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Preliminary in vitro cytotoxic assay of human liver carcinoma cells (HepG2) of organotin(IV) complexes: Synthesis and characterization of organotin(IV) complexes of 2,4-dinitrobenzoic and 3,5-dinitrobenzoic acids

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A total of five organotin(IV) carboxylate complexes was successfully synthesized and characterized quantitatively and qualitatively. Results of the infrared spectroscopy of the parent acids and complexes showed that the coordination took place via oxygen atoms from the carboxylate group. From the preliminary in vitro cytotoxic assay study, triorganotin(IV) complexes (2 and 5) were found to exhibit better activity as compared to diorganotin(IV) complexes (1, 3 and 4) but lower activity as compared to the reference drug. In addition, within the diorganotin(IV) complexes, monomeric type (3) exhibited a slightly better activity as compared to the organodistannoxane dimer types (1 and 4).

Key words: Preliminary in vitro cytotoxic assay, organotin(IV) complexes, comparison study.

INTRODUCTION

Although, the first organotin(IV) compound was successfully isolated in 1850s, it did not gain any commercial significance in industrial applications until almost a hundred years later (Blunden et al., 1985). Since then, the study of organotin(IV) complexes have received considerable attention due to the vast applications in industrial as well as its biological properties against bacterial, fungal and cancer cells lines (Gielen et al., 2000; Mahmood et al., 2003, 2004; Khan et al., 2004; Xanthopoulou et al., 2008; Hadi et al., 2009; Hanif et al., 2010). The history and discovery of cis-platin and its platinum derivatives as anti tumor drugs are a major breakthrough in combating certain human cancers (Bonire and Fricker, 2001; Pruchnik et al., 2003; Clarke et al., 1999). However, the side-effects of cis-platin have led to the search of new anti tumor drugs which possess high anti tumor properties with less side-effects. Hence, new compounds analogous to cis-platin such as organotin(IV) compounds with the general formula of R2SnX2Ln or R2SnL2 (R = alkyl, aryl or phenyl, X= halogen, L= coordinated ligands and n= 1 or 2) are highly targeted for anti tumor screening activity (Clarke et al., 1999; Pruchnik et al., 2003). As a result, numerous in depth study of organotin(IV) carboxylate complexes such as antiproliferative activity and the structural-activity have been carried out (Pellerito et al., 1997; Song et al., 2006; Xanthopoulou et al., 2006; Hadjikakou and Hadjiliadis, 2009). Up to date, organotin(IV) carboxylate complexes are still extensively studied due to their coordination geometries as well as structural diversity (monomer, dimeric, hexameric and oligomeric) which are attributed

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to the coordinating ligands (Zhang et al., 2005; Win et al., 2007; Amini et al., 2008; Zhang et al., 2011; Danish et al., 2011).

In this study, we reported on the synthesis and structural characterization of organotin(IV) carboxylate complexes derived from dinitrobenzoic acids. Moreover, the preliminary in vitro cytotoxic assay on human liver carcinoma cells, HepG2 of the complexes was reported herein.

MATERIALS AND METHODS

Instrumentation

All the reagents, starting materials as well as the solvents were purchased commercially and used without any further purification. The melting points were determined in an open capillary and were uncorrected. Elemental C, H and N analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. Tin was determined gravimetrically by igniting a known quantity of each complex to SnO2. Infrared spectra were recorded using a Perkin-Elmer System 1137 FTIR spectrophotometer as a KBr disc in the frequency range of 4000 to 400 cm^-1. The spectra for 1H, 13C, and 119Sn NMR were recorded on a Bruker AC-P 400 MHz FTNMR Spectrometer and 131C NMR was recorded on a Bruker AC-P 300MHz FTNMR Spectrometer using deuterated CDCl3 and d6-DMSO as the solvent and tetramethylsilane, and TMS as the internal standard.

Preliminary in vitro cytotoxic assay

The in vitro cytotoxic assay was carried out against human liver carcinoma 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 sodium bicarbonate, 100 IU/ml penicillin and 100 μg/ml streptomycin. The cytotoxicity assay was determined using the microtitration 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Mosmann, 1983; Ali et al., 2000). The assay of each concentration for each compound was performed in triplicate. The fraction of surviving cells was measured relative to the untreated control cell population by measuring the absorbance values at 570 nm with a reference at 630 nm using an Enzyme-linked immunosorbent assay (ELISA) microplate reader (Bio Tek EL 340, USA) (Ali et al., 2000). Cytotoxicity was expressed as fifty percent cytotoxic dose (IC50); that is, the concentration causing 50% inhibition of cell growth with reference to the control (untreated cells). The IC50 and the S.E.M. (standard error of the mean) was determined using Probit Analysis (SPSS, version 12.0.1).

Preparation of sodium salts

The sodium salts of the acids were obtained by heating under reflux of a 1:1 molar mixture of sodium hydroxide, NaOH (3 mmol) with the respective acids (3 mmol) in ethanol (50 ml) for two hours. After a few days, white precipitates were obtained. Sodium salt of 2,4-dinitrobenzoic acid: FTIR as KBr disc (cm^-1) selected data: ν(COO)~1659, ν(COO)~1342. Sodium salt of 3,5-dinitrobenzoic benzoic acid: FTIR as KBr disc (cm^-1) selected data: ν(COO)~1624, ν(COO)~1346.

Synthesis of complexes

**Bis(2,4-dinitrobenzoato)tetrabutyldistannoxane(IV) dimer, [(2,4-(NO2)2C6H4COO)(C4H9)2Sn]2O2 (1)**

The complex was obtained by heating under reflux of a 1:1 molar mixture of dibutyltin(IV) oxide (0.75 g, 3 mmol) and 2,4-dinitrobenzoic acid (0.64 g, 3 mmol) in toluene/ethanol mixture (2:3, 50 ml) for three hours. A clear yellow transparent solution was isolated by filtration and kept in a bottle. After few days, yellow crystals (1.19 g, 87.2 % yield) were collected. The melting point was 197.8 to 198.6°C. Analysis for C56H54O10Sn2: C, 40.11; H, 3.00; N, 4.91; Sn, 21.03 %.

**2,4-Dinitrobenzoatotriphenyltin(IV),2,4-(NO2)2C6H4COOC6H5Sn (2)**

Complex 2 was prepared by heating under reflux of a 1:1 molar mixture of triphenyltin(IV) hydroxide (1.10 g, 3 mmol) and 2,4-dinitrobenzoic acid (0.64 g, 3 mmol) in ethanol (50 ml) for two hours. A clear yellow solution was isolated by filtration and kept in a bottle. After three days, yellow crystals (1.38 g, 82.3 % yield) were collected. The melting point was 160.4 to 161.2°C. Analysis for C55H52O9Sn: C, 53.51; H, 3.23; N, 4.91; Sn, 21.03 %. FTIR as KBr disc (cm^-1): ν(C-H) aromatic 3069, 3051, 3023; ν(CO2) 1539, ν(CO2) 1345, ν(CO2) 1376, ν(CO2) 1342, ν(CO2) 1599, ν(CO2) 1345, ν(CO2) 1341, ν(Sn-O) 453. 1H-NMR (ppm) (CDCl3): δ: benzene protons 7.78 (d, 7.7 Hz, 4H), 8.56 (d, 6.9 Hz, 4H), 8.75 (s, 4H); butyl, CH2 0.90 (t, 7.3 Hz, 12H), 0.95 (t, 7.4 Hz, 12H); CH2 1.32-1.51 (m, 32H); CH2 1.67-1.85 (m, 16H), 13C-NMR (ppm) (CDCl3): δ: benzene carbons 119.47, 127.21, 130.59, 135.62, 148.04, 148.44; aromatic 3087, 3058, 2963, 2935, 2875; COO (C=O) 202.

**Bis(3,5-dinitrobenzoato) dibutyltin(IV) toluene solvate, [3,5-(NO2)2C6H4COO)(C4H9)2Sn.C6H6 (3)**

Complex 3 was obtained by heating under reflux of a 1:2 molar mixture of dibutyltin(IV) oxide (0.75 g, 3 mmol) and 3,5-dinitrobenzoic acid (1.27 g, 6 mmol) in the mixture of toluene/acetonitrile (3:2, 50 ml) for three hours. A clear yellow solution was isolated by filtration and kept in a bottle. After five days, yellow crystals (0.61 g, 81.0 % yield) were collected. The melting point was 197.1 to 198.6°C. Analysis for C55H50O10Sn: C, 45.90; H, 4.42; N, 7.48; Sn, 15.73 %. FTIR as KBr disc (cm^-1): ν(C-H) aromatic 3025, ν(C-H) saturated 2963, 2935, 2875; ν(CO2) 1629, ν(CO2) 1345, ν(CO2) 1542, ν(0-Sn-O) 644, ν(Sn-C) 544, ν(Sn-O) 467. 1H-NMR (ppm) (CDCl3): δ: benzene protons
9.27 (t, 2.2 Hz, 2H); 9.29 (d, 2.1 Hz, 4H); toluene CH₃ 2.36 (s, 3H); CH₂ 7.13-7.17 (m, 3H); 7.23-7.27 (m, 2H); butyl CH₂ 0.97 (t, 7.5 Hz, 6H); CH₃ 1.50 (sx, 7.1 Hz, 4H); CH₂ 1.82 (q, 7.4 Hz, 4H); CH₂ 1.99 (t, 8.2 Hz, 4H); ³¹C-NMR (ppm) (CDCl₃): δ: benzene carbons 122.92, 130.55, 134.78, 149.09; toluene 21.82, 125.66, 128.59, 129.39, 138.23; butyl 13.87, 26.17, 26.33, 27.10; COO 171.47. ¹¹¹Sn-NMR (ppm) (CDCl₃): δ: -127.78.

**Bis(3,5-dinitrobenzoato)tetraphytidistanoxane(IV) ditoluene solvate dimer,[3,5-(NO₂)₂C₆H₄COO(C₂H₅)Sn]₂O[Sn(C₂H₅)₂] (4)**

Complex 4 was prepared by a similar method with those described for complex 1, except substituting 2,4-dinitrobenzoic acid with 3,5-dinitrobenzoic acid. A mixture of toluene/acetonitrile (3:2, 50 ml) was used as solvent. A clear yellow transparent solution was isolated by filtration and kept in a bottle. After a week, yellow crystals (1.34 g, 90.0% yield) were collected. The melting point was 210.3 to 210.9°C. Analysis for C₇H₇NO₃Sn₂: C, 43.63; H, 4.53; N, 5.61; Sn, 23.25 %. Calculated for C₇H₇NO₃Sn₂: C, 44.61; H, 5.06; N, 5.62; Sn, 23.83 %. FTIR as KBr disc (cm⁻¹): v(C-H) aromatic 3059, v(C-H) saturated 2958, 2928, 2869; v(COO) (as) 1633, 1550; v(COO) (s) 1342, 1400; v(NO₂) (as) 1550, v(NO₂) (s) 1309, v(Sn-O-Sn) 532, v(Sn-C) 533, v(Sn-O) 477. ¹³N-MNR (ppm) (CDCl₃): δ: benzene protons 9.20 (s, 12H); toluene CH₂ 2.37 (m, 6H); CH₂ 7.14-7.19 (m, 6H); 7.24-7.31 (m, 4H); butyl CH₂ 0.83 (t, 7.1 Hz, 12H), 0.96 (t, 6.2 Hz, 12H); CH₃ 1.36-1.48 (m, 16H); CH₂ 1.81-2.03 (m, 32H). ¹²C-NMR (ppm) (CDCl₃): δ: benzene carbons 122.20, 129.96, 137.22, 149.13; toluene 21.76, 125.65, 128.57, 129.38, 138.21; butyl 13.87, 13.96, 27.15, 27.29, 29.79, 28.28, 29.85, 31.11; COO 168.82. ¹¹¹Sn-NMR (ppm) (CDCl₃): δ: -194.27, -203.44.

**3,5-Dinitrobenzoatotriphenyltin(IV),3,5-(NO₂)₂C₆H₄COO(C₂H₅)Sn (5)**

Complex 5 was prepared by a similar method with those described for complex 2, except substituting 2,3-dinitrobenzoic acid with 3,5-dinitrobenzoic acid. Acetonitrile (50 ml) was applied. A clear brown solution was isolated by filtration and kept in a bottle. After eight days, yellow crystals (1.13 g, 79.3 % yield) were collected. The melting point was 174.4 to 175.2°C. Analysis for C₇H₇NO₃Sn: C, 53.48; H, 2.85; N, 4.95; Sn, 21.08 %. Calculated for C₇H₇NO₃Sn: C, 53.51; H, 3.23; N, 5.00; Sn, 21.15 %. FTIR as KBr disc (cm⁻¹): v(C-H) aromatic 3095, 3084, 3086, 3047, 3024; v(COO) (as) 1655, v(COO) (s) 1343, v(NO₂) (as) 1544, v(NO₂) (s) 1444. ¹³N-MNR (ppm) (CDCl₃): δ: phenyl protons 7.49-7.55 (m, 9H); 7.79-7.83 (m, 6H); benzene 9.16 (t, 2.2 Hz, 1H); 9.21 (d, 2.1 Hz, 2H). ¹²C-NMR (ppm) (CDCl₃): δ: phenyl carbons Cₐro 137.40 (644.5 Hz), Cₐro 137.30 (48.9 Hz), Cₐro 130.68 (64.8 Hz), Cₐro 131.26 (131.3 Hz); benzene 122.27, 129.68, 135.73, 148.86; COO 168.10. ¹¹¹Sn-NMR (ppm) (CDCl₃): δ: -85.02.

**2,4-Dinitrobenzoic acid, 2,4-(NO₂)₂C₆H₄COOH**

The 2,4-dinitrobenzoic acid, 2,4-(NO₂)₂C₆H₄COOH was purchased from Acros Organics and used without any further purification. FTIR as KBr disc (cm⁻¹); selected data: v(OH) 2882-2535, v(COO) (as) 1723, v(COO) (s) 1346. ¹³N-MNR (ppm) (d₆-DMSO): δ: benzene protons 8.09 (d, 8.5 Hz, 1H); 8.57 (dd, 2.2 Hz, 8.4 Hz, 1H); 8.76 (d, 2.2 Hz, 1H). ¹²C-NMR (ppm) (d₆-DMSO): δ: benzene carbons 120.25, 128.66, 132.25, 133.52, 148.75, 149.56; COO 165.56.

**3,5-Dinitrobenzoic acid, 3,5-(NO₂)₂C₆H₄COOH**

The respective acid was also purchased from Acros Organics and used without any further purification. FTIR as KBr disc (cm⁻¹); selected data: v(OH) 2884-2465, v(COO) (as) 1701, v(COO) (s) 1348. ¹¹H-NMR (ppm) (d₆-DMSO): δ: benzene proton 8.85 (d, 2.3 Hz, 2H); 8.99 (t, 2.2 Hz, 1H). ¹³C-NMR (ppm) (d₆-DMSO): δ: benzene carbons 122.82, 129.66, 135.01, 149.16; COO 164.68.

**RESULTS AND DISCUSSION**

**Physical and elemental analysis**

In this study, complexes 1 to 5 derivatives of dinitrobenzoic acids were obtained in solid state. The microelemental analyses for C, H, N and Sn data obtained were in agreement with the predicted formula for complexes 1 to 5. Complexes 1 to 5 gave a sharp melting point indicated the isolation of fairly pure complexes. An outline of the proposed structure for complexes 1-5 are depicted in Figure 1.

**Infrared and NMR spectral studies**

The infrared spectra of complexes 1 to 5 revealed the distinct differences from those of their parent acids. The v(O-H) bands of parent acids which appeared in the range of 2884 to 2465 cm⁻¹ were absent in the infrared spectra of the dinitro salts and complexes 1 to 5, indicating the deprotonation and coordination of the carboxylate anions to the tin(IV) moiety. The infrared spectra of complexes 1 to 5 also revealed that the v(COO) (s) was shifted to a lower wave number as compared to the parent acids, signifying that the coordination took place via the oxygen atoms of the carboxylic anions (Mahmood et al., 2004; Hanif et al., 2010).

The magnitude of Δν= [ν(COO) (as) - ν(COO) (s)] value is useful to determine the bonding properties of carboxylate anion to tin(IV) moiety in organotin(IV) carboxylate complexes (Sandhu and Verma, 1987). Normally, two Δν values for organodistannoxane dimer type complexes indicate that the carboxylate anions were coordinated to the tin(IV) moiety in either a monodentate or bidentate manner (Sandhu and Verma, 1987). From the infrared spectra of complexes 1 and 4, two Δν values (313 and 163 cm⁻¹ for 1 and 291 and 150 cm⁻¹ for 4) were observed. For complex 1, the first Δν value (313 cm⁻¹) was larger than the Δν value of the sodium salts by about 86 cm⁻¹ while the second Δν value (163 cm⁻¹) was lower than the sodium salt. Hence, the two carboxylate anions were bonded to the tin(IV) moiety in a monodentate manner, while the other two carboxylate anions were bonded to the tin(IV) moiety in a bidentate manner. As a
result, all the tin(IV) moiety in complex 1 were five-coordinated and exhibited distorted trigonal bipyramidal geometry. For complex 4, both \( \Delta \nu \) values were either comparable or lower than the \( \Delta \nu \) of the sodium salt of the respective acids, indicating that the carboxylate anions were bonded to the tin(IV) moiety in a bidentate manner. Hence, the two tin(IV) moiety exhibited distorted trigonal bipyramidal geometry, while the other two tin(IV) moiety exhibited distorted octahedral geometry in complex 4. Complex 3 obtained as a monomeric type and based on the infrared study indicated that the carboxylate anions bonded to the tin(IV) moiety in bidentate manner, resulting to the tin(IV) moiety that exhibited distorted octahedral geometry. For complexes derived from triphenyltin(IV) carboxylate, \( \Delta \nu \) below 200 cm\(^{-1}\) would be expected for bridging or chelating carboxylates, but greater than 200 cm\(^{-1}\) for the monodentate bonding carboxylate anions (Yeap and Teoh, 2003). Hence, the carboxylate anion in complexes 2 and 5 would be expected to bond to the tin(IV) moiety in monodentate manner since both the \( \Delta \nu \) values above 200 cm\(^{-1}\).

The \(^1\)H NMR spectra of complexes 1 to 5 revealed some similarities with their parent acids. Complexes 1 and 4 consisted of dibutyl groups (distannoxane dimer types) and found in the upfield region in the NMR spectra. Theoretically, the butyl groups should exhibit four signals corresponding to the protons, with multiplicities of triplet, sextet, quintet and triplet with integration values of 3:2:2:2, respectively. However, these complexes only exhibited three sets of signals in the range of 0.83 to 0.90 ppm (\( \text{CH}_3 \), triplet), 1.31 to 1.51 ppm (\( \text{CH}_2 \), multiplet) and 1.67 to 2.03 ppm (\( \text{CH}_2 \), multiplet) respectively, due to the methylene protons having very similar environment causing their signals to overlap with each other in the \(^1\)H NMR spectra (Danish et al., 1995; Win et al., 2008). For complexes 2 and 5, the resonances appeared as two well separated sets of multiplets in the regions centering around 8 \( \approx 7.50 \) and 7.77 ppm (downfield) with integration values of 9:6, respectively, ascribed to the aromatic protons of the phenyl group (Sau and Holmes, 1981).

The \(^1\)H NMR spectra of complexes 3 and 4 showed the
occurrence of extra signals which was due to the presence of the toluene molecule centered at $\delta \approx 2.36$, 7.15 and 7.27 ppm. Based on the integration, complex 3 (Win et al., 2007) consisted of one toluene molecule, while complex 4 consisted of two toluene molecules. It was believed that the toluene molecules were trapped in the crystal lattice since toluene (solvent) was used during the preparation of complexes 3 to 4 (Win et al., 2007). Based on the integration values, the number of protons in complexes 1 to 5 was in accordance with the number of protons proposed.

The formation of the complexes was evident from the $\delta$(COO) values in the $^{13}$C NMR spectra. All the complexes exhibited a $\delta$(COO) signal in the range of 168.56 to 169.67 ppm. The chemical shift of the $\delta$(COO) signal in each complex was shifted downfield as compared to that of their respective parent acids, indicating the participation of the carboxylate anions in the coordination of the tin(IV) moiety. This phenomenon resulted from the decrease of the electron density in the carboxylate anions upon coordination with the tin(IV) moiety during complex formation. Complex 3 exhibited only one set of butyl signals, whereas complexes 1 and 4 derivatives of the organodistannoxane dimer type exhibited two sets of butyl signals in the $^{13}$C NMR spectra. These two sets of butyl signals were attributed to the butyl groups linked to the exo- and endocyclic tin(IV) moiety, respectively (Danish et al., 1995; Win et al., 2008). Complexes 2 and 5 revealed the chemical shifts of the $\delta^{(13)}$(C)$_{ipso}$ at 137.68 and 137.40 ppm, respectively, indicative of a four-coordinated tin(IV) moiety (Holecék et al., 1983a, b).

The $^{13}$C NMR spectra of complexes 3 and 4 also exhibited five extra signals due to the occurrence of the toluene molecule trapped within the respective complexes. The methyl group of the toluene molecule revealed a signal centered at $\delta \approx 21.50$ ppm. The benzene ring of the toluene molecule exhibited four signals in the range of 125.65 to 138.23 ppm in the $^{13}$C NMR spectra of complexes 3 and 4.

For diorganotin(IV) carboxylate complexes, the $\delta^{(119)}$(Sn) value for five-coordinated complexes is between -90 and -190 ppm and for six-coordinated complexes between -210 and -400 ppm (Holecék et al., 1986). Complexes derivatives of the organodistannoxane dimer types usually exhibit two well resolved $\delta^{(119)}$(Sn) signals ($1 = -190.69, -193.80$ ppm and $4 = -194.27, -203.44$ ppm). Based on the $^{119}$Sn NMR values, all the tin(IV) moiety in complexes 1 and 4 were five-coordinated and each exhibited a distorted trigonal bipyramidal geometry. In addition, the $^{119}$Sn NMR study also indicated that the tin atom in complex 3 was five-coordinated. This phenomenon maybe due to the bidentate bonding manner of the carboxylate anions disassociated with complexes 3 and 4 upon dilution during the preparation of the NMR sample.

The chemical shifts $\delta^{(119)}$(Sn) of triphenyltin(IV) carboxylate complexes lie in a broad range between -40 and -260 ppm (Holecék et al., 1983b). However, for four-coordinated triphenyltin(IV) carboxylate complexes, the chemical shifts $\delta^{(119)}$(Sn) lie between -40 and -120 ppm (Holecék et al., 1983a, b). Complexes 2 and 5 exhibited the $\delta^{(119)}$(Sn) values at -81.04 and -85.02 ppm, respectively, which lie in the range of -40 to -120 ppm, indicating that the tin(IV) moiety were four-coordinated and have a distorted tetrahedral geometry.

### Preliminary in vitro cytotoxic assay

The preliminary in vitro cytotoxic assay of parent acids and complexes 1 to 5 are given in Table 1. Based on the data given in Table 1, it was found that both the parent acids and dibutyltin(IV) oxide are inactive against HepG2 cell line. Complexes 1, 3 and 4 consisted of dibutyltin(IV) derivatives and based on the structural study, complex 3 was obtained as a simple monomer, whereas complexes 1 and 4 were obtained as a bulky organodistannoxane

<table>
<thead>
<tr>
<th>Complexes</th>
<th>IC$_{50}$ (µg/ml)</th>
<th>Human liver hepatocellular carcinoma cells, HepG2</th>
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<tbody>
<tr>
<td>2,4-(NO$_2$)$_2$C$_6$H$_5$COOH</td>
<td></td>
<td>Inactive (start at 1.0)</td>
</tr>
<tr>
<td>[(2,4-(NO$_2$)$_2$C$_6$H$_5$COO(C$_6$H$_5$)$_3$Sn)$_2$O]$_2$, 1</td>
<td>0.404 ± 0.015</td>
<td></td>
</tr>
<tr>
<td>2,4-(NO$_2$)$_2$C$_6$H$_5$COO(C$_6$H$_5$)$_3$Sn, 2</td>
<td>0.093 ± 0.006</td>
<td></td>
</tr>
<tr>
<td>3,5-(NO$_2$)$_2$C$_6$H$_5$COOH</td>
<td></td>
<td>Inactive (start at 1.0)</td>
</tr>
<tr>
<td>(3,5-(NO$_2$)$_2$C$_6$H$_5$COO)[(C$_6$H$_5$)$_3$Sn.C$_6$H$_5$, 3</td>
<td>0.291 ± 0.010</td>
<td></td>
</tr>
<tr>
<td>[(3,5-(NO$_2$)$_2$C$_6$H$_5$COO(C$_6$H$_5$)$_3$Sn)O]$_2$, C$_6$H$_5$, 4</td>
<td>0.500 ± 0.020</td>
<td></td>
</tr>
<tr>
<td>3,5-(NO$_2$)$_2$C$_6$H$_5$COO(C$_6$H$_5$)$_3$Sn, 5</td>
<td>0.174 ± 0.007</td>
<td></td>
</tr>
<tr>
<td>Dibutyltin(IV) oxide</td>
<td>Inactive (start at 1.0)</td>
<td></td>
</tr>
<tr>
<td>Triphenyltin(IV) hydroxide</td>
<td>0.043 ± 0.018</td>
<td></td>
</tr>
<tr>
<td>Vincristine sulphate</td>
<td>0.042 ± 0.013</td>
<td></td>
</tr>
</tbody>
</table>

IC$_{50}$ (µg/ml) = the concentration that yields 50% inhibition of the cell when compared with untreated control. The cytotoxicity values are expressed as mean ± S.E.M. from the triplicate. Reference drug = vincristine sulphate.
dimer types in solution form. Hence, complex 3 was more easily transported to the receptor (active sites) of the cells by the ligands (parent acids), in turn exhibiting lower IC_{50} value (0.291 µg/mL) as compared to complexes 1 and 4. Moreover, based on the data in Table 1, the in vitro cytotoxic activity of complex 3 was found to be lower as compared to complexes 2 (0.093 µg/mL) and 5 (0.174 µg/mL). This is due to the fact that complexes 2 and 5 were derivatives of triorganotin(IV) complexes which is more active as compared to the diorganotin(IV) which is generally known (Rehman et al., 2005; Shahid et al., 2006; Ahmad et al., 2007). In addition, based on the structural-activity study in solution form, the tin(IV) molety of complexes 2 and 5 were four-coordinated, exhibited distorted tetrahedral geometry (sp^3) and exist as a simple monomer, making them to be more active as compared to diorganotin(IV) (Danish et al., 1995). However, the activity of triphenyltin(IV) hydroxide was found to be slightly better than that of complexes 2 and 5 since the structure of triphenyltin(IV) hydroxide is much more simple and less bulkier. Overall, the preliminary in vitro cytotoxic activity could be arranged as triorganotin(IV) > diorganotin(IV).

Conclusion

Complexes 1 to 5 have been successfully synthesized. The structural as well as the coordination number of tin(IV) moieties of complexes 1 to 5 have been successfully characterized quantitatively and qualitatively. Based on the preliminary in vitro cytotoxic assay on human liver hepatocellular carcinoma cells (HepG2), complexes 2 and 5 [triphenyltin(IV)] showed better activity as compared to complexes 1, 3 and 4 [diorganotin(IV)] but lower activity as compared to the reference drug. Within the diorganotin(IV) complexes, monomeric type (3) exhibited a slightly better activity as compared to the organodistannoxane dimer types (1 and 4).

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