

Microwave Synthesis, Characterization, Biological Activity of N- (p-Chlorophenyl)-N'-Benzoyl Thiourea and its Complexes

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Abstract

A derivative of thiourea ligand N-(p-chlorophenyl)-N'-Benzoyl thiourea (PCBT) in equimolar ratio 1:1 and its transition metal complexes Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} were synthesized by microwave (green chemistry). The structure of ligand and its complexes have been characterized by using elemental analysis, mass Spectroscopy, FT-IR, UV-Vis., ¹HNMR and ¹³CNMR. The geometry of the proposed structures of the chelates based on their electronic spectra, electron spin resonance (ESR) and magnetic susceptibility. The stability of complexes was studied by TGA analysis (Thermal studies). The free derivative thiourea ligand (PCBT) and its complexes were studied for antimicrobial and antifungal activity.

Keywords: Thiourea; Transition metals complexes; Microwave irradiation; Green chemistry; Biological activity; Antimicrobial activity; Antifungal activity

Introduction

Coordination compounds attracted great attention due to their structural variety, interesting physical & chemical properties and promising applications in many fields. Metal ions play an important role in the structure and function of many bio macromolecules and have important roles in the biological processes of metabolism as well as in pharmaceutical chemistry due to their chemical properties. Compounds bearing carbonyl and thio carbonyl groups are used as potential donor ligand for the preparation of complexes [1,2]. Among these, thiourea and its derivatives are versatile ligands that coordinate to form stable compounds. Thiourea (NH₂)₂C=S is a compound where the oxygen atom of urea compound replaced by a Sulphur atom. They are able to coordinate with metal either as neutral or mono-anion or dianion ligand [3,4]. Chemotherapy concerned in treatment of disease in which a chemical is specifically targeted for a microbial agent or a specific tissue. These thiourea ligands and their metal complexes were reported to act as antimicrobial, antibacterial, antifungal, antimalarial, anti-tuberculous and anticancer activities [7]. They also form a variety of complexes of different symmetries with various metal ions [7,8]. In view of the importance of thiourea and their derivatives it was worth interesting to synthesize N-substituted thiourea ligand and their complexes with transition metal elements because it was observed that this activity was enhanced by complexing with certain transition metal elements [3,9,10]. Complexes were synthesized using microwave-assisted irradiation. Microwave gives shorter reaction times, clean, high yields, and low cost [11].

Materials and Experimental Method

All purchased chemicals were of Annular AR grade and were obtained from Sigma Aldrich and all Metals salts were purchased from ADWIC. The

Microwave-assisted synthesis was carried out in a domestic microwave energy output 900 W. Purity of Schiff base ligand and its complexes were detected by using thin-layer chromatography (TLC) technique. Melting points were recorded in open capillaries with Barnstead Thermolyne Mel-temp 1001D Electrothermal Melting Point. Elemental analysis was done on automatic analyzer CHNS Vario El III-Elementar, Germany. The FT-IR spectra samples were ground with (CsBr) powder. Then pressed into a disk and recorded on Shimadzu FTIR spectrometer. Mass spectra were determined by using Mass GC-2010 Shimadzu instrument. Metals content were determined by complexometric titration using xylenol orange (XO) as indicator and hexamine as a buffer (p^H = 6). Electronic absorption spectra in DMF were measured using automated UV/Vis-NIR 3101 PC Shimadzu spectrophotometer ranged from 200-900 nm. ¹HNMR spectra for Schiff base ligand was recorded in 300MHz Varian-Oxford Mercury in DMSO-d₆ as solvent and the chemical shifts were recorded in ppm relative to TMS as an internal standard. Magnetic susceptibility of complexes was measured on powdered samples using the faraday method. Thermal analysis measurements (TGA) were carried out with Shimadzu thermal analyzer model 50 at Microanalytical. The ESR spectra of the powdered Cu^{II} complex recorded at room temperature by X-band EMX spectrometer (Bruker, Germany) using a standard rectangular cavity of ER 4102 with 100 KHz frequency.

Schiff base ligand and their metal complexes were screened for *in-vitro* antibacterial activity against two species of Gram-positive bacteria and two species of Gram-negative bacteria as well as two species of fungi. All of these were carried out in faculty of Science, Cairo University.

Chemicals

All consumed chemicals were from analytical grade and were used as received without further purifications. Chemicals used are Benzoyl chloride,

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ammonium thiocyanate, p-chloro anilin, acetone, cobalt acetate, nickel acetate, copper acetate, zinc acetate and methanol.

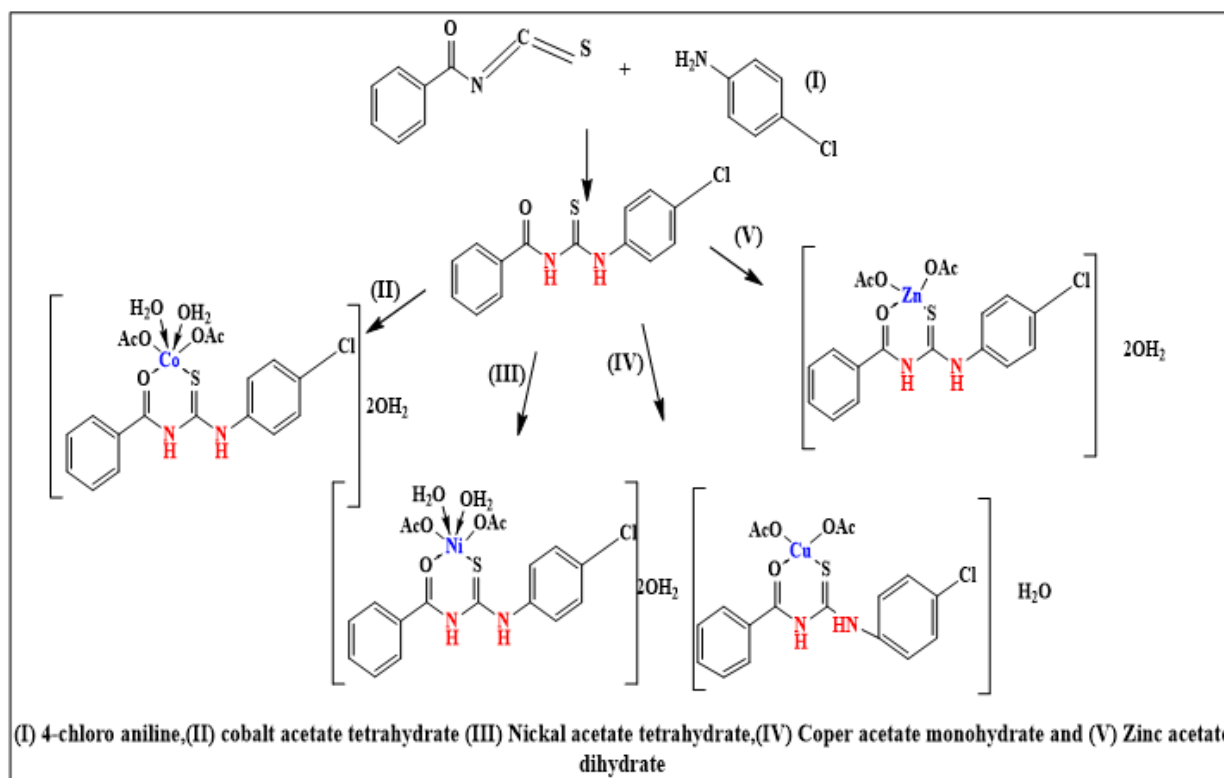
Synthesis of N- (p-chlorophenyl)-N'-Benzoyl thiourea (PCBT)

0.1 m of ammonium thiocyanate (7.6 gm) dissolved in 50 ml of acetone then added drop by drop to 0.1 m of benzoyl chloride (14.06 gm) (11.62 ml) taken in 3 neck flask with continuous stirring. The mixture is refluxed for 1 hour with continuous stirring. After 45 minutes white ppt (ammonium chloride) appeared and then disappeared at 1 hr. The mixture left in room temp until the precipitate appears again completely. Filtration done and precipitate washed by acetone to get all the filtrate (Benzoyl thiocyanate). The filtrate added drop by drop in a 3-neck flask contains 0.1 m (12.75 gm) of para chloro anilin dissolved in 25 ml acetone with continuous stirring. The mixture refluxed for 2 hrs with continuous stirring. The mixture transferred to a baker and covered for two days for complete precipitation. Then the

Precipitate was filtrated and washed by ethanol and acetone. Purity of ligand achieved by recrystallization using ethanol and dried over anhydrous CaCl_2 in a desiccator to give the pure ligand (PCBT).

Synthesis of metal complexes

The prepared ligand and the acetate salts of the metal Co $(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$, Ni $(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$, Cu $(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$ and Zn $(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ were mixed in (1:1) ratio. The reaction mixtures were then irradiated by the microwave oven by using drops of methanol as a solvent. The reaction was completed in a short time (3-5 min) with higher yields. The resulting product washed by hot methanol and ether and finally dried under reduced pressure over anhydrous CaCl_2 in a desiccator. The progress of the reaction and purity of the product was monitored by TLC using silica gel (yield: 78-83 %). The synthetic route of the prepared compounds is illustrated in Scheme 1.



Scheme 1. Synthesis of N- (p-chlorophenyl)-N'-Benzoyl thiourea (PCBT) and its metal Complexes.

mass spectra, UV-Vis and NMR studies. This data is compatible with the required product. Analytical and physical properties of prepared compounds tabulated in Table 1.

Results and Discussion

The structure of the prepared ligand N- (p-chlorophenyl)-N'-Benzoyl thiourea (PCBT) was characterized by melting point, elemental analysis, IR,

Table 1. Analytical and physical properties of the prepared compounds (CPDs).

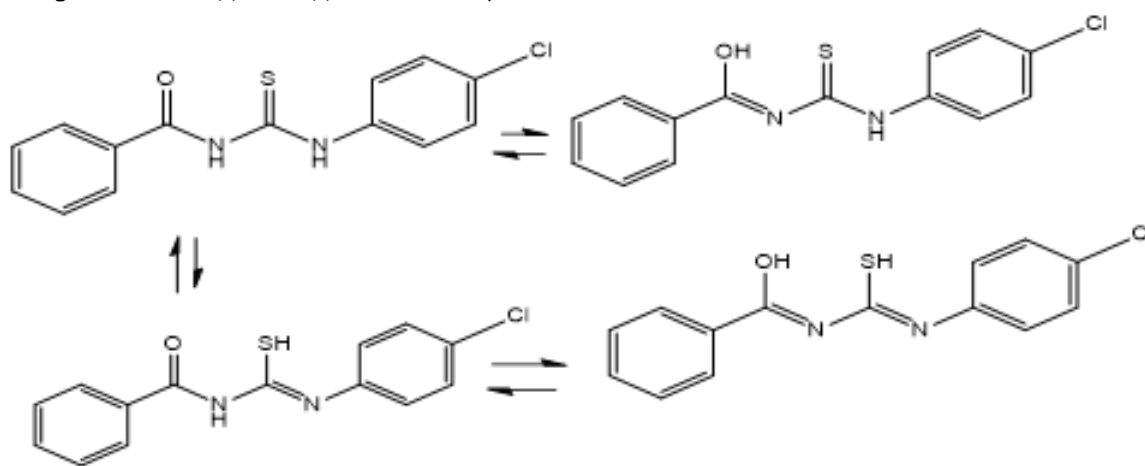
Compd.	Molecular formula	M.Wt.	Yeild%	M.P. °C	Color	%C	%H	%N	%M
PCBT	$\text{C}_{14}\text{H}_{11}\text{ON}_2\text{SCl}$	290.8	86.3	140	Pale yellow	57.83 (57.57)	3.81 (3.96)	9.63 (10.06)	

Co-PCBT	CoC ₁₈ H ₂₅ O ₉ N ₂ SCl	539.58 (539.33)	79.8	320	Dark (pink)	40.03 (41.47)	3.79 (4.6)	5.16 (5.2)	
Ni-PCBT	NiC ₁₈ H ₂₅ O ₉ N ₂ SCl	539.21	81.3	310	Dark Green	40.06 (43.08)	3.68 (4.6)	5.2 (5.87)	10.88 (11.28)
Cu-PCBT	CuC ₁₈ H ₁₉ O ₈ N ₂ SCl	490.1	82.42	330	Greenish	44 (43.21)	3.72 (3.8)	5.72 (5.7)	
Zn-PCBT	ZnC ₁₈ H ₂₁ O ₇ N ₂ SCl	510	82.27	305	White	42.35 (43.7)	3.27 (4.01)	5.58 (5.49)	12.81 (14.31)

IR spectra

The characteristic IR bands of all thiourea ligands showed the expected frequencies of ν (C=O), ν (N-H), ν (C-N) and ν (C=S). The coordinative behavior of present ligand, towards Zn (II) and Ni (II) ions to form complexes

is difficult to establish, as this ligand is capable of exhibiting three tautomeric forms as clear from Scheme 2 due to presence of [-NH-C(=S)] and [-NH-C(=O)] functional groups.



Scheme 2. Tautomeric forms of the prepared ligand.

However, the lack of the characteristic vibrations of ν (S-H) around 2500–2600 cm^{-1} [10] and presence of a peak at 3251 cm^{-1} characteristic of ν (N-H) [11] confirmed the absence of tautomeric form (N=C-SH) and (N=C-OH). Two sharp intense bands observed at 1670 and 1341 cm^{-1} can be ascribed to the stretching vibration of carbonyl group ν (C=O) and thionyl group ν (C=S) respectively [12,13]. These observations confirmed the ketonic– thion form of the ligand in the solid-state. Moreover, the ν (C-Cl) stretching frequency was observed at 765 cm^{-1} , while this band appearing at 678–686 cm^{-1} assigned to the usual modes of phenyl ring vibration,

respectively [14,15]. On the other hand and upon coordination of the metal center to ligand, the characteristic bands of ν (C=O) and ν (C=S) present in the spectrum of the free ligand at 1670 and 1341 cm^{-1} were found to be shifted to a lower frequency and appear from 1535 to 1605 for C=O and from 1273 to 1250 cm^{-1} for C=S. This finding may be taken as an evidence for the coordination of the carbonyl oxygen and thionyl Sulphur atoms with the metal ions. The IR spectra for ligand and complexes are shown in Figures 1, 2, 3, 4 and 5 the data are tabulated in Table 2.

Table 2. Important FT-IR bands of the prepared compounds (CPd).

Cpd.	ν OH (H ₂ O)	ν N-H	ν C-H Aromatic	ν OAc Assym. /Sym.	ν C=O	ν C=S	ν Ph-Cl	ν M-O	ν M-S
PCBT	--	3251	3020	--	1670	1341	765	--	--
PCBT-Co	3742	3348	3148	1396	1550	1273	679	609	501
PCBT-Ni	3850	3441	2993	1412	1535	1250	686	609	509
PCBT-Cu	3700	3487	3148	1442	1605	1273	694	625	501

PCBT-Zn	3850	3464	3009	1342	1535	1250	686	609	501
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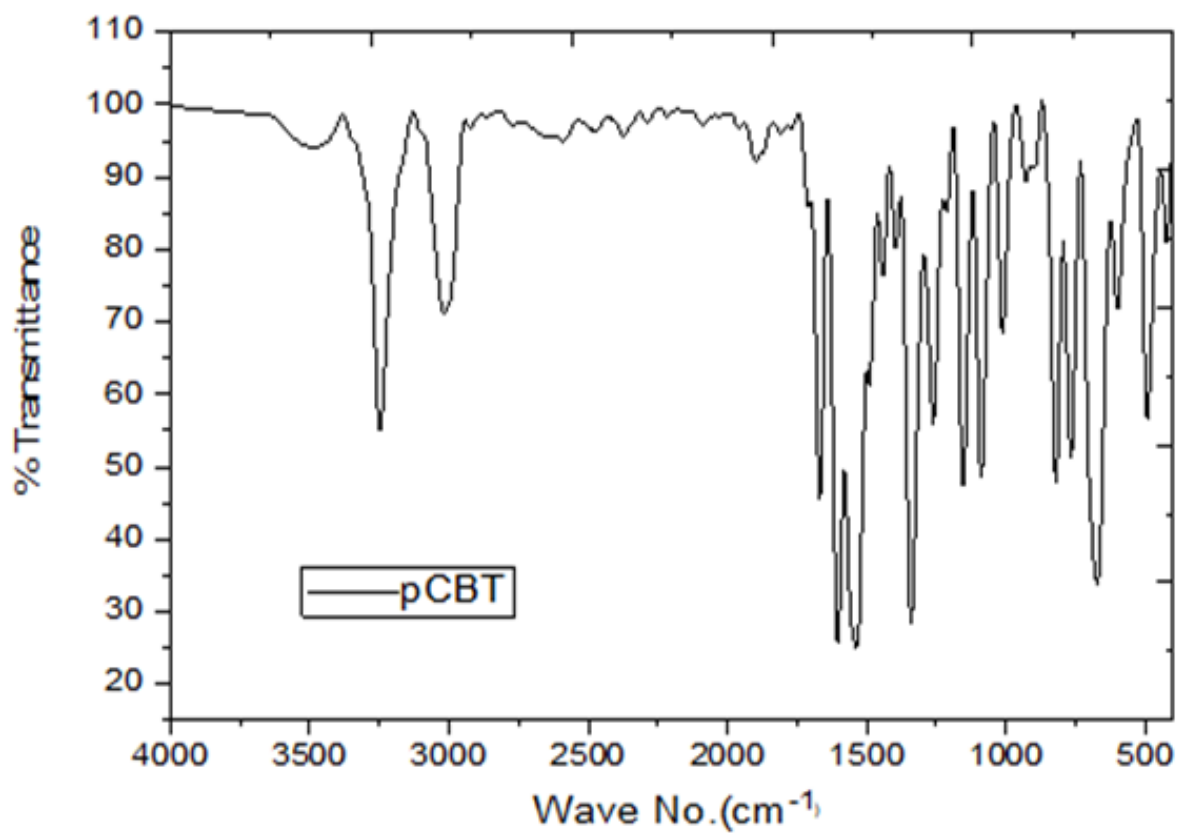


Figure 1. IR spectra of the prepared PCBT.

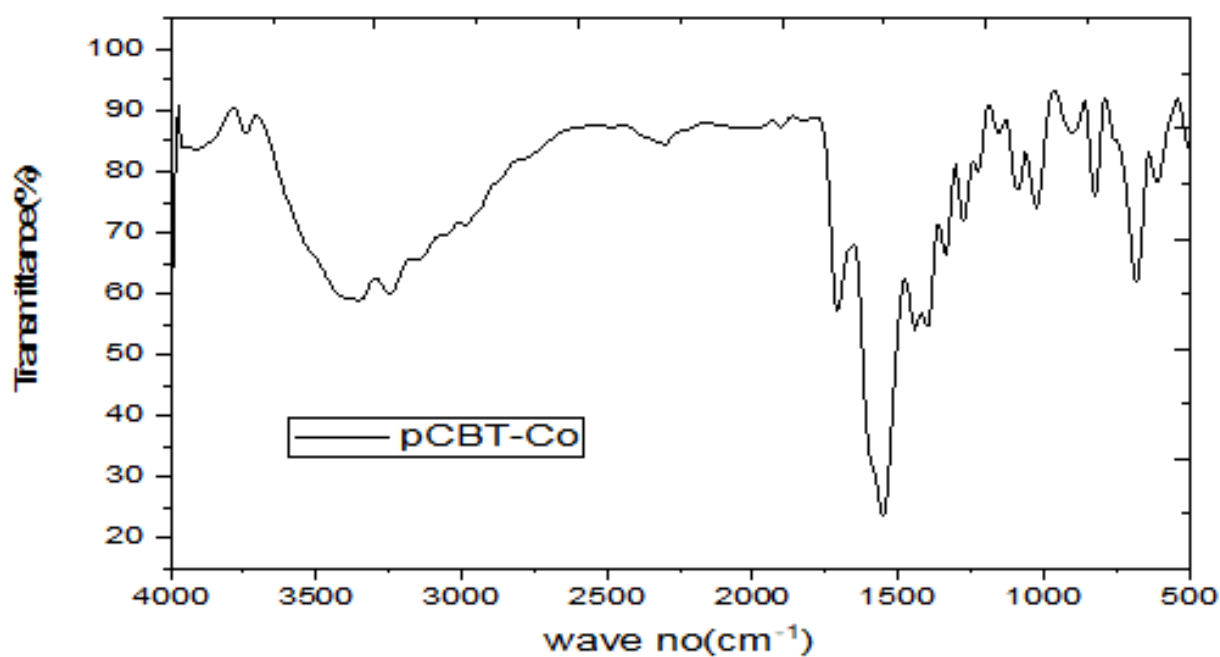


Figure 2. IR spectra of the prepared PCBT-Co.

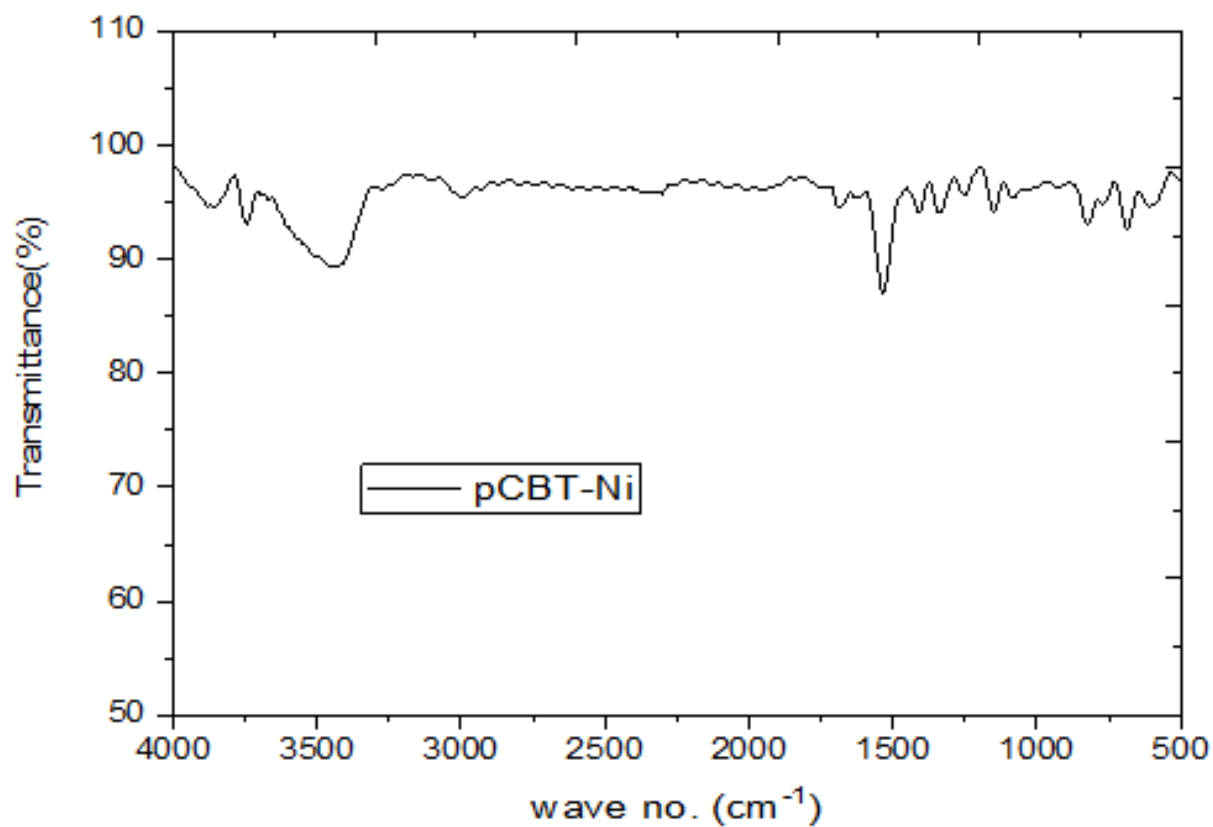


Figure 3. IR spectra of the prepared PCBT-Ni.

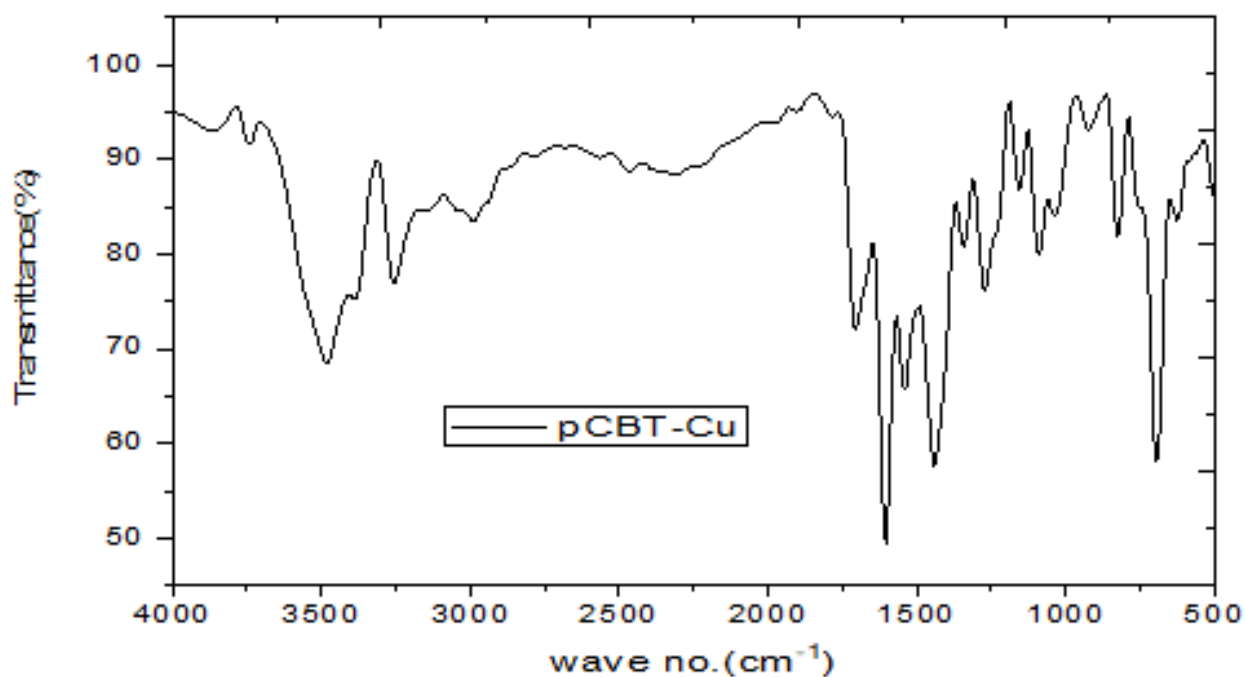


Figure 4. IR spectra of the prepared PCBT-Cu.

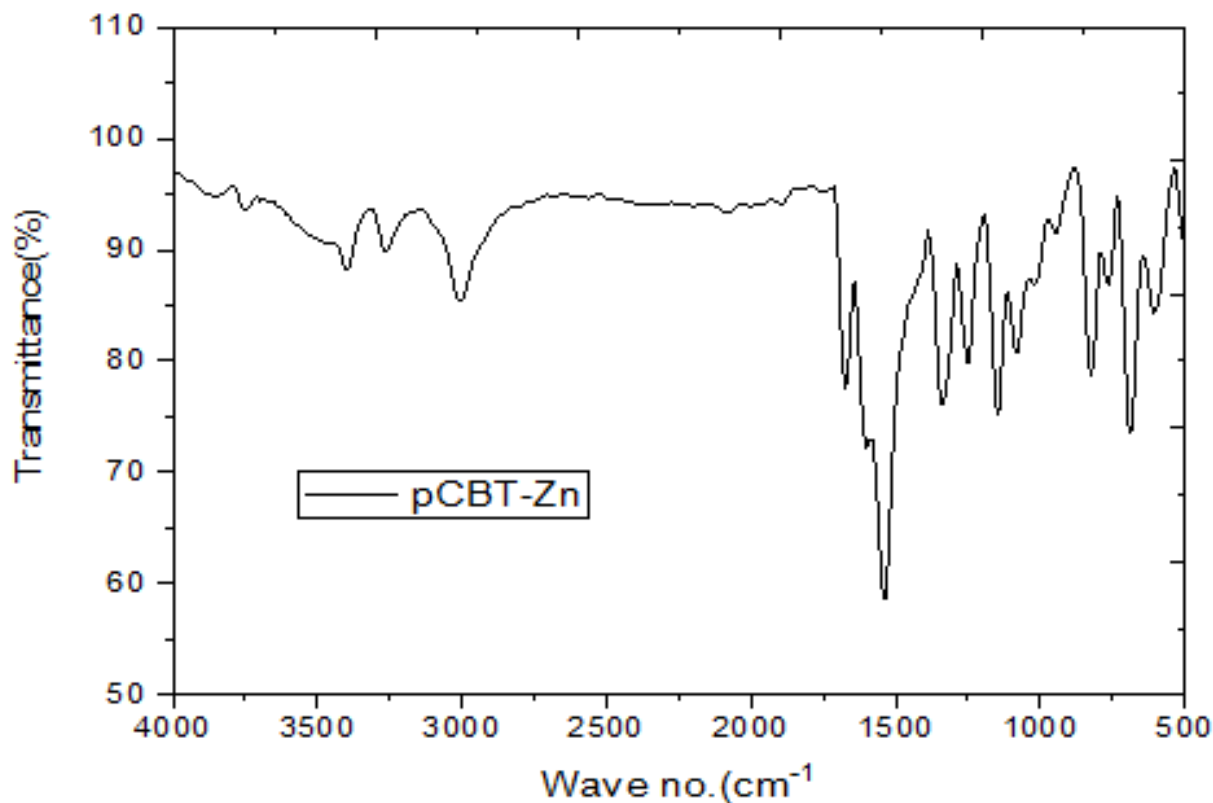


Figure 5. IR spectra of the prepared PCBT-Zn.

Mass spectra

The fragmentation patterns of N- (p-chlorophenyl)-N'-Benzoyl thiourea is shown in Figure 6 and Scheme 3.

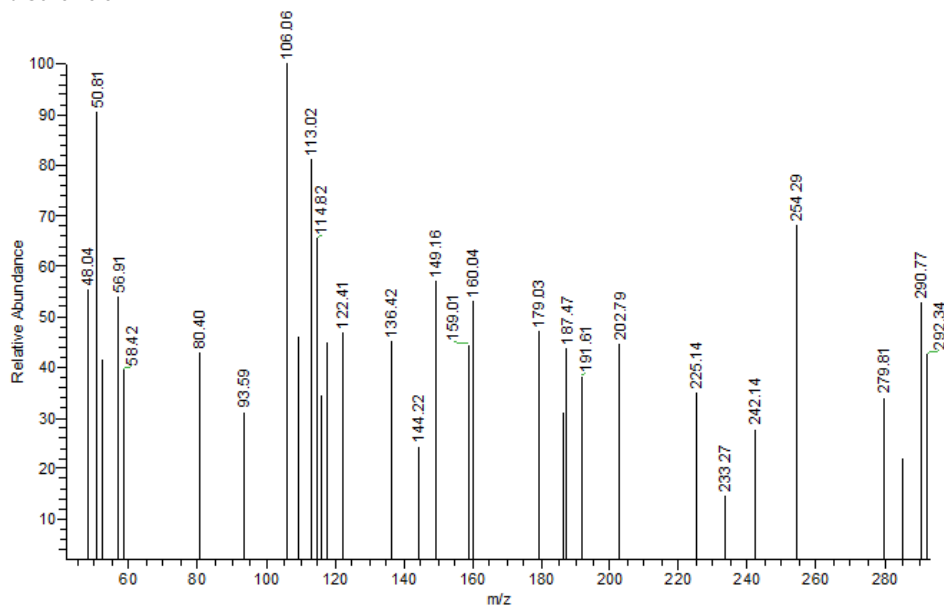
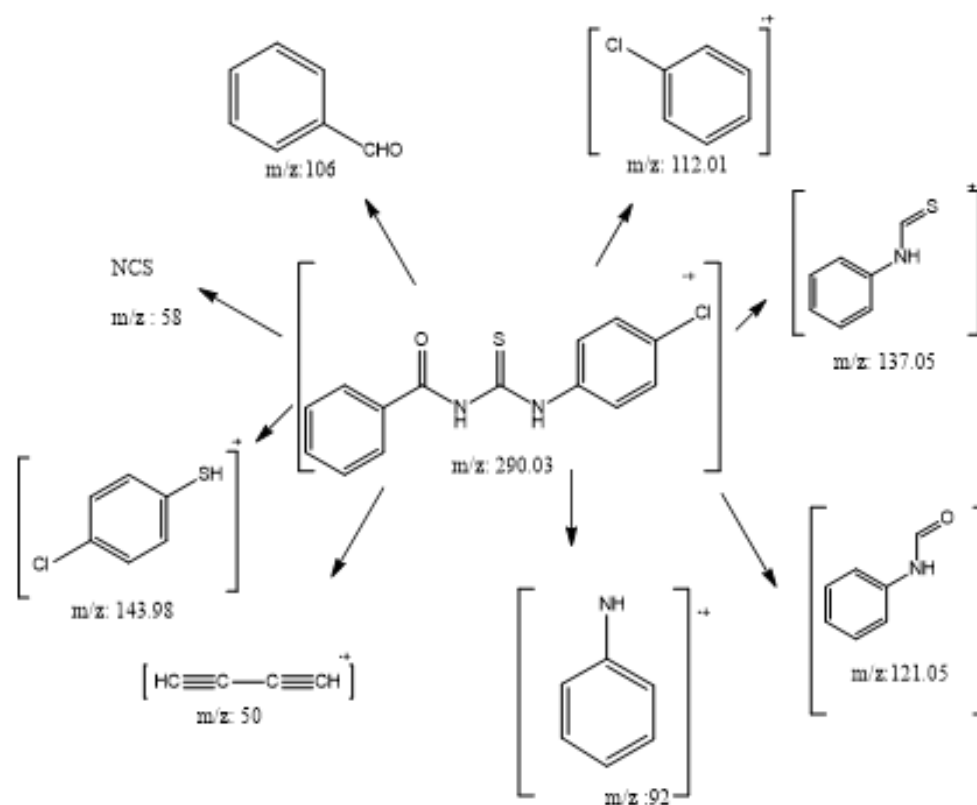


Figure 6. Mass spectra of the prepared ligand (PCBT).

The recorded mass spectra of the ligand (Scheme 3) showed a peak at m/z (relative abundance) 292.34 (42.56%) which is the molecular peak of ($C_{14}H_{11}N_2OSCl$). The ion peak at $m/e = 144.22$ (42 %) is due to M^+ (C_6H_5SCl), while the ion peak at $m/e = 106.06$ (100%) corresponds to M^+ (C_7H_6O) which is the base peak, the ion peak at $m/e = 136.4$ (45.08%)

corresponds to M^+ (C_7H_7NS), the ion peak at $m/e = 122.4$ (46.88%) is due to M^+ (C_7H_7ONCl), the ion peak at $m/e = 113.02$ (80.97 %) points to M^+ (C_6H_5Cl). The ion peak at $m/e = 58.42$ (39.44%) refers to M^+ (NCS), the ion peak at $m/e = 93.59$ (31.09%) corresponds to M^+ (C_6H_6N) the ion peak at $m/e = 50.81$ (90.46%) refers to M^+ (C_4H_2).



Scheme 3. Suggested mass fragmentation patterns of the prepared ligand (PCBT).

The fragmentation patterns of Co^{II} complex shown in Figure 7 and Scheme 4.

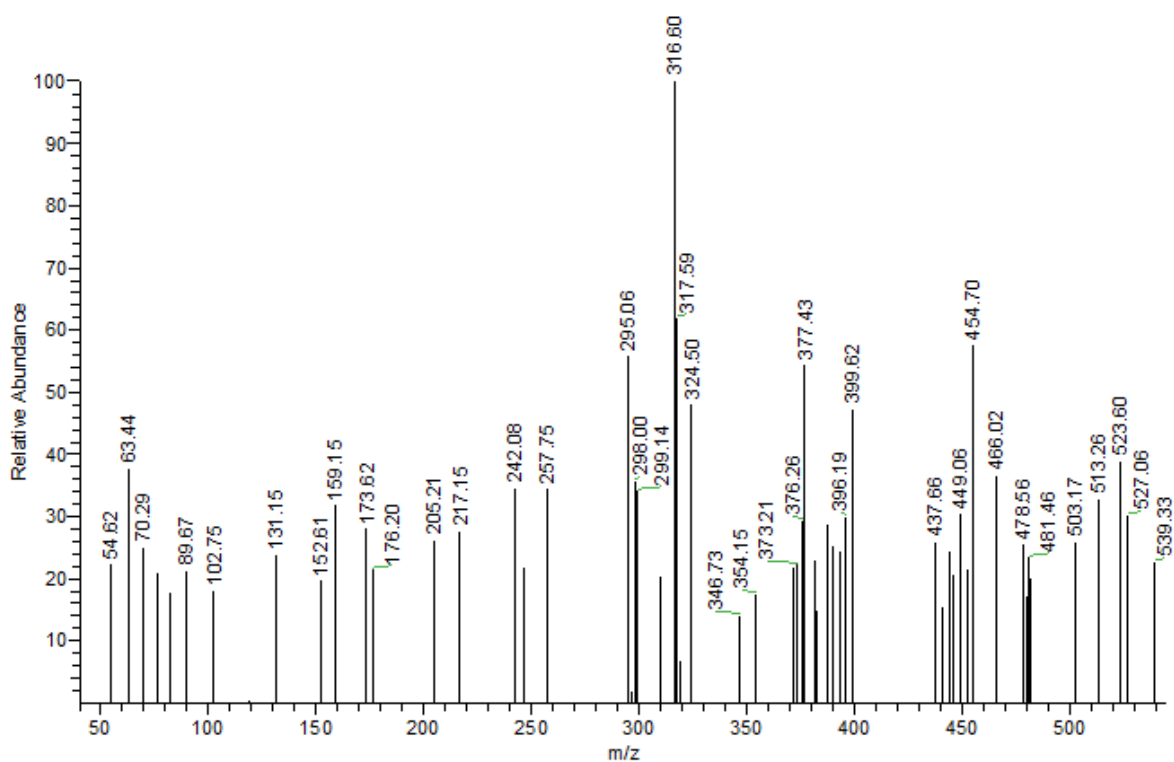
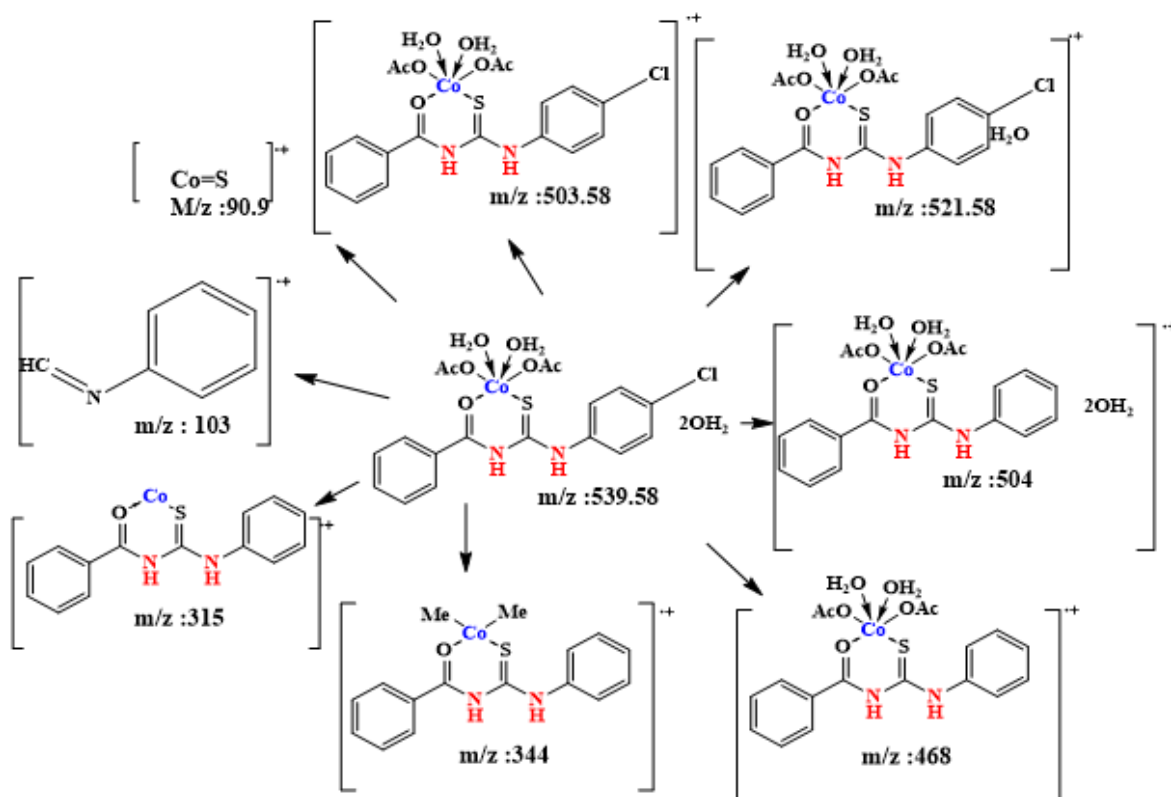


Figure 7. Mass spectra of the prepared Co^{II} complex.

The mass spectra of the PCBT-Co complex (Scheme 4) showed peak at m/z (relative abundance) 539.33 (22.52%) as the molecular peak of $(\text{CoC}_{18}\text{H}_{25}\text{O}_9\text{N}_2\text{SCl})$. The ion peak at $m/e = m/z$ 523.6 (38.74%) is due to M^+ $(\text{Co.C}_{18}\text{H}_{23}\text{O}_8\text{N}_2\text{SCl})$, while the ion peak at m/e 503.17 (25.69%) corresponds to M^+ $(\text{Co.C}_{18}\text{H}_{21}\text{O}_7\text{N}_2\text{SCl})$, the ion peak at $m/e =$

346.73 (13.98%) is due to M^+ $(\text{Co.C}_{16}\text{H}_{16}\text{ON}_2\text{S})$, the ion peak at $m/e =$ 102.75 (18.07%) points to M^+ $(\text{C}_7\text{H}_6\text{N})$, the ion peak at $m/e = 316.6$ (100%) refers to $(\text{Co.C}_{14}\text{H}_{12}\text{ON}_2\text{S})$ which is the base peak, the ion peak at $m/e = 89.67$ (21.15) refers to (CoS) .



Scheme 4. Suggested mass fragmentation patterns of the prepared Co (II) complex.

^1H NMR spectra

The assignments of the main signal in the ^1H NMR spectra of the ligand given in Figure 8 recorded in DMSO-d_6 as a solvent with TMS internal

standard, displays some groups of signals corresponding to the various protons [16-21].

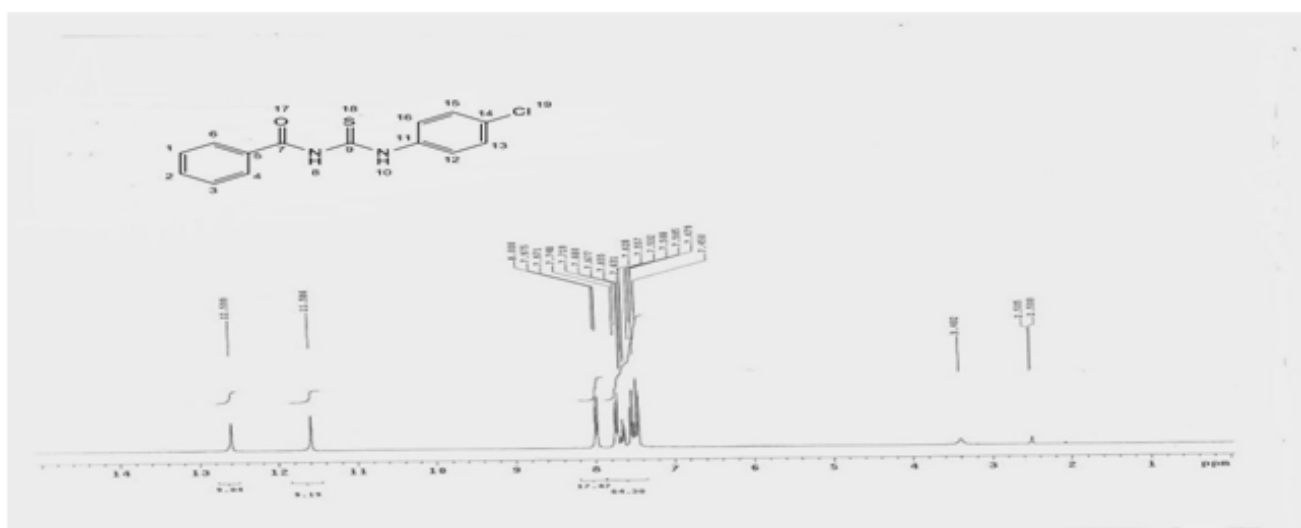


Figure 8. ^1H NMR spectra of the ligand (PCBT).

The chemical shifts were expressed in ppm. The spectrum of the ligand (PCBT) give two singlet signals, one at δ 11.58 ppm assigned to (S,1H, N8-H) and the other at δ 12.59 ppm assigned to (S,1H, N10-H) [22] (which

were also identified by D_2O exchange). The multiplets observed at δ 7.450 – 8.000 ppm are attributed to the phenyl protons [16].

^{13}C NMR spectra

The ^{13}C NMR spectra of the synthesized ligand (PCBT) given in Figure 9 showed peaks at 179.347 ppm assigned to (C=O), 168.207 ppm assigned to

(C=S), 136.958 ppm to (C11) 133.133 ppm to (C14), 132.63 ppm to (C5), 130.257 ppm to (C2), 130.257 ppm to (C12, C16) and at 128.694 ppm (C13, C15), 128.550 ppm (C1, C3), 126.167 ppm (C4 and C6).

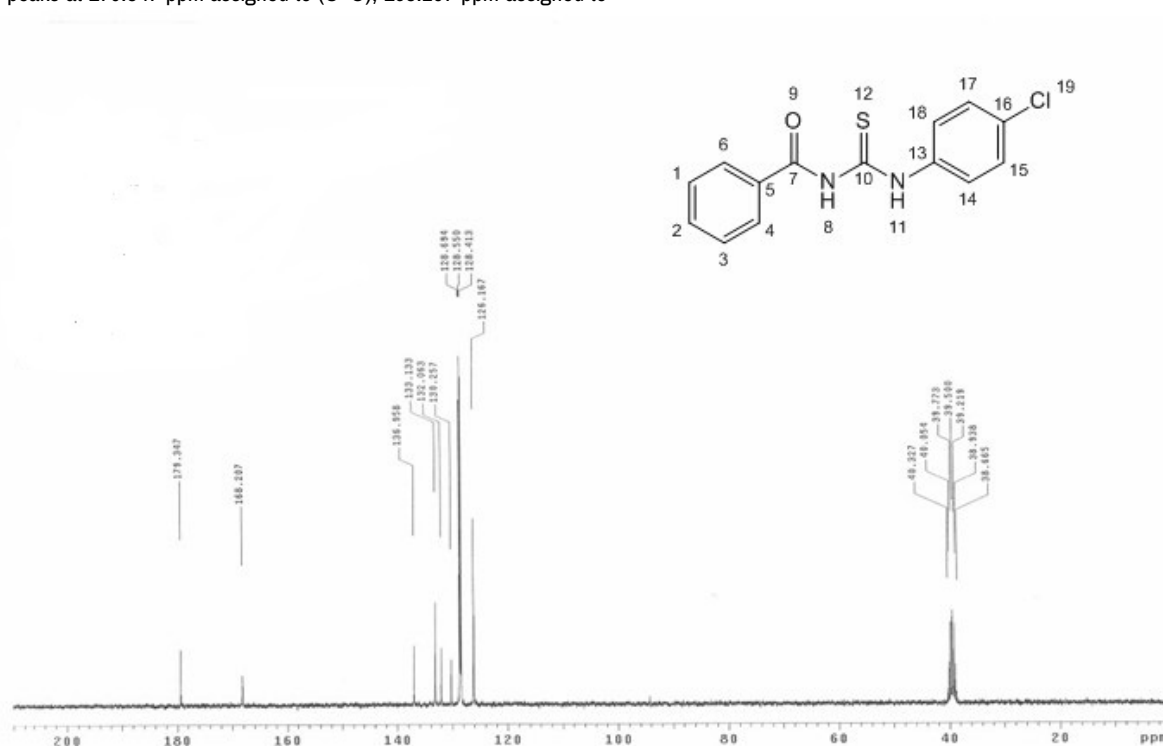


Figure 9. ^{13}C NMR Spectra of PCBT.

Electronic and magnetic properties of the prepared compounds

The stereochemistry of the metal ions in the complexes can be assigned via the electronic spectral measurements.

The diffuse solid reflectance spectra of the ligand and its complexes in solid-state showed a number of bands in the UV-Vis region (200-800 nm).

In the spectrum of the free ligand

Three absorption bands were observed at 258, 277 and 325 nm. The first band can be assigned to $\pi-\pi^*$ transitions originated from aromatic moieties, and the third band can be assigned to $n-\pi^*$ transitions originated from C=O and C=S groups.

The latter band is due to the intermolecular charge transfer interaction from aromatic groups to C=O and C=S group [17,18].

The cobalt (II) complex spectrum showed

Absorption bands from 425 to 650 nm assigned to $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{1g}(\text{P})$ and $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{2g}$ transitions are respectively.

The measured magnetic moments 5.95 B.M., falls in the range reported for octahedral geometry.

The nickel (II) complex spectrum showed

Three electronic bands from 450 to 750 nm due to the transition $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{2g}(\text{F}) (\nu_1)$, $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F}) (\nu_2)$ and $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P}) (\nu_3)$, respectively and LMCT suggesting high-spin octahedral for Ni (II) complex [19].

The measured magnetic moments, 3.9 B.M., falls in the range reported for octahedral geometry.

The copper (II) complex spectrum showed

The electronic spectra of the copper complexes revealed bands from 425 to 750 nm assigned to the transitions ($^2\text{B}_2 \rightarrow ^2\text{E}$) [19].

The measured magnetic moments, 1.89 B.M., falls in the range reported for tetrahedral geometry.

The zinc (II) complex spectrum showed

Absorption bands from 560 to 720 (nm) which can be assigned to metal ligand charge transfer MLCT in a low spin tetrahedral geometry of Zn (II) complex confirmed by the diamagnetic properties. The assignments of the observed electronic transitions apart from that together with the geometry and the magnetic moment values [20,21] are listed in Table 3.

Table 3. Spectral and magnetic properties of the prepared compounds (CPD).

Cpd	λ max(nm)	Assignments	μ eff.(B.M)	Suggested Structure
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pCBT	325 277 258	(n- π^* , C=O), (n- π^* , C=N), (π - π^* , aromatic ring)	--	-
pCBT-Co	425-650	$^4T_{1g}(F) \rightarrow ^4T_{1g}(P) \rightarrow ^4T_{1g}(F) \rightarrow ^4T_{2g}$	5.95	Octahedral
pCBT-Ni	450-750	$^3A_{2g} \rightarrow ^3T_{1g}(P)$ $^3A_{2g} \rightarrow ^3T_{2g}$	3.9	Octahedral
pCBT-Cu	425-750	$^2B_2 \rightarrow ^2E$	1.89	Tetrahedral
pCBT-Zn	560-720	MLCT	Di	Tetrahedral

The most essential features of the spectrum of the complex are entirely different when compared to that of the free ligand. Upon interaction of the ligand with metal ions; there are some shifts in bands positions in the spectra of the complexes. This change can be taken as a positive evidence of complex formation. In addition, appearance of new bands at longer wavelength assigned to ligand metal charge transfer (LMCT) and d-d transitions is another confirmation to complex formation, which gives evidence for the coordination of the ligands to the metal ions. All spectra data were tabulated in Table 3.

Electron spin resonance Spectrum (ESR)

The spectra of copper complex exhibit single broad signal with hyper structure indicating the contribution of free acetate ligand with complex formation. The spectra showed broad signals with two "g" values (g_{\parallel} , g_{\perp}) Figure 10. For all complexes the value of $g_{\parallel} < g_{\perp} < 2.3$ characteristic of complexes with $^2B_1(dx^2-y^2)$ orbital ground state. The average g values were calculated according to the equation $g_{av} = 1/3 [g_{\parallel} + 2g_{\perp}]$ and it was equal to 2.107 for PCBT-Cu.

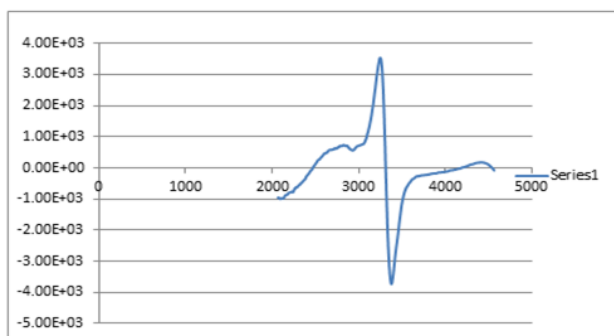


Figure 10. ESR for Cu-PCBT.

Thermal Analysis (TGA)

TGA data of the thermal decomposition of the prepared complexes are shown in Table 4, Figures 11, 12 and Scheme 5.

Table 4. Thermo gravimetric data of Thermal decomposition of of NiII and ZnII Complexes

Cpd.	Molecular formula	MWt	Steps	Ti	Tf	Calc.mass (%)	Found mass (%)	Assignment
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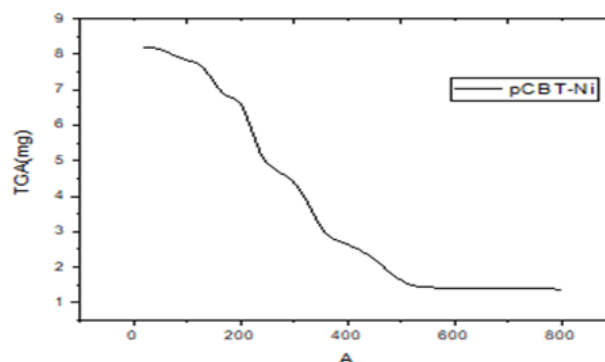


Figure 11. Thermal analysis of PCBT-Ni.

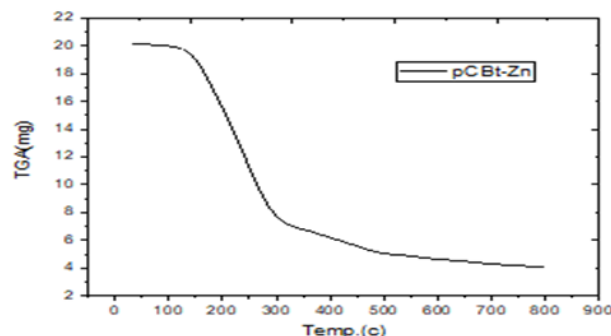
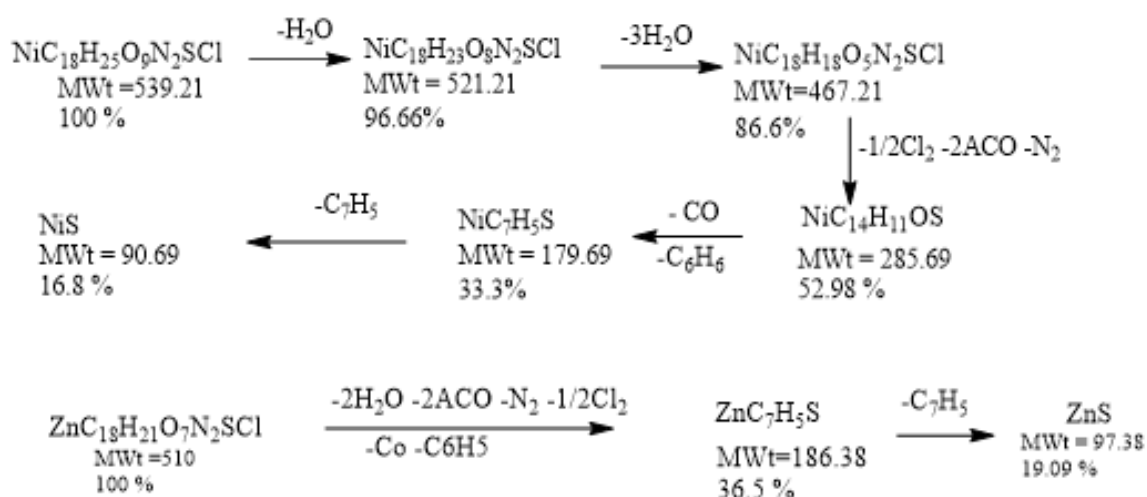


Figure 12. Thermal analysis of PCBT-Zn.

PCBT-Ni	$\text{NiC}_{18}\text{H}_{25}\text{O}_9\text{N}_2\text{SCL}$	539.21	1 st	30	105	96.66	96.05	H_2O
			2 nd	105	180	86.6	84.01	$3\text{H}_2\text{O}$
			3 rd	180	280	52.98	55.65	2ACO
			4 th	280	370	33.3	34.7	N_2
			5 th	370	611	16.8	17.24	$1/2\text{Cl}_2$ CO C_7H_5
PCBT-Zn	$\text{ZnC}_{18}\text{H}_{21}\text{O}_7\text{N}_2\text{SCL}$	510	1 st	40	320	19.09	21.1	$2\text{H}_2\text{O}$
			2 nd	320	450	36.5	35.34	2ACO
								N_2, CO
								C_6H_6
								$1/2\text{Cl}_2$ C_7H_5



Scheme 5. Thermal decomposition of Ni^{II} and Zn^{II} Complexes.

The TGA curves indicate that the loss of weight starts around 205°C and continues to about 300°C at which point most of the organic part of the compounds have been lost.

This sharp decomposition period brings about 78% weight losses in the complexes and led to the complete formation of sulphide.

Biological Activity

Antibacterial and anti-fungal effect

Some chelates exhibited a moderate inhibitory activity of complexes than that of the corresponding free ligands.

The free ligand (PCBT) and its metal complex Co^{II} in addition to the standard drugs were screened separately for their antibacterial activity against *Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans* (ATCC: 25175) (Gram-positive bacteria), *Escherichia Coli* (ATCC:9637) and *Klebsiella Pneumonia* (ATCC:10031) (Gram-negative bacteria) and antifungal

activity against *Aspergillus Nigar* (ATCC:32856) and *Candida albicans* (ATCC:6538) fungi.

The antimicrobial activity against the growth of various microorganisms were determined by measuring the inhibition zone in millimeters around the well, also the activity index data was calculated [22].

The result is recorded in Table 5. As we can observe from the results metal complexes act as more powerful bactericides and fungicides agents and they may serve as a vehicle for activation of ligand where the metal ions being more hypersensitive against the microbial cells.

This behaviour of the metal complexes may be a result to the modification in structure upon coordination and formation of metal organic framework and can be explained on the basis of the overtone concept and chelation theory.

In general, the easy penetration of the metal complexes into lipid membranes, disturbance of the respiration process of the cell and blocking the synthesis of proteins are restrict further growth of the organism and lead to enhance of activity of metal complexes compared with the organic ligand

[23-31]. We did different fungi and ligand interactions with proper docking of the compound.

Table 5. Antibacterial and antifungal assay of ligand and its ZnII complex.

Cpd.	Recorded zone diameter (mm) for each test microorganism					
	BACTERIA			FUNGI		
	Gram-positive		Gram-negative			
	Streptococcus Mutans	Staphylococcus aureus	Escherichia Coli	Klebsilla pneumonia	Asperagillus Nigar	Candida Albicans
pCBT	0	0	0	0	0	0
pCBT-Co	25	35	25	31	0	25
St.	03	22	27	25	21	21
	Gentamicin			Nystain		

Conclusion

Complexes were synthesized successfully and fully characterized by chemical and spectroscopic methods. Then biological activity was studied and compared between the ligand itself and the Zn^{II} complex. The study showed that the prepared compounds have an appreciable activity and can consider as an effective inhibitor towards the different microbial strains. Generally such activity enhanced upon complexation where metal complexes show better activity than their parent ligand.

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