

Preliminary communication

Synthesis and evaluation of the in vivo trypanocidal activity of water soluble organotin compounds

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Abstract – A series of (3-(2-methoxy)ethoxypropyl)tin derivatives were synthesized as potential trypanocidal drugs. The series included an alkyltin trichloride, a dialkyltin dichloride and the corresponding dialkyltin oxide, and six dialkyltin dithio derivatives. Compounds were evaluated for trypanocidal activity using in vitro cultures of *Trypanosoma equiperdum* and mice infected with the same strain of parasite for in vivo tests. Two of the title derivatives, the bis (3-(2-methoxy)ethoxypropyl)tin dichloride **2** and the corresponding bis (3-(2-methoxy)ethoxypropyl)tin oxide **3**, appeared to be water soluble reagents. Furthermore, they are the first examples of organotin compounds presenting interesting in vivo trypanocidal activity. © 1999 Éditions scientifiques et médicales Elsevier SAS

organotin / in vivo trypanocidal activity / water solubility

1. Introduction

Trypanosomal diseases are one of the major health problems in tropical areas of Africa (human sleeping sickness and domesticated live stock 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. Organoarsenical compounds such as Arsobal (figure 1) are still the most commonly used drugs to treat the second stage of the disease when trypanosomes invade the central nervous system in humans [2, 3]. Although these drugs have great potency, they are very toxic for the patient (nearly 5% die during the treatment) due to the presence of the arsenic moiety [4, 5]. Cymelarsan (figure 1) has been recently developed to treat canine heartworm disease caused by *Dirofilaria immitis*, and also to treat camels infected with *Trypanosoma evansi*.

Previously, we had shown that organotin compounds could exhibit strong trypanocidal potency [6]. Some of

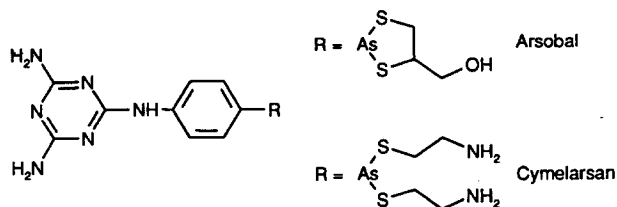


Figure 1. Organoarsenical derivatives commonly used as trypanocides in chemotherapy.

the tin derivatives already presented therein (figure 2) showed as good activity levels as Arsobal or Cymelarsan under in vitro conditions.

Unfortunately, this in vitro activity was not retained under in vivo conditions, and none of the organotin derivatives gave positive results when tested on infected mice. This loss of activity seemed to be connected to the lack of water solubility of these molecules. Since most of

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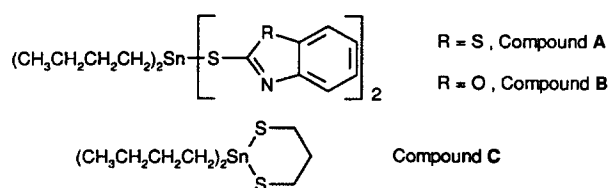


Figure 2. Organotin compounds which have been shown to demonstrate strong in vitro trypanocidal activity, namely bis (2-benzothiazolylthio)dibutyltin (**A**), bis (2-benzoxazolylthio)dibutyltin (**B**) and 2,2-dibutyl-2-stanna-1,3-dithiane (**C**).

the *Trypanosoma* population is present in the bloodstream, water solubility of the drug is necessary for activity.

Therefore, we were interested in increasing the hydro-solubility of our organotin compounds, by introducing hydrophilic groups in the molecule.

2. Chemistry

In 1990, Light and Breslow described tris(3-(2-methoxy)ethoxypropyl)tin hydride as a water soluble tin reagent [7]. Accordingly, our work was initiated from the reasonable assumption that other organotin compounds containing the same dioxalkyl moiety could likewise be water soluble.

Thus, we first synthesized (3-(2-methoxy)ethoxypropyl)tin trichloride **1** and bis (3-(2-methoxy)ethoxypropyl)tin dichloride **2** via a disproportionation reaction between tetrakis (3-(2-methoxy)ethoxypropyl) tin and tin tetrachloride (figure 3) [8–11].

These two tin chlorides **1** and **2** have proven to present a hexacoordinated metal atom in the solid state, studied

by X-ray crystallography, and to be water soluble [8]. Furthermore, we have shown that tin hexacoordination was retained upon dissolution of the derivatives, whatever the solvent used [8].

According to the in vitro results obtained with the previous series of organotin compounds, in which the presence of two Sn-S bonds appeared to be of major importance [12], we decided to transform the tin dichloride **2** into its corresponding dithio derivatives. The reaction usually employed for this purpose requires one equivalent of tin dichloride and two equivalents of thiol in the presence of Et_3N to trap the HCl formed during the reaction [13, 14].

Surprisingly, no expected dithio derivative was formed, although this kind of reaction is known to occur very rapidly, affording good yields [14]. So, we tried more vigorous experimental conditions, i.e. refluxing toluene and direct reaction of a sodium thiolate on the tin dichloride, but all these modifications were unsuccessful. In fact, the absence of reactivity of this particular tin dichloride towards thiols seems to be related to the very specific hexacoordinated structure of the tin atom.

Consequently, the required dithio derivatives had to be synthesized by another method. The tin dichloride **2** was transformed successfully into the corresponding oxide **3** by reaction in a boiling solution of sodium hydroxide (figure 4) [15].

The desired tin oxide **3** was recovered by hot filtration of the aqueous medium. Surprisingly, this compound was insoluble in hot water but appeared to become soluble when the temperature dropped.

Mass spectra analysis [16] gave an answer to this unusual behaviour: upon cooling, the oxide (mol. mass = 369) is transformed into the corresponding dihydroxide derivative (mol. mass = 387), which is soluble in cold water.

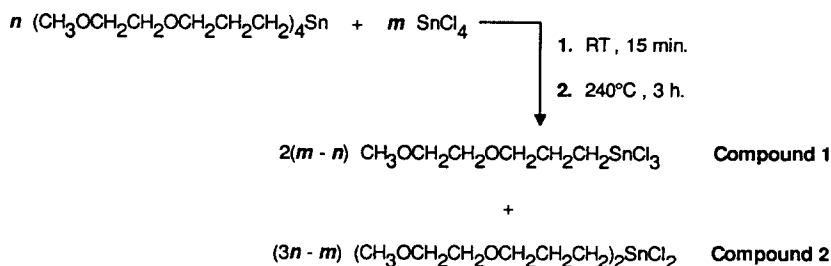


Figure 3. Synthesis of (3-(2-methoxy)ethoxypropyl)tin trichloride **1** and bis (3-(2-methoxy)ethoxypropyl)tin dichloride **2**, via a redistribution reaction between tetrakis (3-(2-methoxy)ethoxypropyl)tin and tin tetrachloride, with $m > n$.

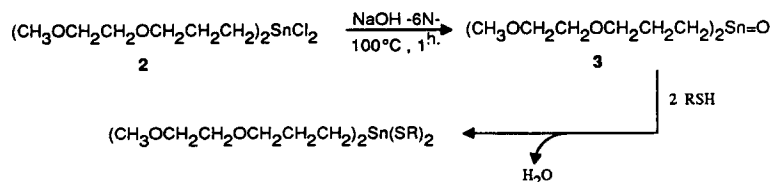


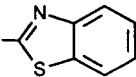
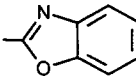
Figure 4. The first step corresponds to the transformation of the tin dichloride **2** into its corresponding tin oxide **3** in an aqueous alkaline medium. The second one describes the synthesis of the desired dithio derivatives **4–9** by reaction between the tin oxide **3** and different thiols in refluxing toluene and using a Dean-Stark trap.

The last step to perform was then to convert this tin oxide **3** into the desired dithio derivatives, according to *figure 4* [14, 17].

For this reaction, one equivalent of the tin oxide was reacted with two equivalents of the selected thiol (except for compound **9** which only requires one equivalent of a dithiol), in refluxing toluene. A Dean-Stark trap was used to continuously remove the water formed during the reaction. The dithio compounds synthesized according to *figure 4* are listed in *table I*.

The thiol groups were chosen with regard to the in vitro test results of a previous series of compounds [6]. Thiol groups of compounds which presented the greater in vitro activities were also used in this study. Two heterocyclic rings, 2-mercaptobenzothiazole and 2-mercaptobenzoxazole (for **7** and **8**), cysteamine (for **6**) and a tin containing ring formed with 1,3-dimercaptopropane (**9**) were studied.

Table I. Dithio organotin compounds synthesized according to *figure 4* and corresponding to the general formula: $(\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2)_2\text{Sn}(\text{SR})_2$.

Compound	R	Yield (%)
4	$-\text{CH}_2\text{CH}_2\text{CH}_3$	96
5	$-(\text{CH}_2)_7\text{CH}_3$	96
6	$-\text{CH}_2\text{CH}_2\text{NH}_2$	92
7		95
8		92
9	$-(\text{CH}_2)_3-$	97

We imagined, for compounds **4–9**, that the alkoxyalkyl part of the molecule should maintain some water solubility. In fact, although we did not perform detailed studies on this point, it appeared clearly that the presence of the thiol part made this hydrosolubility decrease (approximately $< 10^{-3}$ M).

3. Biology

3.1. In vitro trypanocidal activity

The trypanocidal activity tests were carried out in vitro on cultures of *Trypanosoma equiperdum* [18, 19]. Indicated values for the activities correspond to the minimum amount required to cause death of all trypanosomes within 24 h (*table II*).

3.2. In vivo trypanocidal activity

Tests were carried out on mice infected with *Trypanosoma equiperdum* [20]. Each drug was administrated intraperitoneally, at a dose of 1 mg per injection. Follow-

Table II. MEC values for compounds **1–9**.

Compound	MEC (nM)	Compound	MEC (nM)
1	29 000	8	7 600
2	5 900	9	5 400
3	6 800	A	0.7
4	2 500	B	0.7
5	7 800	C	5.5
6	4 900	Arsobal	5
7	3 600	Cymelarsan	0.6

MEC is the minimal efficient concentration which allows complete depletion of the trypanosoma population. The tests were carried out three times for each sample and the average value was tabulated. The values concerning the arsenical derivatives Arsobal and Cymelarsan (presented in *figure 1*), together with the organotin compounds described as potent in vitro trypanocidal agents [6] (**A**, **B** and **C**, presented in *figure 2*), are also reported.

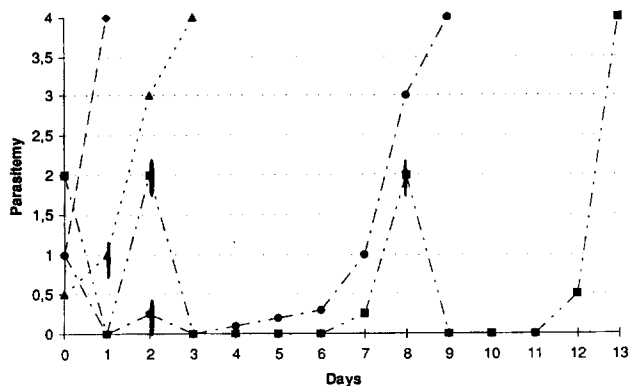


Figure 5. Evolution of the parasitemia in mice infected by *Trypanosoma equiperdum*. Correspondance of the curves: ◆ is for compound 1, ■ for 2, ● for 3 and ▲ for 9. Each compound was tested on three different mice. The evolution of the parasitemia was noted in each case and the average behaviour is reported through these curves. When reaching level 4, parasitemia is too high and the mouse dies rapidly. | represents each new injection of 1 mg of the considered compound.

ing drug treatment, wet amounts of peripheral blood were examined each day for the presence of trypanosomes. The results are presented in figure 5.

The mouse treated with 1 mg of 1 died within 24 h, its parasitemia rising very rapidly. During the same time, the parasitemia of the mouse treated with 9 also increased a little, so a second dose of 1 mg of 9 was injected into the mouse. Despite this, the parasites went on developing until they reached level 4 and the mouse died the next night. Similar results were obtained for the five other dithio organotin compounds (4–8), so details have not been included.

On the contrary, during the first 24 h, mice treated with the dioxalkyltin dichloride 2 and the corresponding oxide 3 saw a decrease in the parasite levels, and no trypanosome could be detected in the rodents blood.

After 48 h, parasites reappeared in the mouse treated with 2, and they rapidly reached level 2 of infection. After the same period, only a few trypanosomes could be detected in the blood of the mouse treated with 3. Then, each mouse was injected with 1 mg of the corresponding compound, and a new drop in the parasitemia was observed within a few hours (the sample was taken 2 h after the injection). No parasite could then be detected in their blood for a period of 3 d.

However, trypanosomes reappeared on the fourth day. At this stage of the experiment, we decided to dissociate

the treatments: the mouse treated with 2 received a new dose of 1 mg, though nothing was given to the one treated with 3. As a result, the former presented an undetectable parasite level once again, while the latter saw its parasitemia rising very rapidly, to reach the critical level 4 causing its death the next day.

The mouse treated with 2, the last one alive, was given no more treatment. After 2 d, parasites reappeared, grew rapidly and caused the death of the rodent.

4. Discussion

4.1. In vitro trypanocidal tests

The values presented in table II clearly indicate that the new series of organotin compounds exhibit low levels of in vitro activity compared to the ones for the arsenicals Arsobal and Cymelarsan, and the three organotin derivatives A, B and C [6].

It is clear from these values that the alkyltin trichloride 1 is by far the least active molecule of the new series. This confirms previous reports of the low biological potency observed for monoalkyltin trichlorides [21].

For all the other derivatives studied, the MEC values are very similar. So, it seems that the in vitro activity of compounds 2–9 depends on the dioxalkyltin part of the molecule, with no involvement of the other groups linked to the metal atom.

4.2. In vivo trypanocidal tests

Results obtained demonstrate that for all the compounds which are not water soluble (compounds 4–9), no in vivo activity can be expected. So, it can be concluded that hydrosolubility is a necessary condition for these molecules to exhibit in vivo activity. However, water solubility is not sufficient to predict a good activity, as compound 1 is water soluble, and it is totally devoid of activity. This absence also confirms the very limited biological properties of alkyltin trichlorides [21].

The most remarkable result obtained from these tests is the discovery of organotin compounds (2 and 3) having in vivo trypanocidal activity. All other organotin derivatives previously tested in vivo appeared devoid of activity, even when they presented strong in vitro potencies [6]. The two molecules 2 and 3 presented herein exhibit an interesting in vivo trypanocidal activity.

Moreover, we have to point out that all the tested molecules appear to be well tolerated by the rodent organisms. Additional studies were carried out for all compounds on non infected mice. The same drug doses

were administrated to the uninfected mice for the same time period, and none of them died, nor presented any trouble.

The good results obtained for these methoxyethoxy derivatives are comparable to the encouraging results obtained for phenoxyphenoxy compounds against *Trypanosoma cruzi* [22].

As organoarsenicals (Arsobal and Cymelarsan) are supposed to interact with trypanothione (N-1,N-8 bis glutathionylspermidine) by a transthilation mechanism [12, 23, 24], one can ask oneself whether the specific parasite cofactor undergoes the same kind of interaction with **2** and **3** or not (the mechanism becoming then a simple thilation).

The cyclic return of the parasites, after periods of undetectable levels, clearly shows that the depletion of the trypanosomes is not total. It seems that the mouse blood is "washed" of its parasites within a few hours after injection of the drug. Contaminating parasites may remain in tissues unreachable by **2** and **3**, due to their strong water solubility and poor lipophilicity.

These molecules may also lack targeting towards the parasites. It has been observed before that triazinyl or adenosyl moieties show some specificity towards *Trypanosoma* via recognition of an adenosine transporter present in the membrane of the parasite [25–27].

Our present efforts are focussed on the parasite by introducing specific groups, and the modulation and control of water solubility vs. lipophilicity.

5. Experimental protocols

5.1. Biology

5.1.1. Cultivation of bloodstream forms of trypanosomes

Trypanosoma equiperdum was cultivated in vitro according to Baltz et al. [19]. 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 d 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 foetal calf serum.

5.1.2. In vitro drug sensitivity tests

Drugs were dissolved in DMSO (10 mg/mL) and diluted to an appropriate concentration in culture medium in 12-well tissue culture plates. To the first well containing 2 mL culture medium, 20 µL 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 so diluted from 10 µg/mL to 2.44 ng/mL. 2×10^4 trypanosomes 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 trypanosome population by 100%) was determined after 24 h. After treatment, killed trypanosomes appeared totally lysed under microscopic observation. 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 determined the cytotoxic effect of the compounds, as only viable motile trypanosomes are counted (killed parasites are no longer motile).

5.1.3. In vivo drug sensitivity tests

Female Swiss mice, weighing 20–25 g, were used for the in vivo drug tests [20]. Mice were infected by intraperitoneal inoculation (i.p.) with $1\text{--}2 \times 10^5$ trypanosomes, and treated 24 h after inoculation. Each drug was administered i.p. to the mice at a dose of 50 mg/kg per injection. Hydrosoluble compounds (**1**, **2** and **3**) were dissolved in water, the other ones into DMSO. Following drug treatment, wet amounts of peripheral blood were examined each day for the presence of trypanosomes which were counted on a Malassez haemocytometer. Their amount was then brought back to an average value per surface unit of the cell. The (arbitrary) levels of parasitemia were then established as follows:

Level 1: from 1–5 trypanosomes per surface unit.

Level 2: from 6–10 trypanosomes per surface unit.

Level 3: from 11–15 trypanosomes per surface unit.

Level 4: more than 16 trypanosomes per surface unit.

Reaching level 4, the parasitemia is too high and the mouse dies within a few hours without treatment. For the control mouse, this level was reached within the first 24 h.

5.2. Chemistry

¹H, ¹³C and ¹¹⁹Sn NMR spectra were recorded on a Bruker AC 200 spectrometer operating respectively at 200.13, 50.32 and 74.54 MHz. For ¹H and ¹³C, chemical shifts are given in ppm downfield from tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. For ¹¹⁹Sn, chemical shifts are given in ppm with tetramethyltin as reference. Mass spectra were recorded on a Finnigan Mat TSQ 70 triplequadrupole mass spectrometer in fast atom

bombardment (FAB) mode. All elemental analyses were performed by the Laboratoires du CNRS, BP 22, 69390 Vernaison, France. The results were within $\pm 0.4\%$ of the theoretical values except where otherwise stated.

5.2.1. Bis (3-(2-methoxy)ethoxypropyl)tin oxide **3**

Bis (3-(2-methoxy)ethoxypropyl)tin dichloride **2** (250 mg, 0.6 mmol) was placed in 5 mL of an aqueous solution of 6 N NaOH. The mixture was stirred for 1 h at 100 °C. A white solid appeared, which was filtered off by hot filtration (letting the mixture cool led to resolubilization of the oxide by transformation into the corresponding di(OH)). The white solid was then dried by lyophilization affording 210 mg of product (Yield = 95%). Anal. ($C_{12}H_{26}O_5Sn$) C, H. 1H NMR (D_2O) δ 1.20 (4H, t, H-1); 1.90 (4H, m, H-2); 3.35 (6H, s, H-6); 3.5–3.7 (12H, m, H-3, H-4, H-5). ^{13}C NMR (D_2O) δ 20.5 (C-1, $^1J(^{13}C-^{119}Sn) = 705.0$ Hz, $^1J(^{13}C-^{117}Sn) = 674.4$ Hz); 26.8 (C-2, $^2J(^{13}C-^{119}Sn) = 30.5$ Hz); 60.7 (C-6); 71.8; 73.4 (C-4, C-5); 75.4 (C-3, $^3J(^{13}C-^{119}Sn) = 82.4$ Hz). ^{119}Sn NMR (D_2O) δ 201.8. MS m/z (%): 387 (39, corresponds to the dihydroxyl form); 369 (21); 237 (24).

5.2.2. General procedure for the synthesis of the dithio derivatives **4–9**

Compounds **4–8** were synthesized by reacting two equivalents of thiol with one equivalent of the dioxalkyltin oxide **3**. Compound **9** was obtained by reacting one equivalent of dithiopropane with one equivalent of the tin oxide **3**. In every case, the reaction was performed in refluxing toluene, using a Dean-Stark trap, so that the water generated during the reaction was continuously removed.

5.2.3. Bis (3-(2-methoxy)ethoxypropyl) bis (propylthio) tin **4**

Tin oxide **3** (111 mg, 0.3 mmol) was reacted with 46 mg of propanethiol (0.6 mmol) in 25 mL of toluene according to the general procedure. The solvent was then evaporated to leave a colourless liquid (145 mg; yield = 96%). Anal. ($C_{18}H_{40}O_4S_2Sn$) C, H. 1H NMR ($CDCl_3$) δ 0.9 (6H, t, H-3'); 1.4 (4H, t, H-1); 1.6 (4H, m, H-2'); 2.0 (4H, q, H-2); 2.6 (4H, t, H-1'); 3.3 (6H, s, H-6), 3.4–3.6 (12H, m, H-3, H-4, H-5). ^{13}C NMR ($CDCl_3$) δ 13.5 (C-3'); 17.4 (C-1); 25.8 (C-2); 27.5 (C-2'); 29.5 (C-1'); 58.9 (C-6); 70.3; 71.8 (C-4, C-5); 72.9 (C-3). ^{119}Sn NMR ($CDCl_3$) δ 183.3. MS m/z (%): 427 (36); 387 (8); 237 (100).

5.2.4. Bis (3-(2-methoxy)ethoxypropyl) bis (octylthio) tin **5**

Compound **3** (111 mg, 0.3 mmol) was reacted with 88 mg of octanethiol (0.6 mmol) in 25 mL of toluene

according to the general procedure. The solvent was then evaporated to afford a colourless liquid (185 mg; yield = 96%). Anal. ($C_{28}H_{60}O_4S_2Sn$) C, H. 1H NMR ($CDCl_3$) δ 0.9 (6H, t, H-8'); 1.1–1.3 (20H, m, H-3', H-4', H-5', H-6', H-7'); 1.5 (4H, t, H-1); 1.7 (4H, app. q, H-2'); 2.1 (4H, q, H-2); 2.8 (4H, t, H-1'); 3.35 (6H, s, H-6); 3.45–3.6 (12H, m, H-3, H-4, H-5). ^{13}C NMR ($CDCl_3$) δ 14 (C-8'); 17.5 (C-1); 22.5; 28.5; 28.7; 29.1; 29.3 (C-3', C-4', C-5', C-6', C-7'); 25.9 (C-2); 31.5 (C-2'); 34.0 (C-1'); 58.8 (C-6); 70.4; 71.9 (C-4, C-5); 72.5 (C-3). ^{119}Sn RMN ($CDCl_3$) δ 101.0. MS m/z (%): 499 (100).

5.2.5. Bis (3-(2-methoxy)ethoxypropyl) bis (2-aminoethylthio) tin **6**

Compound **3** (111 mg, 0.3 mmol) was reacted with 68 mg of cysteamine (0.6 mmol) in 40 mL of toluene according to the general procedure. The solvent was then evaporated to leave a yellow and very viscous liquid (160 mg; yield = 92%). Anal. ($C_{16}H_{38}N_2O_4S_2Sn$) C, H, N. 1H NMR ($CDCl_3$) δ 1.35 (4H, t, H-1); 2.05 (4H, q, H-2); 2.7 (4H, t, H-1'); 2.9 (4H, t, H-2'); 3.30 (6H, t, H-6); 3.40–3.60 (12H, m, H-3, H-4, H-5); 5.30 (4H, bs, $-NH_2$). ^{13}C NMR ($CDCl_3$) δ 17.5 (C-1); 25.7 (C-2); 28.8 (C-1'); 43.9 (C-2'); 58.9 (C-6); 70.2; 71.8; 72.9 (C-3, C-4, C-5). MS m/z (%): 506 (6); 430 (100); 237 (1).

5.2.6. Bis (3-(2-methoxy)ethoxypropyl) bis (2-benzothiazolylthio) tin **7**

Tin oxide **3** (111 mg, 0.3 mmol) was reacted with 100 mg of 2-mercaptobenzothiazole (0.6 mmol) in 20 mL of toluene according to the general procedure. The solvent was then evaporated to afford a viscous brownish compound (195 mg; yield = 95%). Anal. ($C_{26}H_{34}N_2O_4S_4Sn$) C, H, N. 1H NMR ($CDCl_3$) δ 1.40 (4H, t, H-1); 2.0 (4H, m, H-2); 3.30 (6H, s, H-6); 3.4–3.7 (12H, m, H-3, H-4, H-5); 7.20–7.50 (8H, m, H-arom.). ^{13}C NMR ($CDCl_3$) δ 17.9 (C-1); 25.8 (C-2); 58.8 (C-6); 70.3; 71.8 (C-4, C-5); 72.9 (C-3); 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'); 172.9 (C-2'). MS m/z (%): 518 (100); 353 (8).

5.2.7. Bis (3-(2-methoxy)ethoxypropyl) bis (2-benzoxazolylthio) tin **8**

Compound **3** (111 mg, 0.3 mmol) was reacted with 91 mg of 2-mercaptobenzoxazole (0.6 mmol) in 20 mL of toluene according to the general procedure. The solvent was then evaporated to leave a viscous compound (180 mg; yield = 92%). Anal. ($C_{26}H_{34}N_2O_6S_2Sn$) C, H, N. 1H NMR ($CDCl_3$) δ 1.40 (4H, t, H-1); 2.0 (4H, m, H-2); 3.30 (6H, s, H-6); 3.4–3.7 (12H, m, H-3, H-4, H-5); 7.15–7.45 (8H, m, H-arom.). ^{13}C NMR ($CDCl_3$) δ 18.2 (C-1); 25.9 (C-2); 58.9 (C-6); 70.4; 71.9 (C-4, C-5); 73.1

(C-3); 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'). MS m/z (%): 502 (100); 384 (13); 353 (13).

5.2.8. 2,2-bis (3-(2-methoxy)ethoxypropyl)-2-stanna-1,3-dithiane **9**

Compound **3** (148 mg, 0.4 mmol) was reacted with 40 μ L of 1,3-propanedithiol (0.4 mmol) in 20 mL of toluene according to the general procedure. The solvent was then evaporated to afford a yellow liquid (170 mg; yield = 97%). Anal. ($C_{15}H_{32}O_4S_2Sn$) C, H. 1H NMR ($CDCl_3$) δ 1.40 (4H, t, H-1); 1.75 (2H, m, H-2'); 2.0 (4H, m, H-2); 2.85 (4H, t, H-1', H-3'); 3.30 (6H, s, H-6); 3.4–3.6 (12H, m, H-3, H-4, H-5). ^{13}C NMR ($CDCl_3$) δ 17.2 (C-1, $^1J(^{13}C-^{119}Sn) = 448.6$ Hz, $^1J(^{13}C-^{117}Sn) = 428.8$ Hz); 24.0 (C-1', C-3'); 25.9 (C-2, $^2J(^{13}C-^{119}Sn) = 30.5$ Hz); 29.2 (C-2'); 58.8 (C-6); 70.2; 71.7 (C-4, C-5); 77.0 (C-3, $^3J(^{13}C-^{119}Sn) = 44.3$ Hz). ^{119}Sn NMR ($CDCl_3$) δ 183.2.

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