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Synthesis, structural characterization and cytotoxic activity of organotin derivatives of indomethacin†

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The synthesis, characterization and cytotoxic properties *in vitro* of tri-*n*-butyltin 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetate (1), tri-phenyltin 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetate (2), tetra-*n*-butyltin[bis-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetato]distannoxane (3) and di-*n*-butyltin bis-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetate (4) are described. These compounds have been characterized by ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy in solution and ^{119}Sn NMR in the solid state, infrared spectroscopy, elemental analysis and X-ray diffraction for compound 1. The growth inhibition effects of compounds 1–4 against the lung adenocarcinoma cell line SK-LU-1 as well as the cervical cancer cell line HeLa were determined. Compounds 1 and 2 exhibit cytotoxic activity, whereas compounds 3 and 4 are inactive.

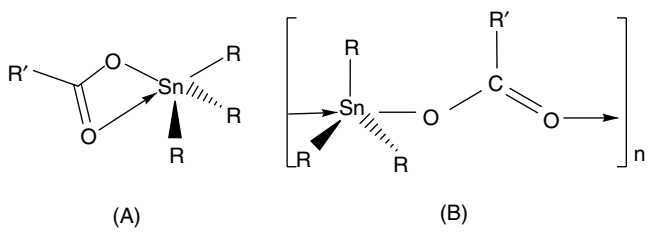
Keywords: organotin; carboxylates; indomethacin; cytotoxic

Introduction

The organotin(IV) carboxylates have been one of the most extensively studied classes of anticancer compounds since it was observed that they significantly reduce the growth of tumors when they are tested *in vivo*;[1–5] the di-*n*-butyl-, tri-*n*-butyl- and tri-phenyl-tin derivatives have also shown high cytotoxic activity with different cell lines of human origin as described in the literature.[1–7] Previously, the antitumor activity of indomethacin has been reported.[8,9] This compound contains an indole group in its structure, which is useful in the treatment of different types of cancer.[10–12] The indomethacin has a synergetic action along with the *cis*-platin on the gastric cancer cell line MGC803.[9] We decided to prepare and study several organotin carboxylates of indomethacin, which include the mentioned substituents, in order to know more about its structural chemistry, if there is a synergetic effect and if the new complexes could exhibit cytotoxic activity.

Triorganotin carboxylates $R'CO_2SnR_3$ are known to adopt a variety of motifs in the solid state,[13,14] and the preference for a five-coordination in derivatives in which the organic moiety does not contain an additional potential donor atom is well known. The structures have been shown to adopt mainly one of two basic motifs, A or B, in which the tin atom is five-coordinated. Motif A is monomeric, while motif B is polymeric, see Scheme **1**. However, in solution, such structures appear as four-coordinate species, because the oxygen atoms of the carboxylic group are non-coordinated to the tin atom.

Dicarboxylatotetraorganodistannoxane dimers of the type $\{R'COO(R_2Sn)\text{-}O\text{-}(SnR_2)OOCR'\}_2$ have structural diversities in the crystalline state[13,15,16] and exhibit interesting biological activities



Scheme 1. Motifs in the solid state for triorganotin carboxylates RCO_2SnR_3.

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† *In honor of Professor Rosalinda Contreras on the occasion of her 60th birthday.*

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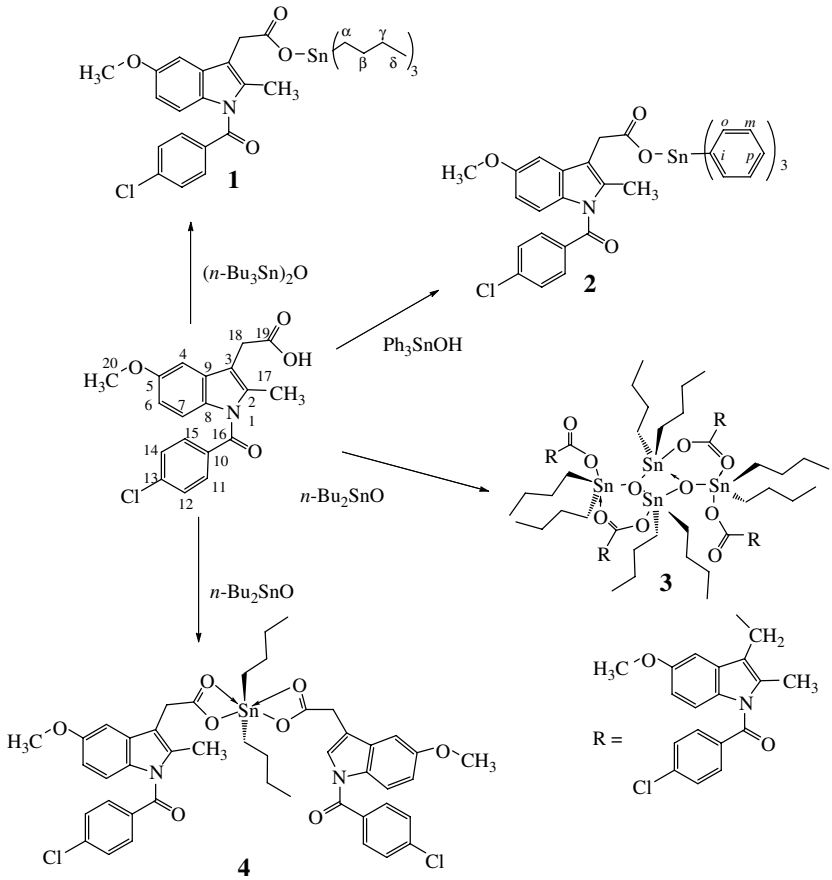

Scheme 2. Synthesis and structures of compounds **1-4**.

as cytotoxic compounds.[17–19] Also diorganotin dicarboxylates of the type $(R'COO)_2SnR_2$ are active cytotoxic compounds.[20]

We report herein the synthesis, characterization and properties of two triorganotin(IV) carboxylates (compounds **1** and **2**), the distannoxane **3** (described in the literature),[21] and one diorganotin(IV) dicarboxylate **4**, all being derivatives of indomethacin. Compounds **1–4** have been characterized by ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy in solution and ^{119}Sn NMR in the solid state, mass spectrometry, infrared spectroscopy, elemental analysis and X-ray diffraction for compound **1**. The cytotoxic activity *in vitro* of these compounds has been examined against both the lung cancer cell line SK-LU-1 and the cervical cancer cell line HeLa.

Table 1. ^{1}H NMR data of compounds **1–4**

Compound	1	2	3	4
CH(11,15)	7.44 A_2B_2 (8.7)	7.55 A_2B_2 (8.4)	7.61 A_2B_2 (8.5)	7.45 A_2B_2 (8.7)
CH(12,14)	7.64 A_2B_2 (8.7)	7.40 A_2B_2 (8.4)	7.42 A_2B_2 (8.5)	7.64 A_2B_2 (8.7)
CH(4)	6.98 d (2.5)	6.86 d (2.4)	6.92 d (2.0)	6.96 d (2.4)
CH(7)	6.87 d (9.0)	6.96 d (9.0)	6.76 d (9.0)	6.85 d (9.0)
CH(6)	6.64 dd (9.0, 2.4)	6.63 dd (9.0,2.4)	6.60 dd (9,0, 2.4)	6.65 dd (9.0, 2.7)
CH_3(20)	3.81 s	3.62 s	3.76 s	3.79 s
CH_2(18)	3.64 s	3.57 s	3.51 s	3.71 s
CH_3(17)	2.36 s	2.15 s	2.38 s	2.38 s
$CH_2(\alpha)$	1.25–1.34 m		1.38–1.62 m	1.57–1.65 m
$CH_2(\beta)$	1.50–1.65 m		1.07–1.35 m	1.47–1.57 m
$CH_2(\gamma)$	1.25–1.34 m		1.07–1.35 m	1.25 qt (7.5, 7.2)
$CH_3(\delta)$	0.85 t (7.3)		0.80, 0.73 t (7.2)	0.76 t (7.3)
CH(*o*)		7.70 b m		
CH(*m*, *p*)		7.38–7.30 b s		

Solvent $CDCl_3$. Chemical shifts in ppm with respect to TMS; coupling constants in Hz, $^{n}J(^{1}H-^{1}H)$ Hz in parentheses. Abbreviations: s = singlet; m = complex pattern; b = broad; t = triplet; tq = triplet of quartets.

Results and Discussion

Synthesis

Compounds **1–4** are prepared by condensation of indomethacin with bis-tri-*n*-butyltin oxide, triphenyltin hydroxide and di-*n*-butyltin oxide to afford compounds **1, 2** and **3,4** respectively. The synthesis and structures of the compounds are shown in Scheme **2**.

^{1}H, ^{13}C and ^{119}Sn NMR spectrocopy

The ^{1}H NMR assignments of compounds **1–4** are based on ^{1}H–^{13}C HMQC experiments, Table 1. The ^{13}C NMR data are given in Table 2. The ^{13}C NMR assignments of indomethacin are based on the previous report[22] as well as ^{1}H–^{13}C HMQC experiments. The assignment of ^{13}C NMR resonances of the *n*-butyltin group in compounds **1** and **4** is straightforward from the $^{n}J(^{13}C-^{119/117}Sn)$ coupling constants. For compound **2**, the aromatic resonances of the triphenyltin moieties are assigned on the basis of aromatic $^{n}J(^{13}C-^{119/117}Sn)$ coupling constants. The chemical shift of the *ipso*-carbon, around 138 ppm, suggests a characteristic tetrahedral tin atom;[23] five-coordinated triphenyltin carboxylates have indeed been observed at approximately 4 ppm to higher frequencies.[24]

The ^{119}Sn NMR data are listed in Table 2. Compounds **1** and **2** exhibit a single resonance in solution, with chemical shifts of +114.7 and −105.9 ppm, respectively, which is characteristic of four-coordinated tri-*n*-butyl- and triphenyl-tin compounds in solution. Accordingly, a tetrahedral geometry is proposed for **1** and **2** in solution.[24,25] Compounds **1** and **2** exhibit in the solid state a single resonance at −13.7 and −425.0 ppm respectively, which suggests a higher coordination number, see Scheme **1**. Compound **3** is a dimeric compound in solution and it shows two equally intense ^{119}Sn resonances at −213.2 and −217.1 ppm, characteristic for five-coordinate endocyclic (Sn1) and exocyclic (Sn2) atoms in the dimeric carboxylatodistannoxanes[13,17,25,26] and in the solid state **3** gives rise two signals at −207.7 and

Table 2. ^{13}C and 119Sn NMR data of compounds **1–4**

Compound	Indomethacin	1	2	3	4
C19	176.5	175.9	175.3	176.9	181.0
C16	168.2	168.2	167.7	168.1	168.3
C5	155.9	156.0	155.5	156.0	156.2
C8	139.2	138.9	139.0	139.0	139.3
C2	136.1	135.2	135.3	135.3	135.9
C13	133.6	134.3	134.3	134.1	134.1
C11, C15	131.1	131.0	131.0	131.0	131.2
C10	130.7	130.9	130.8	130.9	130.9
C9	130.3	n. o.	129.07	n. o.	130.7
C12, C14	129.0	128.9	129.00	129.0	129.2
C3	115.0	114.8	114.8	114.8	115.1
C7	111.7	114.5	113.8	114.3	113.0
C6	111.6	111.5	112.0	111.0	111.7
C4	101.1	101.6	101.6	102.0	101.5
C20	55.7	55.6	55.6	55.5	55.7
C18	29.9	30.9	30.4	32.2	30.1
C17	13.3	13.4	13.2	13.3	13.4
Cα		16.5[356/340]		29.2[743/713] 27.9 [n.r.]	25.23[572/544]
Cβ		27.7[20]		27.6 [n.r.] 27.2 [n.r.]	26.75[37]
Cγ		26.8[95]		26.5 [n.r.] 26.7 [n.r.]	26.2[99]
Cδ		13.2		13.4 13.3	13.4
C*i*			138.2[n.o.]		
C*o*			136.7[48]		
C*m*			128.8[63]		
C*p*			130.1[13]		
^{119}Sn		114.7 (−13.7)	−105.9 (−425.0)	−213.2 (−207.7) −217.1 (−219.6) {119}	−140.1 (−196.5)

Solvent $CDCl_3$. Chemical shifts in ppm with respect to TMS, $^{n}J(^{13}C-^{117/119}Sn)$ Hz coupling constants are given between square brackets. n.r. = not resolved. n.o. = not observed. ^{119}Sn chemical shifts in ppm with respect to $(CH_3)_4Sn$. $^{2}J(^{119}Sn-O-^{117/119}Sn)$ coupling constants between braces, NMR in solid state between parentheses. For compound **3**, the α, β and γ carbons of the *n*-butyl moieties appear as pairs of ^{13}C resonances with very similar chemical shifts, with the consequent overlapping precluding the observations of the corresponding $^{n}J(^{13}C-^{119/117}Sn)$. The α-CH_2 moieties show broad ^{13}C NMR resonances.

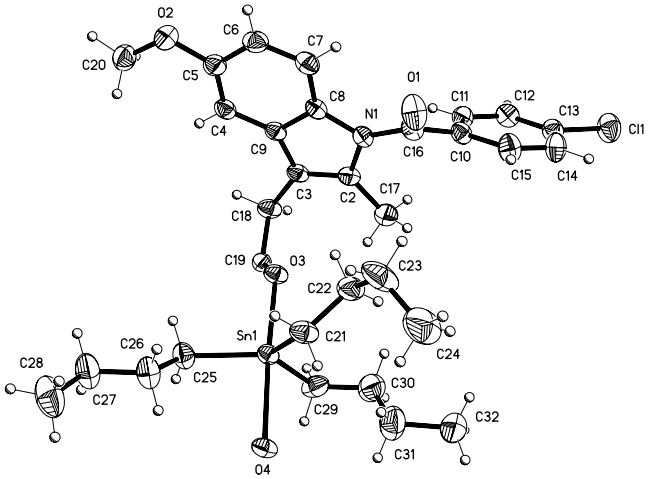

Figure 1. Crystal structure of compound **1**.

−219.6 ppm, which support the same structure in the solid state and in solution, see Scheme 2. These NMR results contrast with the crystal structure reported in the literature[21] for **3**, which reveals Sn-O secondary interactions (>2.5 Å),[21,27,28] for the endocyclic tin atoms. Compound **4** exhibits in solution a single resonance at −140.1 ppm, which is found in the characteristic range of the six-coordination and it is comparable with several di-*n*-butyltin dicarboxylates reported in the literature.[29,30] This chemical shift suggests a coordination between the oxygen donor atoms of the carbonyl groups and the tin atom, see Scheme 2. In the solid state, **4** exhibits a single resonance at −196.5 ppm, also suggesting also a six-coordinated tin compound. The $\Delta\delta$ between ^{119}Sn chemical shifts of **4** in solid state and in solution ($\Delta\delta$ = 56.4 ppm) is similar to other molecules reported in the literature[31] and suggests that there is no change in the coordination number, as well as no interaction with the solvent, or intramolecular interactions with the highly funcionalized indomethacin. The study of **4** in $CDCl_3$ by ^{119}Sn NMR at low temperatures (+20 and −60 °C) shows the same chemical shift (δ −140.1 ppm).

X-ray diffraction

Single crystals of **1** and **3**[21] were obtained by recrystallization. The X-ray diffraction study of **1** shows a polymeric structure; the monomeric fragment is shown in Fig. 1. The crystal data are given in Table 3 and selected bond lengths and angles in Table 4. The structure shows the predominant motif found for triorganotin carboxylates, namely the polymeric five-coordinated *trans*-R_3SnO_2 geometry. The crystalline structure is comparable with other structurally characterized analogues reported in the literature.[31,32] The five-coordinate tin atom shows a distorted trigonal bipyramidal geometry, with a trigonal plane defined by the three butyl substituents. The equatorial plane is formed by the atoms Sn(1), C(21), C(25) and C(29) with bond angles subtending at the tin atom ranging from 117.8(13)° to 121.00(15)°. The axial positions are occupied by the oxygen atoms. The O(3)–Sn(1)–O(4) diaxial angle is 174.12(6)°. The Sn atom lies 0.1305(0) Å out of the trigonal plane in the direction of the more strongly bound O(3). The Sn(1)–O(3) and Sn(1)–O(4) distances are 2.190(2) and 2.496(2) Å, respectively.

Table 3. Crystal and data collection parameters for compound **1**

Empirical formula	$(C_{31}H_{42}ClNO_4Sn)_n$	
Formula weight	646.80	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P\,2_1/n$	
Unit cell dimensions	a = 15.501(1) Å	$\alpha = 90^\circ$
	b = 10.520(1) Å	$\beta = 95.174(1)^\circ$
	c = 19.348(1) Å	$\gamma = 90^\circ$
Volume	3142.2(4) Å^3	
Z	4	
Density (calculated)	1.367 mg/m^3	
Absorption coefficient	0.932 mm^{-1}	
F(000)	1336	
Crystal size/color/shape	0.276 × 0.158 × 0.058 mm/pale-yellow/prism	
Theta range for data collection	1.61–25.38°	
Index ranges	$-18 \le h \le 18$, $-12 \le k \le 12$, $-23 \le l \le 23$	
Reflections collected	25 438	
Independent reflections	5777 [R(int) = 0.0442]	
Completeness to theta = 25.38°	99.6%	
Measurement device	Bruker Smart Apex CCD diffractometer	
Absorption correction	Analytical	
Max. and min. transmission	0.9527 and 0.7910	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5777/147/400	
Goodness-of-fit on F^2	0.884	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0316, $wR2$ = 0.0646	
R indices (all data)	$R1$ = 0.0446, $wR2$ = 0.0680	
Largest difference peak and hole	0.701 and −0.245 e Å^{-3}	
Remarks	Main residue disorder: 14%	

Infrared Spectroscopy

The OH absorption between 3300 and 2800 cm^{-1} due to the acid group is missing in complexes **1–4**, which indicates the deprotonation of the acid during the complex formation.

It has been reported[33] that the difference between asymmetric and symmetric O–C=O vibrations has been used to determine the mode of coordination with metals. Differences larger that 250 cm^{-1} are indicative of tetrahedral structures, while $\Delta\upsilon$ values in the range 150–250 cm^{-1} are indicative of compounds with bridged structures and a difference shorter than 150 cm^{-1} is assigned to chelated structures. The $\Delta\upsilon = \upsilon_{asy}(OCO) - \upsilon_{sym}(OCO)$ for compounds **1–4** is the following: $\Delta\upsilon$ = 1560 − 1379 = 181 (**1**), 1577 − 1395 = 182 (**2**), 1569 − 1402 = 167 (**3**) and 1595 − 1396 = 199 (**4**); these results shown that in solid state the compounds have bridged structures. The NMR in solid state and X-ray diffraction of **1** and **3**[21] agree with the infrared results.

Table 4. Selected bond lengths (Å) and angles (deg) for compound **1**

Sn(1)–C(25)	2.118(3)	C(29)–Sn(1)–C(21)	120.02(14)
Sn(1)–C(29)	2.120(3)	C(21)–Sn(1)–O(3)	91.07(10)
Sn(1)–C(21)	2.131(3)	C(25)–Sn(1)–O(4)	89.01(10)
Sn(1)–O(3)	2.190(2)	C(29)–Sn(1)–O(4)	87.27(10)
Sn(1)–O(4)	2.496(2)	C(21)–Sn(1)–O(4)	83.10(10)
O(3)–C(19)	1.266(3)	O(3)–Sn(1)–O(4)	174.12(6)
O(4)–C(19)	1.242(3)	C(19)–O(4)–Sn(1)	144.59(19)
		C(22)–C(21)–Sn(1)	117.0(5)
C(25)–Sn(1)–C(29)	121.00(15)	C(22)–C(21)–Sn(1)	114.7(11)
C(25)–Sn(1)–C(21)	117.86(13)	C(26)–C(25)–Sn(1)	117.9(2)
C(25)–Sn(1)–O(3)	94.40(11)	C(30)–C(29)–Sn(1)	120.7(4)
C(29)–Sn(1)–O(3)	95.04(11)	C(30)–C(29)–Sn(1)	111.8(7)

In vitro cytotoxic screening

Compounds **1–4** were evaluated for *in vitro* cytotoxic activity against HeLa and SK-LU-1 cell lines and compared with the reference compound *cis*-platin. Table 5 shows the primary screen against HeLa cells, where compounds **1** and **2** were more active than *cis*-platin. Comparatively, compound **1** showed around 1.3 times more activity than compound **2** against HeLa cell lines, whereas, against SKLU-1 cell lines, **2** was 2.9 times more effective than compound **1**. Compounds **3** and **4** showed no activity for both cell lines.

Experimental

Bis-*n*-tributyltin oxide, triphenyltin hydroxide and di-*n*-butyltin oxide were purchased from Aldrich and were used without further purification. Indomethacin 99% was purchased from Auzohu-Konch Pharmaceutica. ^{1}H and ^{13}C NMR spectra were recorded with a Varian spectrometer operating at 300 MHz using $CDCl_3$ as solvent. ^{119}Sn-spectra were recorded with a Bruker Advance Instrument. X-ray diffractometry was determined with a Bruker Smart Apex CCD diffractometer. IR-spectra were obtained on a Nicolet FT-55X apparatus. Melting points were measured on a Melt Temp II Laboratory Devices USA. Electrospray Mass spectra were recorded with a Jeol JMS AX505HA spectrometer.

Compound 1

A mixture of 0.5 g (1.39 mmol) of indomethacin and 0.414 g (0.695 mmol) of $(n\text{-}Bu_3Sn)_2O$, in 3 ml of absolute ethanol and 12 ml of dry toluene were placed in a flask equipped with a Dean–Stark moisture trap, which was filled with dry toluene. The mixture was stirred and refluxed for 24 h. After reflux the toluene was evaporated, giving a yellow solid product. Purification was achieved by recrystallization from methylene dichloride–hexane (3 : 1). E. anal. found (calcd for $C_{31}H_{42}ClNO_4Sn$): C 57.36 (57.56), H 6.44 (6.54), N 2.16 (2.17). M.p.: 75–76 °C. Yield: 67.5%.

IR (KBr disk) cm^{-1}: 3105 w, 3079 w, 2957 s, 2921 s, 2853 m, 1672 s, 1583 s, 1560 s 1477 m, 1457 m, 1379 m, 1357m, 1324 s, 1284 w, 1230 s, 1178 w, 1150 w, 1085 m, 1065 m, 1034 w, 915 w 876 w, 835 m, 807 w, 694 w, 668 w, 600 w.

Electrospray mass (masses given based on ^{1}H, ^{12}C, ^{16}O, ^{14}N and ^{120}Sn): the isotopic distributions were compared with the calculated, for compounds **1–4**. Only tin-containing fragments are given: $M + Bu_3Sn^+$ 936 (100%), M^+ 647 (5%).

Table 5. Inhibitory concentration 50

Compound	Cell line	I_C50 (μg/ml)	μM
2	HeLa	2.72	4.2×10^{-6}
1	HeLa	4.01	5.6×10^{-6}
2	SKLU-1	16.21	2.5×10^{-5}
1	SKLU-1	6.15	8.7×10^{-6}
cis-platin	HeLa	27.14	9.2×10^{-5}
cis-platin	SKLU-1	Inactive	

I_c50 = the 50% growth inhibition parameter.

Compound 2

The procedure described for compound **1** was followed for compounds **2, 3** and **4**. Indomethacin: 0.5 g (1.39 mmol), Ph_3SnOH: 0.51 g (1.39 mmol), 3 ml of absolute ethanol, and 12 ml of dry toluene. The product is a pale yellow solid. Recrystallization from methylene dichloride–hexane (3 : 1). E. anal. found (calcd for $C_{37}H_{30}ClNO_4Sn$): C 62.54 (62.87), H 4.53 (4.27), N 1.84 (1.98). M.p. 105 °C. dec. Yield: 66.8%.

IR (KBr disk) cm^{-1}: 3058 w, 2985 w, 2957 w, 2929 w, 2832 w, 1729 w, 1680 s, 1592 m, 1577 m, 1535 s, 1477 s, 1428 s, 1395 m, 1359 m, 1325 m, 1258 w, 1231 m, 1178 w, 1148 w, 1070 m, 1037 w, 1018 w, 995 w, 917 w, 882 w, 853 w, 833 w, 806 w, 731 s, 697 s, 660 w, 600 w, 545 w.

Electrospray mass: $M+Ph_3Sn^+$ 1056 (60%), M^+ 707 (2%), Ph_3Sn^+ 351 (35%).

Compound 3

Indomethacin: 0.5 g (1.39 mmol), $n\text{-}Bu_2SnO$ 0.346 g (1.39 mmol), 3 ml of absolute ethanol, and 12 ml of dry toluene. The product is a bright yellow solid product. Recrystallization from methylene dichloride–hexane (3 : 1). E. anal. found (calcd for $C_{108}H_{132}Cl_4N_4O_{16}Sn_4$): C 54.30 (54.25), H 5.87 (5.56), N 2.29 (2.34). M.p. 183–184 °C. Yield: 63.2%.

IR (KBr disk) cm^{-1}: 3043 w, 2958 s, 2929 s, 2867 m, 1683 s, 1623 m, 1569 s, 1479 s, 1461 m, 1402 m, 1363 s, 1316 s, 1289 w, 1260 w, 1227 s, 1180 w, 1145 w, 1091 m, 1070 m, 1041 w, 1018 w, 924 w, 857 w, 836 w, 799 w, 755 w, 676 w, 637 m, 547 w.

Electrospray mass: $[RCOOBu_2SnOSnBu_2OSn(Bu)CH{=}CH_2]^+$ 1059 (52%), $[RCOOBu_2SnOSnBu_2]^+$ 838 (100%).

Compound 4

Indomethacin: 1.00 g (2.78 mmol), $n\text{-}Bu_3Sn$ 0.346 g (1.39 mmol), 3 ml of absolute ethanol, and 12 ml of dry toluene. The product is a pale yellow solid. Recrystallization from methylene dichloride–hexane (3 : 1). E. anal. found (calcd for $C_{46}H_{48}Cl_2N_2O_8Sn$): C 58.63 (58.37), H 4.94 (5.11), N 3.26 (2.95). M.p. 201–202 °C. Yield: 65.2%.

IR (KBr disk) cm^{-1}: 2958 m, 2928 m, 2866 w, 1729 w, 1683 s, 1595 s, 1478 s, 1459 s, 1396 m, 1363 s, 1320 s, 1258 m, 1228 s, 1178 w, 1147 w, 1088 m, 1068 m, 1037 w, 1016 w, 995 w, 923 w, 834 w, 754 m, 721 w, 674 w.

Electrospray mass: $[M + Sn(Bu)CH{=}CH_2]^+$ 1148 (26%), $[M + SnCH_2CH_2CH_3]^+$ 1107 (19%).

Measurements of cell growth inhibition

Details of measuring cell growth inhibition are described elsewhere.[1] Briefly, 2×10^4 cells/well were plated in a 96-well microplate with D-MEM supplemented with 10% BFS, and allowed to attach, incubating at 37 °C and 5% CO_2 for 24 h. At the end of incubation time, the medium was put under vacuum and the cells were exposed to drugs in five different logarithmic concentrations (0, 0.1, 1 and 10 µg/mL) for 24 h under the conditions mentioned above. Cell growth was determined according to the sulforhodamine B assay, described by Skehan.[34,35] Absorbance was measured at 564 nm (microplate reader Bio-Rad 550) and the percentage cell growth for each concentration of drug was calculated as: percentage growth $= 100 \times [T/C]$, where T is the absorbance of treated wells and C is the absorbance of untreated wells. The 50% growth inhibition parameter (Ic50) was computed for each drug employing the software PROBIT (log probit analysis by maximum likelihood).[36]

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