American Journal of Applied Sciences 7 (8): 1047-1052, 2010
ISSN 1546-9239

Synthesis and Characterization of Organotin(IV) N-Benzyl-N-Isopropyldithiocarbamate Compounds: Cytotoxic Assay on Human Hepatocarcinoma Cells (HepG2)

[1]Normah Awang, [2]Ibrahim Baba,
[3]Nor Syaidatul Akmal Mohd Yousof and [1]Nurul Farahana Kamaludin
[1]Environmental Health Programme, Faculty of Allied Health Science,
University Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia
[2]Department of Chemistry, School of Chemical Sciences and Food Technology,
Faculty of Science and Technology, University Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[3]Department of Biomedical Science, Faculty of Allied Health Science,
University Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia

Abstract: Problem statement: Several studies on organotin(IV) dithiocarbamate compounds have been carried out but not on the synthesis and characterization together with cytotoxic assay of organotin(IV) N-benzyl-N-isopropyldithiocarbamate compounds. **Approach:** Three new organotin(IV) compounds of type N-benzyl-N-isopropyldithiocarbamate have been successfully synthesized by direct reaction between secondary amine with organotin(IV) chloride using *in situ* method. All the compounds were characterized using elemental analysis, gravimetric analysis, infrared spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy. **Results:** Elemental and gravimetric analyses data of these compounds showed that agreed with the predicted formula, $(CH_3)_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$ (1), $(C_4H_9)_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$ (2) and $(C_6H_5)_3Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]$ (3). The infrared spectra of these compounds showed the thioureide bond, ν(C=N) which occurred at 1438-1440 cm^{-1} and the ν(C=S) band appeared in the range of 967-973 cm^{-1}. The presence of the ν(C=N) and ν(C=S) bands in the infrared spectra confirmed the presence of dithiocarbamate ligand in that compounds. The bond between sulphur and tin atom were supported with the presence of peak in the range of 365-445 cm^{-1} that known to be as stretching mode of ν(Sn-S). The most important signal in the ^{13}C NMR spectra was the chemical shift of NCS_2 group. The ^{13}C NMR spectra of these compound showed a chemical shift in 195.06-202.65 ppm range, which is attributed to the carbon atom of NCS_2 group. The crystal structure of compound 2 (dibutyltin(IV) N-benzyl-N-isopropyldithiocarbamate) has been determined by X-ray single crystal analysis, which shows unsymmetrical nature of the ligand towards coordination to tin. It crystallizes in triclinic P1 space group with the crystal cell parameter: a = 17.7745 (2) (Å), b = 19.5463 (3) (Å), c = 26.2062 (4) (Å), α = 102.5254 (7)°, β = 95.1492 (7)°, γ = 110.2569 (8)°, Z = 10, V (Å^3) = 8202.1 (2) and R = 0.028. In addition, these compounds were screened for their cytotoxic activity on Human Hepatocarcinoma Cells (HepG2). Based on the cytotoxic activity, compounds 2 and 3 showed cytotoxic activity but compound 1 is inactive against HepG2 cells. **Conclusion:** The results of this study showed that the studied compounds might indeed be potential sources of anticancer agents and these would further enable us to evaluate their utility in biomedical field.

Key words: Dithiocarbamate, organotin, X-ray, cytotoxic, NMR

INTRODUCTION

Organotin(IV) compounds are extensively studied due to the applications in industrial as well as biocide properties (Gielen *et al*., 2000). Numerous studies on organotin(IV) compounds have been carried out in order to study its biological properties against bacterial (Jamil *et al*., 2009), fungus and cancer cells line (Crouse *et al*., 2004; Novelli *et al*., 1999). Several organotin compounds exhibit promising *in vitro* antitumor activities against human tumor cell lines (Gielen, 1996).

Corresponding Author: Normah Awang, Environmental Health Programme, Faculty of Allied Health Science,
University Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia

Moreover, the biological activity of organotin(IV) dithiocarbamate compounds are greatly influenced by the structure of the molecule as well as the coordination number of the tin moiety. The search for organometallic compounds as a new alternative drug in combating human cancers has been initiated due to certain side-effects of cis-platin and carboplatin as antitumor drugs (Mansouri-Torshizi *et al*., 2010; Khan *et al*., 2000).

In our previous works (Awang *et al*., 2003a, 2003b; 2003c), we have reported the crystal structure of three organotin (IV) dithiocarbamate compounds which were prepared using *in situ* method. As a continuation of our interest in sulfur-containing ligands, we have synthesized a new series of organotin(IV) dithiocarbamate compounds using the same procedure. All these compounds have been characterized by elemental analyses, infrared spectra (IR) and Nuclear Magnetic Resonance (NMR) (^{1}H and ^{13}C). The crystal structure of compound 2 has been determined by X-ray diffraction study. In addition, the cytotoxic assay of the compounds obtained was screened against human hepatocarcinoma cells, HepG2 and the results are reported herein.

MATERIALS AND METHODS

All chemicals and solvents were of analytical grade. The N-benzylisopropylamine, dimethyltin(IV) chloride, dibutyltin(IV) chloride and triphenyltin(IV) chloride were purchased from Fluka while chloroform and ethanol were supplied by Merck. All the chemicals were used as supplied. Melting points were determined using an Electrothermal IA9100 instrument and elemental analysis with a Fison 1108 CHNS-O microanalyzer. Tin was determined gravimetrically by igniting a known quantity compound to SnO_2. The infrared spectra were recorded on a Perkin Elmer FT-IR Model GX spectrophotometer using KBr discs in the range 4000-400 cm^{-1} and nujol in polyethylene for the wave number range between 400-250 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Joel JNM-LA 400 spectrometer with TMS as the standard. Single crystal X-ray diffraction study was carried out using SMART APEX CCD diffractometer.

Synthesis of organotin(IV) benzylisopropyldithiocarbamate compounds: Compound 1 was prepared by addition of CS_2 (30×10^{-3} mol) to an ethanolic solution of N-benzylisopropylamine (30×10^{-3} mol) under stirring at 5°C. After one hour stirring, the addition of dimethyltin(IV) dichloride (15×10^{-3} mol) yielded to a white solution and still left stirring for another hour. A white solid was obtained and filtered off and then washed with cold ethanol and dried in vacuo. Recrystallization from a $CHCl_3$: C_2H_5OH = 1:1 (v: v) mixture yielded colorless crystal. Compounds 2 and 3 were prepared by the same procedure, but dibutyltin(IV) dichloride (15×10^{-3} mol) or triphenyltin(IV) chloride (30×10^{-3} mol) was used. Compounds 1-3 were in white solid and highly soluble in chloroform. A general reaction scheme for the above preparation was given as below:

$R_mSnCl_{m-1} + nHN(C_7H_7)(i\text{-}C_3H_7) + nCS_2\ EtOH \rightarrow R_mSn(S_2CNR'R'')_n + nHCl$ (m = 1, R = C_6H_5; m = 2, R = CH_3 or C_4H_9)

Crystallographic studies: A single crystal of compound 2 was mounted on glass fiber. Diffraction data were recorded on a Bruker SMART Apex system equipped with a graphite monochromatized Mo K_α radiation (λ = 0.71073 Å). The data were collected using SMART (Siemens, 1996). The data integration was performed using SAINT (Siemens, 1996). An empirical absorption correction was carried out using SADABS (Sheldrick, 1996). The structure was solved with the direct methods and refined by full matrix least square methods based on F^2, using the structure determination and graphics package SHEXTL (Sheldrick 1997a) based on SHELX 97 (Sheldrick, 1997b).

***In vitro* cytotoxic assay:** The *in vitro* cytotoxic assay was carried out on human hepatocarcinoma cells line, HepG2. The cells were maintained in Eagle's Minimum Essential Medium (MEM) supplemented with 2 mM of L-glutamine, 1 mM of sodium pyruvate, 0.1 mM of non-essential amino acid, 1.5 μg mL^{-1} sodium bicarbonate, 100 IU mL^{-1} penicillin and 100 μg mL^{-1} streptomycin. The cytotoxic assay was determined using the microtitration 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Sheldrick, 1997b). The assay of each concentration for each compound was performed in triplicate. The fraction of surviving cells was measured relative to the untreated cell population by measuring the absorbance values at 570 nm with reference at 630 nm using an ELISA microplate reader (Bio Tek EL 340, USA). Cytotoxicity was expressed as 50% cytotoxic dose (IC_{50}), i.e., the concentration causing 50% inhibition of cell growth with reference to the control (untreated cells). The IC_{50} and the Standard Error of the Mean (SEM) were determined using Probit Analysis (SPSS, version 12).

RESULTS

The synthesized compounds (1-3) are stable in the air, soluble in chloroform and dichloromethane. Elemental analysis and physical properties data are given in Table 1. The percentage of tin element in the compound was determined gravimetrically by igniting a known quantity of each compound to SnO_2. The elemental analysis data of the compounds are in agreement with the general formula $R_mSn(S_2CNR'R'')_{4-m}$ (m = 3, R = C_6H_5, R' = C_7H_7, R" = i-C_3H_7; m = 2, R = CH_3 or C_4H_9; R' = C_7H_7, R" = i-C_3H_7).

Infrared spectra: The important IR peaks of the compounds 1-3 were listed in Table 2. The type of bonding between the dithiocarbamate ligand and the tin atom was deduced using the ν_{C-N} and ν_{C-S} vibrations.

^{1}H NMR spectra: The selected ^{1}H NMR chemical shifts of the compounds were given in Table 3. The ^{1}H spectra of the compounds 1-3 were recorded in $CDCl_3$. Table 4 showed the selected ^{13}C chemical shift data for compound 1-3. The ^{13}C NMR spectrum of the organotin(IV) benzylisopropyldithiocarbamate compounds exhibited a signal for methyl carbon of isopropyl group in the range 20.50-20.74 ppm while the chemical shift for carbon which directly attached to the N atom was found in the region 55.94-58.41 ppm. The important chemical shift of the carbon in dithiocarbamate compound was thione carbon (NCS_2). In compounds 1, 2 and 3, the chemical shift of CS_2 were observed at 195.06, 202.65 and 198.43 ppm respectively. The CS_2 resonance for compounds 2 and 3 were shifted to downfield due to electron donating effect by the butyl and phenyl groups. The high value of thione carbon chemical shift could be explained by an increase of π-bond order in the whole NCS_2 moiety (Nomura *et al*., 1989).

Crystal structure of $(C_4H_9)_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$: Suitable crystals for X-ray crystallographic studies of compound 2 were obtained by slow evaporation of a chloroform: Ethanol mixture at room temperature. The details of the crystal data and refinement parameters for compound 2 are listed in Table 5 while selected geometric parameters are listed in Table 6. The crystal structure of compound 2 shows that the tin atom has six coordination number (Fig. 1). The IC_{50} values for compounds 1-3 were given in Table 7.

DISCUSSION

Infrared spectra: Chatt *et al.* (1956) suggested resonance structures on the basis of an intense band in the region 1550-1480 cm^{-1} due to a C-N stretching vibration. Bradley and Gitlitz (1969) studied IR bands in several metal N,N-dialkyldithiocarbamates and reported the thioureide (C⋯N) band near 1500 cm^{-1} as a characteristic for the $(S_2)C{=}NR'R''$ bond. We have observed ν(C⋯N) band in the 1427-1444 cm^{-1} region, which matches well with the literature value. The observed ν_{C-N} vibrations lie between the range for C-N single bonds (1250-1360 cm^{-1}) and C-N double bonds (1640-1690 cm^{-1}). This suggests that the C⋯N bonds have some partial double bond character. Another strong band in the 1148-1165 cm^{-1} may be attributed to N-C_2 for all of the compounds. Strong bands at 953-997 cm^{-1} were due to ν(C⋯S) bond of the chelating character of the dithiocarbamate ligand in all cases (Bonati and Ugo, 1967). Besides this, far IR spectra of the compounds showed a band in the region of 355-377 cm^{-1} was assigned to μ(Sn-S) stretching vibration. Thus lending support to the proposed coordination in the compounds (Soliman and Mohamed, 2004).

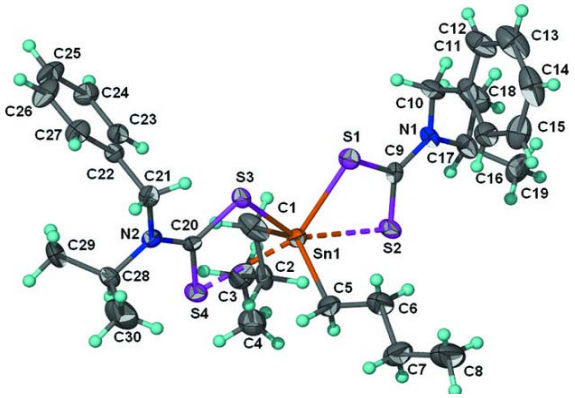

Fig 1: ORTEP plot of compound 2 at 50% probability level

Table 1: Physical and elemental analysis data of organotin(IV) N-benzyl-N-isopropyl dithiocarbamate compounds

				Found (calculated) (%)				
Molecular formula	Color	Yield (%)	Melting point (°C)	C	H	N	S	Sn
$(CH_3)_2Sn[S_2CN(C_7H_7)(iC_3H_7)]_2$ (1)	Colorless	83	132.1-133.7	47.88 (48.24)	5.70 (5.74)	4.48 (4.69)	19.31 (21.47)	20.35(19.86)
$(C_4H_9)_2Sn[S_2CN(C_7H_7)(iC_3H_7)]_2$ (2)	Colorless	79	111.1-112.8	53.09 (52.86)	6.26 (6.80)	4.03 (4.11)	16.48 (18.82)	18.87(17.41)
$(C_6H_5)_3Sn[S_2CN(C_7H_7)(iC_3H_7)]$ (3)	Colorless	76	128.1-130.2	60.53 (60.64)	4.88 (5.04)	2.21 (2.44)	10.11 (11.16)	21.29(20.72)

Table 2: The important infrared absorption bands (cm^{-1})

	Frequency (cm^{-1})				
Compound	ν(C-H)	ν(C ---- N)	ν(N-C)	ν(C ---- S)	ν(Sn-S)
1	2978	1444	1148	997	377
2	2969	1427	1165	956	355
3	2954	1443	1162	953	356

Table 3: Selected ^{1}H NMR spectra data of compounds 1-3 (δ, ppm)

	Chemical shift, δ (ppm)			
Compound	$CH_{aromatic}$	-NCH	$-NCH_2$	$-CH_3$
Benzylisopropylamine	7.17-7.30	2.79	3.71	1.07 (1.05)
1	7.36-7.49	5.10	5.07	1.26 (1.24)
2	7.23-7.29	5.47	5.16	1.18 (1.16)
3	7.26-7.39	5.35	5.10	1.18 (1.16)

Table 4: The selected ^{13}C NMR spectra data of compounds 1-3 (δ, ppm)

	Chemical shift (δ, ppm)			
Compound	NCS_2	$-C_6H_5$	$-NCH_2$	$i\text{-}C_3H_7$
1	195.06	135.95	130.29	128.95
	128.22	58.41	57.37	20.50
2	202.65	137.13	128.58	127.13
	126.69	55.94	51.56	20.64
3	198.43	136.90	129.26	128.69
	126.65	57.89	52.79	20.74

^{1}H NMR spectra: The results were compared with the benzylisopropylamine which used as the starting material to prepare these compounds. A number of signals have been observed on complexation shifts from their original position. A downfield shift in the resonance signals of the compounds in comparison to the starting material was due to bonding between the dithiocarbamate ligand to the tin metal. The aromatic proton signals, which appear in the form of a complex multiplet at δ 7.17-7.30 ppm, shifts to δ 7.23-7.49 ppm due to deshielding on complexation. These results were in agreement as reported by Domazetis *et al.* (1977) at 7.15-7.60 ppm.

Crystal structure of $(C_4H_9)_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$: The Sn-S bonds (Sn(1)-S(1) 2.529(1) Å and Sn(1)-S(2) 2.887(1) Å) lies closely to the analogues complex $Bu_2Sn[S_2CNC_6H_{12}]_2$ (Rehman *et al*., 2006). Thus shorter bond length was closed to the sum of the covalent radii of tin and sulphur (2.42 Å) (Shahzadi *et al*., 2008). The bond distances of S(2) and S(4) with Sn were at 2.887(1) and 3.031(1) Å respectively, which were too long to be strong covalent bonds. However, these Sn-S distances were shorter than the sum of the van der Waals radii (4.0 Å) for these atoms. Thus, these bonds may be considered weak. There were two important reasons for this: first, the strong electron-withdrawing nature of isopropyl, $i\text{-}C_3H_7$ will decreases the electron density on the S atom at C-S and reduces its ability to coordinate to the tin atom.

Table 5: Crystallographic data and refinement parameters for compound 2

Compound	2
Chemical formula	$Sn(C_4H_9)_2(C_{11}H_{14}NS_2)_2$
Formula weight	681.62
Crystal system	Triclinic
Space group	P1
a (Å)	17.7745 (2)
b (Å)	19.5463 (3)
c (Å)	26.2062 (4)
α (º)	102.5254 (7)
β (º)	95.1492 (7)
γ (º)	110.2569 (8)
V ($Å^3$)	8202.1 (2)
Mo Kα (Å)	0.71073
Z	10
D/Mgm^{-3}	1.380
μ (mm^{-1})	1.06 mm^{-1}
F (000)	3540
Color	Colorless
Crystal size (mm)	0.3 x 0.3×0.1 mm
Temperature (K)	123
θ range (º)	2.2-28.3
Index ranges (±h, ±k, ±l)	-23/23, -24/25, -32/34
Total no. reflections collected	23409
Independent reflections	36923 [R_{int} = 0.028]
No. of data used for refinement	36923
No. of parameter refined	96
Largest and smallest peak (e $Å^{-3}$)	2.53 and -1.45

Table 6: Selected bond lengths (Å) and bond angles (º) for compound 2

Bond length (Å)	Bond angles (º)		
Sn(1)-C(1)	2.141(5)	C(1)-Sn(1)-C(5)	129.0(2)
Sn(1)-C(5)	2.146 (4)	C(1)-Sn(1)-S(1)	108.14(1)
Sn(1)-S(1)	2.529(1)	C(5)-Sn(1)-S(1)	115.24(11)
Sn(1)-S(2)	2.887(1)	C(1)-Sn(1)-S(3)	105.81(13)
Sn(1)-S(3)	2.536(1)	C(5)-Sn(1)-S(3)	106.94(13)
Sn(1)-S(4)	3.031(1)	S(1)-Sn(1)-S(3)	79.95(3)
S(1)-C(9)	1.757(4)	C(1)-Sn(1)-S(2)	86.46(13)
S(2)-C(9)	1.686(4)	C(5)-Sn(1)-S(2)	87.93(11)
S(3)-C(20)	1.738(4)	S(1)-Sn(1)-S(2)	65.65(3)
S(4)-C(20)	1.695(4)	S(3)-Sn(1)-S(2)	145.60(3)
N(1)-C(9)	1.342(5)	C(1)-Sn(1)-S(4)	80.36(12)
N(2)-C(20)	1.351(5)	C(5)-Sn(1)-S(4)	80.46(11)
N(1)-C(10)	1.469(5)	C(2)-C(1)-Sn(1)	102.3(3)
N(1)-C(17)	1.491(5)	C(3)-C(2)-C(1)	111.9(5)
N(2)-C(21)	1.469(5)	C(6)-C(5)-Sn(1)	119.0(3)
N(2)-C(28)	1.488(5)	C(7)-C(6)-C(5)	112.9(3)

Table 7: Cytotoxic assays, IC_{50} of compounds 1-3

	IC_{50} (μg mL^{-1})
Compounds	Human hepatocarcinoma cells, HepG2
1	Inactive
2	4.771±0.601
3	1.435±0.667
Etoposide	0.600±0.130

IC_{50} (μg mL^{-1}): The concentration that yields 50% inhibition of the cell compared with untreated control. The cytotoxicity values are expressed as mean ± SEM from the triplicate. Reference drug = Etoposide

Second, the steric interaction of the two bulky butyl groups and four-membered chelating ring may be

prevented the formation of the Sn(1)-S(2) and Sn(1)-S(4) bonds. The C(1)-Sn(1)-C(5) linkage was not linear, having an angle of 129.0(2)°, which was much smaller than the value expected for a regular bipyramidal. The Sn atom exists in a tetrahedral C_2S_2Sn coordination geometry. The best coordination geometry described as distorted towards skew-trapezoidal-bipyramidal owing to the proximity of the double-bonded S atoms.

From the data in Table 7, it was found that compound 1 was inactive against HepG2 cells compared to compounds 2 and 3. Compound 3 showed a significant cytotoxic activity with a lower IC_{50} value of 1.435 μg mL^{-1} compared to compound 2 (4.771 μg mL^{-1}). This was due to compound 3 was derived from triphenyltin(IV) (triorganotin(IV)) which was more active compared to the diorganotin(IV) (compounds 2). Hence, the cytotoxic activity of organotin(IV) obtained in this study could be arranged as: triorganotin(IV) > diorganotin(IV).

CONCLUSION

A new series of organotin(IV) dithiocarbamate compounds has been successfully synthesized and characterized. Elemental analysis C, H, N, S and Sn data obtained were in agreement with the predicted formula. The spectroscopic data supported by crystallographic data indicates that the dithiocarbamate groups form bidentate chelates with the organotin(IV) moieties. The crystallographic information obtained for the dibutyltin(IV) benzylisopropyldithiocarbamate clearly showed that the benzylisopropyldithiocarbamate ligand did indeed chelate as a bidentate entity. The bidentate chelation was unequivalent as demonstrated by the Sn-S bond distances. Based on the cytotoxic activity, compound 3 showed significant cytotoxic activity compared to compound 2 but slightly lower compared to the reference drug and believed to possess a significant role in the medicinal area in the future.

ACKNOWLEDGEMENT

The researcher would like to thank the School of Chemical Sciences and Food Technology, Faculty of Science and Technology for support and the provision of laboratory facilities. We also like to thank Higher Education Ministry, Malaysia for the financial support under the research grant UKM-NN-FRGS0003-2007 and Prof. Ng Seik Weng from Chemistry Department, University of Malaya for crystallographic studies.

REFERENCES

Awang, N., I. Baba, M.M.S. Yusof and B.M. Yamin, 2003a. Bis(N-cyclohexyl-N-methyldithiocarbamato) dimethyltin(IV). Acta Crystallogr. E, 59: 348-349. DOI: 10.1107/S1600536803010420

Awang, N., I. Baba, M.M.S. Yusof and B.M. Yamin, 2003b. (N-cyclohexyl-N-methyldithiocarbamato) triphenyltin(IV). Acta Crystallogr. E, 59: 414-415. DOI: 10.1107/S1600536803011991

Awang, N., I. Baba, M.M.S. Yusof and B.M. Yamin, 2003c. (N-cyclohexyl-N-ethyldithiocarbamato) triphenyltin(IV). Acta Crystallogr. E, 59: 594-595. DOI: 10.1107/S1600536803015277

Bonati, F. and R. Ugo, 1967. Organotin(IV) N,N-disubstituted dithiocarbamates. J. Organomet. Chem., 10: 257-268. DOI: 10.1016/S0022-328X(00)93085-7

Bradley, D.C. and M.H. Gitlitz, 1969. Preparation and properties of NN-dialkyldithiocarbamates of early transition elements. J. Chem. Soc. A, 84: 1152-1156. DOI: 10.1039/J19690001152

Chatt, J., L.A. Duncanson and L.M. Venanzi, 1956. Electronic structure of dithiocarbamate and xanthates. Nature, 177: 1042-1043. DOI: 10.1038/1771042b0

Crouse, K.A., K.B. Chew, M.T.H. Tarafder, A. Kasbollah and A.M. Ali, 2004. Synthesis, Characterization and Bio-activity of S-2-Picolyldithiocarbazate (S2PDTC), some of its Schiff bases and their Ni(II) complexes and x-ray structure of S-2-picolyl-β-N-(2-acetylpyrrole)dithiocarbazate. Polyhedron, 23: 161-168. DOI: 10.1016/j.poly.2003.09.025

Domazetis, G., R.J. Magee and B.D. James, 1977. Synthesis and structure of some triphenyltin(IV) dithiocarbamate compounds. J. Organomet. Chem., 141: 57-69. DOI: 10.1016/S0022-328X(00)90667-3

Gielen, M., 1996. Tin-based antitumour drugs. Coord. Chem. Rev., 151: 41-51. DOI: 10.1016/S0010-8545(96)90193-9

Gielen, M., M.D.V. Biesemans and R. Willem, 2000. Synthesis, characterization and *in vitro* antitumor activity of di- and triorganotin derivatives of polyoxa- and biologically relevant carboxylic acids. J. Inorg. Biochem., 79: 139-145. DOI: 10.1016/S0162-0134(99)00161-0

Jamil, K., M. Bakhtiar, A.R. Khan, F. Rubina and R. Wajid *et al*., 2009. Synthesis characterization and antimicrobial activities of noval organotin compounds. Afr. J. Pure Applied Chem., 3: 66-71. http://www.academicjournals.org/AJPAC/PDF/pdf 2009/April/Jamil%20et%20al.pdf

Khan, S.R.A., S. Huang, S. Shamsuddin, S. Inutsuka and K.H. Whitmire, 2000. Synthesis, characterization and cytotoxicity of new platinum(IV) axial carboxylate complexes: Crystal structure of potential antitumor agent [Pt^{IV}(trans-1R,2R-diaminocyclohexane)trans(acetate)$_2Cl_2$]. Bioorg. Med. Chem., 8: 515-521. DOI: 10.1016/S0968-0896(99)00313-2

Mansouri-Torshizi, H., M. Saeidifar, A. Divsalar and A.A. Sabour, 2010. Spectrochimica acta part A: Molecular and biomolecular spectroscopy. Spectrochimica Acta Part A, 77: 312-318. DOI: 10.1016/j.saa.2010.05.029

Nomura, R., S. Fujii, A. Takabe and H. Matsuda, 1989. Preparation of novel metal dithiocarbamate complexes containing ω-OH group. Stabilization effect of the OH group on the $HNCS_2$-Mt linkage. Polyhedron, 8: 1891-1896. DOI: 10.1016/S0277-5387(00)86410-4

Novelli, F., M. Recine, F. Sparatore and C. Juliano, 1999. Triorganotin compounds as antimicrobial agents. IL Farmaco, 54: 237-241. DOI: 10.1016/S0014-827X(99)00020-8

Rehman, Z., S. Shahzadi, S. Ali, A. Badshah and G.X. Jin, 2006. Crystal structure of 1,1-dibutyl-1,1-bis[(4-methyl-1-piperidinyl) dithiocarbamato)] tin(IV). J. Iran. Chem. Soc., 3: 157-160.

Sheldrick, G.M., 1996. SADABS, program for empirical absorption correction of area detector data. University of Göttingen.

Sheldrick, G.M., 1997a. SHELXTL V5 1 software reference manual. Bruker AXS Inc.

Sheldrick, G.M., 1997b. SHELX97 programs for crystal structure analysis. University of Gottingen, Germany.

Siemens, S., 1996. SMART and SAINT area detector control and integration software. Siemens Analytical X-Ray Systems Inc.

Soliman, A.A. and G.G. Mohamed, 2004. Study of the ternary complexes of copper with salicylidene-2-aminothiophenol and some amino acids in the solid state. Thermochimica Acta, 421: 151-159. DOI: 10.1016/j.tca.2004.03.010

Shahzadi, S., S. Ali and M. Fettouhi, 2008. Synthesis, spectroscopy, *in vitro* biological activity and X-ray structure of (4-Methylpiperidine-dithiocarbamato-S, S′)triphenyltin(IV). J. Chem. Crystallogr., 38: 273-278. DOI: 10.1007/s10870-007-9295-5