SYNTHESIS, SPECTRAL CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF ORGANOTIN(IV) COMPLEXES HETEROCYCLIC-\(\bar{N}(4)\)-CYCLOHEXYLTHIOSEMICARBAZONE LIGAND

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This Final Year Project is submitted in partial fulfilment of the requirement for the degree of Bachelor of Sciences with Honours

( Resource Chemistry)

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Declaration

No portion of the work referred to in this dissertation has been submitted in support of an application for another degree of qualification of this or any other university or institution of higher learning.

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<tr>
<td>Sn(IV)</td>
<td>Tin(IV) atom</td>
</tr>
<tr>
<td>(HPCCT)</td>
<td>2-pyridinecarbaxaldehyde</td>
</tr>
<tr>
<td></td>
<td>(N(4)\text{-cyclohexylthiosemicarbazone})</td>
</tr>
<tr>
<td>[MeSnCl(_2)(PCCT)]</td>
<td>Methyltin(IV) dichloride complex</td>
</tr>
<tr>
<td>[BuSnCl(_2)(PCCT)]</td>
<td>Butyltin(IV) dichloride complex</td>
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Synthesis, Spectral Characterization and Biological Activities of Organotin(IV) Complexes with Heterocyclic-N(4)-cyclohexylthiosemicarbazone Ligand

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ABSTRACT
The reaction of organotin(IV) chloride(s) with 2-pyridinecarboxaldehyde-N(4)-cyclohexylthiosemicarbazone [HPCCT, (1)] ligand under a nitrogen atmosphere in absolute methanol lead to the formation of seven new organotin(IV) complexes of the type [MeSnCl₂(PCCT)] (2), [BuSnCl₂(PCCT)] (3), [PhSnCl₂(PCCT)] (4), [Me₂SnCl(PCCT)] (5), [Bu₂SnCl(PCCT)] (6), [Ph₂SnCl(PCCT)] (7), and [Ph₃Sn(PCCT)] (8). The ligand [HPCCT] (1) and its organotin(IV) complexes (2-8) were characterized by CHN analysis, molar conductivity, UV-Vis, FT-IR, and \(^1\)H NMR spectral studies. Results of spectroscopic data subjected that [HPCCT] (1) is coordinated to the tin(IV) through the thiolate-S, azomethine-N and pyridine-N atoms. Six coordinated molecular structure has been proposed for the synthesized organotin(IV) complexes. The preliminary toxicity test of ligand (1) as well as its organotin(IV) complexes (2-8) have been evaluated against Artemina Salina. Toxicity assay results showed that the organotin(IV) complexes (2-8) exhibited better toxicity activity than free ligand.

Key words: Heterocyclic-N(4)-cyclohexylthiosemicarbazone, organotin(IV) complexes, spectra analysis, cytotoxicity

ABSTRAK
Tindakbalas organostanum(IV) kloride dengan ligand 2-pyridine-N(4)-cyclohexylthiosemicarbazone [HPCCT, (1)] di bawah nitrogen gas di dalam absolute metanol menghasilkan tujuh jenis kompleks organostanum(IV) baru seperti [MeSnCl₂(PCCT)] (2), [BuSnCl₂(PCCT)] (3), [PhSnCl₂(PCCT)] (4), [Me₂SnCl(PCCT)] (5), [Bu₂SnCl(PCCT)] (6), [Ph₂SnCl(PCCT)] (7), dan [Ph₃Sn(PCCT)] (8). Ligand [HPCCT] (1) dan kompleks organostanum(IV) telah dicirikan menggunakan analisis unsur, molar conductivity, UV-nampak, IR, dan \(^1\)H RMN pembelajaran spektal. Keputusan data spektroskopik menunjukkan ligand [HPCCT] (1) berkodinasi pada stanum(IV) melalui thiolate-S, azomethine-N dan pyridine-N atom. Kompleks organostanum(IV) dicadangkan mempunyai enam kordinasi. Ujian ketosikan ligand (1) dan kompleks organostanum(IV)(2-8) dinilai menggunakan Artemina Salina. Assay ketosikan menunjukkan kompleks organostanum(IV) (2-8) mempamerkan kesan ketosikan yang baik daripada ligand bebas.

Kata kunci: Heterocyclic-N(4)-cyclohexylthiosemicarbazone, kompleks organostanum(IV), analisis spektra, ketosikan.
1.0 Introduction
1.1 Background of thiosemicarbazone ligands and their organotin(IV) complexes

Thiosemicarbazone is a chemical compound possessing several donor atoms and generally bind to metal atom through N and S donor atoms. Heterocyclic thiosemicarbazones are interested because of their metal chelating ability and their ability to coordinate in either neutral or deprotonated forms. From the previous studies, the coordination chemistry of thiosemicarbazone with transition metal ions has been widely studied. However, thiosemicarbazones and their organotin(IV) complexes have a great pharmacological interest among the inorganic chemist (Affan et al., 2012). This is due to the marked and various biological activities such as anticancer, antibacterial, antiviral antifungal and anti-inflammatory (David et al., 2005; Singh et al., 2011). For the past few years, a large amount of works have been paid on the studies of the transition metals such as palladium, rubidium, iron, copper, zinc and cobalt with thiosemicarbazone ligands.

Sen and his co-workers (2009) have reported the tin(IV) complexes containing ONS coordination mode of dimethyl-(4)-cyclohexylthiosemicarbazone as a novel of antitumor agent. The biological activity of compound is often related with chelating effect that available with metal ions. Therefore, a better understanding of both ligand and organotin(IV) complexes are required in order to synthesize a highly active compound.

In fact and up to date, organotin(IV) complexes are still extensively studied due to their coordination geometries as well as structural diversity. Thiosemicarbazone ligands have shown various geometry structure depend on the functional behavior of ligand. Gerimario and his members (2001) have studied the five coordinated diphenyltin(IV) complex with N-heterocyclic thiosemicarbazone ligand containing ONS-donor atom which suggested that, the
diphenyltin(IV) complex exhibit trigonal pyramidal geometry. In addition, instead of organotin(IV) complexes the transition element of thiosemicarbazone has also been used as device for the application of optical computing, telecommunication, optical storage and optical information processing (Maniran & Jayabalakrishna., 2011).

Meanwhile, organotin(IV) compound is a type of organometallic compound that showed wide application as catalyst and stabilizer. However, certain derivative is used as agrochemical and antifouling paint due to their low phototoxicity and favourable environmental degradation with non-toxic inorganic residue (Awang et al., 2011). Organotin(IV) complexes have also been studied in order to identify their biological activity against fungi, bacterial and cancer illness (Singh et al., 2011). The tin(IV) complexes have also been proposed as potential therapeutic alternative to replaced cisplatin and similar anticancer agent, since the cisplatin (platinum based compound) has contribute severe effect to patients (Jamieson & Lippard., 1999). Therefore, an interest in organotin(IV) complexes has rised among the researcher. At least 195 of organotin(IV) complexes have been studied from 2003-2007 as antiproliferatives properties against various types cell lines (Hadjikakou & Hadjiadiis., 2009)

Triorganotin(IV) complexes have also displayed higher biological activity than di and mono-organotin(IV) complexes (Elliot et al., 1979). Nevertheless, it has been observed that several diorganotin complexes shown potential of antineoplastic and antituberculosis agent (Demetrzi., 2006). The biological effect of organotin(IV) are greatly influences by the structure of the molecule as well as the coordination number of tin moiety (Amini et al., 2009; Win et al., 2008). Therefore, both thiosemicarbazone ligand and organotin(IV) complexes
have highest demanding due to the various application in industrial and agricultural applications (Singh et al., 2011).

From the literature review, organotin(IV) complexes of $N(4)$-heterocyclic thiosemicarbazone have received less attention there is still limited research has been carried out with organotin(IV) chloride(s). Therefore, organotin(IV) complexes derived from heterocyclic $N(4)$-cyclohexyltiosemicarbazone ligand containing $NNS$-donor atom are still lacking. From the above consideration, the author has decided on the synthesis, spectral characterization and toxicity activity of organotin(IV) complexes of 2-pyridinecarbaxaldehyde-$N(4)$-cyclohexylthiosemicarbazone ligands in order to expand the chemistry and biological studies of the organotin(IV) complexes.
1.2 Objective

The general aim of the work described in this project was the synthesis and structural characterization of organotin(IV) complexes with heterocyclic-\(N(4)\)-cyclohexylthiosemicarbazone ligand as well as their biological activities. In specific terms, the objectives of the work were:

1) to synthesise heterocyclic-\(N(4)\)-cyclohexylthiosemicarbazone ligand

2) to synthesise the organotin(IV) complexes with heterocyclic-\(N(4)\)-thiosemicarbazone ligand

3) to characterize the heterocyclic-\(N(4)\)-thiosemicarbazone ligand and its organotin(IV) complexes by elemental analyses, UV-Visible, FT-IR, and \(^1\)H NMR spectral analyses

4) to determined the molar conductances values of the synthesized organotin(IV) complexes

5) to evaluate the toxicity of heterocyclic-\(N(4)\)-thiosemicarbazone ligand and its organotin(IV) complexes
2.0 Literature review

2.1 Thiosemicarbazone with organotin(IV) complexes

Affan and his co-workers (2012) have reported the synthesis and characterization of organotin(IV) complexes of 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone (Figure 1). The ligand have showed tautomerization environment. In their work, organotin(IV) complexes were obtained by reacting organotin(IV) chloride(s) with 2-hydroxyacetophenone and N(4)-cyclohexylthiosemicarbazone (Figure 3). The X-ray structure of diphenyltin(IV) showed that the tin(IV) atom is located in distorted trigonal bipyramidal environment with thiosemicarbazone, where the ligand acted as dinegative tridentate ONS-chelating agent.

Figure 1: Molecular structure of diphenyltin(IV) complex
Figure 2: Structure of 2-hydroxylacetophenone-\textit{N}(4)-cyclohexylthiosemicarbazone ligand

Figure 3: Structure of organotin(IV) complexes of 2-hydroxylacetophenone-\textit{N}(4)-cyclohexylthiosemicarbazone

\[ \text{RX} \text{Sn} \text{HX} \]

- R = Me, X = Cl
- R = Bu, X = Cl
- R = Ph, X = Cl
- R = Ph, X = Ph
Meanwhile, for the biological activity of the compound, Affan and his co-workers have also studied the toxicity effect against brine shrimp (*Artemia salina*). They also evaluated from the study, the *in vitro* antibacterial activity of the complexes. The results obtained from the study indicated all the organotin(IV) complexes have higher potential antibacterial activity than free thiosemicarbazone ligand.

Recently, Affan *et al.*, (2011) have reported the synthesis and spectroscopic characterization of organotin(IV) complexes with 2-benzoylpyridine-\(N(4)\)-cyclohexylthiosemicarbazone. All organotin(IV) complexes were obtained by direct reaction of 2-benzoylpyridine-\(N(4)\)-cyclohexylthiosemicarbazone with equimolar ratio of both component (Figure 4). The results revealed that the ligand acted as a mononegative tridentate chelating agent and the central tin(IV) atom is six coordinated with a distorted octahedral geometry.

![Figure 4: Proposed structure of organotin(IV) complexes of 2-benzoylpyridine-\(N(4)\)-cyclohexylthiosemicarbazone](image)

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>X</th>
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</thead>
<tbody>
<tr>
<td>Me</td>
<td>Cl</td>
<td>Cl</td>
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<tr>
<td>Ph</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>Cl</td>
<td>Ph</td>
<td>Ph</td>
</tr>
</tbody>
</table>

Figure 4: Proposed structure of organotin(IV) complexes of 2-benzoylpyridine-\(N(4)\)-cyclohexylthiosemicarbazone
Affan et al., (2009) have synthesized pyruvic acid thiosemicarbazone ligand. The ligand has been prepared by the condensation reaction of equimolar of thiosemicarbazide and pyruvic acid. They reported that the ligand exist in the thione tautomer when it is in solid form and in the thiol tautomer when it is in solution (Figure 6).

![Tautomerization of the thiosemicarbazone ligand](image)

Figure 5: Molecular structure of phenyltin(IV) complex

Figure 6: Tautomerization of the thiosemicarbazone ligand
The metal complexes of pyruvic acid thiosemicarbazone have been synthesized by the direct reaction of ligand with appropriate organotin(IV) salts under N\textsubscript{2} atmosphere (Figure 7). The entire coordination mode was difference in all the organotin(IV) complexes (Affan \textit{et al.}, 2009). The molecular structure of dimethyltin(IV) has revealed the complexes exist as trigonal pyramidal with dinegative tridentate pattern through ONS-donor atom. The central tin(IV) moiety was exhibited five coordination number.

Figure 7: Organotin(IV) complexes of pyruvic acid thiosemicarbazone
They have also investigated the biological activity of ligand with different organotin(IV) complexes to determine the toxicity of each compound (Affan et al., 2009). They found that, di-methyltin(IV) complex is much less toxic compared to other bulky di-organotin(IV) complexes as the methyl group is a weaker electron donor compared to di-butyl organotin(IV) complexes, thus it might not accelerate much the \( \pi \)-electron delocalization and subsequently decrease its toxicity.

Singh et al., (2011) have synthesized semicarbazone and thiosemicarbazone ligands. The ligand was prepared by the condensation reaction of 4-hydroxyl-3-methoxybenzaldehyde with semicarbazide in the presence of sodium acetate compound \( L^1 \) was prepared by the reacting 4-hydroxyl-3-methoxybenzaldehyde with semicarbazide. Meanwhile, compound \( L^2 \) were prepared by reacting 4-hydroxyl-3-methoxybenzaldehyde with thiosemicarbazide. The structure of ligands is shown in Figure 8 and Figure 9.

Based on the biological activity they demonstrated that all the complexes have activity against tested bacteria whereas the both ligands showed no activity. Therefore, organotin(IV) complexes are more active than free ligand, which indicated that metalation increased antimicrobial activity. The tributyltin(IV) thiosemicarbazone complexes have shown the potential to inhibit the growth of all bacterial strain. This study also indicates the organotin(IV) complexes of thiosemicarbazone are more active than semicarbazone organotin(IV) complexes.
Figure 8: 4-hydroxy-3-methoxybenzaldehyde

Figure 9: 4-hydroxyl-3-methoxybenzaldehyde

L¹

L²

thiosemicarbazon
Figure 10: Structure of diorganotin(IV) complexes

Figure 11: Structure of triorganotin(IV) complexes
Sen et al., (2008) have synthesized and evaluated the anti-tumor properties of dimethyl tin(IV)-4-cyclohexylthiosemicarbazone complexes. The ligand of 4-cyclohexyl thiosemicarbazone (D4-t) was prepared by the condensation reaction between cyclohexyl thiosemicarbazide and salicyl aldehyde with yielded 80% of colored solid compound (Scheme 1). The D4-t complexes have shown 80% of inhibition of anti-tumor agent. In addition, D4-t also works effectively without causes severe toxicity. This result indicated promising therapeutic of dimethyl tin 4-cyclohexylthiosemicarbazone.

![Chemical Structures](attachment:Scheme_1.png)

**Scheme 1:** Synthesis of 4-cyclohexyl thiosemicarbazone ligand and organotin(IV) complexes