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Cytotoxic Effect of Organotin(IV) Benzylisopropyldithiocarbamate Compounds on Chang Liver Cell and Hepatocarcinoma HepG2 Cell

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Abstract: Cancer is one of the main causes of mortality and morbidity in world. New compounds are currently being synthesized to combat this disease. The organotins are gaining more attention as anti-cancer agents due to their potent cytotoxicity properties. In this study, a series of newly synthesized organotins namely dimethyltin (IV) (compound 1), dibutyltin (IV) (compound 2) and triphenyltin (IV) benzylisopropyldithiocarbamate (compound 3) were assessed for their cytotoxic activities against human Chang liver cells and hepatocarcinoma HepG2 cells. The cytotoxicity of these organotins in both cells upon 24 h treatment was assessed using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Compound 2 and 3 exhibited potent cytotoxic activities towards both cells where the IC_{50} values were less then 10 μM. The IC_{50} value for compound 2 was 2.5 μM in Chang liver cells and 7.0 μM in HepG2 cells whereas compound 3 exhibited an IC_{50} value of 1.5 μM in Chang liver cells and 2.5 μM in HepG2 cells. Therefore, compound 2 and 3 were more toxic against human Chang liver cells as compared to hepatocarcinoma HepG2 cells. Interestingly, compound 1 did not have any IC_{50} value in both cells and hence can be classified as non-toxic. In conclusion, organotin (IV) benzylisopropyldithiocarbamate with insertion of dibutyl and triphenyl functional group possess potent cytotoxicity properties. Structural modification of these compounds can be carried out in further studies to produce less or non toxic effects towards normal human cell.

Key words: Cytotoxicity, organotin (IV), dithiocarbamate, hepatocarcinoma HepG2 cells, chang liver cells

INTRODUCTION

Organotin (IV) compounds are characterized by the presence of at least a bond between carbon (C) and tin (Sn) which are attached covalently. The compounds contain tetravalent (Sn) centres and are classified as mono-, di-, tri and tetraorganotin (IV), depending on the number of alkyl or aryl moieties attached to the tin atom (Pellerito *et al*., 2006). General formula for organotin (IV) is R_nSnX_{4-n} (Xanthopoulou *et al*., 2006), where R is the hydrocarbon group while X is the inorganic entities. Organotin (IV) compounds are gaining more attention nowadays due to their wide use in the Biomedical and commercial field. Most organotin (IV) compounds are generally very toxic, even at low concentrations, whereas dithiocarbamate compounds with diorganotin (IV) species showed various structural and biological activities (Sanuddin *et al*., 2006). Furthermore, the structural chemistry of organotin (IV) compounds of amino acids also exhibit various features in structural motif research (Ashfaq *et al*., 2004a).

General formula for dithiocarbamate is-S_2CNR_2 (Tiekink, 2008). The applications of dithiocarbamate have been widely used in variety of substances as it has the potential to be used as a chemotherapeutic, pesticide and fungicide (Heard, 2005). Most of the metals bind tightly to the thiol group (sulfhydryl). The thiol group is regularly found on various kinds of important enzymatic active sites, including enzymes which are involved in cellular energy generation and oxygen transportation. In addition, neutral organometallic compounds tend to dissolve in lipid and thus enhance their movement across the biological membranes (Manahan, 2003).

Previous studies showed that dibutyltin (IV) and triphenyltin (IV) compounds gave high cytotoxicity and showed very promising anti tumor properties against

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various human cancer cell lines (Gielen *et al*., 2000; Gielen, 2002; Abdellah *et al*., 2009). Interestingly, in some cases, organotin(IV) complexes also showed their potential to be developed as a new chemotherapy agent as they provide acceptable antiproliferative activity *in vivo* (Nagy *et al*., 2000; Nath *et al*., 2001). Furthermore, some studies related to organotin (IV) also showed lower median inhibitory concentration against various human cancer cell lines as compared to the current clinical drugs used in cancer treatment (Gomez-Ruiz *et al*., 2008; Yin and Xue, 2006).

In an attempt to identify new organotin compounds with cytotoxic potential, a series of newly synthesized organotin (IV) benzylisopropyldithiocarbamate compounds were screened in human hepatocarcinoma HepG2 cells and human Chang liver cells (normal liver cells). This study was conducted by using three compounds namely dimethyltin (IV) (compound 1), dibutyltin (IV) (compound 2) and triphenyltin (IV) benzylisopropyldithiocarbamate (compound 3) to evaluate the cytotoxicity of these compounds on both cells.

MATERIALS AND METHODS

This study was conducted from August 2010 to February 2011.

Test compounds: A series of organotin (IV) benzylisopropyldithiocarbamate were synthesized at School of Chemical Sciences and Food Technology, Faculty of Science and Technology, UKM Bangi.

Cell culture and reagents: Hepatocarcinoma HepG2 cells and Chang liver cells were purchased from the American Type Culture Collection (ATCC) and were cultured at Biocompatibility and Toxicology Lab, Faculty of Allied Health Sciences, UKM Kuala Lumpur. HepG2 cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) containing L-glutamine, with high glucose, sodium bicarbonate ($NaHCO_3$), 1% penicillin/streptomicin and 10% Foetal Bovine Serum (FBS) (GIBCO, USA). Meanwhile, Chang liver cells were maintained in Roswell Park Memorial Institute 1640 (RPMI 1640) supplemented with L-glutamine, sodium bicarbonate ($NaHCO_3$), 1% penicillin and streptomicin and 10% Foetal Bovine Serum (FBS) (GIBCO, USA). All cell lines were grown at 37°C in a humidified atmosphere with 5% CO_2 and were in exponential phase of growth at the time of inclusion in cytotoxicity assays.

Assessment of cytotoxicity using MTT assay: Cellular viability for hepatocarcinoma HepG2 and Chang liver cells was determined by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The assay was conducted as described by Mosmann (1983). Dimethyltin (IV), dibutyltin (IV) and triphenyltin (IV) benzylisopropyldithiocarbamate were dissolved in dimethyl sulphoxide (DMSO), diluted in culture media and used to treat model cell lines. The maximum percentage of DMSO present in any well was 0.1%. Both cells were treated with all three organotin (IV) compounds along with menadione as positive control. Both cells were treated using seven different concentrations for 24 h. The concentrations used include 1.563, 3.125, 6.250, 12.500, 25.000, 50.000 and 100.000 μM. Cells were seeded in sterile 96 well flat-bottomed plates (Nunc, Denmark) at a density of 5×10^4 cells mL^{-1} and grown in 5% CO_2 at 37°C. In metabolically active cells, MTT is reduced by the mitochondrial enzyme succinate dehydrogenase to form insoluble purple formazan crystals that are subsequently solubilised and the Optical Density (OD) measured spectrophotometrically. Therefore, drug treated cells were assayed by the addition of 20 μL of 5 mg mL^{-1} MTT in 0.1 M phosphate buffer saline (PBS), pH 7.4. Following incubation for 4 h at 37°C, the overlying medium was aspirated with a micropipette and 180 μL of DMSO was added to dissolve the formazan crystals. Plates were agitated using orbital shaker for 3 to 5 min to ensure complete dissolution of crystals and OD was measured at 570 nm using ELISA Microplate Reader (Labsystem Multiscan Multisoft, Finland). Each compound concentrations had five replicates per assay and each experiment was carried out on at least three separate occasions. The IC_{50} value was calculated for each compound and used as a parameter to compare the relative cytotoxicity of each test compound. Consequently, the IC_{50} was defined as the drug concentration (μM) causing a 50% reduction in cellular viability (Thati *et al*., 2007).

Statistical analysis: Statistical evaluation of the percentage of viable cells along with concentration of compounds used to treat the cells was calculated using Statistical Package for Social Science (SPSS) version 18.0 by employing one-way ANOVA (analysis of variance). A probability of 0.05 or less was deemed statistically significant.

RESULTS AND DISCUSSION

The graph for cytotoxic effect against hepatocarcinoma HepG2 cells after 24 h treatment using all three compounds are presented in Fig. 1. Figure 1 showed

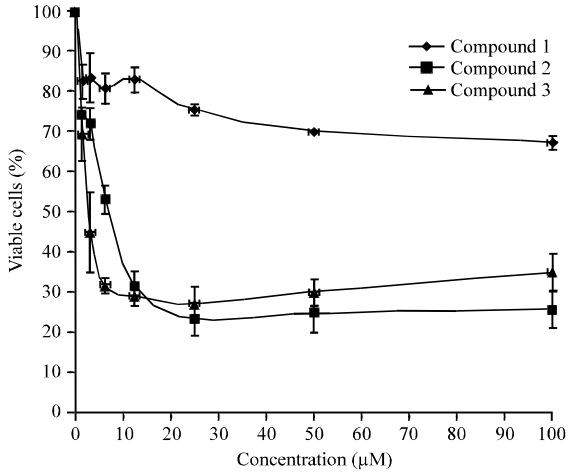

Fig. 1: Cytotoxic effect of organotin (IV) benzylisopropyldithiocarbamate against, hepatocarcinoma HepG2 cells upon 24 h treatment using MTT assay, (Mean±SEM)

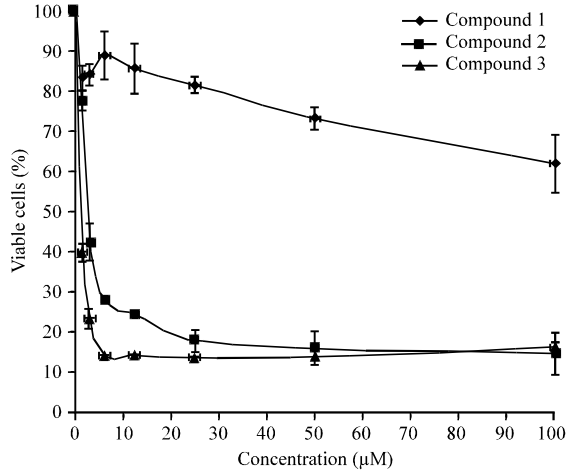

Fig. 2: Cytotoxic effect of organotin (IV) benzylisopropyldithiocarbamate against Chang, liver cells upon 24 h, treatment using MTT assay (Mean±SEM)

that only 2 compounds were able to effectively kill half of the cell population, whereas for compound 1, it has been shown that almost 70% of cells were still alive even during treatment at the highest concentration of 100 μM. Out of all three compounds, compound 1 did not give an IC_{50} value whereas compound 2 and 3 showed high cytotoxicity in both cell lines. Based on the data from the experiment, compound 3 showed higher cytotoxic effect against HepG2 cells as compared to compound 2. The IC_{50} value for compound 3 was 2.5 μM whereas the

Table 1: IC_{50} values for compounds 2 and 3

	IC_{50} (μM)	
Compounds	HepG2	Chang
2	7.0	2.5
3	2.5	1.5

IC_{50} value for compound 2 was 7.0 μM. Compound 1 did not have IC_{50} value even though the cells were treated with a concentration of up to 100 μM.

Figure 2 showed the data obtained for Chang liver cells upon 24 h of treatment. The figure showed that the dimethyltin(IV) compound was not able to kill half of the cell population and had clearly shown that almost 60% of cells population were alive at 100 μM concentration. Similar to hepatocarcinoma HepG2 cells, only two compounds, dibutyltin (IV) and triphenyltin (IV) gave IC_{50} values against Chang liver cells, whereas no IC_{50} value was obtained for dimethyltin (IV). The IC_{50} values for both compounds were less than the IC_{50} values obtained from hepatocarcinoma HepG2 cells where the IC_{50} value for compound 2 was 2.5 μM and 1.5 μM for compound 3. The IC_{50} values determined from both graphs are presented in Table 1.

The morphological changes between HepG2 cells before and after treatment for compound 2 and 3 are shown in Fig. 3. Statistical analysis using one-way ANOVA showed significant differences in HepG2 cells viability (%) between compound 1 and 3 ($p<0.05$) whereas there was no significant differences between compound 2 with compound 1 and 3 where $p>0.05$.

Figure 4 shows the morphological changes in Chang liver cells for both compounds tested before and after treatment. There was significant differences in Chang liver cells viability (%) between compound 1 with compound 2 and 3 ($p<0.05$). Otherwise, compound 2 and 3 showed no significant differences where $p = 0.120$.

As a whole, the percentage of viable cells after treatment with compound 1 was smaller in normal cells as compared to cancerous cells except concentration at 25 μM, where the percentage of viable cells in HepG2 cells was smaller as compared to Chang liver cells. Up to 100 μM, compound 1 did not give IC_{50} values in both cell lines. Compounds with IC_{50} values higher than 25 μg cm^{-3} (41.9 μM for compound 1) are classified as non-toxic (How *et al*., 2008).

In contrast to compound 1, compound 2 was categorized as a highly toxic compound with IC_{50} value of less than 5.0 μg cm^{-3} (<7.34 μM for compound 2). How *et al*. (2008) classified compounds with IC_{50} values of less than 5.0 μg cm^{-3} as very toxic compounds. The results showed that dibutyltin (IV) were very toxic against both cell lines but the IC_{50} value for Chang liver cells (2.5 μM) was smaller than for hepatocarcinoma HepG2 cells (7.0 μM). Thus, compound 2 was found to be

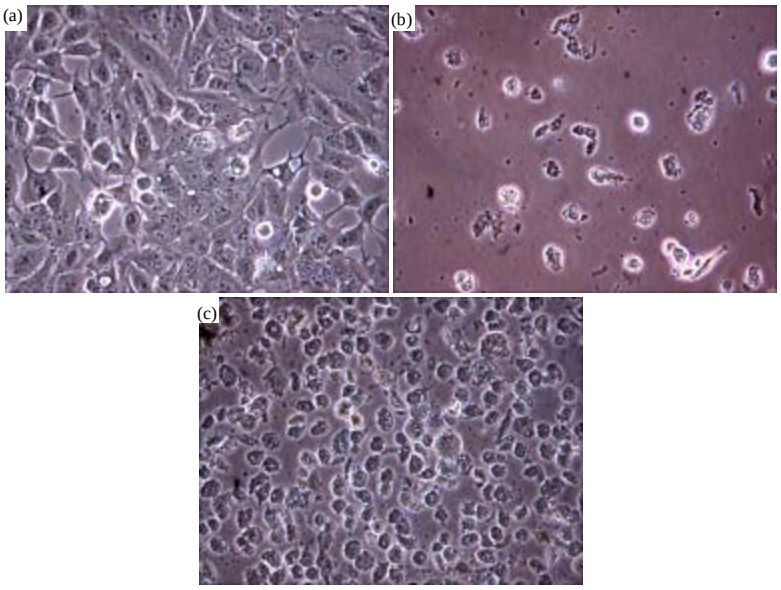

Fig. 3(a-c): Hepatocarcinoma HepG2 cells 24 h after treatment (10×40), (a) Negative control, (b) Treated with compound 2 and (c) Treated with compound 3

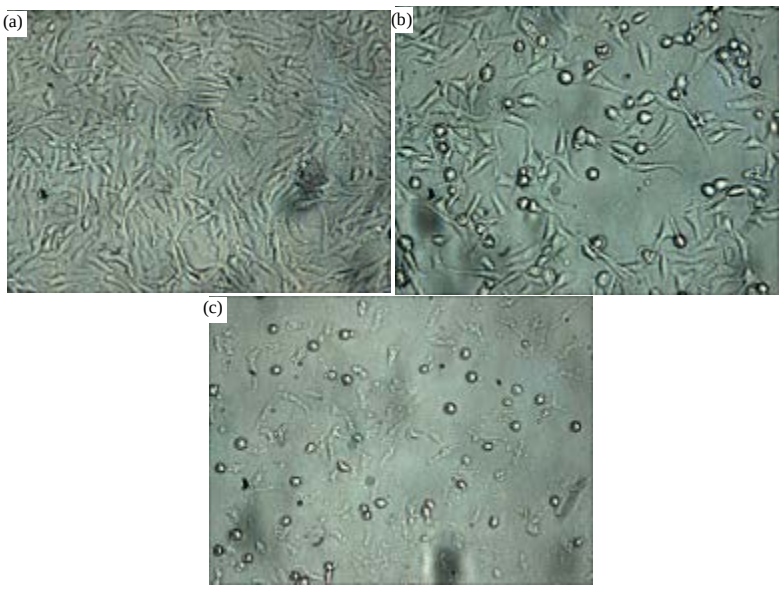

Fig. 4(a-c): Chang liver cells 24 h after treatment (10×40), (a) Negative control, (b) Treated with compound 2 and (c) treated with compound 3

most toxic toward human normal liver cells. A study by Girasolo *et al.* (2010) also showed the similar as all dimethyltin (IV) compounds tested *in vitro* exhibited lower cytotoxic activity than dibutyltin(IV) compounds.

Similar to compound 2, compound 3 also gave IC_{50} values of less than 5.0 μg cm^{-3} (<8.71 μM for compound 3) and therefore also classified as very toxic. Compound 3 was also found to have higher cytotoxic

activity towards Chang liver cells. Based on the data obtained from both cells, the IC_{50} values for both compounds showed that the IC_{50} values obtained for compound 3 was lower than the IC_{50} values for compound 2 in both cell lines. The possible reason in influencing the varying degrees in toxicological properties of organotin (IV) compounds was the nature of the compounds and the number of alkyl groups attached to the Sn (IV) atom (Syng-ai *et al*., 2002). The bulkiness of the functional group R' attached to Sn (IV) is believed to induce and enhance the *in vitro* toxicity against the cell lines tested and have the tendency in increasing the hydrophillicity and finally boost up the bioactivity of these complexes. The increase in hydrophilicity of these compounds were found to be in the same order with their bioactivity (Hadjikakou and Hadjiliadis, 2007).

As in this study, compound 3 was found to have three hydrocarbon groups (phenyl) attached to Sn (IV) atom compared to only two hydrocarbon groups (butyl) attached to tin (IV) atom of dibutyltin (IV). The data gained from the experiment showed that triphenyltin (IV) was more toxic than dibutyltin (IV). This was found to be related to the presence of more R' functional groups attached to tin (IV) atom in compound 3 as compared to compound 2. A research previously done by Awang *et al*. (2011) showed a similar trend where the triorganotin (IV) complex was the most active compound among its series and also showed a very good cytotoxic effect as compared to the clinical drug used, etoposide.

These results were also supported by Jain *et al*. (2004), who conducted a study to identify the influence of R functional groups towards organotin (IV). The tin (II) complexes tested did not have the alkyl group attached to tin atom and the results showed that tin (II) complexes were less toxic in that series. Thus, they suggested that the presence of organic groups attached directly to the tin atom was the most significant factor that influences the increase of organotin (IV) complexes activities.

Several studies have proven that organotin (IV) complexes have the ability to induce apoptotic cell death (Girasolo *et al*., 2010; Alama *et al*., 2009). However, the mechanism of toxic effect of organotin (IV) compounds is fairly complicated. Nowadays, some researchers assume that these compounds have the capability to react with cell membranes thus leading to their decay, enhancing the ion exchange processes and finally the inhibition of oxidative and photochemical phosphorylation (Pellerito *et al*., 2006).

Organotin (IV) compounds could be involved in other biological processes occuring in cells, specifically in peroxide oxidation of lipids. Acceleration of peroxide oxidation of lipids in cells leads to accumulation of hydroperoxides, decay of cell membranes and various pathologies in living bodies. As organotin (IV) compounds exhibit electron acceptor properties, it was presumed that their toxicity originates from interaction with electron-donor groups in biomolecules. Reactions of organotin (IV) compounds with phosphorus containing biomolecules, such as phospholipids, ATP and nucleic acids, were shown to inhibit the synthesis of phospholipids and their intracellular transport, which may be responsible for the antiproliferative activity of organotin (IV) derivatives (Das, 1996).

Based on the results obtained from this study, triphenyltin (IV) benzylisopropyldithiocarbamate was found to be more toxic than dibutyltin (IV) benzylisopropyldithiocarbamate, thus their toxicities can be ranked in this order: $R_3SnX>R_2SnX$. This finding was supported by Attar (1996) which stated that among $R_nSnX_{(4-n)}$ compounds, the most toxic are the R_3SnX. Win *et al*. (2010) previously used diorganotin (IV) and triorganotin (IV) derivatives in their research and also claimed higher cytotoxic effect associated with triorganotin (IV) compound rather than diorganotin (IV) derivatives. This is because the tin moiety nature exists as four-coordinated with distorted tetrahedral geometry which will enhance the cytotoxic activity of a complex (Ashfaq *et al*., 2004b).

According to Pellerito *et al*. (2006), triorganotin (IV) compounds appear to inhibit the mitochondrial function in at least three ways; by causing large-scale swelling at high concentrations, mediating Cl^-/OH^- exchange across membranes and inhibiting oxidative phosphorylation or ATP hydrolysis. The triorganotin (IV) mediated anion exchange across the mitochondrial membrane may also interfere with ATP synthesis or hydrolysis. These factors might be the reasons for higher cytotoxic effect found in triphenyltin (IV) as compared to dibutyltin (IV) benzylisopropyldithiocarbamate.

CONCLUSION

This study showed that a series of organotin (IV) benzylisopropyldithiocarbamate have the ability to reduce the percentage of viable cells, but dimethyltin (IV) was classified as non-toxic compound as it did not have IC_{50} value in both cell lines tested. In contrast, dibutyltin (IV) and triphenyltin (IV) were found to be very toxic against both cancerous and normal liver cells. In comparison between both compounds, triphenyltin (IV) gave higher toxic effect toward both cells, but they were both found to be more toxic toward Chang liver cells compared to hepatocarcinoma HepG2 cells. Thus, structural modification of these compounds will be carried out in further studies to produce less or non toxic effects towards normal human cells.

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REFERENCES

Abdellah, M.A., S.K. Hadjikakou, N. Hadjiliadis, M. Kubicki and T. Bakas *et al*., 2009. Synthesis, characterization and biological studies of organotin (IV) derivatives with o- or p-hydroxybenzoic acids. Bioinorganic Chem. Appl., 2009: 1-12.

Alama, A., B. Tasso, F. Novelli and F. Sparatore, 2009. Organometallic compounds in oncology: Implications of novel organotins as antitumor agents. Drug Discovery Today, 14: 500-508.

Ashfaq, M., M.I. Khan and M.K. Baloch, 2004a. Investigation of novel bio-diorganotin (IV) esters of N-maleoylglycine. J. Med. Sci., 4: 36-40.

Ashfaq, M., M.I. Khan, M.K. Baloch and A. Malik, 2004b. Biologically potent organotin (IV) complexes of 2-maleimidoacetic acid. J. Organomet. Chem., 689: 238-345.

Attar, K.M., 1996. Analytical methods for speciation of organotins in the environment. Appl. Organomet. Chem., 10: 317-337.

Awang, N., I. Baba, b.M. Yamin, M.S. Othman and N.F. Kamaludin, 2011. Synthesis, characterization and biological activities of organotin (IV) methylcyclohexyldithiocarbamate compounds. Am. J. Applied Sci., 8: 310-317.

Das, V.G.K., 1996. Main Group Elements and Their Compounds. Springer, New Delhi, India, ISBN: 9783540614258, pp: 422.

Gielen, M., 2002. Review: Organotin compounds and their therapeutic potential: A report from the organometallic chemistry department of the free university of Brussels. Applied Organomet. Chem., 16: 481-494.

Gielen, M., M. Biesemans, D. De Vos 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.

Girasolo, M.A., S. Rubino, P. Portanova, G. Calvaruso, G. Ruisi and G. Stocco, 2010. New organotin (IV) complexes with l-Arginine, Nα-t-Boc-l-Arginine and l-Alanyl-l-Arginine: Synthesis, structural investigations and cytotoxic activity. J. Organomet. Chem., 695: 609-618.

Gomez-Ruiz, S., G.N. Kaluderovic, S. Prashar, E. Hey-Hawkins, A. Eric, Z. Zizak and Z.D. Juranic, 2008. Study of the cytotoxic activity of di and triphenyltin(IV) carboxylate complexes. J. Inorg. Biochem., 102: 2087-2096.

Hadjikakou, S.K. and N. Hadjiliadis, 2007. Antiproliferative and anti-tumor activity of organotin compounds. Coord. Chem. Rev., 253: 235-249.

Heard, P.J., 2005. Main Group Dithiocarbamate Complexes. In: Progress in Inorganic Chemistry, Karlin, K.D. (Eds.). Vol. 53. John Wiley and Sons Inc., London, UK., ISBN: 9780471463702, pp: 2-68.

How, F.N.F. K.A. Crouse, M.I.M. Tahir, M.T.H. Tarafder and A.R. Cowley, 2008. Synthesis, characterization and biological studies of S-benzyl-&beta-N-(benzoyl) dithiocarbazate and its metal complexes. Polyhedron, 27: 3325-3329.

Jain, A., S. Saxena, A.K. Rai and P.N. Saxena, 2004. Assessment of toxicity of some penta-and hexacoordinated organotin (IV) and tetracoordinated tin (II) complexes of heterocyclic &beta-diketones. Bioinorganic Chem. Appl., 2006: 1-4.

Manahan, S., 2003. Toxicological Chemistry and Biochemistry. 3rd Edn., CRC Press, Boca Raton, FL., USA., ISBN: 9781566706186, pp: 425.

Mosmann, T., 1983. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. J. Immunol. Method, 65: 55-63.

Nagy, L., A. Szorcsik and K. Kovacs, 2000. Tin compounds in pharmacy and nutrition. Acta Pharm. Hung., 70: 53-71.

Nath, M., S. Pokharia and R. Yadav, 2001. Organotin (IV) complexes of amino acids and peptides. Coord. Chem. Rev., 215: 99-149.

Pellerito, C., L. Nagy, L. Pellerito and A. Szorcsik, 2006. Biological activity studies on organotin (IV)$^{n+}$ complexes and parent compounds. J. Organomet. Chem., 691: 1733-1747.

Sanuddin, M., M.Y. Farina, B. Yamin and I. Baba, 2006. Synthesis and characterization of diorganotin (IV) dithiocarbamate complexes. Sains Malaysiana, 34: 107-112.

Syng-ai, C., T.S. Basu Baul and A. Chatterjee, 2002. Antiproliferative and cytotoxic effect of a novel organotin compound on mammalian cells both *in vitro* and *in vivo*. Mutation Res./Genet. Toxicol. Environ. Mutagen., 513: 49-59.

Thati, B., A. Noble, B.S. Creaven, M. Walsh and M. McCann *et al*., 2007. *In vitro* anti-tumour and cyto-selective effects of coumarin-3-carboxylic acid and three of its hydroxylated derivatives, along with their silver-based complexes, using human epithelial carcinoma cell lines. Cancer Lett., 248: 321-331.

Tiekink, E.R.T., 2008. Tin dithiocarbamates: Applications and structures. Applied Organomet. Chem., 22: 533-550.

Win, Y.F., S.G. Teoh, T.S. Tengku-Muhammad, Y. Sivasothy, S.T. Ha, 2010. Synthesis and characterization of organotin(IV) complexes derived of 3-(Dimethylamino)benzoic acid: Cytotoxic assay on human liver carcinoma cells (HepG2). Am. J. Applied Sci., 7: 301-308.

Xanthopoulou, M.N., S.K. Hadjikakou, N. Hadjiliadis, E.R. Milaeva and J.A. Grachev *et al*., 2006. Biological studies of new organotin (IV) complexes of thioamide ligands. Eur. J. Med. Chem., 43: 327-335.

Yin, H.D. and S.C. Xue, 2006. Synthesis and characterization of organotin complexes with dithiocarbamates and crystal structures of $(4\text{-}NCC_6H_4CH_2)_2Sn(S_2CNEt_2)_2$ and $(2\text{-}C_1C_6H_4CH_2)_2Sn(Cl)S_2CNBz_2$. Applied Organomet. Chem., 20: 283-289.