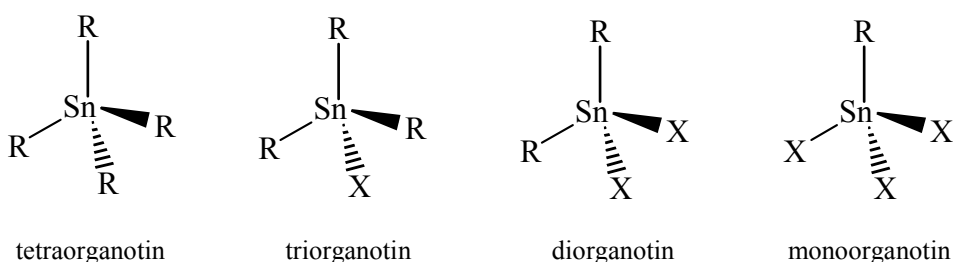


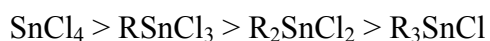
1.1 GENERAL OVERVIEW OF ORGANOTIN COMPOUNDS

Organotin compounds are compounds containing at least one tin-carbon bond and can be classified into four major types depending on the number of tin-carbon bonds. Organotin compounds containing one tin-carbon bond are known as monoorganotins while those with two, three and four tin-carbon bonds are called diorganotins, triorganotins and tetraorganotins respectively. The general formula for the organotin compounds is represented by R_nSnX_{4-n} where $n = 1$ to 4 ; X can be halide or pseudohalide such as CN^- and NCS^- , carboxylate ($OCOR$), phosphate and thiolate.

The structural formula of the four types of organotin compounds are shown below:



As tin is not acidic, its ability to form complexes and adducts is, to a large extent, dependent upon the electronegativity of the substituent groups such as halides and pseudohalides. Generally, the acceptor strength of tin(IV) declines according to the following sequences when the chlorine atoms of stannic chloride, $SnCl_4$ are replaced by relatively electropositive organic groups [Poller 1970].



Tetraorganotins which are the precursors for the preparation of triorganotins, diorganotins and monoorganotins are expected to be tetrahedral in geometry. Most of the molecular structures of tetraorganotin compounds have been reported to have the tetrahedral geometry. A few of the examples are tetraphenyltin [Akhmed and Aleksandrov 1970], tetra(4-methylphenyl)tin(IV) [Karipides and Wolfe 1975], tetra(3-methylphenyl)tin(IV) [Karipides and Oertel 1977], tetra(*p*-chlorophenyl)tin(IV) [Ng 1997], tetra(2-thienyl)tin(IV) [Karipides *et al.*, 1977] and tetrakis(4-methyl-2-thienyl)tin(IV) [Yap *et al.*, 2008b]. Although tetraorganotins do not have the ability to expand their coordination number to beyond four, several five-coordinated and six-coordinated tetraorganotins have been reported in literature. Several examples of five-coordinated tetraorganotins are *bis*[3-(2-pyridyl)-2-thienyl]tri-*p*-tolylstannane [Kumar Das *et al.*, 1987a], methyltriptychstannolidine [Tzschach and Jurkschat 1986], [2-(triphenylstannyl)vinyl]4-estren-17-ol [Pan *et al.*, 1990] and methyl 4,6-*O*-benzylidene-3-deoxy-3-triphenylstannyl- α -*D*-altropyranoside [Doidge-Harrison *et al.*, 1991]. Several rare examples of six-coordinated tetraorganotins have also been reported, namely, *bis*[3-(2-pyridyl)-2-thienyl]diphenylstannane [Kumar Das *et al.*, 1987b] and *bis*[3-(2-pyridyl)-2-thienyl]di-*p*-tolylstannane [Lo *et al.*, 1993] whereby the structures display a distorted octahedral geometry at tin.

Triorganotins show a strong tendency to increase their coordination numbers of tin from four to five or six by reacting with monodentate and bidentate ligands. Five-coordinated triorganotins usually adopt the trigonal bipyramidal geometry with either three R groups (*trans*), two R groups and one X group (*cis*) or one R group and two X groups (*meridional*) occupying an equatorial plane. Triorganotins with coordination number higher than five are less common and not many known crystal structures are found in the literature. An example of six-coordinated triorganotin is the triphenyltin

acetate which has a *meridional* Ph_3SnO_3 geometry whereby the carboxylate groups link together to form a polymeric unit [Molloy *et al.*, 1984]. There are also reports on triorganotin which are expected to be seven-coordinated based on their infrared and ultraviolet spectroscopies evidence [Sengupta *et al.*, 1982].

Diorganotins usually react with donor ligands to form six-coordinated or tin structures with octahedral geometry. They have either the *cis*- or *trans*- $[\text{Sn-R}_2]$ skeletal configurations. There are several examples of diorganotins having the trigonal bipyramidal geometry, which are usually coordinated to tridentate ligands. As compared to triorganotins, diorganotins are stronger Lewis acids and hence will coordinate easily with monodentate, bidentate or tridentate ligands, leading to five, six or seven-coordinated organotin complexes.

Monoorganotins also show a strong tendency to form four, five, six or seven-coordinated tin structures. Similarly to diorganotins, six-coordinated monoorganotins are more common as the stronger Lewis acidic monoorganotins can readily react with monodentate or bidentate ligands. Some examples of monoorganotins are dichloromethyl[1-(2-pyridyl)ethanone benzoylhydrazonato]tin(IV) [Affan *et al.*, 2004], *trans*-(2-acetylpyridine-2-furylhydrazonato)dichlorophenyltin(IV) dichloromethane solvate [de Sousa *et al.*, 2006] and chloromonophenyltin *bis*(*N,N'*-diethyldithiocarbamate) [Harrison and Mangia 1976].

The importance of organotin chemistry was most felt with the discovery of the industrial uses of organotin species a century later after the report of the first organotin compound in 1849. In the late 1950s, the biocidal properties of the organotins were discovered at the TNO Institute, Utrecht, Holland [Van der Kerk and Luitjen, 1954]

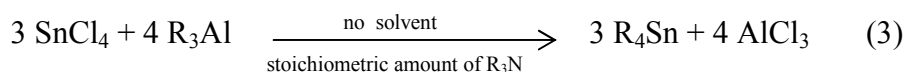
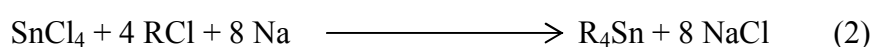
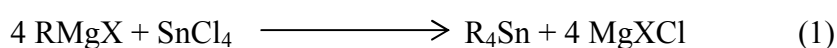
where it was found that the triorganotins in particular *bis*(tributyltin) oxide (TBTO) was a good timber preservative. Wood which was impregnated with TBTO was found to be effectively protected against fungi and insects.

Depending on the nature of its organic groups, triorganotins are generally potential bactericides and fungicides. Trialkyltins, for example tributyltins (TBT), are used as industrial biocides especially as antifungal agents in textiles, paper, wood pulp, paper mill systems, breweries, and industrial cooling systems. Tributyltins are also used in marine anti-fouling paint and in recent years, there have been many debates on the effects of the toxicity of organotins to humans and environment. One example is the leaching of TBT from marine paints into the aquatic environment, causing irreversible damage to the aquatic and marine life. Tributyltins have also been linked to obesity in humans, as they trigger genes that cause the growth of fat cells. However, a recent review has indicated that many marine bacterial strains have an inherent capability to degrade organotin compounds which have high toxicity; for example tributyltins that enter into the environment in the form of insecticides, fungicides and antifouling paints as a result of anthropogenic and industrial activities. The significant degradation of these compounds in the ambient environment may take several years [Dubey and Roy, 2002]. Triphenyltins are found to be an active component in antifungal paints and agricultural fungicides. Other triorganotins are used as miticides and acaricides [Saxena 1987].

On the other hand, diorganotins have low antifungal activity, low toxicity, and low antibacterial activity. Diorganotins are mainly used in polymer manufacturing, as PVC heat stabilizers, catalysts in the manufacturing of polyurethane and silicone curing. However, dibutyltin oxide is immunotoxic, and it has been suggested as a link to auto-

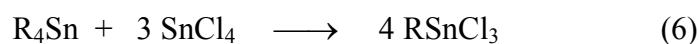
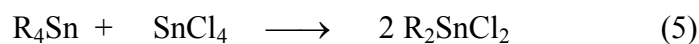
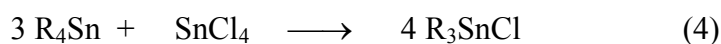
immune related diseases. Monoorganotins have no biocidal activity and their toxicity to mammals are very low. Methyltin, butyltin, octyltin and monoestertins are used as PVC heat stabilizers.

There are various methods for preparing organotin compounds. In general, tetraorganotins are the target products since it is difficult to stop the alkylation at a predetermined stage. The general reaction for preparing tetraorganotins is *via* the Grignard process. This reaction is usually carried out at about 80°C in tetrahydrofuran (THF) or diethyl ether as the solvent or, on the industrial scale in toluene containing the minimum amount of ether to solvate the Grignard reagent. If the R group is a bulky alkyl group, the yield of R₄Sn obtained could be low and it may be advisable to use other methods such as the Wurtz method (equation 2) which is based on the *in situ* reaction of sodium, alkyl halide with stannic chloride or the alkylaluminium reagents (equation 3) to prepare the tetraorganotins. Alkylation of tin tetrachloride with organoaluminium compounds has the advantage that it can be carried out in the absence of solvent.

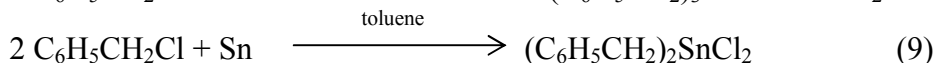
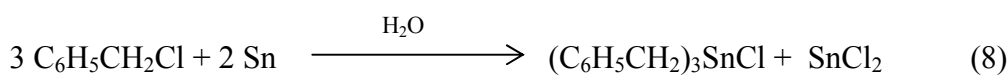
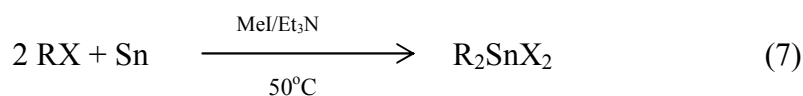


Generally, tetraorganotins are very stable molecules with low toxicity and low biological activity unlike triorganotins and diorganotins. Tetraorganotins have been used as catalysts in numerous chemical reactions. Also, tetraorganotins are used as precursor for the preparation of triorganotins, diorganotins and monoorganotins. Hence, the subsequent reaction of the tetraorganotins with stannic chloride in the

appropriate molar ratio will yield the organotin halides as shown by the reactions below:



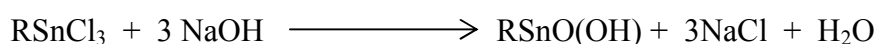
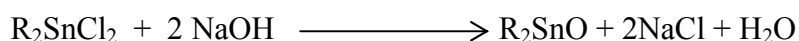
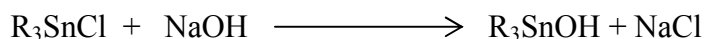
In addition, the direct reaction of tin (as foil, alloy or powder) with organic halides has been used in the laboratory to produce organotin halides. One example of the direct method is the synthesis of dimethyltin dichloride, $(CH_3)_2SnCl_2$ from tin foil and CH_3Cl with $Ph_3CH_3P^+Br^-$ as catalyst and KI as promoter at $180-190^\circ C$ (equation 7). The dominant products from direct synthesis are usually diorganotin dihalides. The direct synthesis of organotin compounds from tin and organic halides originated from the report by Frankland, and many other researchers. The reaction of substituted benzyl chloride on tin powder yielded the substituted tribenzyltin chloride and substituted dibenzyltin dichloride and the yields obtained were satisfactory (equation 8 and equation 9) [Sisido *et al.*, 1961].



Various catalyst/promoter systems such as zinc and copper halides and Lewis bases such as amines, alcohols or ethers have been employed for less reactive halides.

Direct synthesis method is the only method which does not require the use of SnCl₄ as the reactant.

The organotin halides are easily hydrolysed to yield the hydroxides and oxides as exemplified by the following equations:-



1.2 CHARACTERIZATION TECHNIQUES FOR ORGANOTIN COMPLEXES

Organotin compounds could be characterized by several spectroscopic techniques, namely infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy and ¹¹⁹m Mössbauer spectroscopy. Organotin compounds which are crystalline are further characterized by using the single crystal X-ray crystallographic technique, whereby the absolute structure of the complexes and their molecular packing could be determined.

1.2.1 Infrared spectroscopy

Infrared (IR) spectroscopy is a useful spectroscopic technique to characterize the various functional groups in organotin compounds even though rigorous assignments of the stretching band are not possible. Most of the fundamental stretching vibrations involving tin atom are found at frequencies below 650 cm⁻¹. Generally, the frequencies

of the Sn-C stretching vibrations are not affected by the changes in the coordination number of tin. However, the Sn-X stretching modes are very sensitive to the changes in the coordination number of tin from 4 to 6. In principle, the geometry of the R_nSnX_{4-n} moiety could be indicated by the number of the $\nu(\text{Sn-C})$ and the $\nu(\text{Sn-Cl})$ bands in the spectra.

The tin-oxygen stretching frequencies could be observed over a wide range of frequencies depending on the environment of the Sn-O groups in the complexes. The tin-nitrogen stretching frequencies have also been reported to be in a wide range, from 200-700 cm^{-1} . In most diorganotin complexes, the stronger absorption at around the 600-700 cm^{-1} is assigned to Sn-O stretching frequencies while the weaker or medium-intensity band at around 400-500 cm^{-1} could be assigned to Sn-N stretching frequencies. These assignments are quite consistent with those found in a number of organotin derivatives [Liu *et al.*, 1989, Wang *et al.*, 1989, Yin *et al.*, 2005a, Yin *et al.*, 2005b, Yin *et al.*, 2005c, Yin *et al.*, 2007, Yin *et al.*, 2008].

Infrared spectroscopy is particularly useful in the study of organotin complexes of Schiff base ligands. The azomethine C=N stretching vibrations of the Schiff bases are usually observed in the 1580-1680 cm^{-1} region. As the ligand has been inferred to coordinate to the tin atom through the azomethine nitrogen atom, a slight decrease or increase in the frequency of C=N stretching vibrations could be observed. The C-O stretching vibrations of the phenolic group could be found in the 1200-1300 cm^{-1} region. Similarly, the frequency of C-O stretching vibrations is shifted to a higher wave number indicating its participation in coordination [Pellerito *et al.*, 1974, Cunningham *et al.*, 1977]. The C=C stretching vibrations could also be found in the same region as C=N stretching vibrations, but with lower intensities.

1.2.2 Nuclear Magnetic Resonance (NMR) spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy is used in the elucidation of the structural formula of the organotin complexes. Organotin complexes could be characterized by using the ^1H , ^{13}C , ^{119}Sn NMR spectroscopies and sometimes ^{15}N , or ^{19}F spectroscopies. Structural information of the complexes was obtained from two parameters: chemical shifts, δ (normally expressed as ppm with relative to standard nucleus, eg. tetramethylsilane, SiMe_4) and coupling constant, J (normally expressed as Hz).

The coupling constant involving tin and carbon $^1J(^{119}\text{Sn}-^{13}\text{C})$ and $^2J(^{119}\text{Sn}-^{13}\text{C} - ^1\text{H})$ had been measured to describe the structure and bonding in organotin complexes [Holeček *et al.*, 1983a, Holeček *et al.*, 1983b]. The magnitude of the coupling constant was used to draw the inference concerning the geometry of the organotin compounds. Six-coordinated compounds had 1J values which were greater than 800 Hz while tetrahedral compounds had $^1J(^{119}\text{Sn}-^{13}\text{C})$ in the range of 400-600 Hz in non-coordinating solvents.

In ^1H NMR, the sharp singlet was observed in the region 8.50-9.20 ppm due to presence of the azomethine protons of the ligands. Coordination through the azomethine nitrogen for the complexes could be observed as there was a shift to higher field in the chemical shift of the spectra of the complex. The phenolic proton of the ligand displayed a weak peak around the region 13.00-15.00 ppm and broadened on complex formation. This observation could be due to the weakening of the O-H bond upon coordination to the tin atom and which in turn, resulted in the strengthening of the C=N---H hydrogen bond [Khoo *et al.*, 1982, Khoo *et al.*, 1987]. The phenolic proton of

the ligand could also be observed in the region of 5.00-6.00 ppm depending on the environment of the phenoxy oxygens. The amine proton of the ligand displayed a stronger peak in the region of 10.00-12.00 ppm. The coordination through oxygen and nitrogen could be confirmed by the comparison of the ^{13}C NMR spectral data of the ligands with spectral data of the complexes.

Relative to ^1H NMR chemical shifts, the ^{13}C NMR chemical shifts were observed over a wider range from 0-200 ppm. For example, the chemical shifts for the alkyl carbons could be found in between 10-100 ppm while for aryl carbons, the chemical shifts were higher, from 110-150 ppm. The ^{13}C NMR chemical shifts depended very much on the nature and the position of the organotin substituents. The most noticeable feature of the effect would be the downfield shift of the *ipso*-carbon and a similar downfield shift for the carbon *ortho* to the tin substituents. The imine carbons and carbon which were bonded to halogens were more deshielded and usually observed in the low field region between 155-175 ppm.

^{119}Sn NMR was mostly used in the study of organotin compounds. However, it was also applicable to inorganic tin compounds. Tin was unique as it had no less than three NMR active spin $\frac{1}{2}$ nuclei, ^{115}Sn , ^{117}Sn and ^{119}Sn , that yielded narrow signals over a very wide chemical shift range. ^{119}Sn was slightly more sensitive than both ^{117}Sn and ^{115}Sn , therefore ^{119}Sn was usually the preferred nucleus in the NMR spectroscopy. Each type of tin compound had its characteristic chemical shift range, from -1900 ppm to 700 ppm. The ^{119}Sn NMR chemical shifts had been an indicator to predict the coordination environment of tin in the complexes and there were several reports on the ^{119}Sn NMR spectroscopy [Nádvorník *et al.*, 1984, Lyčka *et al.*, 1985a, Holeček *et al.*, 1986, Holeček *et al.*, 1987, Lyčka *et al.*, 1987, Holeček *et al.*, 1988].

1.3 GENERAL OVERVIEW OF SCHIFF BASE LIGANDS

Schiff bases are usually formed from the condensation reaction between aldehydes or ketones with primary amines. They contain an imine or azomethine group and Schiff base ligands are found to be able to coordinate to metals through the imine nitrogen and phenoxyl oxygen from the aldehydes or ketones. Schiff base was named after German chemist, Hugo Schiff who first reported the condensation process of primary amines with carbonyl compounds in 1864.

Schiff base ligands have been used in coordination chemistry and the ligands have found many applications in numerous fields [Dubay *et al.*, 1993]. In the early 20th century, research on Schiff base ligands with metal complexes has increased significantly with the publications of works from various research groups including Pfeiffer and his co-researchers [Pfeiffer *et al.*, 1931, Pfeiffer and Pfitzner 1936, Pfeiffer *et al.*, 1937]. The ligands have been used extensively due to the ease of synthesizing the materials and their abilities to be varied electronically and sterically. Most of the research on Schiff base ligands is focused on the chelation of the synthesized ligands with metal complexes and their characteristics.

The chemistry of Schiff base ligands is very diverse and it can be coordinated to metal complexes in a monodentate, bidentate, tridentate and also tetradentate. One of the most commonly studied group of Schiff base ligands are tridentate and they vary from *O,N,O*, *O,N,N* and *O,N,S*, types. Some examples of *O,N,O* Schiff base ligands are 1-(2-hydroxy-5-methylphenyl)ethanone[(1*H*-indol-3-yl)acetyl]hydrazone [Ali *et al.*, 2008] and *N*-(2,5-dihydroxybenzylidene)-2-hydroxy-3-methylbenzohydrazide [Han *et al.*, 2010]. Also, examples of *O,N,S* Schiff base ligands are 3-methoxybenzaldehyde

thiosemicarbazone [Zhang *et al.*, 2009] and 2-hydroxy-5-nitrobenzaldehyde thiosemicarbazone [Alhadi *et al.*, 2008]. Common examples of tetradentate Schiff base ligand are those derived from ethylenediamine or the more general term SALEN-type which have an *O,N,N,O* coordination, such as 2,2'-[(1,2-cyclohexanediyl)*bis*(nitrilomethylidyne)]*bis*phenol and 2,2'-[(1,2-cyclohexanediyl)*bis*(nitriloethylidyne)]*bis*phenol [Cannadine *et al.*, 1996]. An example of metal complex with SALEN-type ligands is [NN'-ethylene*bis*(salicylideneiminato)]dimethyltin(IV) [Calligaris *et al.*, 1974].

In recent studies, interest on Schiff base ligands and their metal complexes has shifted to the biological activities as Schiff bases displayed good remarkable biological properties especially in anticancer [Collins *et al.*, 2000], antifungal [Pannerselvam *et al.*, 2005], antioxidant [Dutta *et al.*, 2005], antibacterial [Mohd. Ali *et al.*, 2004] and antiviral properties [Gökçe *et al.*, 2005]. A good example of the importance of Schiff bases would be those derived from benzoylhydrazones and acylhydrazone. The interest in benzoylhydrazone and acylhydrazone Schiff base ligands lay mainly due to the versatility of the Schiff base itself and the prepared metal complexes in exhibiting biological activities. Some of these works were reported and published by several research groups [Ainscough *et al.*, 1995, Ainscough *et al.*, 1998, Ainscough *et al.*, 1999, Koh *et al.*, 1998, Raparti *et al.*, 2009].

Also, various research groups had studied and found Schiff base ligands derived from salicylaldehyde to have potential biological properties. Metal complexes with Schiff base ligands derived from salicylaldehyde have the ability to specially cleave DNA [Routier *et al.*, 1996, Gravert and Griffin 1993]. Also, substituted

salicylaldehydes have been widely used as polydentate ligands in the preparation of metal complexes.

The reactions of organotin halides and hydroxides with Schiff base ligands have also been studied extensively. These could be due to the presence of more than one donor site in the ligands. The Schiff base ligands which were of particular interest in this project were those containing oxygen, nitrogen and sulphur donor atoms.

In literature, many different organotin complexes had been synthesized and studied in anticancer therapy, observing that their cytotoxicity and selectivity towards cancer cell was higher than that of *cisplatin* [Crowe *et al.*, 1982, Crowe *et al.*, 1984, Gielen 1994, Gielen 1996].

In our research, the focus was on the synthesis of three different groups of Schiff bases; firstly those derived from *tris*(hydroxymethyl)aminomethane; secondly, those derived from 3-hydroxy-2-naphthoic hydrazide and lastly, Schiff bases derivatives from [2-(3,5-di-*tert*-butyl-4-hydroxybenzyl)sulfanyl]acetatohydrazine.

Tris(hydroxymethyl)aminomethane belongs to the aminoalcohol group, which has been widely used in medicine, biochemistry, analytical and coordination chemistry. The presence of an amino and several hydroxyl groups enables it to undergo condensation reactions with carbonyl groups which led to the changes in their physical and biological properties.

The Schiff bases derived from 3-hydroxy-2-naphthoic hydrazide were synthesized and studied for their biological properties. Schiff base ligands with naphthalene rings had been reported to have good antimicrobial activities [Dogan *et al.*,

1998a, Dogan *et al.*, 1998b]. Also, transition metal complexes of some of these Schiff bases have been tested and reported for their antifungal properties [Mohd. Ali *et al.*, 2004a, Mohd. Ali *et al.*, 2004b].

At present, *tris*(3,5-di-*tert*-butyl-4-hydroxybenzyl)isocyanurate has been used as an antioxidant commercially. The last types of the prepared Schiff bases are derived from [2-(3,5-di-*tert*-butyl-4-hydroxybenzyl)sulfanyl]acetatohydrazide and they contain both the nitrogen and sulphur donor atoms. These ligands have several potential sites for coordination, including the sulphur, imine nitrogen and phenoxy oxygen from the substituted salicylaldehyde ring.

1.4 OBJECTIVE OF RESEARCH

In this research, the project aims to synthesize, characterize and determine the structures of various Schiff bases containing different donor atoms such as O, N and S and their organotin complexes. In addition, the anticancer properties of some of the Schiff base ligands and their organotin complexes have been determined and reported in chapters 3, 4 and 5.