Synthesis and characterization studies of 5-chloro 2-furaldehyde thiosemicarbazone and its Ni, Cu and Zn complex

Abstract

The synthesisand characterization of Ni(II), Cu(II)and Zn(II) complexes of 5-chloro 2-furaldehyde thiosemicarbazone were studied. Elemental analysis, and spectral (IR, UV, Mass and ^{1}H NMR) measurements were used to characterize the ligand and its metal complexes, the results obtained showed that the ligand and its Ni(II), Cu(II), Zn(II) and Co(II) complexes of 5-chloro 2-furaldehyde thiosemicarbazone were prepared successfully.

Keywords: Synthesis and characterization, thiosemicarbazone, Ni complex, Cu and zinic complex, 5-chlolro 2-furaldehyde

1. Introduction

The drugs used in human medicine cover the whole range of chemical structure types, but a majority are heterocyclic small molecules or have heterocyclic structural components [1]. Heterocyclic thiosemicarbazone, their derivatives as well as their complexes with transition metal has been one of the most class of compounds received extensive studies during the recent years, owing to the variety of whys, such as present of several donor sites, variable bonding properties, structural diversity and pharmacological aspects [2].They present a variety of biological activities, including anticancer and anti-inflammatory activities [3-5]. Heterocyclic thiosemicarbazone showed higher activity compared with aromatic thiosemicarbazones[6]. Thiosemicarbazone even increase their antitumour activity by their ability to form chelates with specific metal ions[7]. It was reported that the anticancer activities of thiosemicarbazones were closely related to the parent aldehyde or ketone group, metal chelation ability and terminal amino substitution. Among them, the parent aldehyde or ketone group was considered critical for the anticancer activity of thiosemicarbazones. The activity of these compounds is dependent on the nature of the hetroaromatic ring and the position of attachment of the ring as well as on the form of the thiosemicarbazone moiety[8]. There were several studies involving thiosemicarbazones with different metal ions[9-12]. However, only a few reports described studies on substituted thiosemicarbazone complexes were found. Hence as part of ongoing research regarding thiosemicarbazone complexes, the synthesisand characterization of 2-furaldehyde thiosemicarbazone and its Ni, Cu and Zn complexes are reported herein the present paper.

Comment [BN1]:

1.***The study done by the authors are innovative and not reported this kind. Recommended to include the literature comparison in the introduction part previously studied molecules with these metal complexes.***

2. May be, the title is suitable. Refer the points 5.1 and 5.2.

3. The abstract should be re-written with objective, methods, results and its conclusion.

4. Yes, it is appropriate. Check the accuracy of the numbering for the sections.

5.1. Yes, it is. Recommended to include the justification of characterization with respect to their mass spectra which will give huge impact to the result outputs. If not provided, change the title as follows.

"Synthesis and characterization studies of 5-chloro 2-furaldehyde thiosemicarbazone and its Ni, Cu and Zn complex by Elemental analysis and IR Spectroscopy"

5.2. Importantly, the theoretical CHNS values to be calculated with respect to their water content of the complexes. The reason is that the difference between theoretical and experimental values should be not more than 0.4. But most of the values are exceeding 0.4. So, kindly look into it carefully and include accordingly. If not provided the justification, change the title as follows.

"Synthesis and characterization studies of 5-chloro 2-furaldehyde thiosemicarbazone and its Ni, Cu and Zn complex by IR Spectroscopy"

5.3. Limitation of this study to be provided in the conclusion part for further research.

6. Yes.

7. Figures of IR spectra to be captured for each complex.

8. References, Punctuations and formatting to be done as per the journal guidelines.

Comment [BN2]: The abstract should consists of objective (O), methods (M), results (R), and conclusion (C) in brief manner. Recommended to re-write the abstract with diligent manner by considering the above mentioned OMRC.

Comment [BN3]: To be corrected as "Zinc"

Comment [BN4]: To be mentioned as "5-chloro-2-furaldehyde thiosemicarbozone"

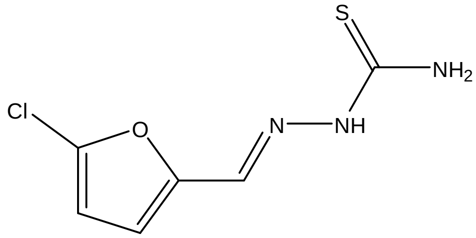


Fig (1): The structure of 5-Chloro-2-furaldehyde thiosemicarbazone((E)-2-(5-chlorofuran-2-yl)methylene)hydrazine-1-carbothioamide)

Comment [BN5]: Include "or" after thiosemicarbozone

2. Material and Methods

2.1. Materials

All the reagents used in this study were chemically pure. The solvents were used as received. $CuCl_2.2H_2O$, $NiCl_2$, $ZnCl_2$, Thiosemicarbazide 98% were purchased from Sigma-Aldrich. 5-Chloro-2-furaldehyde were purchased from (Merck) and used as received.

Comment [BN6]: Name of the solvents used, grade and its manufacturer name to be included

2.2Preparation of the ligand 5-Chloro-2-furaldehyde thiosemicarbazone (HL^2)

A solution of thiosemicarbazide (0.182 g, 0.002 mmol) in 40 mL of dry methanol was prepared with stirring and warming (about 40 ^{0}C) during 1 h. To the warm thiosemicarbazide solution, 5-Chloro-2-furaldehyde (0.26 g, 0.002 mmol) in 10 mL of dry methanol was added followed by a 12 h reflux. The mixture was then slowly cooled down to room temperature until needle crystals were obtained.

Comment [BN7]: Recommended to mention as "ambient temperature"

2.3. General procedure for the preparation of the metal complexes (1–4).

Complexes 1–4 were prepared by direct reaction between theligand and the corresponding metal salts.

Comment [BN8]: Explain or Provide the name of the Complexes 1 - 4 in this place, not referred in the following sections.

2.3.1 Synthesis of [Ni (C_6 H_6 ClN_3 SO)$_2$]

The hexahydrated nickel chloride, $NiCl_2.6H_2O$ (0.0005 mmol, 119 g), was dissolved in 30ml distilled water. An ethanolic solution of 5-Chloro-2-furaldehyde thiosemicarbazone (0.204g, 0.001 mmol) in 10ml was added slowly while stirring. The mixture was refluxed for 3 h. After cooling at room temperature, pale brownprecipitate appeared. It was filtered, washed with small amounts of absolute ethanol and finally dried in vacuum over silicagel. All the compounds were washed and dried in the same way.

Comment [BN9]: Recommended to mention the name of the solvent

Comment [BN10]: Recommended to mention as "ambient temperature"

2.3.2 Synthesis of [Zn (C_6 H_6 ClN_3 SO)$_2$]

0.136g, 0.001mol $ZnCl_2$was dissolved in 20 ml warm absolute ethanol with stirring. To a solution containing 0.429g, 0.002 mol 5-Chloro-2-furaldehyde thiosemicarbazonedissolved in

Comment [BN11]: How this solution is prepared?

20 ml of absolute ethanol NaOH (1M) was added drop wise. The mixture was reflexed for two hours. The separated dark black to brown powder was filtered washed with ethanol and dried in air.

2.3.3 Synthesis of [Cu (C_6 H_6 ClN_3 SO)$_2$]

A quantity of 5-Chloro-2-furaldehyde thiosemicarbazone (0.408g, 0.002 mol) was dissolved in 10 mL ethanol and was added to a solution of (0.134 g 0.001mol) of the metal salts $CuCl_2.2H_2O$ in 10 mL ethanol. Although the complex appeared instantaneously the reflex was maintained for one hour. After recrystallization in ethanol a dark green micro crystalline product was obtained.

Comment [BN12]: How this solution is prepared?

2.3.4 Synthesis of [Cu (C_6 H_6 ClN_3 SO)]

A quantity of 5-Chloro-2-furaldehyde thiosemicarbazone (0.204g, 0.001 mol) was dissolved in 10 mL ethanol andwas added to a solution of (0.134 g 0.001mol) of the metal salts $CuCl_2.2H_2O$ in 10 mL ethanol. Although the complex appeared instantaneously the reflex was maintained for one hour. After recrystallization in ethanol a dark green micro crystalline product was obtained.

Comment [BN13]: How this solution is prepared?

2.4Physical measurements

- **Elemental analyses** for (C, H, N and S) were performed using a Heraeus Carlo Erba 1108 elemental analyzer.

-**Melting points** were determined with a digital melting point apparatus using capillary technique.

-**Mass spectra** were recorded with a Micromass LCT electrospray (Qtof Micro YA263) mass spectrometer.

-**NMR spectra** were recorded in DMSO-d6 solution on a Bruker Avance DPX 300 NMR spectrometer.

Comment [BN14]: "Subscript"

-**IR spectra** were obtained on a Perkin Elmer Spectrum Two IR spectrometer with samples prepared as KBr pellets.

3. Results and discussion

3.1. Synthesis and Physical Properties of the Complexes

Firstly the ligands5-Chloro-2-furaldehyde thiosemicarbazone (HL^2) or (C_6 H_6 ClN_3 SO) was prepared form the reaction between 5-Chloro-2-fuaraldehyde and thiosemicarbazide in alcoholic medium, brown ppt was obtained, the melting point of (HL2)= 152^0C. The elemental analytical calculation for the ligand was found C, 34.98, H, 3.46; N, 23.22 ;S, 17.6%, it’s quite agreed with literature.

Comment [BN15]: "Superscript"

After thatthe preparative reactions for the complexes can be represented by the following equations:

1- $NiCl_2.6H_2O + C_6 H_6 ClN_3 SO \xrightarrow{EtOH} [Ni (C_6 H_6 ClN_3 SO)_2]$

2- $ZnCl_2 + C_6 H_6 ClN_3 SO \xrightarrow{EtOH/NaOH} [Zn(C_6 H_6 ClN_3 SO)_2]$

3- $CuCl_2.2H_2O + C_6 H_6 ClN_3 SO \xrightarrow{EtOH} [Cu(C_6 H_6 ClN_3 SO)_2]$

4- $CuCl_2.2H_2O + C_6 H_6 ClN_3 SO \xrightarrow{EtOH} [Cu(C_6 H_6 ClN_3 SO)]$

Note that all these reaction needed areflux for certain time as metioned in the above procedures(2.3.1-2.3.4).

All the complexes are microcrystalline or amorphous powder, stable in the normal laboratory atmosphere, and slightly soluble in common organic solvent but completely soluble in DMF and DMSO.

The results of elemental analysis of the ligand 5-Chloro-2-furaldehyde thiosemicarbazone (HL^2) alone and its Ni, Cu and Zn complexes were shown in table(1) below.All the analytical data are in good agreement with the empirical formulas as given in Table(1).

Table (1) Analytical data

Compound	Elemental analysis found (Cal) C (%)	H (%)	N (%)	S (%)
5ClFTSC	34.98(35.38)	3.46(2.94)	23.22(20.63)	17.6(15.72)
$[Ni (C_6 H_6 ClN_3 SO)_2]$	31.35(30.92)	2.82(2.57)	14.61(18.06)	6.54(13.76)
$[Cu (C_6 H_6 ClN_3 SO)]$	24.11 (23.08)	2.38 (1.77)	15.25 (12.42)	9.79 (9.46)
$[Cu(C_6 H_6 ClN_3 SO)_2]$	27.43(26.6)	2.70(2.59)	17.13(16.80)	12.30(12.8)
$[Zn(C_6 H_6 ClN_3 SO)_2]$	27.24(26.5)	3.38(3.55)	16.26(16.62)	7.86(8.16)

Comment [BN16]: The % difference between theoretical values of CHNS and experimentally obtained values of CHNS should be not more than 0.4.
It is recommended to calculate the theoretical CHNS values with respect to the water content of each complex and 5ClFTSC.
If not, these results are unacceptable.

3.2 Results of Spectroscopic study

As all thiosemicarbazones, can exhibit thione-thiol tautomerism, since it contains a thioamide –NH–C=S functional group[13]. There is no IR band at 2500–2600 cm^{-1} in the spectrum of the free ligand (5ClFTSC), and this indicates the absence of S–H grouping in the free ligand. However, there are bands in the regions of 855 and 3150 cm^{-1}, characteristic of v(C=S) and ν(N–H), respectively, indicating that the ligand remains as the thione tautomer. This is supported by the H^1 NMR spectrum which does not show any peak at 4 ppm attributable to the S–H proton, but it shows a singular peak at 11.45 ppm relative to the NH next to C=Sin ^1H NMR spectrum of (5ClFTSC), while the signal of the proton on C=N double bond appears at 7.50 ppm. It is interesting to note the presence of two broad singlets for the two NH2 protons, respectively at 7.84 and 8.22 ppm: it means that the free rotation around the C=N bond is blocked because of its partial double bond character.

.The bands appearing around 1345 and 785 cm^{-1} in the spectrum of the ligand are either weakened or shifted to higher wave numbers in all the complexes[14,15] and this shift can be assigned to ν(C=S) vibration. On the other hand, the bands in the region 3440–3270 cm^{-1} attributed to symmetrical and asymmetrical stretching mode ν (NHS) 2 in the spectra of the ligand, undergo appreciable change in the spectra of the complexes. This is due to the coordination of sulfur from the C=S (NH) group as reported earlier[16]. This coordination is confirmed by the presence of a new band at 405–449 cm^{-1}[17], which is assigned to ν(M–S) for all the complexes. In ligand spectra, the strong band observed at 1600 cm^{-1} is corresponds to n(C=N) vibration band[16]. This band shifts to a higher region [14,16] , in the spectra of Ni– nickel complexes and this indicates the coordination of nitrogen of the azomethine group in coordination[17]. In the spectra of complexesfor the ligand 5-Chloro-2-furaldehyde thiosemicarbazone the absorption band at 1465cm^{-1} is assigned to ν (NH2)sym.str.vib , the band at 1587 cm^{-1} is assigned to ν (C=N)sym.str.vib, the band at 838 cm^{-1} is assigned to ν (C=S)sym.str.vib , and the band at 3145cm^{-1} is assigned to ν (NH)sym.str.vib .

Comment [BN17]: Correct as " IR spectrum"

The Infra-red spectral data of the free ligand 5-Chloro-2-furaldehyde thiosemicarbazone (HL^2), shows strong absorption band at 1587 cm^{-1} due to the azomethine ν(C=N) group. This band is shifted to a higher frequency in the complex [Ni(C6H6N3SO)2] assigned at 1625 cm^{-1}. This indicates coordination of the azomethine nitrogen to the metal ion. The ν(C=S) band that appeared at 838 cm^{-1} in the free ligand is shifted to 835 cm^{-1} indicating coordination of the ligand with Ni(II) ion through the sulfur atom.In the complex of copper(II) with the ligand HL2, [Cu(C6H6N3SO)2 Cl2], the band at 1587 cm^{-1} assigned to ν (C=N) is shifted to 1612 cm^{-1}, indicating coordination of the ligand through the azomethine nitrogen. The band assigned to ν (C=S) is shifted from 838 cm^{-1} to 933 cm^{-1} indicating the involvement of sulfur atom in complexation.

Comment [BN18]: Molecular formula to be mentioned in the correct format throughout the article.

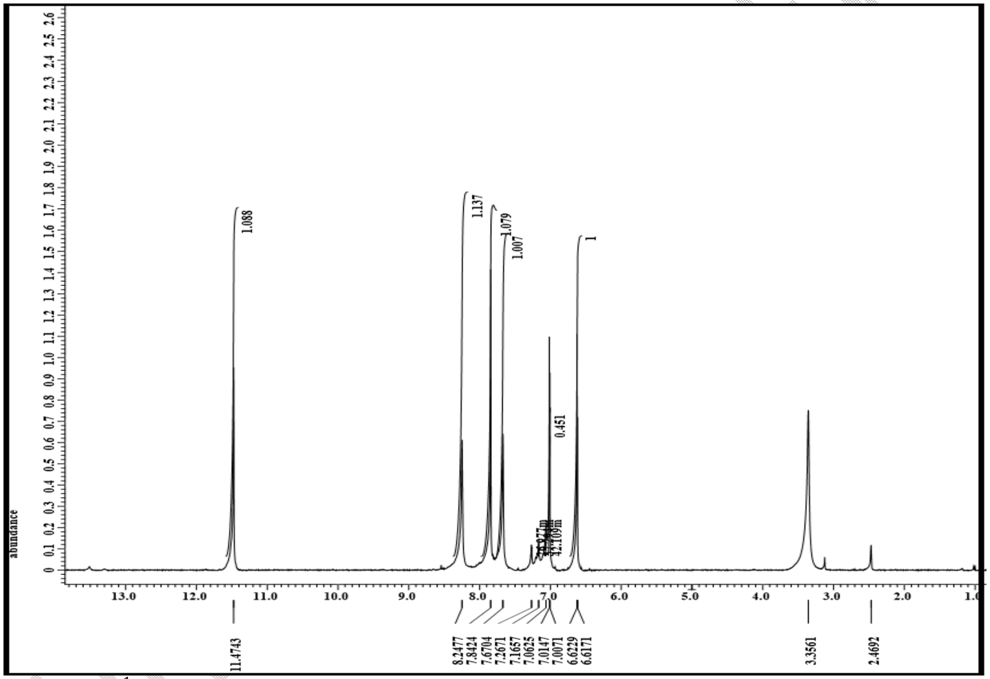
Comment [BN19]: Characterisation is explained with IR mainly, but it will also give huge impact with respect to mass spectrum of the complexes. So, mention the characterisation output based on the theoretical and experimental mass values in the context or in the table 2.
Good to see the mass spectra of the complexes, recommended to include one of the image with high resolution image.

The IR spectral data for the complex [Cu $(C_6H_6N_3SO)$ Cl_2] and [Zn$(C_6H_6N_3SO)_2$ Cl_2]and all the other prepared complexes were showed in table 2

Table (2) Main IR spectral vibrations(cm^{-1})

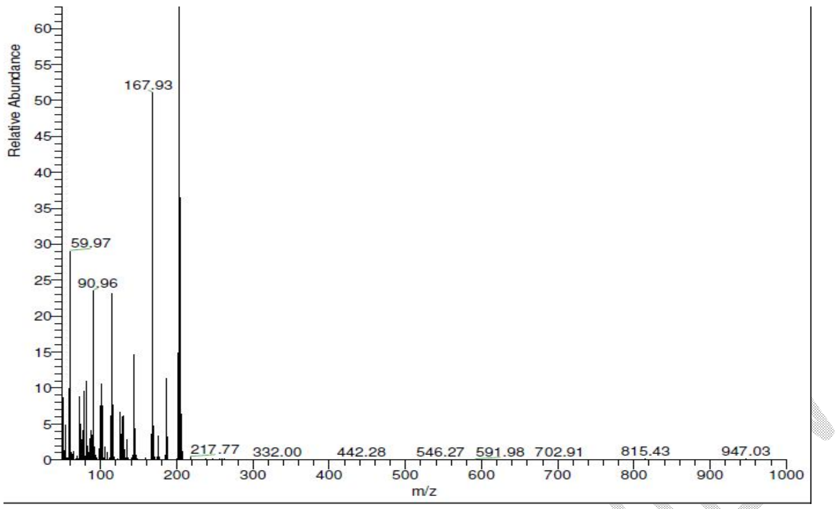
Compound	v(NH_2)	V(C=S)	V(C=N)	V(N-N)	Ring breath	V(C-O-C)	V(M-N)	V(M-S)
5ClFTSC	3145	725	1587	925	1020	1271	499	443
[Ni (C_6H_6 ClN_3 $SO)_2$]	3352	784	1673	927	1022	1271	491	435
[Cu (C_6H_6 ClN_3 SO)]	3379	779	1612	935	1014	1282	503	433
[Zn (C_6 H_6 ClN_3 SO)]	3473	786	1610	937	1016	1201	432	405
[Cu(C_6H_6 ClN_3 $SO)_2$]		783	1539	933	1014	1276	501	449

Comment [BN20]: No figures for IR spectrum. Please capture with the high resolution images.

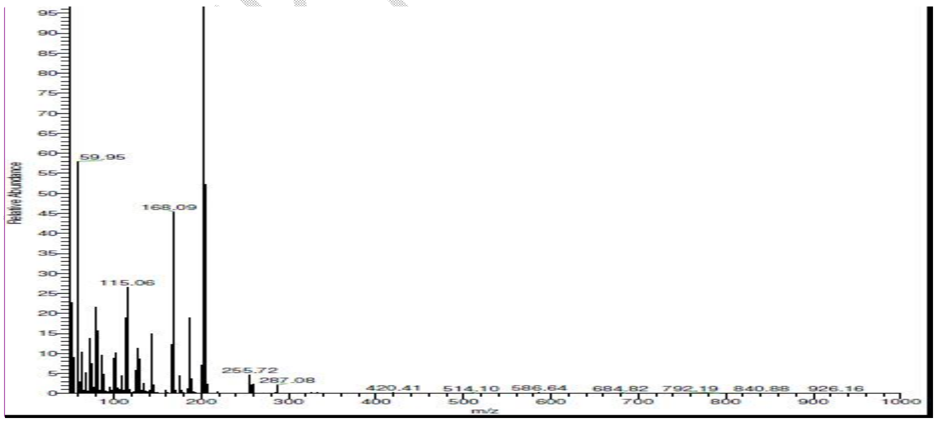


Fig(2) The ^{1}H NMR spectrum of (5ClFTSC)

Figs (3) to (7) showed the mass spectrum of the ligand and metal(Ni,Zn and Cu) complexes all the expected fragmentations and the molecular ion peak and m/z peaks appeared successfully



Fig(3) Mass spectrum of 5ClFTSC



Fig(4) Mass spectrum of Ni($C_6H_6ClN_3SO$)$_2$

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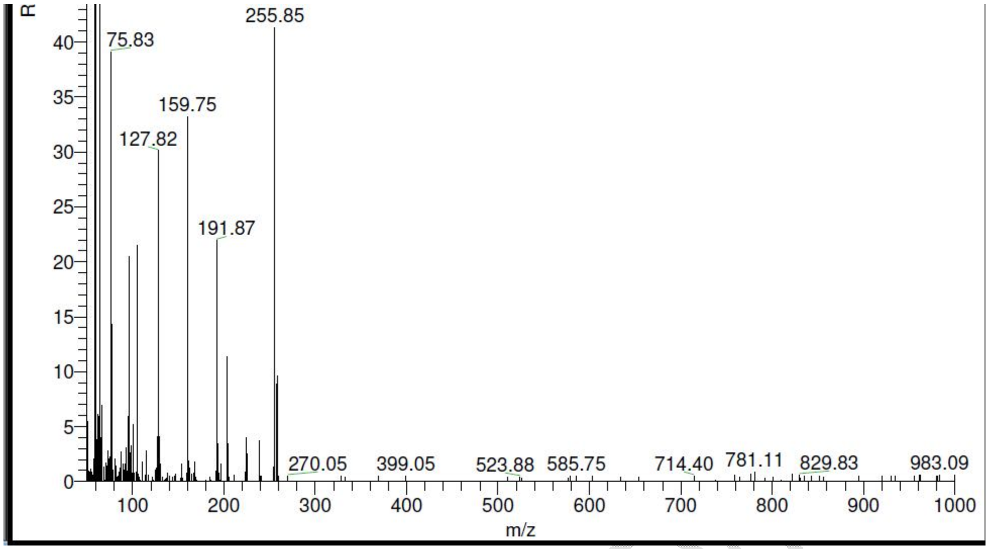
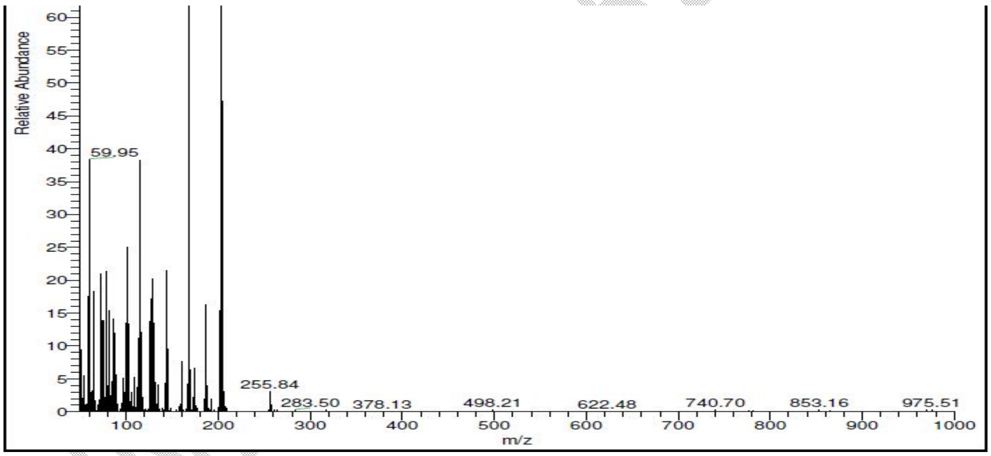
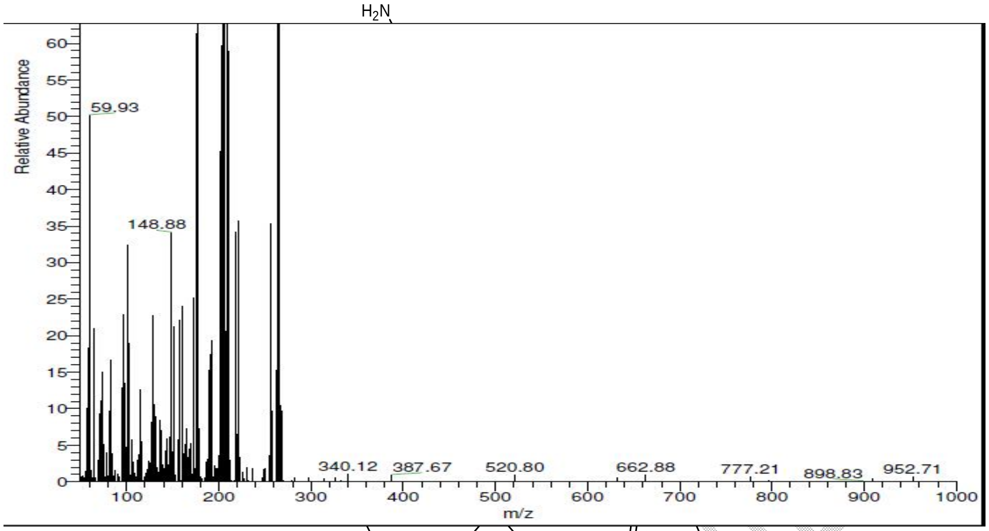


Fig(5) Mass spectrum of Zn($C_6H_6ClN_3SO)_2$

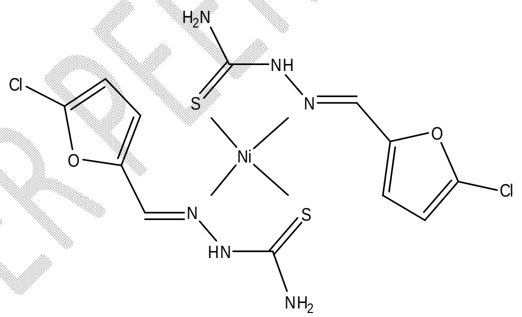


Fig(6) Mass spectrum of Cu($C_6H_6ClN_3SO)_2$

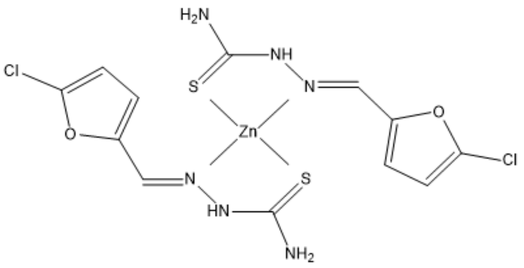


Fig(7) Mass spectrum of Cu($C_6H_6ClN_3SO$)

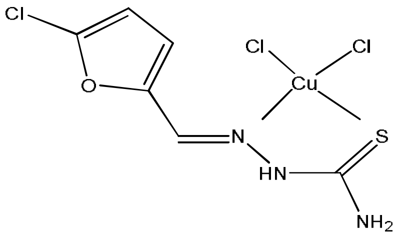
From the spectral results the proposed structure for the different metals 5-Chloro-2-furaldehyde thiosemicarbazone complexes were suggested as follow



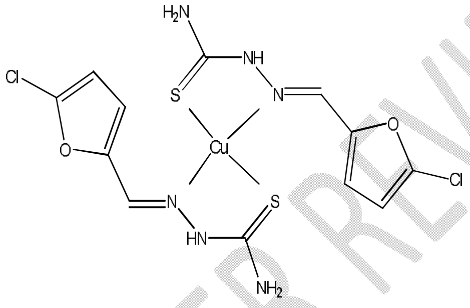
Fig(8) Structure of [Ni($C_6H_6ClN_3SO$)$_2$]



Fig(9) Structure of [Zn($C_6H_6ClN_3SO$)$_2$]



Fig(10) Structure of [Cu($C_6H_6Cl_3N_3SO$)]



Fig(11) Structure of [Cu($C_6H_6Cl_2N_3SO$)$_2$]

5. Conclusions

The spectral data analysis confirmed the newly structures. The coordination ability of the ligand has been proved in complexation reaction with Ni(II), Zn(II) and Cu(II) ions. In all complexes, the ligand acts as mononegative bidentate, around the metallic ion.

Comment [BN22]: Recommended to include the limitation of this study which leads to do the research further. Also, endorse the conclusion part in somewhat detailed manner with more words.

References

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