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Organic ligand 1-(1-morpholino-1-(thiophen-2-yl) ethyl)-3-phenylurea: Synthesis, Characterization, Derivatives and Exploration of Bioactivity

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Abstract

Organic compounds possessing a comparatively greater number of nitrogens, fascinating attention in the upcoming field of medicine and its research. Synthesizing new drugs with a greater number of nitrogen atoms in their structure skeleton place challenges. Unique feature say lipophilicity carried by Mannich bases and their bivalent metal coordination complexes claim themselves to be potential sources [1-3]. Heterocyclic organic compounds rooted through amines and amides possess enhanced absorption through bio-membranes because of its lipohilicity which results in boundless pharmaceutical applications [4-11]. They considerably shorten the duration of therapy too. Mannich base and its coordination complexes with a range of first transition bivalent metals, such as, $Co^{2+,}$ Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} are reported along with DPPH free radical scavenging activity and anti-inflammatory activity. The scheme sequenced with 2-acetylthiophene, morpholine and phenyl urea was not yet described, the new Mannich base, 1-(1-morpholino-1-(thiophen-2-yl) ethyl)-3-

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phenylurea (L), was synthesized. The compound and all the complexes were characterized.

Keywords: Metal complexes; 2-acetylthiophene; Mannich base; Morpholine derivatives; DPPH free radical scavenging activity; anti-inflammatory activity.

1. Introduction

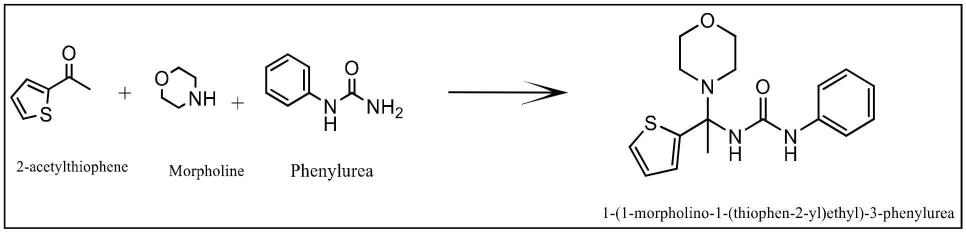
The tendency of Mannich bases to create metal stable complexes has been discovered to have therapeutic potential [1–16]. They are readily absorbed by disease-causing microorganisms through biomembranes [17–23]. A previously unknown mixture of 2-acetylthiophene, morpholine, and phenyl urea was used to synthesize 1-(1-morpholino-1-(thiophen-2-yl) ethyl)-3-phenylurea (L). In this paper, a Mannich base ligand (L) and its bivalent metal complexes (Co^{2+}, Mn^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) are synthesized, characterized, DPPH free radical scavenging activity and anti-inflammatory studies are covered (II).

2. Materials and Methods

When necessary, chemicals of the AR grade were utilized without any filtration. A Shimadzu FT-IR 8300 spectrometer was used to record IR spectra in KBr, Bruker Advance II equipment at Varian 400 MHz were used to record 1H NMR and 13C NMR spectra using DMSO-d6 as a medium, mass spectrum was recorded using HPLC, PDA, and MS.

2.1 Synthesis of Mannich base ligand L

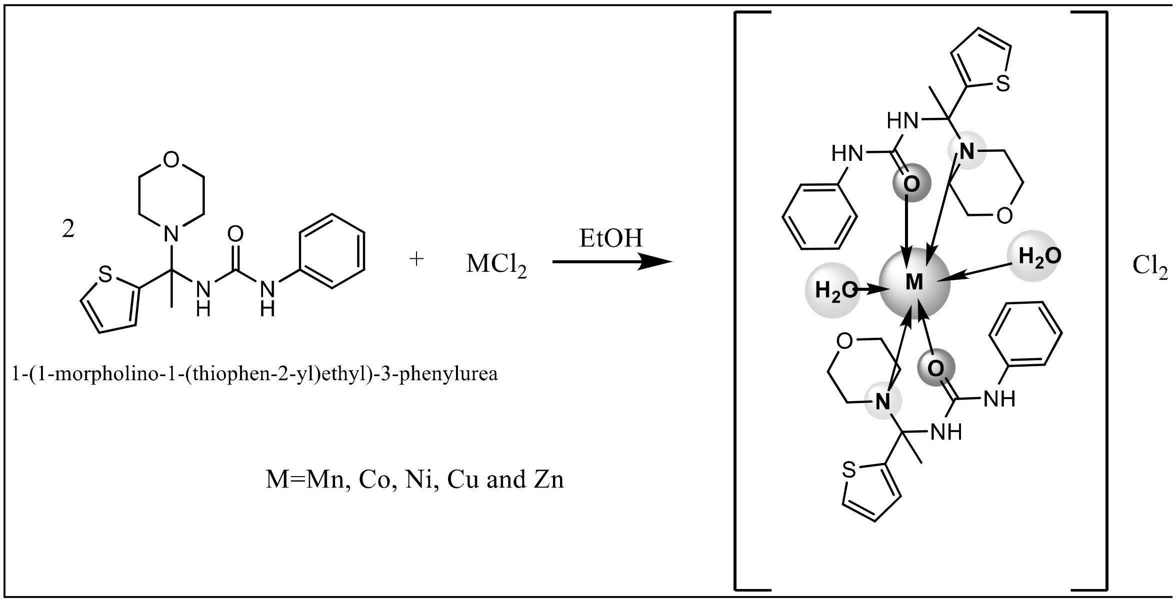
In a 1:1:1 mixture, 2-acetylthiophene, morphine, and phenyl urea were administered. 10 mL of EtOH and 1.3 mL of 2-acetylthiophene were introduced to a flask with a round bottom. 1 mL of morpholine in ethanol was added to this solution, and the combination was thoroughly stirred for 15 minutes while being stirred on a magnetic stirrer. Pellets of NaOH were added to the fluid to make it alkaline. Ethanolic solution of 1.4 g of phenyl urea was added to this mixture and stirred well on a magnetic stirrer. For about 8 hours, stirring was carried out in an ice-cold environment. The resulting substance was filtered, cleaned, and recrystallized with ethanol (Scheme-1).



Scheme-1. Synthesis of Mannich base ligand L

2.2 Synthesis of some first transition bivalent metal complexes of 1-(1-morpholino-1-(thiophen-2-yl) ethyl)-3-phenylurea

A round-bottomed beaker was filled with a mixture of 0.1M methanolic solution of bivalent metal chlorides (MCl2; M=Co2+, Mn2+, Ni2+, Cu2+, and Zn2+) and 0.2M 1-(1-morpholino-1-(thiophen-2-yl)ethyl)-3)-phenylurea in ethanol. For an hour, the mixture was vigorously stirred using a magnetic stirrer (Scheme-2). Filtered, distilled water was used to wash the complex, and pure alcohol was used to crystallise it.



Scheme-2. Synthesis of metal complexes

2.3 In vitro studies

Antioxidant and anti-inflammatory activities were carried out, since the aminoalkyl chain has been a key feature of numerous drugs.

2.3.1 Antioxidant activity

Free radicals, which are created during metabolism as a result of oxidation, play a significant part in food spoilage, chemical degradation, and the development of more than 100 human diseases that are typically treated with antioxidants. By using the Brand-Williams method's DPPH free radical test, the effectiveness of antioxidant activity was evaluated [1].

2.3.2 Anti-inflammatory Activity

It was done to test how well it could prevent protein denaturation. Numerous Mannich bases, which are known for having an aminoalkyl chain, are used in medicine today. The absorbances of BAS solution at various concentrations were measured using a UV-Vis spectrophotometer with a 660 nm wavelength [1].

3. Data, Value and Validation

3.1 Elemental Analysis

The synthesized compound and its complexes molecular formulae, colour, yield, molecular mass, elemental analysis data and conductance were examined and presented in Table 1. All of the bivalent metal complexes had a 1:2 (metal: Ligand) stoichiometry, according to the findings of the CHNO elemental analysis. Evidence that metal complexes are electrolytic can be found in the high molar conductance of the chelates in DMF [24–27].

3.2 FT-IR spectra

Table 2 summarizes the FT-IR results for the compound and its complexes (Fig. 1a – 1f). In the region of 3322-2924 cm^{-1}, the vC-H vibrations of the aromatic and aliphatic compounds are present. The bands seen at 1655 cm^{-1} and 1258 cm^{-1}, respectively, have verified the existence of C=O and C-N-C. The ligand's C=O was discovered to be displaced by 62 cm-1 in bivalent metal complexes, representing that the metal ion and the carbonyl group oxygen atom were coordinated. In the spectra of the complexes, the CNC of morpholine is reduced by 132 cm^{-1}, demonstrating that the coordination is carried out through the morpholine moiety's N-atom. Additional proof that the M-O and M-N bond in bivalent metal complexes, formed may be found in the presence of medium-intensity bands that were observed in the vicinity of 581 and 550 cm^{-1} for all of the complexes respectively [28–30].

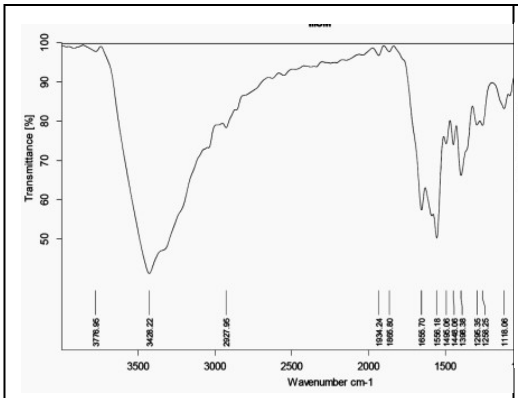
Molecular formula	Color	Yield %	Mol mass	Elemental analysis %				Conductance ($\Omega^{-1}cm^2mol^{-1}$in 10^{-3})
				C	H	N	O	
$C_{17}H_{21}O_2SN_3$	Pale Yellow	96	331	61.6	6.3	12.6	9.6	--
$[C_{34}H_{46}O_6S_2N_6Mn]Cl_2$	Deep brown	94	792	51.5	5.8	10.5	12.1	198
$[C_{34}H_{46}O_6S_2N_6Co]Cl_2$	Pale pink	95	796	51.2	5.7	10.55	12.06	184
$[C_{34}H_{46}O_6S_2N_6Ni]Cl_2$	Pale green	92	796	51.2	5.7	10.55	12.06	182
$[C_{34}H_{46}O_6S_2N_6Cu]Cl_2$	Black	93	801	50.9	5.7	10.4	11.9	166
$[C_{34}H_{46}O_6S_2N_6Zn]Cl_2$	Yellow	90	802	50.8	5.7	10.47	11.9	164

Table 1 – Elemental Analysis

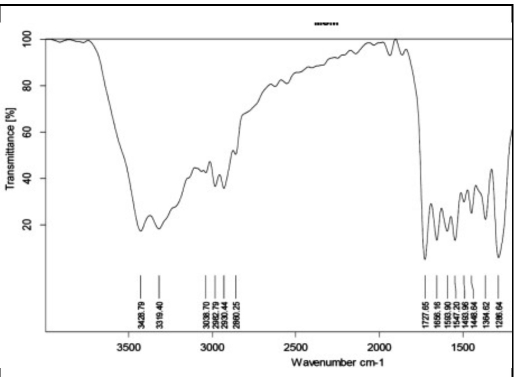
Table – 2. FT-IR bands of synthesized Ligand C17H21O2SN3 and its bivalent metal complexes

Ligand/Complexes	Assignment and frequencies						
	υNH	-*C-H	υC-H	υC=O	υC-N-C	υC-O-C	υC-S
C17H21O2SN3	3428	3040	2927	1655	1258	1118	752
[C34H46O6S2N6 Mn]Cl2	3428	3319	2930	1593	1126	1074	749
[C34H46O6S2N6 Co]Cl2	3427	3318	2929	1598	1126	1074	749
[C34H46O6S2N6 Ni]Cl2	3424	3322	2928	1592	1127	1076	751
[C34H46O6S2N6 Cu]Cl2	3426	3320	2927	1596	1125	1075	748
[C34H46O6S2N6 Zn]Cl2	3426	3320	2983	1596	1127	1075	751

*Aromatic



1a



1b

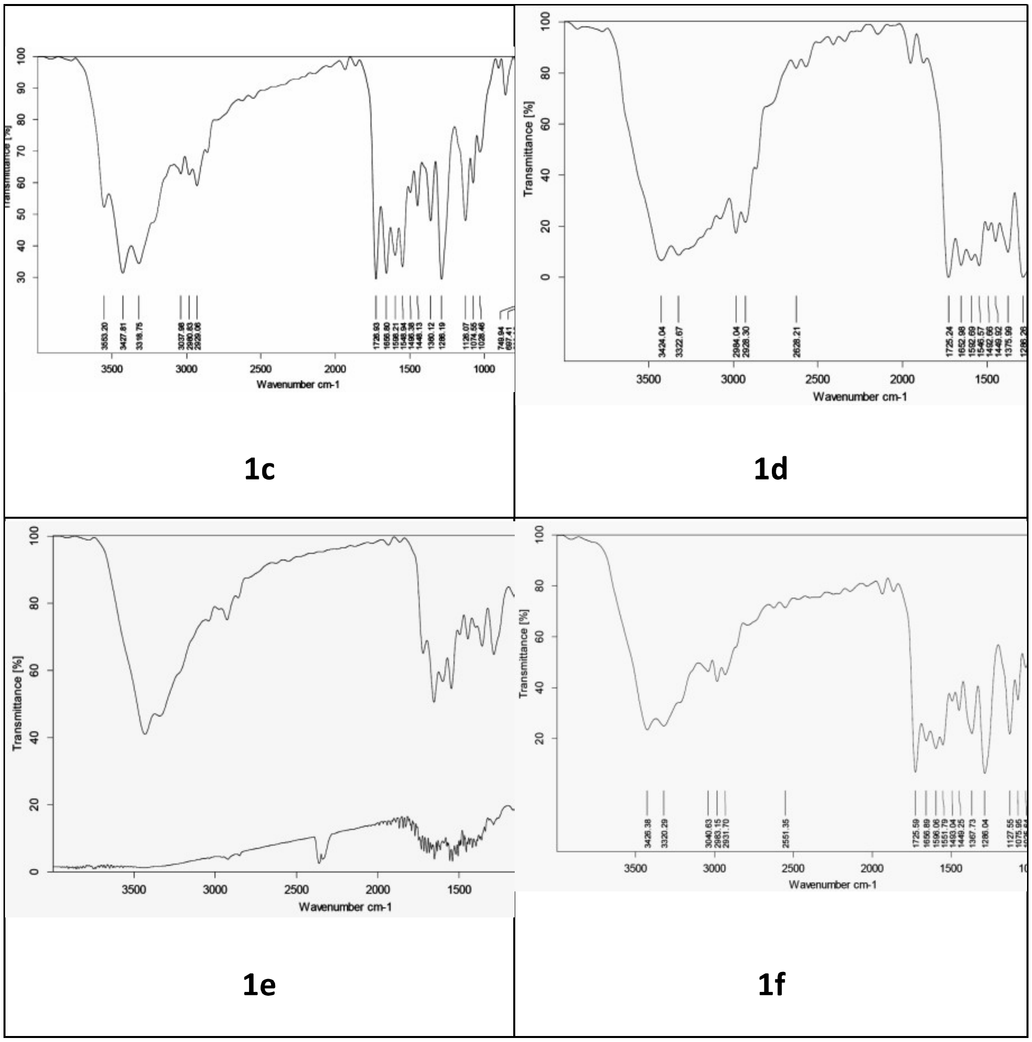


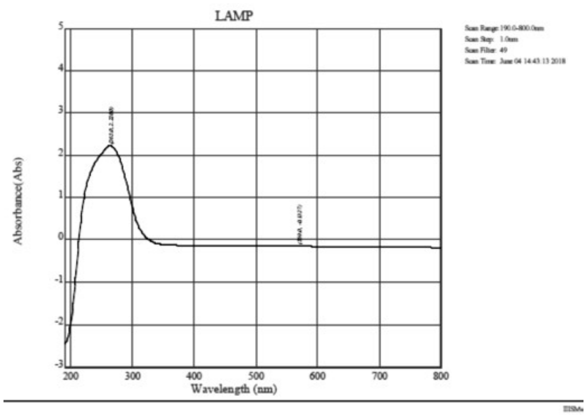
Figure-1. FT-IR spectrum of (1a) Ligand, (1b) [MnL2]Cl2, (1c) [CoL2]Cl2, (1d) [NiL2]Cl2, (1e) [CuL2]Cl2, (1f) [ZnL2]Cl2

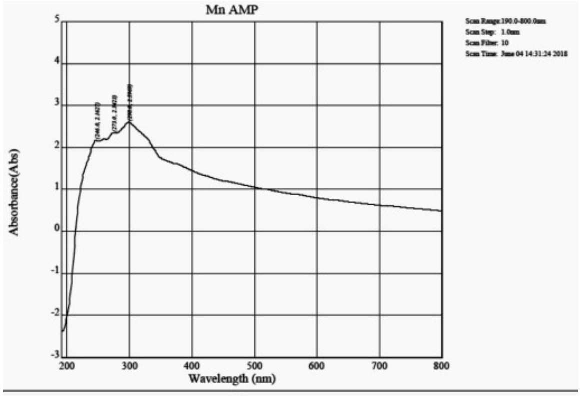
3.3 Electronic spectra

The readings of the UV-visible spectra (Figures 2a–2f) supported the interpretation of FT-IR. Complexes' electronic absorption bands were captured using DMSO as a solvent at room temperature. It was detected between 250 and 900 nm wavelengths. Table 3 provides an overview of the degree of absorption and the associated electronic changes [31–34].

Table-3. UV-Visible Spectral data of complexes

Compounds	nm	Transition	Magnetic moment (BM)
Ligand	263	π →π*	-
	569	n →π*	
$[MnL_2]Cl_2$	246	π →π*	5.82
	568	n →π*	
$[CoL_2]Cl_2$	245	π →π*	3.84
	570	n →π*	
$[NiL_2]Cl_2$	245	π →π*	2.86
	577	n →π*	
$[CuL_2]Cl_2$	246	π →π*	2.74
	542	n →π*	
$[ZnL_2]Cl_2$	249	π →π*	-
	572	n →π*	





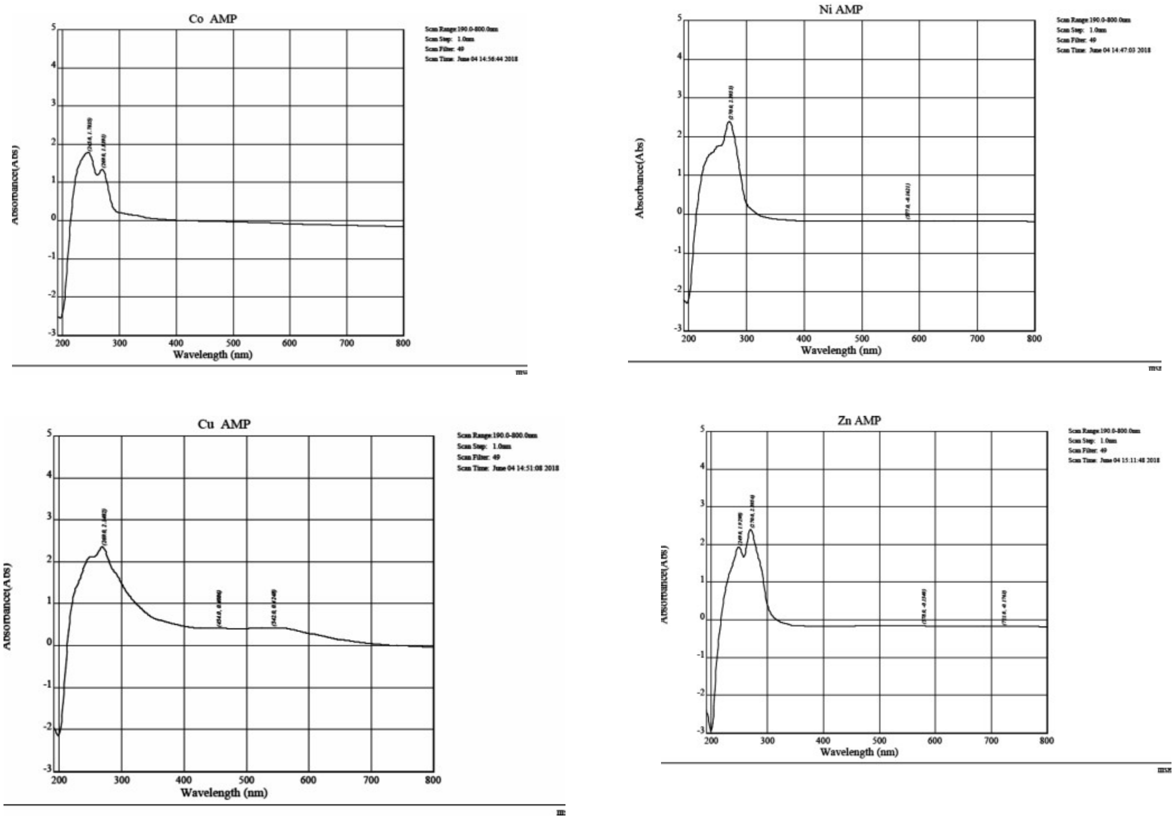


Figure 2. UV Spectrum of (1a) Ligand, (1b) [MnL2]Cl2, (1c) [CoL2]Cl2, (1d) [NiL2]Cl2, (1e) [CuL2]Cl2, (1f) [ZnL2]Cl2

3.4 1H NMR spectrum

1H NMR spectrum of the Mannich base ligand is shown in Figure-3. The multiplets appeared in the range of 7.22 ppm to 7.421 ppm attributed to the aromatic protons of the phenyl ring. The shift observed at 8.7 ppm, indicated the -NH proton attached to phenyl ring. The -NH proton was found at 6.86 ppm. The five-membered ring protons were observed at 6.88 ppm, 6.89 ppm and 7.20 ppm. Methylene protons from the morpholine moiety ($-CH_2-O-CH_2-$ and $-CH_2-N-CH_2-$) are responsible for the triplet peaks seen at 3.43 and 2.50 ppm. The singlet found at 1.73 ppm was assigned to methyl protons.

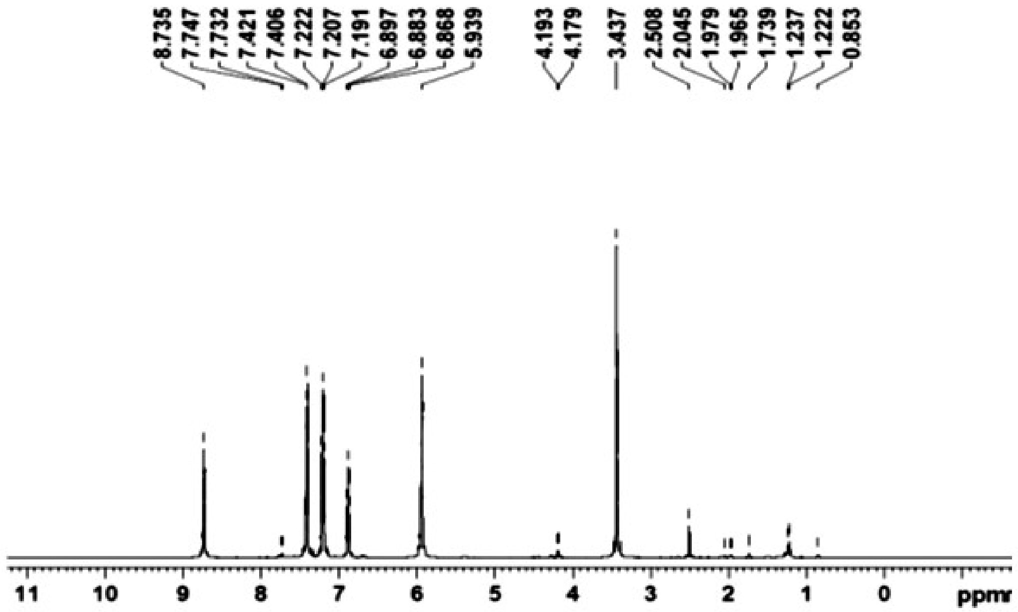


Figure-3. 1H NMR spectrum of Ligand

3.5 13C NMR spectrum

The 13C NMR spectrum of the synthesized Mannich base ligand is shown in Figure-4. 13C NMR spectrum advocated the presence of 17 carbons in its skeleton. The peaks observed at 121.45 ppm, 129.02 ppm, 129.50 ppm and 133.99 ppm are assigned to the aromatic carbons of phenylurea. The carbonyl carbon was responded at 156.62 ppm. The carbons of thiophene ring were found at 126.88 ppm, 128.21 ppm and 141.10 ppm. The methylene carbons of the morpholine moiety (CH2-N-CH2 and CH2-O-CH2 are responsible for the peaks at 49.61 ppm and 66.81 ppm, respectively. There were aliphatic carbons present, as evidenced by the chemical change at 93.3 ppm and 27.5 ppm.

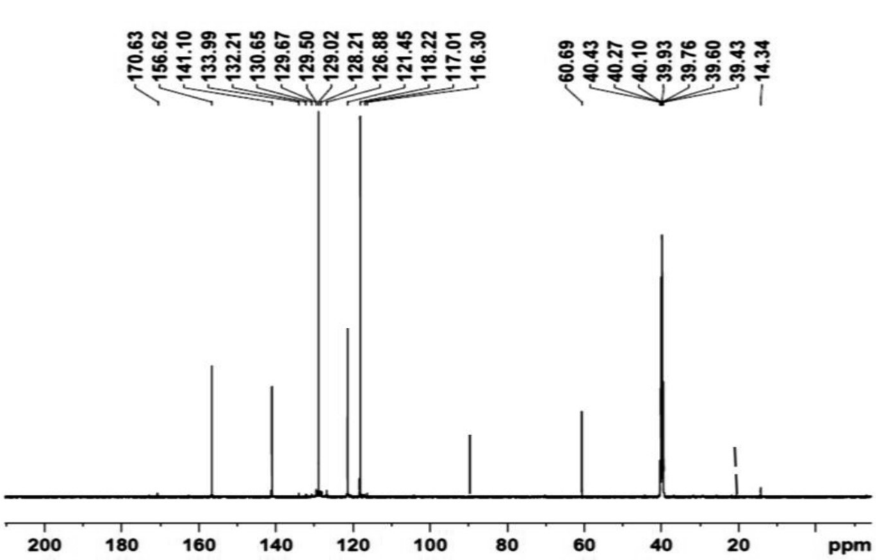


Figure-4. 13C NMR spectrum of Ligand

3.6 Mass spectrum (LC-MS)

Figure 5 displays the ligand's mass spectrum. The molecular weight was verified by the molecular ion peak at m/z=330. The final fragment left over after the elimination of the thiophene and phenyl urea units is what causes the signal at m/z=100 (Scheme 3).

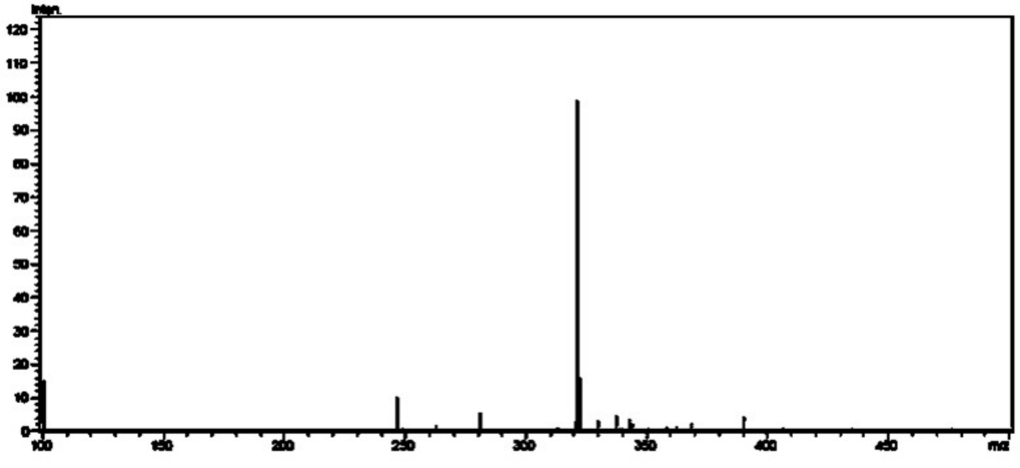
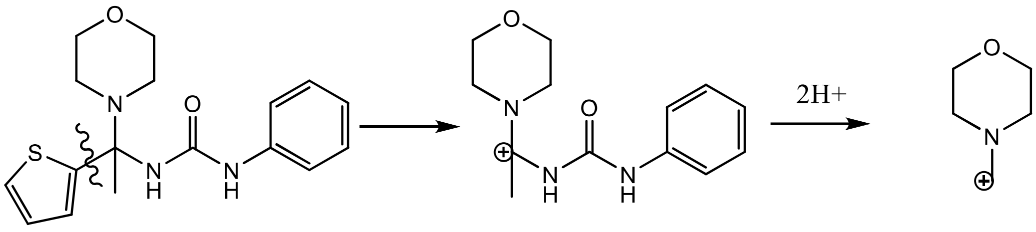


Figure-5. Mass spectrum of Ligand



Scheme 3. The fragmentation scheme proposed for Ligand

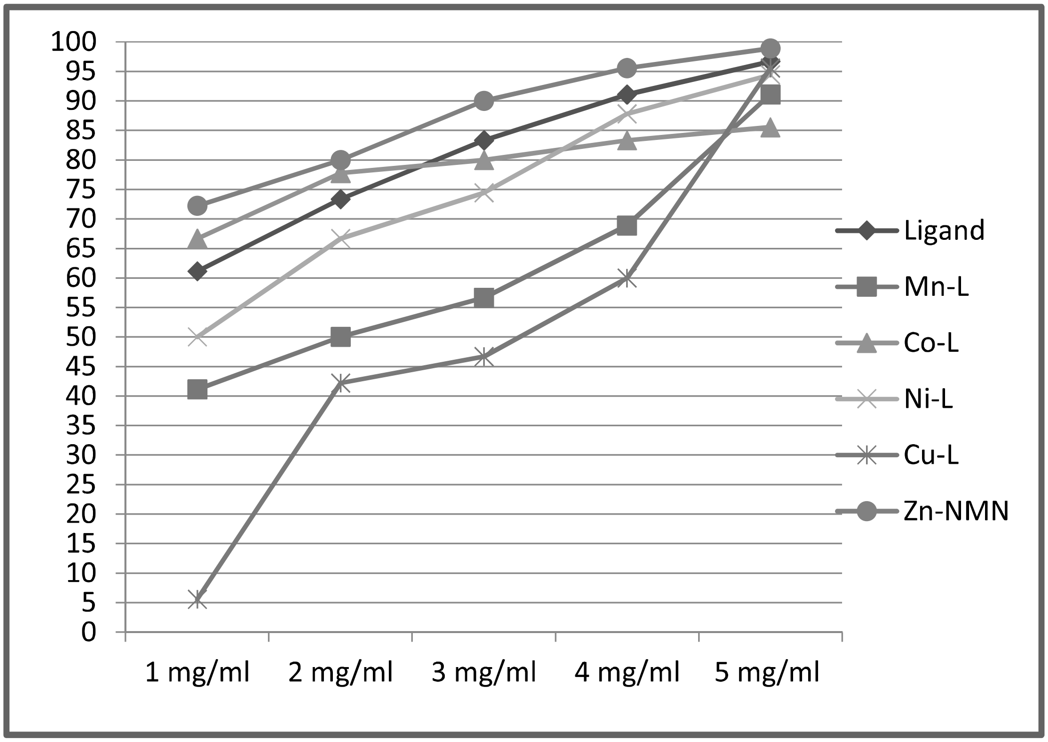
3.8 Antioxidant activity

The Table 4 illustrations the summarized data of the effect of Mannich base ligand and its metal (II) complexes at different concentration in DPPH [1]. Increased effectiveness with respect to concentration was recorded, Figure 5a – 5f. In the concentration of 5 mg/mL, the highest DPPH scavenging activity was perceived in the $[ZnL_2]Cl_2$ (98.89 %) followed by Mannich base Ligand (96.67 %), $[CuL_2]Cl_2$ (95.56 %), $[NiL_2]Cl_2$ (94.44 %), $[MnL_2]Cl_2$ (91.11 %) and $[CoL_2]Cl_2$ (85.56 %). The effectiveness was arranged in an order as, $[ZnL_2]Cl_2 > L > [CuL_2]Cl_2 > [NiL_2]Cl_2 > [MnL_2]Cl_2 > [CoL_2]Cl_2$ (Graph 1). The heteroatoms combined with an amide group of phenyl urea moiety might also proliferate antioxidant activity of the synthesized Mannich base ligand (L) and its metal (II) complexes [35].

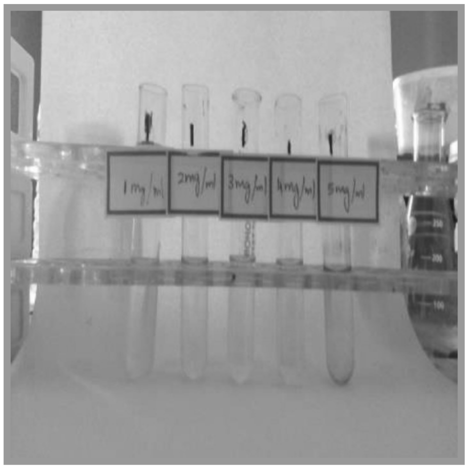
Table-4. Antioxidant activity of Mannich Base Ligand and its Metal (II) complexes

Compound(s)	Concentration (mg/mL)	% of Inhibition (%)	EC_{50} (mg/mL)
Ligand	1	61.11	<1
	2	73.33	
	3	83.33	
	4	91.11	
	5	96.67	
$[MnL_2]Cl_2$	1	41.11	2
	2	50.00	
	3	56.67	
	4	68.89	

Compound(s)	Concentration (mg/mL)	% of Inhibition (%)	EC_{50} (mg/mL)
	5	91.11	
$[CoL_2]Cl_2$	1	66.67	<1
	2	77.78	
	3	80.00	
	4	83.33	
	5	85.56	
$[NiL_2]Cl_2$	1	50.00	1
	2	66.67	
	3	74.44	
	4	87.78	
	5	94.44	
$[CuL_2]Cl_2$	1	5.56	2.99
	2	42.22	
	3	46.67	
	4	60.00	
	5	95.56	
$[ZnL_2]Cl_2$	1	72.22	<1
	2	80.00	
	3	90.00	
	4	95.56	
	5	98.89	



Graph – 1. Antioxidant activity of Ligand and its bivalent metal complexes



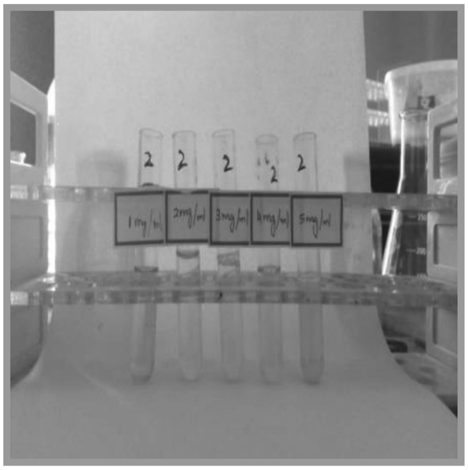


Fig 5a DPPH activity of Ligand

Fig 5b DPPH activity of $[MnL_2]Cl_2$

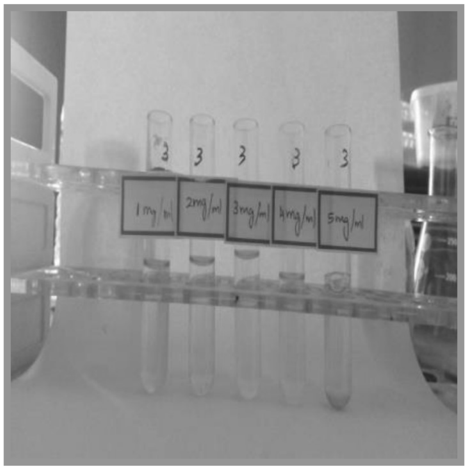


Fig 5c DPPH activity of $[CoL_2]Cl_2$

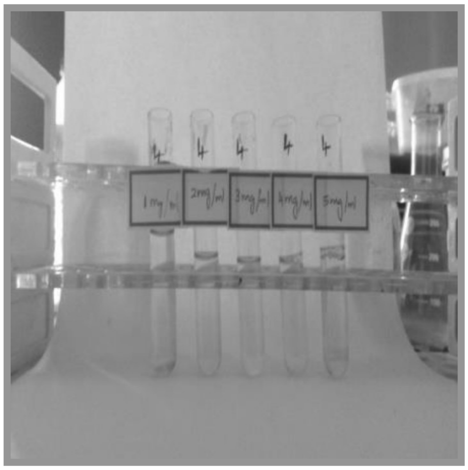


Fig 5d DPPH activity of $[NiL_2]Cl_2$

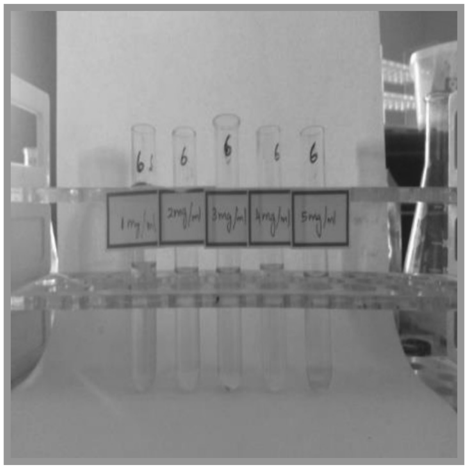


Fig 5e DPPH activity of $[CuL_2]Cl_2$

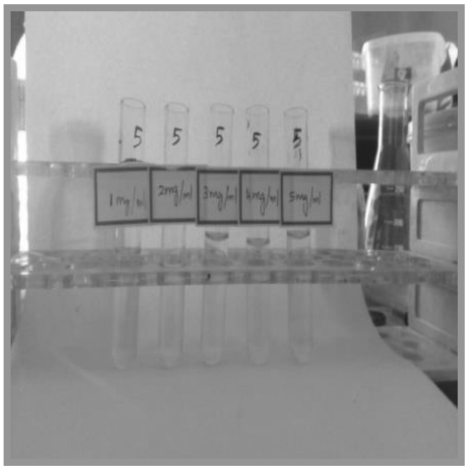


Fig 5f DPPH activity of $[ZnL_2]Cl_2$

3.9 Anti-inflammatory Activity

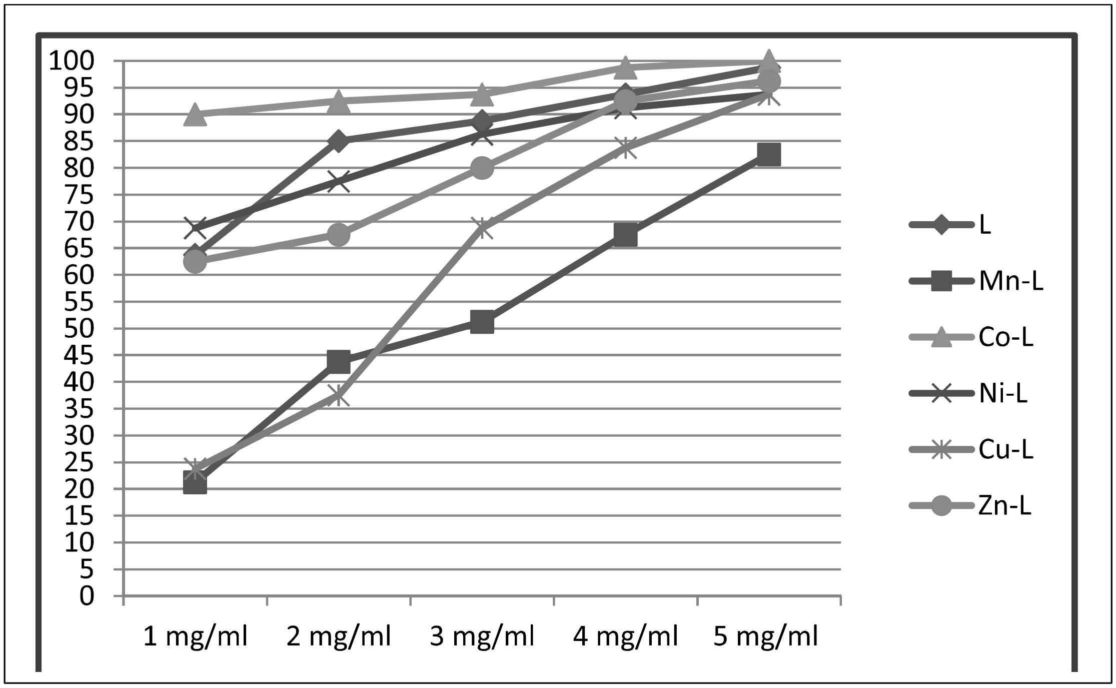
The effectiveness of anti-inflammatory activity of ligand and its complexes were recorded [1], Figure 6a – 6e. Table-5 shows the summarized data of anti-inflammatory activity at a range of concentration. The interpretation shows that the concentration influences in effectiveness, Graph 2, and form an order as; $[CoL_2]Cl_2$> L > $[ZnL_2]Cl_2$ > $[NiL_2]Cl_2$ > $[CuL_2]Cl_2$ >$[MnL_2]Cl_2$.

$[NiL_2]Cl_2$						
$[CuL_2]Cl_2$						

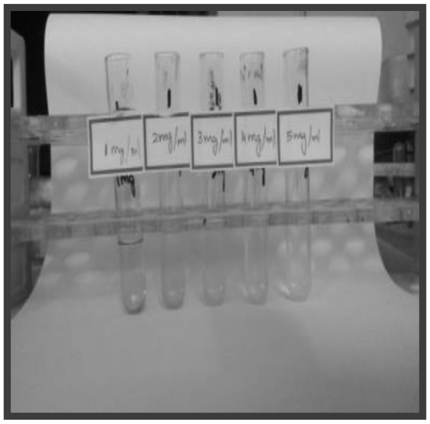
Table – 5. Anti-inflammatory activity of Ligand and its metal (II) complexes

Compound(s)	Concentration (mg/mL)	% of Inhibition (%)	EC_{50} (mg/mL)
Ligand	1	63.75	<1
	2	85.00	
	3	88.75	
	4	93.75	
	5	98.75	
$[MnL_2]Cl_2$	1	21.25	2.78
	2	43.75	
	3	51.25	
	4	67.50	
	5	82.50	
$[CoL_2]Cl_2$	1	90.00	<1
	2	92.50	
	3	93.75	
	4	98.75	
	5	100	
$[NiL_2]Cl_2$	1	68.75	<1
	2	77.50	
	3	86.25	
	4	91.25	
	5	93.75	
$[CuL_2]Cl_2$	1	23.75	2.98
	2	37.50	
	3	68.75	
	4	83.75	

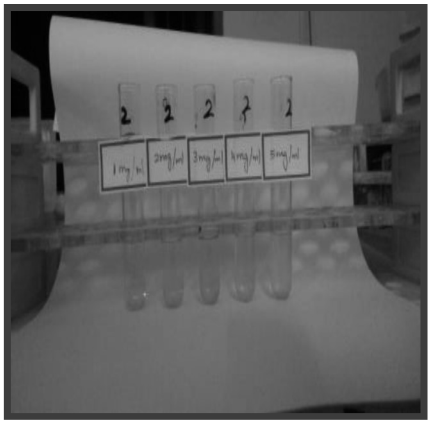
Compound(s)	Concentration (mg/mL)	% of Inhibition (%)	EC_{50} (mg/mL)
	5	93.75	
$[ZnL_2]Cl_2$	1	62.50	<1
	2	67.50	
	3	80.00	
	4	92.50	
	5	96.25	



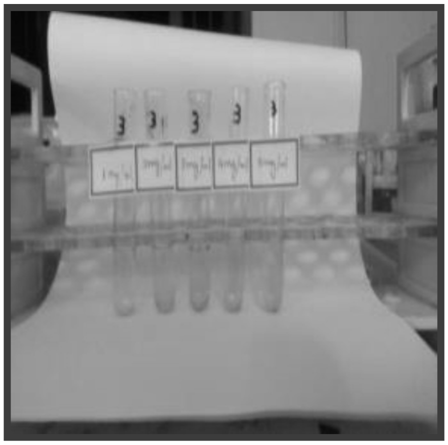
Graph-2. Anti-inflammatoty activity of Ligand and its bivalent metal complexes



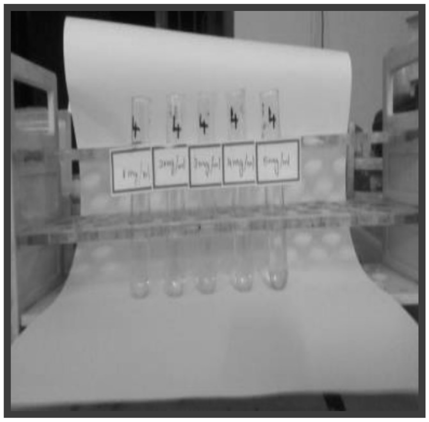
Anti-inflammatory -L



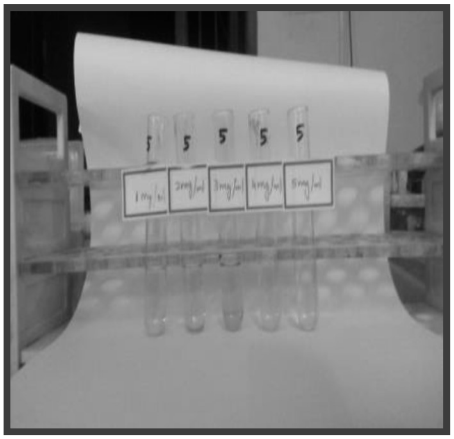
Anti-inflammatory -[MnL_2]Cl_2



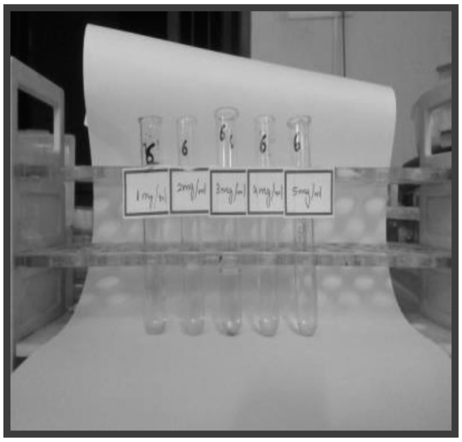
Anti-inflammatory - [CoL_2]Cl_2



Anti-inflammatory
[NiL_2]Cl_2



Anti-inflammatory [CuL_2]Cl_2



Anti-inflammatory [ZnL_2]Cl_2

4. Conclusions

The synthesized ligand and its complexes have been elucidated structurally. The analytical data advocated the structural framework which is a key factor for complexation and bioactivity. The biology of these compounds proved their excellency on antioxidant and anti-inflammatory activities. The outcome of this investigation could be a source for commercial attention to both pharmaceutical concerns and research organizations for exploring new drugs.

Acknowledgements

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