

**SYNTHESIS, SPECTRAL CHARACTERIZATION AND BIOLOGICAL
ACTIVITIES OF ORGANOTIN(IV) COMPLEXES HETEROCYCLIC-N(4)-
CYCLOHEXYLTHIOSEMICARBAZONE LIGAND**

TUAN SAHIKRA AKMAR BINTI TUAN WILL (25313)

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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.

Tuan Sahikra Akmar Bt Tuan Will

Chemistry department

Faculty of Resource Science and Technology

University of Malaysia Sarawak.

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List of Abberiviation

Sn(IV)	Tin(IV) atom
(HPCCT)	2-pyridinecarbaxaldehyde <i>N</i> (4)cyclohexylthiosemicarbazone
[MeSnCl ₂ (PCCT)]	Methyltin(IV) dichloride complex
[BuSnCl ₂ (PCCT)]	Buthyltin(IV) dichloride complex
[PhSnCl ₂ (PCCT)]	Phenyltin(IV) dichloride complex
[Me ₂ SnCl(PCCT)]	Dimethyltin(IV) chloride complex
[Bu ₂ SnCl(PCCT)]	Dibutyltin(IV) chloride complex
[Ph ₂ SnCl(PCCT)]	Diphenyltin(IV) chloride complex
[Ph ₃ Sn(PCCT)]	Triphenyltin(IV) complex

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Synthesis, Spectral Characterization and Biological Activities of Organotin(IV) Complexes with Heterocyclic-*N*(4)-cyclohexylthiosemicarbazone Ligand

Tuan Sahikra Akmar Binti Tuan Will

Resource Chemistry Programme
Faculty of Resource and Sciences Technology
Universiti Malaysia Sarawak

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 ¹H 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), and [Ph₃Sn(PCCT)] (8). Ligand [HPCCT] (1) dan kompleks organostanum(IV) telah dicirikan menggunakan analisis unsur, molar conductivity, UV-nampak, IR, dan ¹H RMN pembelajaran spektal. Keputusan data spektroskopik menunjukkan ligand [HPCCT] (1) berkordinasi 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 chemical compound possesses 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 risen 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 & Hadjiliadis., 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)-cyclohexylthiosemicarbazone 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-pyridinecarboxaldehyde-*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)-cyclohexylthiosemicarzone 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 ¹H 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.

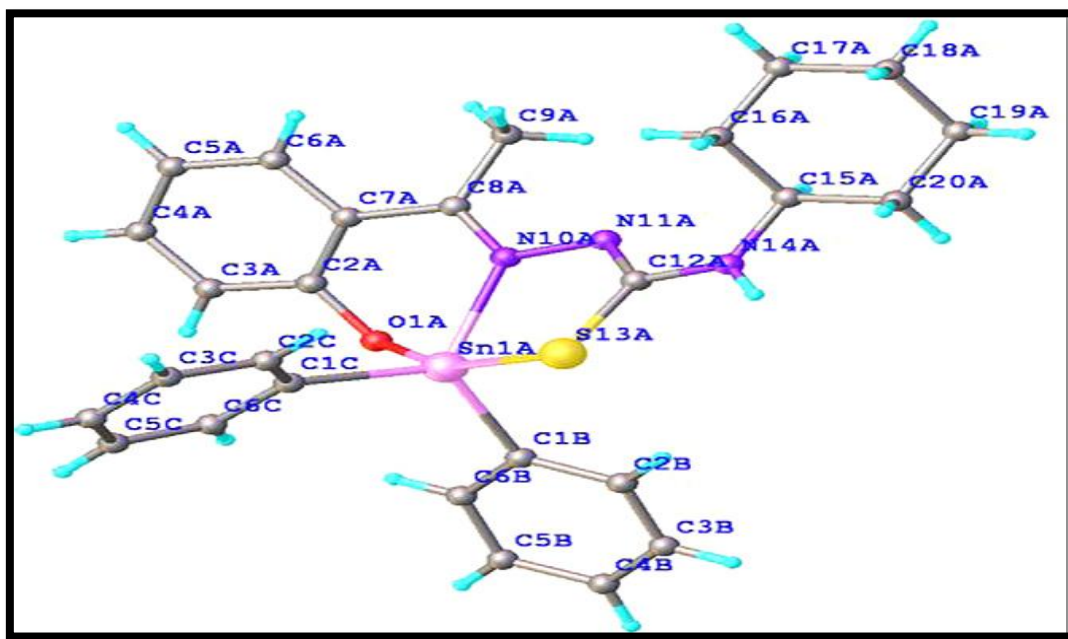


Figure 1: Molecular structure of diphenyltin(IV) complex

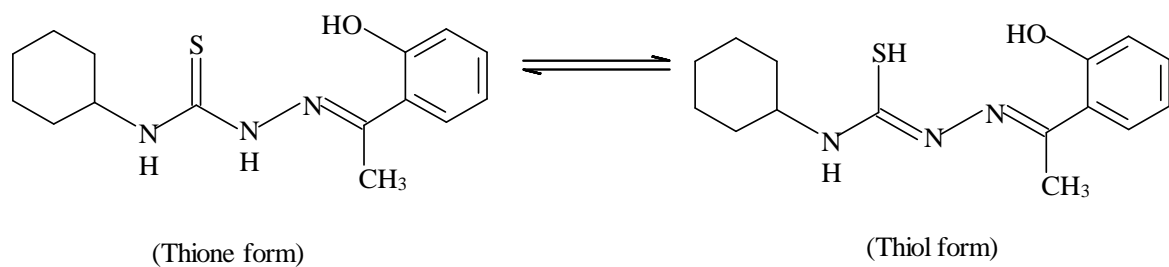


Figure 2: Structure of 2-hydroxyacetophenone-*N*(4)-cyclohexylthiosemicarbazone ligand

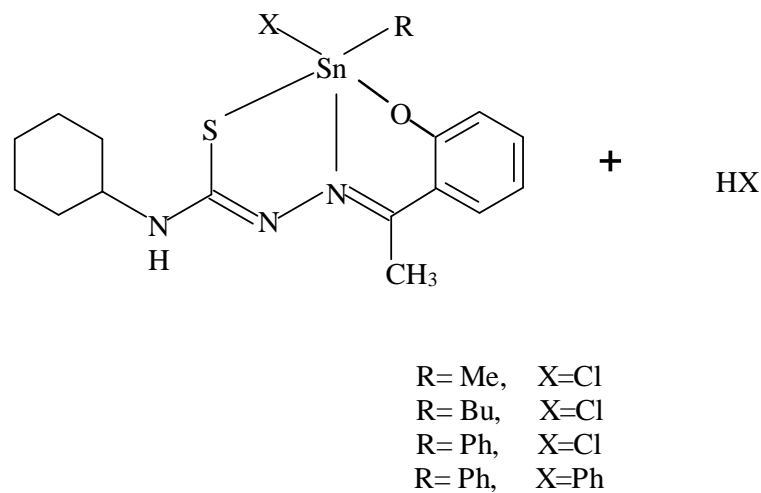


Figure 3: Structure of organotin(IV) complexes of 2-hydroxyacetophenone-*N*(4)-cyclohexylthiosemicarbazone

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.

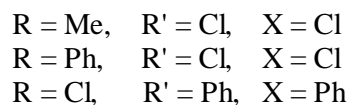
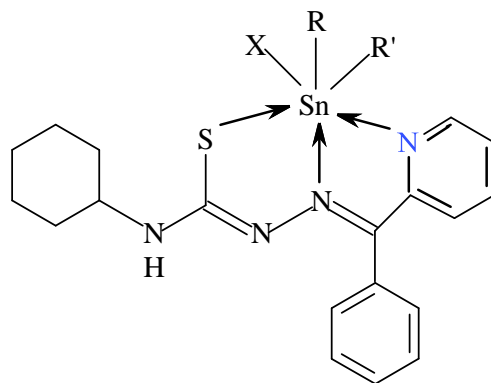


Figure 4: Proposed structure of organotin(IV) complexes of 2-benzoylpyridine-*N*(4)-cyclohexylthiosemicarbazone

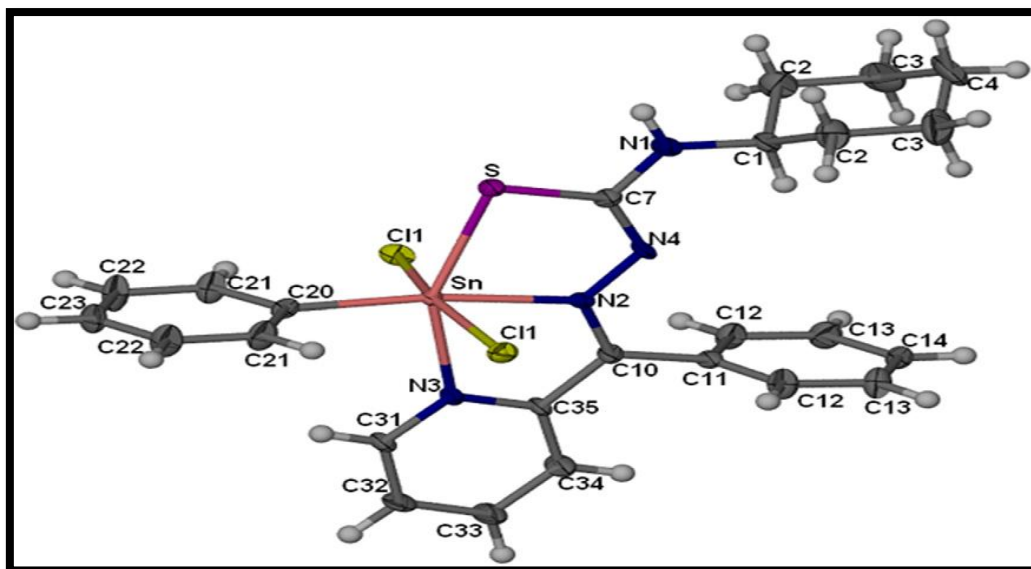


Figure 5: Molecular structure of phenyltin(IV) complex

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).

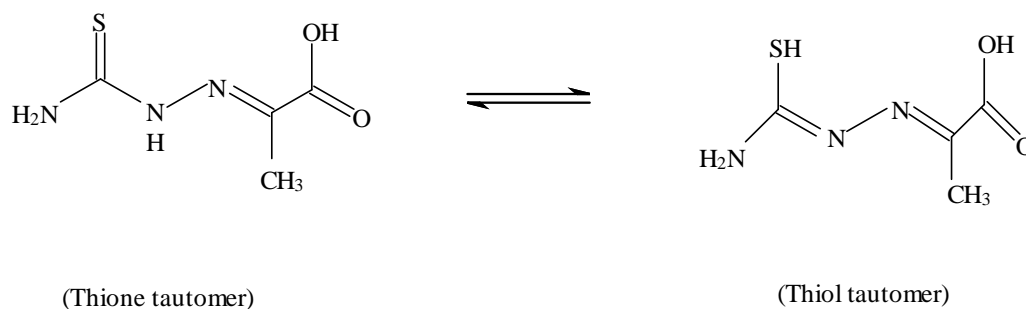
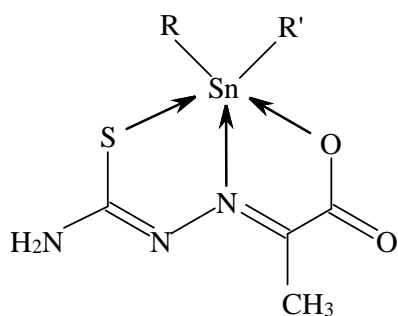


Figure 6: Tautomerization of the thiosemicarbazone ligand

The metal complexes of pyruvic acid thiosemicarbazone have been synthesized by the direct reaction of ligand with appropriate organotin(IV) salts under N₂ atmosphere (Figure 7). The entire coordination mode was difference in all the organotin(IV) complexes (Affan *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.



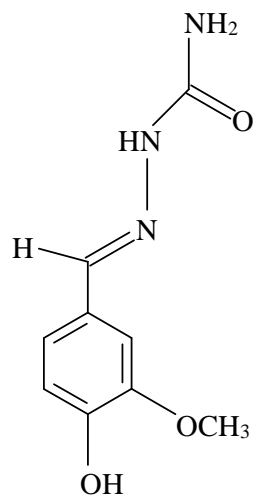
R=Me	R'=Me	n= 2	(2)
R=Bu	R'=Bu	n=2	(3)
R=Ph	R'=Ph	n=2	(4)
R=Me	R'=Cl	n=1	(5)
R=Bu	R'=Cl	n=1	(6)
R=Ph	R'=Cl	n=1	(7)

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 π -electron delocalization and subsequently decrease its toxicity.

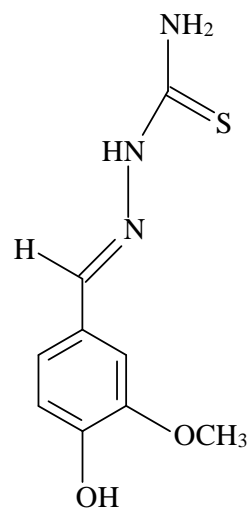
Singh *et al.*, (2011) have synthesized semicarbazone and thiosemicarbazone ligands. The ligand was prepared by the condensation reaction of 4-hydroxyl-3-methoxybenzaldehyde with semicarbazide in the presence of sodium acetate compound L¹ was prepared by the reacting 4-hydroxyl-3-methoxybenzaldehyde with semicarbazide. Meanwhile, compound L² 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.



L¹

Figure 8: 4-hydroxy-3-methoxybenzaldehyde
semicarbazone



L²

Figure 9: 4-hydroxyl-3-
methoxybenzaldehyde
thiosemicarbazone

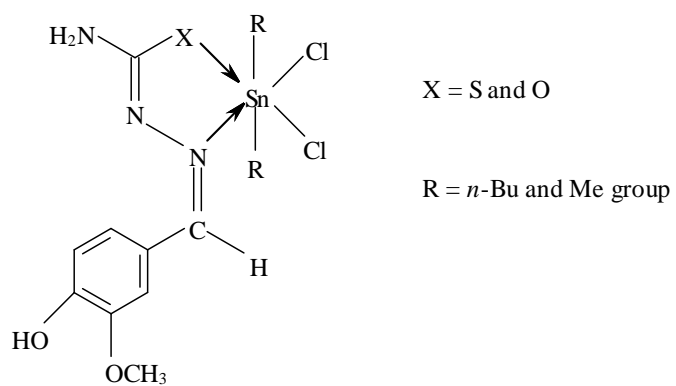


Figure 10: Structure of diorganotin(IV) complexes

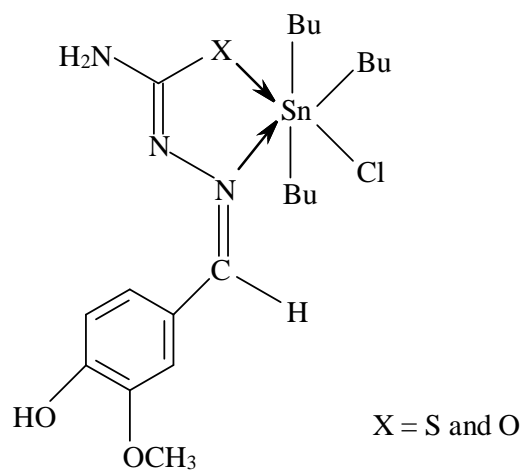
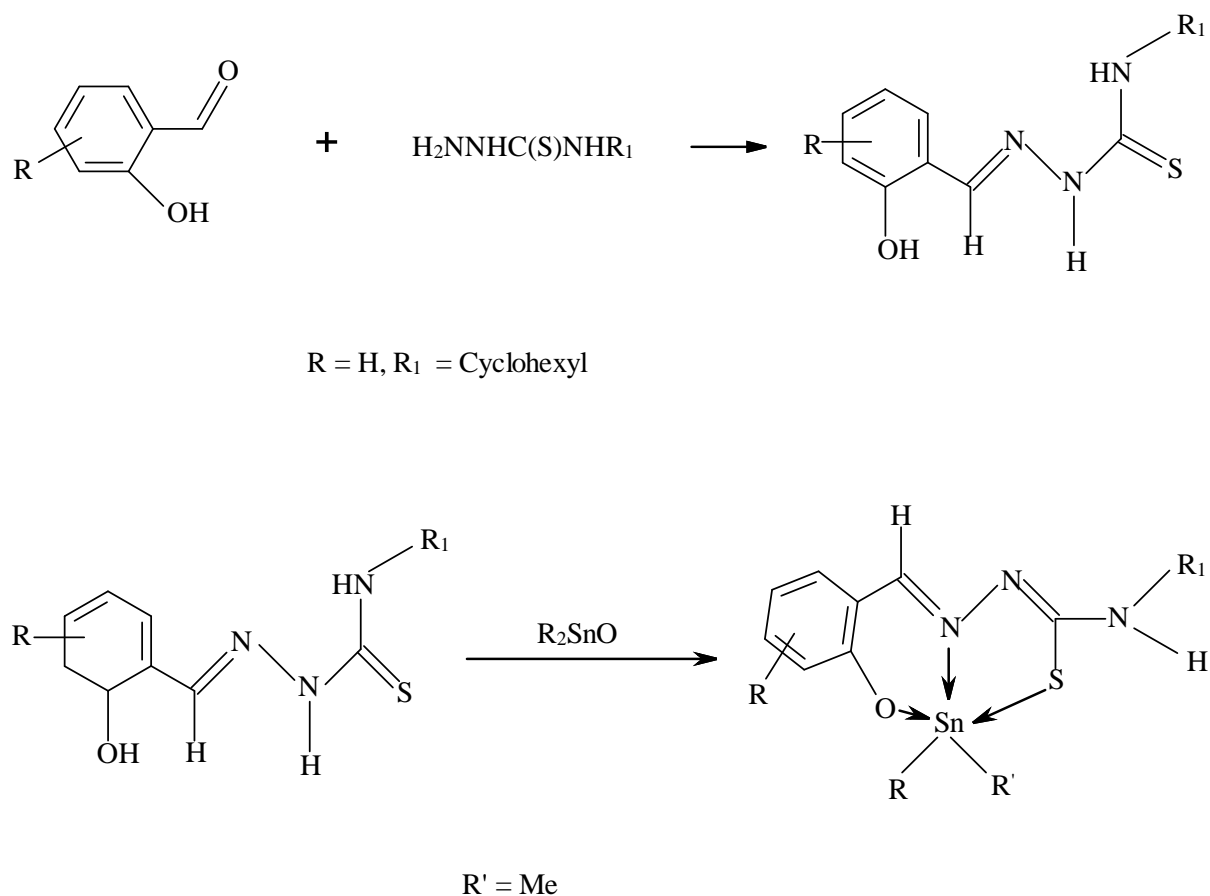


Figure 11: Structure of triorganotin(IV) complexes

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.



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