SYNTHESIS AND CHARACTERIZATION OF TRANSITION AND SOME GROUP 14 METAL COMPLEXES CONTAINING LIGANDS DERIVED FROM 2-ACETYLPYRIDINE AND HYDRAZIDE DERIVATIVES, AND THEIR ANTIPLASMODIUM ACTIVITIES

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PHILIPUS NGHILUKUNANYE HISHIMONE

(200620673)

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Supervisor: Professor E. M. R. Kiremire

Co-Supervisor: Dr. Daniel Likius

ABSTRACT

The synthesis and characterization of two sets of metal complexes containing ligands derived from 2-acetylpyridine and hydrazide derivatives is reported. The first set consists of complexes containing a ligand derived from 2-acetylpyridine and S-methyldithiocarbazate while the second set is of complexes containing a ligand derived from 2-acetypyridine and thiocarbohydrazide. The ligands were synthesized via an acid catalysed condensation reaction and the metal complexes were synthesized by direct mixing of the ligand dissolved in ethanol with a corresponding metal salt dissolved in water. The compounds were characterized by means of Elemental Analysis (EA), Infrared (IR) spectroscopy, Mass Spectroscopy (MS) and proton Nuclear Magnetic Resonance (^{1}HNMR) spectroscopy. Metal complexes with formulas of PbL_2, $Ag(HL)NO_3$ and Sn(L)Cl were obtained from the S-methyldithiocarbazate containing ligand. The thiocarbohydrazone ligand gave bimetallic complexes of manganese(II) and zinc(II) with general formulas that can be represented as $M_2(HL)Cl_3$ (M = Mn or Zn, and HL is the deprotonated ligand)

The ligands and their corresponding metal complexes were tested for antiplasmodial activity against a chloroquine sensitive strain (NF54), of the *Plasmodium falciparum* of the malaria parasite. The NF54:IC_{50} results show that the divalent metallic complexes of the thiocarbohydrazone possess better activity toward this strain better than the parent ligand. The complexes of the S-methyldithiocarbazate containing ligand show lower activity in comparison to their parent ligand.

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HL	2-acetylpyridine S-methyldithiocarbazate
H_2L	bis(2-acetylpridine)thiocarbohydrazone
CQS	Chloroquine sensitive
EA	Elemental Analysis
MS	Mass Spectroscopy
^1H NMR	Proton Nuclear Magnetic Resonance
IR	Infra-red
DMSO	Dimethyl Sulfoxide
Py	Pyridyl

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To my mother, Eufemia Kafute Ndayolanongwe Josef

Conference presentations

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Declarations

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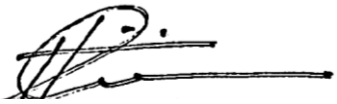

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Philipus Nghilukunanye Hishimone

CHAPTER 1: INTRODUCTION

1.1 General introduction

Cisplatin (*cis*-[$Pt(NH_3)_2Cl_2$], figure 1) which is used in the treatment of testicular cancer was accidentally discovered by Barnett Rosenberg in the 1960s when he was studying the resemblance between the mitotic spindle of dividing cells and the orientation of iron filing around a magnetic field (Alderden, Hall, & Hambley, 2006; Fricker, 2007; Kiremire, 2010). The discovery and development of the antitumor compound cisplatin and its analogues played a very important role in the establishment of the field of medicinal inorganic chemistry (Fricker, 2007; Storr, Thompson, & Orvig, 2006). Various metal complexes have been found to be highly effective against different disease-causing organisms, but due to unacceptable levels of toxicity and drug resistance conditions, their clinical use is limited (Storr et al., 2006).

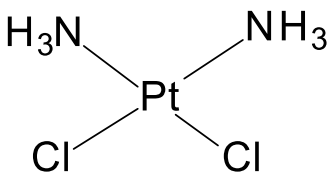


Figure 1. Structure of cisplatin

1.1.1 The importance of transition metal complexes

Transition metals have found noble applications related to human progress ranging from aerospace and electronic industries to health(Medici et al., 2014). Owing to their incomplete d-shells, transition metals bond to a surrounding array of molecules or ions to form metal complexes of coordination compounds.

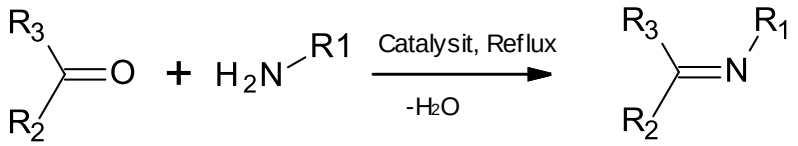
In biological systems, metal ions bond and interact with important biological molecules and they are categorised into three general classes according to their enzymatic roles (that is when the metal acts as an enzyme cofactor and catalyses redox reactions), their structural roles (that is when the metal plays a role contributing to the stability of the biological molecule), and their reactive role (when the metal plays a role in various functions such as the transportation of

oxygen, hydrolysis and group transfer) (Huang, Wallqvist, & Covell, 2005; Ribas, 2008; Sabale, 2012).

Since the discovery of cisplatin, a large number of metal complexes have been synthesized and applied in pharmacological fields as anticancer, anti-inflammatory, antibacterial, and antimalarial drugs just to mention a few (Lippert & Universita, 2013; Medici et al., 2014; Rafique, Idrees, Nasim, Akbar, & Athar, 2010)

1.1.2 Schiff bases

Schiff bases are condensation products of primary amines and carbonyl compounds that are represented by the general formula $R_2R_3C=NR_1$ (**3** in scheme 1) and they were discovered by a German scientist, Hugo Schiff in 1864. The original reaction discovered by Schiff as given in scheme 1 is the most common method of preparing Schiff bases (Qin, Long, Panunzio, & Biondi, 2013)

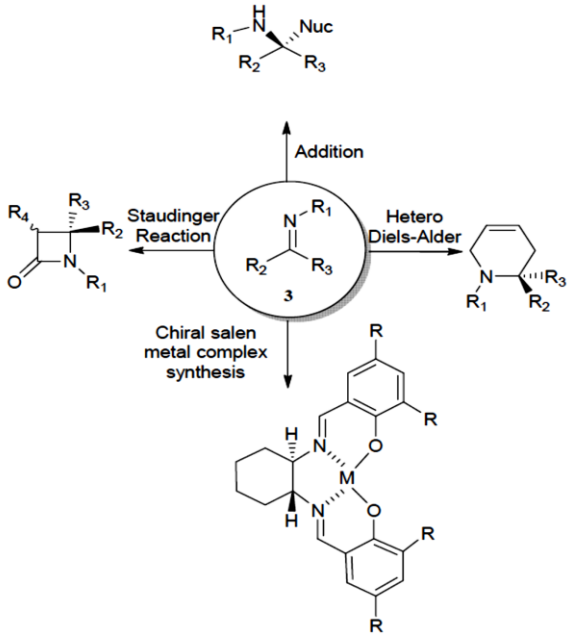


1 **2** **3**

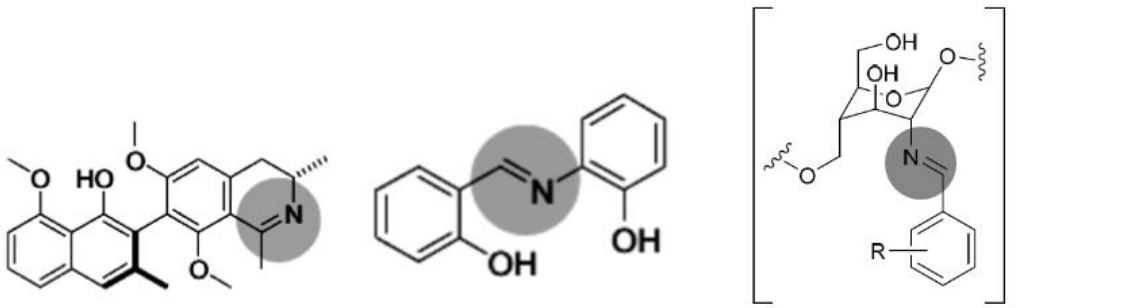
Scheme 1. Schiff reaction for the preparation of Schiff bases

Schiff bases have found vital applications in fields such as organic synthesis, biological applications and pharmaceutical research just to mention a few. The application of these bases in organic synthesis is well summarized by Quin et al (2013) in the form of a chart next page that shows how various organic compounds can be synthesized from Schiff bases.

Chart 1. Application of Schiff bases in organic synthesis(Qin et al., 2013)



The presence of the imine group **–N=CH-** in Schiff bases has been shown to be responsible for various biological activities and other physico-chemical properties, that allow Schiff bases to be used in therapeutic or biological applications either as lead compounds for the treatment of diseases or diagnostic probes and analytical tools (Ashraf, Mahmood, Wajid, Maah, & Yusoff, 2011; Brodowska & Chemistry, 2014; Qin et al., 2013). Examples of some biologically active Schiff bases are given in figure 2 below (highlighting the imine group).



***N*-(Salicylidene)-2-hydroxyaniline (4)**
(Antimalarial activity)

Ancitrocladidine (5)
(Antibacterial activity)

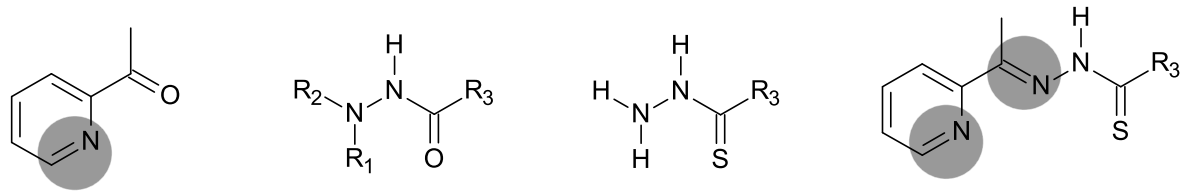
Chitosan-derived Schiff base [R=H or OH] **(6)**
(Antifungal activity)

Figure 2. Examples of biologically active Schiff bases (Brodowska & Chemistry, 2014; Qin et al., 2013)

1.1.3 Schiff base ligands derived from hydrazide derivatives

Schiff bases containing nitrogen and other donor atoms have been found to be among the convenient and attractive ligands for the complexation of some metal ions forming complexes with good biological and industrial application properties (Sathisha, Shetti, Revankar, & Pai, 2008; Wang et al., 2013). It has been reported that these ligands possess excellent selectivity, sensitivity and stability for some metal ions and they have been used as cation carries in potentiometric sensors (Brodowska & Chemistry, 2014).

There are a number of applications of 2-acetylpyridine (**7** in figure 3). Among others, these include being used as a food additive, flavouring substance in tobacco, ice-cream and other food products, and it can also be used as an intermediate to synthesize biologically active chemical compounds (Zhai, Cui, & Liu, 2015). Hydrazide has a general structure represented by **8** in figure 3 and the hydrazide derivative used in this research, the oxygen atom is replaced by a sulphur atom as represented by structure **9**. The combination of 2-acetylpyridine with the chosen hydrazide derivative gives a Schiff base (**10**) with two (2) imine groups as highlighted in figure 3.

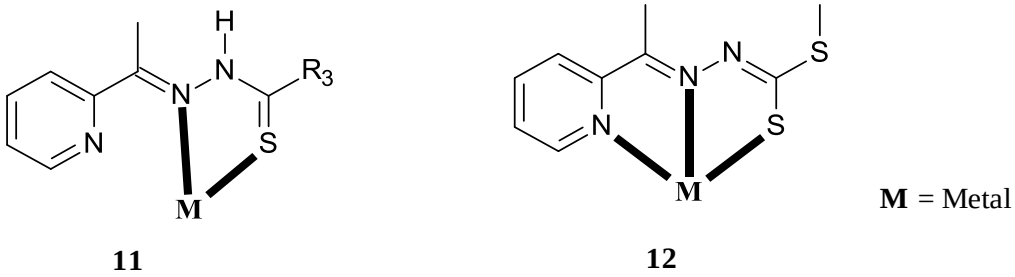


7 **8** **9** **10**

Figure 3. Structure of 2-acetylpyridine **(7)**, hydrazide **(8)**, hydrazide derivative (R_1 &R_2 = H) **(9)** and the Schiff base derived from 2-acetylpyridine and the hydrazide derivative **(10)**

The reactivity of the NH_2 group on the hydrazide derivatives (via condensation reactions) allows for a build-up of different chelate ring size and combinations in Schiff base complexes (Mishra & Kumar, 2014). It can be seen from the structure of the Schiff base ligand (**10** in figure 3), that it can bind to metals as a bidentate ligand using the imine nitrogen and the sulphur atoms as the donor atoms (fig. 4(**11**)) or as a tridentate ligand by using the nitrogen atom on

the pyridine ring in addition to the imine nitrogen and the sulphur atoms (fig. 4(**12**)) forming five membered rings. The other remaining nitrogen atom (NH) is not involved in the coordination because if its involvement would lead to the formation of a three (3) or four (4) membered ring which is less favoured over five (5) membered rings due to steric hindrance (Ribas, 2008).



11 **12**

Figure 4. Schiff base acting as a bidentate ligand (11) and as a tridentate ligand (12).

CHAPTER 2: LITERATURE REVIEW

2.1 Nitrogen-Sulphur based ligands and their metal complexes

In recent years, many studies have highlighted the importance of nitrogen-sulphur based organic compounds due to their potential biological activities(Daniel, 2009; S Kumar & Kumar, 2013; Shalin Kumar, Dhar, & Saxena, 2009; Pelosi, 2010). It has also been observed that the combination of such organic compounds with metal ions to form metal complexes via the chelation of the metal ions by the ligands, greatly affects the biological activities of those compounds (Pelosi, 2010; Storr et al., 2006). Moreover, it was further discovered that the structures of complexes formed by the combination of the metal ions and the organic ligands depend on chelation of the metal by the ligand (Beshir, Guchhait, Gascón, & Fenteany, 2008).

Some metal complexes of nitrogen-sulphur based ligands were reported by Beshir et al. (2008) (figure 5) for biological studies (cell immigration inhibition). Beshir et al. (2008) noted that the biological activities of the metal complexes appear to depend on the complex structure as a whole. Pelosi (2010) reported the synthesis and biological studies (anticancer) of some thio-urea derivative compounds. According to Pelosi (2010), “the structure of the metal complexes also play a major role in their activities”. Furthermore, Pelosi reported that the potency for antitumor activities of the synthesized complexes stems from the presence of a Nitrogen-Nitrogen-Sulphur (NNS) chelating system and an aromatic fragment bound to the sulphur hydrazine moiety.

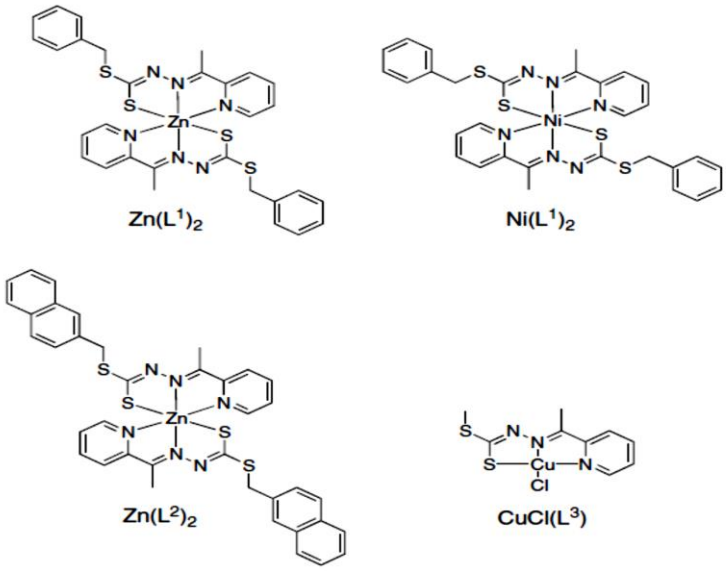


Figure 5. Some metal complexes reported by Beshir et al.

It has also been found that the biological activities of these ligands are either enhanced or reduced in metal complexes compared to non-complexed ligands or the metal ions on their own (C. L. Chen, Zhu, Li, Guo, & Niu, 2011). Further investigation on the biological activities of these complexes revealed that the parent ligand appear to play a role in the overall biological activity (Parul, Subhangkar, & Arun, 2012). The comparison of the biological activities of free ligands to those of their corresponding metal complexes has also been reported in a publication by Kumar and Kumar (2013). The latter shows that when the biological activity of a free ligand as compared to those of its metal complexes, the metal complexes have antimicrobial activities while the free ligand shows no bio-active properties. Therefore, all these activities can be attributed to the chelation of the metal ions by the ligands, a process which changes the biological activity of the ligands (C. L. Chen et al., 2011; S Kumar & Kumar, 2013; Pelosi, 2010).

2.2 2-acetylpyridine S-methyldithiocarbazate (HL) and its metal complexes

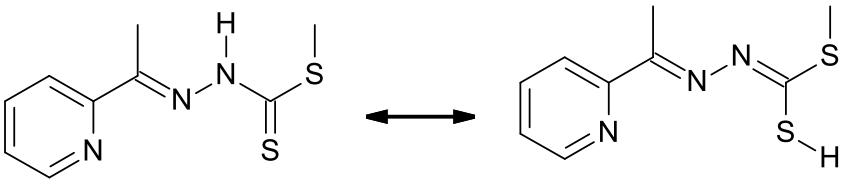
2.2.1 The synthesis of 2-acetylpyridine S-methyldithiocarbazate (HL)

The synthesis of 2-acetylpyridine S-methyldithiocarbazate has been reported in literature (West & Huffman, 1989). Hossain *et al.* (1993) reported the synthesis of this ligand by mixing 2-

acetylpyridine and S-methyldithiocarbazate in ethanol, then boiling the mixture in a water bath for about 10 minutes and reducing the volume to half. The solid that has formed after cooling was then filtered off, washed with ethanol and dried *in vacuo* over P_4O_{10}.

Kumar *et al.* (2014) synthesized the same ligand by mixing the starting material in 2-propanol and stirring the mixture for 2-hours at room temperature and collecting the formed solid by vacuum filtration. Another method of preparing this ligand involves refluxing the mixture of the starting materials in ethanol for a certain period of time and collecting the solid formed upon cooling (C. L. Chen et al., 2011; Mo, Lim, & Koo, 1998).

From literature it can be noted that there are various methods on how to prepare this ligand and they can all be generalised as a condensation reaction between 2-acetylpyridine and S-methyldithiocarbazate in an alcoholic solution (as shown in scheme 2 under the experimental section), forming a compound that may exist in a thione-thiol tautomeric form in solution as shown in figure 6 (Hossain, Begum, & Alam, 1993).



13 **14**

Figure 6. Structures of 2-acetylpyridine S-methyldithiocarbazate in its thione **(13)** and thiol **(14)** tautomeric forms

2.2.2 The synthesis and characterization of HL metal complexes

Metal complexes of ligands derived from S-methyldithiocarbazate have been extensively studied and there are various procedures available in literature for their preparation (C. L. Chen et al., 2011; Hossain et al., 1993; Mo et al., 1998; West & Huffman, 1989). HL has been found to be a tridentate ligand (upon deprotonation) coordinating to metal ions via the pyridyl

nitrogen, azomethine nitrogen, and the sulphur atom (West & Huffman, 1989) as shown in figure 7.

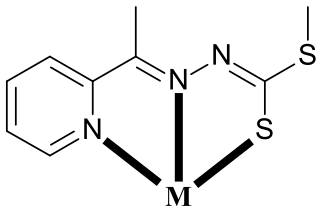


Figure 7. Coordination points deprotonated HL to a metal ion

The synthesis of iron (III), cobalt (II) cobalt (III), copper (II), and nickel (II) complexes containing HL and its deprotonated form has been reported by West & Huffman (1989). In their paper, they reported that all complexes had deprotonated ligands giving octahedral complexes for iron (III) and cobalt (III), and square planar complexes obtained from nickel and copper halides. However, two types of nickel (II) complexes of HL can be obtained depending on the coordinating anions present in the reacting solution (Hossain et al., 1993; West & Huffman, 1989). In the presence of strongly coordinating anions such as Cl^-, Br^-, SCN^-, I^-, etc., square planar complexes of a general formula [Ni(NNS)X] (NNS = the deprotonated ligand, X = the strongly coordinating ligand) can be obtained whereas with weakly anions such as NO_3^- or ClO_4^-, octahedral complexes with a general formula $Ni(NNS)_2$ are obtained (Hossain et al., 1993). The complexes were prepared by mixing ethanolic solutions of metal salts and the ligand in appropriate molar ratios and boiling the mixture on a water bath for about 20 minutes.

Manganese (II) complexes of HL are also reported (C. L. Chen et al., 2011; Mo et al., 1998). The method of preparation reported by Chen et al. was different from the one reported earlier. Here, the mixture was refluxed for at least one hour. Elemental and spectral data suggested that the deprotonated ligand coordinates to the manganese (II) ion with octahedrally hexacoordinate atom via the pyridine nitrogen, azomethine nitrogen, and sulphur atoms (figure 8).

Figure 8. Structure of the Mn(II) complex general structure, R = SCH_3 (Mo et al., 1998)

Kiremire (2011) reported the preparation of HL complexes for nickel (II), manganese (II), iron (II), copper (II), zinc (II), cobalt (II) and cadmium (II). The complexes reported by Kiremire have a general formula ML_2 (M = the metal ion) except the complex prepared from copper (II) chloride and this agrees with the complexes reported by West & Huffman (1989), Hussain *et al.* (1993), and Mo *et al.* (1998). The mode of preparation for the complexes in this case was different from the ones reported by the other authors previously in that, here the metal salts dissolved in water were added to hot ethanolic solutions of the ligand and then the solids formed upon cooling of the mixture.

In contrast to the nickel complexes (square planar) reported by West & Huffman (1989) and Hossain *et al.* (1993), the nickel complex reported by Kiremire had a general formula of $Ni(NNS)_2$ even though $NiCl_2$ was used in both cases. West & Huffman (1989), reported an octahedral complex from nickel chloride that does not involve the deprotonation of the ligand. This complex was isolated from a refluxed aqueous ammonia solution in an attempt to prepare $Ni(NNS)_2$. Therefore, it is interesting to note how West & Huffman (1989) could not obtain a complex with the formula $Ni(NNS)_2$ of HL from nickel (II) chloride and it was easily prepared by Kiremire (2011). Figure 9 shows probable structures for nickel (II) complexes of neutral HL and its deprotonated form reported in literature.

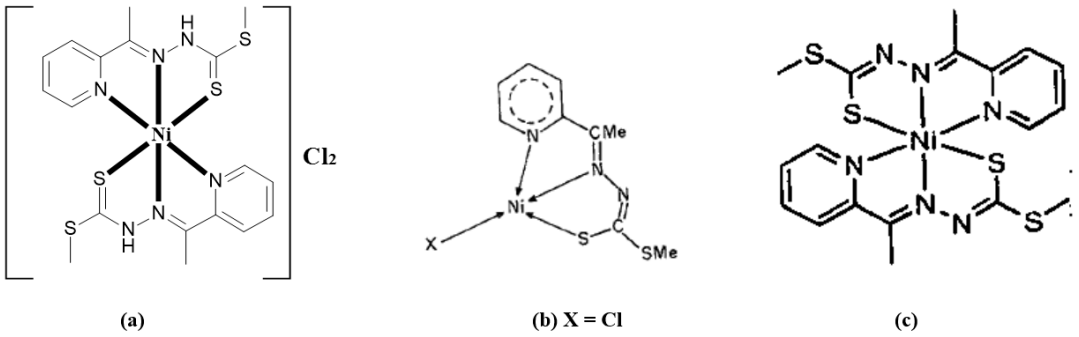


Figure 9. General structures of complexes prepared from nickel (II) chloride (a) aqueous ammonia preparation, (b) ethanol preparation (West & Huffman, 1989), and (c) water/ethanol preparation (Kiremire, 2010).

2.2.3 Biological activities of HL metal complexes

Many complexes of transition metal containing an S donor atom have been described as antimalarial, antileukemic or antiviral agents and several metal complexes containing S-methyldithiocarbazate derivatives possess considerable anti-tumour activity, as well as low toxicity (Daniel, 2009; Gomez-Bosquet, Moreno, Font-Bardia, & Solans, 1998; West & Huffman, 1989).

Hossain *et al.* (1993) reported on the antifungal activity evaluation of nickel (II) complexes containing HL against *A. solani*, *F. equisetti* and *M. phaseolina*. The free ligand was found to possess toxicity levels comparable to that of a commercially available fungicide however, the complexes were reported to be less fungi-toxic than the free ligand. The ligand and its Manganese (II) and cobalt (II) complexes were also tested for their ability to inhibit tumour cell growth (C. L. Chen et al., 2011). The free ligand and the complexes show effective antitumor activity against K562 leukemia cancer cell line and the manganese (II) complex was found to possess increased antitumor activity than the free ligand while the cobalt (III) complex had lower activity than the ligand.

2-acetylpyridine thiosemicarbazone (figure 10) which is structurally similar to HL is known to possess significant antimalarial and antileukemic activity (C. Chen, Chen, Li, & Niu, 2010;

Daniel, 2009; Mo et al., 1998). In addition to this, Kiremire (2011) reported on the metal complexes of HL which were found to possess biological activity against falcipain-2 (fp-2) and falcipain-3 (fp-3) cysteine protease enzymes from malaria parasite *Plasmodium falciparum*. The presence of 2-pyridylalkylidene moiety has been shown to be essential for the antimalarial activity of these complexes (Mo et al., 1998).

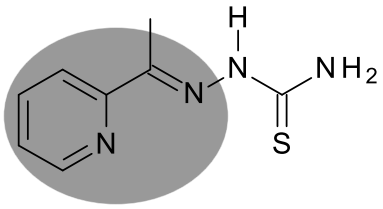


Figure 10. Structure of 2-acetylpyridine thiosemicarbazone highlighting the 2-pyridylalkylidene moiety

2.3 Bis(2-acetylpyridine) thiocarbohydrazone (H_2L) and its metal complexes

2.3.1 The synthesis and characterization of H_2L

Bis(2-acetylpyridine)-thiocarbohydrazone has been synthesized from an acid catalysed condensation of 2-acetypyridine and thiocarbohydrazide (Bacchi, Carcelli, & Pelagatti, 1999; C. Chen et al., 2010; Manoj, 2007). The method of preparation of this ligand involves 2 hour refluxing of an ethanolic mixture of the starting materials in appropriate ratio with a few drops of acetic acid as a catalyst and evaporation of the solvent to get the crystals. Chen *et al.* (2010), reported that the structure of the ligand synthesized contains on bis(2-acetylpyridine)-thiocarbohydrazone and three water molecules. The general structure of the ligand is shown in figure 11.

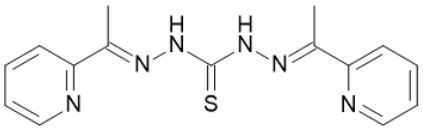
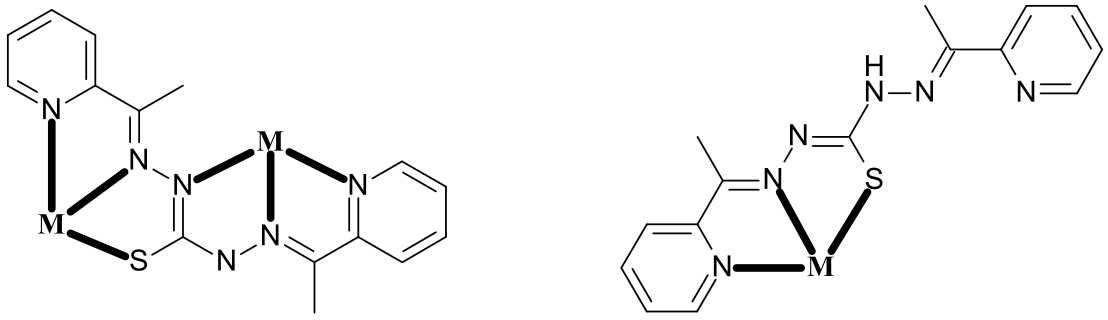


Figure 11. Structure of H_2L, bis(2-acetylpyridine)-thiocarbohydrazone (C. Chen et al., 2010)

The formation of the desired product is confirmed by the absence of the NH_2 group which can be checked by means of IR ($\nu(NH_2)$ at ~ 3280 cm^{-1}) and ^{1}HNMR (broad peak between 4.5 and 5.0 ppm) spectroscopies (Bacchi et al., 1999). The existence of bands in the 3500 ~3100 cm^{-1} (associated with the ν(N-H)) and the absence of any band at 2500 – 2600 cm^{-1} assigned to the ν(S-H) also indicates that in solid state, the compound remains in a thione form (C. Chen et al., 2010).

2.3.2 The synthesis and characterization of H_2L metal complexes

The coordinating properties of H_2L toward copper (II), iron (II),and zinc (II) have been reported (Bacchi et al., 1999). In their report, Bacchi *et al.* represented the ligand as H_2apt and bimetallic or monometallic complexes were obtained with the ligand in the mono- or bi-deprotonated form (figure 12).



(a) **(b)**

Figure 12. Structure of bimetallic (a) and monometallic (b) complexes of H_2L (Bacchi et al., 1999)

Bacchi *et al.* (1999), reported that the copper (II) and iron (II) complexes of H_2L are bimetallic with formulas represented by $Cu_2(Hapt)Cl_3 \cdot 0.5EtOH$ and $Fe_2(apt)Cl_2 \cdot 2H_2O$ respectively. The zinc complex obtained was monometallic, even if the starting metal/ligand molar ratio was 2/1, and this is probably due to its low solubility such that it precipitated immediately in the reaction medium (Bacchi et al., 1999). Although it is clear that at least one pyridine ring and

its imine nitrogen, as well as the sulphur atom are involved in the coordination, the type of coordination in the monometallic complex of H_2L could not be easily assigned due to the flexibility of the ligand and the presence of numerous donor sites (Bacchi et al., 1999).

2.3.3 Biological activities of HL metal complexes

Evaluation of H_2L and its corresponding metal complexes for any biological activity has been reported by Bacchi *et al.* (1999) and by Chen *et al.* (2010) with antimicrobial and antitumor activity being detected respectively. Chen *et al.* compared antitumor activity of the ligand, H_2L to that of 2-acetylpyridine thiosemicarbazone (figure 10), and bis(imidazole-2-carboxaldehyde)thiocarbonohydrazone (figure 13). In both cases, the H_2L shows more significant antitumor activity than the other systems, and the comparison revealed that the biological activity can be increased by changing the substituent group from thiosemicarbazone to thiocarbonohydrazone and also how changing the substituent group in the parent aldehyde or ketone in thiocarbonohydrazone derivatives can influence their antitumor activities.

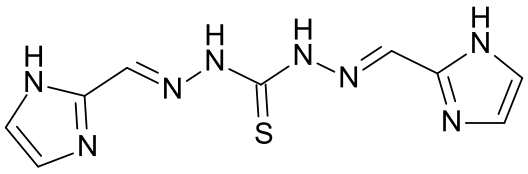


Figure 13. Bis(imidazole-2-carboxaldehyde)thiocarbonohydrazone

Bacchi *et al.* (1999), compared the antimicrobial activity of H_2L (figure 11a) and its copper(II), iron(II), and zinc(II) complexes with that of a corresponding carbonohydrazone, bis(2-acetylpyridine)-carbonohydrazone (figure 14) and its corresponding metal complexes. The thiocarbonohydrazone was found to be more active than the carbonohydrazone and this suggests that the thiocarbo moiety is essential for antimicrobial activity (Bacchi et al., 1999). Also, the corresponding complexes of H_2L reported by Bacchi *et al.* (1999) possess

antimicrobial activity lower than that of the free ligand, suggesting that complexation does not enhance the antimicrobial properties of H_2L.

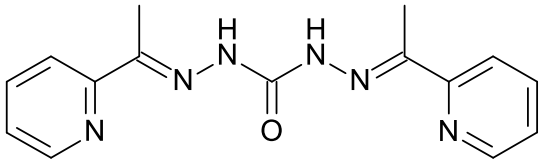


Figure 14. Bis(2-acetylpyridine)-carbonohydrazone

2.4 Statement of the problem

It is estimated that 3.3 billion people were at risk of malaria in 2011 and, 80% of malaria cases and 90% deaths caused by malaria occur in Africa, with children under the age of five and pregnant women being the most severely affected (World Health Organization, 2012). The eradication of malaria and other diseases such as tuberculosis (TB) continues to be frustrated by drug resistance development of the disease-causing organisms.

Drug resistivity of the malaria parasite *P. falciparum* to chloroquine has been reported for decades (Daniel, 2009; Kiremire, 2010; WHO, 2014), however, cases of parasite resistance to the drug currently used, Artemisinin, have been reported in some parts of the world (WHO, 2014). In events of the cases spreading to more parts of the world, public health will be under risk as there is no alternative antimalarial medicine available for at least the next five (5) years (WHO, 2014). This highlights a great need for a continued search for more compounds which are cheaper and more effective against these disease-causing organisms.

2.5 Objectives of the research

The objectives of this research were as follows:

- ✓ to synthesize ligand systems derived from 2-acetylpyridine and thiocarbohydrazide, and S-methyldithiocarbazate.
- ✓ to synthesize the metal complexes using the two ligands mentioned above.
- ✓ to characterize the ligands and their metal complexes
- ✓ to test the ligands and the corresponding complexes for antiplasmodic activities

2.6 Significance of the study

Although a fairly large amount of information is available on the synthesis and characterization of metal chelates derived from nitrogen-sulfur containing ligands, reports of the biological properties 2-acetylpyridine S-methyldithiocarbazate, bis(2-acetylpyridine)-thiocarbonohydrazone, and their corresponding metal complexes are still lacking (Bacchi et al., 1999; C. L. Chen et al., 2011; Daniel, 2009). Therefore, the synthesis of these complexes continues to be of interest in order to evaluate their coordination chemistry and biological activity.

This research is a continuation of work being done on the synthesis and chemical characterization of metal complexes of the nitrogen-sulphur-based ligands at the University of Namibia in the search for bioactive ligands and their complexes.

CHAPTER 3: EXPERIMENTAL

All chemicals used in this research were of analytical reagents grade purchased from commercial sources and they were used without further purification (they are listed in table 1 below). The melting point of the synthesized compounds were taken on a Stuart Melting point SMP-30 and Infra-red analysis was done on a Perkin Elmer FT-IR Spectrometer (both at the University of Namibia). The synthesized compounds were sent to the University of Cape Town for elemental analysis (EA), mass spectroscopy (MS) and, proton-NMR. In addition, the ligands and their corresponding complexes were also evaluated for activities against the *Plasmodium falciparum* NF54 strain of the malaria parasite.

Table 1. List of main chemicals used in this study

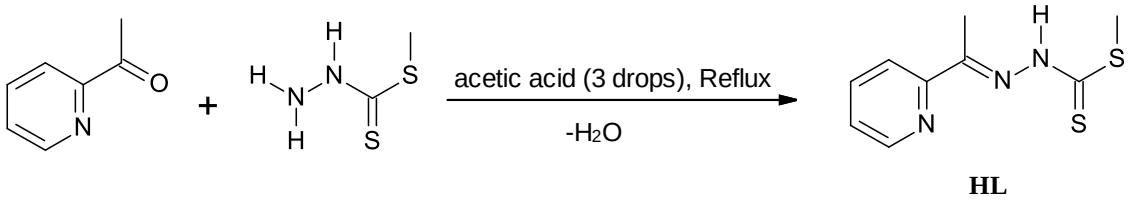
Reagent	**Molecular formula**	**Formula weight (g/mol)**
2-acetylpyridine	C_7H_7NO	121.13
Thiocarbohydrazide	CH_6N_4S	106.15
Hydrazinecarbodithioic acid, methyl ester	$CH_6N_2S_2$	122.21
Cadmium chloride	$CdCl_2$	183.32
Manganese(II) chloride tetrahydrate	$MnCl_2.4H_2O$	197.91
Zinc chloride	$ZnCl_2$	136.28
Lead nitrate	$Pb(NO_3)_2$	331.21
Silver nitrate	$AgNO_3$	169.87
Tin chloride dihydrate	$SnCl_2.2H_2O$	225.63

3.1 Synthesis procedures

3.1.1 Synthesis of ligands

3.1.1.1 Synthesis of the 2-acetylpyridine hydrazinecarbodithioate ligand, HL

Hydrazinecarbodithioic acid, methyl ester (5.0260 g, 0.0409 mol) was dissolved in 100.00 mL of ethanol and mixed with equimolar quantity of 2-acetylpyridine (4.6125 mL, 0.0409 mol) in a 250.00 mL round bottom flask. The mixture was refluxed for 3 hours (3 drops of glacial acetic acid were added when it started boiling) and cooled in an ice-water bath. An orange precipitate formed and it was recovered by Buchner filtration, washed with ice cold ethanol and air dried for 30 minutes (yield: 61%). Scheme 2 below shows the schematic synthesis of the ligand.

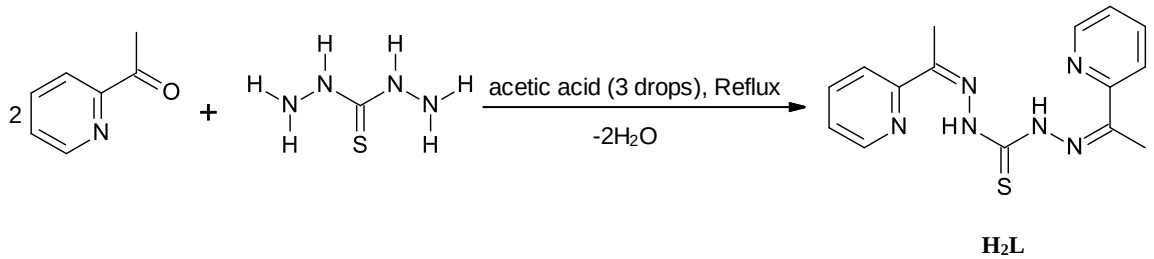


HL

Scheme 2. Synthesis of HL ligand

3.1.1.2 Synthesis of bis(2-acetylpyridine)thiocarbohydrazone, H_2L

Thiocarbohydrazide (2.005 g, 0.01889 mol) was dissolved in 100.00 mL of ethanol and mixed with 2-acetylpyridine (4.30 mL, 0.0383 mol) in a 250.00 mL round bottom flask. After the reflux was started 3 drops of glacial acetic acid were added. During the 3 hours reflux, the mixture changed from clear to pale yellow and upon cooling, a crystalline white precipitate formed and it was recovered by Buchner filtration, washed with ice cold ethanol and air dried for 30 minutes (yield: 74%). The schematic synthesis of this ligand is shown below.



H_2L

Scheme 3. Synthesis of H_2L ligand

3.1.2 Synthesis of metal complexes

3.1.2.1 Synthesis of complexes of the HL ligand

3.1.2.1.1 Synthesis of the Pb(II) complex of HL

A solution of $Pb(NO_3)_2$ (0.7354 g, 0.00222 mol) dissolved in water (10.00 mL) was added slowly with stirring to a hot solution of the ligand HL (1.0000 g, 0.00444 mol) in ethanol (50.00 mL). Upon mixing the two solutions, the colour of the mixture slightly changed to pale yellow and no precipitate formed. Upon the addition of a little amount of water, a yellow precipitate formed. The precipitate was recovered by Buchner filtration, washed with water, ethanol and then air dried for 30 minutes (yield: 36%).

3.1.2.1.2 Synthesis of the Ag(I) complex of HL

A solution of $AgNO_3$ (0.754 g, 0.00444mol) dissolved in water (10.00 mL) was added slowly with stirring to a solution of the ligand HL (1.0000 g, 0.00444 mol) in ethanol (50.00 mL). Upon mixing the two solutions, the solution turned brownish yellow and no precipitate formed. The solution was evaporated and a honey-like product remained. Acetone was added and a brown precipitate was obtained. The precipitate was recovered by Buchner filtration, washed with water, ethanol and then air dried for 30 minutes (yield: 56%).

3.1.2.1.3 Synthesis of the Sn (II) complex of HL

A solution of $SnCl_2.2H_2O$ (0.5010 g, 0.00222 mol) dissolved in water (10.00 mL) was added slowly with stirring to a hot solution of the ligand HL (1.0000 g, 0.00444 mol) in ethanol (50.00 mL). A brown precipitate formed immediately and it was recovered by Buchner filtration, washed with water, ethanol and then air dried for 30 minutes (yield: 52%).

3.1.2.2 Synthesis of complexes of the H_2L ligand

3.1.2.2.1 Synthesis of the Mn(II) complex of H_2L

A solution of $MnCl_2.4H_2O$ (0.6340 g, 0.0032 mol) dissolved in water (10.00 mL) was added drop-wise with stirring to the solution of the ligand H_2L (0.5000 g, 0.0016 mol) in ethanol (35.00 mL). Upon mixing, the mixture turned to orange and no precipitate formed. The mixture was heated and a tan precipitate formed immediately and it was recovered by Buchner filtration, washed with water and air dried for 15 minutes (yield: 44%).

3.1.2.2.2 Synthesis of the Zn(II) complex of H_2L

A solution of $ZnCl_2$ (0.4360 g, 0.0032 mol) dissolved in water (10.00 mL) was added drop-wise with stirring to the solution of the ligand H_2L (0.5000 g, 0.0016 mol) in ethanol (35.00 mL). Upon mixing, no precipitate formed. The mixture was heated to reduce the volume and a deep orange precipitate formed. The precipitate was recovered by Buchner filtration, washed with water and air dried for 30 minutes (yield: 55%).

CHAPTER 4: RESULTS AND DISCUSSION

Under this section, the results obtained from each experimental part will be discussed for each ligand and its metal complexes separately.

4.1 Physical properties and elemental analysis results

4.1.1 HL and its complexes

The physical properties and elemental analysis results of the ligand and its metal complexes are given in table 2 below.

Table 2. Physical properties and elemental analysis results for HL and its metal complexes

Compound	**Colour**	**Melting point, range (℃)**	**Elemental analysis, %found (%calculated)**			**Formula**
			C	**H**	**N**	
HL	Orange	120 - 121	47.2 (48.0)	5.09 (4.90)	21.3 (18.6)	$C_9H_{11}N_3S_2$
PbL_2	Yellow	186 - 190	31.3 (33.0)	3.05 (3.10)	12.6 (12.8)	$C_{18}H_{20}N_6PbS_4$
$Ag(HL)NO_3$	Yellowish brown	148 - 150	29.6 (27.4)	3.04 (2.80)	13.7 (14.2)	$C_9H_{11}AgN_4O_3S_2$
Sn(L)Cl	Brown	110 - 113	28.5 (28.6)	2.65 (2.70)	11.0 (11.1)	$C_9H_{10}ClN_3S_2Sn$

The condensation reaction of 2-acetylpyridine (colourless) and S-methyldithiocarbazate (white) in an ethanolic solution yields an orange ligand, HL. The elemental analysis data are in agreement with the proposed formula for the ligand. the results are shown in table 2. This indicates that 2-acetylpyridine reacts with Hydrazinecarbodithioic acid, methyl ester in a 1:1 mole ratio to give HL, with the formula $C_9H_{11}N_3S_2$ (225.04 g/mol).

The Pb(II) and Ag(II) complexes derived from HL are yellow in colour, while the Sn(II) is brown. The elemental analysis results of HL and its metal complexes are given in table 2 and they are in good agreement with the assigned formulations (table 2). The elemental analysis

results of the Pb complex indicates that HL reacts in a 2:1 ligand to metal ratio giving a complex with the formula PbL_2 indicating that the ligand has been deprotonated in this case.

The results for the Ag(I) and Sn(II) complexes indicates a 1:1 metal to ligand reaction ratio. For Ag (I), the ligand is not deprotonated and the results (both experimental and theoretical) correspond to the formula $Ag(HL)NO_3$. In case of Sn(II), the results are in agreement with the formation of Sn(L)Cl complex indicating that the ligand was deprotonated. Similar results were reported by West & Huffman (1989).

It can be suggested that during complexation, HL reacts with the metal salts in two steps. First, the ligand in its thiol form (in solution) loses the hydrogen from the sulphur to become negatively charged (-1). This anion then reacts with the metal ion (+2) from the solution to give a positively charged complex which is then stabilized by the chloride counter ion.

Solubility tests for the ligand and the complexes were done in order to identify the best solvent to be used for the purification and other spectroscopic measurements and the results are presented in table 3 below.

Table 3. Solubility tests for HL and its metal complexes

	Solvent						
Compound	Water	Ethanol	Methanol	Diethyl ether	Acetone	Chloroform	DMSO
HL	i	sls	sls	sls	s	s	vs
PbL_2	i	sls	sls	i	sls	sls	vs
$Ag(HL)NO_3$	i	sls	sls	i	sls	i	vs
Sn(L)Cl	i	sls	sls	i	vs	vs	vs

Key: i = insoluble, sls = slightly soluble, s = soluble, vs = very soluble

The solubility results show that HL and it its corresponding complexes synthesized in this study are insoluble in water and diethyl ether. All the compounds were found to be slightly soluble in ethanol and methanol. The Pb(II) and Ag(I) complexes were found to be slightly soluble in acetone while the ligand and the Sn(II) complex are soluble and very soluble respectively.

Furthermore, from the results, it is only the silver complex that does not dissolve in chloroform and a close inspection shows that, Pb (II) and Ag (I) complexes have similar solubility characteristics in the solvents used.

4.1.2 H_2L and its metal complexes

The physical properties and elemental analysis results of the ligand and its metal complexes are given in table 2 below.

Table 4. Physical properties and elemental analysis results for H_2L and its metal complexes

Compound	**Colour**	**Melting point, range (℃)**	**Elemental analysis, %found (%calculated)**			**Formula**
			C	**H**	**N**	
H_2L	White	161 - 162	54.3 (57.7)	5.67 (5.2)	30.4 (26.9)	$C_{15}H_{16}N_6S$
$Mn_2(HL)Cl_3$	Brown	170 - 178	33.6 (34.1)	3.69 (2.9)	15.8 (15.9)	$C_{15}H_{15}Cl_3Mn_2N_6S$
$Zn_2(HL)Cl_3$	Yellow	Decomposes	33.53 (32.8)	3.56 (2.76)	16.1 (15.3)	$C_{15}H_{15}Cl_3N_6S\ Zn_2$

HL represents a deprotonated H_2L

For the ligand H_2L, from the elemental analysis, the percentage of carbon, hydrogen and nitrogen found experimentally agrees with the theoretical values. This indicates that 2-acetylpyridine reacts with thiocarbohydrazide in a 2:1 mole ratio to give H_2L, with the formula $C_{15}H_{16}N_6S$ (312.11 g/mol).

The elemental analysis results for the manganese and zinc complexes suggest that the complexes formed by the reaction between the metal ions and the H_2L ligand have a general formula, $M_2(HL)Cl_3$ ($M = Mn^{2+}$ or Zn^{2+}).

Solubility tests results for H_2L and its metal complexes are presented in table 5 below.

Table 5. Solubility tests for H_2L and its metal complexes

	Solvent						
Compound	Water	Ethanol	Methanol	Diethyl ether	Acetone	Chloroform	DMSO
H_2L	i	sls	sls	sls	s	s	vs
$Mn_2(HL)Cl_3$	vs	sls	sls	i	sls	i	vs
$Zn_2(HL)Cl_3$	s	i	sls	i	i	i	vs

HL represents a deprotonated H_2L

The solubility results show that H_2L is not soluble in water but, its metal complexes are soluble. The high solubility of the metal complexes in comparison to the ligand suggests that they might be more polar than the ligand. In other solvents used in the test, the solubility of the metal complexes showed a similar pattern whereby their solubility varied from slightly soluble to being insoluble.

4.2 Proton NMR results

4.2.1 HL and its metal complexes

The proton NMR spectrum of HL in DMSO-d_6 (recorded in ppm, figure 15) exhibits signals due to protons on the pyridine ring as multiplets at 7.64 – 8.75 (4H). The four protons on the pyridine ring are not equivalent and this is why there are four different peaks. The proton attached to the carbon close to the nitrogen atom in the pyridine ring is responsible for the peak at about 8.75 ppm because it is much closer to the electron withdrawing group, which is the nitrogen atom and the other three peaks are for the remaining three protons. The signal at 2.81 is for the protons on the methyl group on the carbon attached to the pyridine ring. For the methyl group attached to the sulphur, the signal for its protons is at 2.26 and the signal for the proton attached to the nitrogen atom, is downfield at 10.05. This proton is directly attached to an

electron withdrawing group therefore it appears in the downfield region of the spectrum (Omar, Ravoof, Tahir, & Crouse, 2013).

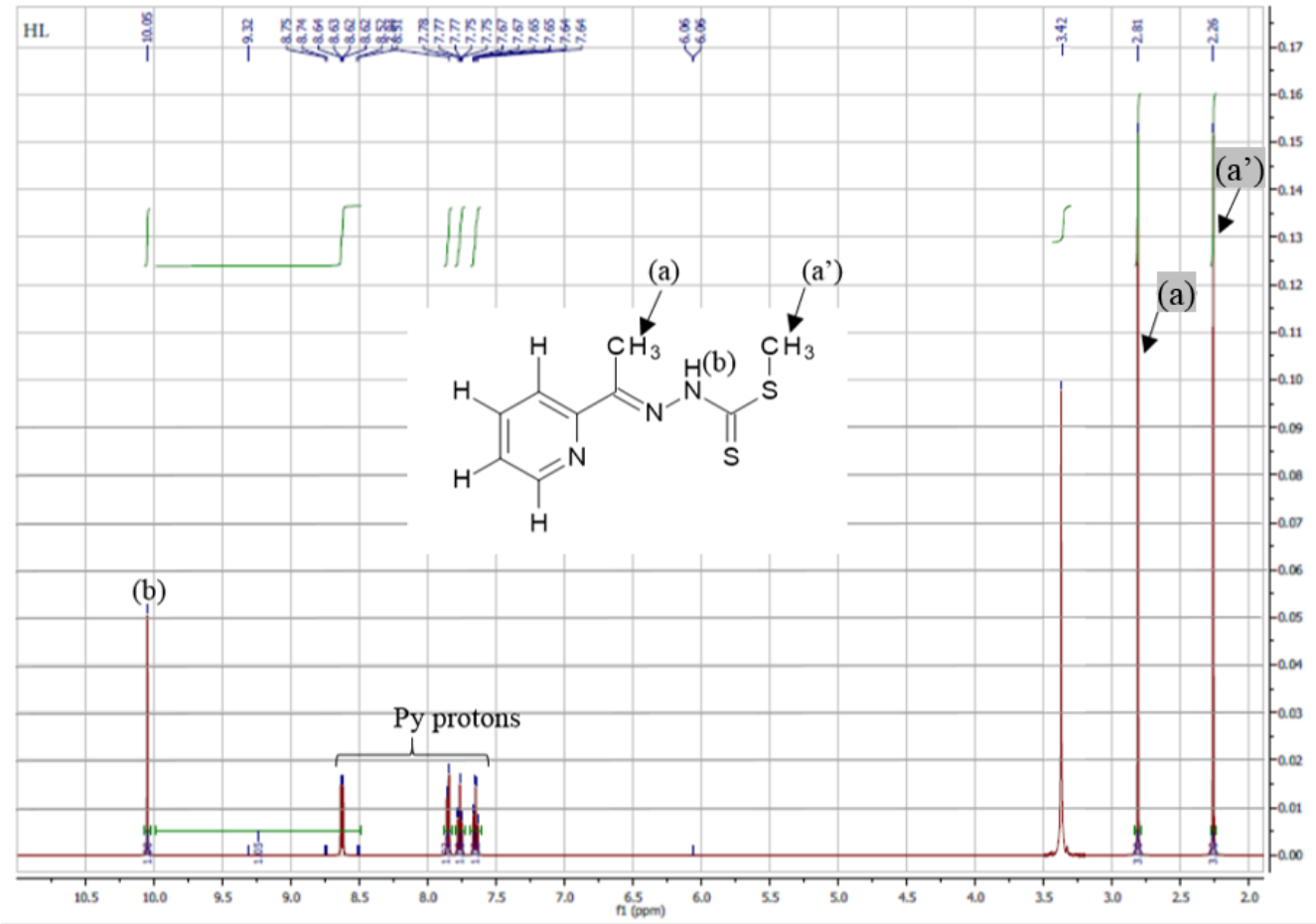


Figure 15. [1]HNMR spectrum for HL

The proton NMR spectra for HL complexes are shown in figures 16-18. The spectrum for lead (II) complex (figure 16) clearly shows the signals for all protons in HL except that of the hydrogen attached to the nitrogen atom. This agrees with the formulated structure that, HL binds to the Pb(II) ion, in a deprotonated form. Therefore, the disappearance of the peak due to this proton in the spectrum of the complex confirms its absence.

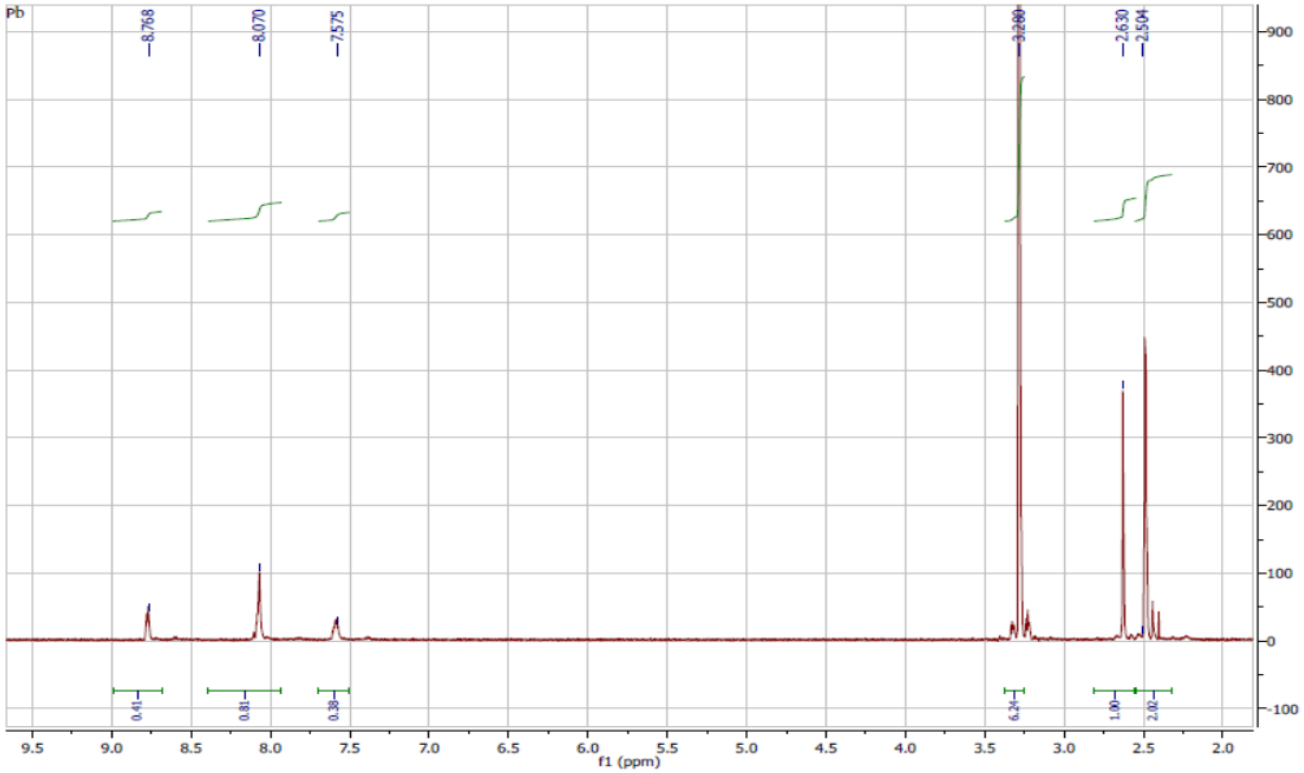


Figure 16. ^{1}HNMR spectrum for PbL_2

The spectra for silver and tin complexes (figure 17 & 18 respectively) are broadened and less resolved than that of the free ligand. The peaks due to protons of the methyl groups of the free ligand can be observed as several multiplets in the silver and tin complexes' spectra and this suggests that the complexation of HL and its deprotonated form with these metals has an effect on these protons.

For the silver complex, the peaks due to the protons on the pyridine ring are broadened and can be observed in the 7.5 ppm to 9.13 ppm range and the peak due to the proton of the –NH group does not show. All these may be attributed to the broadening effect of the Ag(I) ion.

In the spectrum for the tin complex, the peak due to the proton of the –NH group is not observed. Elemental analysis result for this complex suggests that the ligand to be in a deprotonated form when binding to the tin ion.

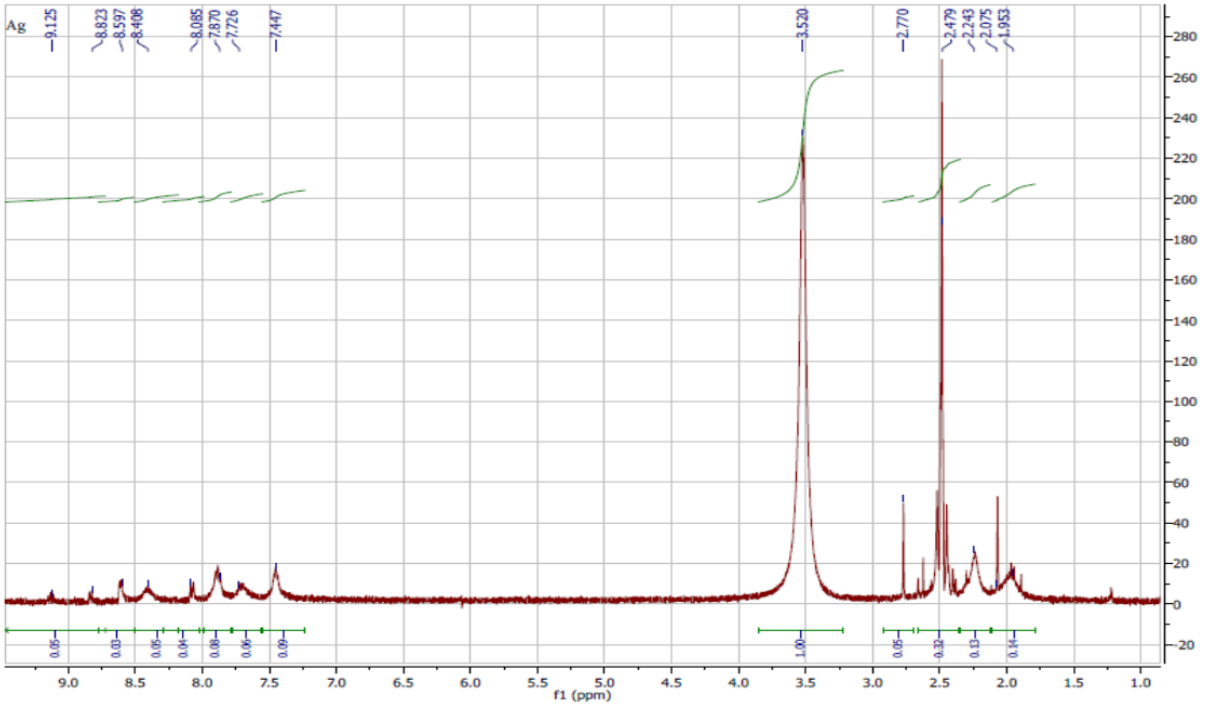


Figure 17. ^{1}HNMR spectrum for Ag(HL)NO_3

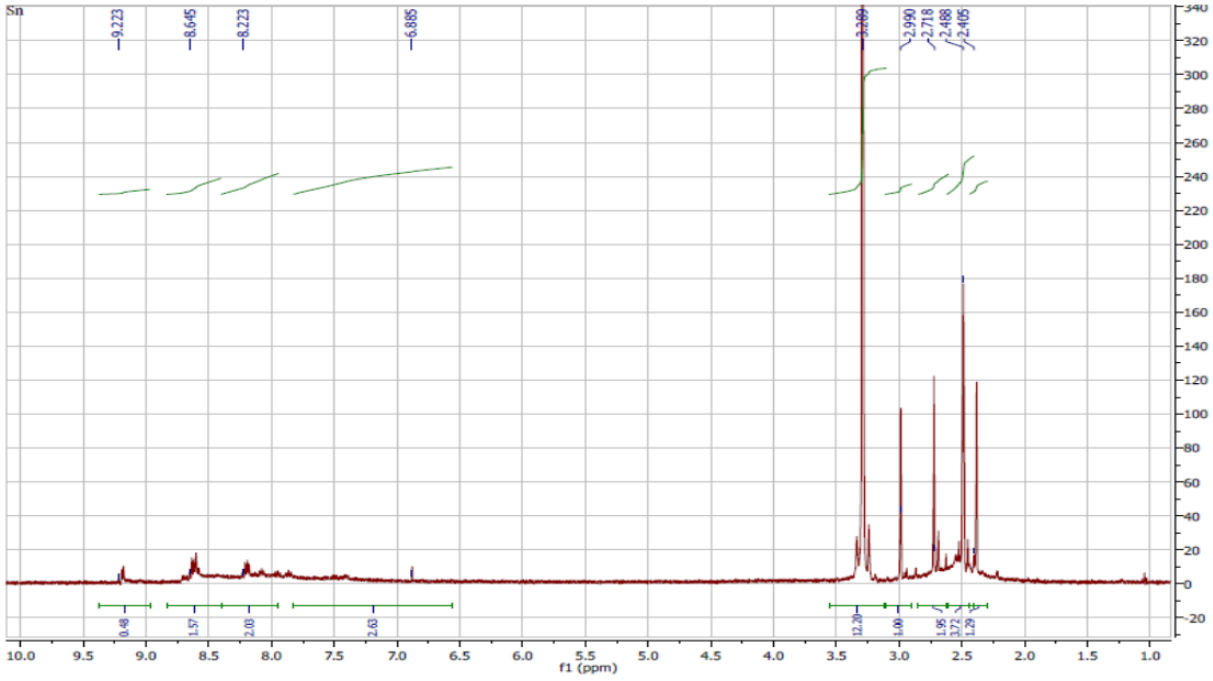


Figure 18. ^{1}HNMR for Sn(L)Cl

4.2.2 H_2L and its metal complexes

The proton NMR spectrum for H_2L is given in figure 19. The spectrum is expected to have six peaks which are, four (4) peaks for the four protons on the pyridine ring, one (1) peak for the proton on the methyl carbon and one (1) for the proton on the nitrogen atom (Bacchi et al., 1999; C. L. Chen et al., 2011; Daniel, 2009; Kiremire, 2010).

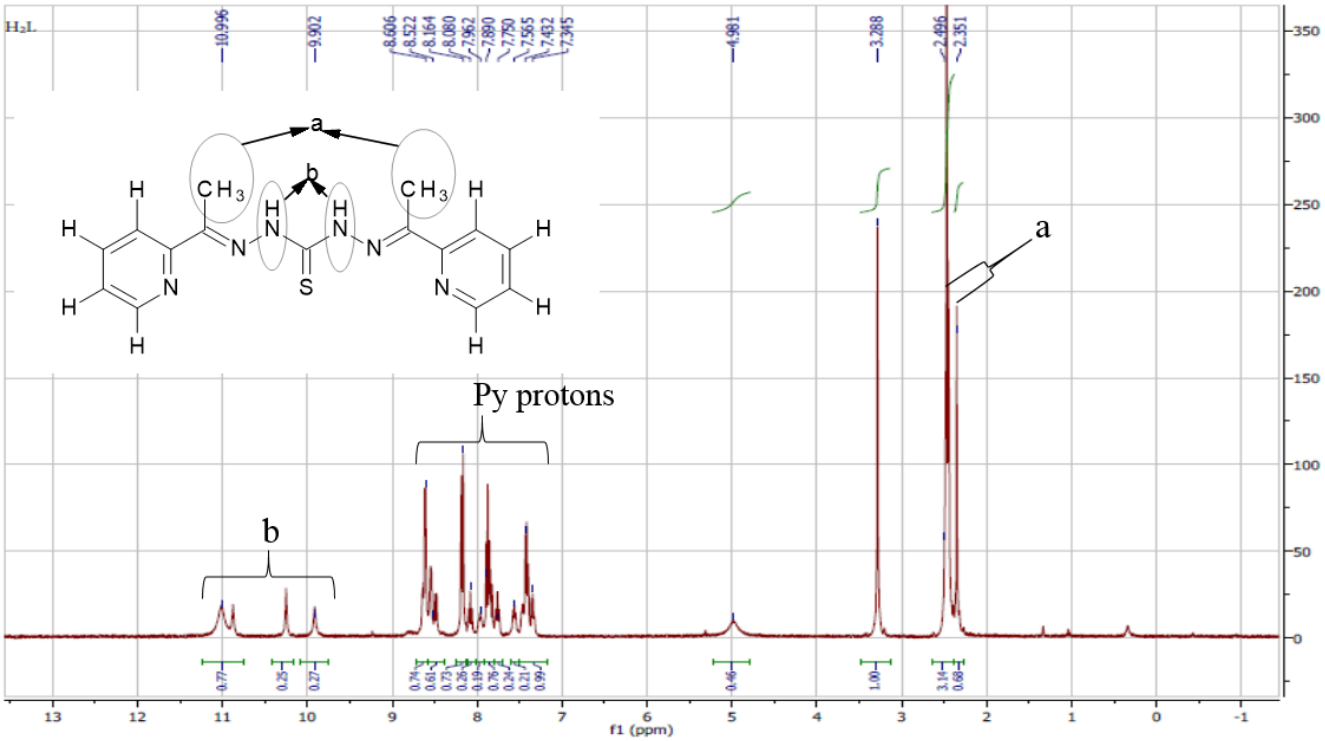


Figure 19. ^{1}HNMR spectrum for H_2L

To help with explanation, the proton NMR spectra for H_2L in DMSO-d6 was interpreted based on the structure given in figure 20 below.

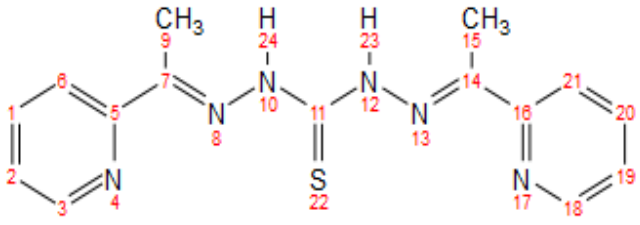


Figure 20. Formulated structure of H_2L

There are four different protons on the pyridine rings of the H_2L ligand and for this reason, there are four peaks appearing in the 7.89 ppm – 8.61 ppm range of the spectrum (figure 19). The methyl hydrogen appear up-field at 2.35 ppm – 2.95 ppm while the protons at position 23 (and 24) (and 18) give peaks at 9.91 ppm -11 ppm.

The zinc spectrum (figure 21), shows peaks for the methyl protons and protons on the pyridine rings appearing as a blips at 2.60 ppm and 7.58 - 8.60 ppm respectively. From the elemental analysis results, the H_2L has lost only one proton from one of the two –NH group. However, the ^{1}NMR spectrum of the zinc complex does not show a peak due to the remaining proton. This implies that the zinc ion, Zn^{2+} despite its filled d-shell (d^{10}) has a broadening influence on the proton signals..

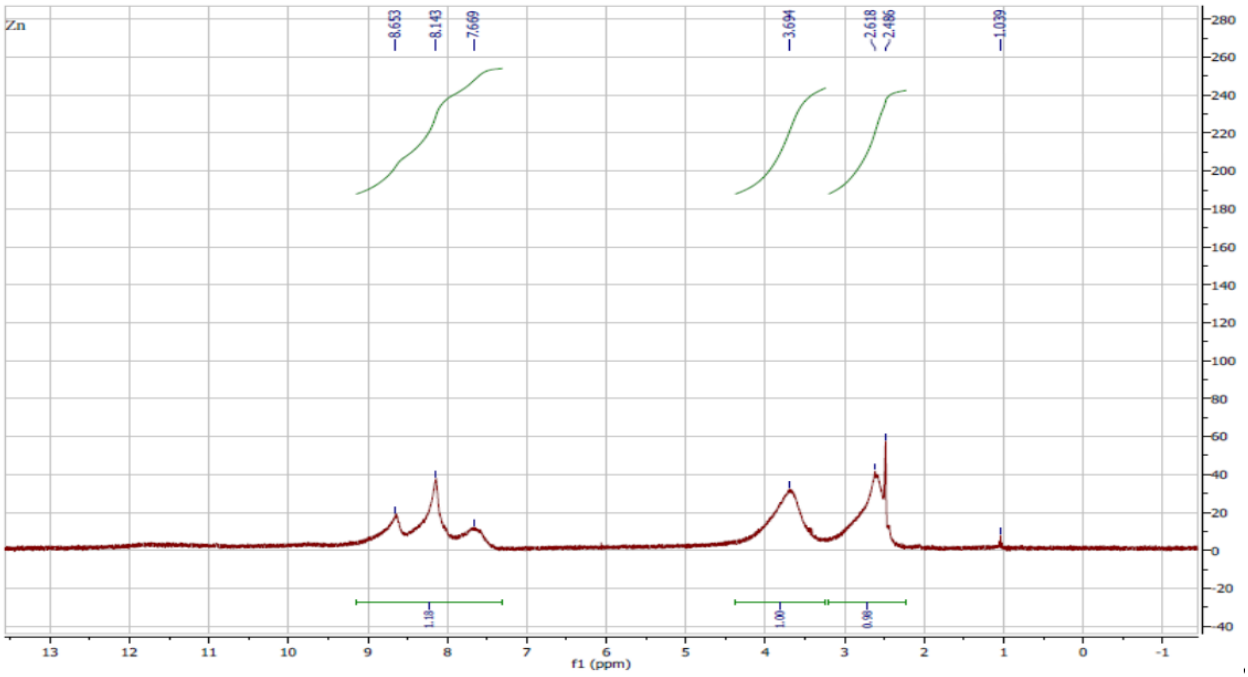


Figure 21. ^{1}HNMR spectrum for $Zn_2(HL)Cl_3$

4.3 Mass spectrometry results

Mass spectrometry is found to be useful for the unequivocal characterization of large molecules (Manoj, 2007), and for this reason, EI^+ mass spectra were generated for the ligands and their corresponding metal complexes.

4.3.1 HL and its metal complexes

The EI^+ mass spectrum for HL (figure 22) shows the presence of four main peaks below the molecular weight of the ligand (calc. 225.33 g/mol). The peak observed at m/z 221 (100%) corresponds to $[M - 4H]^+$, (with M representing the parent molecule). The peak at m/z 207 can be assigned to $[M – (Me +3H)]^+$ and the other two peaks at 147 and 73 assigned to $[M – Py]^+$ and $[NNHCS]^+$ respectively.

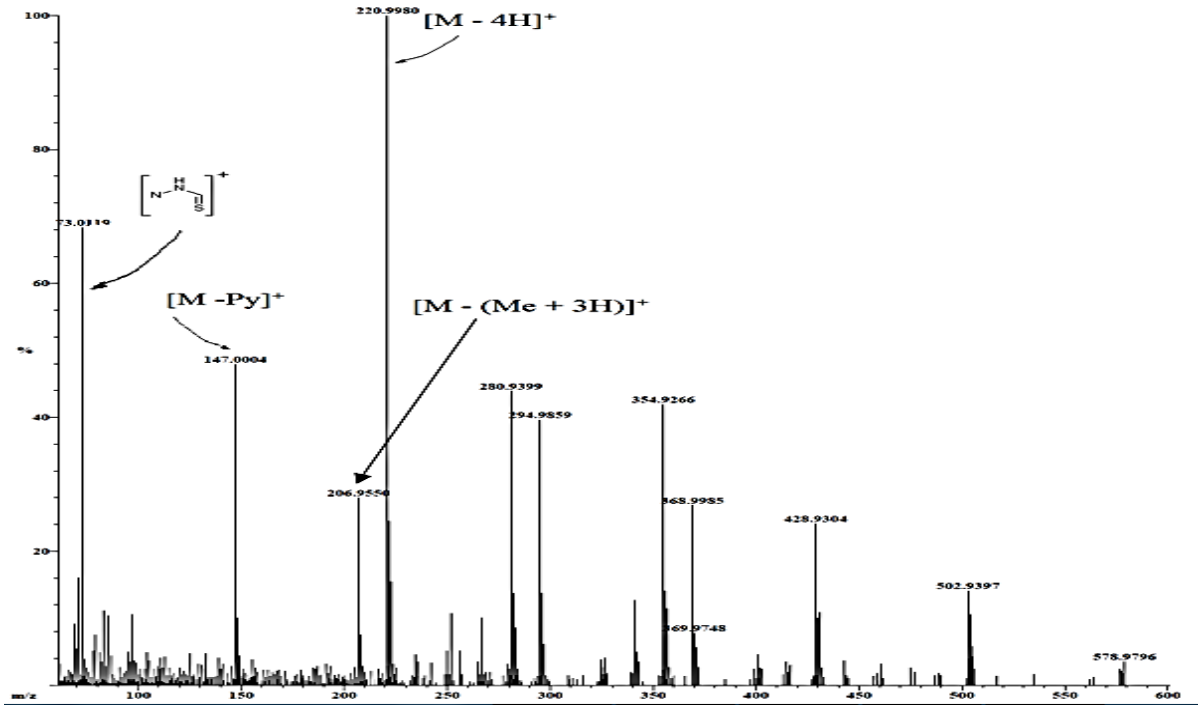
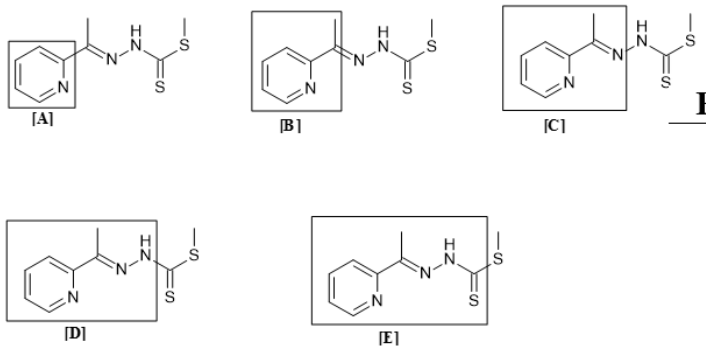


Figure 22. EI^+ mass spectrum for HL

The mass spectra of the metal complexes of HL show common fragments. These probably arise from the free ligand fragmentation. Some of the common peaks appearing in the spectra are the peak at m/z 77 which corresponds to $[Py\text{-}H]^+$, the peak at m/z 177 for $[M – SCH_3]^+$ and the peak at m/z 199 corresponding to the free ligand losing a methyl group and 3 hydrogens, [M –

(CH_3 + 3H)] (here M represents a free ligand (HNNS)). Other common fragments and their peaks are summarized in figure 23 and the mass spectra for the complexes are given in appendices (appendix A_{1-4}).



Fragment	m/z
$[A]^+$	**78**
$[B]^+$	**105**
$[C]^+$	**119**
$[D]^+$	**134** (133 for Sn complex)
$[E]^+$	**178**

Figure 23. Summary of common fragments observed in the mass spectra of HL metal complexes

4.3.2 H_2L and its metal complexes

The EI^+ mass spectrum for H_2L (figure 24) show about six peaks that can be successfully assigned to their corresponding m/z ratios and the molecular ion, $[M]^+$ peak can be clearly observed at m/z 312. The peak at 297 (33.8%) can be assigned to $[M - CH_3]^+$ fragment and the peak at 234 corresponds to $[M – Py]^+$. Other peaks and their corresponding fragments are indicated in the mass spectrum of H_2L.

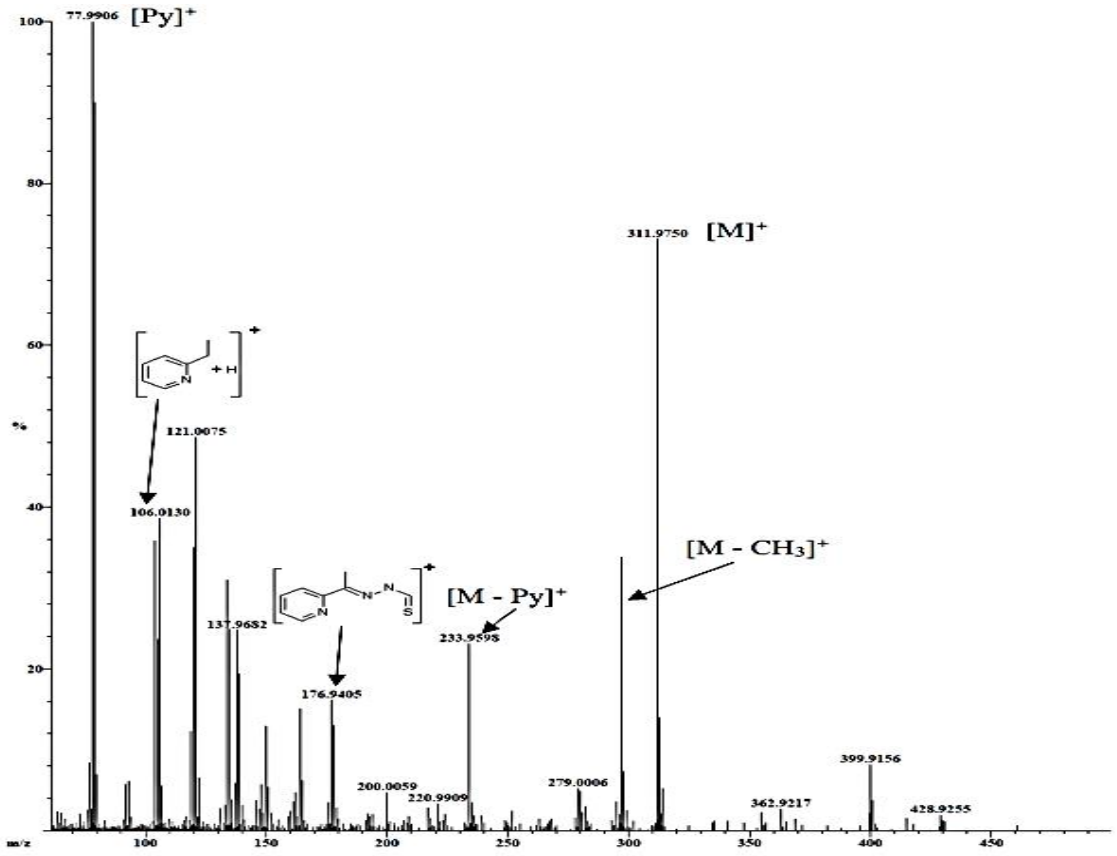
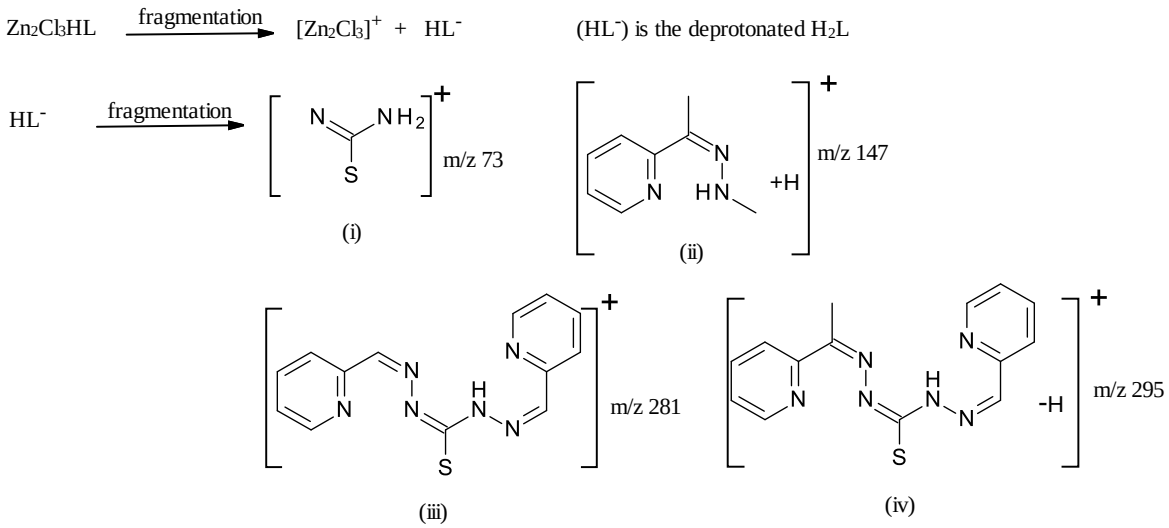


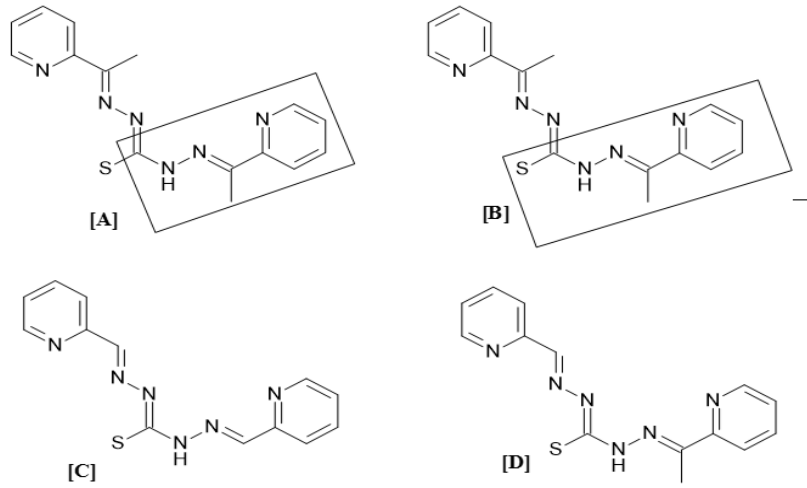
Figure 24. EI^+ mass spectrum for H_2L

The mass spectra of the metal complexes of H_2L show peaks that correspond to fragments of the free ligand. This implies that upon fragmentation, these metal complexes break down in such a way that the ligand is freed and it is then fragmented further to give fragments that are recorded by the analyser. The ESI-MS spectrum of complex $[Zn_2Cl_3HL]$ may be considered to arise from decomposition of $[Zn_2Cl_3HL]$ to form fragments $[Zn_2Cl_3]^+$ and HL^-. The free ligand HL^- breaks down further to give possible fragments (i) to (iv). This is presented in scheme 4.



Scheme 4. Interpretation of ESI-MS of the Zn(II) complex summarized

Some of the common major peaks appearing in these spectra are the peaks at m/z 73 and 235 which correspond to $[NC(S)NH]^+$ and $[M –Py]^+$ respectively. The other common peaks are summarized in figure 25 and the full spectra are given in the appendices (appendix A_{6-7}).



Fragment	m/z
$[NC(S)NH]^+$	73
$[A + H]^+$	147
$[B - H]^+$	177
$[C]^+$	281
$[D + H]^+$	296

Figure 25. Summary of common fragments observed in the mass spectra of H_2L metal complexes

4.4 Infrared spectroscopy results

The data extracted from the spectra of the ligands and their corresponding metal complexes are given in table 6, and the major IR bands of the compounds were identified on the basis of similar compounds (Bacchi et al., 1999; C. L. Chen et al., 2011; Daniel, 2009).

Table 6. Infrared absorption frequencies (cm^{-1}) of the ligands and its corresponding metal complexes

HL	**Complexes**		
	Pb(II)	**Ag(I)**	**Sn(II)**
680(m), 740(m), 780 (vs), 960(s), 990(m), 1050(sh), 1070(vs), 1280(s, b), 1430(s), 1460(vs), 1560(vs), 3150(m)	710(m), 759(m), 780(s), 800(s), 920(vs), 990(vs), 1040(m), 1280(s), 1370(m), 1440(vs), 1490(m), 1550(m), 1580(w)	740(s), 880(s), 990(s), 1040(m), 1360 (s, b), 1400(s), 1450(m), 1510(w), 1650(w), 2820(w), 2870(w)	749(m), 790(s), 810(s), 990(vs), 1000(vs), 1090(w), 1300(m), 1440(vs), 1500(m)

H_2L	**Complexes**	
	Mn(II)	**Zn(II)**
680(s), 750(m), 790(vs), 850(s), 1020(m), 1130(s), 1230(vs), 1430(sh), 1460(vs), 1500(vs), 3050-3200(m, br), 3400(w), 3590(w)	740(s), 782(s), 1017(s), 1070(s), 1105(s), 1147(s), 1213(s), 1255(s), 1441(s), 1472(s), 1520(s), 1560(s), 1600(s), 1716(s), 2952(w), 3091(w), 3383(w)	672(s), 747(s), 782(s), 903(s), 1020(s), 1085(s), 1158(s), 1266(s), 1470(s), 1522(s), 1566(s), 1621(s), 1646(s), 1703(s), 3327(w), 3099(w)

br = broad, sh = shoulder, vs = very strong, s =strong, m = medium, w = weak.

Since the ligands were synthesized by the combination of a ketone (2-acetylpyridine) and the hydrazide derivatives, their formation are confirmed by the absence of peaks at 1750 cm^{-1} and 3200-3180 cm^{-1} assignable to the ν(C=O) and $\nu(NH_2)$ respectively(Daniel, 2009). The bands at about 3590 cm^{-1} and 3050 - 3200 cm^{-1} can be assigned to ν(N-H) and ν(C-H) stretch respectively. The vibrations assignable to the –C-H (of CH_3) bend are also present in all the

spectra at about 1460 cm^{-1}. Other major peaks in the spectrum appear at 1500 - 1560 *ν*(C=N), 1020 -1070 cm^{-1} *ν*(C=S) with contribution from *ν*(C-N), and <700 cm^{-1} *ν*(py) (Bacchi et al., 1999; C. Chen et al., 2010; C. L. Chen et al., 2011; Manoj, 2007). The absence of a band in the region 2500 – 2600 cm^{-1} implies that the ligand retain its thione form in solid state (C. Chen et al., 2010; S Kumar & Kumar, 2013).

In literature, it is indicated that ligands are capable of binding to the metals via the pyridyl nitrogen, the azomethine nitrogen, and the sulphur atom (Bacchi et al., 1999; C. L. Chen et al., 2011; Daniel, 2009) and this implies that changes in frequencies associated with C=S, C=N, C-N, and N-H vibrations are expected. Upon coordination, the strength of a bond between two atoms (of which one is coordinating to the metal) and this leads to a shift to lower frequency of the affected bonds (C. L. Chen et al., 2011; Mo et al., 1998).

For the complexes of HL, it is worth noting the changing of the major bands in the ligands IR spectrum. For instance, the band at *ca.* 3150 cm^{-1} in the free ligand does not appear in the complexes' spectra suggesting possible deprotonation of the ligand (Daniel, 2009). The *ν*(C=S) that appear at about 1070 cm^{-1} in the free ligand, shifted lower frequencies in all the metal complexes of HL and this confirm the participation of the sulphur atom in the coordination of the metals to the ligand (Hossain et al., 1993; West & Huffman, 1989).

IR spectra studies have been found to be very useful for mononuclear or dinuclear complexes of thiocarbohydrazones towards copper (Manoj, 2007), therefore the results obtained for the manganese and zinc complexes of H_2L are expected to give similar information. In these complexes, the presence of the band *ca.* ~3300 cm^{-1} assignable to *ν*(N-H) confirms that the coordination still leaves one free –NH group (Daniel, 2009; Manoj, 2007). Upon deprotonation, the C=S bond in the free ligand becomes a single bond (C-S) in the metal complex and this is supported by the *ν*(C-S) bands in the range 1147 – 1158 cm^{-1} (Manoj, 2007).

The IR spectra for the complexes has a number of bands in the 1520 to 1646 cm^{-1} range and this can be linked to the mixing patterns of C-N, N-N, and C=N groups in complexes and this can be attributed to possible coordination via the azomethine nitrogen (Manoj, 2007). Tentative assignment of bands of ligands and their corresponding metal complexes are given in table 7.

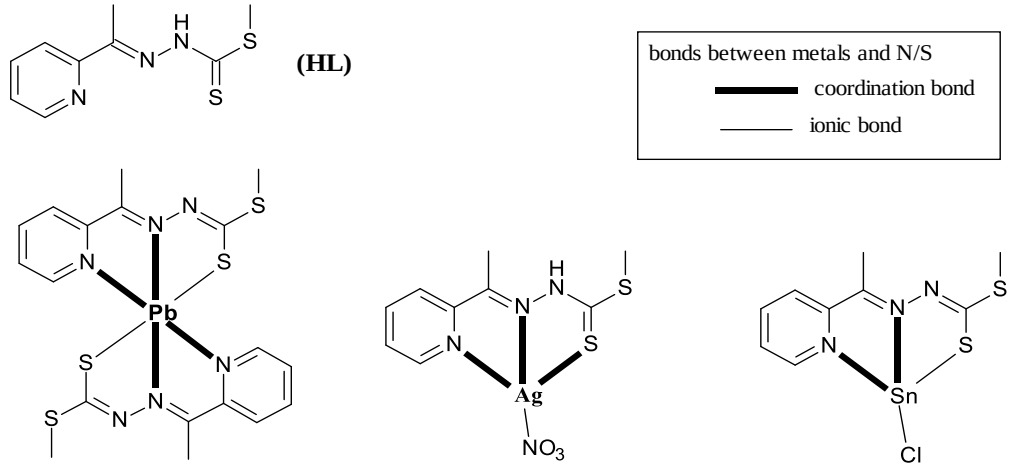
Table 7. Tentative IR spectra assignment for ligands and their corresponding metal complexes (cm^{-1})

C.	*ν*N-H	*ν*C-H	*ν*C=N + *ν*C=C	*ν*N-N	*ν*C-N + *ν*C=S	*ν*C-S	py
LH		3150(w)	1430(s), 1460(vs), 1560(vs)	1280(s b)	1050(sh), 1070(vs)		680(m)
Pb(II) comp.			1440(vs), 1490(m), 1550(m), 1580(w)	1280(s)	1040(m)		
Ag(I) comp.		2820(w), 2870(w)	1450(m), 1510(w	1360(s,br)	1040(m)		
Sn(II) comp.			1440(vs), 1500(m)	1300(m)	1000(vs)		
H_2L	3400(w), 3590(w)	3050-3200(m,br)	1430(sh), 1460(vs), 1500(vs)	1230(vs)	1020(m)		680(m),
Mn(II) comp.	3383(w)	3050-3200(m,br)	1441(s), 1472(s), 1520(s), 1560(s), 1600(s)	1213(s), 1255(s)	1017(s), 1070(s)		
Zn(II) comp.	3327(w),	3099(w)	1470(s), 1522(s), 1566(s), 1621(s), 1646(s)	1266(s),	1020(s), 1085(s)		672(s),

C. = compound, comp. = complex, br = broad, sh = shoulder, vs = very strong, s =strong, m = medium, w = weak.

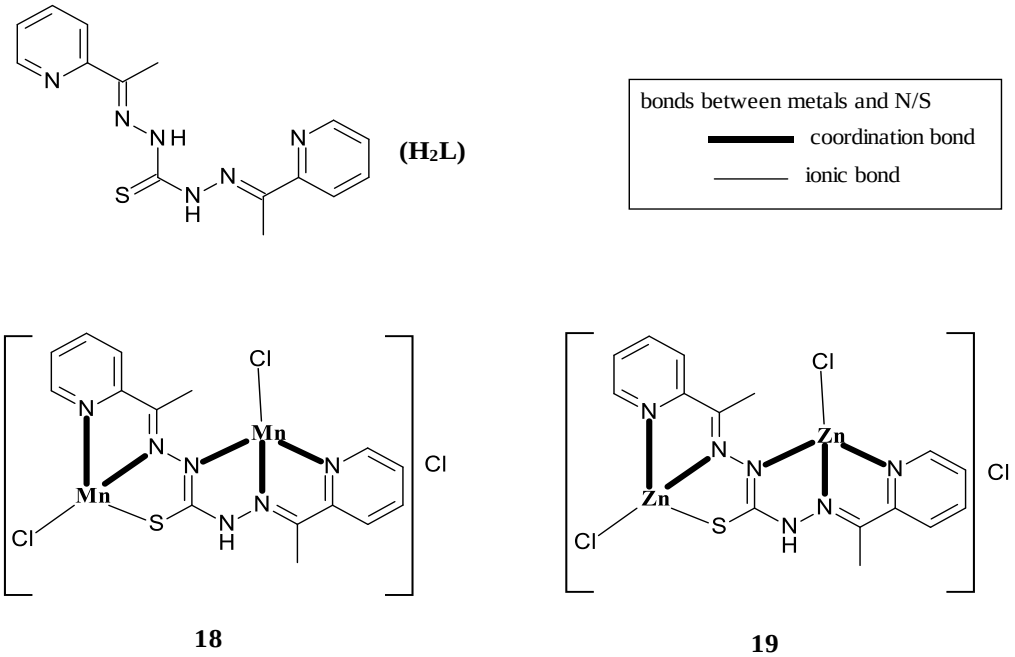
4.5 Suggested structural formulae of the synthesized ligands and their complexes

Combining information obtained from elemental analysis, spectral analysis data and comparing with analogous structures reported in literature, the tentative structure of the metal complexes synthesized in this research may tentatively be formulated as shown in figure 26 and 27.



15 **16** **17**

Figure 26. Tentative structures of $Pb(L)_2$ **(15)**, $Ag(HL)NO_3$ **(16)**, and Sn(L)Cl **(17)** complexes of HL



18 **19**

Figure 27. Tentative structures of $Mn_2(HL)Cl_3$ **(20)**, and $Zn_2(HL)Cl_3$ **(21)** complexes of H_2L

4.6 Antiplasmodial activity results

The ligands and their corresponding metal complexes were screened for antimalarial activity. Using chloroquine and Artesunate as controls, the synthesized compounds were *in vitro* tested for antiplasmodial activity against *P. falciparum* chloroquine sensitive (CQS) NF54 strain. The results are given in table 8 in form of percentage survival and half inhibitory concentration (IC_{50}).

Table 8. In vitro antiplasmodial activity against P. falciparum (CQS) NF54 strain

Compound		**% Survival at 1000ng/ml**	**NF54:IC_{50} (ng/ml)**
HL		8.9	0.74 ± 0.3
HL complexes	**Pb(II)**	0.00	19.9 ± 8.7
	Ag(I)	0.00	17.0 ± 8.8
	Sn(II)	0.00	36.1 ± 5.2
H_2L		29.2	49.9 ± 11.8
H_2L complexes	**Mn(II)**	29.4	21.0 ± 14.5
	Zn(II)	14.6	20.4 ± 5.4
Controls	**CQ**	9.9	3.7 ± 1.5
	Artesunate	5.7	$< 2 \pm \text{ND}$

The results show that HL possesses pronounced activity against the NF54 strain with an IC_{50} value of 0.74 ± 0.3 ng/ml as compared to the activity of chloroquine (3.7 ± 1.5) and artesunate ($< 2 \pm$ND) toward the strain. The complexes synthesized in this study showed low antiplasmodial activity than the free ligand and this implies that complexation decreases the activity of this ligand towards the NF54 strain.

H_2L show low antiplasmodial activity with an IC_{50} value of 49.0 ± 11.8 ng/ml in comparison to the controls. Upon complexation however, the antiplasmodial activity increased tremendously 21 ± 14.5 and 20.4 ± 5.4 ng/ml for the manganese(II) and zinc(II) complexes respectively. H_2L is considered to be hydrophilic and this improves its solubility and transportation across the membranes in biological systems, therefore introducing the metal ions during complexation enhances the lipophilic character of the compounds, increasing their biological activities as a result (Bacchi et al., 1999; Daniel, 2009).

CHAPTER 6: CONCLUSION

In this study, two series of metal complexes were synthesized. The first series focused on metal complexes of 2-acetylpyridine S-methyldithiocarbazate (HL). The ligand and its metal complexes were prepared and characterized using spectroscopic techniques such as proton NMR, infrared (IR) and mass spectroscopy. Of all the metal ions selected for this study, only Pb(II) reacted with HL in a 2:1 ligand to metal ratio to give a complex with a general formula $Pb(NNS)_2$ (NNS represents the deprotonated ligand, tentative structure **15** figure 26). Tin(II) and Ag(I) give complexes with formulas of [Sn(NNS)]Cl (**17**) and $Ag(HNNS)NO_3$ (**16**) respectively.

The second series is constituted of metal complexes of bis(2-acetypyridine) thiocarbohydrazone (H_2L). The ligand and divalent metallic complexes of manganese(II) and zinc(II) were prepared and characterized by similar procedures as the compounds in the first series. H_2L probably binds to the metal ions in the mono-deprotonated form as shown in figure 27 forming bimetallic, uni-charged complexes completed by a chloride counter ion

The ligands and their corresponding metal complexes were evaluated for antiplasmodial activity against the chloroquine sensitive (NF54) strain of *P. falciparum*. The complexes of HL are less biologically active than their parent ligand against the NF54 strain and the silver complex is more active than the lead and tin complexes. For H_2L and its metal complexes, the complexes show better activity than the free ligand. This shows how the formation of metal complexes affect the biological activities of the parent organic molecules or ligands

.

Recommendations

This project confirmed the antiplasmodic activities of metal complexes of nitrogen-sulphur containing ligands as reported in literature. From the biological activity results of metal complexes of 2-acetylpyridine S-methyldithiocarbazate, we observed how the biological activity decreases in the metal complexes and also how the percentage survival of the strain drop from 8.9% in the free ligand to 0.00% in the metal complexes. Metal complexes of this ligand were found to possess better antimalarial activity against a chloroquine resistant malaria strain as reported by Kiremire (2011). Comparing these results, reveals the need to evaluate the activities of metal complexes reported by Kiremire (2011) against the NF54 strain and see how the overall biological activity changes for these compounds. In addition to that, toxicity test of these ligands and their corresponding metal complexes need to be carried out in future studies.

Since the kind of work done in this project involves inorganic and biological sciences expertise, a good collaborative agreement between these two fields will be helpful for a thorough investigation starting from the preparation, characterization and biological evaluation of the compounds.

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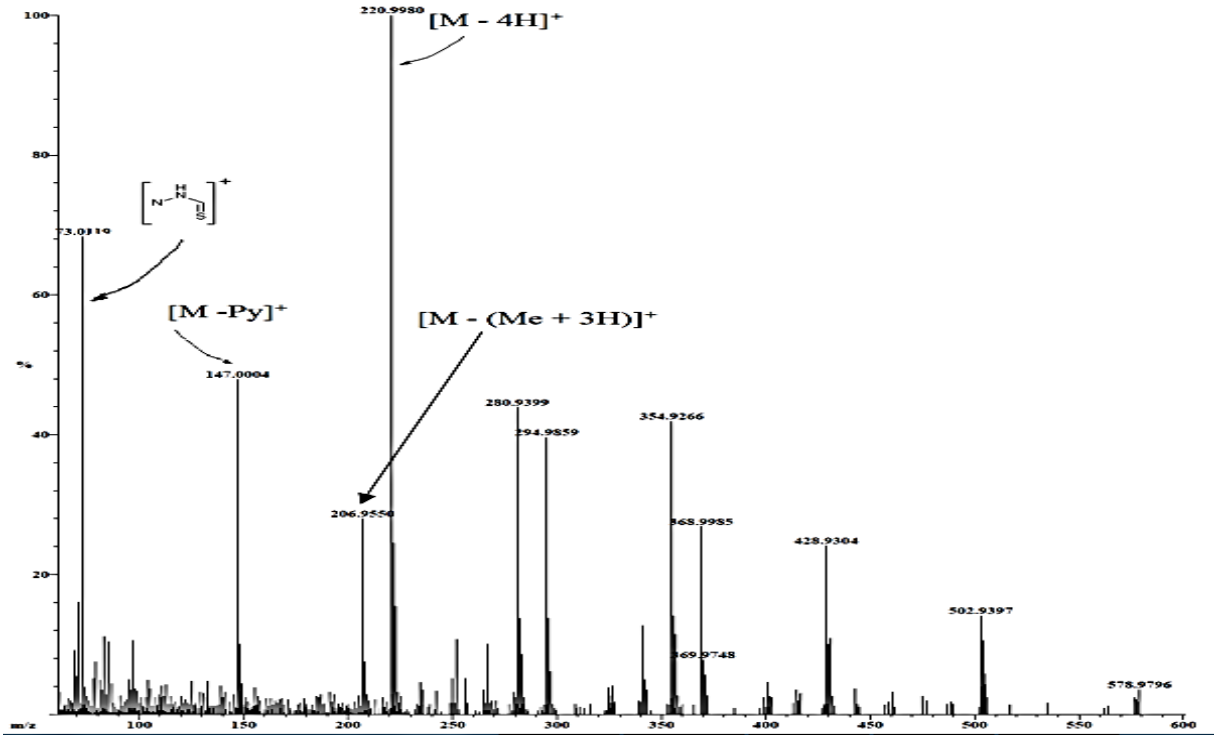
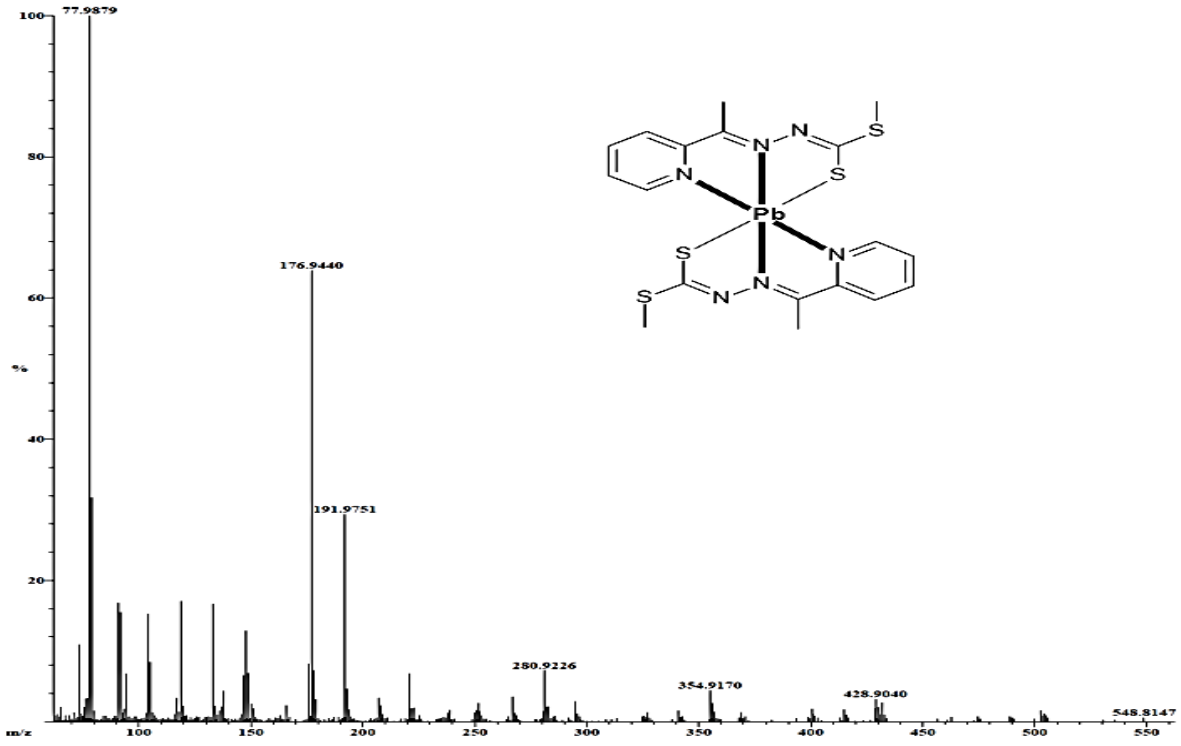
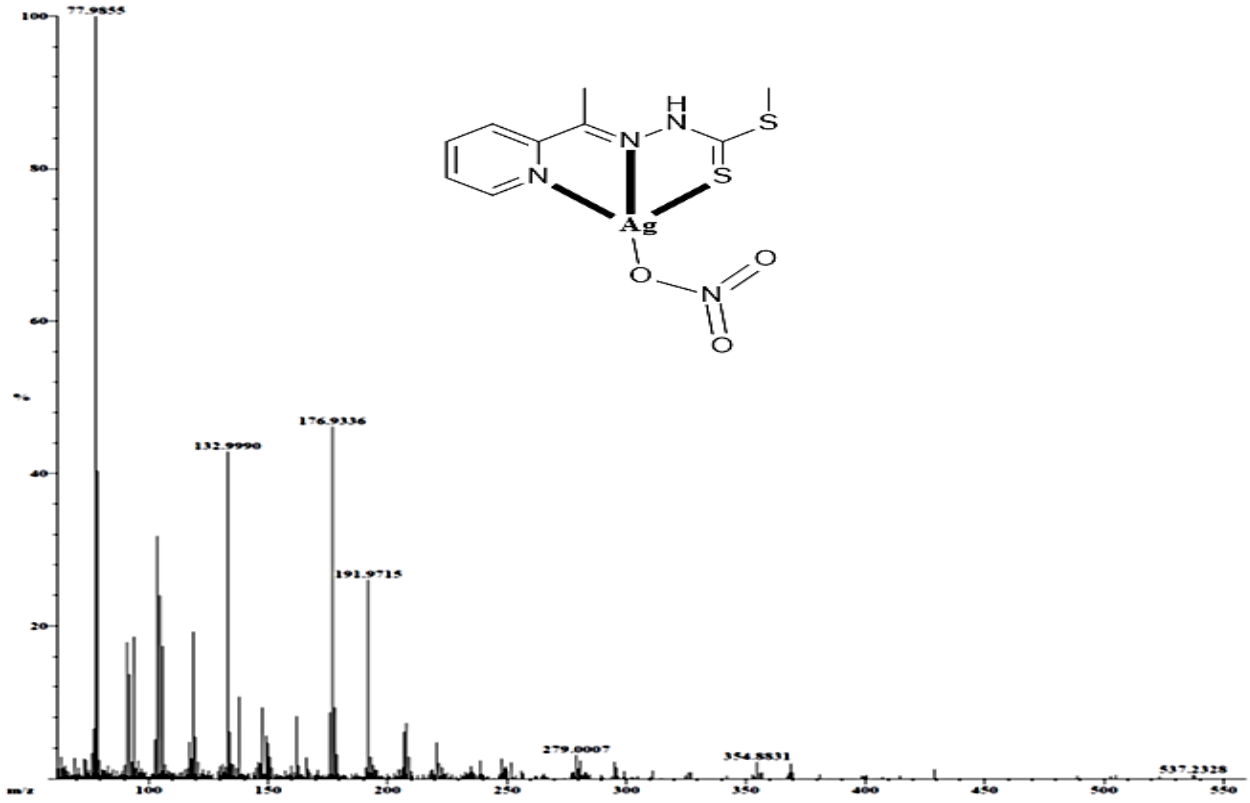
Appendinx A EI^+ mass spectra



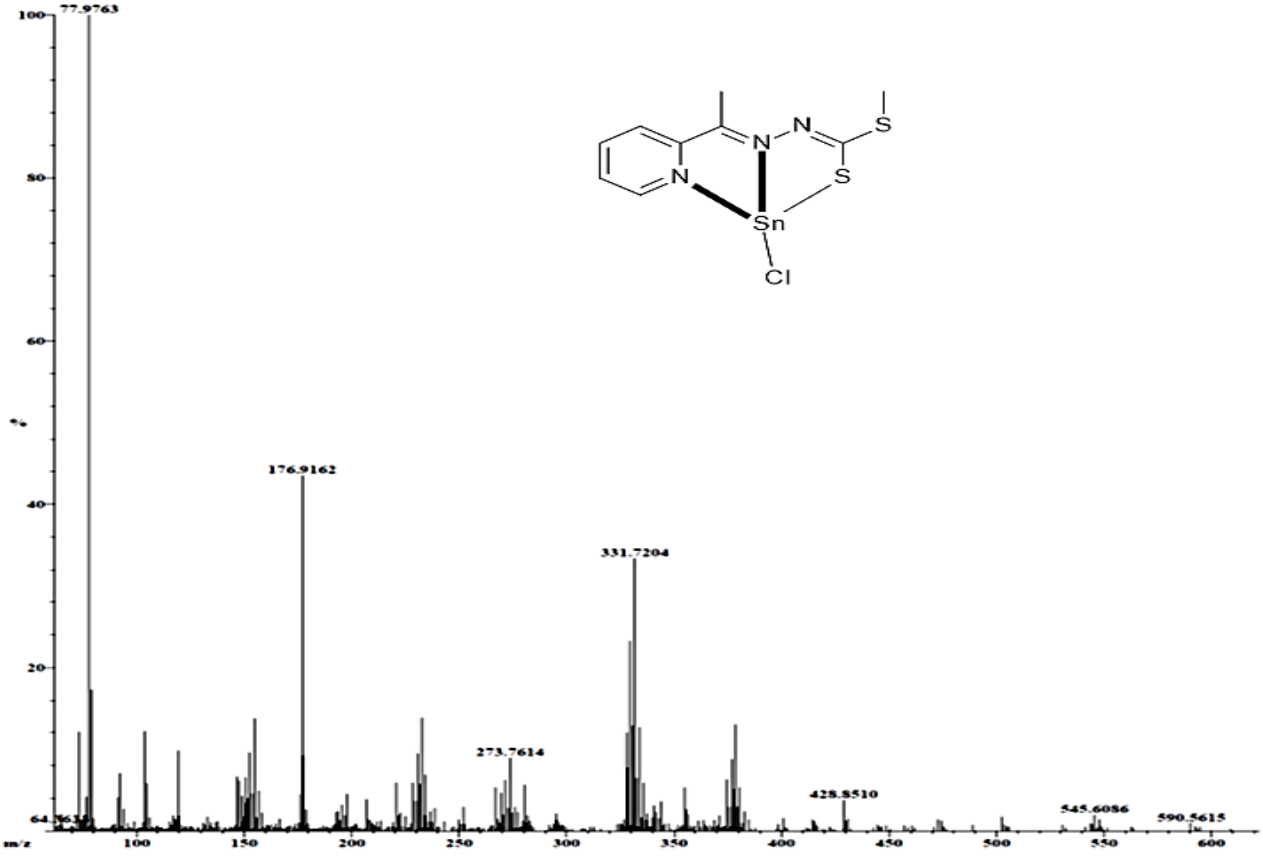
Appendix A 1. EI^+ mass spectrum for HL



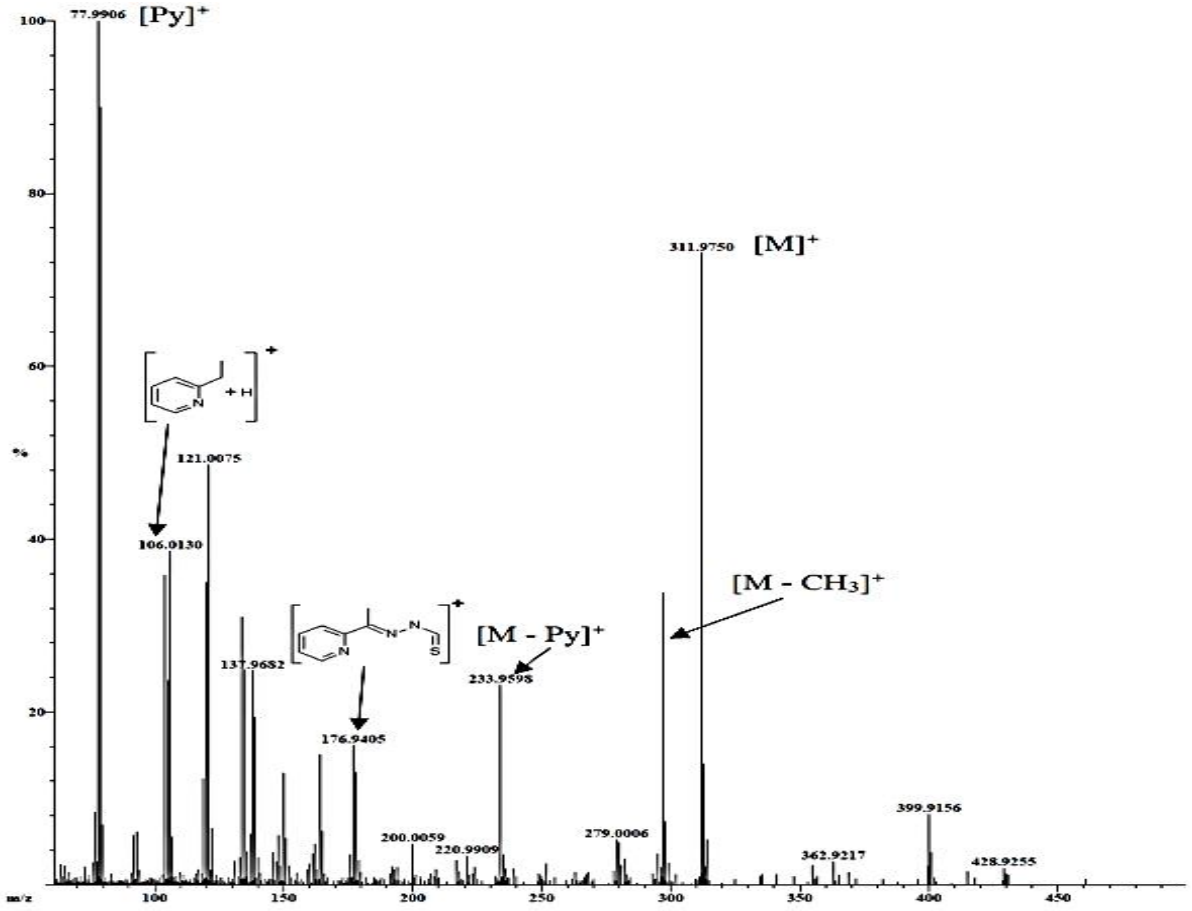
Appendix A 2. EI^+ mass spectrum for the Pb(II) complex of HL



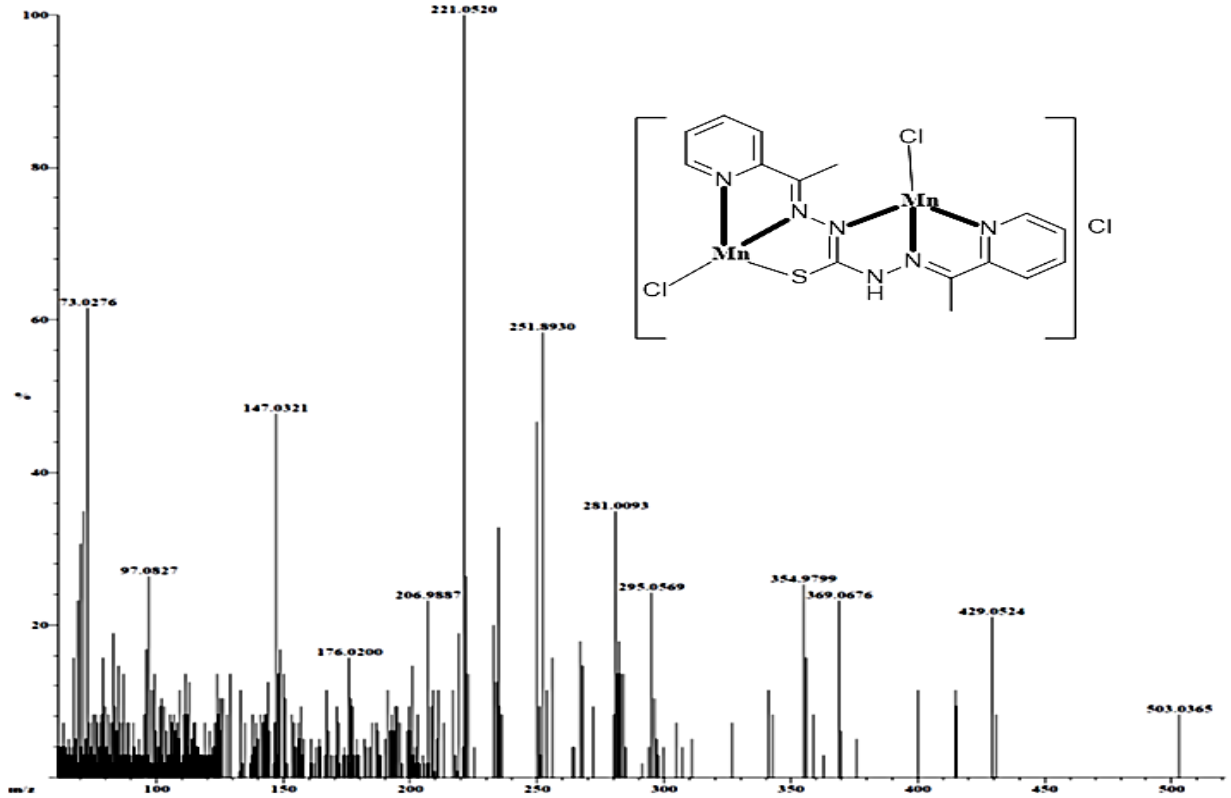
Appendix B *3.* EI^+ mass spectrum for the Ag(I) complex of HL



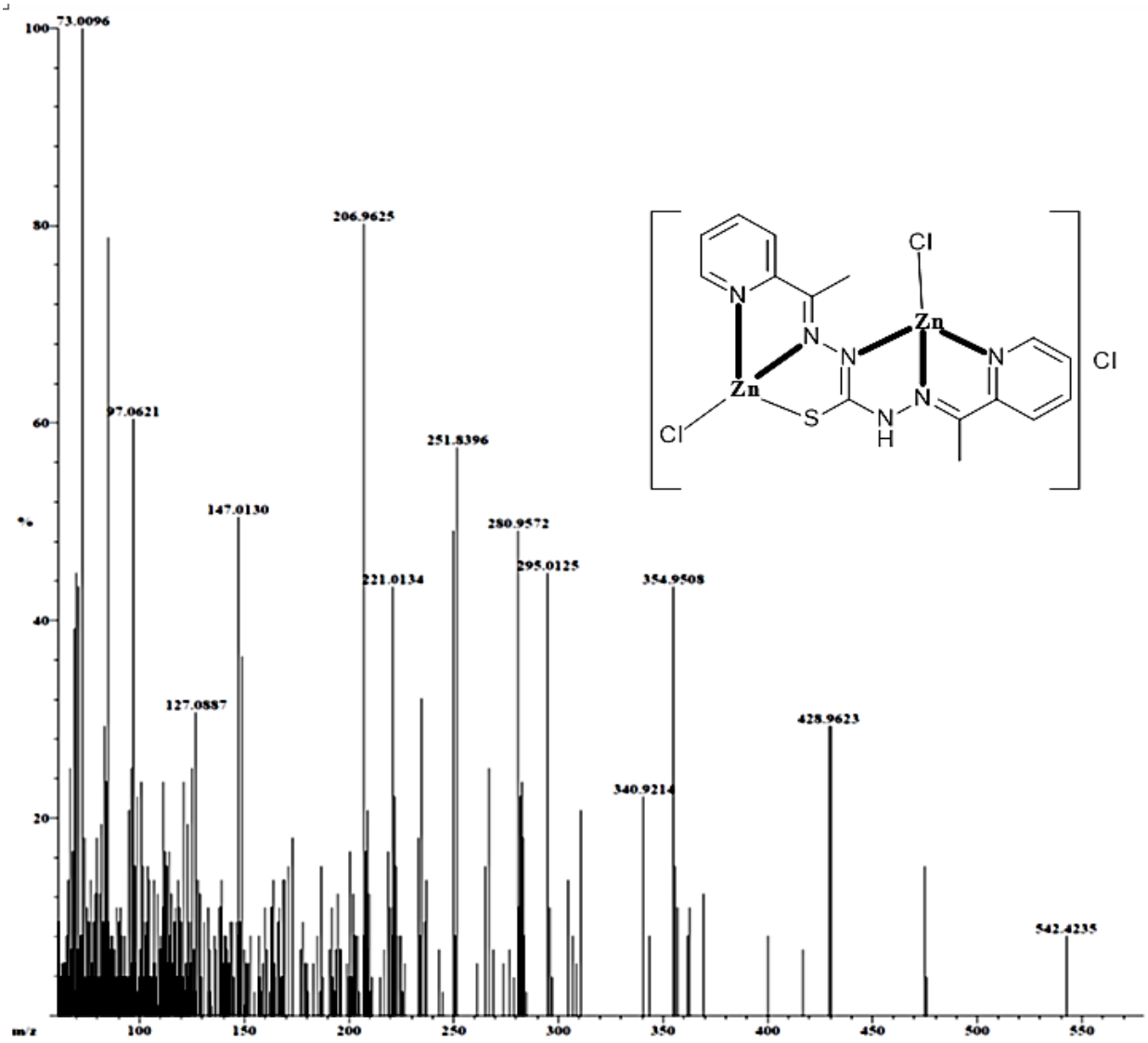
Appendix A *4.* EI^+ mass spectrum for the Sn(II) complex of HL



Appendix A *5.* EI^+ mass spectrum for H_2L



Appendix A *6.* EI^+ mass spectrum for the Mn(II) complex of H_2L



Appendix A *7.* EI^+ mass spectrum for the Zn(II) complex of H_2L