Diorganotin difluorobenzoates: synthesis, spectroscopic characterization and *in vitro* antitumour activity. X-Ray structure determination of bis[di-n-butyl(2,6-difluorobenzoato)tin] oxide

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Abstract

The synthesis and spectroscopic characterization of diorganotin(IV) bis(difluorobenzoates) $[F_2C_6H_3COO]_2SnR_2$ [type **a**] and bis[diorgano(difluorobenzoato)tin(IV)] oxides $\{[(F_2C_6H_3COO)R_2Sn]_2O\}_2$ [type **b**] are described. An X-ray structure study has revealed compound **3b**, $\{[(2,6\text{-}F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$, to be dimeric and built around a planar Sn_2O_2 ring. The crystals are triclinic P$\bar{1}$ with the cell dimensions $a = 11.935(13)$, $b = 12.3675(14)$, $c = 12.974$ Å, $\alpha = 92.89(8)$, $\beta = 84.32(7)$, $\gamma = 67.49(9)°$; $Z = 1$, with the dimer being centro-symmetric. Selected compounds have been tested *in vitro* against two human tumour cell lines, MCF-7 (a mammary tumour) and WiDr (a colon carcinoma), and exhibit promising cytotoxicities.

Introduction

Di-n-butyltin 2,5-bis(trifluoromethyl)benzoate shows rather promising *in vitro* antitumour activities since its ID_{50} values against two human tumour cell lines, MCF-7 and WiDr, have been found to be 48 and 176 ng ml^{-1}, respectively. These results are significantly better than the values of 850 and 624 ng ml^{-1} found for *cis*-platin [1]. Di-n-butyl- and diethyl-tin monofluorobenzoates, either diorganotin bismonofluorobenzoates, compounds of type **a**, or bis(diorgano[monofluorobenzoato]tin) oxides, compounds of type **b**, also gave promising ID_{50} values [2]. We have prepared a series of diorganotin difluorobenzoates in order to find out whether the presence of a second fluorine atom on the phenyl ring of the benzoate ligand could enhance the *in vitro* antitumour activity of diorganotin derivatives of fluorobenzoates.

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Results and discussion

Synthesis

The compounds prepared were $(F_2C_6H_3COO)_2Sn(n\text{-}C_4H_9)_2$ [type **a**] and $\{[(F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$ [type **b**], with $F_2 = 2,3\text{-}F_2$ (compounds **1a** and **1b**), $F_2 = 2,5\text{-}F_2$ (compound **2b**), $F_2 = 2,6\text{-}F_2$ (compounds **3a** and **3b**), $F_2 = 3,5\text{-}F_2$ (compounds **4a** and **4b**), and $(F_2C_6H_3COO)_2Sn(C_2H_5)_2$ [type **a**] and $\{[(F_2C_6H_3COO)(C_2H_5)_2Sn]_2O\}_2$ [type **b**], with $F_2 = 2,5\text{-}F_2$ (compound **6b**), $F_2 = 2,6\text{-}F_2$ (compounds **7a** and **7b**) and $F_2 = 3,5\text{-}F_2$ (compound **8b**).

X-Ray diffraction study

An X-ray diffraction analysis of a single crystal of compound **3b**, $\{[(2,6\text{-}F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$, has been performed. The atomic coordinates obtained are listed in Table 1. The molecular structure of compound **3b** and the numbering scheme used are shown in Fig. 1. Selected bond lengths and angles are given in Table 2.

Compound **3b** adopts the same structural pattern as bis(di-n-butyltin-5-methoxysalicylato) oxides [3], bis(di-n-butyl-3,4,5-trimethoxybenzoatotin) oxide [4] and diethyl-2-methylthio-3-pyridinecarboxylato-tin)oxide [2]. In agreement with Tiekink's statement [5], this is the predominant structure for diorganotin carboxylates of the general formula $[(R_2(R'COO)Sn)_2O]_2$. Compound **3b** is a centrosymmetric dimer built around a planar Sn_2O_2 ring, with two types of tin atoms, the tin atoms of the distannadioxetane ring and those that are substituents of the same ring, and two distinct carboxylate moieties, one bidentate and the other monodentate. The two types of tin atoms are pentacoordinated in a distorted trigonal bipyramidal geometry. Furthermore, the monodentate carboxylate ligand forms a sixth weaker interaction with both tin atoms: Sn(2)···O(3) (2.712(4) Å) is especially short; it induces the opening of the Bu—Sn(2)—Bu angle so that the geometry around Sn(2) can alternatively be described as that of a highly distorted octahedron.

Other bond lengths and angles around tin are, in general, close to the corresponding values found in analogous structures. The main difference with our previous structures [2–4] is the value of the dihedral angle between carboxylate groups and adjacent phenyl (close to 90° here, close to 0° in the three structures described previously).

Spectroscopic data

The ^1H NMR spectra (see Experimental section) of compounds of type **a**, diorganotin dibenzoates, exhibit a single resonance for the methyl group of the diethyltin or dibutyltin moieties. In contrast, for compounds of type **b**, bis(benzoatodiorganotin) oxides, two triplets are observed. The ^{13}C NMR spectra (see Experimental section) also show pairs of signals for the butyl or ethyl carbons in the case of compounds **b** in contrast with the single signals for compounds **a**. Finally, the ^{119}Sn NMR spectra (see Table 3) also exhibit the same dichotomy, a single resonance for compounds **a** and two

TABLE 1

Atomic coordinates ($\times 10^4$, $\times 10^5$ for Sn atoms) of compound **3b**, $\{[(2,6\text{-}F_2C_6H_3COO)\text{-}(n\text{-}C_4H_9)_2Sn]_2O\}_2$, with estimated standard deviations between parentheses[a]

Atom	x/a	y/b	z/c
Sn1	37752(4)	1027(4)	24366(3)
Sn2	38406(4)	12767(3)	−687(3)
F1	7567(6)	−1855(5)	3750(5)
F2	6320(7)	−4681(5)	2373(5)
F3	2369(7)	4458(6)	2940(6)
F4	−212(5)	3048(6)	1395(5)
O1	5097(5)	−1726(5)	2685(4)
O2	6700(5)	−2342(4)	1481(4)
O3	2662(4)	1796(4)	1901(3)
O4	1446(6)	2302(5)	3409(4)
O5	4639(4)	−48(3)	982(3)
C1	6896(6)	−3240(6)	3038(5)
C2	7586(7)	−2969(7)	3725(6)
C3	8317(9)	−3714(9)	4363(7)
C4	8331(9)	−4873(10)	4312(8)
C5	7678(10)	−5198(8)	3645(9)
C6	6968(8)	−4378(7)	3012(7)
C7	6180(6)	−2352(6)	2334(5)
C8	1102(6)	3706(6)	2173(6)
C9	1418(9)	4636(8)	2371(8)
C10	782(11)	5786(8)	2072(9)
C11	−164(12)	5901(11)	1515(10)
C12	−540(9)	5016(10)	1244(9)
C13	127(8)	3937(8)	1614(7)
C14	1779(6)	2499(6)	2559(5)
C15	2363(8)	−559(7)	2498(7)
C16	2186(11)	−1019(10)	3597(9)
C17	1293(15)	−1616(15)	3572(13)
C18	1028(16)	−2024(15)	4642(13)
C19	4576(10)	706(8)	3608(6)
C20	4649(9)	1894(8)	3529(7)
C21	5347(10)	2184(9)	4385(8)
C22	5315(13)	3418(12)	4387(11)
C23	4342(7)	2649(6)	531(6)
C24	5502(8)	2682(8)	−106(7)
C25	5993(9)	3489(9)	502(8)
C26	7110(12)	3557(12)	−180(11)
C27	2275(6)	854(7)	−250(6)
C28	2411(8)	122(8)	−1299(6)
C29	1277(10)	−174(10)	−1359(8)
C30	1451(14)	−945(13)	−2421(11)

[a]Lists of thermal parameters, structure factors, complete tables of bond lengths and angles are available from the authors (J.M.-P.).

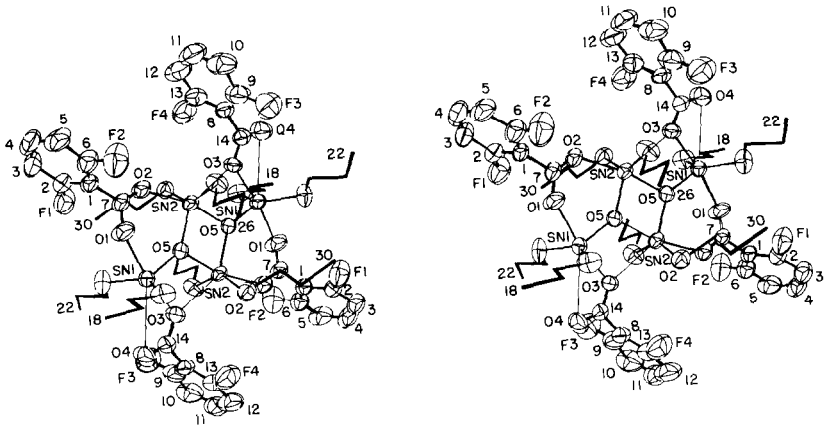


Fig. 1. Molecular structure of compound **3b**, $\{[(2,6\text{-}F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$, and numbering used; the C symbols have been omitted for clarity. Thermal ellipsoids are drawn at 50% probability for all atoms except for some carbon atoms of the butyl groups for which they have been set artificially small. Details of the data collection and structure refinement are reported in Table 3.

TABLE 2

Bond lengths (Å) and angles (°) in compound **3b**, $\{[(2,6\text{-}F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$; atoms denoted with an asterisk are related symmetrically to those without an asterisk through the centre of symmetry

Sn(1)–O(1)	2.269(5)
Sn(1)–O(3)	2.198(4)
Sn(1)–O(4)	3.144(5)
Sn(1)–O(5)	2.023(4)
Sn(1)–C(15)	2.134(8)
Sn(1)–C(19)	2.121(8)
Sn(2)–O(2*)	2.309(5)
Sn(2)–O(3)	2.712(4)
Sn(2)–O(5)	2.177(4)
Sn(2)–O(5*)	2.071(4)
Sn(2)–C(23)	2.141(7)
Sn(2)–C(27)	2.155(7)
O(3)–Sn(1)–O(1)	169.5(2)
O(4)–Sn(1)–O(1)	145.4(2)
O(4)–Sn(1)–O(3)	45.0(2)
O(5)–Sn(1)–O(1)	90.5(2)
O(5)–Sn(1)–O(3)	79.1(1)
O(5)–Sn(1)–O(4)	124.1(2)
C(15)–Sn(1)–O(1)	88.0(3)
C(15)–Sn(1)–O(3)	94.8(3)
C(15)–Sn(1)–O(4)	77.2(3)

TABLE 3

^{119}Sn (chemical shifts versus Me_4Sn, external reference) and ^{19}F (chemical shifts versus $CFCl_3$) NMR parameters for solutions of compounds **1a** to **8b** in $CDCl_3$

Comp. No.	X_2	R	$\delta(^{119}Sn)$ (ppm)	$^2J(Sn-O-Sn)$ (Hz)	$\delta(^{19}F)^1H$ decoupled (ppm)	$\delta(^{19}F)$ undecoupled (ppm)
1a	2,3-F_2	Bu^n	−133.8		−135.3, d (**20**)	dddd (**20**, 6, 6, 1)
					−137.3, d (**20**)	dddd (**20**, 10, 5, 1)
3a	2,6-F_2	Bu^n	−123.1		−109.9, s	dd (7, 6)
4a	3,5-F_2	Bu^n	−138.5		−109.1, s	dd (8, 8)
1b	2,3-F_2	Bu^n	−210.0	120	−137.0, d (**20**)	bs
			−210.6		−138.0, d (**20**)	bs
2b	2,5-F_2	Bu^n	−210.6	123	−116.5, d (**18**)	bs
			−211.2		−119.1, d (**18**)	bs
3b	2,6-F_2	Bu^n	−185.4	123	−112.4, s	bs
			−190.9			
4b	3,5-F_2	Bu^n	−209.8	130	−109.5, s	bs
			−216.1			
7a	2,6-F_2	Et	−129.3		−109.8, s	dd (8, 6)
6b	2,5-F_2	Et	−211.2	134	−116.4, d (**18**)	bs
			−212.5		−118.9, d (**18**)	bs
7b	2,6-F_2	Et	−189.4	135	−112.2, s	bs
			−194.7			
8b	3,5-F_2	Et	−210.6	119	−109.4, s	bs
			−215.3			

[a] $^2J(SnOSn)$ = unresolved $^2J(^{119}Sn-O-^{119}Sn)$ and $^2J(^{119}Sn-O-^{117}Sn)$ satellites; d = doublet; s = singlet; b = broad; the coupling patterns of the ^{19}F data are indicated between parentheses, those in bold referring to $J(^{19}F-^{19}F)$ coupling and the others to $J(^{19}F-^1H)$ couplings.

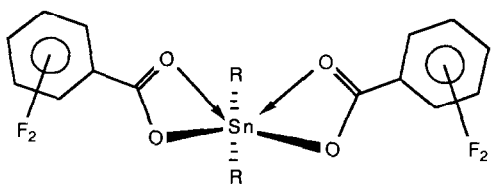


Fig. 2. Structure proposed for the diorganotin bisdifluorobenzoates, compounds of type **a** (R = Et, Bu^n).

signals of identical intensities for the type **b**. The latter exhibit characteristic $^{119}Sn-O-^{117/119}Sn$ coupling satellites.

The structure proposed for compounds **a** from these data, displayed in Fig. 2, is in agreement with previous data [6]. They are likely to have the recently observed strongly distorted square bipyramidal structure, with equatorial bidentate carboxylate groups and apical organic groups bound to tin with unequal carboxylate oxygen–tin bonds [6].

The structure proposed for compounds of type **b** is dimeric, as shown by X-ray diffraction methods [2] (see Fig. 3). One set of resonances is associated with the organotin moieties involved in the dioxadistannetane ring and the second set with the terminal diorganotin moieties. This suggests that the dimeric structures found previously in the solid state [2–4] remain in $CDCl_3$ solution.

Mössbauer spectrometry (see Experimental section) does not discriminate between the two different types of tin atoms typical to compounds of type **b**. This is due to the rather small isomer shift scale, which makes this parameter somewhat insensitive to small variations in the tin environments as already reported [1, 3, 6]. Similarly, the ^{19}F NMR spectra (See Table 3) do not reflect the non-equivalence of the fluorobenzoate ligands in compounds of type **b**. This again is not unexpected since this probe is more sensitive to the local environment of the phenyl ring rather than the tin heterotopicity of quite distant tin atoms.

In vitro *antitumour activity*

The results of *in vitro* tests performed [7] on a selection of these compounds are given as ID_{50} values in Table 4. Data on some compounds currently used clinically as antitumour agents are given for comparison.

From Table 4, it can be deduced that all the tested compounds score analogously against WiDr, i.e. slightly better than *cis*-platin or etoposide. Their activity is comparable to those observed (200–300 ng ml^{-1}) for the monofluorobenzoates [2]. Against MCF-7, they are even more active than doxorubicin. The highest activity is obtained from ethanol solutions, rather than DMSO, especially in the case of compound **3b** which is then as active as mitomycin C. The other compounds of type **b** are also quite active in ethanol solutions.

Compounds **1a** to **4a**, **1b** and **2b** were also tested *in vitro* by the National Cancer Institute (NCI), Bethesda, Maryland, USA, for cytotoxic

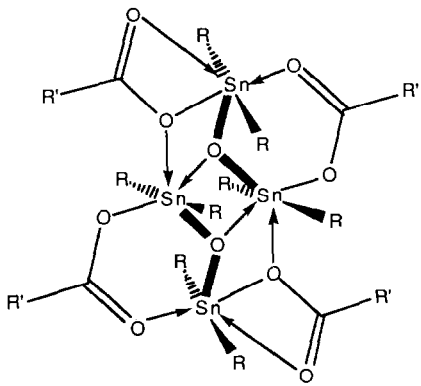


Fig. 3. Structure proposed for the bis(benzoatodiorganotin) oxides, compounds of type **b** (R = Et, Bu^n).

TABLE 4

ID_{50} values (ng ml^{-1}) for compounds of type **a** $(F_2C_6H_3COO)_2Sn(n\text{-}C_4H_9)_2$, **1a**, **3a** and **4a**, of type **b** $\{[(F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$, **1b** to **4b**, and of the reference compounds tested [8] against two human tumour cell lines, MCF-7 and WiDr

Comp. No.	F_2	MCF-7		WiDr	
		DMSO	EtOH	DMSO	EtOH
1a	2,3-F_2	38	23	277	283
3a	2,6-F_2	98		326	
4a	3,5-F_2	52	30	416	407
1b	2,3-F_2	13	9	134	120
2b	2,5-F_2	32	7	353	277
3b	2,6-F_2	25	3	227	174
4b	3,5-F_2	43	11	277	172
'cis-platin' [8]		850		624	
etoposide [8]		187		624	
doxorubicin [8]		63		31	
mitomycin C [8]		3		17	

activity against a panel of *c.* 60 human tumour cell lines. The results obtained are summarized in Table 5. The detailed parameter significance has been presented previously [8]. Briefly, D_{GI50}, D_{TGI} and D_{LC50} are differential cell subpanel sensitivities calculated [9] from the dose–response parameters GI_{50}, TGI and LC_{50} displayed by the tested compounds. These parameters are interpolated values representing the concentrations at which the percentage growth PG is $+50$, 0 and -50, respectively [8].

Computer simulations performed by the NCI suggest that compounds characterized by values of D_{GI50}, D_{TGI} and $D_{LC50} \geqslant 50$ display a statistically significant subpanel sensitivity [9]. The D_H value is a probe to cell panel selectivity of the drug while the MGD_H values are representative of its subpanel selectivity. Computer simulations performed by the NCI suggest that values of D_H and $MGD_H \geqslant 75$ correspond to statistically significant selectivities [9].

Table 5 shows that all compounds of type **a** are characterized by quite similar test results: satisfactory D_{GI50} (>50), D_H and MGD_H (>75) values have been obtained. They show poor results at the levels of D_{TGI} and D_{LC50}. The two compounds of type **b** tested gave satisfactory D_{GI50} and D_{TGI} values (*c.* 50 or more). Compound **1b** is characterized by borderline significant (≈ 75) D_H and MGD_H values, whereas compound **2b** gives lower ones. It is worth noting that all these organotin compounds exhibit very bad LC_{50} values against all leukemiae. This might be correlated with the observation with many organotin compounds tested previously *in vivo* by the NCI that they are only marginally active against P_{388} leukemia in mice.

TABLE 5

Overview of the NCI *in vitro* screening data obtained for some di-n-butyltin bis-difluorobenzoates, compounds **1a** to **4a**, and for some bis(difluorobenzoatodi-n-butyltin) oxides, compounds **1b** and **2b**. Their significance is given in ref. 8

No. Compound	NSC No.	Mean log values			Selectivity analysis[a]			Response parameter	Subpanel sensitivity[b]	$D_{GI_{50}}$ D_{TGI} $D_{LC_{50}}$	D_H MGD_H
		GI_{50}	TGI	LC_{50}	ΔGI_{50}	ΔTGI (range)	ΔLC_{50}				
1a	643842	−6.0	−5.6	−5.2	0.85	0.92	1.01	GI_{50}	LNS	67	83
$(2,3\text{-}F_2PhCOO)_2SnBu_2$					(1.61)	(1.80)	(2.24)	TGI	LNS	19	87
								LC_{50}	LNS	14	
2a	643844	−6.0	−5.6	−5.2	0.97	1.02	1.12	GI_{50}	LNS, REN	74	82
$(2,5\text{-}F_2PhCOO)_2SnBu_2$					(1.85)	(1.96)	(2.31)	TGI	LNS, REN	16	84
								LC_{50}	LNS, REN	22	
3a	643841	−6.1	−5.7	−5.2	0.90	1.02	1.10	GI_{50}	LNS	53	80
$(2,6\text{-}F_2PhCOO)_2SnBu_2$					(1.54)	(2.67)	(2.33)	TGI	LNS	39	79
								LC_{50}	LNS	19	
4a	643843	−6.0	−5.6	−5.2	0.83	0.93	1.06	GI_{50}	LNS	69	85
$(3,5\text{-}F_2PhCOO)_2SnBu_2$					(1.72)	(1.88)	(2.28)	TGI	LNS	19	83
								LC_{50}	LNS	16	
1b	643853	−6.8	−6.1	−5.5	1.24	1.45	1.50	GI_{50}	REN	64	77
$\{[(2,3\text{-}F_2PhCOO)Bu_2Sn]_2O\}_2$					(2.30)	(3.51)	(3.02)	TGI	REN	46	75
								LC_{50}	REN, LNS	25	
2b	643855	−6.7	−6.0	−5.5	1.28	1.55	1.21	GI_{50}	REN	52	68
$\{[(2,5\text{-}F_2PhCOO)Bu_2Sn]_2O\}_2$					(2.34)	(3.60)	(2.71)	TGI	REN	57	53
								LC_{50}	LNS, MEL, REN	27	

[a] ΔGI_{50}, ΔTGI and ΔLC_{50} represent the highest deviations with respect to the mean log values of GI_{50}, TGI and LC_{50} respectively.
[b] Cell line subpanels: LNS = non-small cell lung; MEL = melanoma; REN = kidney.

Experimental

Instruments

X-Ray data were collected on a four-circle diffractometer. Mössbauer spectra were recorded as described previously [3]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 270 instrument at 270.13 and 67.93 MHz, respectively. ^{119}Sn NMR spectra were obtained on a Bruker WM 500 instrument at 186.5 MHz. ^{19}F NMR spectra were recorded on a Bruker AC250 instrument at 235.36 MHz. The FAB mass spectra were recorded on a V.G. Micromass 7070 F instrument (source temperature, 200 °C).

Crystal data

$F_8O_{10}C_{60}H_{84}Sn_4$, triclinic; space group $P\bar{1}$; $a = 11.935(13)$ Å, $b = 12.367(14)$ Å, $c = 12.974(3)$ Å, $\alpha = 92.89(8)°$; $\beta = 84.32(7)°$, $\gamma = 67.49(9)°$, $Z = 1$; $D_c = 1.51$ g cm^{-3}, (MoKα) = 13.53 cm^{-1}; crystal dimensions, parallelepiped, $0.22 \times 0.20 \times 0.35$ mm. Intensity data were collected at 295 K with a Huber four-circle diffractometer using graphite-monochromated MoKα radiation with $\lambda = 0.71069$ Å and employing an ω scan mode of 1.2° width. 6136 independent reflections were measured in the range $3° < 2\theta < 50°$ with $0 < h < 15$, $-13 < k < 13$, $-14 < l < 14$. No absorption corrections were applied to the intensity data. The structure was solved by direct methods using the SHELX86 [10] program. No H atoms were located. All positional parameters and anisotropic thermal parameters for F atoms were refined by a full-matrix least-squares technique (SHELX76 [11]) and isotropic thermal parameters were employed for the 12 C-atoms (C16, 17, 18, 20, 21, 22, 24, 25, 26, 28, 29 and 30) of the butyl groups. The weighting scheme used was $w = [\sigma^2(F) + 0.00453F^2]^{-1}$ and final R, Rw and S values of 0.048, 0.058 and 1.041, respectively, were obtained for 4699 observed reflections ($I > 2.5\sigma$). The maximum and minimum heights in the final ΔF map were 0.94 and -0.51 e Å^{-3}, respectively, with a maximum Δ/σ value of 0.07 in the last cycle.

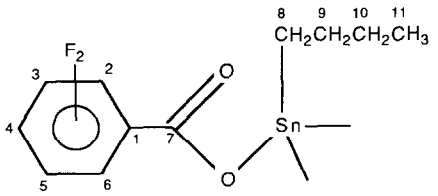
Syntheses

Compounds of type **a** were typically prepared as follows. 1.00 g (4.0 mmol) di-n-butyltin oxide or 0.86 g (4.0 mmol) diethyltin oxide were added to 1.26 g (8.0 mmol) of the appropriate difluorobenzoic acid dissolved in 150 ml of toluene and 50 ml of ethanol. The mixture was refluxed for 6 h and the ternary azeotrope water/ethanol/toluene distilled off via a Dean–Stark funnel. Half of the remaining solution was then evaporated under vacuum. The oily solid obtained was recrystallized from ethanol.

The synthesis of compounds of type **b** was similar but only half the amount of fluorobenzoic acid was used, i.e. 0.63 g (4.0 mmol). The recrystallization solvents are given below in the experimental details for each compound.

Spectroscopic characterization

Abbreviations: b: broad; d: doublet; q: quartet; t: triplet; nr: non-resolved; nv: non-visible; m: complex pattern; ^{n}J(Sn–C): unresolved $^{n}J(^{119}Sn-^{13}C)$ and $^{n}J(^{117}Sn-^{13}$); ^{2}J(SnOSn): unresolved $^{2}J(^{119}Sn-O-^{119}Sn)$ and $^{2}J(^{117}Sn-O-^{119}Sn)$. Coupling constants are given in Hz. Chemical shifts are given in ppm with respect to TMS and $CDCl_3$ taken to be 0.0 and 77.0 ppm for ^{1}H and ^{13}C spectra, respectively, with tetramethyltin in $CDCl_3$ (*c.* 40%) as external reference for ^{119}Sn spectra and with $CFCl_3$ (*c.* 10%) as external reference for ^{19}F spectra. All spectra were recorded in $CDCl_3$. $^{1}H-^{19}F$ couplings are given in bold type.



Compound **1a** (F_2 = 2,3-F_2; R = Bu^n): yield, 58%; m.p. 72–73 °C; recrystallized from petroleum ether. Mössbauer: QS: 3.97; IS: 1.57; Γ_1: 0.92; Γ_2: 0.86 mm s^{-1}. ^{1}H NMR δ: H-4: 7.39 (dddd, **10**, 8, **7**, 2); H-5: 7.17 (dddd, 8, 8, **5**, **2**); H-6: 7.83 (dddd, 8, **6**, 2, **2**); H-8 and H-9: 1.71–1.91 (m); H-10: 1.45 (tq, 7, 7); H-11: 0.90 (t, 7) ppm. ^{13}C NMR δ: C-1: 120.5 [d, $^{2}J(^{19}F-^{13}C)$ = 6 Hz] (calc.: 118.7); C-2: 151.1 [dd, $^{1}J(^{19}F-^{13}C)$ = 249 Hz, $^{2}J(^{19}F-^{13}C)$ = 11 Hz] (152.3); C-3: 150.7 [dd, $^{1}J(^{19}F-^{13}C)$ = 260 Hz, $^{2}J(^{19}F-^{13}C)$ = 13 Hz] (150.1); C-4: 121.6 [d, $^{2}J(^{19}F-^{13}C)$ = 17 Hz] (121.5); C-5: 123.6 [d, $^{3}J(^{19}F-^{13}C)$ = 6 Hz] (125.1); C-6: 127.5 [$^{3}J(^{19}F-^{13}C)$ = 3 Hz] (127.3); C-7: 172.4; C-8: 25.6 [$^{1}J(^{119/117}Sn-^{13}C)$ = 570/545 Hz]; C-9: 26.5 [^{2}J(Sn–C) = 36 Hz]; C-10: 26.2 [^{3}J(Sn–C) = 125 Hz]; C-11: 13.4 ppm.

Compound **3a** (F_2 = 2,6-F_2; R = Bu^n): yield, 97%; m.p. 59–61 °C; recrystallization from ethanol. Mössbauer: QS: 3.56, IS: 1.37, Γ_1: 1.05, Γ_2: 0.91 mm s^{-1}. ^{1}H NMR δ: H-3 and H-5: 6.94 (dd, 8, **8**); H-4: 7.39 (tt, 8, **6**); H-8 and H-9: 1.76–1.96 (m); H-10: 1.46 (tq, 7, 7); H-11: 0.94 (t, 7) ppm. ^{13}C NMR δ: C-1: 111.3 [t, $^{2}J(^{19}F-^{13}C)$ = 19 Hz] (calc.: 104.4); C-2 and C-6: 160.7 [dd, $^{1}J(^{19}F-^{13}C)$ = 256 Hz, $^{3}J(^{19}F-^{13}C)$ = 6 Hz] (166.6); C-3 and C-5: 111.8 [d, $^{2}J(^{19}F-^{13}C)$ = 23 Hz] (110.8); C-4: 132.4 [d, $^{3}J(^{19}F-^{13}C)$ = 10 Hz] (135.8); C-7: 170.8; C-8: 25.8 [$^{1}J(^{119/117}Sn-^{13}C)$ = 556/532 Hz]; C-9: 26.1 [^{2}J(Sn–C) = 38 Hz]; C-10: 26.4 [^{3}J(Sn–C) = 95 Hz]; C-11: 13.3 ppm.

Compound **4a** (F_2 = 3,5-F_2; R = Bu^n): yield, 91%; m.p. 103–105 °C; recrystallized from petroleum ether. Mössbauer: QS: 3.81, IS: 1.55, Γ_1: 0.89, Γ_2: 0.92 mm s^{-1}. ^{1}H NMR δ: H-2 and H-6: 7.65 (dd, **8**, 2); H-4: 7.04 (tt, **9**, 2); H-8 and H-9: 1.66–1.86 (m); H-10: 1.41 (tq, 7, 7); H-11: 0.90 (t, 7) ppm. ^{13}C NMR δ: C-1: 133.4 [t, $^{3}J(^{19}F-^{13}C)$ = 9 Hz] (calc.: 133.0); C-2 and C-6: 113.3 [d, $^{2}J(^{19}F-^{13}C)$ = 26 Hz] (113.0); C-3 and C-5: 162.6 [dd, $^{1}J(^{19}F-^{13}C)$ = 250 Hz, $^{2}J(^{19}F-^{13}C)$ = 12 Hz] (164.4); C-4: 108.4 [t, $^{2}J(^{19}F-^{13}C)$ = 25 Hz] (107.2); C-7: 173.4; C-8: 25.7 [$^{1}J(^{119/117}Sn-^{13}C)$ = 573/

548 Hz]; C-9: 26.5 [^2J(Sn–C) = 35 Hz]; C-10: 26.2 [^3J(Sn–C) = 98 Hz]; C-11: 13.4 ppm.

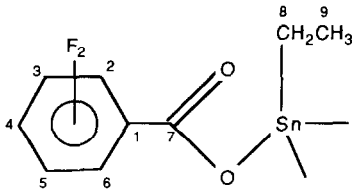
Compound **1b** (F_2 = 2,3-F_2; R = Bu^n): yield, 72%; m.p. 109–110 °C; recrystallized from petroleum ether. Mössbauer: QS: 3.52, IS: 1.36, Γ_1: 1.05, Γ_2: 1.12 mm s^{-1}. ^{1}H NMR δ: H-4: 7.31 (dddd, **10**, 8, **7**, 2); H-5: 7.14 (dddd, 8, 8, **5**, **2**); H-6: 7.64 (dddd, 8, **6**, 2, **2**); H-8 and H-9: 1.58–1.76 (m); H-10: 1.26 (tq, 7, 7) and 1.37 (tq, 7, 7); H-11: 0.78 (t, 7) and 0.87 (t, 7) ppm. ^{13}C NMR: C-1: 124.2 (calc. 118.7); C-2: 151.0 [dd, $^1J(^{19}F–^{13}C)$ = 248 Hz, $^2J(^{19}F–^{13}C)$ = 12 Hz] (152.3); C-3: 150.1 [dd, $^1J(^{19}F–^{13}C)$ = 258 Hz, $^2J(^{19}F–^{13}C)$ = 12 Hz] (150.1); C-4: 120.1 [d, $^2J(^{19}F–^{13}C)$ = 17 Hz] (121.5); C-5: 123.4 (125.1); C-6: 127.7 (127.3); C-7: 169.2; C-8: 29.9 [^1J(Sn–C) = 735 Hz] and 28.3 [^1J(Sn–C) = 697 Hz]; C-9: 27.5 [^2J(Sn–C) = 36 Hz] and 27.2 [^2J(Sn–C) = 30 Hz]; C-10: 26.6 [^3J(Sn–C) = 125 Hz]; C-11: 13.5 and 13.4 ppm.

Compound **2b** (F_2 = 2,5-F_2; R = Bu^n): yield, 62%; m.p. 125–127 °C; recrystallized from petroleum ether. Mössbauer: QS: 3.52, IS: 1.35, Γ_1: 0.97, Γ_2: 1.02 mm s^{-1}. ^{1}H NMR δ: H-3: 7.16 (ddd, 9, **9**, **5**); H-4: 7.10 (ddd, 9, **9**, **5**); H-6: 7.57 (b); H-8 and H-9: 1.56–1.80 (m); H-10: 1.26 (tq, 7, 7) and 1.37 (tq, 7, 7); H-11: 0.79 (t, 7) and 0.87 (t, 7) ppm. ^{13}C NMR δ: C-1: 123.2 (calc.: 118.7); C-2: 157.9 [d, $^1J(^{19}F–^{13}C)$ = 243 Hz] (160.7); C-3: 117.9 [dd, $^2J(^{19}F–^{13}C)$ = 26 Hz, $^3J(^{19}F–^{13}C)$ = 8 Hz] (116.7); C-4: 119.8 [dd, $^2J(^{19}F–^{13}C)$ = 25 Hz, $^3J(^{19}F–^{13}C)$ = 8 Hz] (125.5); C-5: 157.6 [d, $^1J(^{19}F–^{13}C)$ = 253 Hz (158.5); C-6: 118.3 [d, $^2J(^{19}F–^{13}C)$ = 26 Hz] (118.9); C-7: 169.0; C-8: 29.9 [$^1J(^{119/117}Sn–^{13}C)$ = 739/701 Hz] and 28.3 [$^1J(^{119/117}Sn–^{13}C)$ = 720/678 Hz]; C-9: 27.5 [^2J(Sn–C) = nv] and 27.2 [^2J(Sn–C) = 30 Hz]; C-10, 26.6 [^3J(Sn–C) = 125 Hz]; C-11: 13.4 ppm.

Compound **3b** (F_2 = 2,6-F_2; R = Bu^n): yield, 69%; m.p. 136–138 °C; recrystallized from ethanol. Mössbauer: QS: 3.47, IS: 1.34, Γ_1: 0.90, Γ_2: 0.92 mm s^{-1}. ^{1}H NMR δ: H-3 and H-5: 6.88 (dd, **8**, 8); H-4: 7.29 (tt, 8, **6**); H-8 and H-9: 1.47–1.79 (m); H-10: 1.31 (tq, 7, 7) and 1.37 (tq, 7, 7); H-11: 0.84 (t, 7) and 0.89 (t, 7) ppm. ^{13}C NMR δ: C-1: 115.1 [t, $^2J(^{19}F–^{13}C)$ = 39 Hz] (calc.: 104.4); C-2 and C-6: 159.6 [d, $^1J(^{19}F–^{13}C)$ = 245 Hz] (166.6); C-3 and C-5: 111.7 [d, $^2J(^{19}F–^{13}C)$ = 24 Hz] (110.8); C-4: 130.6 [t, $^3J(^{19}F–^{13}C)$ = 19 Hz] (135.8); C-7: 166.8; C-8: 27.8 [$^1J(^{119/117}Sn–^{13}C)$ = 669/640 Hz] and 28.6 [$^1J(^{119/117}Sn–^{13}C)$ = 681/651 Hz]; C-9: 27.0 [^2J(Sn–C) = nv] and 27.2 [^2J(Sn–C) = nv]; C-10: 26.8 [^3J(Sn–C) = 132 Hz]; C-11: 13.4 and 13.5 ppm.

Compound **4b** (F_2 = 3,5-F_2; R = Bu^n): yield, 65%; m.p. 123–125 °C; recrystallization from ethanol. Mössbauer: QS: 3.47, IS: 1.33, Γ_1: 0.86, Γ_2: 0.87 mm s^{-1}. ^{1}H NMR δ: H-2 and H-6: 7.51 (bd, **6**); H-4: 7.03 (bt, **8**); H-8 and H-9: 1.60–1.74 (m); H-10: 1.28 (tq, 7, 7) and 1.38 (tq, 7, 7); H-11: 0.78 (t, 7) and 0.88 (t, 7) ppm. ^{13}C NMR δ: C-1: 136.7 (calc.: 133.0); C-2 and C-6: 112.5 [d, $^2J(^{19}F–^{13}C)$ = 25 Hz] (113.0); C-3 and C-5: 162.7 [dd, $^1J(^{19}F–^{13}C)$ = 250 Hz, $^3J(^{19}F–^{13}C)$ = 12 Hz] (164.4); C-4: 107.4 (t, $^2J(^{19}F–^{13}C)$ = 25 Hz] (107.2); C-7: 170.2; C-8: 28.4 [^1J(Sn–C) ≈ 707 Hz] and 30.6 [^1J(Sn–C) ≈ 670 Hz]; C-9: 27.4 [^2J(Sn–C) = 35 Hz] and 27.7

[^2J(Sn–C) = 37 Hz]; C-10: 26.6 [^3J(Sn–C) = 120 Hz]; C-11: 13.3 and 13.4 ppm.



Compound **7a** (F_2 = 2,6-F_2; R = Et): yield, 91%; m.p. 88–90 °C; recrystallized from toluene/ethanol. Mössbauer: QS: 3.54, IS: 1.38, Γ_1: 0.99, Γ_2: 0.88 mm s^{-1}. ^{1}H NMR δ: H-3 and H-5: 6.94 (dd, **8**, 8); H-4: 7.40 (tt, 8, **6**); H-8: 1.92 [q, 8, ^2J(Sn–^{1}H) = 78 Hz]; H-9: 1.45 [t, 8, $^3J(^{119/117}$Sn–^{1}H) = 144/138 Hz] ppm. ^{13}C NMR δ: C-1: 110.9 [t, $^2J(^{19}$F–^{13}C) = 18 Hz] (calc.: 104.4); C-2 and C-6: 160.7 [dd, $^1J(^{19}$F–^{13}C) = 257 Hz, $^3J(^{19}$F–^{13}C) = 6 Hz] (166.6); C-3 and C-5: 111.9 [d, $^2J(^{19}$F–^{13}C) = 22 Hz] (110.8); C-4: 132.7 [t, $^3J(^{19}$F–^{13}C) = 10 Hz] (135.8); C-7: 170.4; C-8: 18.5 [$^1J(^{119/117}$Sn–^{13}C) = 580/555 Hz]; C-9: 8.6 [^2J(Sn–C) = 46 Hz] ppm.

Compound **6b** (F_2 = 2,5-F_2; R = Et): yield, 84%; m.p. 213–215 °C; recrystallization from toluene/ethanol. Mössbauer: QS: 3.49, IS: 1.34, Γ_1: 0.93, Γ_2: 0.96 mm s^{-1}. ^{1}H NMR δ: H-3: 7.11 (ddd, 9, **9**, **5**); H-4: 7.16 (ddd, 9, **9**, **6**, 3); H-6: 7.63 (ddd, **9**, **6**, 3); H-8: 1.59 [q, 8, ^2J(Sn–^{1}H) = 67 Hz] and 1.62 [q, 8, ^2J(Sn–^{1}H) = 65 Hz]; H-9: 1.33 [t, 8, $^3J(^{119/117}$Sn–^{1}H) = 147/141 Hz] and 1.40 [t, 8, $^3J(^{119/117}$Sn–^{1}H) = 149/143 Hz] ppm. ^{13}C NMR δ: C-1: 122.9 (calc.: 118.7); C-2: 158.0 [d, $^1J(^{19}$F–^{13}C) = 242 Hz] (160.7); C-3: 118.0 [dd, $^2J(^{19}$F–^{13}C) = 26 Hz, $^3J(^{19}$F–^{13}C) = 8 Hz] (116.7); C-4: 120.0 [dd, $^2J(^{19}$F–^{13}C) = 24 Hz; $^3J(^{19}$F–^{13}C) = 9 Hz] (121.5); C-5: 157.9 [d, $^1J(^{19}$F–^{13}C) = 254 Hz] (158.5); C-6: 118.5 [d, $^2J(^{19}$F–^{13}C) = 25 Hz] (118.9); C-7: 169.0; C-8: 20.7 [$^1J(^{119/117}$Sn–^{13}C) = 735/710 Hz] and 22.9 [$^1J(^{119/117}$Sn–^{13}C) = 766/725 Hz]; C-9: 9.5 [^2J(Sn–C) = nv] and 9.8 [^2J(Sn–C) = 45 Hz] ppm.

Compound **7b** (F_2 = 2,6-F_2; R = Et): yield, 80%; m.p. 225–227 °C; recrystallized from petroleum ether. Mössbauer: QS: 3.51, IS: 1.36, Γ_1: 0.96, Γ_2: 0.99 mm s^{-1}. ^{1}H NMR δ: H-3 and H-5: 6.89 (dd, 8, **8**); H-4: 7.30 (tt, 8, **6**); H-8: 1.57 [q, 8, ^2J(Sn–^{1}H) = 79 Hz] and 1.63 [q, 8, ^2J(Sn–^{1}H) = 80 Hz]; H-9: 1.30 [t, 8, $^3J(^{119/117}$Sn–^{1}H) = 145/139 Hz] and 1.40 [t, 8, $^3J(^{119/117}$Sn–^{1}H) = 148/142 Hz] ppm. ^{13}C NMR δ: C-1: 114.7 [t, $^2J(^{19}$F–^{13}C) = 20 Hz] (calc.: 104.4); C-2 and C-6: 159.8 [dd, $^1J(^{19}$F–^{13}C) = 252 Hz, $^3J(^{19}$F–^{13}C) = 7 Hz] (166.6); C-3 and C-5: 111.7 [d, $^2J(^{19}$F–^{13}C) = 24 Hz] (110.8); C-4: 130.8 [t, $^3J(^{19}$F–^{13}C) = 10 Hz] (135.8); C-7: 167.1; C-8: 20.3 [$^1J(^{119/117}$Sn–^{13}C) = 698/668 Hz] and 21.6 [$^1J(^{119/117}$Sn–^{13}C) = 713/679 Hz]; C-9: 9.3 [^2J(Sn–^{13}C) = 41 Hz] ppm.

Compound **8b** (F_2 = 3,5-F_2; R = Et): yield, 82%; m.p. 224–225 °C; recrystallized from chloroform/ethanol. Mössbauer: QS: 3.47, IS: 1.33, Γ_1: 0.96, Γ_2: 1.00 mm s^{-1}. ^{1}H NMR δ: H-2 and H-6: 7.53 (dd, **8**, 2); H-4: 7.02 (tt, **9**, 2); H-8: 1.60 [q, 8, ^2J(Sn–^{1}H) = 85 Hz] and 1.68 (q, 8, ^2J(Sn–^{1}H) = 80 Hz];

H-9: 1.36 [t, 8, $^{3}J(^{119/117}Sn-^{1}H) = 147/140$ Hz] and 1.41 [t, 8, $^{3}J(^{119/117}Sn-^{1}H) = 148/143$ Hz] ppm. ^{13}C NMR δ: C-1: 136.5 (calc.: 133.0); C-2 and C-6: 112.6 [d, $^{2}J(^{19}F-^{13}C) = 25$ Hz] (113.0); C-3 and C-5: 162.7 [dd, $^{1}J(^{19}F-^{13}C) = 250$ Hz, $^{3}J(^{19}F-^{13}C) = 12$ Hz] (164.4); C-4: 107.6 [t, $^{2}J(^{19}F-^{13}C) = 25$ Hz] (107.2); C-7: 170.3; C-8: 20.6 [$^{1}J(^{119/117}Sn-^{13}C) = 727/695$ Hz] and 23.4 [$^{1}J(^{119/117}Sn-^{13}C) = 764/738$ Hz]; C-9: 9.8 [$^{2}J(Sn-^{13}C) = 36$ Hz] and 10.0 [$^{2}J(Sn-^{13}C) = 44$ Hz] ppm.

In vitro *tests*

Drug activity was determined using an automated *in vitro* technique as described previously [7, 8, 12].

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