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Synthesis, structure and *in vitro* cytotoxic activity of two organotin complexes of 2-phenyl-1,2,3-triazole-4-carboxylic acid

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Abstract: Two organotin complexes of 2-phenyl-1,2,3-triazole-4-carboxylic acid, $\{[n\text{-}Bu_2Sn(OOCC_2HN_3Ph\text{-}2)]_2O\}_2$ (**1**) and $(c\text{-}C_6H_{11})_3Sn(OOCC_2HN_3Ph\text{-}2)(C_2H_5OH)$ (**2**), have been synthesized and characterized by means of elemental analysis, FT-IR, NMR (^1H, ^{13}C and ^{119}Sn) spectra and X-ray single crystal diffraction. Compound **1** is a centrosymmetric tetranuclear bis(dicarboxylatotetra-*n*-butyldistannoxane) complex containing two distinct types of carboxylate moieties and tin atoms with $[SnC_2O_3]$ trigonal-bipyramidal and $[SnC_2O_4]$ skew-trapezoidal-bipyramidal geometries. Compound **2** possesses a $[SnC_3O_2]$ trigonal bipyramidal environment with the axial positions occupied by the carboxylate oxygen and hydroxyl oxygen of an ethanol molecule and forms a one-dimensional supramolecular structure by intermolecular O-H···O hydrogen bonds. Bioassay results have shown that the two compounds possess good *in vitro* cytotoxic activity against three human tumor cell lines (HeLa, CoLo205 and MCF-7).

Keywords: crystal structure; cytotoxic activity; organotin; 2-phenyl-1,2,3-triazole-4-carboxylic acid.

Introduction

In recent years, organotin carboxylates have received considerable attention due to their structural interest and various applications (Tiekink, 1991, 1994; Davies et al., 2008). Many researchers have described the preparation and characterization of organotin carboxylates and their activity against tumors, fungi, bacteria and other microorganisms (Shang et al., 2011; Seter et al., 2012; Kaur et al., 2013; Nath et al., 2013, 2014; Dong et al., 2014; Wang et al., 2014; Mao et al., 2015). It has been observed that some di- and triorganotin carboxylates show potential as antineoplastic agents (Hadjikakou and Hadjiliadis, 2009; Amir et al., 2014; Carraher and Roner, 2014). The number and nature of the organic groups bonded to the tin center and the carboxylate ligand appear to play an important role in determining their antitumor activity (Hadjikakou and Hadjiliadis, 2009; Amir et al., 2014). The design and synthesis of new organotin carboxylates by selecting ligands and organotin substrates has been encouraged in order to achieve efficacy. 2-Phenyl-1,2,3-triazole-4-carboxylic acid is an acid containing an N-donor aromatic heterocycle, and we previously reported the synthesis and biological activity of several of its triorganotin complexes (Tian et al., 2005). In order to continue to expand the chemistry and therapeutic potential of the organotin esters of 2-phenyl-1,2,3-triazole-4-carboxylic acid, we synthesized two new organotin complexes of this acid, $\{[n\text{-}Bu_2Sn(OOCC_2HN_3Ph\text{-}2)]_2O\}_2$ and $(c\text{-}C_6H_{11})_3Sn(OOCC_2HN_3Ph\text{-}2)(C_2H_5OH)$, and determined their *in vitro* cytotoxic activity.

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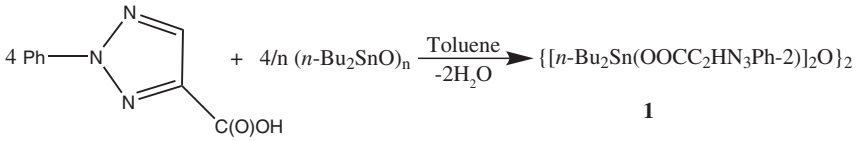
Results and discussion

Synthesis

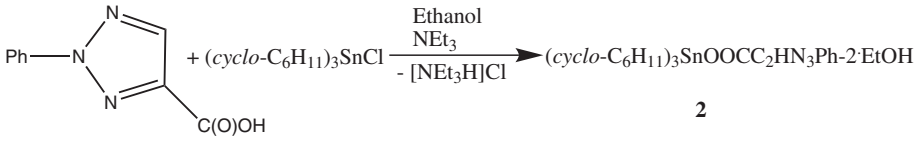
Compound **1** was prepared by azeotropic removal of water from the reaction between di-*n*-butyltin oxide and 2-phenyl 1,2,3-triazole-4-carboxylic acid in the molar ratio 1:1 in toluene (Scheme 1).

Compound **2** was synthesized in ethanol by the reaction of tricyclohexyltin chloride with 2-phenyl 1,2,3-triazole-4-carboxylic acid in the presence of Et_3N (Scheme 2).

When the reaction of di-*n*-butyltin oxide with the ligand acid is performed in the molar ratio 1:2 in toluene, the product $n\text{-}Bu_2Sn(OOCC_2HN_3Ph\text{-}2)_2$ (**3**) should be formed. We tried to isolate and purify compound **3**, but failed. Compound **2** is an ethanol solvate of $(cyclo\text{-}C_6H_{11})_3$



Scheme 1: Synthesis of compound **1**.



Scheme 2: Synthesis of compound **2**.

$Sn(OOCC_2HN_3Ph\text{-}2)$ (**4**) that had been obtained previously by the reaction of tricyclohexyltin hydroxide with 2-phenyl 1,2,3-triazole-4-carboxylic acid in benzene (Tian et al., 2005), and converted readily into **4** when heated at 80°C for 1 h or dried in vacuum for 48 h at room temperature. Both compounds **1** and **2** are white solids and soluble in benzene and in common polar organic solvents such as methanol, ethanol, trichloromethane, acetone and *N*,*N*-dimethylformamide.

Spectroscopic analysis

In the complexes, the strong band at ~1600 cm^{-1} assigned to the stretching vibration of C=N of the triazole ring was almost the same as that of the free 2-phenyl-1,2,3-triazole-4-carboxylic acid, indicating that the N atom of the triazole ring was not coordinated to the tin atom. In organotin carboxylates, IR spectroscopy can provide useful information concerning the coordination mode of the carboxylate group (Deacon and Phillips, 1980; Szorcsik et al., 2004). When the carboxylic group of the ligand coordinates to the metal in the monodentate mode, the difference between the ν_{as}(COO) and ν_s(COO) bands, $\Delta\nu$(COO), is larger than that observed for ionic compounds. When the ligand chelates, $\Delta\nu$ is smaller than that observed for its ionic compounds, whereas for the asymmetric bidentate coordination, the value is in the range characteristic of monodentate coordination. When the carboxylate group bridges metal ions, the $\Delta\nu$ value is higher than that of the chelated ions and nearly the same as that observed for ionic compounds. In **1**, the $\Delta\nu$(COO) value is 284 and 199 cm^{-1}, respectively. The former is larger than that of the sodium salt of the free acid ($\Delta\nu$=208 cm^{-1}), and the latter is less than the $\Delta\nu$ value of the sodium salt, which indicate that there are monodentate carboxylate and weak chelating/bridging bidentate carboxylate groups (see below X-ray crystallography) (Deacon and Phillips, 1980; Chandrasekhar et al., 1988). A strong band of 640 cm^{-1} is assigned to vibration associated with the Sn-O-Sn stretch (Chandrasekhar et al., 1988). In **2**, a broad band at 3446 cm^{-1} was assigned to the ν(OH) mode of ethanol. The magnitude (241 cm^{-1}) of $\Delta\nu$(COO) confirms that the carboxylate group is monodentate coordination to tin, which is in agreement with the solid-state structure shown below.

The ^{1}H NMR spectra show the expected integration and peak multiplicities. Two resonances were observed for the butyl protons and carbon atoms in compound **1**, which is consistent with the presence of a dimer in solution by analogy with related compounds (Baul et al., 2006). This indicates that two types of tin centers are present with non-equivalent surroundings. This was further confirmed by the crystal structure of compound **1**. Although two structurally different carboxylate groups are present in **1**, as revealed by the crystal structure analyses (see below), only a single broad resonance (δ 165.3 ppm) is observed for the *C*(O)O carbon atoms in the ^{13}C NMR spectrum, which might also correspond to the situation when two ^{13}C resonances from two distinct carboxyl groups exist, but the difference between them is rather small in the $CDCl_3$ solution. This could arise in the case of fast intramolecular rearrangement on the NMR time scale, as described by Martins et al. (Martins et al., 2000; Baul et al., 2006). In compound **2**, the cyclohexyl protons show the multiplet in the range 1.31–2.07 ppm. The resonance signals of cyclohexyl carbon atoms appear at 27.2, 29.2, 31.4 and 34.1 ppm, respectively, and the spin-spin coupling constants $^1J(^{119}Sn\text{-}^{13}C)$ and $^3J(^{119}Sn\text{-}^{13}C)$ are 330 and 65 Hz, respectively. The coordination number of the tin atom in organotin compounds has been related to the $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants (Holecek et al., 1983). The $^1J(^{119}Sn\text{-}^{13}C)$ value in **2** is close to that of the corresponding four-coordinate tricyclohexyltin carboxylates, such as $2\text{-}HOC_6H_4N{=}NC_6H_4COOSn(cyclo\text{-}C_6H_{11})_3$ ($^1J(^{119}Sn\text{-}^{13}C)$=335 Hz) (Willem et al., 1998),

(*cyclo*-C_6H_{11})$_3$SnOOCCH$_2$CH$_2$COOSn(*c*-C_6H_{11})$_3$ (^1J(^{119}Sn-^{13}C)= 340 Hz) (Tian et al., 2013) and (*cyclo*-C_6H_{11})$_3$SnOOCCH$_2$CH$_2$COCH$_2$CH$_2$COOSn(*cyclo*-C_6H_{11})$_3$ (^1J(^{119}Sn-^{13}C)=325 Hz) (Chalupa et al., 2006), suggesting that ethanol is free and the tin atom is four-coordinated in the $CDCl_3$ solution.

The ^{119}Sn chemical shifts primarily depend on the coordination number and the nature of the donor atom directly bonded to the central tin atom (Davis, 2004). In $CDCl_3$, the ^{119}Sn NMR spectra of compound **1** display two ^{119}Sn resonances of -194.0 and -205.2 ppm, which are assigned to the endocyclic and exocyclic tin atoms, respectively. Holecek et al. (1986) reported that the four-coordinate di-*n*-butyltin compounds have δ(^{119}Sn) ranging from about +200 to -60 ppm; five-coordinate compounds, -90 to -190 ppm; and six-coordinate compounds, -210 to -400 ppm. Based on the results, five-coordinated endocyclic tin centers and near six-coordinated exocyclic tin centers are present in the $CDCl_3$ solution, which is consistent with the X-ray crystal structure of **1** (below). The ^{119}Sn chemical shift of **2** (17.6 ppm) in $CDCl_3$ is in accord with the value found in (*cyclo*-C_6H_{11})$_3$Sn(OOC$_2$HN$_3$Ph-2) (18.7 ppm) (Tian et al., 2005) and other four-coordinated tricyclohexyltin compounds in solution of non-coordinating solvent (Willem et al., 1998; Chalupa et al., 2006), confirming that the tin atom is four-coordinated in the $CDCl_3$ solution. However, in dimethylsulfoxide-d_6 (DMSO-d_6), the ^{119}Sn chemical shifts appear at -89.6 ppm, which shows that the coordination of the solvent through the oxygen atom to the Sn atom and the tin atom may be five-coordinated (Nadvornik et al., 1984).

Structure analysis of compounds 1 and 2

The structures in the solid state of complexes **1** and **2** are shown in Figures 1–3 and the selected geometric parameters are given in Table 1. Compound **1** crystallizes in the

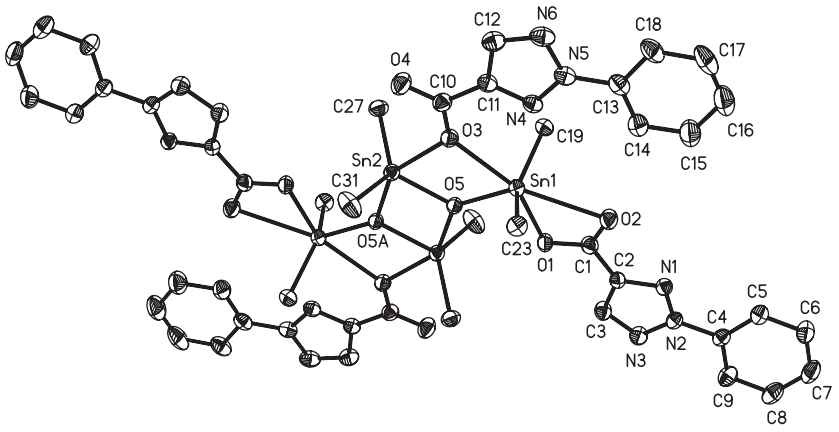


Figure 1: The molecular structure of compound **1**. All hydrogen atoms and partial carbons of butyl bond to Sn atoms are omitted for clarity.

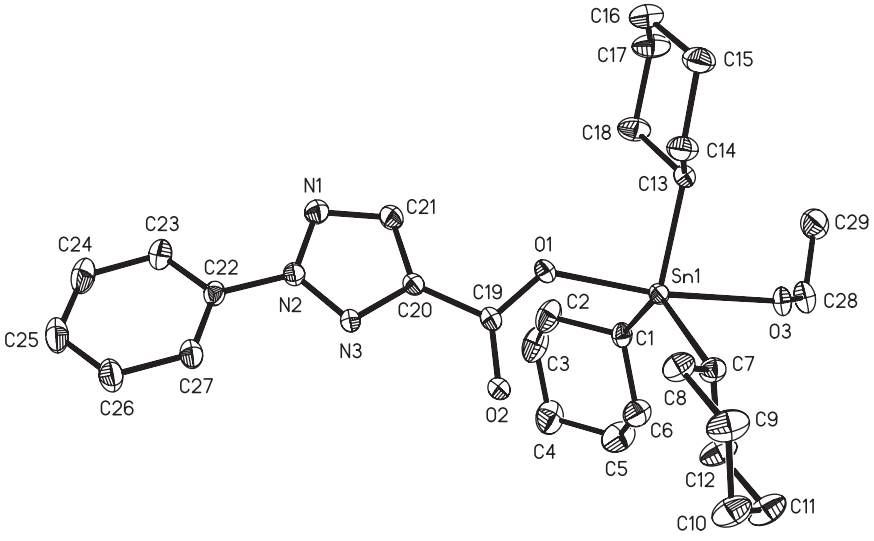


Figure 2: The molecular structure of compound **2**. All hydrogen atoms are omitted for clarity.

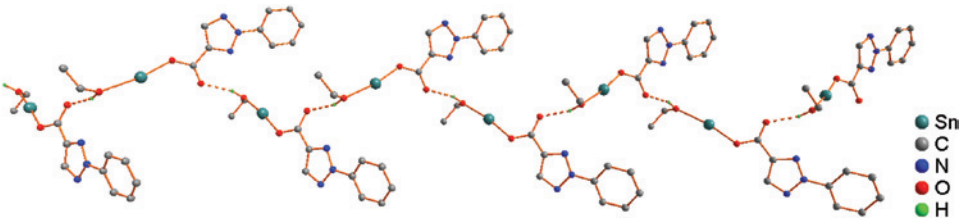
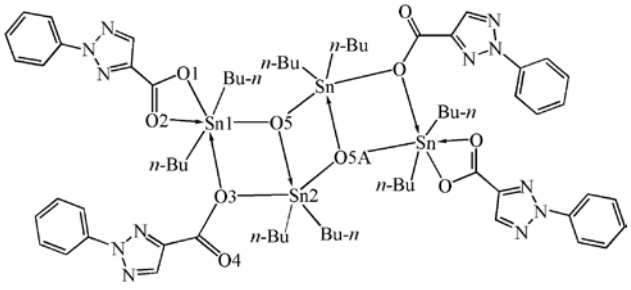


Figure 3: The 1D supramolecular chain of **2** formed by the intermolecular O-H···O hydrogen bonds.

Table 1: Selected bond lengths (Å) and angles (°) for **1** and **2**.

1					
Sn(1)-O(1)	2.155(4)	Sn(1)-C(23)	2.131(5)	Sn(2)-C(31)	2.122(8)
Sn(1)-O(2)	2.675(4)	Sn(2)-O(3)	2.243(4)	C(1)-O(1)	1.291(7)
Sn(1)-O(3)	2.422(4)	Sn(2)-O(5)	2.036(3)	C(1)-O(2)	1.220(7)
Sn(1)-O(5)	2.032(3)	Sn(2)-O(5A)	2.140(3)	C(10)-O(3)	1.305(7)
Sn(1)-C(19)	2.110(6)	Sn(2)-C(27)	2.115(6)	C(10)-O(4)	1.218(7)
O(5)-Sn(1)-C(19)	107.6(2)	O(1)-Sn(1)-O(3)	152.19(13)	C(27)-Sn(2)-C(31)	127.9(4)
O(5)-Sn(1)-C(23)	106.6(2)	O(5)-Sn(1)-O(2)	136.14(14)	O(5)-Sn(2)-O(5A)	74.50(15)
C(19)-Sn(1)-C(23)	142.1(2)	C(19)-Sn(1)-O(2)	84.2(2)	C(27)-Sn(2)-O(5A)	100.18(19)
O(5)-Sn(1)-O(1)	83.01(13)	C(23)-Sn(1)-O(2)	82.6(2)	C(31)-Sn(2)-O(5A)	98.7(3)
C(19)-Sn(1)-O(1)	99.5(2)	O(1)-Sn(1)-O(2)	53.18(13)	O(5)-Sn(2)-O(3)	72.95(13)
C(23)-Sn(1)-O(1)	100.5(2)	O(3)-Sn(1)-O(2)	154.61(13)	C(27)-Sn(2)-O(3)	92.59(19)
O(5)-Sn(1)-O(3)	69.18(13)	O(5)-Sn(2)-C(27)	116.4(2)	C(31)-Sn(2)-O(3)	96.7(3)
C(19)-Sn(1)-O(3)	89.12(19)	O(5)-Sn(2)-C(31)	115.4(3)	O(5A)-Sn(2)-O(3)	147.40(13)
C(23)-Sn(1)-O(3)	87.94(19)				
2					
Sn(1)-C(1)	2.152(4)	Sn(1)-O(1)	2.161(3)	C(20)-N(3)	1.325(4)
Sn(1)-C(7)	2.167(4)	Sn(1)-O(3)	2.518(3)	C(19)-O(1)	1.280(4)
Sn(1)-C(13)	2.145(4)	C(21)-N(1)	1.329(5)	C(19)-O(2)	1.219(4)
C(13)-Sn(1)-C(1)	122.22(17)	C(1)-Sn(1)-C(7)	121.35(16)	C(1)-Sn(1)-O(3)	82.36(13)
C(13)-Sn(1)-O(1)	88.14(14)	O(1)-Sn(1)-C(7)	104.53(14)	O(1)-Sn(1)-O(3)	170.39(10)
C(1)-Sn(1)-O(1)	94.65(14)	C(13)-Sn(1)-O(3)	85.78(14)	C(7)-Sn(1)-O(3)	84.75(14)
C(13)-Sn(1)-C(7)	113.43(17)				

Symmetry code A: -*x*+1, -*y*+2, -*z*+1.



Scheme 3: The coordination mode of the tin atoms in compound **1**.

triclinic space group *P*-1 and possesses the basic type II structural motif described by Tiekink (1991) (Scheme 3). Compound **1** is a centrosymmetric tetranuclear dimer built up around the planar cyclic Sn_2O_2 core in which the two oxygen atoms [O(5) and O(5A), symmetry code A: -*x*+1, -*y*+2, -*z*+1] are tridentate as they link three tin centers – two endocyclic and one exocyclic. The distance between the endocyclic and exocyclic tin atoms is 3.521(1) Å and the distance between the two endocyclic tin centers is 3.325(1) Å. Additional links between the endocyclic and exocyclic tin atoms are provided by the carboxylate O-atoms in an asymmetric μ_2-oxo fashion. The distances of two Sn-O bonds, Sn(1)-O(3) and Sn(2)-O(3), are 2.243(4) and 2.422(4) Å, respectively. The exocyclic Sn(1) atom in **1** is six-coordinated, and the six coordination atoms come from two carbon atoms C(19) and C(23) of *n*-butyl groups, one μ_3-O(5) atom, one μ_2-O(3) atom of one carboxylate and two oxygen atoms O(1) and O(2) of the other carboxylate. Because the two O atoms of carboxylate C(1)O(1)O(2) coordinate, in an asymmetric fashion, to Sn(1) with the

longer Sn(1)-O(2) interaction of 2.675(4) Å and the smaller bite angle O(1)-Sn(1)-O(2) of 53.18(13)°, the environment of the Sn(1) atom may be described as a distorted skew-trapezoidal bipyramid with the *n*-butyl ligands occupying axial positions [C(19)-Sn(1)-C(23) 142.1(2)°]. The Sn(1)···N(4) separation (3.134(2) Å) was smaller than the sum of Van der Waals radii of tin and nitrogen (3.74 Å) (Bondi, 1964), indicating that there was a weak interaction between N(4) and Sn(1). Thus, the N(4) atom also exerted a steric influence and contributed to the distortion of the geometry at the Sn(1) atom. The endocyclic Sn(2) atoms have five-coordination, and the coordination atoms are C(27) and C(31) from two *n*-butyl groups, μ_3-O(5) and μ_3-O(5A) atoms, and the μ_2-O(3) atom of the carboxylate, respectively. The coordination geometry of Sn(2) is a quite distorted trigonal bipyramidal with axial positions occupied by oxygen atoms [O(3)-Sn(1)-O(5A) 147.40(13)°]. The Sn(2) atom lies 0.071(1) Å out of the trigonal plane defined by O(5), C(27) and C(31) in the direction of the atom O(5A). The Sn(2)···O(4) and Sn(2)···O(1A) separations of 3.364(2) and 3.331(2) Å are shorter than the sum of the Van der Waals radii of tin and oxygen (3.73 Å) and much longer than the sum of the covalent radii of tin and oxygen (2.14 Å) (Bondi, 1964), which was not indicative of a significant interaction between these atoms. The major stereochemical role of the O(4) and O(1A) atoms is to distort the bipyramidal geometry by opening up the C(27)-Sn(2)-C(31) angle to 127.9(4)°. In bis(dicarboxylatotetraorganodistannoxanes), $\{[R_2Sn(OOCR')]_2O\}_2$, the type II structural motif displayed by compound **1** occurs less frequently than the more common type I motif (Tiekink, 1991; Chandrasekhar et al., 2002). The structural feature of **1** is similar to that of several reported bis(dicarboxylatotetraorganodistannoxanes) possessing the type II motif (Table 2).

Compound **2** crystallizes in the monoclinic space group $P2_1/n$, and the tin atom is five-coordinated and possesses a distorted $[SnC_3O_2]$ trigonal bipyramidal geometry, formed by a monodentate carboxylate group, three cyclohexyl groups and a coordinated ethanol molecule. The axial sites are occupied by the O atoms of the ethanol and carboxylate [O(1)-Sn(1)-O(3) 170.39(10)°], and the trigonal plane is defined by the three cyclohexyl groups with the C-Sn-C angles in the range of 113.43(17)–122.22(17)°. The bond length of the coordinated Sn(1)-O(3) [2.518(3) Å] is significantly longer than that of the covalent Sn(1)-O(1) [2.161(3) Å], so that the Sn(1) atom is displaced out of the C_3 trigonal plane of the *trans*-C_3SnO_2 trigonal bipyramidal polyhedron in the direction of O(1) by 0.216(2) Å. The Sn-C lengths from 2.145(4) to 2.152(4) Å are similar to those found in other reported five-coordination tricyclohexyltin carboxylates, such as 3-$C_5H_4NCO_2Sn$(*cyclo*-$C_6H_{11})_3(H_2O)$ (Teoh et al., 1999), (4-$MeC_6H_4)_3GeCH(C_6H_4$OMe-4)CH_2CO_2Sn(*cyclo*-$C_6H_{11})_3(H_2O)$ (Din et al., 2003) and $O(CH_2CH_2)_2NC(O)SCH_2CO_2Sn$(*cyclo*-$C_6H_{11})_3(H_2O)$ (Ng, 1996). To the best of our knowledge (CSD version 5.36), this is a first example of structurally characterized tricyclohexyltin carboxylate containing an alcohol coordination to tin. In the crystal, the molecules are linked into a one-dimensional supramolecular chain by the intermolecular hydrogen bond O(3)-H(3)···O(2)^i [*i*: -*x*+1/2, *y*+1/2, -*z*+3/2) (H(3)···O(2) 1.93 Å, O(3)···O(2)^i 2.744(4) Å, O(3)-H(3)···O(2)^i 160.1°] between the ethanol O-H and carbonyl oxygen atom of carboxylate (Figure 3).

In vitro cytotoxicity

Under the experimental conditions, the results of the cytotoxic assay of the compounds against HeLa (cervix tumor cell), CoLo 205 (colon carcinoma cell) and MCF-7 (mammary tumor cell) are shown in Table 3. Compounds **1** and **2** displayed the potent *in vitro* activity, and are more active than clinically used *cis*-platin. The activity of **2** is better than that of **1**, which is consistent with the result

Table 2: X-ray data for some type II diorganotin carboxylates, $\{[R_2Sn(O_2CR')]_2O\}_2$.

Compound[a]	Sn(1)-O(1)	Sn(1)-O(2)	Sn(1)-O(3)	Sn(1)-O(5)	Sn(2)-O(3)	Sn(2)-O(5)	Sn(2)-O(5A)
$[(n\text{-}Bu_2SnL^1)_2O]_2$	2.093(5)	2.746(6)	2.498(5)	2.003(4)	2.206(4)	2.021(4)	2.148(4)
$[(n\text{-}Bu_2SnL^2)_2O]_2$	2.121(6)	2.746(7)	2.517(7)	1.993(6)	2.191(6)	2.047(6)	2.171(6)
$[(n\text{-}Bu_2SnL^3)_2O]_2$	2.104(6)	2.573(6)	2.688(5)	2.009(5)	2.202(6)	2.036(5)	2.166(5)
$[(n\text{-}Bu_2SnL^4)_2O]_2$	2.116(4)	2.771(4)	2.587(4)	2.004(3)	2.239(4)	2.015(3)	2.178(3)
$[(n\text{-}Bu_2SnL^5)_2O]_2$	2.124(2)	2.682(2)	2.647(2)	2.044(2)	2.234(2)	2.011(2)	2.171(2)
$[(n\text{-}Bu_2SnL^6)_2O]_2$	2.124(4)	2.672(2)	2.621(2)	2.051(2)	2.247(2)	2.005(2)	2.171(2)
$[(n\text{-}Bu_2SnL)_2O]_2$	2.155(4)	2.675(4)	2.422(4)	2.032(3)	2.243(4)	2.036(3)	2.140(3)

[a]L^1=4-$FC_6H_4CH_2COO$ (Tiekink et al., 1995); L^2=$C_6H_5COCH_2CH_2COO$ (Ng et al., 1991); L^3=4-$NH_2C_6H_4COO$ (Chandrasekhar et al., 1988); L^4=$C_4H_8NCS_2CH_2COO$ (Yin et al., 2004); L^5=4-(C_6H_5N=N)-2-(HO)C_6H_3COO (Baul et al., 2006); L^6=4-(4-ClC_6H_4N=N)-2-(HO)C_6H_3COO (Baul et al., 2006); L=2-PhC_2HN_3COO (this work).

Table 3: *In vitro* cytotoxicity (IC_{50}, μg/mL) of the compounds.

Compound	HeLa	CoLo205	MCF-7
1	0.315±0.054	1.014±0.094	0.266±0.048
2	0.176±0.031	0.423±0.057	0.230±0.068
cis-platin	1.443±0.332	4.611±0.332	5.457±0.335

Data represent mean±S.D. All assays were performed in triplicate for three independent experiments.

that triorganotin compounds are usually more active than the corresponding diorganotin compounds (Hadjikakou and Hadjiliadis, 2009; Amir et al., 2014). In the 0.1% DMSO solution, compound **1** displays the poor anticancer activity due to the high coordination number and steric hindrance around tin, which limit the access of tin to the target (Amir et al., 2014). The activity of **1** is comparable with that of other di-*n*-butylstannoxanes such as $\{[n\text{-}Bu_2(3\text{-}FC_6H_4COO)Sn]_2O\}_2$ (MCF-7, IC_{50} 0.496 μg/mL) and $\{[n\text{-}Bu_2(2\text{-}HO\text{-}4\text{-}MeOC_6H_3COO)Sn]_2O\}_2$ (MCF-7, IC_{50} 0.131 μg/mL) (Gielen, 2002), but better than that of $\{[n\text{-}Bu_2(2\text{-}O_2NC_6H_4CH{=}CHOO)Sn]_2O\}_2$ (HeLa, IC_{50} 5.717 μg/mL) (Liu et al., 2011). The activity of **2** is similar to that of our previously reported tricyclohexyltin 2-phenyl-1,2,3-triazole-4-carboxylate (Tian et al., 2005) bis(triorganotin) 2,6-pyridinedicarboxylates (Wang et al., 2014), but is lower than triphenyltin 2-phenyl-1,2,3-triazole-4-carboxylate (Tian et al., 2005). Gielen et al. found that the di- and triorganotin steroid carboxylates, crown-ethercarboxylates and fluorine-substituted carboxylates exhibited quite potent cytotoxicities against many human tumor cell lines such as MCF-7, EVSAT, WiDr, IGROV, MI9, A498 and H226 (Gielen, 2002; Gielen et al., 2005). The IC_{50} values of some dibutyl- and triphenyltin derivatives of such ligands against the cell lines were less than 1 ng/mL. Thus, both the organotin moiety and the ligand appear to play an important role in the activity, and further structure modification of organotin compounds is valuable for enhancing cytotoxicity.

Conclusion

In summary, two new di-*n*-butyltin and tricyclohexyltin derivatives of 2-phenyl-1,2,3-triazole-4-carboxylic acid have been synthesized and characterized. The di-*n*-butyltin complex is a centrosymmetric tetranuclear bis(dicarboxylatotetra-*n*-butyldistannoxane) having the basic type II structural motif. The tricyclohexyltin complex possesses a trigonal bipyramidal environment with the axial positions occupied by the carboxylate oxygen and hydroxyl oxygen of an ethanol molecule and forms a one-dimensional supramolecular chain by the intermolecular O-H···O hydrogen bonds. The two compounds have good *in vitro* cytotoxic activity against three human tumor cell lines, i.e. HeLa, CoLo205 and MCF-7, and can be considered as antitumor compounds to further study.

Experimental section

General

2-Phenyl-1,2,3-triazole-4-carboxylic acid was prepared according to the literature procedure (Liu and Cao, 1993). All other chemicals (Sinopharm Chemical Reagent Company Limited, Shanghai, China) were of reagent grade and were used without further purification. Carbon, hydrogen and nitrogen analyses were determined using a Perkin Elmer 2400 Series II elemental analyzer (Perkin Elmer, Waltham, MA, USA). IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer using KBr disks in the range 4000–400 cm^{-1} (Thermo Nicolet Corporation, Madison, WI, USA). ^1H and ^{13}C NMR spectral data were collected using a Bruker Avance DMX500 FT-NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard (Bruker Corporation, Switzerland).

Synthesis of the complex $\{[n\text{-}Bu_2Sn(OOCC_2HN_3Ph\text{-}2)]_2O\}_2$ (1)

To a suspension of di-*n*-butyltin oxide (0.50 g, 2 mmol) in 50 mL of anhydrous toluene was added 2-phenyl-1,2,3-triazole-4-carboxylic acid (0.38 g, 2 mmol). The reaction mixtures were heated under reflux for 6 h with a Dean-Stark separator, and then allowed to cool to room temperature. The solution was filtered and the solvent was removed under reduced pressure by a rotary evaporator. The resulting white solid was recrystallized from trichloromethane/methanol (1:1, V/V). Yield 0.59 g (69%), m.p. 170.9–171.4°C. Anal. calcd. for $C_{68}H_{96}N_{12}O_{10}Sn_4$: C 47.58, H 5.64, N 9.79; found C 47.60, H 5.57, N 9.72%. IR (KBr, cm^{-1}): 2955s, 2926s, 2858s, 1626s [$\nu(COO^-)_{as}$], 1599s (C=N, triazole ring), 1587s [$(\nu(COO^-)_{as})$], 1497s, 1464m, 1425m, 1388s [$\nu(COO^-)_s$], 1342s [$\nu(COO^-)_s$], 1251s, 1139m, 1027m, 966m, 833s, 752s, 640s (Sn-O-Sn). ^1H NMR ($CDCl_3$, δ, ppm): 8.24 (2H, s, CH=N), 8.18 (4H, d, J=7.9 Hz, H-2 of phenyl), 7.51 (4H, t, J=7.8 Hz, H-3 of phenyl), 7.38 (2H, t, J=7.3 Hz, H-4 of phenyl), 1.87–1.28 (24H, m, $CH_2CH_2CH_2Sn$), 0.82 (6H, t, J=7.2 Hz, CH_3), 0.77 (6H, t, J=7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.3 (C=O), 143.8 (C=N), 139.8 (CH=N), 138.3, 129.8, 128.6, 119.6 (phenyl), 28.8, 28.2 (α-C), 27.9, 27.5 (β-C), 27.4, 27.0 (γ-C), 13.8, 13.8 (δ-C) (*n*-butyl). ^{119}Sn NMR ($CDCl_3$, δ, ppm): –194.0, –205.2.

Synthesis of the complex (*cyclo*-$C_6H_{11})_3Sn(OOCC_2HN_3Ph\text{-}2)(C_2H_5OH)$ (2)

To the solution of 2-phenyl-1,2,3-triazole-4-carboxylic acid (0.38 g, 2 mmol) in ethanol (50 mL) was added tricyclohexyltin chloride (0.81 g, 2 mmol) and Et_3N (0.20 g, 2 mmol). The mixture was refluxed

for 2 h and the solvent was removed by evaporation *in vacuo*. The crude products were recrystallized from ethanol. Yield 70.5%, m.p. 78–79°C. Anal. calcd. for $C_{29}H_{45}N_3O_3Sn$: C 57.82, H 7.53, N 6.98; found C 57.68, H 7.27, N 6.82%. IR (KBr, cm^{-1}): 3446bs (O-H), 2921s, 2846s, 1597 (C=N, triazole ring), 1583 [$\nu(COO^-)_{as}$], 1496s, 1446, 1412, 1356, 1342 [$\nu(COO^-)_s$], 1296m, 1269m, 1171m, 1026m, 992m, 965s, 807m, 794s, 756s, 672s. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.17 (2H, d, J=7.8 Hz, H-2 of phenyl), 8.16 (1H, s, CH=N), 7.49 (2H, t, J=7.9 Hz, H-3 of phenyl), 7.38 (1H, t, J=7.4 Hz, H-4 of phenyl), 3.72 (t, J=7.0 Hz, CH_2O), 2.07–1.31 (34H, m, cyclohexyl+OH), 1.24 (3H, t, J=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.3 (C=O), 143.9 (C=N), 139.8 (CH=N), 138.3, 129.7, 128.6, 119.6 (phenyl), 57.9 (CH_2O), 34.1 [$^1J(^{119}Sn\text{-}^{13}C)$=330 Hz, α-C], 31.4 (β-C), 29.2 [$^3J(^{119}Sn\text{-}^{13}C)$=65 Hz, γ-C], 27.2 (δ-C), 18.3 (CH_3). ^{119}Sn NMR ($CDCl_3$, δ, ppm): 17.6.

X-ray crystallography

The colorless single crystal of **1** and **2** was obtained from ethanol by slow evaporation at room temperature. Diffraction measurements were performed on a Bruker Smart Apex imaging-plate area detector (Bruker Corporation, Germany) fitted with graphite monochromatized MoK_α radiation (0.71073 Å) using the φ and ω scan technique. The structures were solved by direct methods and refined by a full-matrix least-squares procedure based on F^2 using SHELXL-97 (Sheldrick, 2008). The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation, with C-H=0.93 Å for aromatic H atoms, C-H=0.96 Å for methyl H atoms, C-H=0.97 Å for methylene H atoms, C-H=0.98 Å for methine H atoms and O-H=0.85 Å for hydroxy H atoms. In complex **1**, the *n*-butyl groups are disordered over two positions, and their site occupancies were refined to 0.64(2):0.36(2) for C(22), 0.50(6):0.50(6) for C(29)-C(30) and 0.51(5):0.49(5) for C(32)-C(34), respectively. In refinements, the C-C bonds and 1,3-distances of the disorderly butyl groups were restrained to 1.53(1) and 2.50(2) Å, respectively. Crystal data, collection procedures and refinement results are shown in Table 4. The crystallographic data of compounds **1** and **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1052854 and 1052855.

In vitro cytotoxicity

Cytotoxic activity was assayed against two human tumor cell lines, Hela (cervix tumor cell) and MCF-7 (mammary tumor cell). The samples were prepared by dissolving the test compounds in DMSO (^{1}H NMR shows that the compounds are stable in the solvent DMSO) and by diluting the resultant solutions with water. In the assays, the final concentration of DMSO was less than 0.1% (the concentration used was found to be non-cytotoxic against tumor cells). *Cis*-platin was purchased from Mayne Pharma Pty Ltd (Australia). The *in vitro* cytotoxic activity of the compounds was measured by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay according to the literature (Denizot and Lang, 1986). All cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% heat-inactivated newborn calf serum at 37°C in a humidified 5% CO_2 incubator and were seeded into each well of a 96-well plate and were fixed for 24 h. The following day, different concentrations of the test compounds were added. After incubation with various concentrations of test compounds for 72 h, the inhibition on cell proliferation was measured. The dose causing 50% inhibition of cell growth (IC_{50}) was calculated.

Table 4: Crystallographic and refinement data of **1** and **2**.

Compound	1	2
Empirical formula	$C_{68}H_{96}N_{12}O_{10}Sn_4$	$C_{29}H_{45}N_3O_3Sn$
Formula weight	1716.33	602.37
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	$P2_1/n$
a (Å)	11.1234(10)	10.744(4)
b (Å)	14.3109(11)	14.270(6)
c (Å)	14.3898(11)	19.662(8)
α (°)	114.2040(10)	90
β (°)	92.938(2)	94.168(5)
γ (°)	108.8450(10)	90
Volume (Å^3)	1932.0(3)	3007(2)
Z	1	4
D_c (g cm^{-3})	1.475	1.331
μ (mm^{-1})	1.338	0.882
F(000)	868	1256
Crystal size (mm)	0.15×0.12×0.08	0.22×0.20×0.18
θ range (°)	1.59–26.00	1.76–26.00
Total reflections	15 238	22 789
Uniq. reflections	7519 (R_{int}=0.0261)	5903 (R_{int}=0.0300)
Reflections with $I>2\sigma(I)$	5336	4666
GOF on F^2	1.009	1.056
R indices [$I>2\sigma(I)$]	*R*=0.0492, *wR*=0.1217	*R*=0.0426, *wR*=0.1054
R indices (all data)	*R*=0.0713, *wR*=0.1365	*R*=0.0573, *wR*=0.1134
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	-0.491, 0.694	-0.379, 0.919

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