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Synthesis, spectral characterization and antibacterial activities of heterocyclic complexes with Schiff base derived from 3-hydroxybenzofuran-2-carbaldehyde and (furan-2-yl)methanamine

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A Schiff base, 2-((E)-((furan-2-yl)methylimino)methyl)benzofuran-3-ol has been synthesized and assessed using elemental analysis, infrared spectroscopy, nuclear magnetic resonance, mass spectroscopy and thermal analysis (TGA). The complexes' analytical results confirm the synthesis of a 1:2 [M:L] ratio of the formula [ML_2], where M corresponds to the ions Cu(II), Ni(II), Zn(II), Mn(II) and L for the deprotonated Schiff base. Metal ions are bidentately coupled to Schiff base *via* azomethine-N and phenolic-oxygen groups, as inferred from infrared spectra. The disc diffusion technique has been used to test the ligands and their metal chelates for their antibacterial properties against specified microorganisms.

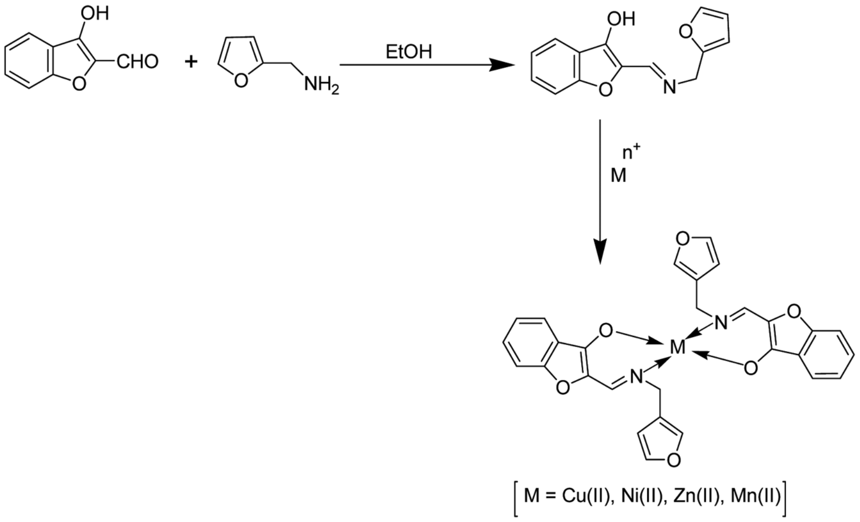
Keywords: Schiff base, Metal complexes, Biological activity

The evolution of coordination chemistry was greatly influenced by Schiff bases, a family of ligands that easily form stable complexes with the majority of transition metals. It is well-known that the consumption of some medications as metal complexes increases their efficacy[1]. Interestingly, research has demonstrated that certain metal chelates may prevent tumor development[2]. In addition to their significant functions in organic synthesis and catalysis, metal complexes of Schiff base ligands have been reported to have a wide range of industrial, biological, therapeutic, analytical and other uses[3-7]. Schiff base metal complexes made from 3-hydroxybenzofuran-2-carbaldehyde have the ability to break DNA in a specific way, according to several research groups[8,9]. The potent antibacterial properties of furan derivatives are well known. Additionally, Schiff base metal complexes containing heterocyclic molecules have medicinal promise[10,11]. Thus, a common issue has been the synthesis of novel Schiff bases and related complexes[12]. Preparative chemistry also relies on knowing a substance's protonation constants[13]. Additionally, protonation of a newly synthesized compound can also give supportive information about its structure[14]. If theoretically calculated protonation constants are in good accordance with the experimental values, it is possible that the proposed structure could be correct[15-17].

The present study expands upon our work by examining the synthesis, characterization, equilibrium study and biological activity of Schiff base ligand and its complexes with various divalent metal ions, as well as 2-((E)-((furan-2-yl)methylimino)methyl) benzofuran-3-ol derivatives. The free Schiff base ligand is protonated, and the researchers display its stepwise stability constants with Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} (Ref. 18). This was accomplished by determining the stability constants of their complexes at various temperatures. We additionally show some relationships between thermodynamic functions and several well-known metal ion characteristics in this expanded version of the paper. The kind and motivations behind the interactions in biological systems may be better understood with this kind of research.

Results and Discussion

The Schiff base compound is produced by condensing 3-hydroxybenzofuran-2-carbaldehyde with (furan-2-yl)methanamine in boiling ethanol. Strong polar solvents like DMSO and DMF in addition to heated ethanol may dissolve the ligand. Since the complexes' melting temperatures are greater than the ligand's, it is evident that the complexes are much more stable. Scheme 1 shows the chemical equations for the creation of the Schiff base and the complexes. The compounds shown were obtained



Scheme 1 — Structure of Schiff base ligand and its metal(II) complexes

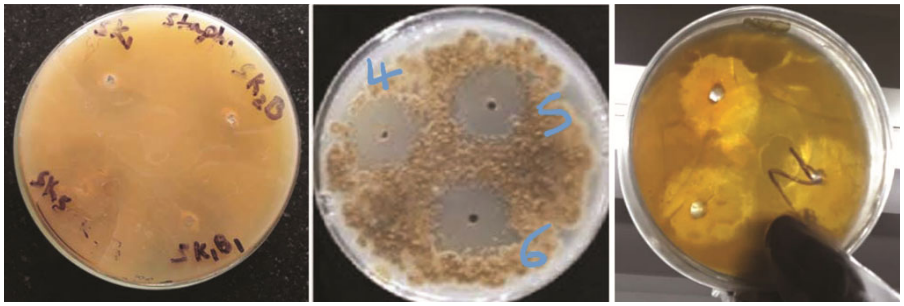


Fig. 1 — Some pictures of anti bacterial activity of metal complexes

by reacting Schiff base ligand with copper(II), nickel(II), zinc(II), manganese chloride in EtOH at a molar ratio of 1:2 under reflux conditions. According to the data, the water molecule is not coordinated to the metal ion since the dehydration temperature of $[Zn(L)_2]\cdot H_2O$ is lower.

To make the Schiff base, an ethanolic solution was mixed with 2.01 g (0.01 mol) of 3-hydroxybenzofuran-2-carbaldehyde and 1.13 g (0.01 mol) of (furan-2-yl)methanamine in a volume of 20 mL of ethanol. This was followed by a refluxing period of 1 hour while stirring the liquid constantly. It was then crystallized from ethanol and allowed to dry at RT, resulting in an 85% yield.

The Schiff base complexes that were meant to be studied were made by combining 25 mL of an ethanolic Schiff base solution (0.01 mol, 2.95), with 25 mL of an ethanolic metal salt solution (0.005 mol), which included $CuCl_2\cdot 2H_2O$ (0.852 g), $Ni(NO_3)_2\cdot 6H_2O$ (1.453 g) and $Zn(NO_3)_2\cdot 6H_2O$ (1.487 g), $MnCl_2\cdot 4H_2O$ (1.465 g) . The final mixture was refluxed for two hours while stirring continuously and then left overnight to ensure all reactions were completed. As a result, the complexes were filtered, collected and washed with hot ethanol on multiple occasions until the filtrate lost all color. The desiccator was used in conjunction with anhydrous calcium chloride to dry the complexes under vacuum. From 75% to 80% was the yield. Elemental analysis and spectral data were examined in the dried complexes. The decomposition of TGA of metal complexes of Cu(II) is 1100°C and Mn(II) is 1000°C.

In vitro antibacterial activity

The bacteria, namely *Escherichia coli*, *Pseudomonas aeruginosa* as Gram −ve, *Staphylococcus aureus* and *Bacillus subtillis* as Gram +ve, were used to test the synthesized Schiff base and its related Cu(II), Ni(II), Zn(II) and Mn(II) complexes for their biological activity *in vitro* (Fig. 1). The test chemical compound's stock solution (1 mg mL^{-1}) was made by dissolving 20 mg of the compound in 20 mL of dimethyl sulfoxide (DMSO) solvent. Sterilized distilled water was used to dilute this stock solution until 30 and 50 g mL^{-1} were produced. To make a sterile distilled water control, 10 mL of solvent was mixed with the stock solution for each dilution. The microorganisms were cultivated in agar. The Petri dishes were kept at 37°C for a duration of 24 hours. Ampicillin is a standard antibacterial antibiotic was also tested under the same configurations. A paper disc with a consistent diameter of 2 cm and made of Whatman filter paper (No. 42) was autoclaved for sterilization. In a clean manner the paper discs were placed in petri dishes that contained nutrient agar media that was seeded with Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtillis separately. The discs were soaked in the complex solutions to the desired concentration. Incubation was carried out at 37 ˚C for the petri dishes. Following 24 hours of incubation, the inhibitory zone's width was determined. The average of three independent tests may be used to determine the antimicrobial activity shown in Table 1. All of the metal complexes showed greater activity against Ampicillin at higher temperatures.

Experimental Section

All compounds were of analytical grade and they were distilled before use in accordance with conventional procedure. Elemental analysis CHN was done using Elementar Vario EL III analyzer. In order to ensure that the results were accurate, the analyses were run twice. The KBr pellets were subjected to infrared spectra recording using a Shimadzu 8001-PC FTIR spectrophotometer. Thermo gravimetric analysis (TGA) was performed using a Universal TGA Q50 equipment, that heated samples at a rate of 2°C/min from 30 to 1000°C. A Bruker ARX-300 apparatus was used to record the ^{1}H NMR and ^{13}C NMR spectra. In the presence of DMSO-*d*$_6$, the chemical changes are expressed as parts per million (δ, ppm) in comparison to tetramethylsilane.

Synthesis of Ligand

A Schiff base was prepared by combining 2.01 g (0.01 mol) of 3-hydroxybenzofuran-2-carbaldehyde and 1.13 g (0.01 mol) of (furan-2-yl)methanamine in a volume of 20 mL of ethanol dissolved in an ethanolic solution. After that, the liquid was refluxed for an hour with continual stirring. Then, it was dried at RT after crystallizing from ethanol. White Crystals. Yield 85%. T$_{\text{m.p}}$: 99.40-101.32°C. IR (KBr): 1670-1680, 1360–1450, 1340-1345 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 7.61 d (*J*= 6.1 MHz, 2H, ArH), 7.47 m (3H, ArH), 6.06 m (3H, Ar-H), 5.72 m (1H, OH), 4.87 s (2H, CH$_2$); ^{13}C NMR (DMSO-*d*$_6$): δ 159.48, 152.54, 148.88, 144.95, 141.63, 129.16, 127.91, 122.51, 121.03, 120.68, 112.38, 111.96, 110.65, 66.83; MS: *m*/*z* 241.10. Found: 241.27. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.75; H, 4.63; N, 5.83%.

Synthesis of Metal complexes

To prepare the Schiff base complexes for the experiment, 25 mL of an ethanolic Schiff base solution (0.01 mol, 2.95), along with 25 mL of an ethanolic metal salt solution (0.005 mol) were mixed. The metal salts used is $CuCl_2.2H_2O$ (0.852 g), $Ni(NO_3)_2.6H_2O$ (1.453 g), $Zn(NO_3)_2.6H_2O$ (1.487 g) and $MnCl_2.4H_2O$ (1.465 g). After two hours of refluxing with constant stirring, the final mixture was allowed to overnight that all reactions had finished. The complexes were then filtered, collected and washed with hot ethanol many times until the filtrate became colorless. To dry the complexes under vacuum, the desiccator was utilized in combination with anhydrous calcium chloride. A yield ranging from 75% to 80% was observed. The dried complexes were subjected to spectrum data and elemental analyses.

Cu(II) Complex

Light blue. Yield 75%. T$_{\text{m.p}}$: >300°C. IR (KBr): 1690-1680, 1380–1350 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 8.45 m (3H, ArH), 8.12 m (3H, ArH), 7.65 d (*J*= 6.1 MHz, 2H, ArH), 7.48 m (3H, ArH), 6.06 m (3H,

Table 1 — Antibacterial activity of Schiff base metal complexes

Compd	*Pseudomonas aereuginosa*		*Salmonella typhi*		*Bacillus subtillis*		*Staphylococcus aureus*	
Conc. (gmL^{-1})	30	50	30	50	30	50	30	50
Ligand	14	16	9	15	13	15	12	14
[Cu(L)$_2$]	16	18	15	19	20	24	13	16
[Ni(L)$_2$]	20	23	20	24	19	22	18	23
[Zn(L)$_2$]	20	25	22	26	15	23	16	27
[Mn(L)$_2$]	22	26	19	25	14	19	13	19
Ampicillin	20	21	15	18	16	17	16	18

Ar-H), 5.72 s (2H, ArH), 4.85 s (4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 163.07, 156.03, 145.02, 142.08, 139.95, 131.63, 124.14, 123.61, 121.03, 118.68, 111.38, 110.62, 107.03, 51.23; MS: *m*/*z* 543.01. Found: 543.43. Anal. Calcd for $C_{28}H_{20}CuN_2O_6$: C, 61.82; H, 3.71; N, 5.15. Found: C, 61.83; H, 3.75; N, 5.20%.

Ni(II) Complex

Light blue. Yield 77%. $T_{m.p}$: 165.32-167.20°C. IR (KBr): 1692-1618, 1389–1332 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.46 m (4H, ArH), 8.10 m (2H, ArH), 7.60 d (*J*= 7.1 MHz, 2H, ArH), 7.45 m (3H, ArH), 6.00 m (3H, Ar-H), 5.52 s (2H, ArH), 4.75 s (4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 162.15, 156.03, 154.02, 145.02, 141.18, 139.95, 131.62, 124.14, 123.61, 122.03, 121.03, 117.65 111.35, 110.62, 107.03, 51.28; MS: *m*/*z* 538.05. Found: 538.27. Anal. Calcd for $C_{28}H_{20}NiN_2O_6$: C, 62.37; H, 3.74; N, 5.20. Found: C, 62.39; H, 3.75; N, 5.25%.

Zn(II) Complex

Light cream. Yield 80%. $T_{m.p}$: 239.20-242.25°C. IR (KBr): 1704-1582, 1380–1321 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.40 m (4H, ArH), 8.07 m (2H, ArH), 7.40 d (*J*= 5.1 MHz, 2H, ArH), 7.23 m (3H, ArH), 6.23 m (3H, Ar-H), 5.35 s (2H, ArH), 4.25 s (4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 165.20, 154.15, 153.12, 145.02, 141.18, 136.92, 131.62, 126.14, 124.63, 123.03, 121.03, 117.65 112.35, 110.62, 102.03, 55.18; MS: *m*/*z* 544.15. Found: 544.37. Anal. Calcd for $C_{28}H_{20}ZnN_2O_6$: C, 61.61; H, 3.69; N, 5.13. Found: C, 61.63; H, 3.72; N, 5.16%.

Mn(II) Complex

Light cream. Yield 78%. $T_{m.p}$: 240.10-242.15°C. IR (KBr): 1604-1682, 1370–1351 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.20 m (3H, ArH), 8.05 m (3H, ArH), 7.20 d (*J*= 4.1 MHz, 2H, ArH), 7.13 m (3H, ArH), 6.23 m (3H, Ar-H), 5.36 s (2H, ArH), 4.20 s (4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 164.20, 153.15, 153.12, 145.02, 140.18, 136.75, 130.62, 126.14, 124.13, 122.63, 121.03, 116.45 110.75, 110.42, 101.03, 59.18; MS: *m*/*z* 535.55. Found: 535.37. Anal. Calcd for $C_{28}H_{20}MnN_2O_6$: C, 62.81; H, 3.77; N, 5.23. Found: C, 62.85; H, 3.79; N, 5.25%.

Conclusion

This study discusses the synthesis, characterisation, and electronic absorption spectra of Schiff base ligand and its complexes. The synthetic process in this study produced compounds with a molar ratio of 1:2 (L:M). The newly synthesized Schiff base functions as a monobasic bidentate ligand. The azomethine nitrogen and phenolic oxygen atoms coordinate the metal ion, generating a stable heterocyclic ring by deprotonation. According to chelation hypothesis, this substance possesses antimicrobial properties. Further, the complexes that were examined had a stronger impact on Gram-positive bacteria compared to Gram-negative bacteria according to the data. There may be a correlation between the structure of the bacteria's cell wall and the antibacterial action of the substances.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Conflict of Interest

The authors confirm that there is no conflicts of interest.

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