*Research Article*

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# Synthesis, crystal structure and *in vitro* anti-tumor activity of dibutyltin complex of 2,4-dichloro-5-fluorobenzoic acid

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**Abstract:** The dibutyltin complex of 2,4-dichloro-5-fluorobenzoic acid, $[(2,4\text{-}Cl_2\text{-}5\text{-}FC_6H_2C(O)OSnBu_2)_2O]_2$ (Bu = $CH_2CH_2CH_2CH_3$) (**1**), has been synthesized and characterized by elemental analysis, FT-IR, $^{119}$Sn NMR spectroscopy, and X-ray single crystal diffraction. Compound 1 is a centrosymmetric dimmer with two distinct types of carboxylate moieties and tin atoms with distorted trigonal bipyramidal geometries. The *in vitro* anti-tumor activity of **1** against two human tumor cell lines was found to be higher than that for cis-platin [*cis*-diaminedichloroplatinum(II)] used clinically.

**Supporting information**: FT-IR, $^{119}$Sn NMR, X-Ray, Proliferation inhibitory rate, Cif file.

**Keywords:** *organotin, 2,4-dichloro-5-fluorobenzoic acid, crystal structure, in vitro anti-tumor activity.*

## 1. INTRODUCTION

Diorganotin carboxylates have drawn great attention because of their structural interest and their varied applications [1]. Some of them were used as the reaction catalysts, PVC stabilizers, and biocides. Recent studies have shown that some diorganotin carboxylates have relatively high *in vitro* anti-tumor activity [2-4]. In general, the organotin moiety, the ligand (carboxylic acid) and the number of tin atom appear to play an important role in anti-tumor activity [2]. Thus, to design and synthesize new diorganotin carboxylates by changing ligands has been encouraged. 2,4-Dichloro-5-fluorobenzoic acid is an important intermediate of fluoroquinolone antibiotics [5], and its diorganotin esters are not reported in the literatures. In the paper, we have synthesized dibutyltin ester of 2,4-dichloro-5-fluorobenzoic acid, $[(2,4\text{-}Cl_2\text{-}5\text{-}FC_6H_2C(O)OSnBu_2)_2O]_2$ (**1**), and determined its *in vitro* anti-tumor activity.

## 2. EXPERIMENTAL

All chemicals were of reagent grade and were used without further purification. Carbon and hydrogen analyses were determined using a Perkin Elmer 2400 Series II elemental analyzer. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000-400 $cm^{-1}$. $^{119}$Sn NMR spectral data were collected using a Bruker Avance DPX300 NMR spectrometer with $CDCl_3$ as solvent and $SnMe_4$ as external standard.

### 2.1 Synthesis of $[(2,4\text{-}Cl_2\text{-}5\text{-}FC_6H_2C(O)OSnBu_2)_2O]_2$

To a suspension of dibutyltin oxide (0.50 g, 2 mmol) in 50 ml of toluene was added 2,4-dichloro-5-fluorobenzoic acid (0.42 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 re-crystallized from methanol. Yield 0.68 g (76%), m.p. 123-124°C. Anal. Found: C, 40.04; H, 4.28. Calcd for $C_{60}H_{80}Cl_8F_4O_{10}Sn_4$: C, 40.13; H, 4.49%. IR (KBr) $cm^{-1}$: 3028 (C-H of benzene ring), 2956, 2926, 2869 (C-H), 1636 [$\nu_{as}$(C(O)O)], 1574 [$\nu_{as}$(C(O)O)], 1541 (C=C), 1400 [$\nu_s$(C(O)O)], 1334 [$\nu_s$(C(O)O)]. $^{119}$Sn NMR ($CDCl_3$) $\delta$: −205.9, −216.1 ppm.

### 2.2 X-ray crystallography

The colorless single crystal of **1** was obtained from chloroform-hexane (1:1, V/V) by slow evaporation at room temperature. Diffractions measurements were performed on a Bruker Smart Apex imaging-plate area detector fitted with graphite monochromatized Mo-Kα radiation (0.71073 Å) using the *j* and *w* 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 [6]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions. In the complex, the *n*-butyl groups are disordered over two positions, and their site occupancies were refined to 0.56(3):0.44(3) for C(2)-C(4), 0.53(4):0.47(4) for C(6)-C(8), 0.51(9):0.49(9) for C(10)-C(12), and 0.63(7):0.37(7) for C(14)-

C(16), respectively. In refinements, the C-C bonds and 1,3-distances of the disorderly *n*-butyl groups were restrained to 1.52(1) and 2.50(2) Å, respectively. Crystal data, collection procedures and refinement results are summarized in Table S1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 926118.

### 2.3 *In vitro* anti-tumor activity

Anti-tumor activity was assayed against two human tumor cell lines, CoLo205 (colon carcinoma cell) and HeLa (cervix tumor cell). The sample was prepared by dissolving compound **1** in ethanol and by diluting the solution obtained with water. *In vitro* cytotoxicity of **1** was measured by the MTT assay according to the literature [7]. The dose causing 50% inhibition of cell growth ($IC_{50}$) was calculated by NDST software (Tables S2 and S3).

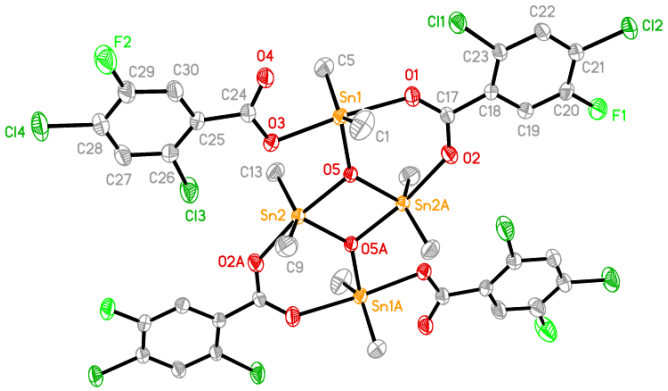


**Figure 1.** The molecular structure of **1**; all hydrogen atoms and partial carbons of butyl bond to Sn atoms are omitted for clarity.

## 3. RESULTS AND DISCUSION

Compound **1** was prepared by azeotropic removal of water from the reaction between the dibutyltin oxide and 2,4-dichloro-5-fluorobenzoic acid in the molar ratio 1:1 in toluene. The compound is white crystals, air stable and soluble in benzene, toluene and in common polar organic solvents.

In organotin complexes of the carboxylate ligand, IR spectroscopy can provide useful information concerning the coordination mode of the carboxylate group. Generally, the difference between the $\nu_{as}$(C(O)O) and $\nu_s$(C(O)O) bands, $\Delta\nu$( C(O)O), of bidentate carboxylate group is below 200 $cm^{-1}$, while unidentate carboxylate is above 200 $cm^{-1}$ [8]. In **1**, the $\Delta\nu$( C(O)O) value is 302 and 174 $cm^{-1}$, respectively, indicating that there are the monodentate carboxylate and bridging bidentate carboxylate groups [8,9]. A strong band of 645 $cm^{-1}$ is assigned to vibrations of associated with the Sn–O–Sn stretch [9]. Two $^{119}$Sn resonances ($\delta$ -216.1, -205.9) are assigned to the endocyclic and exocyclic tin atoms.[10].

The molecular structure of **1** is shown in Figure 1. The selected bond lengths and bond angles are listed in Table 1. The compound crystallizes in triclinic space group *P*-1 and is a centrosymmetric dimer built up around the planar cyclic $Sn_2O_2$ unit.

The two oxygen atoms [O(5) and O(5A), symmetry code A: -*x*+1, -*y*+2, -*z*+1] in this unit are tridentate as they link three tin canters, two endocyclic and one exocyclic. The distance between the endocyclic and exocyclic tin atoms is 3.668(2) Å and the distance between the two endocyclic tin centers is 3.293(2) Å. Additional links between the endo- and exo-cyclic tin atoms are provided by bi-dentate carboxylate ligands with asymmetrical bridges in which the distances of two Sn-O bonds [Sn(1)-O (1) and Sn(2A)-O(2)] and two C-O bonds [C(17)-O(1) and C (17)-O(2)] are 2.301(5) and 2.249(5) Å, 1.212(8) and 1.240(8) Å, respectively. Each exocyclic tin atom is coordinated by a mono-dentate carboxylate ligand. The length of Sn(1)-O(3) bond is 2.209(4) Å, and two C-O bond distances of the monodentate carboxylate are C(24)-O(3) 1.273(8) and C(24)-O(4) 1.225(8) Å, respectively. The coordination geometry about each of the tin atoms is best described as distorted trigonal bipyramidal with axial positions occupied by oxygen atoms [O(3)-Sn(1)-O(1) 171.1(2)° and O(5)-Sn(2)-O(2A) 168.35(18)°]. Atom Sn (1) lies 0.128(1) Å out of the trigonal plane defined by O(5), C (1) and C(5) in the direction of atom O(3), and Sn(2) lies 0.013 (1) Å out of the trigonal plane defined by O(5A), C(9) and C (13) in the direction of atom O(5). Distortions from the ideal geometry arise partly owing to the close intramolecular ap-

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

| | | | |
|---|---|---|---|
| Sn(1)-C(1) | 2.067(10) | Sn(2)-C(9) | 2.110(8) |
| Sn(1)-C(5) | 2.087(9) | Sn(2)-C(13) | 2.097(7) |
| Sn(1)-O(1) | 2.301(5) | Sn(2)-O(2A) | 2.249(5) |
| Sn(1)-O(3) | 2.209(4) | Sn(2)-O(5) | 2.162(4) |
| Sn(1)-O(5) | 2.024(4) | Sn(2)-O(5A) | 2.041(4) |
| O(5)-Sn(1)-C(1) | 106.8(4) | O(5A)-Sn(2)-C(13) | 109.0(3) |
| O(5)-Sn(1)-C(5) | 111.4(4) | O(5A)-Sn(2)-C(9) | 107.3(3) |
| C(1)-Sn(1)-C(5) | 140.6(5) | C(13)-Sn(2)-C(9) | 143.7(4) |
| O(5)-Sn(1)-O(3) | 82.22(15) | O(5A)-Sn(2)-O(5) | 76.87(16) |
| C(1)-Sn(1)-O(3) | 100.8(4) | C(13)-Sn(2)-O(5) | 93.8(3) |
| C(5)-Sn(1)-O(3) | 93.7(3) | C(9)-Sn(2)-O(5) | 95.3(3) |
| O(5)-Sn(1)-O(1) | 89.91(18) | O(5A)-Sn(2)-O(2A) | 91.99(18) |
| C(1)-Sn(1)-O(1) | 85.4(4) | C(13)-Sn(2)-O(2A) | 86.6(3) |
| C(5)-Sn(1)-O(1) | 85.3(3) | C(9)-Sn(2)-O(2A) | 91.3(4) |
| O(3)-Sn(1)-O(1) | 171.1(2) | O(5)-Sn(2)-O(2A) | 168.35(18) |

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

proach of oxygen atoms such that Sn(1)···O(4) is 2.729(3) Å and Sn(2)···O(2A) is 2.919(3) Å. Although these separations are considered too long to represent significant bonding interactions between tin and oxygen, they do exert an important influence on the respective coordination geometries, as seen in the expansion of the C(1)-Sn(1)-C(5) and C(9)-Sn(2)-C(13) angles to 140.6(5) and 143.7(4)° respectively from an ideal value of 120°. Various Sn–C and Sn–O distances are normal and can be compared with the distances reported in related complexes [11,12].

The $IC_{50}$ against CoLo205 and HeLa is 1.113 and 0.329 $\mu g \times ml^{-1}$, respectively, indicating that **1** is active against the two tumor cells, and its activity is higher than that of the reference drug *cis*-platin ($IC_{50}$ 4.027 and 1.377 $\mu g \times ml^{-1}$, respectively). Thus, further studies on the structure and activity are essential in order to obtain the more active organotin complexes.

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