

The in vitro trypanocidal activity of organotin compounds

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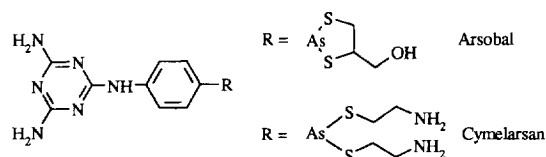
Summary — A series of alkyl (aryl) thio organotin compounds were synthesized as potential trypanocidal drugs. These derivatives were prepared by the treatment of alkyl (or aryl) tin chlorides or oxides with thiols. Compounds were evaluated for trypanocidal activity using in vitro cultures of *Trypanosoma equiperdum*. Their efficiency for killing the parasites appeared to be under control of both the alkyl (or aryl) part of the molecule and the thio moiety. Several of the synthesized compounds exhibited a high in vitro levels of activity compared with the arsenic derivatives used for chemotherapy.

trypanocidal activity / organotin / thio derivative / triazine

Introduction

Trypanosomal diseases are one of the major health problems in tropical areas of Africa (human sleeping sickness and domesticated livestock diseases) [1]. Extensive use of a limited number of commercially available trypanocides has resulted in the appearance of trypanosome strains resistant to these drugs and the discovery of new drugs is lacking. Organoarsenic compounds such as Arsobal are still the most common drugs used for treatment of the second stage of the disease in humans when trypanosomes invade the central nervous system [2, 3]. However, this great potency cannot hide their strong toxicity for the patient (nearly 5% die during the treatment), due to the presence of the arsenic moiety [4, 5]. Cymelarsan has been recently developed to treat canine heartworm disease caused by *Dirofilaria immitis* and camels infected with *Trypanosoma evansi* (scheme 1).

These compounds have been described to interact with trypanothione (*N*-1-, *N*-8-bisglutathionylspermidine), which is the substrate of trypanothione reductase, a central enzyme in parasite metabolism [6]. This interaction appears to occur via the hetero atom which could undergo bonding with the free thiol groups of the two cysteines present in the cofactor.

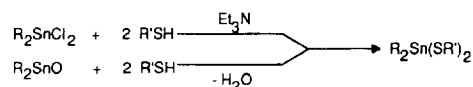


Scheme 1.

Thus, the central atom of a new lead compounds ought to show a great affinity towards sulfur. Moreover, in order to replace the arsenic derivatives with a good efficiency, these derivatives would have to have a lower toxicity. These two parameters led us to select the tin atom as a candidate for synthetic work [7, 8].

Chemistry

Most of the synthesized dialkyl (or diaryl) dithioalkyl (or thioaryl) tin derivatives were obtained according to reactions presented in scheme 2. Two equivalents of thiol were mixed with one equivalent of dialkyl (or diaryl) tin dichloride, and the HCl formed was trapped



Scheme 2.

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with triethylamine. When a tin oxide was used, the water generated during the reaction was continuously removed with a Dean–Stark trap [9–11]. The compounds synthesized are listed in table I.

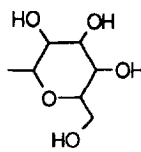
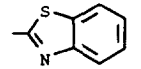
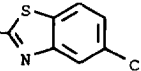
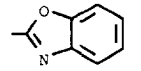
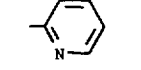
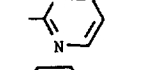
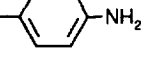
Compounds where a tin atom is included in a ring were synthesized according to scheme 3, reacting 1 mol of a dithiol with 1 mol of disubstituted tin dichlorides (or tin oxides). Compounds **15–22**, synthesized according to this scheme, are summarized in table II.

When dialkyl (or diaryl) tin dichlorides were not commercially available, they were synthesized by a

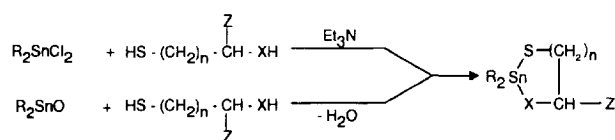
redistribution reaction of the corresponding tetraalkyl (tetraaryl) tin with tin tetrachloride, according to scheme 4 [12]. Substituted tin chlorides yielded by this method were further reacted with thiols.

We described that when R is a 4-(*N,N*-dimethylamino)phenyl group, the three possible compounds could be obtained just by mixing the two reactants in the required proportions at room temperature [13]. The results of further reactions with thiols are summarized in table III; all the compounds correspond to the general formula $R_nSn(SR')_{4-n}$ [13].

Table I. Organotin compounds synthesized according to scheme 2.

Compound	R	R'	Reference ^a	Yield (%)
1	-CH ₃	-(CH ₂) ₂ CH ₃	[16]	99
2	-CH ₃	-(CH ₂) ₇ CH ₃	[17]	92
3	-CH ₃			97
4	-(CH ₂) ₃ CH ₃	-(CH ₂) ₂ CH ₃	[18]	97
5	-(CH ₂) ₃ CH ₃	-(CH ₂) ₇ CH ₃	[19]	95
6	-(CH ₂) ₃ CH ₃		[20]	83
7	-(CH ₂) ₃ CH ₃			94
8	-(CH ₂) ₃ CH ₃			94
9	-(CH ₂) ₃ CH ₃		[21]	93
10	-(CH ₂) ₃ CH ₃			92
11	-(CH ₂) ₃ CH ₃			74
12	-(CH ₂) ₃ CH ₃	-CH ₂ CH ₂ NH ₂ , HCl	[22]	57
13	-C ₆ H ₅	-(CH ₂) ₂ CH ₃	[23]	99
14	-C ₆ H ₅	-(CH ₂) ₇ CH ₃	[24]	97

^aCompounds previously described in the literature.



Scheme 3.

Since Arsobal and Cymelarsan embody one triazinyl moiety, it would be interesting to obtain compounds including this heterocycle. Compound **27** was synthesized according to scheme 5. Two equivalents of 2-chloro-4,6-diamino-1,3,5-triazine were mixed in refluxing DMF with one equivalent of **12**, in the presence of potassium carbonate.

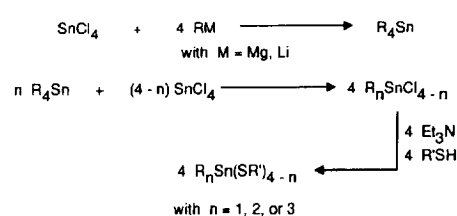
The synthesis of **30** required three steps (scheme 6). Disulfide **28** was first obtained when reacting two equivalents of 2-chloro-4,6-diamino-1,3,5-triazine with one equivalent of (4-aminophenyl)disulfide in acidic water. Thiol **29** was then generated by tributyl phosphine reduction of the resulting disulfide in a methanol/water (9:1) mixture [14]. This was then condensed on tributyltin chloride, in the presence of triethylamine to yield **30**.

Biology: trypanocidal activity

The trypanocidal activity tests were carried out in vitro on cultures of *T. equiperdum* (see *Experimental protocols*) [15, 16]. Values indicated for these activities correspond to the minimum amount required to cause death of all trypanosomes within 24 h (table IV)

Results and discussion

These results show clear evidence of the in vitro trypanocidal activity of organotin compounds, several of them being at least as active as Arsobal or Cymelarsan. Antiparasitic properties cannot be solely



Scheme 4.

a result of the presence of the tin atom as several molecules presented here are totally devoid of activity, even though they contain tin.

Comparison of the respective potency of derivatives containing the same thio part (thiopropyl for example) and a variable alkyl (or aryl) group (methyl for **1**, butyl for **4** and phenyl for **13**) highlights an enhanced activity for butyl-substituted derivatives.

In order to measure the influence of the mercapto group, the analysis of butyl-containing compounds only (since methyl and phenyl compounds are less active) was sufficient to correlate the observed differences of activities with the nature of the thiol linked to tin. Heteroaromatic rings, such as 2-mercaptobenzothiazole and 2-mercaptobenzoxazole, appear to afford a good level of efficiency (**6** and **8**). However **7**, which only differs from **6** by the presence of a chlorine atom on the benzothiazolyl ring, is 70-fold less active. We can also note that monocyclic heteroaromatic structures (**9** and **10**) are totally devoid of trypanocidal potency. Moreover, **27** and **30**, which embody a melaminyl moiety (ie, triaminotriazinyl), exhibit strong activity.

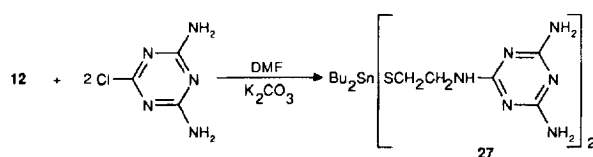
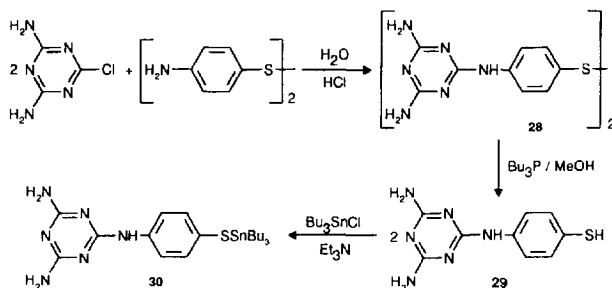
Except for dimethyl tin compounds, which are totally inactive (whatever the thiol), a six-membered cyclic structure including tin appears to improve the efficiency of the derivatives (**18** and **22**). This might be due to the lipophilic properties of the defined structure. Moreover, contraction of this structure into a

Table II. Organotin compounds obtained via scheme 3.

Compound	R	X	n	Z	Reference	Yield (%)
15	-CH ₃	S	1	-H	[25]	77
16	-CH ₃	S	2	-H	[26]	70
17	-(CH ₂) ₃ CH ₃	S	1	-H	[27]	90
18	-(CH ₂) ₃ CH ₃	S	2	-H	[28]	91
19	-(CH ₂) ₃ CH ₃	S	1	-CH ₂ OH	[29]	94
20	-(CH ₂) ₃ CH ₃	O	1	-H	[30]	95
21	-C ₆ H ₅	S	1	-H	[31]	88
22	-C ₆ H ₅	S	2	-H	[32]	77

Table III. Synthesized 4-(*N,N*-dimethylamino)phenyltin compounds (general formula $R_n\text{Sn}(\text{SR}')_{4-n}$).

Compound	R	n	R'	Reference	Yield (%)
23	4-[(CH ₃) ₂ N]C ₆ H ₄ -	1	-(CH ₂) ₂ CH ₃	[13]	62
24	4-[(CH ₃) ₂ N]C ₆ H ₄ -	2	-(CH ₂) ₂ CH ₃	[13]	75
25	4-[(CH ₃) ₂ N]C ₆ H ₄ -	3	-(CH ₂) ₂ CH ₃	[13]	60
26	4-[(CH ₃) ₂ N]C ₆ H ₄ -	3	-(CH ₂) ₇ CH ₃	[13]	65

**Scheme 5.****Scheme 6.**

five-membered ring (**17**, **19**, **20** and **21**) leads to a net decrease of activity.

Selected samples that showed strong in vitro activity were injected intraperitoneally in mice infected with *T. equiperdum*. Injection had to be performed when compounds were suspended in polypropylene glycol because of their lack of water solubility. None of them showed activity or toxicity in vivo. As none of the compounds was active in vivo, we did not test the effect of the vehicle alone or the presence of the drug in the peritoneum. This absence of both activity and toxicity in the experiments in vivo might be due to the absence of water solubility of the tested derivatives, as well as a poor targeting towards the parasite. Our research is now directed towards improvement of these two parameters.

Experimental protocols

Biology

Cultivation of bloodstream forms of trypanosomes

T. equiperdum was cultivated in vitro according to Baltz et al [16]. The cultured medium used consisted of minimum essential medium (MEM) supplemented with 25 mM HEPES, 1 g/L additional glucose, 2.2 g/L NaHCO₃, adjusted to pH 7.3 with 5 M NaOH and sterilized by filtration (0.22 µm), then stored for up to 10 days at 4 °C. Before use, the medium was further supplemented as follows: 0.2 mM 2-mercaptoethanol, 2.0 mM Na-pyruvate, 0.1 mM hypoxanthine and 0.016 mM thymidine. The serum component was 10% heat-inactivated rabbit or fetal calf serum.

Table IV. MEC values for compounds 1–30.

Compound	MEC (nM)	Compound	MEC (nM)
1	8360	15	10 400
2	5700	16	9800
3	18 500	17	30
4	7.8	18	5.5
5	9.2	19	55
6	0.7	20	27.5
7	49	21	3420
8	0.7	22	8
9	170	23	>21 500
10	33	24	2450
11	20	25	>18 000
12	85	26	>16 000
13	59	27	0.8
14	138.5	30	1
Arsobal	5	Cymelarsan	0.6

MEC is the minimal efficient concentration which allows complete depletion of trypanosoma population. The tests were carried out three times for each sample and the average value was tabulated. The values concerning the arsenic derivatives Arsobal and Cymelarsan are also reported.

In vitro drug sensitivity tests

Drugs were dissolved in DMSO (10 mg/mL) and diluted to appropriate concentration in culture medium in 12-well tissue culture plates. To the first well containing 2 mL culture medium, 20 μ L of the selected drug concentration was added. The drug was then diluted serially to the other wells containing 1 mL culture medium. Each drug was thus diluted from 10 μ g/mL to 2.44 ng/mL. Trypanosomes (2×10^4) were added to each well and cultured at 37 °C in a CO₂ atmosphere (4% CO₂/96% air) for 24 h. Control cultures (without drug) were incubated under the same conditions. The MEC (minimal effective concentration which killed the trypanosomes population by 100%) was determined after 24 h. Viable, motile trypanosomes were counted in a Malassez haemocytometer and the relative growth was calculated using the control value as 100%. At least three independent experiments were performed for each measurement. The studies on *in vitro* cultured trypanosomes determine the cytotoxic effect of the compounds as only viable, motile trypanosomes are counted (killed parasites are no longer motile).

Chemistry

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on Bruker AC 200 (¹H: 200.13 MHz; ¹³C: 50.32 MHz). Chemical shifts are given in ppm downfield from tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on a Finnigan Mat TSQ 70 triplequadrupole mass spectrometer in electron impact ionization mode (70 eV). All elemental analyses were performed by the Laboratoires du CNRS, BP 22, 69390 Vernaison, France.

Bis(peracetyl-1-glucosylthio)dimethyltin 3

In order to be more easily analyzed, the glucose moiety in **3** was peracetylated. A solution of dimethylindichloride (150 mg; 0.683 mmol) in 10 mL benzene was added at room temperature to a mixture of peracetyl-1-thioglucofuranose (510 mg; 1.4 mmol) and triethylamine (0.2 mL; 1.4 mmol) in 40 mL benzene. The reaction mixture was stirred for 1 h under reflux. After cooling at room temperature, the triethylamine hydrochloride was filtered off and the solvent was evaporated to leave a white solid (0.58 g; 97% yield) which was analytically pure. ¹H-NMR (CDCl₃) δ 0.89 (6H, s, ²J(¹H-¹³C) = 32.2 Hz, CH₃-); 1.99 (3H, s, CH₃CO-); 2.01 (3H, s, CH₃CO-); 2.06 (3H, s, CH₃CO-); 2.07 (3H, s, CH₃CO-); 3.75 (2H, m, H-5); 4.15 (4H, m, H-6); 4.74 (2H, d, *J* = 9.3 Hz, H-1); 4.95–5.15 (6H, m, H-2, H-3, H-4). ¹³C-NMR (CDCl₃) δ 1.7 (CH₃-, ¹J(¹³C-¹¹⁹Sn) = 430.0 Hz); 20.47; 20.50; 20.70 (CH₃CO-); 61.7 (C-6); 67.9 (C-4); 73.4 (C-2); 73.9 (C-5); 76.4 (C-3); 80.1 (C-1); 169.2; 169.3; 170.0; 170.3(-CO-).

Bis(5-chloro-2-benzothiazolylthio)dibutyltin 7

A mixture of dibutylindichloride (1.52 g; 5 mmol) in toluene (15 mL) was added dropwise, at room temperature and under nitrogen atmosphere, to a solution of 5-chloro-2-mercaptobenzothiazole (2.02 g; 10 mmol) and triethylamine (1.01 g; 10 mmol) in toluene (30 mL). The mixture was first stirred for 15 min at room temperature and then for 12 h refluxing. After cooling at room temperature, the organic solution was washed with aqueous saturated sodium chloride (2 x 25 mL). The aqueous phase was extracted with dichloromethane (3 x 20 mL). All the organic layers were combined, dried over Na₂SO₄, and solvents were removed by rotary evaporation. A brown solid was recovered and recrystallised from a mixture of CH₂Cl₂/C₆H₁₄ (3:7) to obtain slightly brown crystals (2.1 g, 66.2%).

Mp 120 °C. Anal calc C₂₅H₂₄N₂S₄Cl₂Sn: C, 41.66; H, 3.81; N, 4.42; found: C, 41.91; H, 3.80; N, 4.61. ¹H-NMR (CDCl₃) δ 0.83 (6H, t, *J* = 7.3 Hz, H-4); 1.38 (4H, sextet, *J* = 7.3 Hz, H-3); 1.75 (4H, m, H-2); 1.95 (4H, m, H-1); 7.25 (2H, dd, *J* = 2.0 Hz, 8.4 Hz, H-6); 7.60 (2H, d, *J* = 8.4 Hz, H-7); 7.64 (2H, d, *J* = 2.0 Hz, H-4). ¹³C-NMR (CDCl₃) δ 13.5 (C-4); 26.2 (C-3, ³J(¹³C-¹¹⁹Sn) = 98.7 Hz); 28.0 (C-2, ²J(¹³C-¹¹⁹Sn) = 36.6 Hz); 28.7 (C-1, ¹J(¹³C-¹¹⁹Sn) = 501.4 Hz); 119.2 (C-6'); 121.8 (C-7'); 124.2 (C-4'); 132.2 (C-3'a); 135.4 (C-7'a); 152.3 (C-5'); C-2' not found.

Bis(2-benzoxazolylthio)dibutyltin 8

A mixture of dibutylindichloride (1.52 g; 5 mmol) in toluene (15 mL) was added dropwise, at room temperature and under nitrogen atmosphere, to a solution of 2-mercaptobenzoxazole (1.51 g; 10 mmol) and triethylamine (1.01 g; 10 mmol) in toluene (30 mL). The mixture was first stirred for 15 min at room temperature and then refluxed for 12 h. After cooling to room temperature, the organic solution was washed with aqueous saturated sodium chloride (2 x 25 mL). This aqueous phase was extracted with dichloromethane (3 x 20 mL). All the organic layers were combined, dried over Na₂SO₄ and solvents were removed by rotary evaporation. A brown solid was recovered and recrystallised from a mixture of CH₂Cl₂/C₆H₁₄ (2:8) to obtain brown crystals (1.46 g; 54.7%). Mp 98 °C. Anal calc C₂₅H₂₄N₂O₂S₂Sn: C, 49.55; H, 4.91; N, 5.25; found: C, 48.81; H, 5.04; N, 4.95. ¹H-NMR (CDCl₃) δ 0.85 (6H, t, *J* = 7.2 Hz, H-4); 1.40 (4H, sextet, *J* = 7.2 Hz, H-3); 1.83 (4H, m, H-2); 2.01 (4H, m, H-1); 7.15–7.45 (8H, m, H-arom). ¹³C-NMR (CDCl₃) δ 13.5 (C-4); 26.1 (C-3, ³J(¹³C-¹¹⁹Sn) = 103.6 Hz); 27.9 (C-2, ²J(¹³C-¹¹⁹Sn) = 35.6 Hz); 29.2 (C-1, ¹J(¹³C-¹¹⁹Sn) = 506.1 Hz); 110.0; 115.3; 123.5; 124.4 (C-4'; C-5'; C-6'; C-7'); 139.3 (C-3'a); 152.0 (C-7'a); 173.1 (C-2').

Bis(-2-pyrimidinylthio)dibutyltin 10

A mixture of dibutylindichloride (1.52 g; 5 mmol) in toluene (15 mL) was added dropwise, at room temperature and under nitrogen atmosphere, to a solution of 2-mercaptopyrimidine (1.51 g; 10 mmol) and triethylamine (1.01 g; 10 mmol) in toluene (30 mL). The mixture was first stirred for 15 min at room temperature and then for 12 h refluxing. After cooling at room temperature, the organic solution was washed with aqueous saturated sodium chloride (2 x 25 mL). This aqueous phase was extracted with dichloromethane (3 x 20 mL). All the organic layers were combined, dried over Na₂SO₄ and solvents were removed by rotary evaporation. A yellow solid was recovered and recrystallised from a mixture of CH₂Cl₂/C₆H₁₄ (2:8) to obtain pale yellow crystals (1.55 g, 68.1%). Mp 160 °C. Anal calc C₁₆H₂₄N₄S₂Sn: C, 42.21; H, 5.31; N, 12.30; found: C, 41.87; H, 5.40; N, 12.30. ¹H-NMR (CDCl₃) δ 0.81 (6H, t, *J* = 7.2 Hz, H-4); 1.36 (4H, m, H-3); 1.67 (8H, m, H-1, H-2); 6.96 (2H, t, *J* = 4.9 Hz, H-5'); 8.37 (4H, d, *J* = 4.9 Hz, H-4', H-6'). ¹³C-NMR (CDCl₃) δ 13.5 (C-4); 25.4 (C-1, ¹J(¹³C-¹¹⁹Sn) = 534.5 Hz); 26.1 (C-3, ³J(¹³C-¹¹⁹Sn) = 99.8 Hz); 28.2 (C-2, ²J(¹³C-¹¹⁹Sn) = 35.3 Hz); 115.4 (C-5'); 156.5 (C-4'; C-6'); 175.7 (C-2').

Bis(4-aminophenylthio)dibutyltin 11

A mixture of dibutylindichloride (440 mg; 1.44 mmol) in toluene (10 mL) was added dropwise, at room temperature and under nitrogen atmosphere, to a solution of *p*-aminothiophenol (500 mg; 4 mmol) and triethylamine (405 mg; 4 mmol) in toluene (20 mL). The mixture was first stirred for 12 h at room temperature and then for 3 h refluxing. After cooling at room temperature, the organic solution was washed with aqueous saturated sodium chloride (2 x 25 mL). The organic layer was dried over Na₂SO₄ and solvent was removed by rotary evapora-

tion. An orange viscous liquid was recovered, which was recrystallised from a mixture of $\text{CH}_2\text{Cl}_2/\text{C}_6\text{H}_{14}$ (2:8) to obtain yellow crystals (510 mg, 73.6%). Anal calc $\text{C}_{20}\text{H}_{30}\text{N}_2\text{S}_2\text{Sn}$: C, 49.91; H, 6.28; N, 5.82; found: C, 50.16; H, 6.36; N, 5.89. $^1\text{H-NMR}$ (CDCl_3) δ 0.80 (6H, app t, H-4); 1.10–1.30 (8H, m, H-2, H-3); 1.40 (4H, m, H-1); 3.60 (4H, bs, $-\text{NH}_2$); 6.50 (4H, dd, $J = 6.4$ Hz, $J = 2.0$ Hz, H arom); 7.20 (4H, dd, $J = 6.4$ Hz, $J = 2.0$ Hz, H arom). $^{13}\text{C-NMR}$ (CDCl_3) δ 13.5 (C-4); 18.5 (C-1, $^1J(^{13}\text{C}-^{119}\text{Sn}) = 358.6$ Hz); 26.6 (C-3, $^3J(^{13}\text{C}-^{119}\text{Sn}) = 73.25$ Hz); 27.9 (C-2, $^2J(^{13}\text{C}-^{119}\text{Sn}) = 24.4$ Hz); 115.6 (CH arom); 119.4 (C-1'); 135.9 (CH arom); 145.2 (C-4').

Bis(2-melaminylethylthio)dibutyltin 27

A solution of bis(2-aminoethylthio)dibutyltin **12** (1.15 g; 3.25 mmol) in 15 mL DMF was added dropwise at room temperature to a mixture of 2-chloro-4,6-diamino-1,3,5-triazine (946 mg; 6.5 mmol) and potassium carbonate (2.76 g; 20 mmol) in 10 mL DMF. The reaction mixture was left under reflux overnight. The DMF was then distilled off under reduced pressure and the solid recovered was poured into water. A white powder which was still insoluble was filtered off and then chromatographed. Only 180 mg (6% yield) of the desired product was collected (the compound appeared to decompose slowly while going through the column). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 0.84 (apparent t, 6H, H-4); 1.08 (m, 4H, H-1); 1.28 (m, 4H, H-3); 1.50 (m, 4H, H-2); 3.30 (m, 4H); 3.60 (m, 4H); 6.2 (bs, 8H, NH_2); 6.65 (bs, 2H, $-\text{NH}-$). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 13.4 (C-4); 26.3 (C-3); 28.1 (C-2); 37.8 (C-1); 39.4 (C-1'); 43.7 (C-2'); 166.1 (C-3'); 167 (C-4', C-5').

(4-Melaminophenylthio)tributyltin 30

This synthesis was conducted in three steps.

Synthesis of the bis(4-melaminophenyl)disulfide 28. 2-Chloro-4,6-diamino-1,3,5-triazine (1.16 g; 8 mmol) was dissolved in 25 mL water and 1.5 mL of a solution of 2 N HCl (3 mmol) was added. The medium was stirred at room temperature for 15 min. Bis(4-aminophenyl)disulfide (984 mg; 4 mmol) was then added and the mixture was heated at 100°C for 1 h, after which it was cooled to room temperature. It was neutralized with a solution of 1 N NaOH and a pale yellow solid was filtered off (1.7 g, 91.2% yield). It was characterised by NMR as the desired product. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 6.6 (8H, bs, $-\text{NH}_2$); 7.3 (4H, dd, H arom); 7.8 (4H, dd, $J = 2.40$ Hz, $J = 6.80$ Hz, H arom); 9.3 (2H, s, $-\text{NH}-$). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 120.2 (CH arom); 127.6 (C-1), 130.5 (CH arom); 140.9 (C-4); 164.1 (C-7); 165.5 (C-8, C-9).

Synthesis of 4-melaminothiophenol 29. Compound **28** (932 mg; 2 mmol) was dissolved in 40 mL of a MeOH/ H_2O (9:1) mixture and 1 mL (4 mmol) of tributylphosphine was added. The medium was stirred for 1 h at room temperature and the MeOH was evaporated, leaving an aqueous phase with an insoluble compound which was filtered off, washed with ether (to remove excess tributylphosphine) and lyophilized. It was used in the next step with no further purification. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 6.3 (4H, bs, $-\text{NH}_2$); 7.2 (2H, d, H arom); 7.7 (2H, d, H arom); 8.9 (1H, s, $-\text{NH}-$). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 120.8 (CH arom); 122.1 (C-1), 129.3 (CH arom); 138.5 (C-4); 164.4 (C-7); 166.8 (C-8, C-9).

Synthesis of (4-melaminophenylthio)tributyltin 30. Compound **29** (800 mg; 3.4 mmol, 16.6% excess) and 420 μL triethylamine (3 mmol) were mixed into 25 mL toluene. Tributyltinchloride (814 μL , 3 mmol) in 10 mL toluene was then added slowly and the reaction mixture was left at room temperature for 4 h before refluxing for 12 h. The organic layer was washed with water (3 x 20 mL), dried over MgSO_4 and the toluene was

evaporated to obtain a white solid (1.1 g, 70% yield). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 0.80–1.80 (27H, m, H-1, H-2, H-3, H-4); 6.30 (4H, s, $-\text{NH}_2$); 7.15 (2H, d, $J = 9.4$ Hz, H-arom); 7.65 (2H, d, $J = 9.4$ Hz, H-arom); 8.8 (1H, s, $-\text{NH}-$). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 13.5 (C-4); 14.8 (C-1, $^1J(^{13}\text{C}-^{119}\text{Sn}) = 344.0$ Hz); 26.5 (C-3, $^3J(^{13}\text{C}-^{119}\text{Sn}) = 62.0$ Hz); 28.1 (C-2); 119.3 (C-3', C-5'); 126.1 (C-1'); 134.1 (C-2', C-6'); 138.6 (C-4'); 164.6 (C-7'); 167.1 (C-8', C-9').

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