V Luciano, B Elena, S Giuditta, F Maurizio, F Marco, P Sabrina *Bioorg. Med. Chem*, **2007,** 15(23), 7444-7458.
[18] S N Pandeya, D Sriram, G Nath, E D Clercq, *Pharm. Acta Helvetiae*,**1999,** 74(1), 11-17.
[19] V E Kuz'min, V P Lozitsky, G L Kamalov, R N Lozitskaya, A I Zheltvay, A S Fedtchouk, DN Kryzhanovsk, *Acta. Biochim. Pol*, **2000,** 47(3), 867-875.
[20] R Nair, A Shah, S Baluja, S Chanda, *J. Serbian Chem. Soc.* **2006,** 71(7), 733-744.
[21] S Xiao-Hong, T Yan, L Yuan-Fa, C Bang, *Chin. J. Chem*, **2007,** 25(10), 1573-1576.
[22] H H Glenn, D W Leslie, *J. Pharm. Sci*, **1971,** 60(6), 925-927.