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Original article

Novel mixed ligand di-n-butyltin(IV) complexes derived from acylpyrazolones and fluorinated benzoic acids: Synthesis, characterization, cytotoxicity and the induction of apoptosis in Hela cancer cells

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ABSTRACT

Twenty one novel mixed ligand di-n-butyltin(IV) complexes [$^{n}Bu_2SnAL$] (A = substituted 4-acyl-5-pyrazolone, and L = fluorinated benzoic acid) were prepared by condensation of di-n-butyltin(IV) oxide with HL and HA in 1:1:1 molar ratio in refluxing methanol. All of the complexes were characterized by elemental analyses, IR, NMR (^{1}H, ^{13}C, ^{119}Sn) and in four cases by X-ray diffraction. Cytotoxicity of the compounds was studied against two human cancer cell lines (KB and Hela) by means of the MTT assay compared to cisplatin, featuring IC_{50} values in the low micromolar range. Hela cancer cell apoptosis-induced by **2** was examined by flow cytometry analysis, and preliminary results showed that **2** at concentrations of more than 1.0 μM can induce apoptosis.

1. Introduction

The discovery of cisplatin opened a new era of anticancer drug research based on metallopharmaceuticals [1]. In order to search other better metal-based drugs, the biological activity of organotin(IV) complexes derived from various organic ligands such as carboxylates [2–5], oximates [6–12], acylpyrazolones [13–15], amino acids [16,17] and schiff bases [18–20] have been widely investigated during the last few decades.

It is well known that organotin(IV) carboxylates exhibit rather promising *in vitro* antitumor activities against some human tumor cell lines [2–5], and, in particular, the presence of the fluorinated phenyl group can result in an enhanced antitumor activity of such complexes [2]. Meanwhile, there has been much progress in the chemistry of organotin(IV) complexes with acylpyrazolones ligands, and the acyl group on pyrazol ring plays an important role in biological activity aspect [13]. Most of these compounds having been widely studied are diorganotin(IV) complexes with dicarboxylates or dipyrazolones, and less attention has been devoted to the mixed-ligand organotin(IV) complexes containing two types of chelating ligands [21]. Moreover, antitumor activity of organotin(IV) compounds was also confined with an attached R group to tin atom, and it was found in literature that compounds with butyl group on the tin atom had good partition coefficient, thereby increasing the bioactivity [2–12].

Currently, we are interested in the mixed ligand complexes containing two different types of ligands above mentioned. One is substituted 4-acyl-5-pyrazolone (HA), and the other is fluorinated benzoic acid (HL), and hope to introduce them into a Bu_2Sn center to form novel mixed ligand dibutyltin(IV) complexes. These complexes with different donors bear both four-membered chelate ring ligand and six-membered chelate ring ligand connected to the tin center at the same time and whose coordination chemistry and antitumor activity still remain unexplored. Moreover, the presence of the two different chelating ring moieties of the complex can be liable to stepwise dissociation in the formation of a Sn-DNA complex [22], which may be promotes cellular uptake and antitumor action.

In this report we described the synthesis of twenty one novel mixed ligand dibutyltin(IV) complexes of the type [Bu_2SnAL] where HA ligands contain eight 4-acyl-5-pyrazolones derivatives with different acyl groups, and HL ligands differ only in their position and number of phenyl group: 4-F (HL_1), 2,4-F_2 (HL_2) and 3,4-F_2

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(HL_3) (Scheme 1). *In vitro* antitumor activities were carried out on two human cancer cell lines (KB and Hela). In addition, cell apoptosis study of complex 2 with the highest activity on Hela cancer cell lines was also investigated by flow cytometry and provided insight into the initial mechanism of antitumor action.

2. Results and discussion

2.1. Syntheses

Twenty one novel mixed-ligand dibutyltin(IV) complexes [Bu_2SnAL] were prepared by the reaction of the two ligands with Bu_2SnO in methanol solution (Scheme 1). The complexes were isolated as white or yellow solids in different yields (19–90%). They are stable in air, light, moisture and buffer solution. All complexes are insoluble in water and n-hexane, soluble in chloroform, dichloromethane and partly soluble in dimethylsulfoxide, methanol and ethanol.

2.2. Spectral studies

There are a few changes observed in the IR spectra of the complexes with respect to those of the neutral free donors: the band of the carbonyl stretching frequency shifts to lower frequency (from 1620 to 1640 to 1600 cm^{-1} in 4-acyl-5-pyrazolones, from 1690 to 1600 in substituting benzoic acids); the disappearance of the broad absorption between 3200 and 2700 cm^{-1} can be noted, which is due to the absence of strongly hydrogen-bonded band (the loss of the enolic proton upon complexation). These changes suggest deprotonation of the ligand, involvement of both the carbonyl groups in the coordination of the tin (IV) atom, and formation of the six-membered chelate ring involving C_3, C_4, C_6 and the two oxygen atoms and four-membered chelate ring involving Sn and the COO groups. Besides, all complexes showed two or more bands in the region 563–420 cm^{-1}, and we assigned some absorption to the stretching modes of Sn–C and Sn–O on the basis of assignments made from analogous compounds [23–26].

The ^1H NMR spectra display the expected signals of different types of protons present in the complexes. The butyl protons attached to tin exhibit broad resonances in the region δ 1.80–0.68 ppm. The aromatic protons are observed as a complex pattern δ 8.16–6.86 ppm. The other ^1H NMR signals of methyl groups in heterocyclic β-diketones, which show expected signals, are listed in the Section 4.2.1–4.2.21.

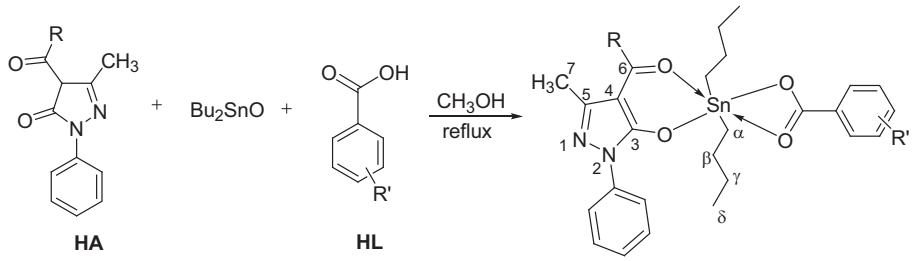
The ^{13}C NMR spectra of the complexes show a downfield shift of δ 2–5 ppm in the position of the carboxylic carbon signal as compared to its position in the parent fluorinated benzoic acid ligands, revealing the bidentate nature of COO group of the ligands. The delocalization of electrons takes place during the complex formation in the acylpyrazolone ligands of these complexes. There is some shifting in the positions of the carbon (C_3, C_4, C_6) signals due to delocalization of electrons. The bidentate nature of acylpyrazolone ligands is suggested. The ^{13}C NMR spectra of all complexes exhibit signals at δ 13.5–27.0 ppm, which can be attributed to the butyl carbons attached to tin atom.

In the ^{119}Sn NMR spectra, there are two or three resonances for the [Bu_2SnLA] complexes with intense signals observed around −230 ppm. The other two weak signals were also observed around −140 and −355 ppm, respectively, indicating the presence of aggregates in solution. The chemical shifts (approximately −140 ppm) are in agreement with the pentacoordinated tin centers, and the resonances around −230 ppm and −355 ppm support hexacoordinated tin centers in these complexes [27], which indicates that the structural character of tin atom in the solid state is not retained in solution. Probably there is a dynamic equilibrium among the three isomeric species due to the presence of high ring tension of four-membered chelate ring resulting in unidentate or weak bidentate bonding to tin(IV) in solution [6,28] (Scheme 2).

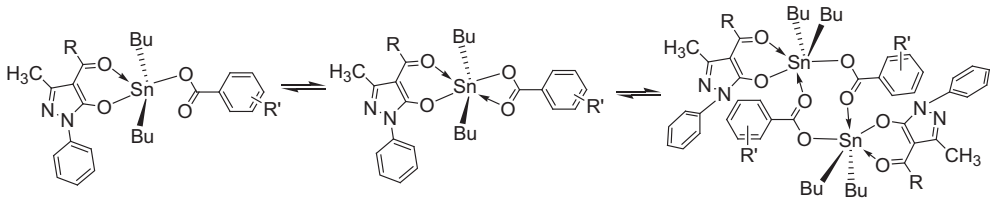
2.3. X-ray diffraction analysis

The molecular structures of the complexes **1**, **8**, **9** and **17** were authenticated by single crystal X-ray diffraction analyses. The most relevant parameters of bond distances and angles are given in the legends of Figs. 1–4.

The structures of complexes **1**, **9** and **17** (Fig. 1 for complex **1**; Fig. 2 for complex **9**; and Fig. 3 for complex **17**) are quite similar. It can be seen that they are monomeric with the tin atoms in distorted octahedral geometries environments formed by four oxygen atoms derived from one acylpyrazolone and one benzoate in the equatorial positions and two carbon atoms of the butyl groups in the *trans* positions (the C–Sn–C′ bond angles in the three derivatives range from 150.4(4)° to 152.4(3)°). This is characterized by two shorter Sn–O and two longer Sn–O bond lengths; e.g. in **1** they



Scheme 1. Synthesis of mixed ligand complexes [Bu_2SnAL] [$Bu_2SnA_1L_1$ (**1**), $Bu_2SnA_2L_1$ (**2**), $Bu_2SnA_3L_1$ (**3**), $Bu_2SnA_4L_1$ (**4**), $Bu_2SnA_5L_1$ (**5**), $Bu_2SnA_6L_1$ (**6**), $Bu_2SnA_7L_1$ (**7**), $Bu_2SnA_8L_1$ (**8**), $Bu_2SnA_1L_2$ (**9**), $Bu_2SnA_3L_2$ (**10**), $Bu_2SnA_4L_2$ (**11**), $Bu_2SnA_5L_2$ (**12**), $Bu_2SnA_6L_2$ (**13**), $Bu_2SnA_7L_2$ (**14**), $Bu_2SnA_1L_3$ (**15**), $Bu_2SnA_2L_3$ (**16**), $Bu_2SnA_3L_3$ (**17**), $Bu_2SnA_4L_3$ (**18**), $Bu_2SnA_5L_3$ (**19**), $Bu_2SnA_6L_3$ (**20**), $Bu_2SnA_7L_3$ (**21**)].



Scheme 2. Equilibrium between pent- and hexacoordinated species of Bu_2SnAL in solution.

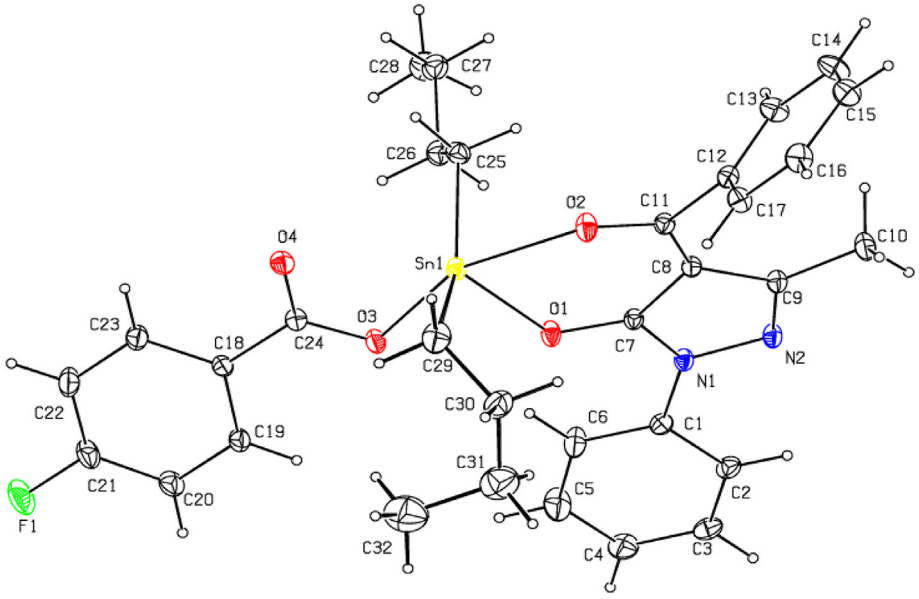


Fig. 1. Molecular structure of **1** showing the labeling scheme of the all atoms. Selected bond lengths (Å) and angles (°): Sn(1)–O(1) 2.103(2), Sn(1)–O(2) 2.350(2), Sn(1)–O(3) 2.163(2), Sn(1)–O(4) 2.656(2), Sn(1)–C(25) 2.106(3), Sn(1)–C(29) 2.184(9), C(7)–O(1) 1.284(3), C(11)–O(2) 1.261(4), C(24)–O(3) 1.292(4), C(24)–O(4) 1.238(4), C(29)–Sn(1)–C(25) 150.4(4), O(1)–Sn(1)–O(2) 79.27(8), O(1)–Sn(1)–O(3) 77.59(8), O(2)–Sn(1)–O(3) 156.46(9), O(1)–Sn(1)–C(25) 100.60(12), O(1)–Sn(1)–C(29) 106.4(2), O(2)–Sn(1)–C(25) 86.94(12), O(2)–Sn(1)–C(29) 84.6(5), O(3)–Sn(1)–C(25) 101.47(11), O(3)–Sn(1)–C(29) 97.4(5).

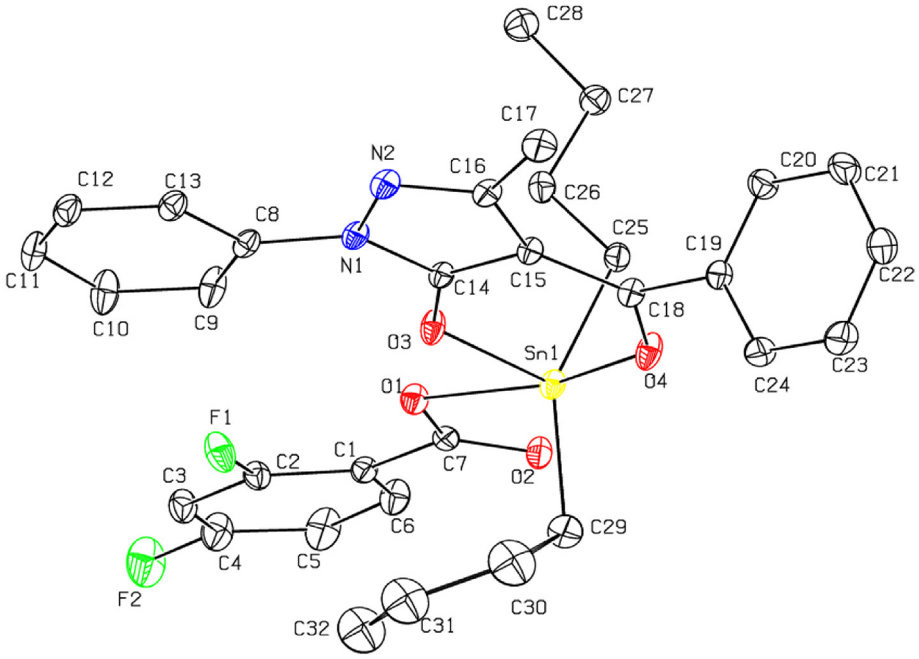


Fig. 2. Molecular structure of **9** showing the labeling scheme of the non-H atoms. Selected bond lengths (Å) and angles (°): Sn(1)–O(1) 2.161(3), Sn(1)–O(2) 2.741(3), Sn(1)–O(3) 2.350(2), Sn(1)–O(4) 2.091(3), Sn(1)–C(25) 2.102(4), Sn(1)–C(29) 2.114(5), O(1)–C(7) 1.262(5), O(2)–C(7) 1.223(5), O(3)–C(14) 1.289(4), O(4)–C(18) 1.254(5), C(25)–Sn(1)–C(29) 151.44(18), O(1)–Sn(1)–O(3) 77.42(10), O(1)–Sn(1)–O(4) 157.18(11), O(3)–Sn(1)–O(4) 79.98(10), O(1)–Sn(1)–C(25) 99.36(14), O(1)–Sn(1)–C(29) 97.66(17).

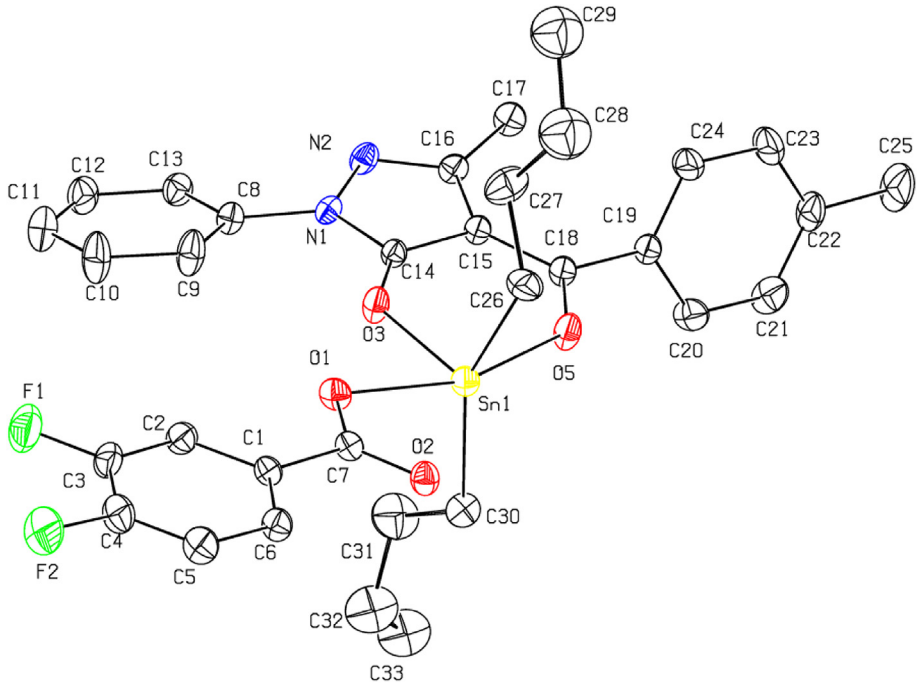


Fig. 3. Molecular structure of **17** showing the labeling scheme of the non-H atoms. Selected bond lengths (Å) and angles (°): Sn(1)–O(1) 2.161(4), Sn(1)–O(2) 2.737(4), Sn(1)–O(3) 2.102(3), Sn(1)–O(5) 2.326(4), Sn(1)–C(26) 2.075(6), Sn(1)–C(30) 2.121(5); C(26)–Sn(1)–C(30) 152.4(3), C(26)–Sn(1)–O(3) 104.6(2), O(3)–Sn(1)–C(30) 101.09(19), C(26)–Sn(1)–O(1) 98.2(3), O(3)–Sn(1)–O(1) 76.74(13), C(30)–Sn(1)–O(1) 97.3(2), C(26)–Sn(1)–O(5) 86.9(3), O(3)–Sn(1)–O(5) 80.16(13), C(30)–Sn(1)–O(5) 87.7(2), O(1)–Sn(1)–O(5) 156.89(14).

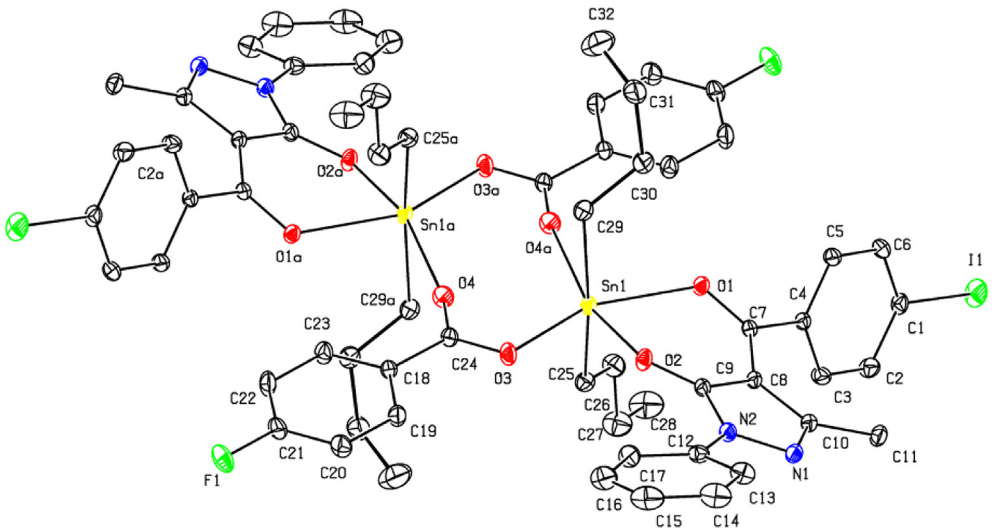


Fig. 4. Molecular structure of **8** showing the labeling scheme of the non-H atoms. Selected bond lengths (Å) and angles (°): Sn(1)–O(1) 2.337(2), Sn(1)–O(2) 2.122(2), Sn(1)–O(3) 2.173(2), Sn(1)–O(4a) 2.649(2), Sn(1)–C(25) 2.116(3), Sn(1)–C(29) 2.108(3), O(1)–C(7) 1.262(3), O(2)–C(9) 1.276(3), O(3)–C(24) 1.283(4), O(4)–C(24) 1.231(4); C(29)–Sn(1)–C(25) 162.71(15), O(2)–Sn(1)–O(1) 78.56(7), O(3)–Sn(1)–O(1) 155.36(8), O(2)–Sn(1)–O(3) 77.21(8), C(25)–Sn(1)–O(1) 86.47(11), C(29)–Sn(1)–O(1) 92.39(11), C(25)–Sn(1)–O(2) 100.04(12), C(29)–Sn(1)–O(2) 96.63(12), C(25)–Sn(1)–O(3) 93.42(11), C(29)–Sn(1)–O(3) 94.72(12).

are [2.103(2), 2.163(2) Å] and [2.350(2), 2.656(2) Å], respectively. The trend is somewhat similar for some organotin(IV) derivatives [6,29]. The two butyl substituents are found to be disordered owing to high thermal motion. These mixed ligand complexes have two different types of organic ligands, acylpyrazolones and fluorinated benzoic acids. Acylpyrazolone is found to be chelating to tin center through the carboxylic oxygen and the enolic oxygen atom, while fluorinated benzoic acid is monodentate, coordinating to the same tin center through the hydroxylic oxygen atom. The tin(IV) complexes with two different types of chelating ligands are very rare [21,29].

Complex **8** is a centrosymmetric dimmer built around an eight-membered $Sn_2O_4C_2$ macrocycle with one type of six-coordinated tin atom (Fig. 4). It features 2-fold linkages of neighboring units via intermolecular weaker contacts (Sn1—O4a) (2.649(2) Å), giving rise to the formation of dimeric tin aggregates. In fact, in complex **8**, there is a bidentate acylpyrazolone ligand chelating to every tin atom, and the monodentate fluorinated benzoic acid ligand is

coordinated to tin center by hydroxylic oxygen, while carboxylic oxygen from fluorinated benzoic acid ligand contacts neighboring tin atom to form the interesting structure. Other band lengths and angles around tin are, in general, close to the corresponding values found in the dibutyltin(IV) biscarboxylates [$Bu_2Sn(L)_2$] [30] or bispyrazolones [$R_2Sn(A)_2$] [31,32].

To the best of our knowledge, no such mixed ligand dibutyltin(IV) complexes containing both monodentate benzoate and bidentate O-donors acylpyrazolone as supporting ligands have ever been reported, thus, complexes **1**, **8**, **9** and **17** are unusual.

2.4. In vitro antitumor activity assays

In order to obtain the information about the antitumor activity of this type of organotin compounds, all of the synthesized mixed ligand dibutyltin(IV) complexes (**1**–**21**) were screened against two human cancer cell lines (KB and Hela) for preliminary *in vitro* antitumor activity by means of the MTT assay with cisplatin as a positive reference compound. As shown in Table 1, all of them exhibit rather promising *in vitro* antitumor activities since their IC_{50} values against two human tumor cell lines, KB and Hela, have been found below 0.55 μM. These results are significantly better than the values of 2.65 μM for KB and above 50 μM for Hela found for cisplatin [33]. All complexes showed a strong antiproliferative activity against the two tumor cell lines being that exhibit an antiproliferative activity range between 0.29 and 0.54 μM for KB and 0.05–0.31 μM for Hela. It may be due to having similar coordinate environment, and such mixed ligand dibutyltin(IV) complexes can be liable to stepwise dissociation *in vivo* [6,15d,21], which might increase the antitumor activity.

Based on the data analysis, we could also recognize as follows: (i) for all twenty one mixed-ligand dibutyltin(IV) complexes, they tend to be more effective towards Hela, exhibiting better activity against Hela in comparison with KB; (ii) complex **2** containing acetylpyrazolone and 4-fluorobenzote ligands is the most active one (IC_{50} = 0.05 μM) against Hela, what suggests that acetyl from acylpyrazolone and para-fluorobenzoate ligand may play a key role for increasing their activity; (iii) although we introduced different acyl groups and number of fluorine atoms into the compounds, variation of the these groups results only in minor differences of antitumor activity, and no conclusive structure–activity relationships in the activity can be deduced in this respect.

Table 1
The *in vitro* antitumor activity of the complexes (**1**–**21**) against two human cancer cell lines (KB and Hela) and normal human cervical epithelial cells (HCvEpCs) (n = 3).

Complex	R	R′	IC_{50} (μM)		
			KB	Hela	HCvEpCs
$Bu_2SnA_1L_1$ (**1**)	C_6H_5	4-F	0.31	0.14	
$Bu_2SnA_2L_1$ (**2**)	CH_3	4-F	0.35	0.05	0.26
$Bu_2SnA_3L_1$ (**3**)	4-$CH_3C_6H_4$	4-F	0.36	0.26	
$Bu_2SnA_4L_1$ (**4**)	4-$CF_3C_6H_4$	4-F	0.32	0.13	
$Bu_2SnA_5L_1$ (**5**)	4-FC_6H_4	4-F	0.34	0.28	
$Bu_2SnA_6L_1$ (**6**)	4-ClC_6H_4	4-F	0.38	0.18	
$Bu_2SnA_7L_1$ (**7**)	4-BrC_6H_4	4-F	0.54	0.16	
$Bu_2SnA_8L_1$ (**8**)	4-IC_6H_4	4-F	0.31	0.23	
$Bu_2SnA_1L_2$ (**9**)	C_6H_5	2,4-F_2	0.29	0.23	
$Bu_2SnA_3L_2$ (**10**)	4-$CH_3C_6H_4$	2,4-F_2	0.44	0.31	
$Bu_2SnA_4L_2$ (**11**)	4-$CF_3C_6H_4$	2,4-F_2	0.51	0.24	
$Bu_2SnA_5L_2$ (**12**)	4-FC_6H_4	2,4-F_2	0.39	0.20	
$Bu_2SnA_6L_2$ (**13**)	4-ClC_6H_4	2,4-F_2	0.37	0.21	
$Bu_2SnA_7L_2$ (**14**)	4-BrC_6H_4	2,4-F_2	0.49	0.25	
$Bu_2SnA_1L_3$ (**15**)	C_6H_5	3,4-F_2	0.54	0.08	
$Bu_2SnA_2L_3$ (**16**)	CH_3	3,4-F_2	0.49	0.15	
$Bu_2SnA_3L_3$ (**17**)	4-$CH_3C_6H_4$	3,4-F_2	0.46	0.28	
$Bu_2SnA_4L_3$ (**18**)	4-$CF_3C_6H_4$	3,4-F_2	0.34	0.15	
$Bu_2SnA_5L_3$ (**19**)	4-FC_6H_4	3,4-F_2	0.35	0.18	
$Bu_2SnA_6L_3$ (**20**)	4-ClC_6H_4	3,4-F_2	0.32	0.18	
$Bu_2SnA_7L_3$ (**21**)	4-BrC_6H_4	3,4-F_2	0.45	0.14	
cisplatin			2.65 [33]	>50	

Table 2
The percentages of apoptosis of in different concentrations with cisplatin as positive control.

Complex	Concentrations (μM)	Q2 (later apoptosis and necrotic cell)	Q4 (early apoptosis)	Total percentage
Control		4.0	3.3	7.3
2	0.05	3.5	3.6	7.1
	1.0	12.2	5.5	17.7
	2.5	16.8	4.9	21.7
Cisplatin	1.0	4.3	3.4	7.7
	2.5	4.3	3.0	7.3

To gain more insights into the possible *in vitro* cytoselectivity of **2** with the highest cytotoxicity for Hela tumor cell lines, MTT assays were also performed in normal human cervical epithelial cells (HCvEpCs) (Table 1). **2** shows the lower cytotoxic activity in the normal human cervical epithelial cell line (IC_{50} = 0.26 μM) than in Hela tumor cell line (IC_{50} = 0.05 μM), which demonstrates the slight specificity for this type of tumor cell and is a positive feature for further development.

2.5. Cell apoptosis analysis by flow cytometry

To gain more insights relative to the antitumor mechanism, compound **2** with good activities was chosen for further experiments. Since Hela cells appeared to be the more sensitive ones to the tested compounds, we carried out flow cytometry assays to determine the apoptosis level of Hela cells exposed to compound **2**.

Early stages of apoptosis are characterized by perturbations in the cellular membrane. It leads to a redistribution of phosphatidylserine (PS) to the external side of the cell membrane, which causes a Ca flux. Annexin V is a Ca-dependent phospholipids binding protein with high affinity for PS. Therefore, fluorescently labeled annexin V can be used to identify early apoptosis cells. Late apoptosis and necrotic cells have lost membrane integrity, and can be stained by propidium iodide (PI). The percentage of apoptosis was presented in Table 2 and Fig. 5 by the region Q4 (early apoptosis) and Q2 (late apoptosis and necrotic cell) and total percentages of apoptosis.

We can see that the total apoptosis percentages of the positive control are 7.7 and 7.3% at the concentration of 1.0 and 2.5 μM, respectively, and nearly equal to the negative control (ca. 7.3%). This indicates cisplatin induced little apoptosis. Probably, for cisplatin, the action mechanism relative to the antitumor activity is not due to cell apoptosis [34]. Complex **2**, at low concentrations (0.05 μM) does not induce apoptosis in Hela cells. With the increase of the concentration of **2**, the apoptosis induction obviously increased. The total apoptosis percentages are 17.7 and 21.7% at the concentration of 1.0 and 2.5 μM, respectively, which is higher than the positive or negative control. These data show complex **2** is able to induce Hela cancer cell apoptosis to some extent, which might partially correlate with the strong antitumor activity of complex **2**. Nevertheless, generalizations have to be taken cautiously before further investigation results have been shown.

3. Conclusions

We have firstly synthesized a series of novel mixed ligand dibutyltin(IV) complexes that combine acylpyrazolone and

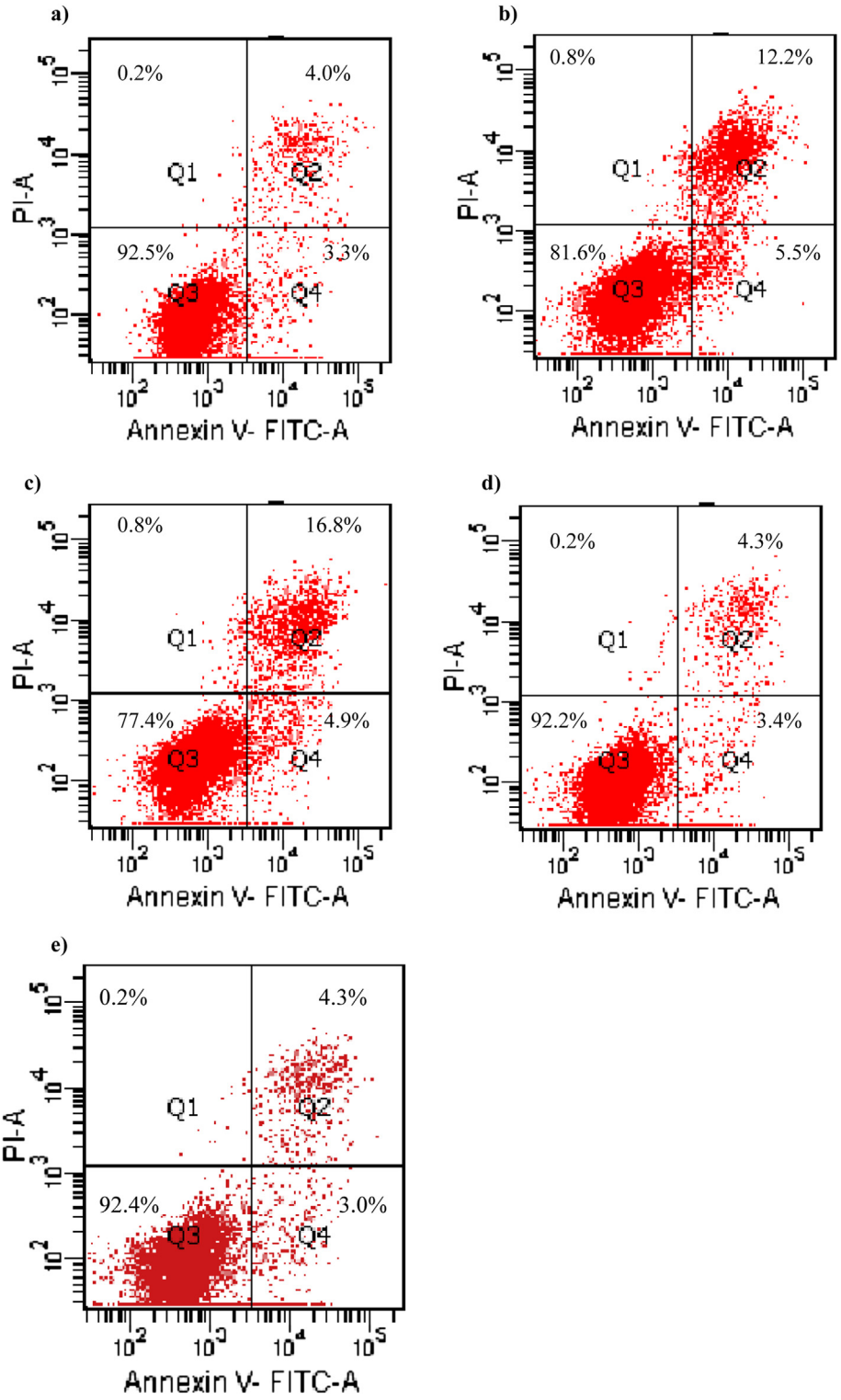


Fig. 5. Apoptosis detection in Hela cells using the Annexin V assay after 24 h. The total percentage of apoptotic cells was considered as Q2+Q4. Plot presents the fluorescence data of propidium iodide (PI) and Annexin V fluoresce in corresponding to (a) 7.3% (control), (b) 17.7% (1.0 μM, **2**), (c) 21.7% (2.5 μM, **2**), (d) 7.7% (1.0 μM, cisplatin), (e) 7.3% (2.5 μM, cisplatin).

fluorinated benzoate ligands, which were fully characterized by elemental analysis, IR, ^{1}H, ^{13}C, ^{119}Sn NMR, and in four cases by X-ray single-crystal diffraction analysis. Their activities were checked against two human tumor cell lines (KB and Hela). All of them are highly cytotoxic compared with cisplatin, with IC_{50} values ranging from 0.05 to 0.54 μM. Between the two human tumor cell lines, Hela cells appeared to be more sensitive to these mixed ligand dibutyltin(IV) complexes than KB. To gain further insights into the mode of action, Hela cancer cell apoptosis-induced by **2** was examined by flow cytometry analysis by means of cell staining with propidium iodide and annexin V FITC. The preliminary results showed that **2** can induce the apoptosis to some extent at

concentrations of more than 1.0 μM, most probably indicating that the antitumor mechanism of such type of complexes partially correlates to the apoptosis mechanism.

4. Experimental section

4.1. Materials and physical measurements

$^{n}Bu_2SnO$ was purchased from Aldrich and used as received. All the other reagents used in the reactions were of analytical grade (Sinopharm Chemical Reagent Co., Ltd., China). The ligands (HA) were prepared according to the previous methods [35]. Elemental analyses were performed on PE-2400-II elemental analyzer. Melting points were determined by X-5 digital melting-point apparatus. IR spectra in the range 4000–400 cm^{-1} were recorded on a Perkin Elmer FT-IR spectrophotometer with samples investigated as KBr discs. ^{1}H, ^{13}C, ^{119}Sn NMR spectra were recorded on a Bruker AM-400 spectrometer (400.0 MHz for ^{1}H, 100.0 MHz for ^{13}C) and a Varian INOVA 600 spectrometer (223.6 MHz for ^{119}Sn) at ambient temperature [δ values in ppm relative to Me_4Si (^{1}H, ^{13}C) or Me_4Sn (^{119}Sn)].

4.2. Synthesis of the dibutyltin(IV) complexes Bu_2SnAL

The detailed methodology for the preparation of mixed ligand di-n-butyltin(IV) complexes [Bu_2SnAL] is described below.

4.2.1. Synthesis of [$Bu_2Sn(A_1)(L_1)$] (**1**)

To a methanol solution (20 ml) of HA_1 (1.0 mmol) and HL_1 (1.0 mmol) was added Bu_2SnO (1.0 mmol). The mixture was refluxed overnight, and then a clear solution was obtained. On removing the excess of solvent under reduced pressure at 50 °C, the pale yellow crystals were isolated which was purified by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 80%. M.p. 118–120 °C. Anal. Calc. for $C_{32}H_{35}FN_2O_4Sn$ (649.31): C 59.19; H 5.43; N 4.31. Found C 59.20, H 5.40, N 4.18. IR (KBr): ν = 1600 s, 1378 s (C=O and OCO), 542 m, 506 s (Sn–C), 425 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ = 0.70–0.88 (br, 6H, δ-H), 1.26–1.43 (br, 4H, γ-H), 1.59–1.85 (m, 11H, α-H, β-H, H-7), 7.13–8.14 (m, 14H, $-C_6\underline{H}_5$, 4-$FC_6\underline{H}_4$–, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$), δ = 174.6 (CO), 162.9 (C-3), 149.4 (C-5), 104.8 (C-4), 16.5 (C-7), phenyl rings skeleton: 167.2, 164.7, 138.4, 133.0, 132.9, 131.4, 129.0, 128.6, 127.8, 127.5, 125.9, 121.0, 115.5, 115.3 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$), δ = −148.6, −232.5, 356.9 ppm.

4.2.2. Synthesis of [$Bu_2Sn(A_2)(L_1)$] (**2**)

Compound **2** was prepared analogously by following the method and conditions described for **1** using HA_2 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The white crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 66%. M.p. 137–139 °C. Anal. Calc. for $C_{27}H_{33}FN_2O_4Sn$ (587.26): C 55.22; H 5.66; N 4.77. Found C 55.22, H 5.56, N 4.73. IR (KBr): ν = 1602 s, 1383 s(C=O and OCO), 544 m, 498 s (Sn–C), 451 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ = 0.73–0.90 (m, 6H, δ-H), 1.32–1.72 (m,12H, α-H, β-H, γ-H), 2.46, 2.38 (d, 6H, 2$C\underline{H}_3$), 7.12–8.13 (m, 9H, 4-$FC_6\underline{H}_4$–, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$), δ = 174.2 (CO), 161.7 (C-3), 148.7 (C-5), 104.6 (C-4), 17.0 (C-7), 27.8 (CH_3) ppm. Phenyl rings skeleton: 166.9, 164.4, 132.7, 132.6, 128.8, 128.7, 126.0, 125.4, 120.9, 115.3, 115.1 ppm. Sn–^{n}Bu skeleton: 13.6 (δ-C), 26.3 (β-C), 26.7 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$), δ = −148.4, −232.8, −357.7 ppm.

4.2.3. Synthesis of [$Bu_2Sn(A_3)(L_1)$] (**3**)

Compound **3** was prepared analogously by following the method and conditions described for **1** using HA_3 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow crystals was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 77%. M.p. 138–140 °C. Anal. Calc. for $C_{33}H_{37}FN_2O_4Sn$ (663.37): C 59.75; H 5.62; N 4.22. Found C 59.88, H 5.62, N 4.13. IR (KBr): ν = 1600 s, 1377 s(C=O and OCO), 545 m, 522 s, 505 s (Sn–C), 423 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ = 0.69–0.91 (m, 6H, δ-H), 1.24–1.43 (br, 4H, α-H), 1.56–1.92 (m, 11H, β-H, γ-H, H-7), 2.45 (s, 3H, 4-CH_3), 7.13–8.14 (m, 13H, 4-$CH_3C_6\underline{H}_4$, 4-$FC_6\underline{H}_4$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$), δ = 174.5 (CO), 162.8 (C-3), 149.4 (C-5), 104.7 (C-4), 16.7 (C-7), 21.7 (4-$\underline{C}H_3$-ph) ppm. Phenyl rings skeleton: 167.2, 164.6, 138.5, 132.9, 132.8, 130.5, 129.2, 129.0, 128.2, 127.6, 125.8, 121.0, 115.5, 115.3 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$), δ = −148.8, −233.3, 357.8 ppm.

4.2.4. Synthesis of [$Bu_2Sn(A_4)(L_1)$] (**4**)

Compound **4** was prepared analogously by following the method and conditions described for **1** using HA_4 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow powder was obtained by recrystallization from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 42%. M.p. 158–160 °C. Anal. Calc. for $C_{33}H_{34}F_4N_2O_2Sn$ (717.34): C 55.25; H 4.78; N 3.91. Found C 55.57, H 4.64, N 4.35. IR (KBr): ν = 1601 s(C=O and OCO), 553 w, 506 s (Sn–C), 463 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ = 0.74–0.92 (br, 6H, δ-H), 1.28–1.43 (br, 4H, γ-H), 1.59–1.82 (m, 11H, α-H, β-H, H-7), 7.13–8.14 (m, 13H, 4-$CF_3C_6\underline{H}_4$, 4-$FC_6\underline{H}_4$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$), δ = 174.8 (CO), 162.9 (C-5), 149.1 (C-3), 104.9 (C-4), 16.7 (C-7), 122.4 (ph-$\underline{C}F_3$) ppm. Phenyl rings skeleton: 167.3, 164.7, 138.2, 133.0, 132.9, 129.1, 128.1, 127.2, 125.7, 121.2, 115.6, 115.4 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$), δ = −148.6, −230.6, 351.5 ppm.

4.2.5. Synthesis of [$Bu_2Sn(A_5)(L_1)$] (**5**)

Compound **5** was prepared analogously by following the method and conditions described for **1** using HA_5 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The milk-yellow solid was recrystallized from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 90%. M.p. 124–126 °C. Anal. Calc. for $C_{32}H_{34}F_2N_2O_4Sn$ (667.33): C 57.59; H 5.14; N 4.20. Found C 57.76, H 5.32, N 3.91. IR (KBr): ν = 1601 s, 1379 s (C=O and OCO), 545 m, 509 s (Sn–C), 454 s, 424 m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.69–0.90 (m, 6H, δ-H), 1.26–1.43 (br, 4H, γ-H), 1.57–1.89 (m, 11H, α-H, β-H, H-7), 7.11–8.14 (m, 13H, 2(4-$FC_6\underline{H}_4$), N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.6 (CO), 162.8 (C-3), 149.0 (C-5), 104.8 (C-4), 16.7 (C-7) ppm. Phenyl rings skeleton: 167.2, 166.1, 164.7, 163.6, 138.3, 133.0, 132.9, 130.5, 130.4, 129.1, 127.3, 126.0, 121.0, 115.9, 115.6, 115.5, 115.3 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −148.7, −231.9, 355.9 ppm.

4.2.6. Synthesis of [$Bu_2Sn(A_6)(L_1)$] (**6**)

Compound **6** was prepared analogously by following the method and conditions described for **1** using HA_6 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The bright yellow crystals was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 85%. M.p. 130–132 °C. Anal. Calc. for $C_{32}H_{34}FClN_2O_4Sn$ (683.78): C 56.21; H 4.01, N 4.10. Found C 55.95, H 5.07, N 4.06. IR (KBr): ν = 1600 s, 1378 s (C=O and OCO), 562 m, 505 s (Sn–C), 474 s 420 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.74–0.92 (br, 6H, δ-H), 1.28–1.42 (br, 4H, γ-H), 1.61–1.79 (br, 8H, α-H, β-H), 1.90 (s, 3H, 7-H), 7.13–8.14 (m, 13H, 4-$ClC_6\underline{H}_4$, 4-$FC_6\underline{H}_4$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.7 (CO), 162.8 (C-3), 149.0 (C-5), 104.8 (C-4), 16.8 (C-7) ppm. Phenyl rings skeleton:

167.2, 164.7, 138.3, 137.8, 133.0, 132.9, 131.8, 129.5, 129.1, 128.9, 128.7, 127.3, 125.9, 121.0, 115.6, 115.3 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −148.4, −231.6, 353.8 ppm.

4.2.7. Synthesis of [$Bu_2Sn(A_7)(L_1)$] (**7**)

Compound **7** was prepared analogously by following the method and conditions described for **1** using HA_7 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The gray solid was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 21%. M.p. 132–134 °C. Anal. Calc. for $C_{32}H_{34}FBrN_2O_4Sn$ (728.24): C 52.78; H 4.71; N 3.85. Found C 52.76, H 4.67, N 3.68. IR (KBr): ν = 1600 s, 1385 s (C=O and OCO), 547 w, 506 s (Sn–C), 447 s, 428 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.72–0.92 (br, 6H, δ-H), 1.27–1.41 (br, 4H, γ-H), 1.64–1.77 (br, 8H, α-H, β-H), 1.90 (s, 3H, H-7), 7.13–8.14 (m, 13H, 4-Br$C_6\underline{H}_4$, 4-F$C_6\underline{H}_4$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.6 (CO), 162.8 (C-3), 149.0 (C-5), 104.8 (C-4), 16.8 (C-7) ppm. Phenyl rings skeleton: 167.2, 164.7, 138.3, 133.0, 132.9, 131.9, 129.6, 129.1, 127.2, 126.2, 126.0, 121.0, 115.6, 115.4 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −230.5, −353.4 ppm.

4.2.8. Synthesis of [$Bu_2Sn(A_8)(L_1)$] (**8**)

Compound **8** was prepared analogously by following the method and conditions described for **1** using HA_8 (1.0 mmol), HL_1 (1.0 mmol) and Bu_2SnO (1.0 mmol). The brown crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 19%. M.p. 118–120 °C. Anal. Calc. for $C_{32}H_{34}FIN_2O_4Sn$ (775.24): C 49.58; H 4.42; N 3.61. Found C 49.51, H 4.39, N 3.53. IR (KBr): ν = 1600 s, 1386 s (C=O and OCO), 543 s, 507 s (Sn–C), 444 s, 425 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.70–0.89 (m, 6H, δ-H), 1.26–1.43 (br, 4H, γ-H), 1.50–1.95 (m, 11H, α-H, β-H, H-7), 7.13–8.16 (m, 13H, 4-I$C_6\underline{H}_4$, 4-F$C_6\underline{H}_4$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.7 (CO), 162.9 (C-3), 149.0 (C-5), 104.7 (C-4), 16.8 (C-7) ppm. Phenyl rings skeleton: 167.2, 164.7, 137.8, 132.9, 132.9, 129.5, 129.1, 127.3, 125.8, 121.0, 115.5, 115.3 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.4 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −149.5, −231.9, −353.5 ppm.

4.2.9. Synthesis of [Bu_2Sn (A_1) (L_2)] (**9**)

Compound **9** was prepared analogously by following the method and conditions described for **1** using HA_1 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 79%. M.p. 113–115 °C. Anal. Calc. for $C_{32}H_{34}F_2N_2O_4Sn$ (667.33): C 57.59; H 5.14; N 4.20. Found C 57.67, H 5.15, N 4.18. IR (KBr): ν = 1600 s, 1378 s (C=O and OCO), 543 m, 512 s (Sn–C), 447 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.71–0.93 (m, 6H, δ-H), 1.28–1.45 (br, 4H, γ-H), 1.58–1.88 (m, 11H, α-H, β-H, H-7), 6.87–8.12 (m, 13H, 2,4-$F_2C_6\underline{H}_3$, –$C_6\underline{H}_5$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.8 (CO), 162.8 (C-3), 149.0 (C-5), 104.8 (C-4), 16.5 (C-7) ppm. Phenyl rings skeleton: 167.1, 166.9, 164.9, 164.7, 164.6, 164.4, 162.3, 162.1, 138.3, 134.9, 134.8, 131.6, 129.1, 128.6, 127.8, 126.1, 120.9, 111.5, 111.3, 105.5, 105.3, 104.9 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −138.3, −228.6, −357.8 ppm.

4.2.10. Synthesis of [Bu_2Sn (A_3) (L_2)] (**10**)

Compound **10** was prepared analogously by following the method and conditions described for **1** using HA_3 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow powder was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 76%. M.p. 128–130 °C. Anal. Calc. for $C_{33}H_{36}F_2N_2O_4Sn$ (681.36): C 58.17; H 5.33; N 4.11. Found C 58.14, H 5.32, N 4.12. IR (KBr): ν = 1601 s, 1376 s (C=O and OCO), 512 m (Sn–C), 441 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.70–0.91 (m, 6H, δ-H), 1.27–1.98 (m, 15H, α-H, β-H, γ-H, 7-H), 2.45 (s, 6H, 2CH_3), 6.86–8.11 (m, 12H, 4-$CH_3C_6\underline{H}_4$, 2,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.7 (CO), 162.7 (C-3), 149.3 (C-5), 104.7 (C-4), 16.6 (C-7), 21.8 (4′-CH_3) ppm. Phenyl rings skeleton: 167.0, 166.9, 164.8, 164.7, 164.5, 164.4, 162.2, 162.1, 138.4, 134.8, 134.7, 130.6, 129.2, 129.0, 128.2, 126.0, 120.9, 111.5, 111.3, 105.5, 105.2, 104.9 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −139.8, −229.8, −358.2 ppm.

4.2.11. Synthesis of [$Bu_2Sn(A_4)$ (L_2)] (**11**)

Compound **11** was prepared analogously by following the method and conditions described for **1** using HA_4 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The milk-yellow solid was obtained by recrystallization from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 40%. M.p. 150–152 °C. Anal. Calc. for $C_{33}H_{33}F_5N_2O_4Sn$ (735.33): C 53.90; H 4.52; N 3.81. Found C 54.11, H 4.66, N 3.95. IR (KBr): ν = 1600 s, 1382 (C=O and OCO), 513 s (Sn–C), 462 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.78–0.93 (br, 6H, δ-H), 1.32–1.44 (br, 4H, γ-H), 1.69–1.84 (br, 11H, α-H, β-H, H-7), 6.88–8.13 (m, 12H, 4-$CF_3C_6\underline{H}_4$, 2,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.1 (CO), 162.8 (C-5), 149.0 (C-3), 104.8 (C-4), 16.6 (C-7), 122.4 (R′-ph-CF_3) ppm. Phenyl rings skeleton: 167.2, 167.1, 164.9, 164.8, 164.6, 164.5, 162.3, 162.2, 138.2, 134.9, 134.8, 129.1, 128.1, 125.7, 125.1, 120.9, 111.6, 111.4, 105.5, 105.3, 105.0 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −138.7, −226.3, −351.7 ppm.

4.2.12. Synthesis of [Bu_2Sn (A_5) (L_2)] (**12**)

Compound **12** was prepared analogously by following the method and conditions described for **1** using HA_5 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 77%. M.p. 122–124 °C. Anal. Calc. for $C_{32}H_{33}F_3N_2O_4Sn$ (685.32): C 56.08; H 4.85; N 4.09. Found C 56.08, H 4.95, N 4.13. IR (KBr): ν = 1601, 1377 s (C=O and OCO), 511 s (Sn–C), 455 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.68–0.94 (br, 6H, δ-H), 1.26–1.45 (br, 4H, γ-H), 1.59–1.92 (m, 11H, α-H, β-H, H-7), 6.87–8.11 (m, 12H, 4-F$C_6\underline{H}_4$, 2,4-$F_2C_6\underline{H}_3$–, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9 (CO), 162.8 (C-5), 148.9 (C-3), 104.7 (C-4), 16.6 (C-7) ppm. Phenyl rings skeleton: 167.1, 166.9, 164.8, 164.7, 164.6, 164.4, 162.2, 162.1, 138.3, 134.9, 134.7, 130.5, 129.0, 126.0, 120.9, 115.8, 115.6, 111.5, 111.3, 105.5, 105.2, 104.9 ppm. Sn–nBu skeleton: 13.6 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −138.7, −228.3, −354.8 ppm.

4.2.13. Synthesis of [Bu_2Sn (A_6) (L_2)] (**13**)

Compound **13** was prepared analogously by following the method and conditions described for **1** using HA_6 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The bright yellow crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 65%. M.p. 119–121 °C. Anal. Calc. for $C_{32}H_{33}F_2ClN_2O_4Sn$ (701.78): C 54.77; H 4.74; N 3.99. Found C 54.85, H 4.86, N 3.68. IR (KBr): ν = 1601 s, 1376 s (C=O and OCO), 561 m, 510 s (Sn–C), 470, 439 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.70–0.92 (br, 6H, δ-H), 1.26–1.44 (br, 4H, γ-H), 1.59–1.95 (m, 11H, α-H, β-H, H-7), 6.87–8.11 (m, 12H, 4-Cl$C_6\underline{H}_4$, 2,4-$F_2C_6\underline{H}_3$–, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9 (CO), 162.6 (C-3), 148.9 (C-5), 104.7 (C-4), 16.9 (C-7) ppm. Phenyl rings skeleton: 167.1, 167.0, 164.9, 164.7, 164.6, 164.5, 162.3, 161.1, 138.3, 134.9, 134.8, 131.8, 129.5, 129.1, 128.9, 128.7, 126.1, 121.0, 111.5, 111.3, 105.5, 105.2, 105.0 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −142.5, −231.1, −353.1 ppm.

*4.2.14. Synthesis of [Bu_2Sn (A_7) (L_2)] (**14**)*

Compound **14** was prepared analogously by following the method and conditions described for **1** using HA_7 (1.0 mmol), HL_2 (1.0 mmol) and Bu_2SnO (1.0 mmol). The bright yellow crystals were obtained by recrystallization from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 24%. M.p. 124–126 °C. Anal. Calc. for $C_{32}H_{33}F_2BrN_2O_4Sn$ (746.23): C 51.50; H 4.46; N 3.75. Found C 51.83, H 4.55, N 3.72. IR (KBr): ν = 1600 s, 1377 (C=O and OCO), 511 s (Sn–C), 444 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.72–0.93 (br, 6H, δ-H), 1.27–1.43 (br, 4H, γ-H), 1.57–1.91 (m, 11H, α-H, β-H, H-7), 6.87–8.11 (m, 12H, 4-Br$C_6\underline{H}_4$, 2,4-$F_2C_6\underline{H}_3$–, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9(CO), 162.8 (C-3), 148.9 (C-5), 104.7 (C-4), 16.7 (C-7) ppm. Phenyl rings skeleton: 167.1, 167.0, 164.9, 164.7, 164.6, 164.5, 162.3, 162.1, 138.2, 134.9, 134.8, 131.2, 129.6, 129.1, 126.1, 121.0, 111.6, 111.5, 111.4, 111.3, 105.5, 105.3, 105.0 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −138.7, −227.7, −353.3 ppm.

*4.2.15. Synthesis of [Bu_2Sn (A_1) (L_3)] (**15**)*

Compound **15** was prepared analogously by following the method and conditions described for **1** using HA_1 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The white solid was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 89%. M.p. 129–131 °C. Anal. Calc. for $C_{32}H_{34}F_2N_2O_4Sn$ (667.33): C 57.59; H 5.14; N 4.20. Found C 57.65, H 5.18, N 4.15. IR (KBr): ν = 1600 s, 1386 s (C=O and OCO), 551 m, 508 s (Sn–C), 438 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.75–0.91 (br, 6H, δ-H), 1.26–1.42 (br, 4H, γ-H), 1.58–1.87 (m, 11H, α-H, β-H, H-7), 7.19–8.12 (m, 13H, $-C_6\underline{H}_5$, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.2 (CO), 162.8 (C-5), 149.4 (C-3), 104.8 (C-4), 16.5 (C-7) ppm. Phenyl rings keleton: 155.0, 154.8, 152.4, 152.3, 151.4, 151.3, 148.9, 148.8, 138.3, 131.6, 129.0, 128.6, 127.8, 127.2, 126.1, 121.0, 119.7, 119.6, 117.3, 117.1 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −142.9, −229.2, −357.4 ppm.

*4.2.16. Synthesis of [Bu_2Sn (A_2) (L_3)] (**16**)*

Compound **16** was prepared analogously by following the method and conditions described for **1** using HA_2 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The white solid was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 81%. M.p. 139–141 °C. Anal. Calc. for $C_{32}H_{32}F_2N_2O_4Sn$ (605.26): C 53.58; H 5.33; N 4.63. Found C 53.41, H 5.38, N 4.62. IR (KBr): ν = 1604 s, 1376 s (C=O and OCO), 563 m, 535 s, 507 s (Sn–C), 450 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.76–0.85 (br, 6H, δ-H), 1.36–1.41 (br, 4H, γ-H), 1.59–1.67 (br, 8H, α-H, β-H), 2.45–2.48 (d, 6H, $2CH_3$-), 7.18–8.07 (m, 8H, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.8 (CO), 161.8 (C-3), 148.9 (C-5), 104.7 (C-4), 17.1 (C-7), 27.8 (-$\underline{C}H_3$) ppm. Phenyl rings skeleton: 154.8, 154.7, 152.3, 152.2, 151.4, 151.3, 148.8, 138.1, 128.9, 127.1, 127.1, 127.0, 126.2, 121.0, 119.6, 119.5, 117.2, 117.0 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.4 (β-C), 26.8 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −143.2, −229.5, −357.0 ppm.

*4.2.17. Synthesis of [Bu_2Sn (A_3) (L_3)] (**17**)*

Compound **17** was prepared analogously by following the method and conditions described for **1** using HA_3 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow crystals were obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 82%. M.p. 144–146 °C. Anal. Calc. for $C_{33}H_{36}F_2N_2O_4Sn$ (681.36): C 58.17; H 5.33; N 4.11. Found C 58.44, H 5.51, N 3.84. IR (KBr): ν = 1599 s, 1385 s (C=O and OCO), 557 m, 514 s (Sn–C), 444 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.69–0.95 (br, 6H, δ-H), 1.25–1.45 (br, 4H, γ-H), 1.54–1.79 (br, 8H, α-H, β-H), 1.93 (s, 3H, H-7), 2.45 (s, 3H, 4-$C\underline{H}_3C_6H_4$), 7.19–8.12 (m, 12H, 4-$CH_3C_6\underline{H}_4$, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.1 (CO), 162.8 (C-5), 148.3 (C-3), 104.7 (C-4), 16.6 (C-7), 21.7 (R′-CH_3) ppm. Phenyl rings skeleton: 154.9, 154.8, 152.4, 152.3, 151.4, 151.3, 148.9, 148.8, 138.3, 129.2, 129.0, 128.3, 127.2, 127.1, 126.2, 121.0, 119.7, 119.5, 117.3, 117.1 ppm. Sn–nBu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0(α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −143.2, −230.5, −359.9 ppm.

*4.2.18. Synthesis of [Bu_2Sn (A_4) (L_3)] (**18**)*

Compound **18** was prepared analogously by following the method and conditions described for **1** using HA_4 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow solid was obtained by recrystallization from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 38%. M.p. 158–160 °C. Anal. Calc. for $C_{33}H_{33}F_5N_2O_2Sn$ (735.33): C 53.90; H 4.52; N 3.81. Found C 53.90, H 4.50, N 3.83. IR (KBr): ν = 1601 s, 1386 s (C=O and OCO), 560 s, 509 s (Sn–C), 463 s, 437 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.75–0.83 (br, 6H, δ-H), 1.29–1.37 (br, 4H, γ-H), 1.63–1.84 (m,11H, α-H, β-H, H-7), 7.20–8.07 (m, 12H, 4-$CF_3C_6\underline{H}_4$–, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.5 (CO), 162.9 (C-3), 149.1 (C-5), 104.9 (C-4), 16.6 (C-7), 122.4 (ph-$\underline{C}F_3$) ppm. Phenyl rings skeleton: 155.1, 154.9, 152.5, 152.4, 151.5, 151.3, 149.0, 148.8, 138.2, 129.1, 128.5, 128.1, 127.3, 127.2, 125.7, 125.2, 121.1, 119.8, 119.6, 117.3, 117.2 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 27.0 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −142.9, −227.4, −351.7 ppm.

*4.2.19. Synthesis of [Bu_2Sn (A_5) (L_3)] (**19**)*

Compound **19** was prepared analogously by following the method and conditions described for **1** using HA_5 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The milk-white solid was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 82%. M.p. 135–137 °C. Anal. Calc. for $C_{32}H_{33}F_3N_2O_4Sn$ (685.32): C 56.08; H 4.85; N 4.09. Found C 56.13, H 4.95, N 4.11. IR (KBr): ν = 1601 s, 1386 s (C=O and OCO), 557 m, 511 s (Sn–C), 454 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.74–0.92 (br, 6H, δ-H), 1.28–1.43 (br, 4H, γ-H), 1.59–1.78 (m, 8H, α-H, β-H), 1.91 (s, 3H, H-7), 7.17–8.07 (m, 12H, 4-$FC_6\underline{H}_4$–, 3,4-$F_2C_6\underline{H}_3$, N–C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.0 (CO), 162.6 (C-3), 148.9 (C-5), 104.6 (C-4), 16.5 (C-7) ppm. Phenyl rings skeleton: 166.0, 163.5, 154.9, 154.7, 152.3, 152.2, 151.3, 151.2, 148.8, 148.7, 138.1, 130.4, 130.3, 128.9, 128.5, 127.1, 127.0, 126.0, 120.9, 119.6, 119.4, 117.2, 117.0, 115.7, 115.5 ppm. Sn–^{n}Bu skeleton: 13.5 (δ-C), 26.2 (β-C), 26.8 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −143.0, −229.4, −355.8 ppm.

*4.2.20. Synthesis of [Bu_2Sn (A_6) (L_3)] (**20**)*

Compound **20** was prepared analogously by following the method and conditions described for **1** using HA_6 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The white solid was obtained by recrystallization from dichloromethane/methanol mixture and dried in vacuo. Yield: 53%. M.p. 132–134 °C. Anal. Calc. for $C_{32}H_{33}F_2ClN_2O_4Sn$ (701.78): C 54.77; H 4.74; N 3.99. Found C 54.74, H 4.96, N 3.50. IR (KBr): ν = 1598 s, 1384 s (C=O and OCO), 558 m, 513 w (Sn–C), 471 s, 440 s (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.74–0.91 (br, 6H, δ-H), 1.28–1.47 (br, 4H, γ-H), 1.57–1.77 (m, 8H, α-H, β-H), 1.91 (s, 3H, H-7), 7.22–8.07 (m, 12H, 4-$ClC_6\underline{H}_4$–, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$) δ = 174.5, 173.1 (CO), 162.7 (C-3), 149.0 (C-5), 104.7 (C-4), 16.7 (C-7) ppm. Phenyl rings skeleton: 155.0, 154.9, 152.5, 151.3, 148.9, 139.5, 138.2, 137.9, 131.3, 129.5, 129.1, 128.9, 128.4, 127.3, 126.1, 121.0, 119.7, 117.2 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −144.5, −229.2, −353.4 ppm.

*4.2.21. Synthesis of [Bu_2Sn (A_7) (L_3)] (**21**)*

Compound **21** was prepared analogously by following the method and conditions described for **1** using HA_7 (1.0 mmol), HL_3 (1.0 mmol) and Bu_2SnO (1.0 mmol). The pale yellow solid was

obtained by recrystallization from dichloromethane/n-hexane mixture and dried in vacuo. Yield: 19%. M.p. 140–142 °C. Anal. Calc. for $C_{32}H_{33}F_2BrN_2O_4Sn$ (746.23): C 51.50; H 4.46; N 3.75. Found C 51.43, H 4.60, N 3.65. IR (KBr): ν = 1598 s, 1385 s (C═O and OCO), 558 m, 509 s (Sn–C), 446 w (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.72–0.88 (br, 6H, δ-H), 1.24–1.44 (br, 4H, γ-H), 1.66–1.74 (m, 8H, α-H, β-H, 7-H), 1.91 (s, 3H, H-7), 7.20–8.03 (m, 12H, 4-Br$C_6\underline{H}_4$–, 3,4-$F_2C_6\underline{H}_3$, N–$C_6\underline{H}_5$) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.3 (CO), 162.8 (C-3), 149.0(C-5), 104.7 (C-4), 16.7 (C-7) ppm. Phenyl rings skeleton: 155.0, 154.9, 152.5, 151.4, 151.3, 148.9, 138.3, 131.9, 129.6, 129.1, 128.6, 127.3, 126.2, 121.0, 119.7, 119.6, 117.3, 117.1 ppm. Sn–^{n}Bu skeleton: 13.7 (δ-C), 26.3 (β-C), 26.9 (α-C, γ-C) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −142.9, −228.7, −353.7 ppm.

4.3. X-ray crystallography

Suitable single crystals of the complexes **1**, **8**, **9** and **17** were mounted in glass capillaries for X-ray structural analysis. Diffraction data were collected on a Bruker SMART CCD diffractometer with Mo Ka (λ = 0.71073 Å) radiation at room temperature. During the intensity data collection, no significant decay was observed. The intensities were collected for Lorentz-polarization effects and empirical absorption with the SADABS program. The structure was solved by direct methods using the SHELXL-97 program. All non-hydrogen atoms were found from the difference Fourier syntheses. The H atoms were included in calculated positions with isotropic thermal parameters related to those of the supporting carbon atoms but were not included in the refinement. All calculations were performed using the Bruker Smart program [36]. Crystallographic details are reported in Table 3.

4.4. In vitro cytotoxic activity

The following cell lines were used for biological assays: human nasopharyngeal carcinoma (KB) and human cervical carcinoma cell line (Hela) cell lines and normal human cervical epithelial cells (HCvEpCs). KB and Hela were grown and maintained in RPMI-1640 medium (Zhejiang Tianhang Biological Technology Co., Ltd., China) supplemented with 10% fetal bovine serum (Thermo Fisher Scientific Biochemical reagent Co., Ltd., China), penicillin (100 U/ml), and streptomycin (100 mg/ml) at 37 °C in humidified incubators in an atmosphere of 5% CO_2. HCvEpCs was grown and maintained in epibasal medium with 5% epi-growth supplement (Cell Applications Inc., USA) at 37 °C in humidified incubators in an atmosphere of 5% CO_2.

The complexes were dissolved in DMSO at a concentration of 10 mM as stock solution, and diluted in culture medium at concentrations of 2.0, 1.0, 0.5, 0.25 and 0.125 μM as working solution. To avoid DMSO toxicity, the concentration of DMSO was less than 0.1%(v/v) in all experiments [37].

The cells harvested from the exponential phase were seeded equivalently into a 96-well plate, 24 h later, added new culture medium to replace the previous and then the complexes were added to the wells to achieve final concentrations. Control wells were prepared by addition of culture medium. Wells without culture medium and cells were used as blanks. All experiments were performed in triplicate. The MTT assay was performed as described by Mosmann [38]. Upon completion of the incubation for 48 h, stock MTT dye solution (20 μl, 5 mg/ml) was added to each well. After 4 h incubation, DMSO (150 μl) was added to solubilize the MTT formazan. The OD of each well was measured on a microplate spectrophotometer at a wavelength of 492 nm. The IC_{50} value was determined from plot of 50% viability against dose of compounds added.

4.5. Cell death by flow cytometry

Hela cells were seeded in sterile twelve-well plates at density of 1×10^6 and grown in 5% CO_2 at 37 °C. After 24 h incubation, cells were exposed to **2** and cisplatin for 24 h at concentrations of 1.0 μM and 2.5 μM. Then the solutions with compound **2** or cisplatin were washed by cold PBS and harvested by trysinisation and collected by

Table 3
Experimental data for crystallographic analyses for compounds **1, 8, 9** and **17**.

Compound	1	8	9	17
Formula	$C_{32}H_{35}FN_2O_4Sn$	$C_{32}H_{34}FIN_2O_4Sn$	$C_{32}H_{34}F_2N_2O_4Sn$	$C_{33}H_{36}F_2N_2O_4Sn$
M (g mol^{-1})	649.31	775.20	667.30	681.33
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Space group	P-1	P-1	P-1	P-1
a (Å)	9.6987(8)	10.2631(10)	9.9927(14)	9.8040(14)
b (Å)	11.2307(9)	13.6590(14)	11.1439(15)	11.5799(17)
c (Å)	14.9526(12)	14.0654(14)	14.935(2)	15.492(2)
α (deg)	78.3050(10)	108.659(2)	77.935(2)	81.366
β (deg)	79.0880(10)	108.875(2)	77.339(2)	74.474
γ (deg)	74.1170(10)	104.042(2)	73.310(2)	78.498
V (Å^3)	1518.4(2)	1630.6(3)	1535.3(4)	1651.8(4)
Z	2	2	2	2
ρ (g cm^{-3})	1.420	1.579	1.444	1.370
μ (mm^{-1})	0.885	1.772	0.882	0.821
F (000)	664	768	680	696
θ range (deg)	1.40–26.00	1.70–27.00	1.41–25.49	1.37–25.00
Index ranges	$-11 \le h \le 11$	$-13 \le h \le 13$	$-12 \le h \le 12$	$-11 \le h \le 11$
	$-13 \le k \le 13$	$-17 \le k \le 17$	$-13 \le k \le 13$	$-13 \le k \le 13$
	$-18 \le l \le 18$	$-10 \le l \le 17$	$-18 \le l \le 17$	$-17 \le l \le 18$
N (R_{int})	5894 (0.0168)	6975(0.0189)	5665(0.0230)	5734(0.0260)
Restraints/parameters	10/387	6/402	10/403	20/441
Completeness (%)	98.9	97.9	99.0	98.5
Goodness-of-fit on F^2	1.130	1.047	1.140	1.114
R_1, wR_2	R_1 = 0.0313	R_1 = 0.0340,	R_1 = 0.0414	R_1 = 0.0532
[$I > 2\sigma$(I)]	wR_2 = 0.0966	wR_2 = 0.0867	wR_2 = 0.1287	wR_2 = 0.1578
R_1, R_2 (all data)	R_1 = 0.0361	R_1 = 0.0387	R_1 = 0.0466	R_1 = 0.0626
	wR_2 = 0.1110	wR_2 = 0.0907	wR_2 = 0.1406	wR_2 = 0.1723
T (K)	296(2)	273(2)	298(2)	298(2)

centrifugation and washed two times with PBS. Re-suspended cells in 300 μl binding buffer and added 5 μl of Annexin V-FITC and 10 μl of PI (MultiSciences Biotech Co., Ltd., China) to cells, and then cells were incubated for 15 min at room temperature in the dark and then analyzed by flow cytometry (Beckman coulter flow cytometry).

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Appendix A. Supplementary data

CCDC-950099 (for **1**), -950100 (for **8**), -950101 (for **9**) and −950102 (for **17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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