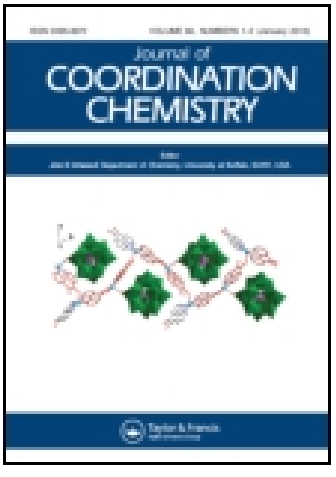

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Polymeric seven-coordinated organotin(IV) complexes derived from 5-amino-2-chlorobenzoic acid and *in vitro* anti-cancer studies

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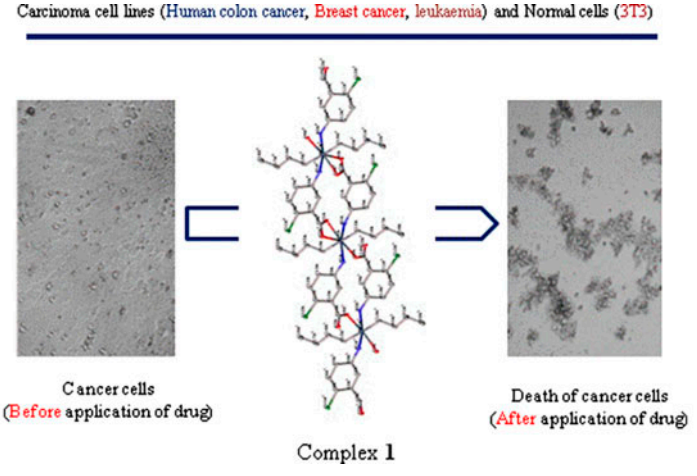

Complex **1**

Cancer cases are alarmingly increasing worldwide, and newer chemotherapeutic agents are needed. Recent analogs of *cis*platin (carboplatin, lobaplatin, nedaplatin and oxaliplatin) and their marketing as advanced chemotherapeutic drugs have furthered the interest in metal-based anti-cancer drugs. In the current study, two new polymeric organotin(IV) carboxylate complexes (**1** and **2**) have been synthesized and characterized. Spectroscopic studies showed that coordination took place via carboxylates. Furthermore, X-ray crystallographic study on **1** indicated that it possesses a monomeric structure and exists in polymeric formation due to additional Sn–N coordination, assigning seven coordinations to each metal ion. Both the complexes were tested against three cancerous (human colon cancer, HCT 116; breast cancer, MCF-7; and leukemia, K562) and one non-cancerous (3T3-L1) cell lines.

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Complex **1** showed exceptional cytotoxicity against cancerous cell lines (IC_{50} = 1.0 μM for HCT 116; 258.7 nM for MCF-7; and 46.7 nM K562) and remained comparatively non-toxic against normal cells (IC_{50} = 37.0 μM). This shows that both complexes have selective cytotoxicity against cancer cells.

Keywords: Organotin(IV) carboxylate complexes; 5-Amino-2-chlorobenzoic acid; Cytotoxicity; Anti-cancer

Introduction

Tin is a biocompatible metal [1–3]. In recent years, a number of organotin complexes have been screened for possible anti-microbial [4–17] and anti-cancer [8, 18–23] activities. Organotin complexes offer unique coordination chemistry as well as structural diversity which could expand from simple monomeric to polymeric structures [4, 24–31] and may give biological adoptability to these complexes.

Organotin(IV) complexes, possessing various coordination features, have been studied against a range of cancerous cell lines like human lung tumor (A549), cervix tumor (HeLa), kidney cancer (A498), breast cancer (EVSA-T, MCF-7), lung cancer (H226), ovarian adenocarcinoma (IGROV, A2780), melanoma (M19 MEL), colon cancer (WIDR, SW480), hepatocellular liver carcinoma (HepG2), endometrial cancer (HEC-1B), and bladder carcinoma (T24) [18, 19, 21, 23, 31, 32].

In the current study, we report the synthesis of two new organotin(IV) carboxylate complexes (**1** and **2**, scheme 1) derived from 5-amino-2-chlorobenzoic acid (**HL**) and their cytotoxicity against three cancerous cell lines (breast cancer MCF-7, human colorectal cancer HCT 116, and leukemia HL-60) and one non-cancerous cell line (3T3-L1) to study the effect of synthesized compounds on cancerous and non-cancerous cells. The complexes have seven coordinations which have been rarely reported for tin complexes [33, 34].

Experimental

General and instrumental

Chemicals were purchased commercially and used without purification. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. Tin was assessed gravimetrically by igniting a known quantity of each complex to SnO_2. The melting points were determined in an open capillary tube. Infrared spectra were recorded using a Perkin-Elmer System 2000 FTIR spectrophotometer as KBr disks from 4000 to 400 cm^{-1}. ^{1}H, ^{13}C, and ^{119}Sn NMR spectra were recorded on a Joel JNM-ECX 400 FT NMR spectrometer using deuterated d_6-DMSO as the solvent and tetramethylsilane, TMS, as the internal standard.

Single-crystal X-ray diffraction data were collected on an APEX II Duo CCD area-detector diffractometer operating at 50 kV and 30 mA using Mo Kα radiation (λ = 0.71073 Å). Diffraction data for **1** was collected with the Oxford Cryosystem Cobra low-temperature attachment at 100 K [35]. Data collection and reduction were performed using APEX2 and SAINT software. SADABS was used for absorption correction. All structures were solved by direct methods, and refinement was carried out by full-matrix least squares on F^2 using SHELXTL [36]. All non-hydrogen atoms were refined anisotropically, whereas hydrogens were refined isotropically. All N-bound hydrogens were located in different Fourier

maps and fixed at their found positions and refined with U_{iso} (H) = 1.2 U_{eq} (N). Hydrogens bound to carbon were positioned geometrically with U_{iso} (H) = 1.2 or 1.5 U_{eq} (C). A rotating-group model was applied for the methyl groups.

5-Amino-2-chlorobenzoic acid (HL)

HL was purchased from Acros Organics and was used without purification. FTIR as KBr disk (cm^{-1}): selected data: ν(OH) 2923–2597, $\nu(COO)_{as}$ 1624, $\nu(COO)_s$ 1371, and $\Delta\nu$ = 253. ^{1}H NMR (ppm) (d_6-DMSO): δ: benzene protons 6.64 (dd, 2.4 Hz, 8.6 Hz, 1H); 6.91 (d, 3.0 Hz, 1H); and 7.06 (d, 9.2 Hz, 1H). ^{13}C NMR (ppm) (d_6-DMSO): δ: benzene carbons 115.8, 117.6, 118.1, 131.3, 131.9, and 147.9; COO 166.9.

Preparation of dimethyltin(IV) oxide, Me_2SnO

Dimethyltin(IV) dichloride was dissolved in distilled water and stirred for 16 h. Colorless solution was obtained. White precipitates formed after the addition of ammonia solution (60%). The precipitates were placed in an oven (60 °C) for a few days to dry.

Preparation of sodium salt (NaHL)

The sodium salt of the acid was obtained by refluxing a 1 : 1 M mixture of sodium hydroxide and 5-amino-2-chlorobenzoic acid in ethanol (50 mL) for 2 h. After a few days, white precipitate of sodium 5-amino-2-chlorobenzoate was obtained. FTIR as KBr disk (cm^{-1}, selected data): $\nu(COO)_{as}$ 1565, $\nu(COO)_s$ 1387, $\Delta\nu$ = 178.

Synthesis of complexes

Preparation of (5-NH_2-2-Cl-$C_6H_3COO)_2(C_4H_9)_2Sn$ (1). Complex **2** was obtained by refluxing a 1 : 2 M mixture of dibutyltin(IV) oxide (0.75 g, 3 mM) and 5-amino-2-chlorobenzoic acid (1.03 g, 6 mM) in methanol (50 mL) for 4 h. A transparent solution was separated by filtration and kept in a bottle. After a few days, needle brown crystals (1.34 g, 78.0% yield) were collected. Melting point: 121–123 °C. Analysis for $C_{22}H_{28}N_2O_4Cl_2Sn_1$: C, 45.77; H, 3.81; N, 4.06; Sn, 19.03%. Calculated for $C_{22}H_{28}N_2O_4Cl_2Sn_1$: C, 46.03; H, 4.91; N, 4.88; Sn, 20.68%. FTIR as KBr disk (cm^{-1}): $\nu(COO)_{as}$ 1592; $\nu(COO)_s$ 1385, $\Delta\nu$ = 207; ν(O–Sn–O) 660, ν(Sn–C) 597, ν(Sn–N) 502, and ν(Sn–O) 447. ^{1}H NMR (ppm) (d_6-DMSO): δ: benzene protons 6.60 (d, 6.7 Hz, 2H); 6.90 (s, 2H); and 7.03 (d, 8.6 Hz, 2H); butyl, CH_3 0.78 (t, 6.6 Hz, 6H), CH_2 1.24 (sx, 7.3 Hz, 4H); CH_2 1.43–1.49 (m, 4H); and CH_2 1.52–1.59 (m, 4H). ^{13}C NMR (ppm) (d_6-DMSO): δ: benzene carbons 115.9, 117.6, 131.1, 133.0, and 147.9; butyl 13.9, 14.0, 26.2, 27.3, and 30.8; COO 172.3. ^{119}Sn NMR (ppm) (d_6-DMSO): δ: −260.7.

Preparation of (5-NH_2-2-Cl-$C_6H_3COO)_2(CH_3)_2Sn$ (2). Complex **1** was obtained by refluxing a 1 : 2 M mixture of dimethyltin(IV) oxide (0.50 g, 3 mM) and 5-amino-2-chlorobenzoic acid (1.03 g, 6 mM) in acetonitrile (50 mL) for 4 h. A transparent solution was separated by filtration and kept in a bottle. After a few days, white precipitates (1.25 g,

85.0% yield) were collected. Melting point: 204–206 °C. Analysis for $C_{16}H_{16}N_2O_4Cl_2Sn_1$: C, 38.97; H, 3.01; N, 4.98; Sn, 24.22%. Calculated for $C_{16}H_{16}N_2O_4Cl_2Sn_1$: C, 39.23; H, 3.29; N, 5.72; Sn, 24.23%. FTIR as KBr disk (cm^{-1}): $\nu(COO)_{as}$ 1594; $\nu(COO)_s$ 1385, $\Delta\nu$ = 209; ν(O–Sn–O) 663, ν(Sn–C) 577, and ν(Sn–O) 448. ^{1}H NMR (ppm) (d_6-DMSO): δ: benzene protons 6.58 (dd, 2.8 Hz, 8.7 Hz, 2H); 6.87 (s, 2H); and 7.02 (d, 8.7 Hz, 2H); methyl 0.83 (s, 6H). ^{13}C NMR (ppm) (d_6-DMSO): δ: benzene carbons 115.7, 117.4, 131.0, 133.9, and 147.8; methyl 11.79, COO 171.79. ^{119}Sn NMR (ppm) (d_6-DMSO): δ: −288.5.

In vitro *anti-cancer studies*

Source of cell lines, culture conditions, preparation of cell culture, and MTT assay were performed according to our previously reported procedure for these cell lines [37–40]. The procedure has been additionally described in the supplementary file.

Results and discussion

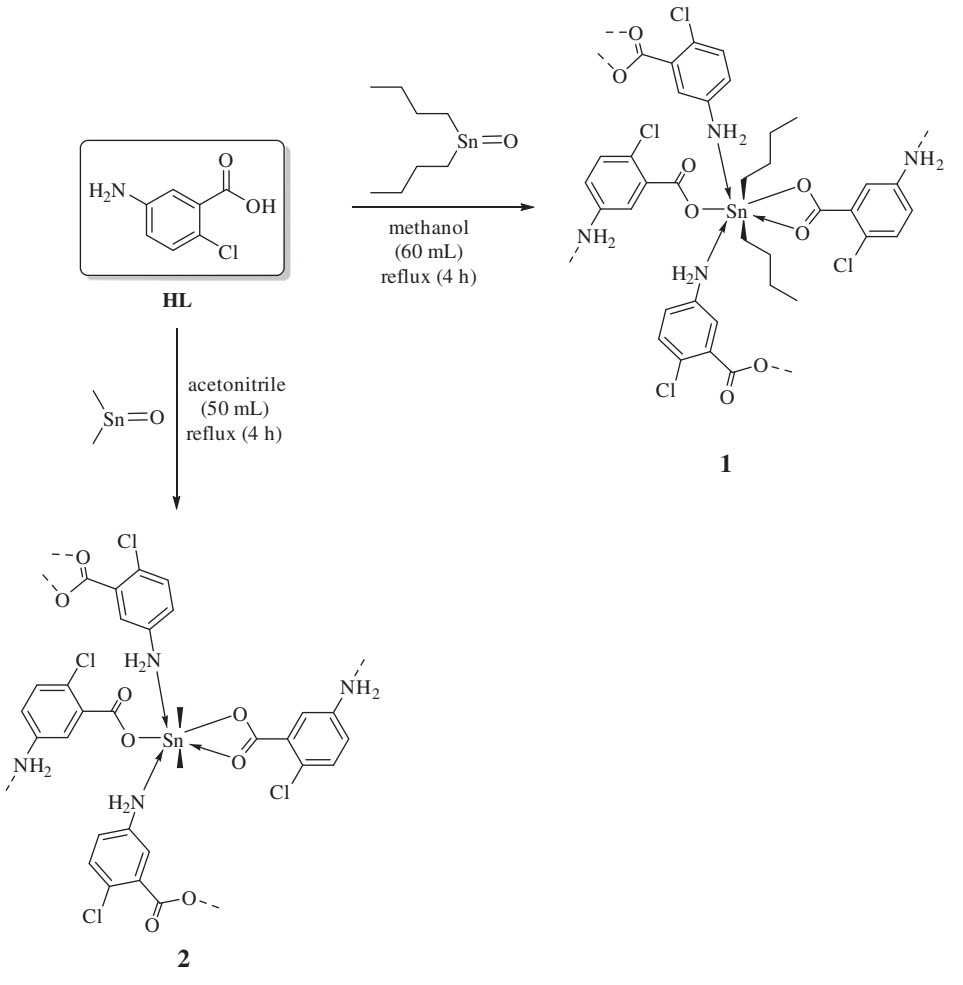
In this study, **1** and **2** have been obtained in the solid state. The complexes have sharp melting points (with a range of less than 3 °C), indicating isolation of pure complexes. An outline of the proposed structures for complexes has been depicted in scheme 1. The micro-analytical data obtained is in agreement with the predicted formulas of **1** and **2**.

Spectroscopy (FTIR, ^{1}H, ^{13}C, ^{119}Sn NMR)

The ν(O–H) bands in **HL** were absent in the infrared spectra of salt (**NaL**) and **1** and **2** which indicated deprotonation and coordination of the carboxylate. Complexes revealed that $\nu(COO)_{as}$ shifted to a lower wave number ($\Delta\nu$) compared to **HL** which signifies that coordination took place via the oxygens of carboxylates. Complexes **1** and **2** were isolated as polymeric complexes, and their $\Delta\nu$ values were 209 and 207 cm^{-1}, lower than the sodium salt ($\Delta\nu$ = 178 cm^{-1}) of 5-amino-2-chlorobenzoic acid, indicating that the carboxylates were bidentate to tin(IV). Further evidence of the coordination to tin(IV) via oxygens was revealed by the presence of ν(O–Sn–O)/ν(Sn–O–Sn) and ν(Sn–O) stretching bands in the FTIR spectra of **1** and **2**.

^{1}H NMR spectra of **1** and **2** exhibited similarities to **HL**. The only exceptional differences were the appearance of new ^{1}H NMR signals for coordinated methyl and butyl moieties at δ 0.83 ppm for **1** and δ 0.75–1.60 ppm for **2**. Further evidence for formation of the complexes was provided by ^{13}C NMR studies. The ^{13}C NMR spectra of **1** and **2** showed that the δ(COO) signals shifted downfield (~172 δ ppm) from that of **HL** (~167 δ ppm), indicating the carboxylate bonding to tin(IV). Also, **1** exhibited a sharp signal at 11.7 ppm, indicating the presence of the methyl groups in the $SnMe_2$ moiety, whereas **2** exhibited a set of signals in the upfield region, indicating the presence of the butyl groups of $SnBu_2$.

The $\delta(^{119}Sn)$ values of four-coordinate complexes fall in the range +200 to −60 ppm; the five-coordinate complexes fall between −90 and −190 ppm, and the six- and seven-coordinate complexes fall between −210 and −400 ppm [41, 42]. The $\delta(^{119}Sn)$ values of **1** and **2** were −288.5 and −260.7 ppm, respectively, indicating that tin(IV) in both **1** and **2** remained six-coordinate in solutions. However, the crystallographic information revealed seven coordinations, which may be acquired during crystallization.



Scheme 1. Synthesis of tin complexes **1** and **2**. The dashed lines represent the extended units in order to generate a polymeric formation.

Crystallography

Complex **1** was isolated, and its molecular structure was studied using single-crystal X-ray diffraction technique. Single-crystal X-ray determination revealed that the crystal system of the complex is triclinic with space group $P\bar{1}$ and unit cell parameters $a = 7.5585(4)$ Å, $b = 16.4261(9)$ Å, $c = 20.4598(11)$ Å, $\alpha = 68.216(1)°$, $\beta = 89.882(1)°$, and $\gamma = 82.410(1)°$. Summary of the crystallographic data for **1** at 100.0 K is depicted in table 1 and selected bond lengths (Å) and angles (°) are listed in table 2. The hydrogen-bond geometry (Å, °) of **1** is given in table 3. The structural elucidation provided two crystallographically different units (A and B) having slightly different geometrical parameters. The literature shows that in some cases, crystallographically different units of the same molecule have some significant differences (bond distances and angles) to be discussed in detail [43–45]. However, in the current case, both the units (A and B) have almost similar geometries (figure S1, see

Table 1. Crystallographic data of **1**.

Parameter	$(5\text{-}NH_2\text{-}2\text{-}Cl\text{-}C_6H_3COO)_2(C_4H_9)_2Sn$
Empirical formula	$C_{22}H_{28}Cl_2N_2O_4Sn$
Formula weight	574.05
Temperature (K)	100
Radiation/wavelength	Mo Kα/0.71073 Å
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	$a = 7.5585(4)$ Å $\alpha = 68.216(1)°$ $b = 16.4261(9)$ Å $\beta = 89.882(1)°$ $c = 20.4598(11)$ Å $\gamma = 82.410(1)°$
Volume (Å^3)	2335.1(2)
Z, Calculated density (Mg m^{-3})	4, 1.633
Absorption coefficient (mm^{-1})	1.350
Crystal size (mm)	0.53 × 0.15 × 0.14
Crystal morphology/color	Needle/brown
θ range for data (°)	3.5–32.6
Limiting indices	$-9 \le h \le 9$, $-21 \le k \le 21$, $-26 \le l \le 26$
Reflections collected/unique	41,033/10,517
R (int)	0.027
Completeness	98.1%
Max and min transmission	0.828 and 0.534
Goodness of fit	1.12
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$	0.029, 0.074
Largest difference between peak and hole (e Å^{-3})	1.26, −1.17

online supplemental material at http://dx.doi.org/10.1080/00958972.2014.963571), except the terminals of the alkyl chains which might have less significance in both, biological activities and metal coordination geometries. Furthermore, there is no interconnection between polymer chains comprised of unit A and unit B which keeps them independent moieties. In addition, the crystal packing for both of the units is comparable where it is reflected by the similar hydrogen-bonding geometries (table 3). Hence, only one of the units (A) was selected to be discussed in detail. Figure 1 exhibits the molecular structure of **1** with its numbering scheme, while the molecular packing diagram is depicted in figure S2 (supplementary file).

Based on the crystal structure depicted in figure 1, the tin is seven coordinate [33, 34, 46], bonded to three oxygens (Sn–O) of the carboxylate anions and two bonds from bonding of butyl groups to tin (Sn–C). Another two bonds attributed to Sn–N result in tin(IV) being seven coordinate in a distorted pentagonal–bipyramidal geometry. Due to the Sn–N bonding, **1** forms a polymeric chain propagating in [0 1 0] instead of simple monomeric as reported earlier [24, 47].

In the crystal, the polymeric chains are further consolidated by intermolecular N–H···Cl, N–H···O and C–H···O hydrogen bonds (table 3).

Based on the spectroscopic study, carboxylates are bonded bidentate to tin(IV) and the overall structure would be simple monomeric type. However, based on the single crystal structure determination, it was confirmed and have a clearer view that a new structure of dibutyltin(IV) dicarboxylate has been obtained which existed in the polymeric form and possessed distorted pentagonal bipyramidal geometry.

Anti-cancer studies

The mortality rate due to cancer is increasing worldwide due to the rapid growth of world population as well as adoption of cancer-causing behaviors [48, 49]. According to GLOBOCAN 2008 estimate, 7.6 million cancer deaths occurred worldwide labeling breast cancer as

Table 2. Bond lengths (Å) and angles (°) of **1**.

Bond lengths			
Sn(1A)–C(15A)	2.133(2)	Sn(1B)–C(15B)	2.142(2)
Sn(1A)–C(19A)	2.135(2)	Sn(1B)–C(19B)	2.143(2)
Sn(1A)–O(1A)	2.2629(16)	Sn(1B)–O(1B)	2.2495(16)
Sn(1A)–O(4A)	2.2648(16)	Sn(1B)–O(4B)	2.2521(15)
Sn(1A)–N(1A)	2.4045(18)	Sn(1B)–N(1B)	2.4012(18)
Sn(1A)–N(2A)	2.4433(18)	Sn(1B)–N(2B)	2.4339(18)
Bond angles			
C(15A)–Sn(1A)–C(19A)	177.69(8)	C(15B)–Sn(1B)–C(19B)	178.34(8)
C(15A)–Sn(1A)–O(1A)	88.43(7)	C(15B)–Sn(1B)–O(1B)	94.02(7)
C(19A)–Sn(1A)–O(1A)	93.45(7)	C(19B)–Sn(1B)–O(1B)	84.86(7)
C(15A)–Sn(1A)–O(4A)	93.31(7)	C(15B)–Sn(1B)–O(4B)	88.30(7)
C(19A)–Sn(1A)–O(4A)	85.22(7)	C(19B)–Sn(1B)–O(4B)	93.07(7)
O(1A)–Sn(1A)–O(4A)	165.06(6)	O(1B)–Sn(1B)–O(4B)	166.74(6)
C(15A)–Sn(1A)–N(1A)	92.93(8)	C(15B)–Sn(1B)–N(1B)	92.45(8)
C(19A)–Sn(1A)–N(1A)	88.84(8)	C(19B)–Sn(1B)–N(1B)	88.81(8)
O(1A)–Sn(1A)–N(1A)	75.20(6)	O(1B)–Sn(1B)–N(1B)	91.40(6)
O(4A)–Sn(1A)–N(1A)	89.89(6)	O(4B)–Sn(1B)–N(1B)	75.45(6)
C(15A)–Sn(1A)–N(2A)	85.00(7)	C(15B)–Sn(1B)–N(2B)	85.47(7)
C(19A)–Sn(1A)–N(2A)	92.87(7)	C(19B)–Sn(1B)–N(2B)	93.04(7)
O(1A)–Sn(1A)–N(2A)	121.60(6)	O(1B)–Sn(1B)–N(2B)	73.76(6)
O(4A)–Sn(1A)–N(2A)	73.73(6)	O(4B)–Sn(1B)–N(2B)	119.46(6)
N(1A)–Sn(1A)–N(2A)	162.92(6)	N(1B)–Sn(1B)–N(2B)	164.80(6)
C(7A)^{i}–O(1A)–Sn(1A)	103.14(13)	C(14B)^{iii}–O(1B)–Sn(1B)	129.95(13)
Bond angles			
C(14A)^{ii}–O(4A)–Sn(1A)	103.14(13)	C(7B)^{iv}–O(4B)–Sn(1B)	105.62(13)
C(6A)–N(1A)–Sn(1A)	122.15(14)	C(6B)–N(1B)–Sn(1B)	121.41(14)
Sn(1A)–N(1A)–H(1NA)	102.8	Sn(1B)–N(1B)–H(1NB)	108.1
Sn(1A)–N(1A)–H(2NA)	105.9	Sn(1B)–N(1B)–H(2NB)	100.6
C(8A)–N(2A)–Sn(1A)	121.40(13)	C(8B)–N(2B)–Sn(1B)	119.43(13)
Sn(1A)–N(2A)–H(3NA)	94.8	Sn(1B)–N(2B)–H(3NB)	97.2
Sn(1A)–N(2A)–H(4NA)	94.8	Sn(1B)–N(2B)–H(4NB)	106.5
C(16A)–C(15A)–Sn(1A)	116.33(15)	C(16B)–C(15B)–Sn(1B)	114.64(15)
Sn(1A)–C(15A)–H(15A)	108.2	Sn(1B)–C(15B)–H(15C)	108.6
Sn(1A)–C(15A)–H(15B)	108.2	Sn(1B)–C(15B)–H(15D)	108.6
C(20A)–C(19A)–Sn(1A)	117.72(15)	C(20B)–C(19B)–Sn(1B)	116.22(15)
Sn(1A)–C(19A)–H(19C)	107.9	Sn(1B)–C(19B)–H(19A)	108.2
Sn(1A)–C(19A)–H(19D)	107.9	Sn(1B)–C(19B)–H(19B)	108.2

Note: Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $-x+1, -y+2, -z$; (iv) $-x+1, -y+1, -z$.

a leading cause of cancer deaths [48]. The discovery of *cis*platin as an anti-cancer drug and recently its improved analogs (Carboplatin, Lobaplatin, Nedaplatin, Oxaliplatin) as marketing chemotherapeutic drugs give interest in exploration of metal-based anti-cancer drugs [50–56]. Several new organometallic compounds have been reported as anti-carcinogenic agents [8, 10, 18, 19, 21, 32, 40, 57–99], which indicate the bright future of metal-based drugs.

The current study reports *in vitro* anti-cancer potential of **1** and **2**. Each complex was tested against three cancer cell lines (human colon cancer HCT 116, breast cancer MCF-7, and leukemia K562) and one normal cell line (3T3-L1). The IC_{50} values are shown in table 4 and the dose-dependent graphs as figure 2. The table shows that **1** imparted significant activity ($IC_{50} = 1.0$ μM) compared to **2** ($IC_{50} = 177.5$ μM) against HCT 116 cell line. Such a significant difference in the IC_{50} values of both the complexes

Table 3. Hydrogen-bond geometry (Å, °) of **1**.

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N1*A*–H1*NA*···Cl1*A*^{i}	0.91	2.82	3.637(2)	150
N1*A*–H2*NA*···O2*A*^{i}	0.87	2.57	3.171(3)	126
N1*A*–H2*NA*···O3*A*^{ii}	0.87	2.04	2.831(3)	149
N2*A*–H3*NA*···O3*A*^{iii}	0.90	2.07	2.893(2)	150
N1*B*–H1*NB*···O2*B*^{iv}	0.87	2.36	3.072(3)	140
N1*B*–H1*NB*···O3*B*^{v}	0.87	2.22	2.871(3)	132
N2*B*–H4*NB*···O3*B*^{vi}	0.89	2.04	2.889(2)	160
C1*A*–H1*AA*···O1*A*	0.93	2.42	3.059(3)	126
C1*B*–H1*BA*···O4*B*	0.93	2.45	3.037(3)	121

Note: Symmetry codes: (i) $-x+2, -y, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $-x, -y+1, -z+1$; (iv) $-x+2, -y+1, -z$; (v) $-x+1, -y+2, -z$; (vi) $-x, -y+2, -z$.

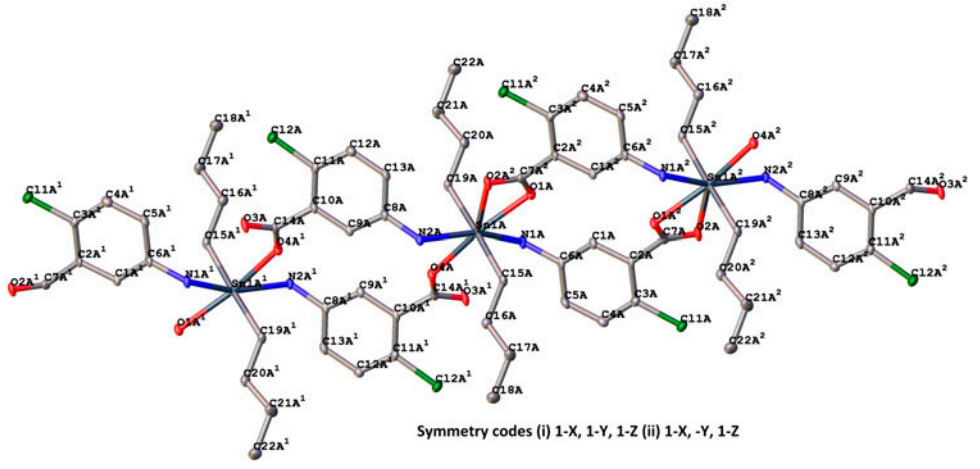


Figure 1. Crystal structure of **1** drawn using Olex2 software and labeled according to the CIF data file. The ORTEP picture of molecular structure (figure S4) and crystal packing (figure S2) has been additionally provided in supplementary file.

Table 4. The IC_{50} values of **1** and **2**.

Cell lines		Carcinoma cell lines HCT 116	MCF 7	K562	Normal cell line 3T3-L1
Complexes	**1**	1.0*	258.7**	46.7**	37.0*
	2	177.5*	49.7*	40.7*	136.0*
Standards		*5-FU*	*Tamoxifen*	*Betulinic acid*	*Betulinic acid*
		8.1*	8.7*	15.0*	44.0*

*μM.
**nM.

may be due to the different geometrical orientations and substitutional effects. This is further evident from their IC_{50} values on MCF-7 cell line where again **1** showed results better than **2** (IC_{50} of **1** = 258.7 nM and **2** = 49.7 μM). This also shows that a complex

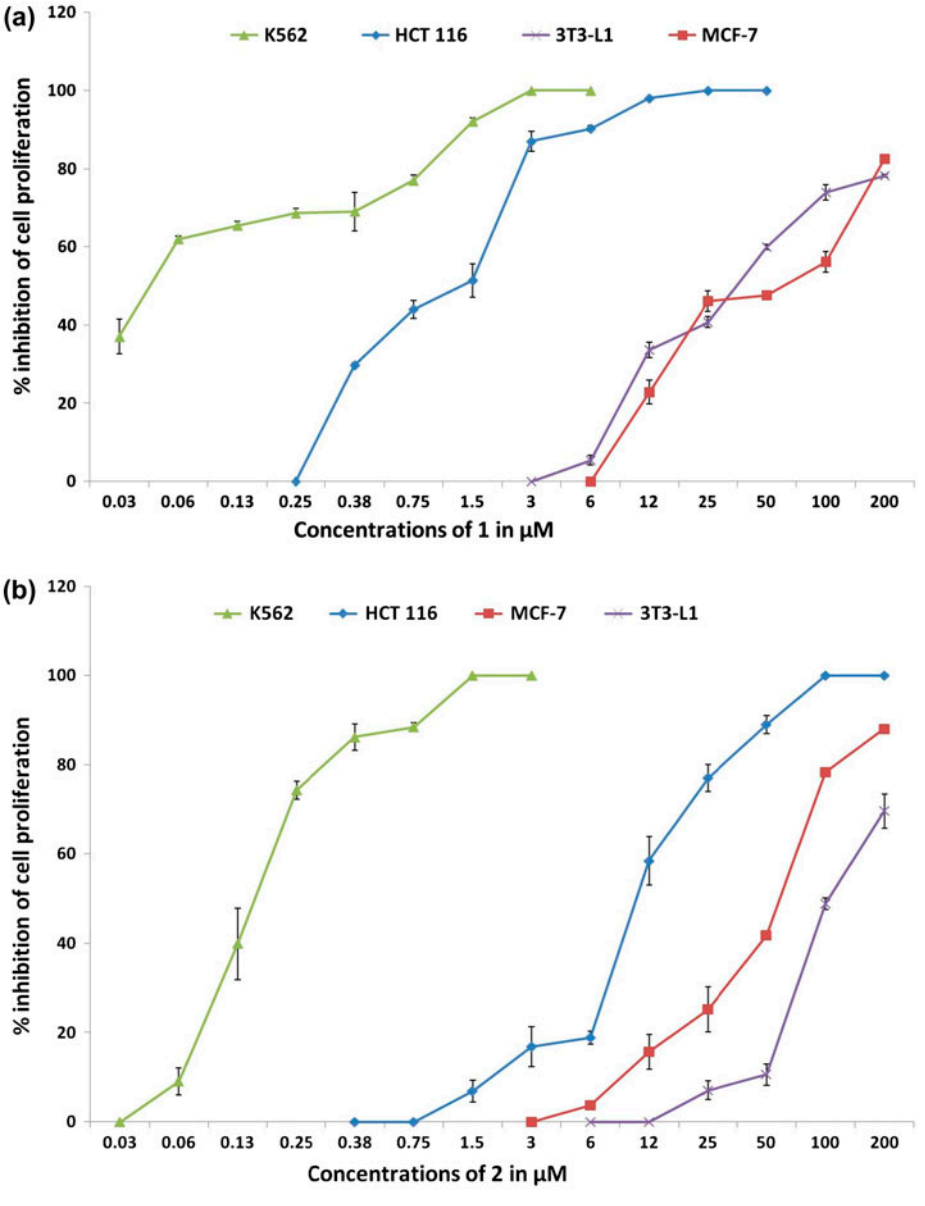


Figure 2. Dose-dependent anti-proliferative effect of **1** (a) and **2** (b) on human colorectal cancer (HCT 116), breast cancer (MCF-7), leukemia (K562), and normal cell line (3T3-L1).

may show lower cytotoxicity or may be inactive against one cell line, but may have observable activity against the other type of cell line. Furthermore, on K562 cell line, similar results were obtained (IC_{50} of **1** = 46.7 nM and **2** = 40.7 µM) which label both the complexes as anti-carcinogenic agents with an exception of **2** as almost inactive against HCT 116 and moderately active against the other two cell lines. Additionally, compared to their cytotoxicity against carcinoma cell lines, each of the complexes

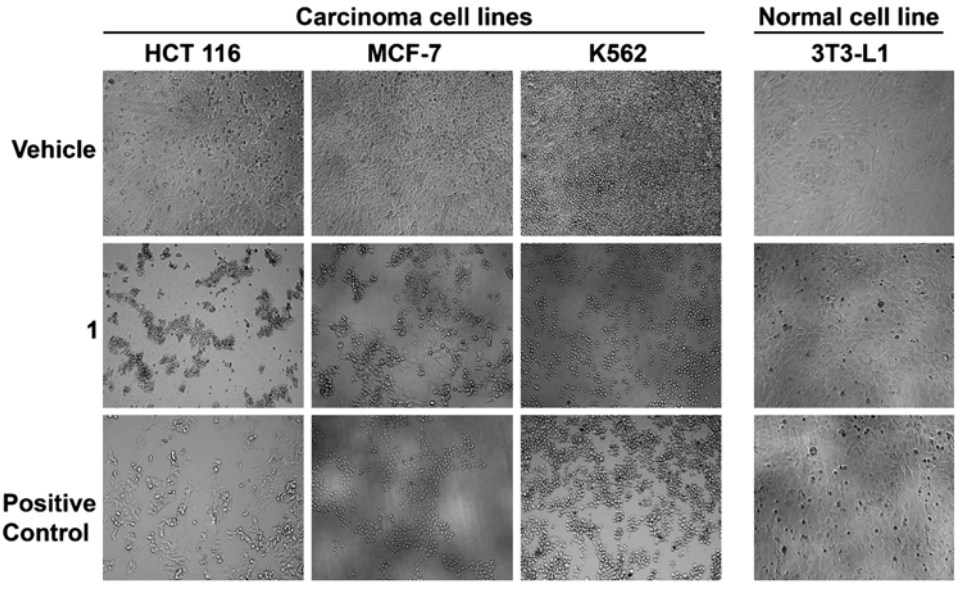


Figure 3. Photomicrographic images of the cell lines, taken under an inverted phase-contrast microscope at ×200 magnification using a digital camera at 48 h after treatment with the vehicle/negative control (0.1% DMSO), **1**, and controls/standards (5-FU for HCT 116, Tamoxifen for MCF-7, Betulinic acid for K562 and 3T3-L1 cells). All the cells treated with the vehicle (0.1% DMSO) showed confluent layer of aggressively proliferating cells for all four cell lines, whereas treatment with **1** showed significant ($p < 0.01$) inhibitory effect on proliferation of HCT 116, MCF-7, and K562 cancer cell lines with IC_{50} 1.0 μM, 258.7 nM, and 46.7 nM, respectively. The pictures reveal that the population of the treated cells reduced noticeably when compared to that of negative control. However, the complex demonstrated less cytotoxicity toward normal cell line (3T3-L1), as the selective index (SI = ratio of the IC_{50} obtained from the test on normal cell (3T3-L1) *vs.* the IC_{50} for cancer cell) was more than 10 except HCT 116 (SI is 8.1). Complex **1** showed a pronounced anti-proliferative effect than the respective standard reference drugs.

showed very low cytotoxicity against normal cells (3T3-L1, IC_{50} for **1** = 37.0 μM and **2** = 136.0 μM). This indicates that complexes are selectively toxic against cancer cells. The photomicrographs of cells are shown in figure 3.

Conclusion

Complexes **1** and **2** have been synthesized, and the molecular structure of **1** has been characterized by X-ray crystallographic technique, representing a seven-coordinate geometry. The complexes were tested against three cancerous and one non-cancerous cell lines. Complex **1** showed cytotoxicity significantly better than **2** which may be due to geometrical and substitutional differences. Finally, both the complexes have selective toxicity against cancer cells and remained safe against normal cells.

Supplementary material

The article contains supplementary file. Also, CCDC 983681 contains the supplementary crystallographic data for **1**. The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336-033; or E-mail: deposit@ccdc.cam.ac.uk.

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