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Synthesis, Diagnoses, and Biological Evaluation of New Ligand Derived from Mesalazine and acetyl isothiocyanate with their metal ion complexes

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Abstract

Mesalazine ligand (ML) having the isothiocyanate has been synthesis via reaction of mesalazine with acetyl isothiocyanate using absolute ethanol to give 5-(3-acetylthioureido)-2-hydroxybenzoic acid (ML) ligand in one step, then the two step involved the reaction of (ML) ligand with ionic salts as Ni (II), Cu (II), Co (II), and Zn(II) via two sites for coordination (O, S) to prepared five complexes in good yield. The synthesized ligand and complexes were branded using (FTIR), (1H-NMR,13CNMR), UV-vis spectroscopy, and (CHNS), as well as molar conductivity, magnetic susceptibility of complexes in their solid state, and atomic absorption, in addition to measuring melting points.

From the results, we note that the molar ratio (M:L) is (1:2) for all the prepared complexes. From our results, the expected geometry for all chelating complexes is octahedral. The same synthesis of five complexes (ML1 - ML5) was used to measure biological activity via two types of bacteria, and showed excellent results compared to the Ciprofloxacin drug.

Keywords: Biological activity, isothiocyanate, mesalazine, (ML)ligand complex, ethanol.

Introduction

Mesalazine (known as mesalamine) is 5-aminosalicylic acid (5-ASA). A crucial and significant component of plants' regulatory processes is salicylic acid. It has anti-disease properties for both plants and animals and is extracted from willow trees (1).

Mesalamine is one of salicylic acid's derivatives. It has been used as a medication for colon diseases and as an anti-inflammatory (2).

Mesalazine has been widely used for 45 years, and it also has side effects, including diarrhea, nausea, vomiting, abdominal pain, headache, pancreatitis, and blood disorders (3).

Mesalazine is also used as the main drug to treat ulcerative colitis and inflammatory bowel disease (IBD) (4). It also has antioxidant properties that reduce tissue injury, a role in inhibiting T-cell activation and proliferation (5). Do not use medication containing mesalazine to treat myocarditis and pericarditis.

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Isothiocyanates (ITCs) are a group of natural products and contain a highly reactive electrophilic functional group −N=C=S. (6)

It is a small molecular weight compound containing sulfur and a group with a side chain, that may be aryl, phenyl, etc., or it may be aliphatic, and it participates in several special reactions in biological systems. (7)

Through the study, they found that complexes of 5-aminosalicylic acid with its transition element ions have greater antimicrobial activity than the 5-aminosalicylic acid drug (8) because it reduces side effects for therapeutic radiation (9).

It is a good antioxidant for many activities (10), such as anti-tumor (11,12), and anti-microbial. (13) . It also reduces soil-borne plant diseases, especially fungi, such as root rot. (14). To get rid of chemical compounds affecting plants, element ions were added to biologically active organic compounds because they are environmentally friendly and have been shown as antioxidants, for their antifungal properties, (15)

5-aminosalicylic acid. (Mesalamine) with acetyl isothiocyanide and its complexes with elements Co 2+, Ni 2+, Cu 2+ and Zn +2. The ligand and its metal complexes were identified by various analytical and spectroscopic techniques. And their applications as inhibitors for fungi.

2. Materials and Methods

The chemicals provided from B.D.H., Sigma Aldrich, Merck and Fluorochem, the all compounds were measured of melting point ("Stuart CL7-9"), FTIR ("BRUKER, type: Tensor27, TNo: 3534"), UV-Visible spectra ("UV_6100PC Double beam spectrophotometer, EMC LAB, Germany") in (200-800) range, 1HNMR,13CNMR "(Varian-500 Hz, 200Hz)" in Tehran University, molar electrical conductivity ("Conductivity Meter 740, WTW, Germany") in Babylon university, (C.H.N) ("the Eager 300 for EA1112"), ("Atomic Absorption Spectrophotometer AA_6300, Shimadzu, Japan") in Baghdad.

2.1. Preparation of the Compound (ML)(16)

The Compound (ML) was prepared via reaction of mesalazine (0.01 mol, 1.53 g) with (0.01 mol,1.00 g) acetyl isothiocyanate in 20 mL of absolute ethanol. The mixture was refluxed with stirring for 3 hr. The product, filtered, washed (ethanol), and then crystallized with ethanol. Physical properties in Table 1.

2.2. Preparation of Metal Salt Solution

The prepared salt solutions 1×10-3 M of (CoCl2.6H2O), (NiCl2.6H2O), (CuCl2.2H2O), and $ZnCl_2$.2H2O) from dissolving (0.0273gm, 0.0237 gm, 0.0170 gm, and 0.0415gm in 100ml of the buffer solutions, then (1×10-5-1×10-4) M were prepared from diluting the standard solution.

2.3 Preparation of solid complexes (ML1-5)

The complexes (ML1-ML5) were prepared by adding (0.01mole, 2.54 g) of compound (ML) dissolved in (25ml) absolute ethanol.

The complexes were prepared for Co(II), Ni(II), Cu(II), Zn(II) ions in molarities [M:L] at [1:2] of the Ni and complexes, Cu(II), Co(II), was [1:2], via adding each ligand solution in (50) ml of absolute ethanol to salts metal ions solutions Co(II), Ni(II), Cu(II), and Zn (II), refluxed for 3hr, the colored solid complexes cooled(ice bath), filtered, dried. Table (1).

2.4 Measurements of Conductivity

The molar electrical conductivity was measured for solutions of chelate complexes prepared in (DMSO and DMF) solvents at a concentration of (1×10-3) molarity and a temperature of (25) °C.

Table 1: Analytical and physical data of 5-ASA and its metal complexes

Complex (formula)	M.p. (^{0}C)	M.Wt	Color (%Yield)	% Found (Calc.)			
				C	H	N	M
ML $C_{10}H_{10}N_2O_4S$	248	254	brown	74.24 73.02	3.96 3.21	11.02 11.12	
ML1 C21H23Cl2CoN4O8S2	290	653	Dark brown	38.60 37.81	3.55 3.14	8.57 8.34	9009 9.22
ML2 C21H23Cl2N4NiO8S2	278	653	Reddish brown	38.62 38.01	3.56 3.44	8.58 7.50	8.99 8.89
ML3 C21H23Cl2CuN4O8S2	>300	658	Yellowish brown	38.33 37.93	3.52 3.55	8.51 8.70	9.66 9.51
ML4 C21H23Cl2N4O8S2Zn	>300	659	White	38.33 38.12	3.51 3.02	8.49 8.56	9.91 9.87

3. Results and Discussion

3.1 Synthesis of Compound (ML)

The formation of metallocomplexes from the organic compound mesalazine with acetyl isothiocyanate using absolute ethanol has long been recognized, but medicines contain metal ions to form binary complexes. which didn't study. It is important for biological activity.

The solubility of the prepared complexes was studied. We notice its ability to dissolve in acidic and basic solutions and some solvents (such as ethyl and methyl alcohol, $CHCl_3$, DMF, and dimethyl sulfoxide and is not soluble in water.

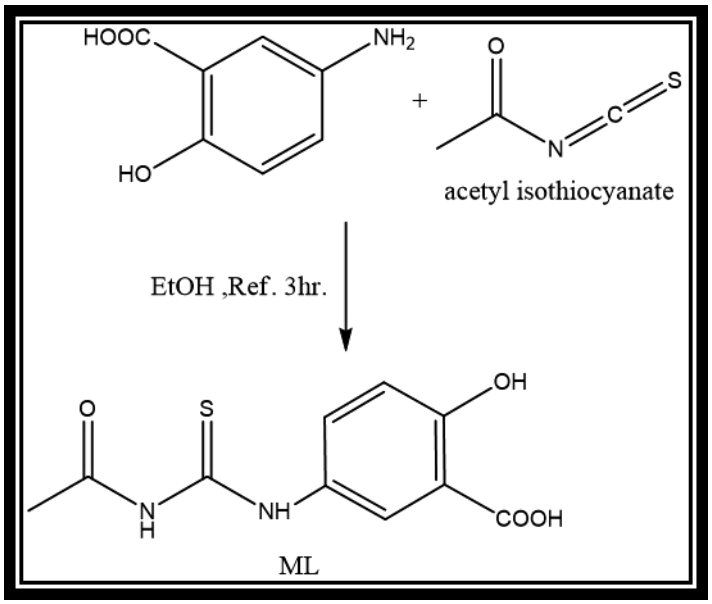
The spectra of the mixture of metals with the ligand:

The UV-vis spectrum of the ligand prepared in ethanol was studied, and three absorption peaks were shown:430nm refers to n→ π* transitions, 222, 291 nm refer to π→ π*. In Fig. 1:

By comparing the color and absorption peaks of the prepared ligand with the spectra of solutions of the mixture of metal ions, there is a difference in the color of the complexes and also a shift of the absorption peaks to longer wavelengths (17), and this indicates the occurrence of coordination and formation of complexes between those ions and the prepared ligand.in Fig. 2.

Determine the structures of potential complexes:

The method ("Yeo & Jone") was used to determine the molar ratios, and it is done by fixing the number of moles of the metal ion while changing the moles of the ligand. The ratios were (1:2) for all dissolved complexes (M: L).



Scheme 1: Preparation of ligand (ML).

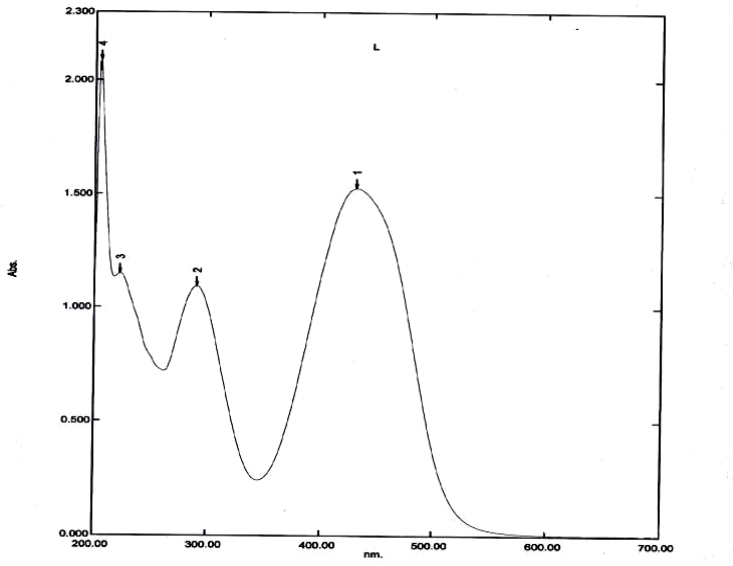


Fig. (1): UV-vis spectrum of (ML).

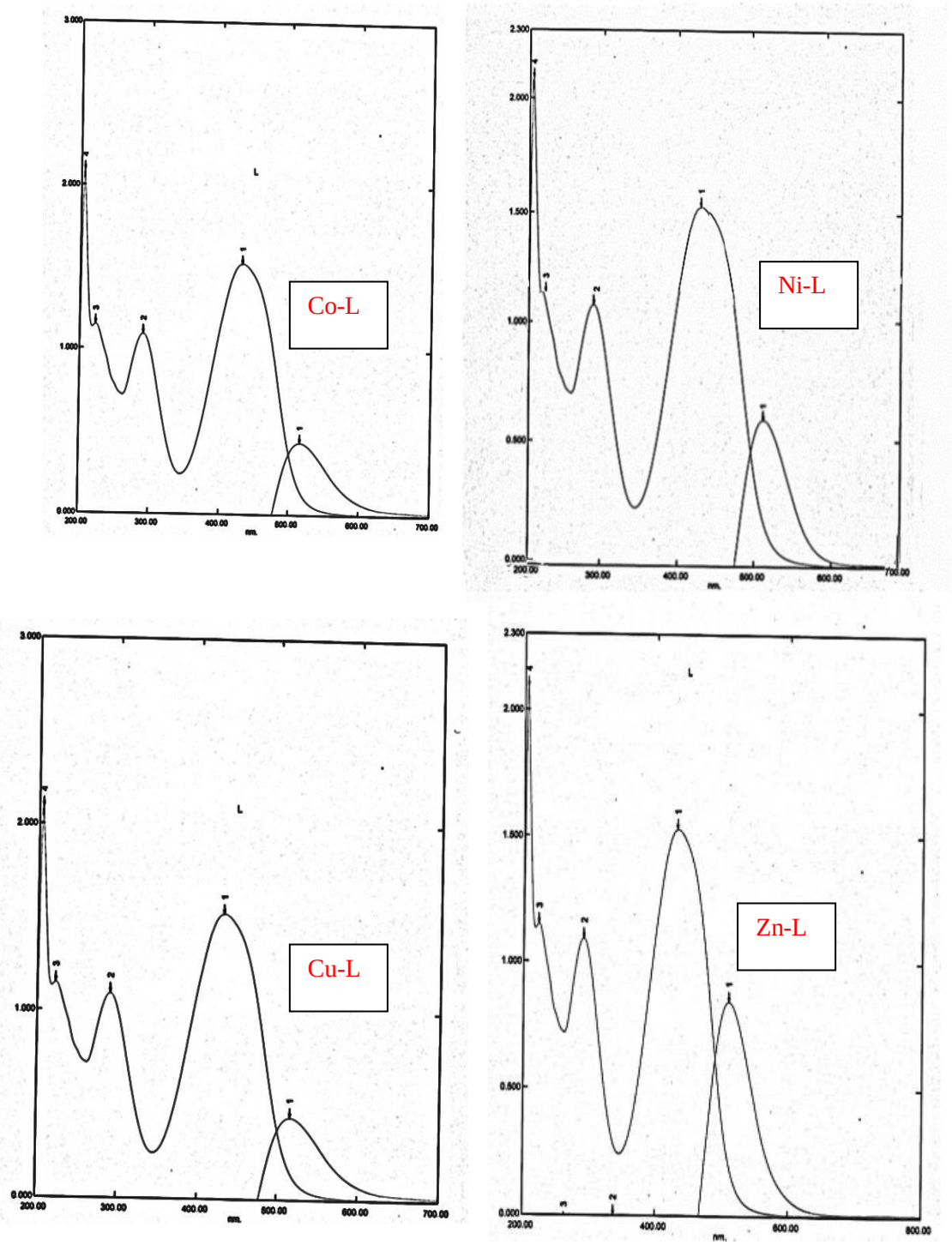


Fig. (2): UV-vis spectrum of complex Co, Ni, Cu, Zn with (ML).

Table 2: The best conditions for concentration and maximum wavelength

Co (II)	Ni (II)	Cu (II)	Zn (II)
516nm	509nm	528nm	513nm
4×10^{-5} M	3×10^{-4} M	2×10^{-5}M	4×10^{-5} M

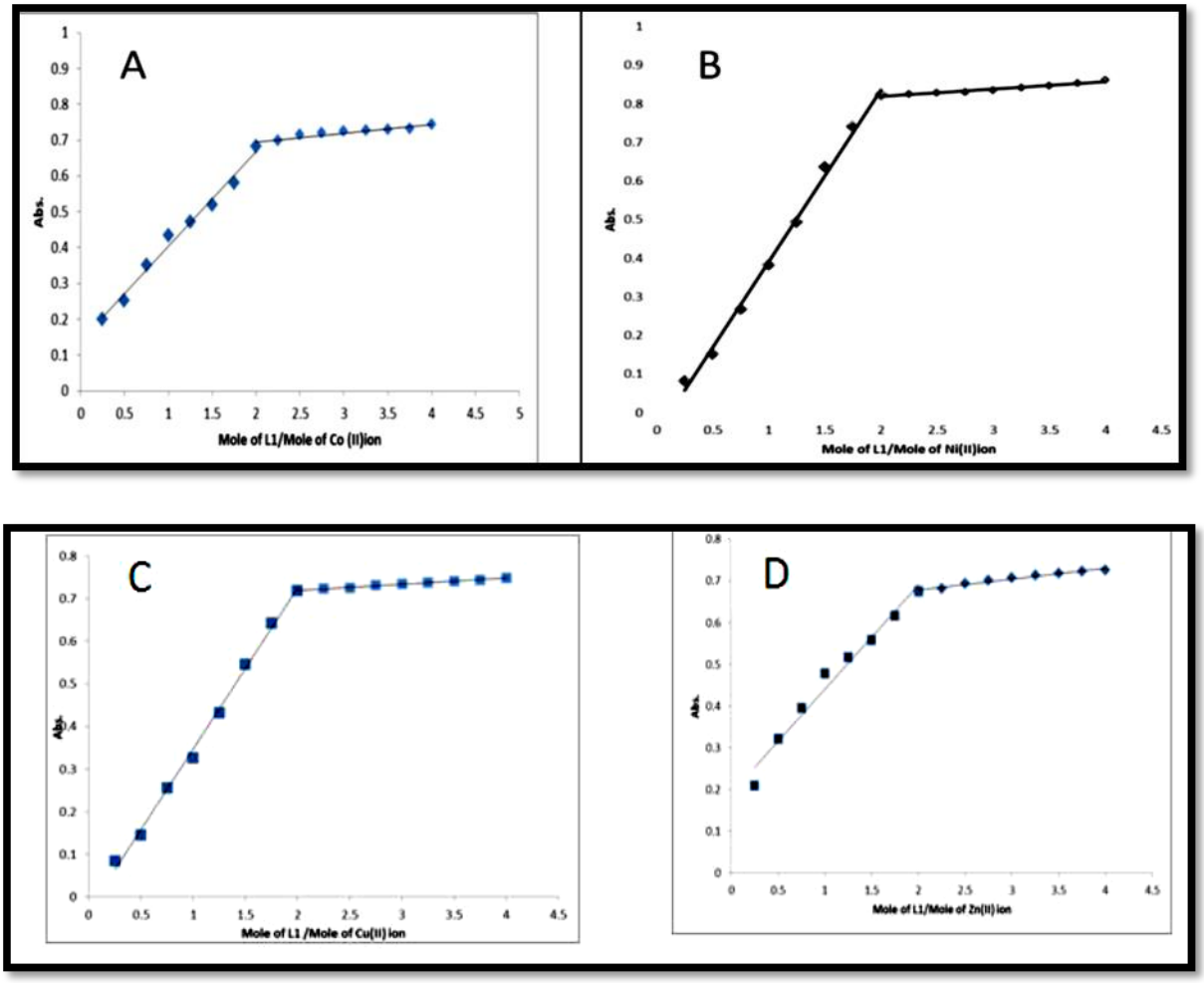


Fig. (3): molar ratio of complex A(Co), B(Ni), C(Cu), D(Zn) with ML.

(FTIR) (KBr): ν (cm-1): 2492-3416 (OH, NH), 1661 (C=O amid), 1716 (C = O), 3091 (CHar.),2995 (CH al.), 1601 (C=C ar), 1209.4-1307 (C-N, C–O, C-S).

for every complex, indicating that the C=O group's (O atom) is not taking part in chelation. Also, C=S and C=O are partaking in the complex formation.

1HNMR (500 MHz, DMSO-d6) δ (ppm): 13.1 (s, 1H, COOH), 4.99 (s, 1H, OH), 8.3 (s, 1H, NH), 4.0 (s, 1H, NH), 2.1(s,3H, CH_3), (7.0(s, 1H, CHar),7. 9, 6.8) (d, 2H, CHar), 2.99 (DMSO).

13CNMR (DMSO): δ 156(C1), (118 -134(CH ar.),21(CH_3),

169 (COOH), 128 (C=S), 163 (C=Oamide),158(C-O), 40((DMSO).

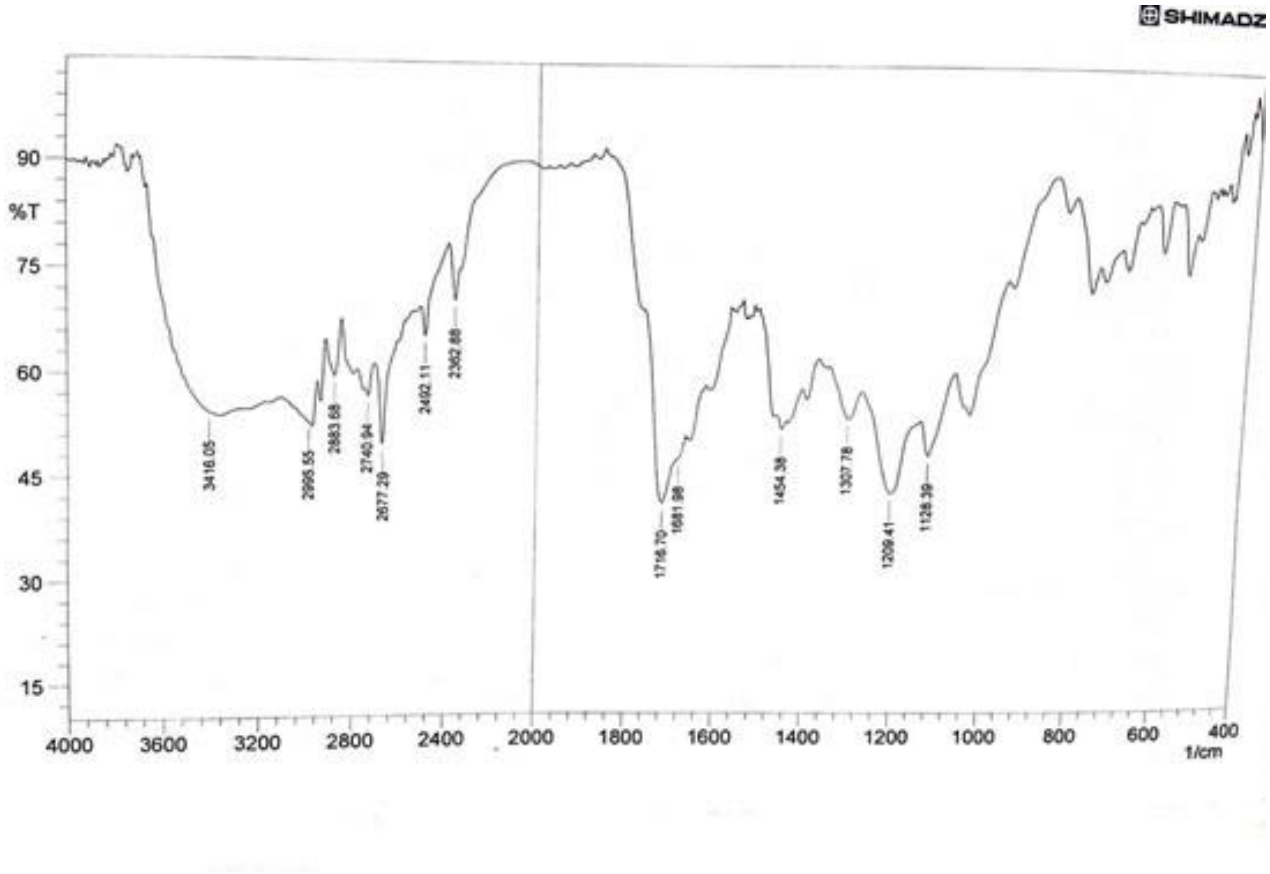


Fig. 4: FTIR for (ML) Compound.

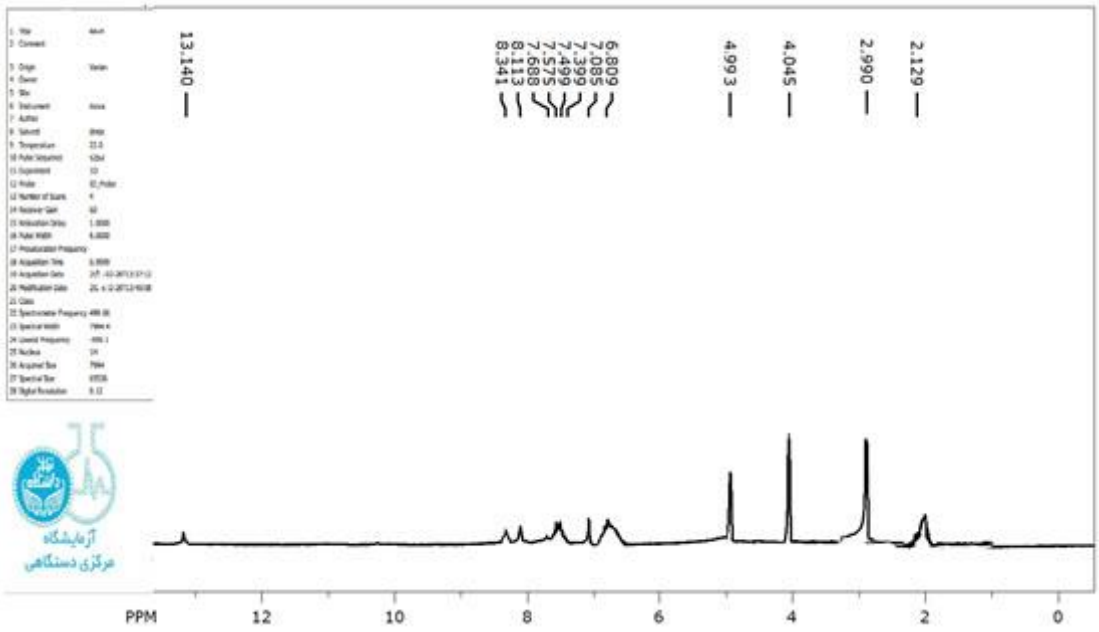


Fig. (5): ^{1}HNMR for (ML)Compound.

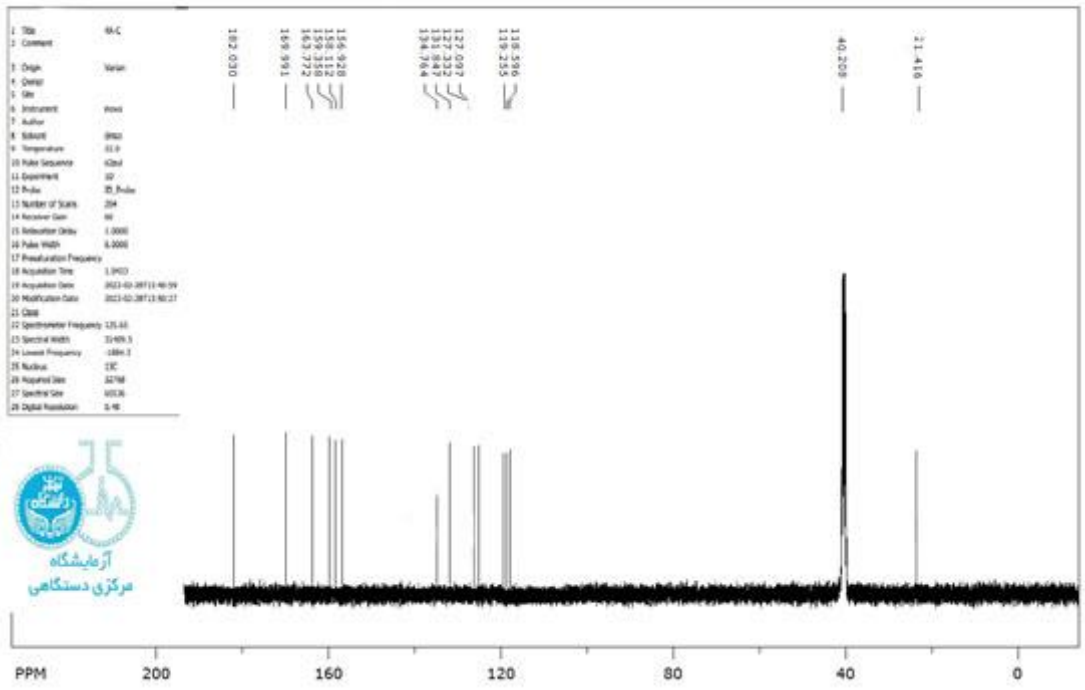


Fig. (6): ^{13}CNMR for (ML)Compound.

3.2 Synthesis of metal complexes (ML1-ML5)

Metal complexes were synthesized via reaction of the (ML) ligand with metals $CoCl_2$.6H2O, $NiCl_2$.4H2O, $CuCl_2$.2H2O, and $ZnCl_2$.2H2O in ethanol.

We show the appearance of an absorption band when which indicates that the NH and OH groups are not bonded to the metal ion in all complexes, but rather the bond is through the carbonyl and sulfur groups to the thio group.

Co^{2+} complex [Co (ML)2 Cl2]:

IR (υ, cm-1): 3400(NH), 2362-3346 (OH, acid and Phenol),2945 (CH al.), 1716(C=O), 1654 (C=O amid), 1606 (C=C ar.), 1217-1341 (C-N, C-S), 637 (M-Cl);, 483 (Co–O), and (428 Co–S)

1HNMR: 12.3 (s, 1H, COOH), 5.7,5.5 (s, 2H, OH), 8.7 ,9.4 (s, 2H, NH), 4.69, 4.5 (s, 2H, NH), 2. 5 (s,3H,CH_3), (6.8- 7.5) (d, 3H, CHar), 2.5 (DMSO).

13CNMR: 156,158(C-NH), (115 -138(CH ar.),29.2(CH_3), 174.2 (COOH), 182.8 (C=S), 169 (C=Oamide),166,163(C-OH), 40 ((DMSO).

Ni^{2+} complex [Ni (ML)2 Cl2]:

IR (υ, cm-1): 3290(NH), 2362-3346 (OH, acid and Phenol),2995 (CH al.), 1720(C=O), 1658 (C=O amid), 1606 (C=C ar.), 1213-1307 (C-N, C-S), 625 (M-Cl);, 487 (Ni–O), and (429 Ni–S)

1HNMR: 12.6 (s, 1H, COOH), 9.2 (s, 1H, OH), 8.7 (s, 1H, NH), 4.6 (s, 1H, NH) , 2. 0 (s,3H,CH_3), (6.7- 7.5) (d, 3H, CHar), 2.5 (DMSO).

13CNMR: δ 156,157(C1), (107 -138(CH ar.),26.1(CH_3), 174 (COOH), 182(C=S), 167 (C=Oamide),147(C-O), 40 ((DMSO).(

Cu^{2+} complex [Cu (ML)2 (Cl2)]:

IR (υ, cm-1): 3148(NH), 2495-3435 (OH, acid and Phenol),2906 (CH al.), 1720(C=O), 1612 (C=O

amid), 1531 (C=C ar.),1220 -1301(C-N, C-S), 625 (M-Cl); , 556 (M–O); 410 (M–S)
1HNMR: 11.1 (s, 1H, COOH), 10.6 (s, 1H, OH), 8.6 (s, 1H, NH), 4.83 (s, 1H, NH), 1. 9(s,3H, CH_3), (6.6- 7.7) (d, 3H, CHar), 2.5 (DMSO).

13CNMR: δ 156,158(C1), (117 -137(CH ar.),22.7(CH_3), 170 (COOH), 185(C=S), 165 (C=Oamide),142(C-O), 40 ((DMSO).(

Zn^{2+} complex [Zn (ML)2 (Cl2)]:
IR (υ, cm-1): 3354(NH) ,2492-3356 (OH, acid and Phenol),2941(CH al.), 1735(C=O), 1651 (C=O amid), 1604 (C=C ar.),1210-1172 (C-N,C-S), 634 (M-Cl); , 535 (M–O); 415 (M–S)

1HNMR: 12.4 (s, 1H, COOH), 5.9 (s, 1H, OH), 9.2 (s, 1H, NH), 4.23 (s, 1H, NH), 2. 0(s,3H,CH_3), 7.27(s, 1H, CH ar)(6.9- 7.8) (d, 3H, CHar), 2.5 (DMSO).

13CNMR: δ 156(C1), (116 -138(CH ar.),23.9(CH_3),
178 (COOH), 183(C=S), 165 (C=Oamide),158(C-O), 40 ((DMSO).

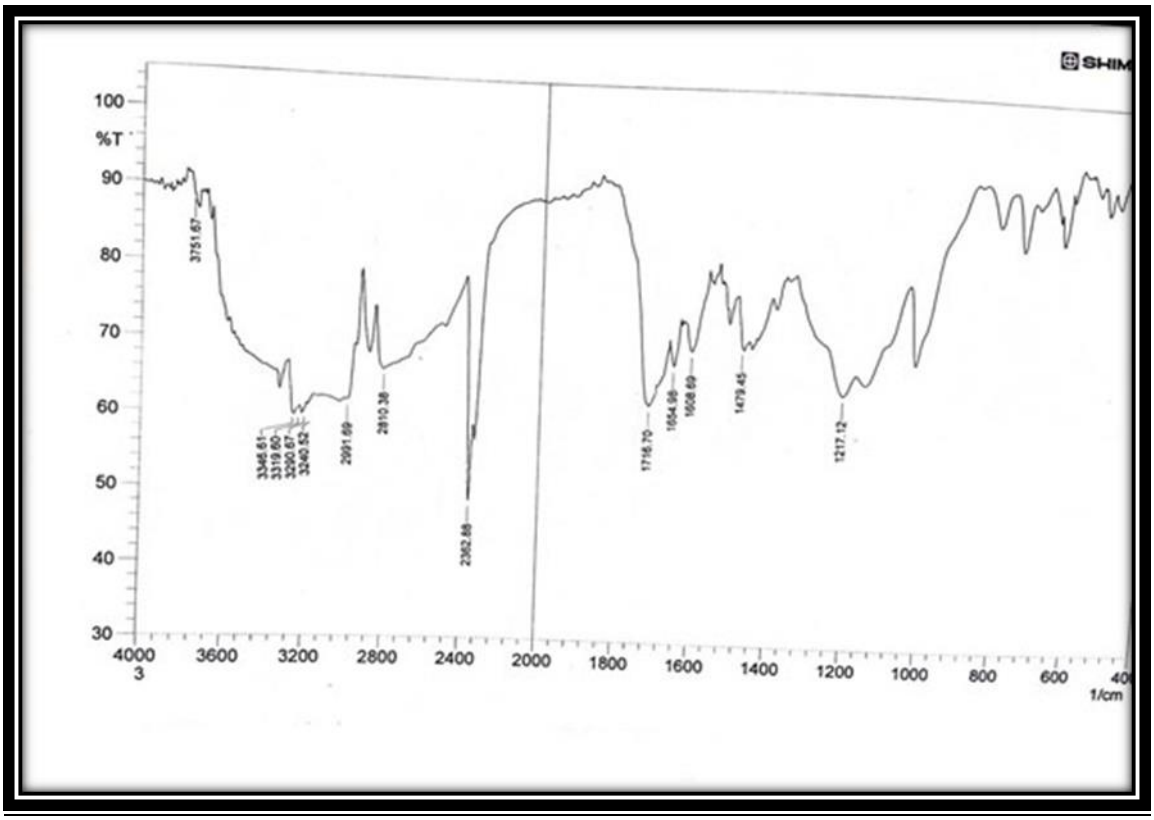


Fig (7): FTIR of complex (Co-ML)

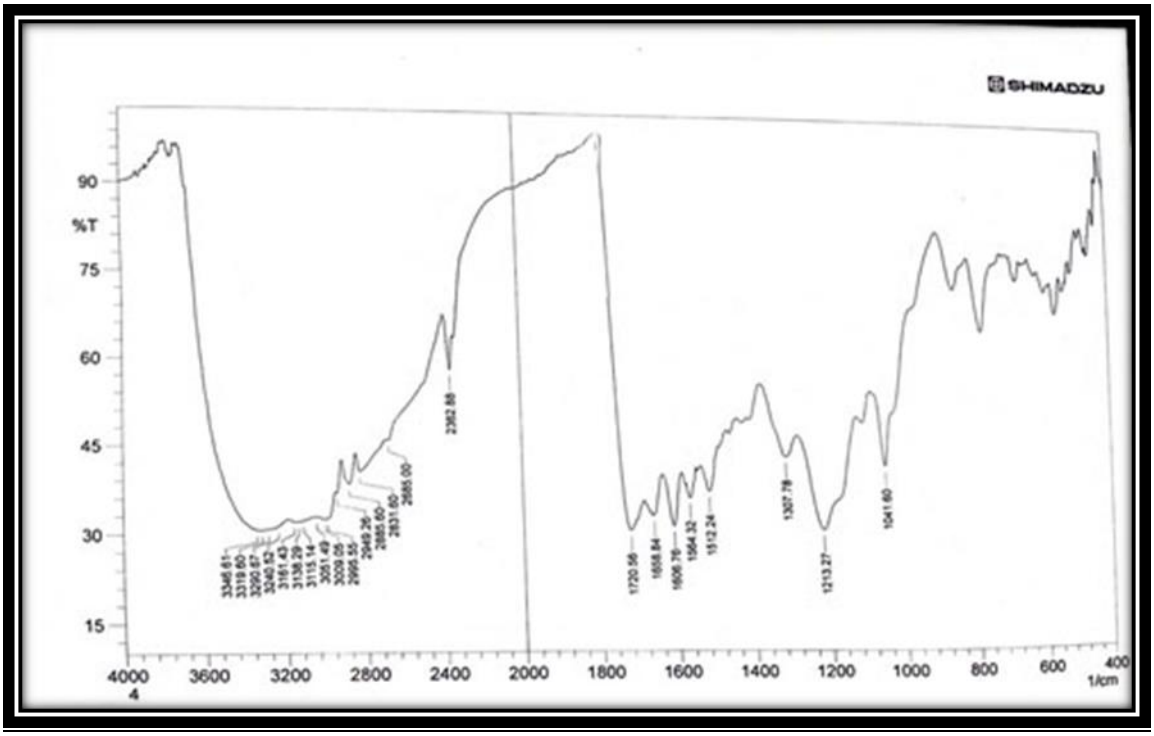


Figure 8: FTIR of complex (Ni-ML)

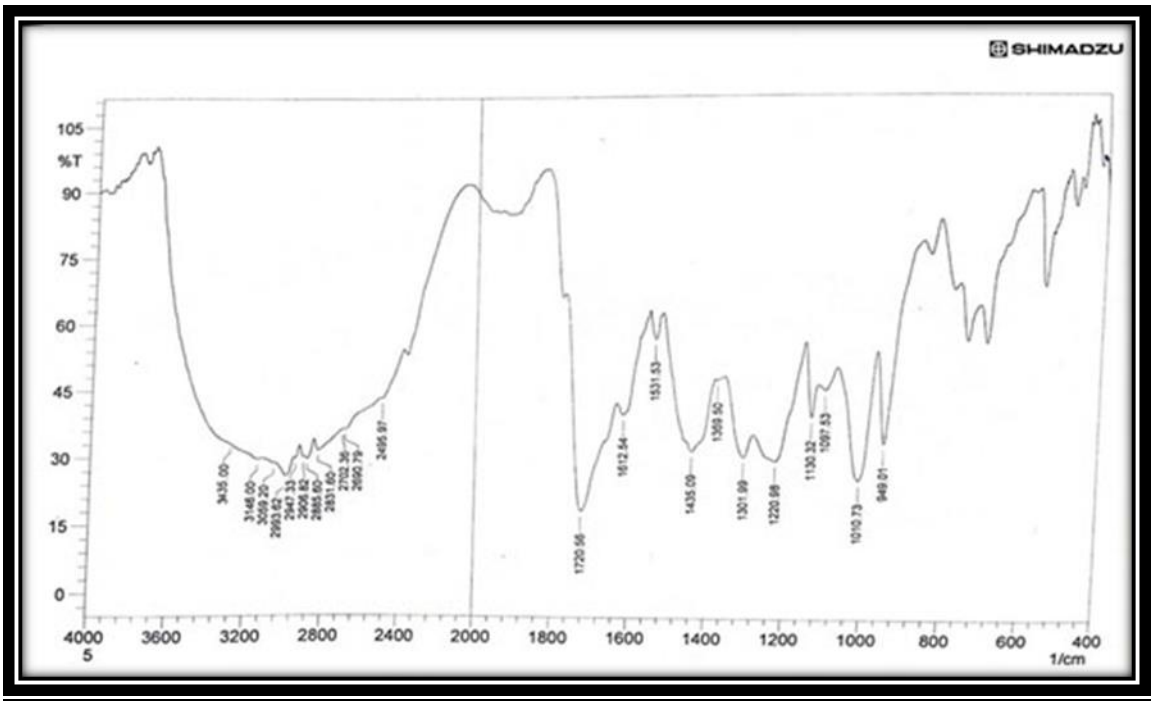


Figure 9: FTIR of complex (Cu-ML)

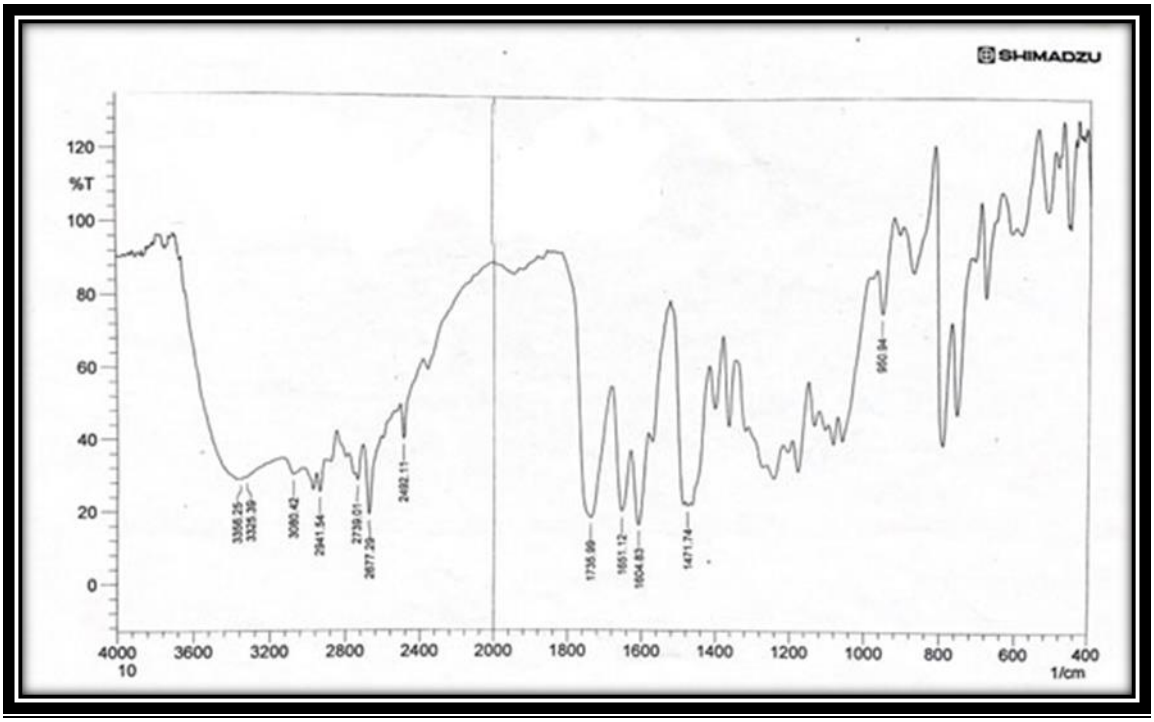


Fig (10): FTIR of complex (Zn-ML)

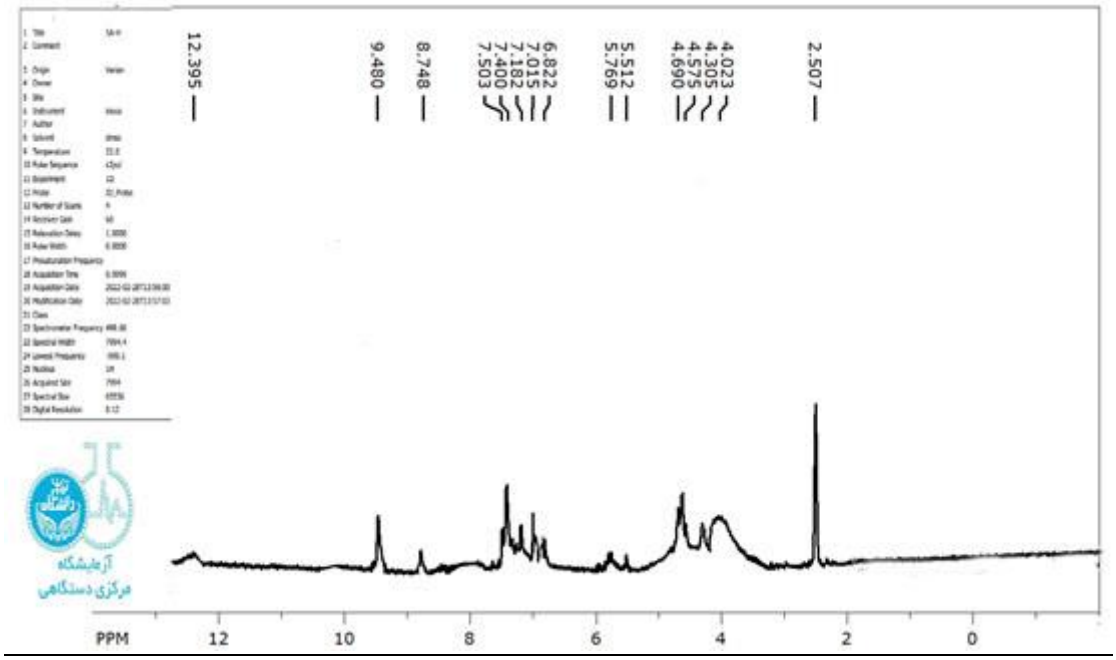


Fig (11): 1HNMR of complex (Co-ML)

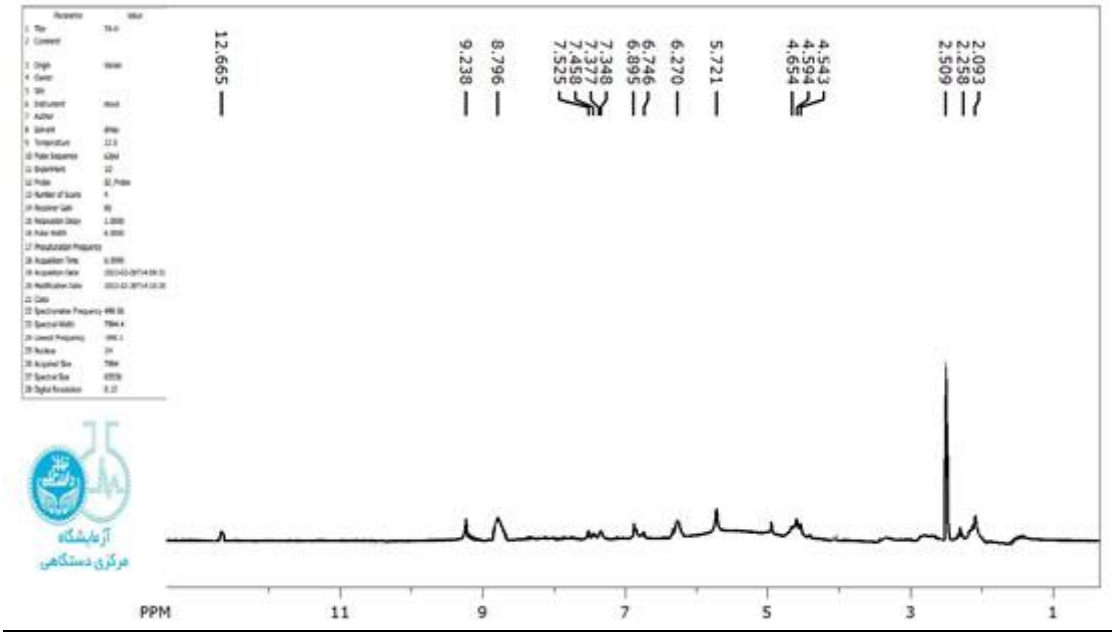


Fig (12): 1HNMR of complex (Ni-ML)

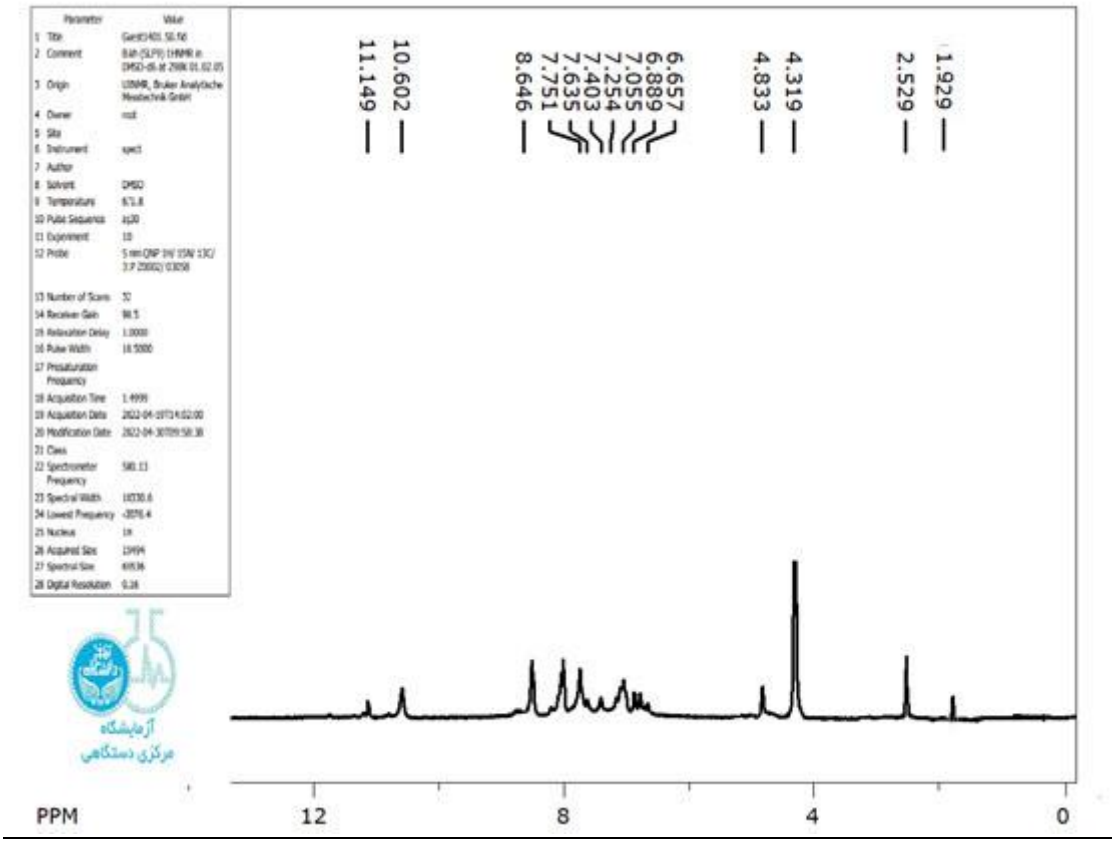


Fig (13): 1HNMR of complex (Cu-ML)

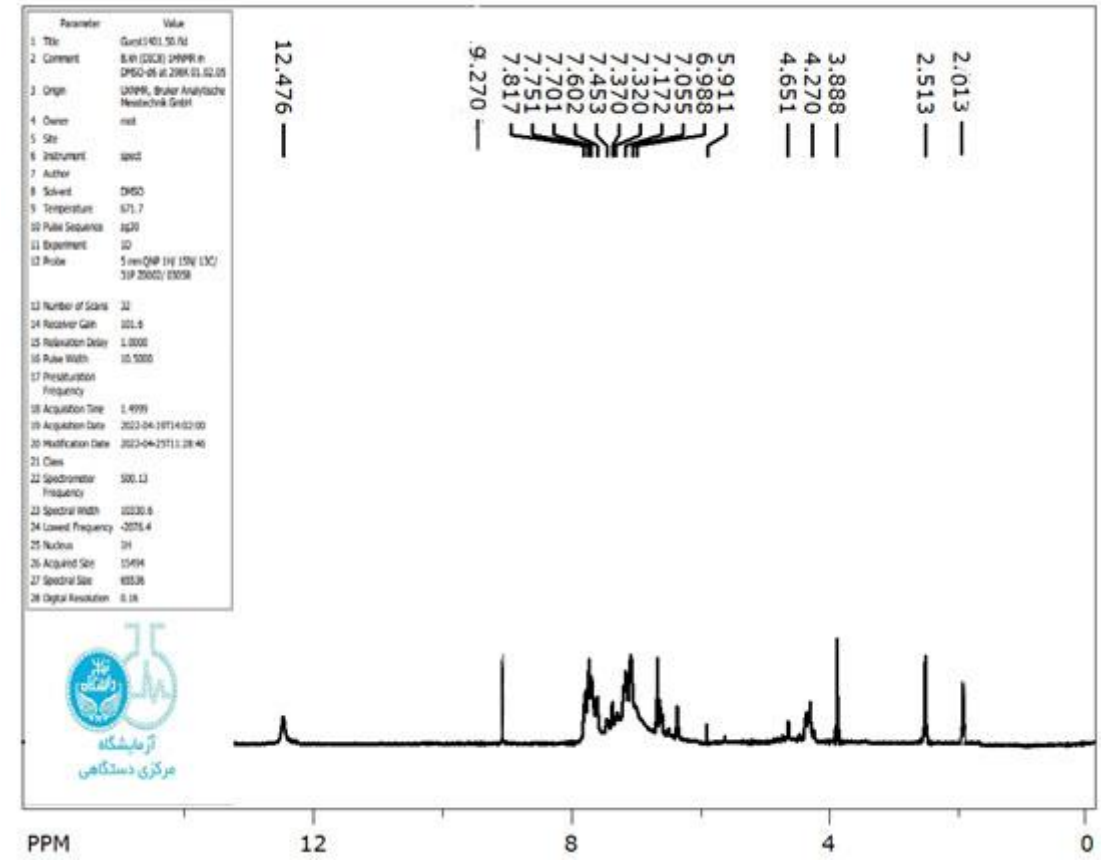


Fig (14): 1HNMR of complex (Zn-ML)

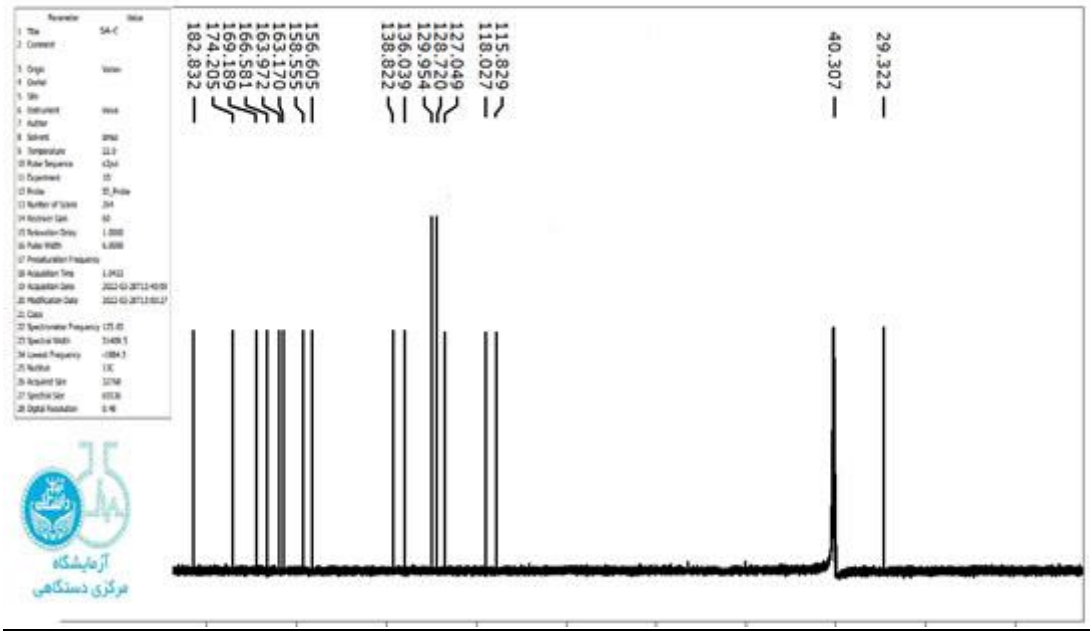


Fig (15): 13CNMR of complex (Co-ML)

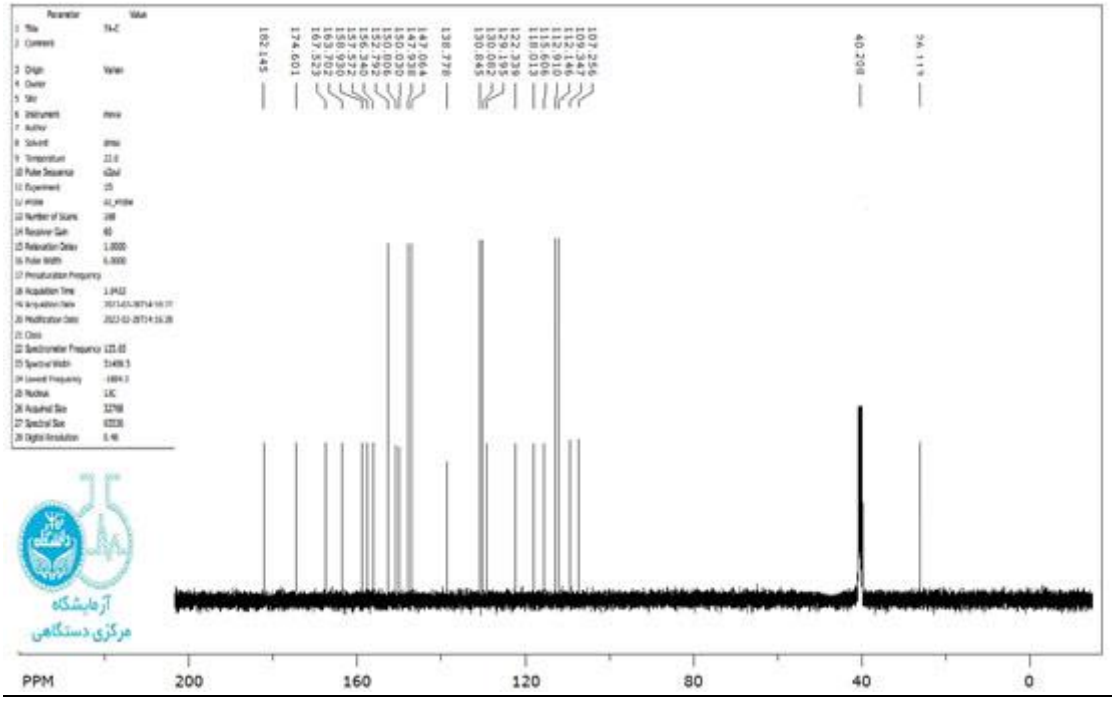


Fig (16): 13CNMR of complex (Ni-ML)

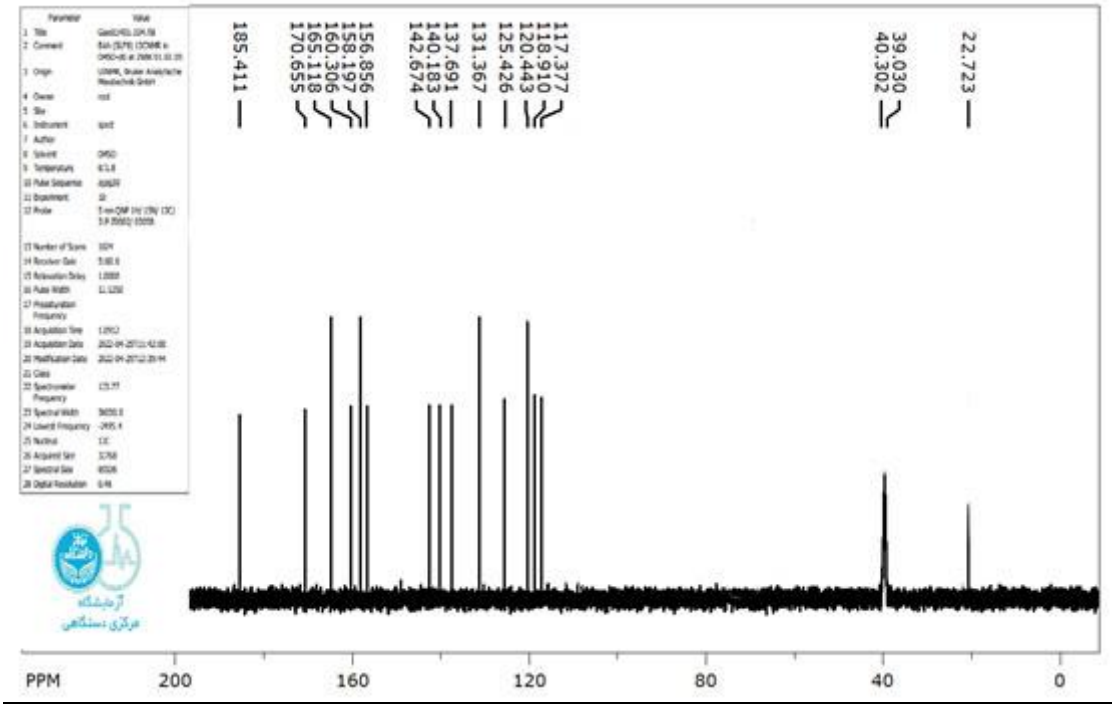


Fig (17): 13CNMR of complex (Cu-ML)

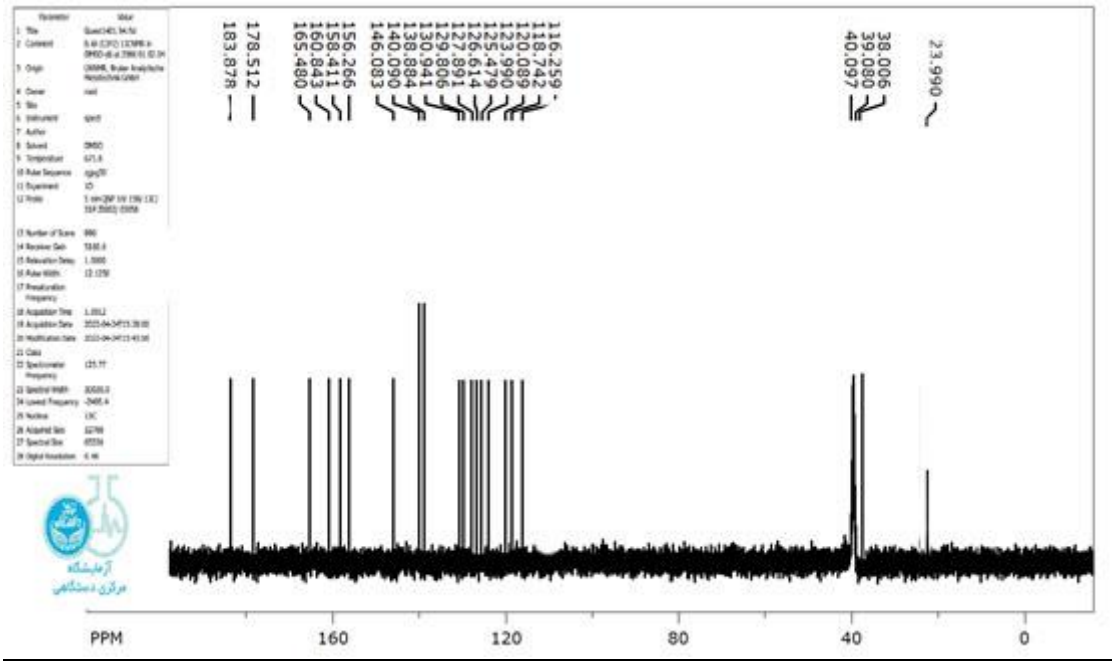


Fig (18): 13CNMR of complex (Zn-ML)

Biological evaluation

The antibacterial activity of the prepared complexes was evaluated using two types of bacteria (+ve) *S. aureus* and *E. coli*; (-ve) and compared to a drug Ciprofloxacin [18,19]. Using the plate method, using focus and distance incubation period, the complexes ML1, ML3, and ML4 showed good action towards *S. aureus*, and complexes ML1, ML2, and ML3 towards *E. coli* showed high action.

Molar conductivity:

Based on the results of measuring the molar electrical conductivity, the geometric structures of the complexes can be suggested, prepared, and through the ionic formulas of solutions of solid complexes, because they are compatible.

It is directly proportional to the charged species in the solution, and its value is in solutions that do not have a low ionic character or are close to zero.

The prepared complexes do not have properties in ethanol and DMF solvents at a concentration of 1M.

Magnetic susceptibility:

Magnetic susceptibility was measured to propose the stereoscopic shapes of metal complexes prepared from studying the effects of the outer shells filled with electrons, knowing the electronic structure and oxidative state of the transition metal atoms, and the high or low state of the spin of the number of individual electrons for the metal ion and after correcting for the diamagnetism of the atoms in organic compounds, and metal ions using Pascal's tables,

Proposed geometric shapes:

Through the results of the values of precise elemental analysis, flame atomic absorption, knowledge of the metal: ligand ratios, magnetic susceptibility, molar conductivity, and spectra, we arrived at a proposal. the geometric shape of all the prepared complexes is octahedral.

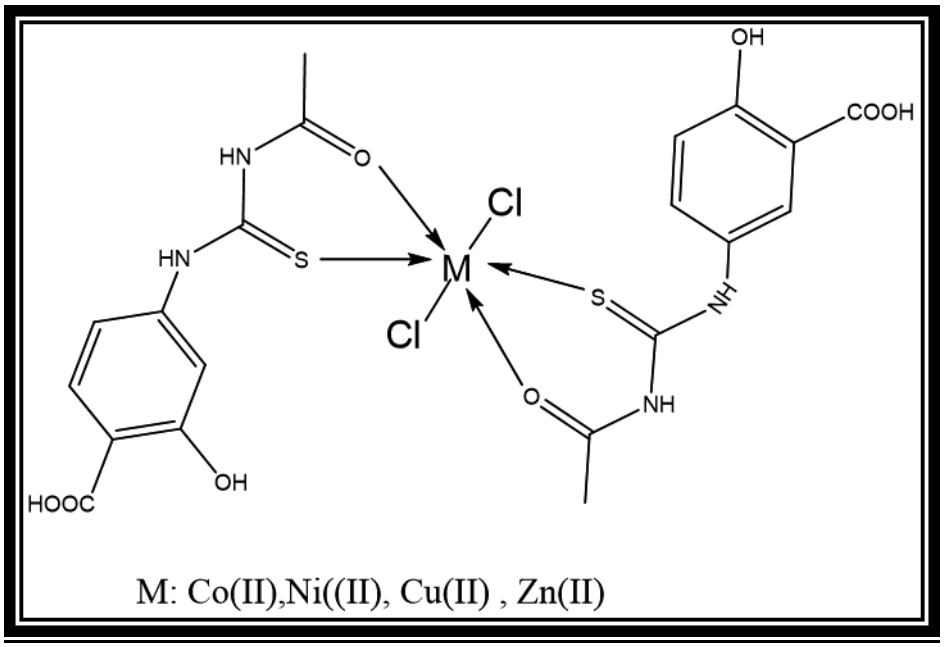


Table 3. Biological actions of prepared compounds

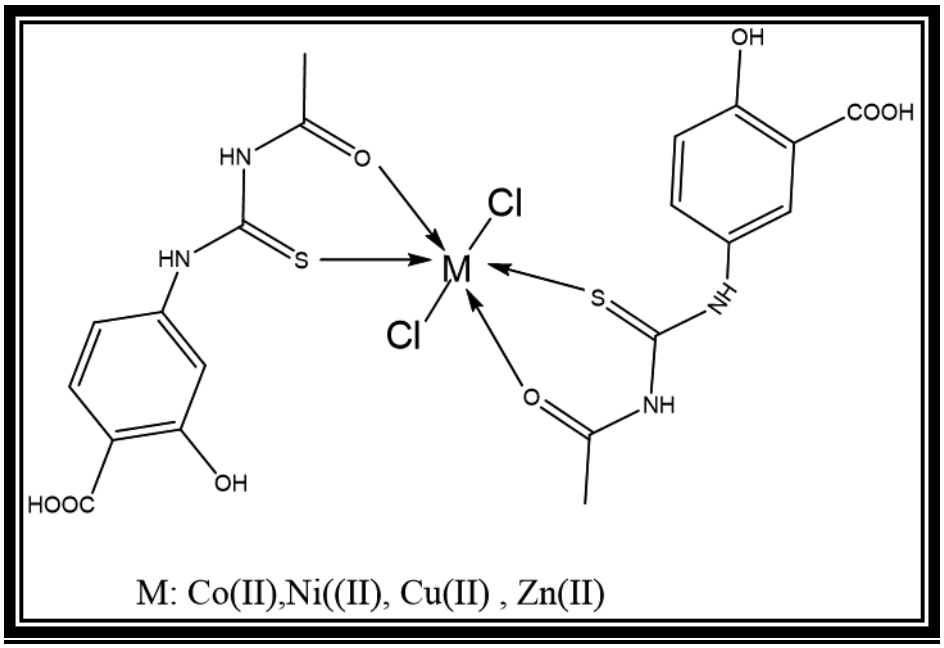
Comp.	*S. aureus*	*E-coli*
Ciprofloxacin	*3*	*4*
ML	3	2
ML1	6	7
ML2	3	5
ML3	20	17
ML4	8	4

Table (4): Molar conductivity values for the prepared complexes.

Complex	Λm ($S.mol^{-1}.cm^2$)	
	In (EtOH)	In (DMF)
[Co(ML)2Cl2]	3.28	15.83
[Ni(ML)2Cl2]	3.54	22.11
[Cu(ML)2Cl2]	2.75	25.55
[Zn(ML)2Cl2]	2.73	12.80

Table 5. Magnetic susceptibility of the complex:

Complex	μeff(B.M)
[Co(ML)2Cl2]	4.34
[Ni(ML)2Cl2]	3.14
[Cu(ML)2Cl2]	1.73
[Zn(ML)2Cl2]	Dia



Conclusion

Through the study and results of the prepared complexes, we concluded that the preparation of the ligand is easy through the reaction of mesalazine with acetyl, and the preparation of complexes Co (II), Ni (II), Co (II), Zi (II), with ligand With a good product, the spectroscopic results, molar ratios and sensitivity, we arrived at the shape of the compounds, which are octahedral and their connection through oxygen and sulfur with the ligand.

Conflict of interest: **NIL**

Funding: **NIL**

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