Design, synthesis, spectral characterization and antibacterial studies of transition metal complexes of benzothiophene Schiff base

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Abstract

In the present work, a series of benzothiophene based Schiff base ligands 2-((E)-(1-methyl-3-nitro-1H-pyrazol-5-ylimino)methyl)benzo[b]thiophen-3-ol and their Cu(II), Co(II) and Ni(II) complexes were synthesized and characterized by physical, analytical and spectral data such as elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, ESI-Mass, UV-vis studies. Spectro-analytical experimental data confirms that all of these metal complexes have a square planar shape.

The synthesized Schiff base coordinates to the metal through imine nitrogen and phenolic oxygen atoms, making it a monobasic bi-dentate ligand. In addition, five different bacterial species were tested for metal complexes in the antibacterial tests.

Keywords: Pyrans, Multicomponent reaction, Antioxidant activities.

Introduction

The synthesis of a new class of Schiff base benzothiophene metal complexes has been our primary focus[1]. The pharmacological actions of Schiff bases[2] which include antibacterial, anticancer, anti-inflammatory, anti-tuberculosis, antioxidant, anticonvulsant and antihelmintic[3-9] etc. have attracted the greatest attention in medicinal chemistry[10]. Schiff bases have several applications including those of dyes, catalysts, chemical synthesis intermediates and polymer stabilizers[11-14]. In addition, benzothiophenes are well recognized as bioactive chemicals within the heterocyclic chemistry class[15] and they exhibit a wide variety of biological actions[16]. Moreover, Schiff base produced from benzothiazole is finding uses in the analytical, biological, inorganic, medical and pharmaceutical industries[17]. Because of their many biological activities including antioxidant, antifungal, anti-inflammatory, antibacterial, anticancer and cytotoxic benzothiophene Schiff bases are also valuable for pharmacological research[18-20].

Material and Methods

Infrared spectra were collected using a Perkin-Elmer Infrared Model 337 spectrophotometer with KBr pellets and then transformed using the Fourier transform (FTIR). A Bruker-Avance-III 400 MHz digital NMR apparatus was used to record the proton ^{1}H NMR and carbon ^{13}C NMR Fourier transform spectra of Schiff base with tetramethylsilane (TMS) serving as the internal standard. The mass spectra of all substances were obtained using an ESI-MS instrument from VG Scientific. The Perkin Elmer 240C (USA) elemental analyser was used to determine the concentrations of C, N, H and S. Using Polmon-MP-96 equipment, we determined the melting points of the compounds. Fluorescence was studied using DMSO in a JASCO FP-8500 spectrofluorimeter and electronic absorption spectra were acquired on a Shimadzu UV-vis 2600 spectrophotometer across a wavelength range of 200-800 nm.

Antibacterial activity: Five different bacterial organisms including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*, were obtained and tested *in vitro* for their susceptibility to the Schiff base ligand 6-((E)-(1-methyl-3-nitro-1H-pyrazol-5-ylimino)methyl)benzo[b] thiophen-5-ol and its metal complexes. Micro centrifuge tubes containing 40% sterile glycerol were used to store the bacterial cultures at 20 °C until use. The drugs' inhibitory action was examined using either a well plate or disc diffusion assay. Mueller Hinton agar, Trypton soy agar, or Nutrient agar were used to make the wells. The test organisms were already present in the medium.

The culture volumes for McFarland 0.5 turbidity standard inoculation of diffusion plates range from 1-2x108 CFU/mL of bacteria. The plates were incubated at 37 °C for 24 hours after all of the test substances were injected into the wells. Each experiment was performed three times with a control group in between. A zone of inhibition was measured in diameter to quantify microbial growth. Tube dilution methods were used to establish the minimal inhibitory concentration. Single dilutions of each component have been made to achieve a range of concentrations. Each compound's minimum inhibitory concentration was determined by determining the lowest concentration at which the inoculated test organisms failed to develop or produce turbidity in broth culture.

Each substance was also tested against a tube containing only water as a control. Standard organisms are those exposed to the antibiotic ciprofloxacin. All pathogens were treated with substances at concentrations between 1 and 100 g/mL. The Muller-Hinton agar technique was first used to measure the zone of inhibition and the measured diameters were then rounded to the closest full millimeter for analysis. When tested against bacteria that are sensitive to antibiotics, the concentrations of both the synthesized Schiff base ligand

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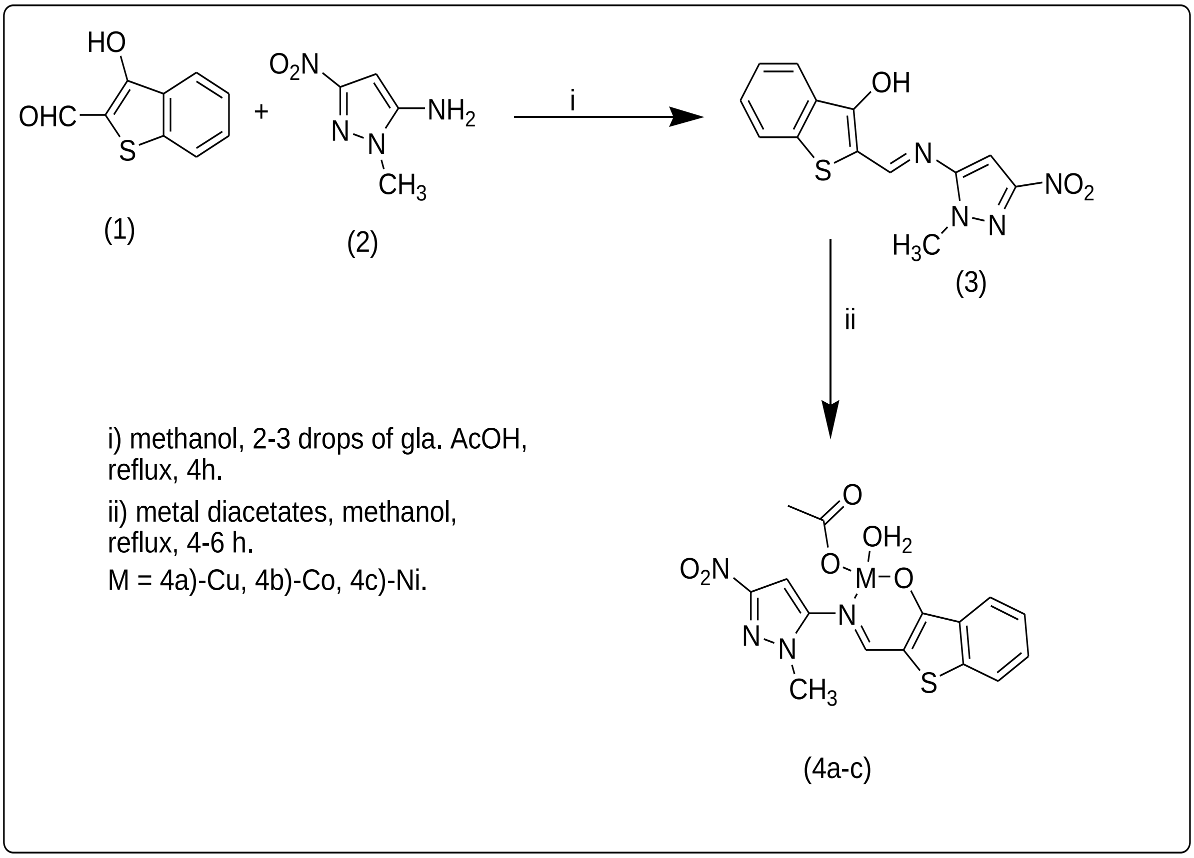
and their metal complexes revealed MICs (in g/mL) that were in orders of magnitude greater than those of the well-known antibiotic ciprofloxacin.

Synthesis of Schiff base ligand: One mole of 3-hydroxybenzo[b]thiophene-2-carbaldehyde (1) (0.167 g, 2 mmol) and one mole of 1-methyl-3-nitro-1H-pyrazol-5-amine (2) (0.194 g, 2 mmol) were added to a solution of hot methanol (10 ml). The final mixture went through a four-hour period of refluxing. A firm, yellowish precipitate appears after the reaction is complete. Drying occurred in a desiccator over anhydrous $CaCl_2$ after filtration and rinsing with cold methanol.

Yield: 85%; M.P. 232–234 °C; IR (KBr, cm^{-1}): ν (H_2O) 3452, ν (C=O) 1641, ν (C = N) 1620; ^1H NMR spectrum (DMSO 400 MHz) δ/ppm: 3.96 (s, 3H, CH_3), 5.28 (s, 1H, OH), 7.40 (s, 1H, CH), 7.48 (s, 1H, CH), 7.59 (s, 1H, CH), 7.65 (s, 1H, CH), 8.26 (s, 1H, CH), 8.71 (s, 1H, CH); ^{13}C NMR spectrum (DMSO 400 MHz): δ/ppm: 37.17, 99.37, 110.54, 113.03, 116.22, 122.35, 128.94, 129.77, 141.54, 150.64, 156.59, 159.22, 163.79; ESI-MS (m/z): Calcd: 302.05 Found: 302.90 $[M + H]^+$; Anal. Calcd (%) for $C_{13}H_{10}N_4O_3S$; C, 51.65; H, 3.33; N, 18.53; Found: C, 51.67; H, 3.35; N, 18.54.

Synthesis of transition metal complexes: 2-((E)-(1-methyl-3-nitro-1H-pyrazol-5-ylimino)methyl)benzo[b]thiophen-3-ol (0.343 g, 10 mmol), The ligand Schiff base was dissolved in 10 ml of hot methanol. Drop by drop, solution was added to a 10 ml solution of metal salts in hot methanol with copper acetate monohydrate $[Cu(CH_3COO)_2.H_2O]$, cobalt acetate tetrahydrate $[Co(CH_3COO)_2.4H_2O]$ and nickel acetate tetrahydrate $[Ni(CH_3COO)_2.4H_2O]$. After the reaction was complete, the solid precipitate was washed with cold methanol and dried in vacuum under desiccators over anhydrous $CaCl_2$ (Scheme 1).



i) methanol, 2-3 drops of gla. AcOH, reflux, 4h.

ii) metal diacetates, methanol, reflux, 4-6 h.

M = 4a)-Cu, 4b)-Co, 4c)-Ni.

Scheme 1: Synthesis of Schiff base ligand and its metal complexes.

Table 1
Bacterial minimum inhibitory activity of Schiff base ligand and their metal complexes (MIC Value in μg/mL)

Compound	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pyogenes*
3.	9.2 ± 0.82	8 ± 0.66	11.1 ± 0.19	9.4 ± 0.21	12.8 ± 0.27
4a.	7.9 ± 0.44	9.3 ± 0.39	8.5 ± 0.33	7.9 ± 0. 17	9.0 ± 1.58
4b.	6.0 ± 0.35	6.9 ± 0.98	10.6 ± 1.73	8.9 ± 0.24	10 ± 1.12
4c.	6.8 ± 0.29	6.0 ± 0.50	8.0 ± 0.24	8.5 ± 0.39	8.0 ± 0.05

(4a) [Cu(II)(L)(CH_3COO)(H_2O)]: Yield: 71%; M.P. 262–264°C. Anal. Calcd (%) for $C_{17}H_{16}CuN_2O_6S$: C, 46.41; H, 3.67; N, 6.37. Found: C, 446.43; H, 3.69; N, 6.40 % IR (KBr /cm^{-1}): ν (H_2O) 3407, ν (C=O) 1650, ν (C = N) 1620, ν (M-O) 525, ν (M-N) 435. UV–vis (nm): 270, 299, 353, 390. ESI-MS (m/z): Calcd: 439.32. Found: 439.63 $[M+H]^+$.

(4b) [Co(II)(L)(CH_3COO)(H_2O)]: Yield: 80%; M.P. 260–262°C. Anal. Calcd (%) for $C_{17}H_{16}CoN_2O_6S$: C, 46.90; H, 3.70; N, 6.44. Found: C, 46.92; H, 3.73; N, 6.46 %. IR (KBr /cm^{-1}): ν (H_2O) 3397, ν (C = N) 1601, ν (C=O) 1148, ν (M-O) 524, ν (M-N) 441. UV–vis (nm): 278, 303, 550, 469. ESI-MS (m/z): Calcd: 435.01 Found: 435.32 $[M+H]^+$.

(4c) [Ni(II)(L)(CH_3COO)(H_2O)]: Yield: 72%; M.P. 256–258°C. Anal. Calcd (%) for $C_{17}H_{16}N_2NiO_6S$: C, 46.93; H, 3.71; N, 6.44. Found: C, 46.95; H, 3.75; N, 6.46 %. IR (KBr /cm^{-1}): ν (H_2O) 3420, ν (C = N) 1601, ν (C=O) 1170, ν (M-O) 520, ν (M-N) 420. UV-Vis (nm): 256, 354, 387. ESI-MS (m/z): Calcd: 434.01. Found: 434.08 $[M+H]^+$.

Results and Discussion

FT-IR spectroscopy: FT-IR spectra were taken in the region of 4000-250 cm^{-1} of a newly synthesized Schiff base ligand and its associated metal complexes. Table 1 displays the findings of the experiments. Free ligand IR spectra revealed a wide bond at 3406 cm^{-1} that corresponds to phenolic H_2O bonds and a significant absorption band at 1620 cm^{-1} that was attributed to azomethine -C=N bonds.

This indicates that the nitrogen of azomethine is coordinated to the metal ion, since the metal complexes have been moved down in frequency by 16–20 cm^{-1} of the azomethine frequency. Another indicator that the oxygen of the H_2O group has been coordinated, is a decrease in the stretching frequency of (C=O) and at 1650 cm^{-1} for ligand in complexes. In addition, the creation of metal-ligand bonds is supported by the appearance of additional bands at lower frequency area between 418 and 527 cm^{-1}, owing to the stretching frequency of (M-N) and (M-O) respectively.

ESI mass spectral studies: The mass spectrum may be used as an initial reference for determining a compound's structure. There was a dominant base peak at m/z = 302.05 in the ESI mass spectra of the ligand (3), which corresponds with the predicted mass $[M+H]^+$ peak. Peaks at m/z = 439.32 [M+H] for 4a, 435.01 $[M+H]^+$ for 4b and 434.01 $[M+H]^+$ for 4c were seen in the ESI mass spectra of metal complexes. All of the metal complexes had a metal-to-ligand molar ratio of 1:1 [M: L], as predicted by the analytical data of molecular ions of complexes.

Electronic absorption study: Electronic absorption spectroscopy in the ultraviolet-visible range is a widely used tool for investigating metal complexes. The addition mode featuring strong stacking interaction between azomethine (N=C) and aromatic chromophores in the ligand led to hypochromism and wave length shift with red shift/ bathochromic in the absorption bands of complexes. The partial filling of orbitals by electrons is thought to be a major contributor to the reduction of transition energy while connecting the orbital of the incorporated ligand of the complexes lowering the transition probabilities: UV absorbance at 260 nm and 280 nm for (4a) and (4b) and (4c) at 250nm.

Conclusion

In this work, we have synthesized and studied Schiffbases based on benzothiophenes, as well as their metal complexes. Electronic absorption, FTIR, Mass, ^1H NMR and ^{13}C NMR tests and analyses have made it clear that all metal complexes also shown higher activity than their equivalent ligands in tests of antibacterial efficacy. When compared to the other complexes, the Cu complex had the most impressive activity.

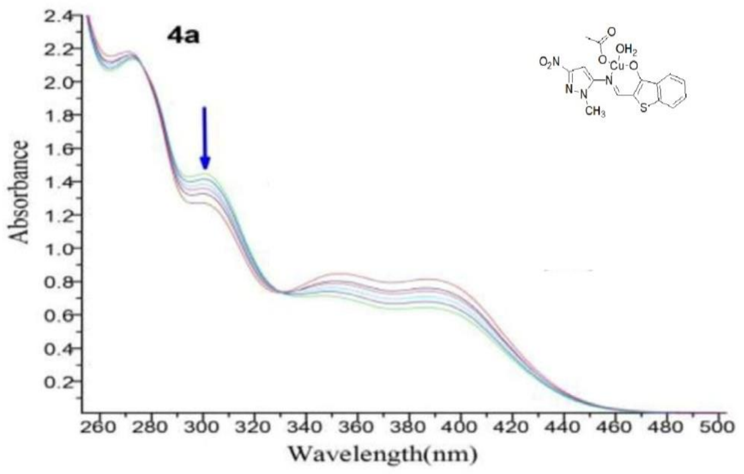


Figure 1: Electronic spectra of Cu-Complex

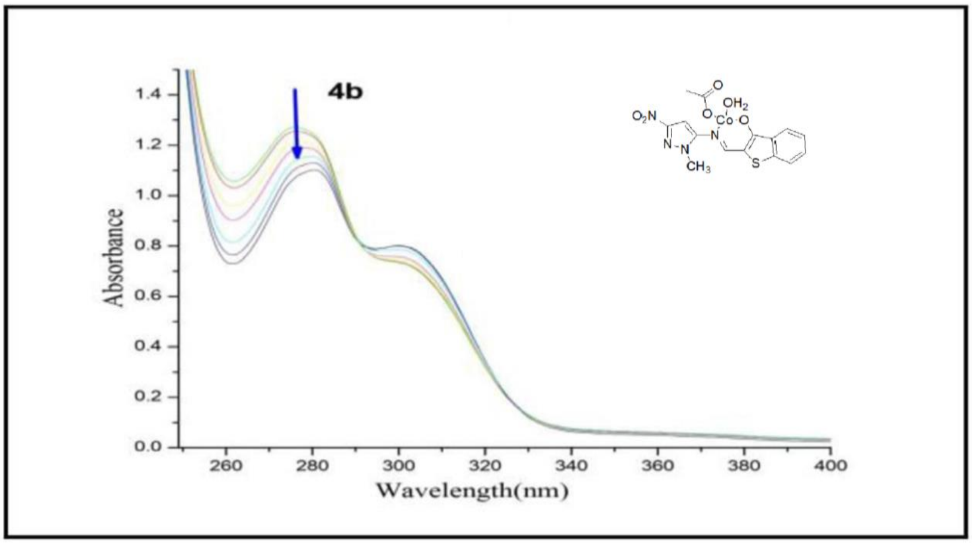


Figure 2: Electronic spectra of Co-Complex

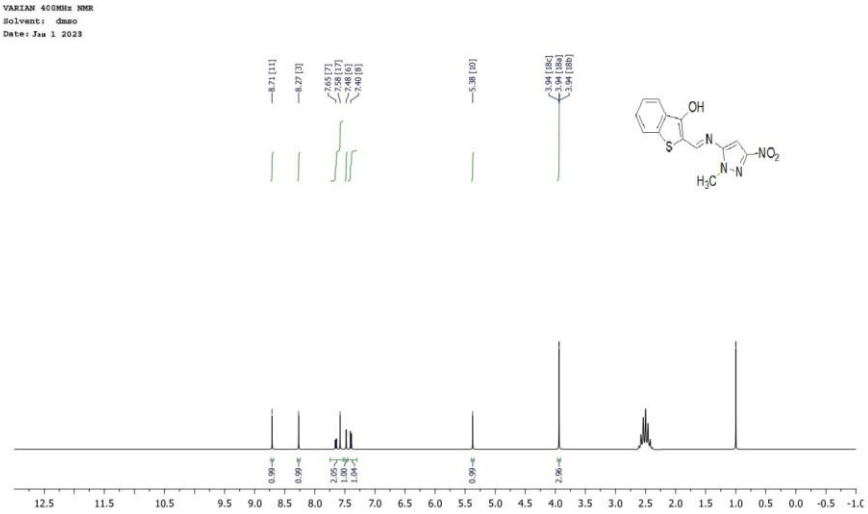


Figure 3: ^{1}H NMR spectra of Ligand

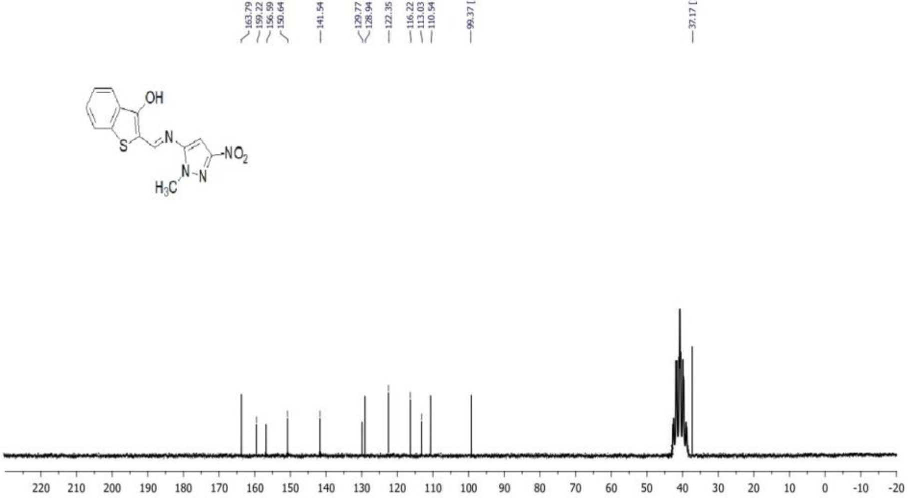


Figure 4: ^{13}C NMR spectra of Ligand

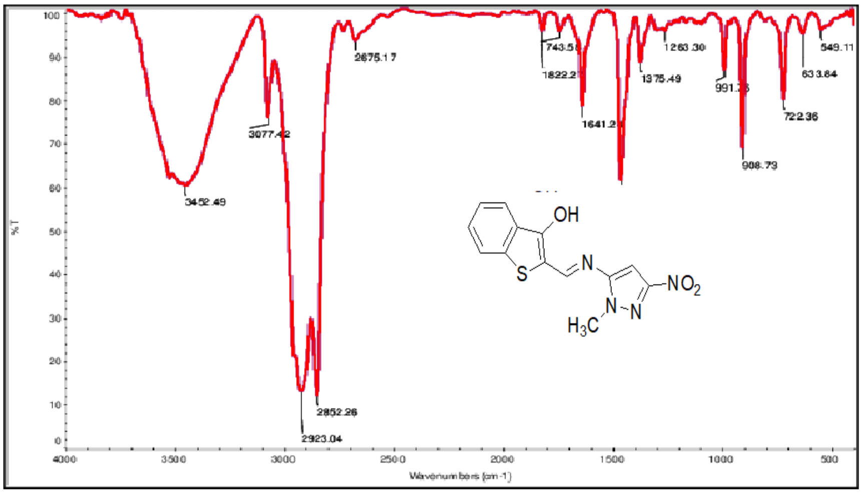


Figure 5: IR spectra of Schiff base Ligand

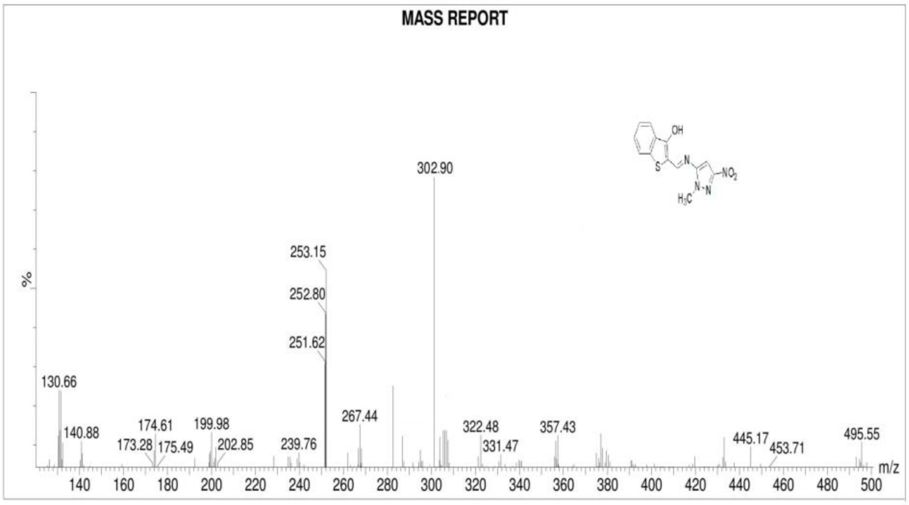


Figure 6: Mass spectra of Schiff base Ligand

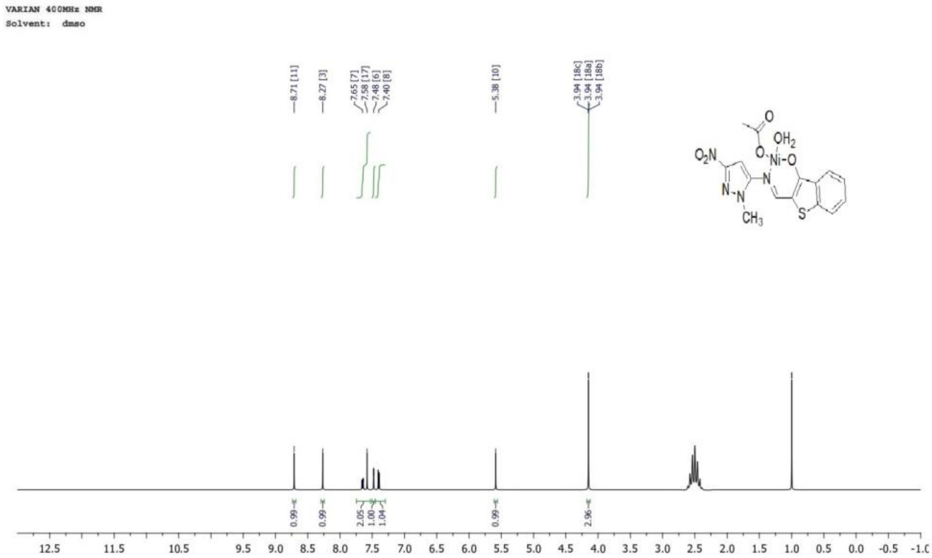


Figure 7: ^{1}H NMR spectra of Ni- Complex

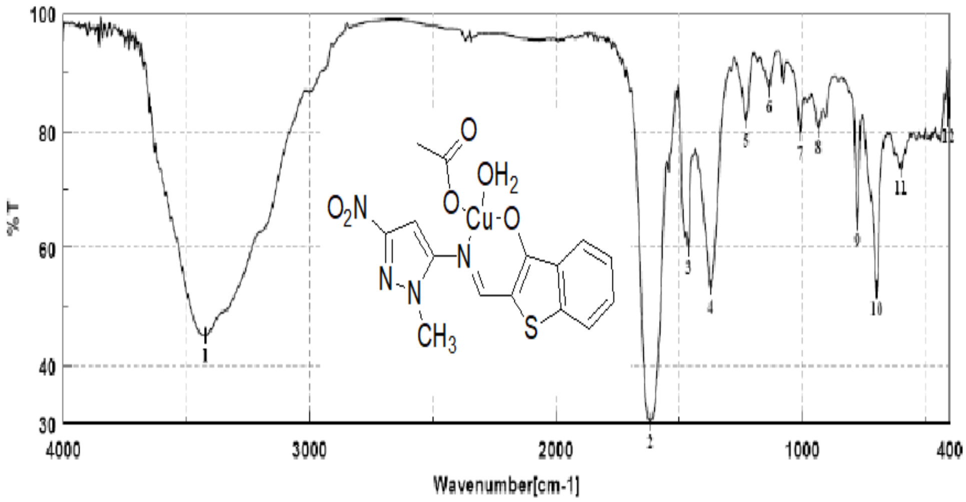


Figure 8: IR spectra of Cu – Complex

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