

SYNTHESIS, CHARACTERISATION AND STRUCTURAL ELUCIDATION OF NOVEL 4-TERT-BUTYLBENZOHYDRAZONE AND ITS Cu(II), Ni(II), Co(II) AND Mn(II) COMPLEXES

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ABSTRACT. 4-Tert-butylbenzohydrazone ligand was synthesised by reacting 4-tert-butylbenzohydrazide with dehydroacetic acid. Afterward, the Cu(II), Ni(II), Co(II), and Mn(II) complexes of 4-tert-butylbenzohydrazone were synthesised. All the synthesised compounds were characterised using elemental analysis, ESI-MS, IR, ¹H-NMR and ¹³C-NMR spectroscopic methods. ESI-MS studies revealed ligand to metal stoichiometry of 1:1 for the Cu(II) complex, 2:1 for the Ni(II), Co(II), and Mn(II) complexes. IR studies showed that the ligand was coordinated to the metal ions through ONO donor atoms. The ¹H NMR revealed that deprotonation did not occur in the ligand. Thus, the hydroxyl oxygen and the secondary amine nitrogen did not participate in the coordination. The proposed structures of the compounds conform with the analytical results.

KEY WORDS: 4-Tert-butylbenzohydrazone, Metal complexes, Structure, Elucidation

INTRODUCTION

Good health has remained one of the primary needs of mankind. For some decades now, infectious diseases have been effectively treated using antibiotics. Nevertheless, antibiotics overuse has resulted to a drastic decline in their potency against microbes [1-3]. This has prompted researchers to the design and synthesis of hydrazone Schiff-bases and their metal complexes.

Hydrazone Schiff-bases and their metal complexes have shown a broad spectrum of biological activities which include antibacterial, antifungal, antitubercular, anti-inflammatory, anthelmintic, anticonvulsant, analgesic, antidepressant, and antioxidant activities [4-13]. The antimicrobial activities of hydrazones and their metal complexes are owing to their high lipophilicity which enables them to penetrate/cross the lipid membrane that envelops the cell of microbes [14]. Sequel to this, they block the metal active binding sites on specific enzymes of some microorganisms [15-16] and disrupt the respiratory process of the cell [17]. Hydrazones' antimicrobial activity may result from their inherent azomethine group that could interfere with the cell multiplication (division) mechanism of the microbes and stop their further growth. Hydrazones and their metal complexes have been found to exhibit cytotoxic activity against human cancer cell lines and hence portraying them as good anticancer agents. El-Tabl *et al.* synthesised a novel hydrazide hydrazone 2-hydroxyl-3-(hydroxyimino)-4-oxopentan-2-ylidene benzohydrazide. Screening alongside with its Co(II) and series of Cu(II) complexes exhibited high cytotoxic activities against human liver cancer HepG2 cell line and abolished cell growth in comparison with Sorafenib (Nexavar) [18]. Apart from the rich bioactivity of hydrazones and their metal complexes, the ease of their synthesis and stable complex formation have drawn the interest of researchers.

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In this present research, we report the synthesis, spectroscopic characterization and structural elucidation of a novel hydrazide hydrazone 4-*tert*-butyl-*N*-[(1*E*)-1-(2-hydroxy-6-methyl-4-oxo-4*H*-pyran-3-yl)ethylidene] benzohydrazide and its Cu(II), Ni(II), Co(II) and Mn(II) complexes.

EXPERIMENTAL

Materials

The 4-*tert*-butylbenzohydrazide and sodium bicarbonate used were Sigma-Aldrich products. Dehydroacetic acid used was purchased from Merck (Darmstadt, Germany). Nickel (II) chloride hexahydrate and manganese(II) chloride tetrahydrate were acquired from Guangdong Guanghua Sci-Tech Co. Ltd. Copper(II) chloride dihydrate and cobalt(II) chloride hexahydrate were sourced from Sure Chem. Products (SCP Ltd., England) and Cartivalue Chemicals (Cartivalue Chemicals Ltd., Mumbai, India), respectively. The methanol and the chemicals used were of analytical grade.

Physical methods

The ESI mass spectra of the compounds were recorded with a Waters Micromass Mass Spectrometer in the positive ion mode. Elemental analyser (Elementar, VarioEL Cube) was used to determine the C, H, N elemental compositions of the compounds. The infrared spectra of the compounds were recorded on a Bruker FTIR Spectrophotometer using KBr disc, in 4000–400 cm^{-1} region. The ^1H and ^{13}C NMR spectra were recorded on Bruker-400 MHz NMR Spectrophotometer, in DMSO- d_6 solvent.

Syntheses

Synthesis of 4-tert-butyl-N-[(1E)-1-(2-hydroxy-6-methyl-4-oxo-4H-pyran-3-yl)ethylidene] benzohydrazide (HL)

(3500 mg, 20.82 mmol) of dehydroacetic acid was dissolved in 50 mL methanol and heated for 3 min on a magnetic-stirrer hot plate. (4000 mg, 20.82 mmol) of 4-*tert*-butylbenzohydrazide was added followed by sodium bicarbonate (1750 mg, 20.82 mmol) and the mixture was refluxed for 1 h. The resulting lime green precipitate was cooled, filtered, and washed with methanol. The residue was thereafter dried and collected at room temperature.

Yield: 70%; colour: lime green; selected IR data (KBr, v/cm^{-1}): 3444b $\text{v}(\text{O}-\text{H str})$, 2848 m, 2915 m $\text{v}(\text{aliphatic C}-\text{H str})$, 1634.89 s $\text{v}(\text{C}=\text{O str})$, 1568 m $\text{v}(\text{C}=\text{N})$, 1443 m, 1489 m, 1509 m $\text{v}(\text{C}-\text{C str, benzene ring})$, 1335 m, 1421 m $\text{v}(\text{C}-\text{C str, pyrone ring})$, 1044 m, 1275 m $\text{v}(\text{C}-\text{O str})$, 749 s $\text{v}(\text{wagging N}-\text{H})$. $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , ppm): 15.56 (s, 1H, OH), 12.46 (s, 1H, -NH), 7.90–7.31 (d, 4H, ArH *tert*-butylbenzene), 5.61 (s, 1H, ArH pyrone), 2.70 (s, 3H, CH_3 pyrone), 2.54 (s, 3H, $\text{CH}_3-\text{C}=\text{N}-$), 1.43 (s, 9H, $-\text{C}(\text{CH}_3)_3$ *tert*-butylbenzene). $^{13}\text{C NMR}$ (400 MHz, DMSO- d_6 , ppm): 180.86 (C, $\text{C}=\text{O pyrone}$), 166.59 (C, $-\text{NH}-\text{C}=\text{O}$), 164.22 (C, $\text{C}-\text{OH}$), 159.73 (C, $-\text{C}=\text{N}-$), 151.55–124.48, 34.78, 31.63 (C atoms, *tert*-butylbenzene), 19.52 (C, CH_3 pyrone), 17.25 (C, CH_3 attached to azomethine). ESI-MS (m/z): (343 $[\text{M}+\text{H}]^+$, 50%, 365 $[\text{M}+\text{Na}]^+$, 100%), calc. = 342. Anal. calc. for $\text{C}_{19}\text{H}_{22}\text{O}_4\text{N}_2$ (342): C, 66.67; H, 6.43; N, 8.19. Found: C, 54.20; H, 5.93; N, 5.88%.

Synthesis of metal(II) 4-tert-butyl-N-[(1E)-1-(2-hydroxy-6-methyl-4-oxo-4H-pyran-3-yl)ethylidene] benzohydrazide

Cu(HL) synthesis. (1000 mg, 2.92 mmol) of HL was dissolved in 20 mL of methanol and heated for 2 min on a magnetic-stirrer hot plate. Copper(II) chloride dihydrate (500 mg, 2.92 mmol) was

added gradually to the stirred solution of the ligand and the mixture was refluxed for 2 h. The resulting moss green precipitate was cooled, filtered, and washed with methanol. The residue was subsequently dried and collected at room temperature.

Yield: 60%; colour: moss green; selected IR data (KBr, ν/cm^{-1}): 3444b $\nu(\text{O-H str})$, 2848 m, 2919 m, $\nu(\text{aliphatic C-H str})$, 1641.61 s, 1726.10 m $\nu(\text{C=O str})$, 1559 m $\nu(\text{C=N})$, 761 m $\nu(\text{wagging N-H})$, 611 m $\nu(\text{M-Cl str})$, 538 m $\nu(\text{M-N str})$, 432 m $\nu(\text{M-O str})$. ESI-MS (m/z): (482.00 $[\text{M+Na}]^+$, 100%), calc. = 459. Anal. calc. for $\text{C}_{19}\text{H}_{24}\text{O}_5\text{N}_2\text{ClCu}$ (459): C, 49.67; H, 5.23; N, 6.10. Found: C, 42.28; H, 1.28; N, 3.99%.

Ni(HL)₂ synthesis

(1000 mg, 2.92 mmol) of HL was dissolved in 20 mL of methanol and heated for 2 min on a magnetic-stirrer hot plate. Nickel(II) chloride hexahydrate (350 mg, 1.46 mmol) was added gradually to the stirred solution of the ligand and the mixture refluxed for 2 h. The resulting eton blue precipitate was cooled, filtered, and washed with methanol. The residue was then dried and collected at room temperature.

Yield: 73%; colour: eton blue; selected IR data (KBr, ν/cm^{-1}): 3465b $\nu(\text{O-H str})$, 2848 m, 2919 m, $\nu(\text{aliphatic C-H str})$, 1637.77 s $\nu(\text{C=O str})$, 1539 m $\nu(\text{C=N})$, 749 s $\nu(\text{wagging N-H})$, 670 m $\nu(\text{M-N str})$, 424 m $\nu(\text{M-O str})$. ESI-MS (m/z): (765.76 $[\text{M+Na}]^+$, 45%), calc. = 742.69. Anal. calc. for $\text{C}_{38}\text{H}_{44}\text{O}_8\text{N}_4\text{Ni}$ (742.69): C, 61.40; H, 5.92; N, 7.54. Found: C, 58.51; H, 5.72; N, 6.48%.

Co(HL)₂ synthesis

(1000 mg, 2.92 mmol) of HL was dissolved in 20 mL of methanol and heated for 2 min on a magnetic-stirrer hot plate. Cobalt(II) chloride hexahydrate (350 mg, 1.46 mmol) was added gradually to the stirred solution of the ligand and the mixture refluxed for 2 h. The resulting chocolate coloured precipitate was cooled, filtered, and washed with methanol. The residue was then dried and collected at room temperature.

Yield: 74%; colour: chocolate; selected IR data (KBr, ν/cm^{-1}): 3434b $\nu(\text{O-H str})$, 2848 m, 2919 m, $\nu(\text{aliphatic C-H str})$, 1633.84 s, 1644.95 s, $\nu(\text{C=O str})$, 1534 m $\nu(\text{C=N})$, 749 s $\nu(\text{wagging N-H})$, 529 m $\nu(\text{M-N str})$, 420 m $\nu(\text{M-O str})$. ESI-MS (m/z): (819.96 $[\text{M+2K-H}]^+$, 40%), calc. = 742.93. Anal. calc. for $\text{C}_{38}\text{H}_{44}\text{O}_8\text{N}_4\text{Co}$ (742.93): C, 61.38; H, 5.92; N, 7.54. Found: C, 56.46; H, 5.46; N, 6.25%.

Mn(HL)₂ synthesis

(1000 mg, 2.92 mmol) of HL was dissolved in 20 mL of methanol and heated for 2 min on a magnetic-stirrer hot plate. Manganese(II) chloride tetrahydrate (290 mg, 1.46 mmol) was added gradually to the stirred solution of the ligand and the mixture refluxed for 2 h. The resulting light yellow coloured precipitate was cooled, filtered, and washed with methanol. The residue was dried and collected at room temperature.

Yield: 81%; colour: light yellow; selected IR data (KBr, ν/cm^{-1}): 3434b $\nu(\text{O-H str})$, 2852 m, 2918 m, $\nu(\text{aliphatic C-H str})$, 1626.13 s, 1668.47 s $\nu(\text{C=O str})$, 1538 s $\nu(\text{C=N})$, 750 s $\nu(\text{wagging N-H})$, 583 s $\nu(\text{M-N str})$, 435 s $\nu(\text{M-O str})$. ESI-MS (m/z): (779.29 $[\text{M+ONa}]^+$, 42%), calc. = 739.64. Anal. calc. for $\text{C}_{38}\text{H}_{44}\text{O}_8\text{N}_4\text{Mn}$ (739.64): C, 61.65; H, 5.95; N, 7.57. Found: C, 57.71; H, 5.51; N, 6.40%.

RESULTS AND DISCUSSION

General synthesis

The novel hydrazone ligand was synthesised from a condensation reaction between dehydroacetic acid and 4-tert-butylbenzohydrazide in methanolic solution in the presence of sodium bicarbonate as a catalyst (Figure 1). The Cu(II), Ni(II), Co(II) and Mn(II) complexes of the ligand were synthesised by complexing the latter with copper(II) chloride dihydrate, nickel(II) chloride hexahydrate, cobalt(II) chloride hexahydrate, and manganese(II) chloride tetrahydrate, respectively. The compounds were characterized using elemental analysis, ESI-MS, IR, ^1H NMR and ^{13}C NMR spectroscopic methods.

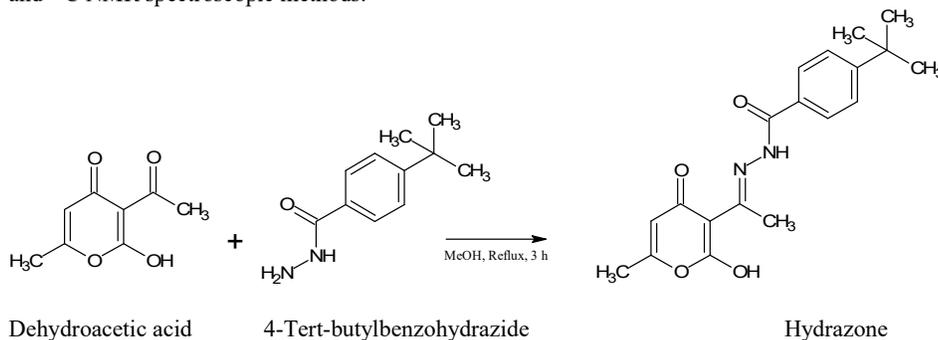


Figure 1. Synthesis of 4-tert-butyl-N-[(1E)-1-(2-hydroxy-6-methyl-4-oxo-4H-pyran-3-yl)ethylidene] benzohydrazide (**HL**).

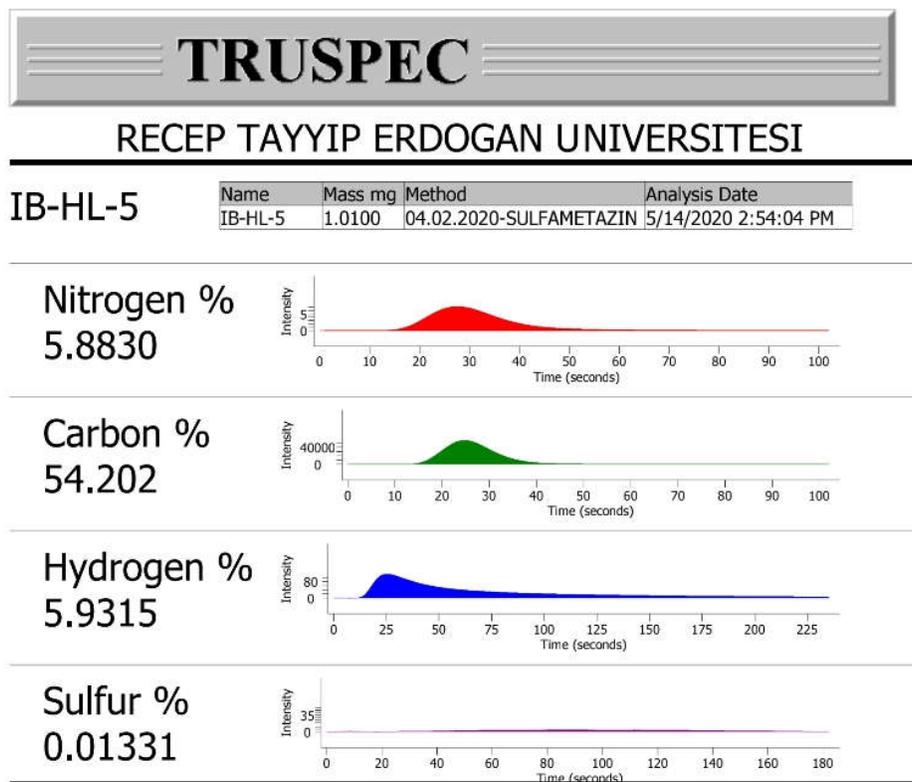
^1H and ^{13}C -NMR spectra of the ligand (HL) and complexes

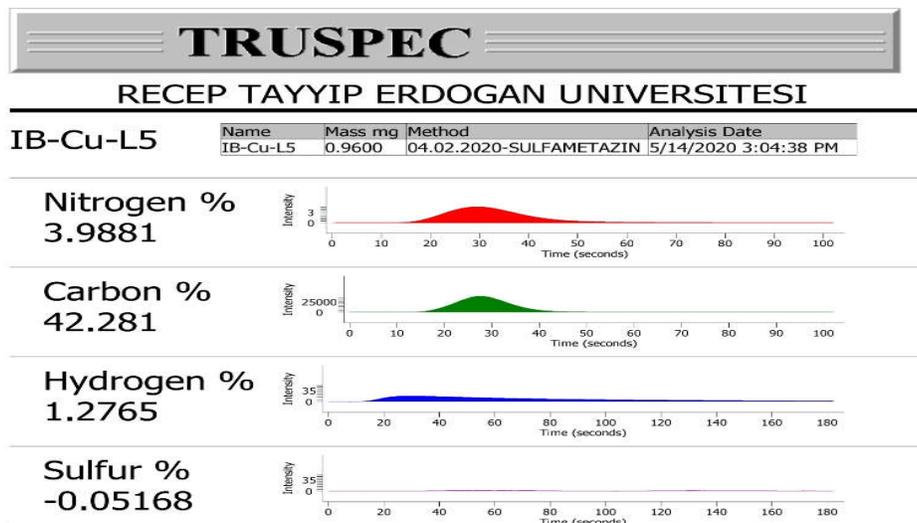
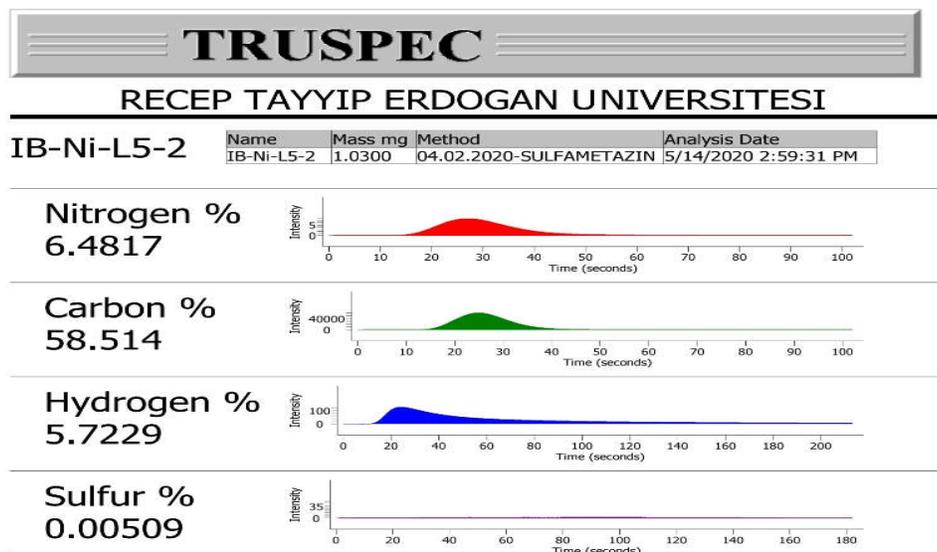
The ^1H NMR spectrum of the ligand gave a singlet peak at 15.56 ppm attributed to the proton of the hydroxyl group. This peak was also found present in the spectra of its complexes showing that no deprotonation occurred. Hence, the hydroxyl oxygen seems not participate in coordination in all the complexes. The signal at 12.46 ppm was given by the proton of the secondary amine group and was also found in the spectra of the complexes. This is indicative of the non-participation of the amine nitrogen in coordination in all the complexes. The four aromatic protons of the tert-butylbenzene ring gave doublets at 7.90, 7.73, 7.46, and 7.31 ppm. The aromatic proton of the pyrone ring gave a singlet at 5.61 ppm. The signal due to the protons of the methyl group of the pyrone ring was found as singlet at 2.70 ppm, while the singlet at 2.54 ppm was given by the protons of the methyl group attached to the azomethine group. The protons of the three methyl groups of the tert-butylbenzene gave a singlet at 1.43 ppm.

The ^{13}C -NMR spectrum of the ligand was used to support the inferences drawn from its ^1H -NMR spectrum. The carbon atoms of the two carbonyl groups gave signals at 180.86 and 166.59 ppm. The signal seen at 164.22 ppm is owing to the carbon atom of the C–OH group. The carbon atom of the azomethine group gave a peak at 159.73 ppm, showing that the ligand formed. The carbon atoms of the tert-butylbenzene which are in six different carbon environments gave signals at 151.55, 136.57, 127.62, 124.48, 34.78 and 31.63 ppm. The signal at 19.52 ppm was contributed by the carbon atom of the methyl group attached to the pyrone ring while that at 17.25 ppm was exhibited by the carbon atom of the methyl group attached to the azomethine group.

Mass spectra and elemental analysis

The ESI-MS molecular ion signals of the ligand and its complexes conformed with their proposed formulas (structures). HL ligand gave molecular ion signals at 343 = $[M+H]^+$, and 365 = $[M+Na]^+$ (base peak) which agree with a calculated value of 342. Its Cu(II), Ni(II), Co(II), and Mn(II) complexes gave molecular ion peaks at 482.00 $[M+Na]^+$ (base peak), 765.76 $[M+Na]^+$, 819.96 $[M+2K-H]^+$, and 779.29 $[M+ONa]^+$, respectively, which are in agreement with their calculated molecular masses of 459, 742.69, 742.93, and 739.64, respectively. The consensus between the calculated values and the molecular ion signals of the complexes confirms 2:1 ligand to metal coordination for the Ni(II), Co(II), and Mn(II) complexes and 1:1 for the Cu(II) complex. The peaks due to the loss of the coordinated chlorine atom and water molecule were found in the Cu(II) complex spectrum. Generally found in the spectra of the complexes are peaks which could result from other minor fragments and thus could not be identified. The results of the elemental analyses (Figures 2-6) of the ligand and its complexes are not so much in conformity with the calculated elemental compositions of the compounds. This could be attributed to the impure nature of the compounds, also revealed by the IR spectra of the compounds.

Figure 2. Spectrum of elemental analysis of HL₅ ligand.

Figure 3. Spectrum of elemental analysis of Cu(HL₅).Figure 4. Spectrum of elemental analysis of Ni(HL₅)₂.

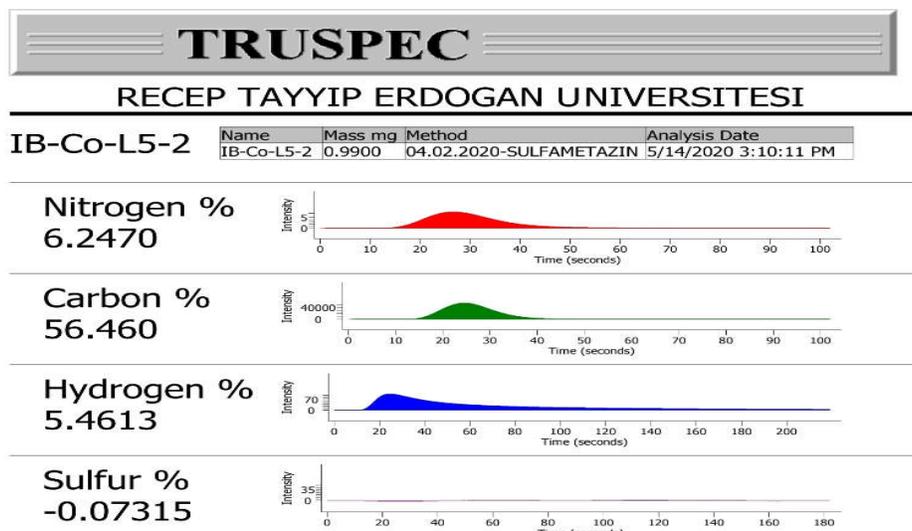


Figure 5. Spectrum of elemental analysis of $\text{Co}(\text{HL}_5)_2$.

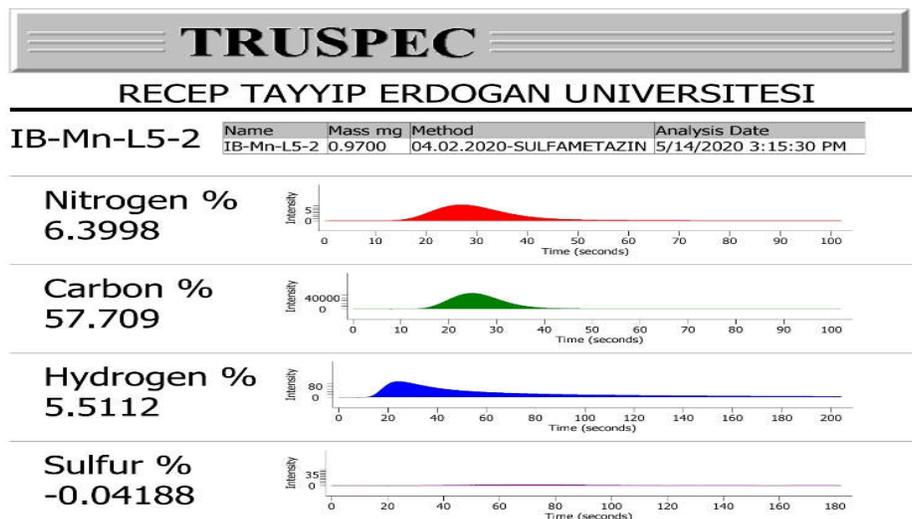


Figure 6. Spectrum of elemental analysis of $\text{Mn}(\text{HL}_5)_2$.

Infrared spectra of the ligand (HL) and metal complexes

The infrared absorption data of the ligand and its complexes are showed in Table 1. The formation of the ligand, its coordination with metal ions, and their mode of binding can be revealed by the IR spectra of the ligand and its complexes.

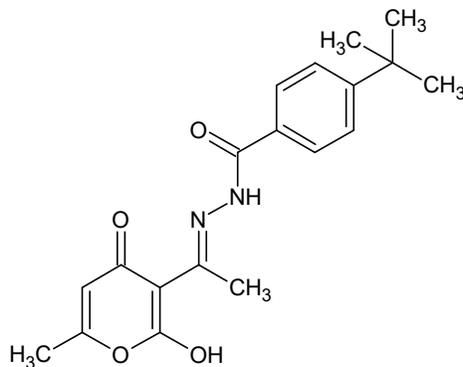
Table 1. Infrared absorption data for ligand and complexes.

S/N	Wave number (cm ⁻¹)	Functional group
Ligand		
1	3444	O–H stretching
2	1634	C=O stretching
3	1568	C=N stretching
4	749	N–H of the secondary amine
5	1443, 1489, 1509	C–C stretching of the benzene
6	1335, 1421	C–C stretching of the pyrone
7	1044, 1275	C–O stretching of the pyrone
8	2915	Aliphatic C–H stretching of the tert-butyl
9	2848	Aliphatic C–H stretching of the methyl
Metal complexes		
Cu(HL)		
1	3444	O–H stretching
2	1641, 1726	C=O stretching
3	1559	C=N stretching
4	761	N–H of the secondary amine
5	611	M–Cl stretching
6	538	M–N stretching
7	432	M–O stretching
8	3729–3929	O–H stretching (coordinated water molecule)
9	2919	Aliphatic C–H stretching of the tert-butyl
10	2848	Aliphatic C–H stretching of the methyl
Ni(HL) ₂		
1	3465	O–H stretching
2	1637	C=O stretching
3	1539	C=N stretching
4	749	N–H of the secondary amine
5	670	M–N stretching
6	424	M–O stretching
7	2919	Aliphatic C–H stretching of the tert-butyl
8	2848	Aliphatic C–H stretching of the methyl
Co(HL) ₂		
1	3434	O–H stretching
2	1633, 1644	C=O stretching
3	1534	C=N stretching
4	749	N–H of the secondary amine
5	529	M–N stretching
6	420	M–O stretching
7	2919	Aliphatic C–H stretching of the tert-butyl
8	2848	Aliphatic C–H stretching of the methyl
Mn(HL) ₂		
1	3434	O–H stretching
2	1626, 1668	C=O stretching
3	1538	C=N stretching
4	750	N–H of the secondary amine
5	583	M–N stretching
6	435	M–O stretching
7	2918	Aliphatic C–H stretching of the tert-butyl
8	2852	Aliphatic C–H stretching of the methyl

In the IR spectrum of the ligand, a broad peak was observed at 3444 cm^{-1} attributed to the O–H stretching vibration. The peak at 1634 cm^{-1} was given by the stretching vibrations of the C=O groups. The C=N stretching vibration of the azomethine group was found at 1568 cm^{-1} which indicates that the ligand formed. The wagging vibration of N–H of the secondary amine group gave a band at 749 cm^{-1} . The three C–C stretching vibrations in the benzene ring were seen at 1443 , 1489 , and 1509 cm^{-1} while the two C–C stretching vibrations in the pyrone ring were found at 1335 and 1421 cm^{-1} . The C–H stretching vibrations of the tert-butyl group gave a band at 2915 cm^{-1} while that of the methyl groups was found at 2848 cm^{-1} . The two C–O stretching vibrations of the pyrone ring gave bands at 1044 and 1275 cm^{-1} .

In the spectra of the complexes, the hydroxyl and secondary amine bands were still present, indicative of the non-participation of the hydroxyl oxygen and the amine nitrogen in the coordination. However, the bands of the carbonyl and azomethine groups experienced a shift in their vibrational frequencies, indicative of the participation of the carbonyl oxygen and the azomethine nitrogen in the coordination. Also found in the spectra of the complexes are the M–O and M–N vibrational peaks in the range; $420\text{--}435\text{ cm}^{-1}$ and $529\text{--}670\text{ cm}^{-1}$, respectively which are sufficient evidence of coordination. Note that these bands were absent in the spectrum of the ligand. In the Cu(II) complex spectrum, the M–Cl band was found at 611 cm^{-1} while the bands due to the coordinated water molecule and hydrogen bonding were found at $3729\text{--}3929\text{ cm}^{-1}$. Suffice to mention are the bending vibrational peaks found in the spectrum of all the compounds. Besides, there are other unidentified bands attributed to the existence of overtones and out-of-plane bands. The assignment of these bands was done with respect to the existing literature [19–23].

From the coordinated ligand atoms mentioned above, it could be deduced that the ligand is tridentate. The proposed structures of the ligand and its metal complexes are shown in Figure 7.



HL ligand

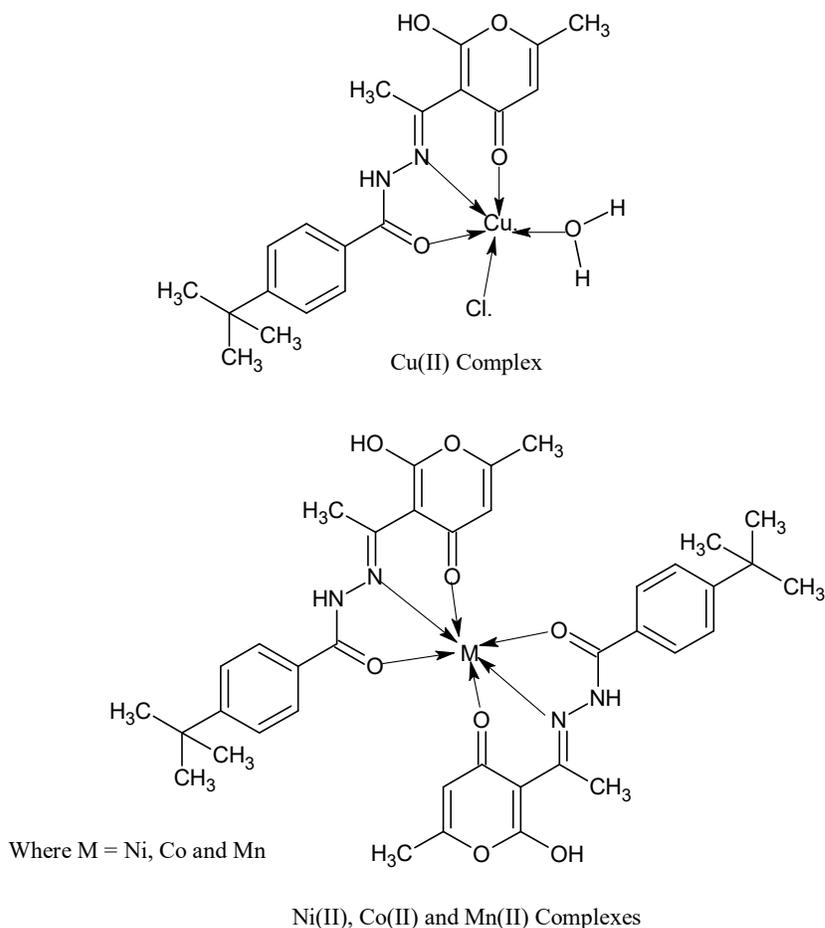


Figure 7. Proposed structures of HL ligand and its Cu(II), Ni(II), Co(II), and Mn(II) complexes.

CONCLUSION

The ligand and its Cu(II), Ni(II), Co(II) and Mn(II) complexes were successfully synthesized. The characterisation studies by spectroscopic techniques gave results that are in conformity with the proposed structures of the compounds. However, the elemental analysis results of the compounds did not agree so much with their calculated elemental compositions, indicative of the impure nature of the synthesized compounds.

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