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Synthesis, Single Crystal X-Ray and Biological Study of Transition Metal Complexes of N, N-Donor Schiff Base Ligand: N1 , N2 -Bis[(4-Methoxyphenyl) Methylidene]-1,2-Ethanediamine

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Abstract

A Schiff base ligand, N 1 , N2 -bis[(4-methoxyphenyl) methylidene]-1,2-ethanediamine (SBL), was derived by the condensation of 4-methoxybenzaldehyde with ethylene diamine followed by complexation with divalent transition metals. The synthesized Schiff base ligand (SBL) and its complexes 1-5 were characterized on the basis of IR, 1H-NMR, 13C-NMR, MS spectral, molar conductance and elemental analyses data. The structure of Schiff base ligand (SBL) was also confirmed by single crystal x-ray crystallographic study. The conductivity data suggests non-electrolytic nature of these complexes. The complexes have higher antibacterial activity than the parent Schiff base ligand. . Abstract A Schiff base ligand, N 1 , N2 -bis[(4 methoxyphenyl) methylidene]-1,2-ethanediamine (SBL), was derived by the condensation of 4-methoxybenzaldehyde with ethylene diamine followed by complexation with divalent transition metals. The synthesized Schiff base ligand (SBL) and its complexes 1-5 were characterized on the basis of IR, 1H-NMR, 13C-NMR, MS spectral, molar conductance and elemental analyses data. The structure of Schiff base ligand (SBL) was also confirmed by single crystal x-ray crystallographic study. The conductivity data suggests non-electrolytic nature of these complexes. The complexes have higher antibacterial activity than the parent Schiff base ligand

Keywords: schiff base ligand; x-ray diffraction;enzyme inhibition; antioxidant activity; antibacterial activity

Introduction

The most important aspect of today research in the field of chemistry has focused its dimensions and orientations towards the synthesis of novel compounds which could be used as templates against harmful pathogens. The development of new templates is based on the fact that different strains of bacteria and fungi have developed immunity against the commonly used antibacterial and antifungal agents (Dueke-Eze et al, 2011). In this context, Schiff bases have been found as promising antimicrobial agents. These compounds were first of all reported by Hugo (Schiff, 1864). Schiff bases are compounds having azomethine (-C=N-) functionality. Literature shows that these compounds are antibacterial, herbicidal (Zhu et al, 2016), antifungal (Zhang et al, 2006) and anti-tumor (Billman & Schmidgall, 2006) agents. Moreover, there is an increased use of these Schiff bases as ligands in making mononuclear and as well as polynuclear complexes with transition metals (Adsule et al, 2006). The remarkable development in the field of Schiff base chemistry has turned the attention of scientific community to synthesize more and more Schiff base ligands with novelty and diversity in structural aspects which may act as models for various biologically significant systems after complexation (Dharmaraj et al, 2001). The Schiff bases have been used as templates in electroluminescent complexes of zinc (Yu et al, 2007). Schiff bases have found their use as carriers of potentiometric sensors for determination of cations and anions (Shamspur et al, 2005). Aroyl hydrazones have been used as ligands in corrosion inhibition, antimicrobial and tuberculosis activity. The medicinal importance of Schiff bases has encouraged the researchers to use them for designing medicinal compounds (Patole et al, 2006). Due to versatile biological and chemical significance of Schiff bases, prompted us to synthesize new Schiff base ligands and their metal complexes. Herein, we report the synthesis of Schiff base ligand, N 1 , N 2 - bis[(4-methoxyphenyl) methylidene]-1,2 ethanediamine (SBL) from the condensation of 4- methoxybenzaldehyde with ethylene diamine and its complexes with Co (II), Cu (II), Pb (II), Ni (II) and Cd (II) metal ions, their structure elucidation and biological potentials such as antibacterial, antioxidant, lipoxygenase and urease inhibition.

2.Experimental

2.1 Materials and methods

All the chemicals and solvents used for the synthesis were purchased from the Merck and as such. The hydrated metal (II) salts were used in chlorides or acetates form [CoCl2.6H2O, CuCl2.2H2O, Pb(OOCCH3)2.3H2O, Ni(OOCCH3)2.4H2O and Cd(OOCCH3)2.2H2O].

2.2 Physical measurement

The TLC was performed on aluminium plates coated with silica gel G-25-UV254 and detection was done under UV lamp at 254 and 366 nm. FTIR were recorded at Thermo Nicolet Avatar 320 spectrophotometer via KBr pellet. Melting points were measured at Gallenkamp apparatus and are uncorrected. For the elemental analyses, Perkin Elmer 2400 series II elemental analyser is used and conductances in DMSO solution (1×10-3 M) at room temperature. The mass spectra were recorded through FAB (Fast atomic bombardment) on JEOL SX102/DA-6000 mass spectrometer, using glycerol as matrix and ions are given in m/z (%). The H-NMR spectra were recorded on a Bruker AMX-400 spectrometer in DMSO-d6. The chemical shifts (δ) are given in ppm, relative to tetramethylsilane as an internal standard, and the scalar coupling constants (J) are reported in Hertz. Single-crystal x-ray diffraction data was collected on Bruker Smart APEX II, CCD 4-K area detector diffractometer (Madison, 1996). Data reduction was performed by using SAINT program. The structure was solved by direct method (Altomare et al, 1993), and refined by full-matrix least squares on F2 by using the SHELXTL-PC package (GM, 1997). The figures were plotted with the aid of ORTEP program (CK, 1976)

2.3 Synthesis

2.3.1 Synthesis procedure of Schiff base ligand (SBL)

The methanol solution of 4-methoxybenzaldehyde (0.02 mol) was refluxed with the methanol solution of ethylenediamine (0.01 mol) for 4 hours at 100 oC with constant stirring on water bath. The resulting reaction mixture was concentrated to one-third of its original volume by rotary evaporator. Then added the ethyl acetate and petroleum ether (1:1) and cold on ice-water. The concentrated resulting mixture was kept at room temperature and light yellow transparent crystals were observed after five days. The obtained crystals were filtered, washed with cold methanol, dried and recrystallized with methanol and then dried over anhydrous CaCl2. The purity of the product was checked by TLC (Fig., 1). N 1 ,N2 -Bis[(4-methoxyphenyl)methylidene]-1,2-ethanediamine (SBL): Light yellow crystals; yield: 87 %; m.p.: 110 oC; IR (KBr) υmax cm-1 : 2841 (C-H), 1638 (C=N), 1459 (C=C); 1H-NMR (DMSO-6d, 400 MHz) δ: 8.23 (2H, s, H-7, -7′), 7.63 (4H, d, J = 8.8 Hz, H-2, -6, -2′, -6′), 6.95 (4H, d, J = 8.8 Hz, H-3, -5, -3′, -5′), 3.79 (4H, s, H-9, -9′), 3.70 (6H, s, OMe (4, 4′)); 13C-NMR (DMSO 6d, 400 MHz) δ: 165.4 (C-7, -7′), 163.6 (C-4, -4′), 131.0 (C-2, -6, -2′, -6′), 129.7 (C-1, -1′), 115.1 (C-3, -5, -3′, -5′), 61.9 (C-9, -9′), 55.9 (OMe (4, 4′)); FAB-MS (+ve) m/z: 297.2 [M+H]+ (calcd. 296.1 for C18H20N2O2); Elemental analysis (%C 72.93, H 6.92, N 9.50 (clacd. C 72.95, H 6.80, N 9.45) Figure 1: Synthesis of Schiff base ligand (SBL)

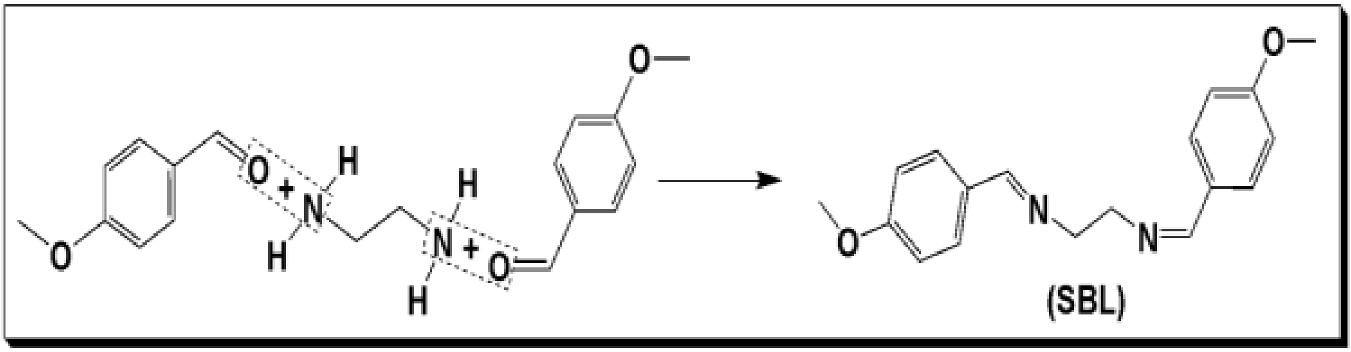


Figure 1: Synthesis of Schiff base ligand (SBL)

2.3.2 General Procedure for the Synthesis of Metal Complexes (1-5)

The methanol solution of the respective metal salt [CoCl2.6H2O, CuCl2.2H2O, Pb(OOCCH3)2.3H2O, Ni(OOCCH3)2.4H2O, Cd(OOCCH3)2.2H2O] was added slowly to a hot methanol solution of ligand (SBL) with stirring in 2:1 (L:M) ratio. The reaction mixture was further refluxed for 45 min. The pH of the reaction mixture was maintained by drop wise adding 1M NaOH in MeOH for the complex formation and the precipitation of complex. The precipitates of the complexes were filtered, washed with cold methanol and dried over anhydrous CaCl2 under reduced pressure. [Pb(BMBE)2(OAc)2] (1): White solid; yield: 78 %; m.p.: 284 oC (decomp.); IR (KBr) υmax cm-1 : 2924 (C-H), 1641 (COO)as, 1545 (C=N), 1390 (C=C), 1246 (COO)s, 519 (Pb-N); Molar conductance (DMSO) λm (Ohm-1 cm2mol-1): 5.93; FAB-MS (+ve) m/z: 919.5 [M+H]+ (calcd. 918.3 for C40H46N4O8Pb); Elemental analysis (%):C 52.38, H 5.12, N 6.17, Pb 22.61 (clacd. C 52.33, H 5.05, N 6.10, Pb 22.57) [Ni(BMBE)2(H2O)2] (2): Stonewash green solid; yield: 81 %; m.p.; 201 oC (decomp.); IR (KBr) υmax cm-1 : 3286 (OH), 2928 (C-H), 1554 (C=N), 1404 (C=C), 523 (Ni-N); Molar conductance (DMSO) λm (Ohm1 cm2mol-1): 10.12; FAB-MS (+ve) m/z: 687.4 [M+H]+ (calcd. 686.2 for C36H44N4O6Ni); Elemental analysis (%):C 62.92, H 6.53, N 8.20, Ni 8.59 (clacd. C 62.90, H 6.45, N 8.15, Ni 8.54) [Co(BMBE)2(H2O)2] (3): Fatigue green solid; yield: 79 %; m.p.: 245 oC (decomp.); IR (KBr) υmax cm-1 : 3495 (OH), 3094 (C-H), 1569 (C=N), 1461 (C=C), 577 (Co-N); Molar conductance (DMSO) λm (Ohm1 cm2mol-1): 7.91; FAB-MS (+ve) m/z: 688.3 [M+H]+ (calcd. 687.2 for C36H44N4O6Co); Elemental analysis (%):C 62.89, H 6.53, N 8.18, Co 8.58 (clacd. C 62.87, H 6.45, N 8.15, Co 8.57) [Cu(BMBE)2(H2O)2] (4): Dark chocolate solid; yield: 72 %; m.p.: 258 oC (decomp.); IR (KBr) υmax cm1 : 3364 (OH), 2974 (C-H), 1604 (C=N), 1462 (C=C), 583 (Cu-N); Molar conductance (DMSO) λm (Ohm1 cm2mol-1): 12.61; FAB-MS (+ve) m/z: 692.3 [M+H]+ (calcd. 691.2 for C36H44N4O6Cu); Elemental analysis (%):C 62.49, H 6.51, N 8.13, Cu 9.23 (clacd. C 62.46, H 6.41, N 8.09, Cu 9.18) [Cd(BMBE)2(H2O)2] (5): Light yellow solid; yield: 69 %; m.p.: 204 oC (decomp.); IR (KBr) υmax cm-1 : 3599 (OH), 2909 (C-H), 1551 (C=N), 1401 (C=C), 514 (Cd-N); Molar conductance (DMSO) λm (Ohm1 cm2mol-1): 12.13; FAB-MS (+ve) m/z: 743.4 [M+H]+ (calcd. 742.2 for C36H44N4O6Cd); Elemental analysis (%):C 58.39, H 6.02, N 7.59, Cd 15.19 (clacd. C 58.34, H 5.98, N 7.56, Cd 15.17)

2.4 Biological studies

The antioxidant potential with DPPH scavenging and urease inhibition activity were measured by reported protocol (Ferheen et al, 2009), while lipoxygenase (LOX) inhibiting activity was measured by reported modified method (Ali et al, 2009). The antibacterial activity was measured as diameter of zone of inhibition to calculate the % inhibition by using modified method (Bibi et al, 2011).

3. Results and Discussion

The reaction of 4-methoxybenzaldehyde (anisaldehyde) with ethylene diamine produces the Schiff base ligand, N 1 ,N2 -bis[(4- Aslam et al., Journal of Natural and Applied Sciences Pakistan, Vol 5 (1), 2023 pp1222-1231 1226 methoxyphenyl)methylidene]-1,2-ethanediamine (SBL), while treatment of this Schiff base with metal (II) salt resulted in the formation of complexes (1-5). The melt points of complexes (1-5) were provide clear evidence that the complexes (1-5) are fairly stable.

3.1 Infrared spectra

The absence of characteristic bands of the carbonyl group ν(C=O) of 4-methoxybenzaldehyde and the amino group ν(-NH2) of free ethylene diamine revealing the complete condensation taken place, and the absorption band at 1638 cm-1 further revealed the formation of azomethine bond. The binding positions of the Schiff base ligand with the metal ion in complexes were revealed by comparing the IR spectra of the ligand with the IR spectra of all the complexes. In the IR spectra of the complexes, the shifting of SBL band from 1638 cm-1 to 1545- 1604 cm-1 indicating the formation of coordinate covalent bond between nitrogen of the C=N group and the metal atom. This can be explained by the donation of electrons from nitrogen to the d-orbital of the metal atom (Zhu et al, 2006). Furthermore, the appearance of band with medium intensity at 514- 583 cm-1 is assigned to ν(M-N) (Chohan and Pervez, 1993), confirmed the formation of complexes. The absorption bands at 1641 and 1246 cm-1 in IR of complex 1 were assigned to the ν(COO-)as asymmetric stretching vibrations and to the ν(COO-)s symmetric stretching vibration of the acetate ion, respectively. This indicates that the acetate group was present in the complex (Fig., 2). In complexes 2-5, the presence of broad band at 3286-3599 cm suggesting the presence of water in the complexes (Fig., 2) (Nakanishi and Solomon, 1977).

3.2 1H-NMR

spectra In the 1H-NMR spectrum of the ligand (SBL), the singlet at 8.23 ppm of methane proton revealing the formation of azomethine bond in the Schiff base ligand. The down field signals at 7.63 and 6.95 ppm were of aromatic ring protons and the signals at 3.79 and 3.70 ppm were of -CH2 and -OCH3, respectively.

3.3 Molar conductance

The molar conductivities of the complexes 1-5 of 1×10-3 M DMSO solutions were measured at room temperature. The observed molar conductance value for complex 1 was 5.93 ohm-1 cm2mol-1 , showing the non-ionic nature while complexes 2-5 have molar conductance values in the range of 7.91-12.61 ohm1 cm2mol-1 , revealing the ionic nature of these complexes (Geary, 1971).

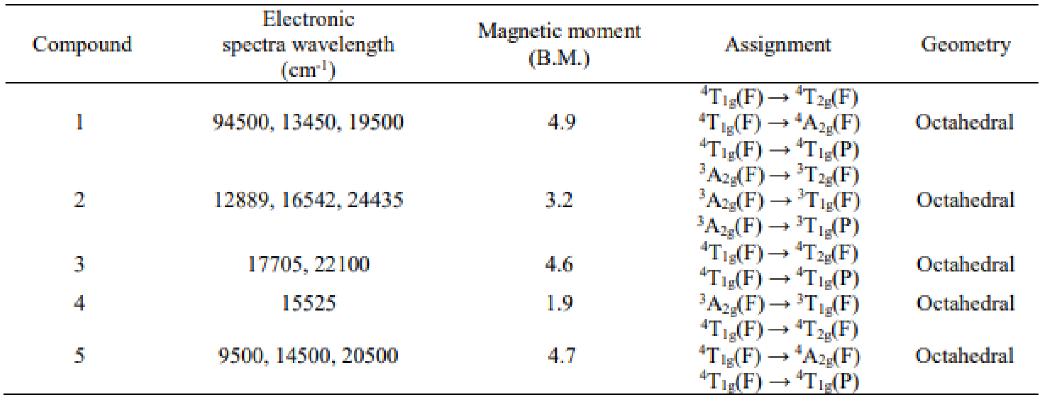
3.4 FAB mass spectra

The masses of the ligand (SBL) and the complexes 1-5 were determined through the FAB (positive mode) mass spectra. A molecular ion peak [M+H]+ was observed at m/z 297.2 which revealed the ligand and confirms the molecular weight i.e., 296.1. The observed molecular ion peaks for the complexes 1- 5, confirming the complexes with metal to ligand ratio 1:2. The elemental analysis values are also in good agreement with these values.

3.5 Electronic spectra and magnetic moment

The position, number of d-d transitions and charge transfer formed the basis of geometry of metal ions in complexes 1-5 and geometry was assigned by observing electronic spectra. The octahedral geometry was suggested for all complexes by Aslam et al., Journal of Natural and Applied Sciences Pakistan, Vol 5 (1), 2023 pp1222-1231 1227 observing electronic spectra and magnetic moment values (Table 1), which was further strengthened by the low value of molar conductance, indicating the nature of complexes as non-electrolytic. Table 1:

Table 1: Electronic and magnetic moment data of ligand and complexes



Compound	Electronic spectra wavelength (cm^{-1})	Magnetic moment (B.M.)	Assignment	Geometry
1	94500, 13450, 19500	4.9	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	Octahedral
2	12889, 16542, 24435	3.2	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$	Octahedral
3	17705, 22100	4.6	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	Octahedral
4	15525	1.9	$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$	Octahedral
5	9500, 14500, 20500	4.7	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	Octahedral

3.6 Proposed molecular structure of metal complexes (1-5)

On the bases of analytical and spectral data, it is imagining that the metal ions are bonded to the Schiff base ligand (SBL) via the nitrogen atom; the tentative proposed structures of the complexes are illustrated in Figure 2.

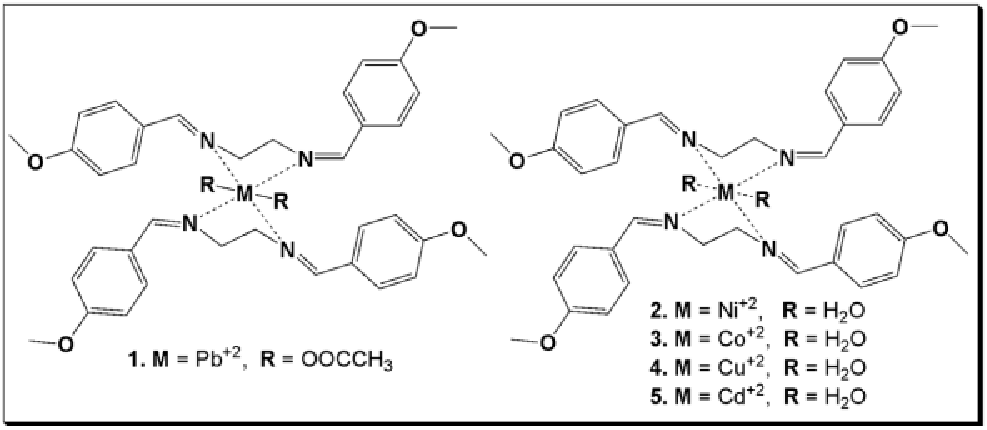


Figure 2: Proposed structure complexes 1-5

3.7 Single crystal XR

The crystal structure of ligand (SBL) (Fig., 3) iscentrosymmetric with a centre of inversion locatedin the midpoint of the compound. Therefore, thecomplete molecule of the Schiff base ligand, C18H20N2O2 is generated by the application of a centre of inversion. The azomethine double bond adopts an E-configuration, with torsion angle of 179.54(13)o C8/N1/C6-C7. The phenyl group (C1---C6) and azomethine moiety, C6/N1/C7---C8, are each planar with a dihedral angle between their least square planes being 7.44 (18)o. The bond lengths and angle were similar to the reported structurally related compounds (Cox et al, 2008). The bond length of azomethine bond was found to be 1.249(2) Å. In the crystal structure of the ligand, the molecules were arranged in parallel sheets along b-axis without any classical hydrogen bonding betweenmolecules. Crystal data of Schiff base ligand (SBL):

C18H20N2O2, Mr = 296.36, Monoclinic, space group P21/n, a = 10.2089(8) Å , b = 7.9659(7) Å , c =

10.6366(9 Å , β = 111.747(2)o, V= 803.44(12)Å 3, Z= 2, □calc= 1.225 mg/m3, F(000) = 316, µ (Mo Kα)= 0.71073 Å, max/min transmission 0.9896/0.9570crystal dimensions 0.55 x 0.26 x 0.13, 2.36◦ < □ <25.5◦, 4577 reflections were collected, of which 1464 reflections were observed (Rint = 0.0141). TheR values were: R1 = 0.0438, wR2 = 0.1239 for I □ 2□(I), and R1 = 0.0515, wR2 = 0.1334 for all data; max/min residual electron density: 0.160 / -0.143 eA˚−3

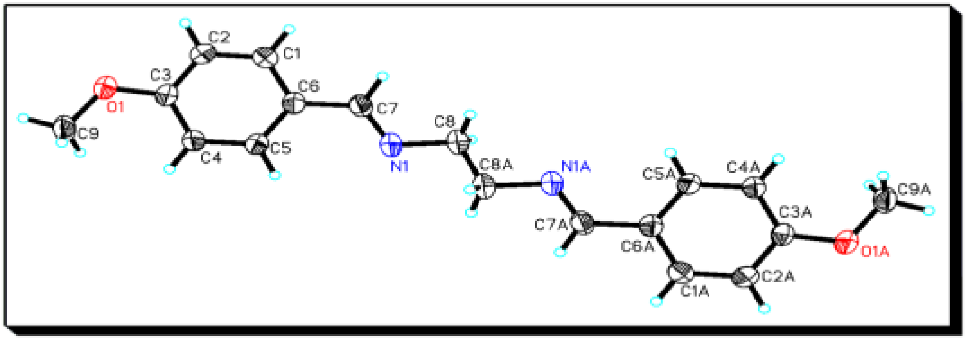


Figure 3: The molecular structure (ORTEP) of Schiff base ligand (SBL) with displacement ellipsoids drawn at 30% probability level.

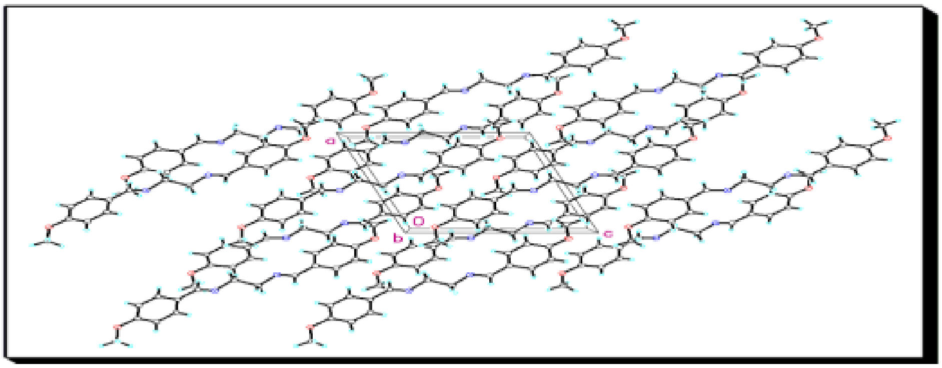
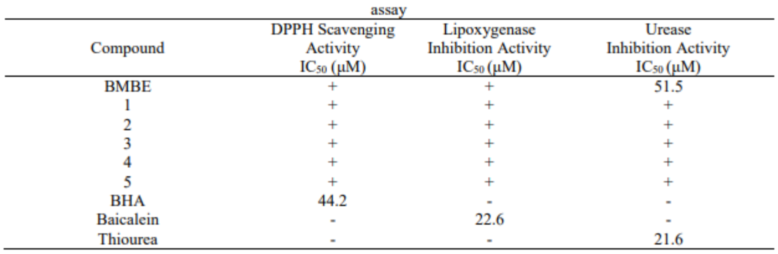


Figure 4: The crystal packing of the ligand (SBL)

3.8 Biological studies

The Schiff base ligand (SBL) and its complexes 1-5 were screened out for antioxidant, lipoxygenase, urease inhibition and antibacterial activities. The results of Schiff base ligand (SBL) and complexes 1- 5 of DPPH scavenging antioxidant, lipoxygenase and urease inhibition activities are summarized in Table 2. When IC50 values SBL and complexes 1-5 were compared with the standard, it can be seen that the Schiff base ligand (SBL) has good IC50 value only in urease inhibition activity while its complexes 1-5 have non-significant IC50 values. The potential of the Schiff base ligand (SBL) and its complexes 1- 5 was checked against various microorganisms such as S. intermedius, B. subtilis, S. aureus, E. coli and S. typhi in order to establish its bioactivities and results are summarized in Table 3. The antibacterial activity was evaluated by measuring the diameter of the zone of inhibition in mm and then percentage of growth inhibition was calculated. In order to compare the results obtained, the gentamicin was used as a standard drug. The result obtained showed that Schiff base ligand (SBL) and its complexes (1- 5) have good activity against B. subtilis and S. aureus while moderate activity against S. intermedius, E. coli and S. typhi as compared to the standard drug, proposed that the oxygen of –OCH3 may bind with the bacteria leading to such kind of results of biological activity. In the mode of action of the Schiff base ligand, may involve the formation of hydrogen bond through the azomethine group with the active Centre of cell constitutes resulting in interference with the normal cell process.

Table 2: IC50 (µM) values of Schiff base ligand (SBL) and complexes (1- 5) in the antioxidant, lipoxygenase and urease



assay

Compound	DPPH Scavenging Activity IC_{50} (µM)	Lipoxygenase Inhibition Activity IC_{50} (µM)	Urease Inhibition Activity IC_{50} (µM)
BMBE	+	+	51.5
1	+	+	+
2	+	+	+
3	+	+	+
4	+	+	+
5	+	+	+
BHA	44.2	-	-
Baicalein	-	22.6	-
Thiourea	-	-	21.6

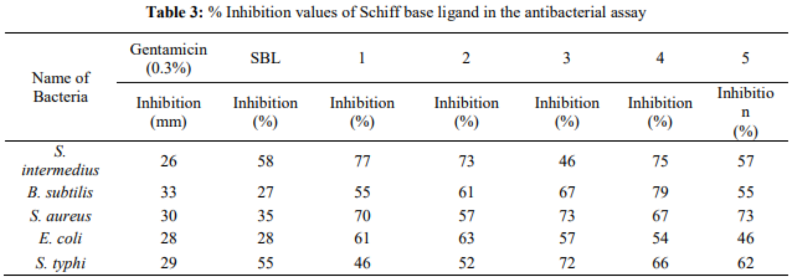


Table 3: % Inhibition values of Schiff base ligand in the antibacterial assay

Name of Bacteria	Gentamicin (0.3%)	SBL	1	2	3	4	5
	Inhibition (mm)	Inhibition (%)	Inhibition (%)	Inhibition (%)	Inhibition (%)	Inhibition (%)	Inhibitio n (%)
S. intermedius	26	58	77	73	46	75	57
B. subtilis	33	27	55	61	67	79	55
S. aureus	30	35	70	57	73	67	73
E. coli	28	28	61	63	57	54	46
S. typhi	29	55	46	52	72	66	62

4. conclusions:

schiff base ligand and complexes were derived from 4-methoxybenzaldehyde with ethylene diamine, and metal (II) salts, respectively. They characterized by various spectroscopic and analytical techniques. FAB-MS and elemental analyses of the complexes were confirmed its bidentate nature, and stoichiometry was observed as 1:2 (M:L) and its non-electrolytic nature has been deduced from conductance data. The metal complexes have nonsignificant antioxidant, lipoxygenase and urease inhibition activities and have higher antibacterial activity than the Schiff base ligand.

5. Supplementary material:

CCDC-881753 contains the supplementary crystallographic data for Schiff base ligand (SBL). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrievinghtml by e-mailing: deposit@ccdc.cam.ac.uk; or by contacting: The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0)1223-336-033.

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