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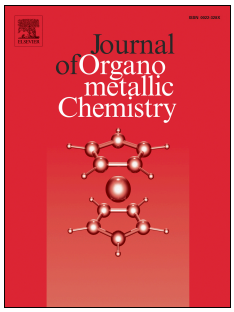

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Organotin(IV) compounds derived from ibuprofen and cinnamic acids, an alternative into design of anti-inflammatory by the cyclooxygenases (COX-1 and COX-2) pathway

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Abstract

New tributyl-, dibutyl- and diphenyl-tin(IV) complexes derived from ibuprofen and cinnamic acids were synthesized. All compounds were structurally characterized by FT-IR, multinuclear ^{1}H, ^{13}C, ^{19}F and ^{119}Sn NMR and corroborated by 2D spectra. The NMR data in $CDCl_3$ revealed several hexacoordinated compounds with octahedral geometry. Moreover, in DMSO-d_6 some of these complexes switched to heptacoordination with a pentagonal-bipyramidal geometry due to the inclusion of a solvent's molecule; their ^{119}Sn signals moved up field by around 58 ppm compared to their chemical shifts in non-coordinated solvent $CDCl_3$. The structural results were supported by Density Functional Theory (DFT) computational calculations. In addition, a docking study was performed to evaluate the ability of ligands to interact within the active site of cyclooxygenases (COX-1 and COX-2). Docking results showed a possible binding of stannoxanes theoretically more selective towards COX-2 than ibuprofen.

Keywords: Stannoxanes; Ibuprofen; Coordination; DFT; Docking; Cyclooxygenase.

1. Introduction

Tin compounds offer a large structural variety due to the range of coordination numbers that the tin atom can adopt (4-8). This leads to different chemical shifts in ^{119}Sn NMR spectroscopy, ranging of +800 to -600 ppm [1-3]. The type and size of the substituents attached to the tin(IV) atom determines the spatial geometry, as well as their industrial and biological applications. It is well known that an increase in the coordination number of the tin atom is related to an increase in electron shielding around the nucleus, that is monitored by the NMR spectra of ^{119}Sn, as well as the $^{n}J(^{13}C\text{-}^{117/119}Sn)$ coupling

constants [3-5]. These increases involve intra- or inter-molecular interactions by varying the solvent, temperature or steric factors of substituents at the metal center. An increase in the coordination number depends of the acidity of tin atom and the availability of the substituents as electron donors [3, 4]. Diverse studies have determined that an increase in the size and number of the substituents on the tin atom, increases the lipophilicity and decreases the toxicity of the compound in biological systems [6-11]. Particularly, organotin(IV) carboxylates' monomers have shown a wide variety of coordination geometries, such as tetrahedral, trigonal bipyramidal and octahedral [12, 13].

The study of organotin's biological activity began with Gielen and coworkers, who tested a set of compounds as antitumor agents [14-17]. Some organotin(IV) compounds exhibit a better *in vitro* antitumor activity than the cisplatin or carboplatin [3,7]. In addition, organotin compounds have been explored as acaricide [3], anthelmintic [18], cytotoxic [19,20], antibacterial [21,22], antifungal [22], antimicrobial [23], anti-tuberculosis [24], antioxidants and anti-inflammatory [25], agents.

Ibuprofen (Figure 1) is one of the best-selling NSAIDs (Nonsteroidal anti-inflammatory drugs) worldwide and it is marketed as a racemic mixture, but its overconsumption has been linked to gastric ulcers and other side effects [26,27].

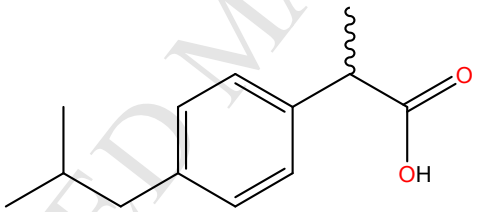


Figure 1. Chemical structure of (*R,S*)-ibuprofen.

On the other hand, the *trans*-cinnamic acids and their derivatives have received attention because their functional properties like antioxidant, antibacterial, antifungal, and their importance in food supplements, cosmetics and pharmaceuticals [28-32]. Furthermore, these compounds offer a great structural diversity when attached to metals [33]. Moreover the spacer groups play an important role in prodrug conjugation and design, as well as in drug delivery systems. The glycol spacers increase the degrees of freedom and modify the solubility with the aim of reduce adverse effects, in some NSAIDs the use of these groups decreases gastric damage by esterification of the carboxylic acid [34-35]. Based on the aforementioned, the present work reports the synthesis and structural characterization of a new group of organotin(IV) compounds by means the NMR spectra in $CDCl_3$ and DMSO-d_6. This study focuses on the ability of the tin atom to increase its coordination number in the presence of a coordinating agent, in addition, a study to the *in silico* affinity and selectivity was carried out of each complex towards cyclooxygenases, important enzymes of the inflammatory process.

2. Results and discussion

2.1 Synthesis

A series of ibuprofen and cinnamic acid derivatives organotin(IV) carboxylates compounds (**1-13**) were synthesized according to **Scheme 1** and **Scheme 2** (see experimental section). All compounds were air-stable, soluble in common organic solvents and they could be isolated up to 82% of yield. Some of *n*-butyl derivatives (**2**, **3**, **4**, **7**, **8** and **9**) were solids and melted at range of 45-90 °C, the rest of the compounds were liquids. This is because the presence of two *n*-butyl groups bonded to tin atom, these groups decrease the formation of intermolecular interactions by steric hindrance [3]. The NMR spectra of ^{1}H, ^{13}C and ^{119}Sn indicate the presence of only one species in solution, these were obtained in a noncoordinating solvent ($CDCl_3$) and a coordinating (DMSO-d_6), with the aim of analyze the tin atom ability to increase its coordination sphere and the chemical behavior of this metal in different conditions.

2.2 Spectroscopy

In the infrared spectra, an explicit feature of all the studied compounds is the band that corresponds to the Sn-O bond, which appears in the region of 400 to 500 cm^{-1}. This, along with the absence of a broad band in the region 2600-3000 cm^{-1} corresponding to the stretching vibration of the hydroxyl group ν(O-H) in carboxylic acids, is an indication of the deprotonation of the COOH moiety [36,37]. Furthermore, the bands in the 507-594 cm^{-1} and 511-631 cm^{-1} regions are assigned to the symmetrical and asymmetrical stretching of the Sn-C bond [38]. In addition, dicarboxylic stannoxanes (**1-9**) displayed two intense bands in the range of 1550 to 1700 cm^{-1} due to the stretching vibration of the carbonyl groups ν(C=O). However, one of these carbonyl stretching bands disappears for compounds **10-13**.

A comparative analysis of the Δ**ν** (ν_{asym}COO- ν_{sym} COO-) values of the sodium carboxylates and complexes **1-9** indicates the type of coordination between the tin atom and the carboxylate substituent, differentiating between monodentate, bidentate and bidentate bridge modes [39]. The Δ**ν** for compounds **1-4**, **7** and **8** is lower than those corresponding to the respective free ligands by 84 to 124 cm^{-1}. This is representative of the bidentate chelating mode. In the case of **5**, **6** and **9** complexes, the values of Δ**ν** correspond to those found in a bidentate bridge mode for the carboxylic ligands in them (see experimental section) [40,41].

The signal corresponding to the COOH proton of the raw organic acids is absent in the ^{1}H NMR spectra of compounds **1-13** ($CDCl_3$) and **1a-13a** (DMSO-d_6). This coincides with the observed data in IR. The chemical shifts for *n*-butyl protons show a shielding

effect in DMSO-d_6 solution, which may be related to the changes in the electronic environment of the tin atom caused by coordinating solvent. The H7, H7', H8 and H8' protons of the α, β-unsaturated double bonds do not exhibit significant changes in molecules **1-4**, **1a-4a**, **6-9** and **6a-9a**. For compounds **5**, **10-13**, **5a**, and **10a-13a**, the positions H7 and H8 exhibit a deshielding effect, because of the tin atom presence. Figure 2 shows the numbering scheme for the stannoxanes.

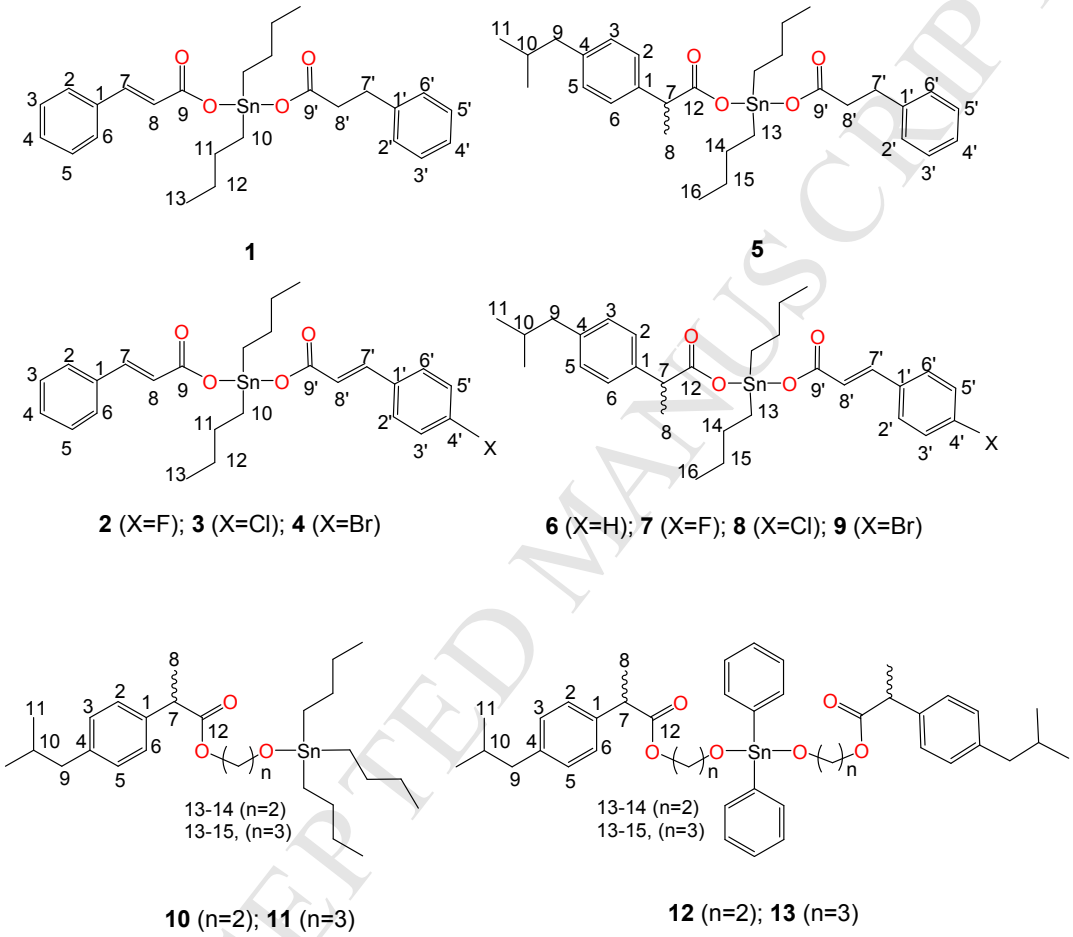


Figure 2. Organotin(IV) compounds and numbering sequence.

The ^{13}C NMR spectra data confirms the exchange of the acidic proton (-COOH) by tin atom (-COOSn-) with the carbonyl signals appearing between 172.1 and 185.0 ppm, because of the substituent (Table 1). For compounds **1-9**, the carbonyl chemical shifts give important information of the chemical environment surrounding the tin atom when is compared to the raw materials. The carbonyl chemical shifts in $CDCl_3$ show a deshielding effect in comparison with their free ligands. For the hydrocinnamic and ibuprofen carbonyl groups, displacements of 4-6 ppm to higher frequencies were observed, whereas this change was greater than 10 ppm for the *trans*-cinnamic ligands. The above changes suggest that the *trans*-cinnamic carboxylates had a stronger coordination with tin(IV) atom, due to a

lesser steric hindrance. These data confirmed the carboxylate oxygen's bidentate chelating and bridge modes of coordination with the tin atom, as previously observed through FT-IR spectra. On the other hand, for the compounds **10-13** was not observed the interaction and coordination of the carboxylate oxygen with the tin atom.

Table 1. Chemical shifts δ (ppm) of the carbonyl groups in $CDCl_3$ y DMSO-d_6 for the **1-13** compounds.

	1	**1a**	**2**	**2a**	**3**	**3a**	**4**	**4a**		
9	176.2	173.0	176.1	173.8	176.3	173.3	176.4	172.6		
9'	182.9	180.0	176.3	173.8	175.9	174.1	175.9	172.7		
	5	**5a**	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**9a**
12	185.0	181.6	184.8	181.0	185.0	172.3	185.0	172.7	184.9	172.1
9'	183.0	179.4	176.1	172.5	175.9	172.3	175.9	172.7	172.7	172.1
	10	**10a**	**11**	**11a**	**12**	**12a**	**13**	**13a**		
12	175.1	175.0	175.2	175.0	175.1	175.1	175.3	175.1		

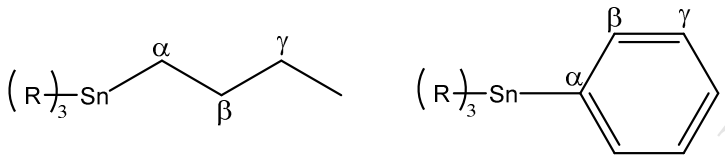
***#a** = chemical shifts in DMSO-d_6*

When this analysis was done in a coordinating solvent, DMSO-d_6, the carbonyl groups had a deshielding effect with respect to the free ligands. However, compounds **1a-13a** carbonyl signals appear at lower frequency than those of **1-13**, an effect attributed to DMSO-d_6 interaction to the tin atom. This disturbs the structure's geometry around the metallic nucleus, weakening the interaction between the carboxylate oxygen and the tin atom. The ibuprofen carbonyl of compounds **7a-9a** display the largest changes; 12.7 ppm, 12.3 ppm and 12.8 ppm respectively.

The ^{119}Sn spectroscopy data of the studied compounds (**1-13** and **1a-13a**) are presented in Table 2. The ^{119}Sn chemical shifts for compounds **1-9** appear in the region of -+145 ppm to -150 ppm confirming that all of them are hexacoordinate systems. For compounds **10-13**, simple signals were observed around of +156 ppm for tributyltin derivatives and chemical shifts at -46 ppm for diphenyltin derivatives, both in accord with reported tetracoordinate tin atom [25, 32]. The ^{119}Sn signals are shifted to lower frequencies in DMSO-d_6, because of a shielding effect by the solvent surrounding the metal. Comparing the ^{119}Sn chemical shifts in both solvents, compounds **1** and **4** had the largest differences, $\Delta\delta^{119}$Sn = 57.7 and $\Delta\delta^{119}$Sn = 58.8 respectively. These changes have been previously related to changes in the coordination number of the metal, with the solvent acting as a ligand in this case (Table 2) [4].

The carbon atoms (α, β and γ) coupled with the metallic nucleus in systems **1-13** are shown in Figure 3. The corresponding $^{n}J(^{13}C\text{-}^{117/119}Sn)$ coupling constants are quite informative regarding the interactions between the nuclei, their chemical and magnetic

environments, as well as the geometry, hybridization and number of substituents of the tin atom. In $CDCl_3$, the alpha carbon has an average $^{2}J(^{13}C\text{-}^{117/119}Sn)$ coupling constant of 580 Hz for products **1-9**, 337 Hz for **10** and **11**, and 620 Hz in systems **12** and **13**. In comparison, the same coupling constant was greater than 850 Hz in compounds **1a-9a**.



1-11 **12, 13**

Figure 3. Important positions near the tin atom for **1-13** compounds.

Table 2. Selected Chemical shifts δ (ppm) of ^{13}C and ^{119}Sn for **1-13** and **1a-13a** compounds.

Compounds	α	β	γ	$\delta^{119}Sn$	$\Delta\delta^{119}Sn$
1	25.2 (569.5/562.4)	26.3 (95.5)	26.6 (35.2)	-146.9	57.7
1a	29.9 (855.2/827.1)	26.2 (138.8)	27.2 (50.3)	-204.6	
2	25.4 (586.8/560.5)	26.4 (97.6)	26.6 (34.5)	-147.4	46.0
2a	26.2 (835.1/820.0)	26.2 (137.8)	27.3 (62.3)	-193.4	
3	25.9 (585.6/561.5)	26.4 (98.6)	26.7 (35.2)	-147.8	58.0
3a	30.0 (851.2/814.0)	26.1 (137.8)	27.2 (57.3)	-205.8	
4	25.4 (584.6/559.4)	26.4 (99.6)	27.7 (35.2)	-149.6	48.8
4a	29.3 (855.2/854.2)	26.2 (139.8)	27.2 (72.4)	-198.4	
5	25.0 (580.5/554.4)	26.3 (93.5)	25.6 (37.2)	-145.9	21.5
5a	30.2 (867.3/847.2)	26.1 (142.8)	27.2 (27.6)	-167.4	
6	26.5 (583.6/557.5)	26.2 (97.6)	25.1 (36.2)	-150.1	22.0
6a	30.3 (856.3/839.1)	26.2 (144.8)	27.3 (34.1)	-172.1	
7	26.6 (584.6/559.5)	26.4 (98.6)	25.1 (36.2)	-149.5	19.4
7a	30.2 (857.3/813.0)	27.4 (140.8)	26.2 (35.1)	-168.9	
8	25.1 (568.5/555.5)	26.2 (97.6)	26.6 (37.2)	-149.4	20.5
8a	30.3 (850.2/825.1)	26.1 (139.8)	27.5 (36.2)	-169.9	
9	25.1 (571.5/558.2)	26.2 (96.5)	26.4 (36.2)	-149.3	33.8

9a	0.3 (868.3/822.0)	26.1 (138.8)	27.4 (37.3)	-183.1	
10	17.6 (337.1/332.0)	26.9 (63.4)	27.8 (22.1)	+156.4	7.5
10a	7.7 (343.2/327.0)	26.8 (64.3)	27.9 (23.1)	+148.9	
11	18.3 (337.1/332.0)	26.8 (64.4)	27.7 (22.1)	+156.2	12.4
11a	17.9 (339.1/NA)	26.8 (64.6)	27.8 (23.1)	+143.8	
12	137.4 (619.8/NA)	129.2 (58.3)	136.5 (48.3)	-46.6	17.1
12a	137.5 (627.9/NA)	129.1 (62.4)	136.1 (42.3	-63.7	
13	137.4 (631.9/NA)	129.2 (63.4)	136.1 (49.3)	-46.2	27.4
13a	138.3 (NA)	129.1 (104.6)	136.2 (49.3)	-73.6	

***#a** (DMSO-d_6); (${}^{n}J({}^{13}C\text{-}{}^{117/119}Sn)$)*

For compounds **1a-4a**, the difference between the coupling constants in DMSO-d_6 and $CDCl_3$ is 285.7, 248.3, 265.6 and 270.6 Hz respectively. This, jointly with a change in the chemical shift of tin ($\Delta\delta^{119}Sn$) larger than 45 ppm and slight variations in the carbonyl groups' chemical shifts, confirm the coordination of a dimethylsulfoxide's oxygen atom with the tin atom [42, 43]; a contrast of hexacoordination in chloroform with heptacoordination in DMSO-d_6.

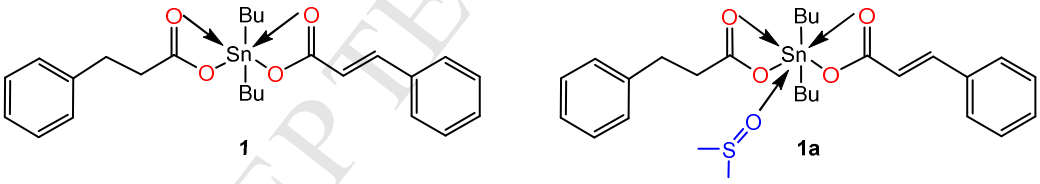


Figure 4. Coordination for compound **1** in $CDCl_3$ and DMSO-d_6. This change in the coordination number was observed for **2a-4a** compounds as well.

The coupling constant (${}^{2}J({}^{13}C\text{-}{}^{117/119}Sn)$) is around 300 Hz for compounds **5a** and **6a**. However, $\Delta\delta^{119}Sn$ is smaller than 25 ppm and the chemical shifts for the, respectively, carbonyl groups do not show any significant changes. This indicates a weak interaction between a DMSO-d_6 molecule and these compounds, contrary to the coordination with the metallic nucleus presented in **1a-4a**. To further support these conclusions, DFT theoretical computations were performed. Figure 5 shows the resulting optimized geometry for compound **5a** with a DMSO molecule. Of all the atoms interacting with the tin atom, the solvent's oxygen atom is the furthest from the metallic nucleus, in concordance with the NMR data.

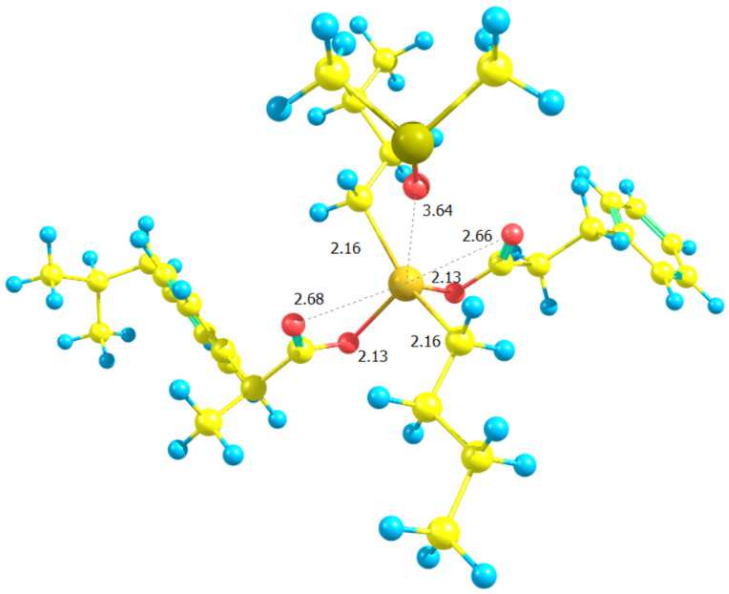


Figure 5. Optimized geometry of compound **5a** with a DMSO molecule. Displayed interatomic distances in angstroms.

Systems **7a-9a** (Figure 6) had similar ($^{2}J(^{13}C\text{-}^{117/119}Sn)$) coupling constants, and $\Delta\delta^{119}Sn$, however, the chemical shift for the ibuprofen's carbonyl group was displaced to lower frequencies by 12 ppm (Table 1). This reflects the molecules' structural rearrangement due to the DMSO's oxygen atom taking the tin atom to heptacoordination. The structure of compound **8a** was optimized utilizing computational calculations, where a single solvent molecule was included. The results show the solvent oxygen atom and the carbonyl oxygen atoms are at a similar distance from the tin nucleus (Figure 7). When compared with the calculations for compound **5a**, the solvent has a stronger interaction with the tin atom in **8a**. These results further supports the heptacoordination suggested by NMR data.

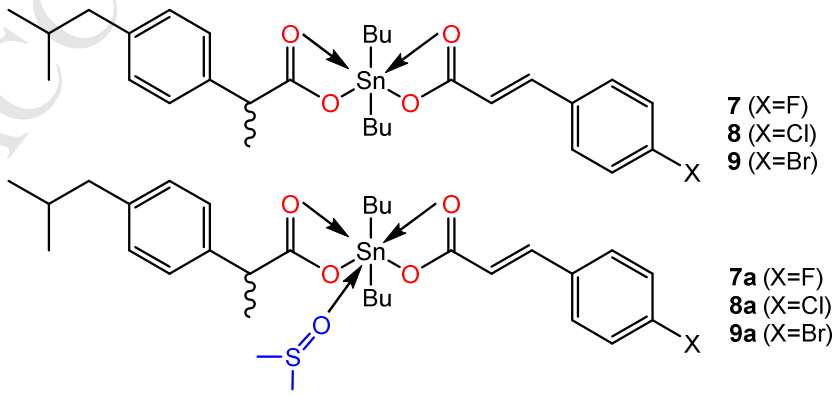


Figure 6. Coordination number for **7-9** and **7a-9a** compounds in $CDCl_3$ and DMSO-d_6.

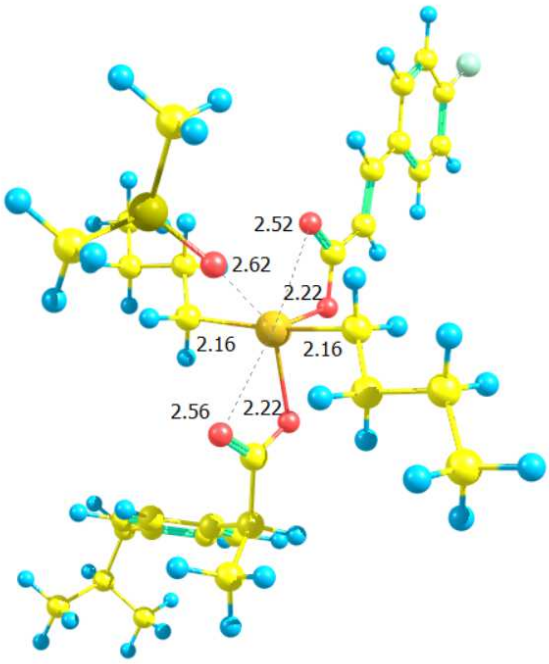


Figure 7. Optimized geometry of compound **8a**.

Compounds **10a** through **13a** did not show any significant changes that would indicate an alteration in the tin's coordination number. The spacer group pushes the carbonyl fragment away from the metallic nucleus, effectively inhibiting any possible coordination. Furthermore, the three butyls present on systems **10a** and **11a**, hinders any approach to the tin center by any DMSO molecule.

2.3 Molecular docking

To explore the effect of the tin atom in combination with the *trans*-cinnamic acid (TCA), hydrocinnamic acid (HCA) and ibuprofen a docking study towards cyclooxygenase (COX) isoforms was carried out.

Only compounds which bear at least one (*S*)-ibuprofen moiety –which is biologically active in COX inhibition– were selected to discuss their binding modes [44, 45]. Additionally, as a second criteria, only those systems that were able to interact with Arg513 and His90 residues, were discussed; these residues are only reached by COX-2 selective inhibitors [46]. Arg513 and His90 are key residues, which provide access to the lipophilic pocket formed by Val523, hence a COX-2 selective inhibitor needs to interact favorably with them to accommodate into the pocket [46, 47].

Compounds **5** (*S*), **7** (*S*), **9** (*S*), **10** (S), **11** (*S*), **12** (*S, S*), **12** (*S, R*) and **13** (*S, R*) were found to meet the criteria described. The interactions of tin derivatives with the constriction channel (CC; Arg120, Glu524 & Tyr355), lateral pocket (LP; Ala527, Leu531, Ser530 & Val349) and lipophilic pocket (LiP; Val 523) residues of COX-2 are shown in Table 3 and compare to ibuprofen's and celecoxib's, COX-2 reference inhibitors.

Table 3. Summary of the interactions of selected compounds with Arg513 & His90, LP, CC and LiP (COX-2).

	5*S*	**7***S*	**9***S*	**10***S*	**11***S*	**12** (*S, S*)	**12** (*S, R*)	**13** (*S, R*)	**Ibu.**	**Cel.**
Ala527	-9.92	-7.80	-7.55	-0.77	-0.32	-10.20	-10.82	-7.30	-13.60	-15.33
Arg120	---	-9.64	-22.60	-28.85	-32.60	-18.70	-15.10	-12.90	-9.10	-2.20
Arg513	-10.25	-6.30	-2.46	-2.68	-0.37	-11.22	-13.10	-5.06	-1.20	-5.08
Glu524	---	---	-1.44	-4.32	-0.95	-8.70	-9.61	-0.98	1.70	---
His90	-5.21	-5.30	-2.14	-4.31	-2.20	-15.33	-13.1	-3.70	-0.45	-3.64
Leu531	-7.00	-7.63	-9.70	-3.92	-1.11	-13.43	-2.96	-2.50	-3.40	-2.70
Ser530	-17.70	-8.80	-6.33	-1.66	-2.02	-1.41	----	-13.72	-4.18	-4.43
Tyr355	-6.41	-16.84	-13.11	-9.51	-12.60	-13.80	-30.50	-9.80	-10.30	-12.53
Val349	---	-12.70	-12.20	-6.33	-10.12	-11.80	-7.80	-3.20	-11.43	-11.13
Val523	---	-22.90	-17.70	-16.76	-14.25	-24.40	-22.92	-22.61	-6.80	-18.31

Ibu*: ibuprofen;* ***Cel****: celecoxib*

The stannoxanes bind to COX-2's active site mainly by forming steric interactions with key residues; their binding mode is also driven by the formation of hydrogen bonds (HB). In general terms, the presence of a tin atom, in combination with ibuprofen, HCA and TCA moieties, exert a favorable influence in their binding modes with COX-2 and allow them to reach Arg513 and His90.

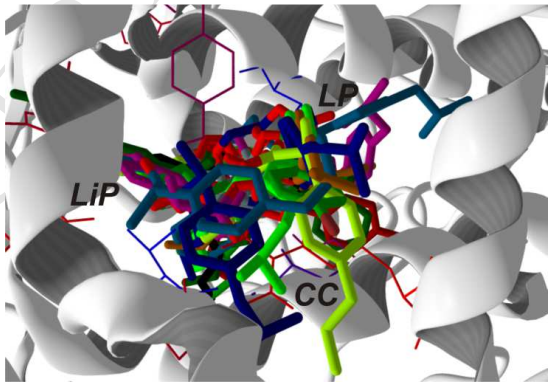


Figure 8. Binding of selected compounds into COX-2 active site.

Compound **7** (*S*) and **12** (*S, S*) displayed remarkable interaction values in comparison to reference inhibitors and the other stannoxanes (Figure 9). The presence of fluoro-*trans*-cinnamic acid and ibuprofen moieties in **7** (*S*), favors higher interaction

energies than those of reference inhibitors with Arg513, His90, Leu531, and Val523. Its binding mode locates the fluoro-*trans*-cinnamic acid moiety reaching towards the LiP, His90 and Arg513. The ibuprofen moiety accommodates and interacts with LP's residues Ala527 and Leu531. The carboxyls accept HBs from Tyr355 and Ser353. The butyl groups and tin atom face the Ser530, Val349, and Ala527 residues.

On the other hand, compound **12** (*S, S*), which bears two phenyl rings bound to the tin atom, shows higher interaction energy with Arg513, His90, and Leu531 than reference inhibitors and **7** (*S*). It binds to COX-2 facing each ibuprofen moiety to opposite directions. One is facing the Arg513, His90 and Glu524 residues, whereas the other reaches towards LP residues (Leu531 and Val349). The phenyl groups and tin atom reach the LiP and Ala527, while also interacting with Val523 and His90.

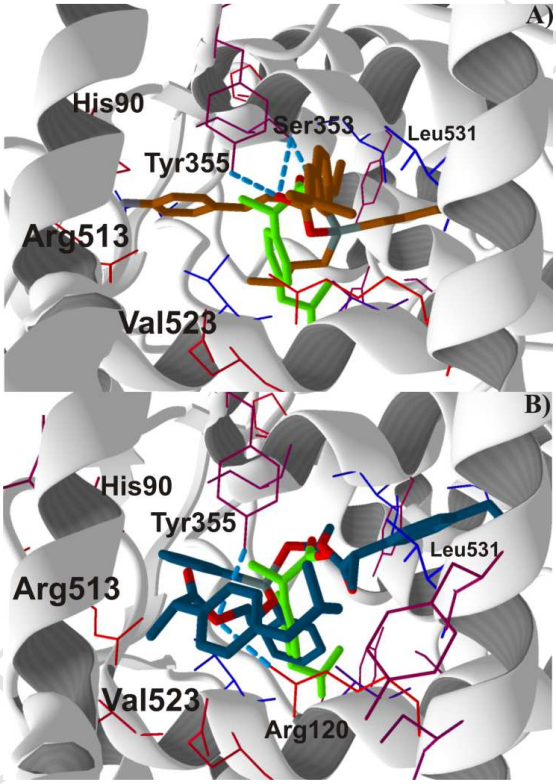


Figure 9. Comparison of the binding modes of compounds **7** (*S*), A) and **12** (*S, S*), B) to ibuprofen (green). The blue dashed lines represent the HB.

Besides, the interaction with Val523, His90 and Arg513 is often related to a tight and durable binding to COX-2, which is only achieved by time-dependent and selective COX-2 inhibitors [46-48]. On the other hand, Leu531 is key to COX-2 selectivity, since it needs to reach a conformational change that allows the accommodation of an inhibitor [49]. In this sense, compounds **7** & **12** show favorable interactions to the mentioned residues, which suggest that they may interact with COX-2 in a similar manner to reference

compounds. The interactions values of compounds with key residues of COX-1 are shown in Table 4.

Table 4. Summary of the interactions of selected compounds with LP, CC and Ile523 (COX-1).

	5*S*	**7***S*	**9***S*	**10***S*	**11***S*	**12** (*S, S*)	**12** (*S, R*)	**13** (*S, R*)	**Ibu.**	**Cel.**
Ala527	-11.50	-7.40	-13.00	-13.60	-12.02	-9.30	-12.72	-11.90	-12.72	-13.04
Arg120	-0.73	---	-12.60	-9.54	-2.43	-17.10	-1.60	-8.70	-15.95	-1.35
Glu524	---	---	---	---	---	-1.21	---	-3.81	1.86	---
Ile523	-13.20	-17.40	-7.00	-19.64	-13.90	-27.40	-12.03	-16.50	-7.16	-15.80
Leu531	-7.82	-5.84	-7.92	-14.70	-11.33	-18.34	8.62	-6.97	-5.50	-4.56
Ser530	-10.10	-18.30	-5.13	-15.98	-18.00	-15.10	-9.20	-6.10	-4.74	-3.11
Tyr355	-11.10	-4.95	-9.10	-19.12	-12.71	-14.10	-21.74	-4.80	-10.80	-12.93
Val349	-16.50	-17.20	-9.60	-20.54	-16.90	-13.42	-20.40	-11.20	-10.40	-11.30

Ibu*: ibuprofen;* ***Cel****: celecoxib*

Similarly to COX-2, the selective binding to COX-1 relies on the interaction with key residues of its active site. Key residues are similar in both isoforms, they have in common the LP and CC. However, COX-1 lacks of a lipophilic pocket, which is the main difference between isoforms and it is due to the presence of Ile523 & His513 instead of Val523 and Arg513 [47]. The interaction with Ile523 is important because it controls the access to the COX-1 active site; Ile523 must reach a conformation that allows the ligands to accommodate favorably into the site [50].

In general, the selected derivatives **5** (*S*), **7** (*S*), **9** (*S*) - **11** (*S*), **12** (*S, S*), **12** (S, R) and **13** (*S, R*) bind into COX-1 active site mainly by forming steric interactions; they were more prone to form steric clashes when binding to COX-1 than to COX-2. In contrast to COX-2, the binding of **7** (*S*) and **12** (*S, S*) to COX-1 shows some important differences. In this regard, compound **7** (*S*) accepts a HB from Tyr355 and Arg120 and binds facing its ibuprofen to reach towards Ser530, whereas the fluoro-*trans*-cinnamic acid moiety interacts with Ala527 and Val349; butyl chains interact with Ile523. The binding mode favors the interaction with Ile523, which is higher in energy than Ibuprofen´s and Celecoxib´s. Compound **12** (*S, S*) binds into COX-1 by accepting a HB from Ser530 and Arg120. However, it clashes with Val349; its interactions with Ile523 are higher than celecoxib´s and ibuprofen´s.

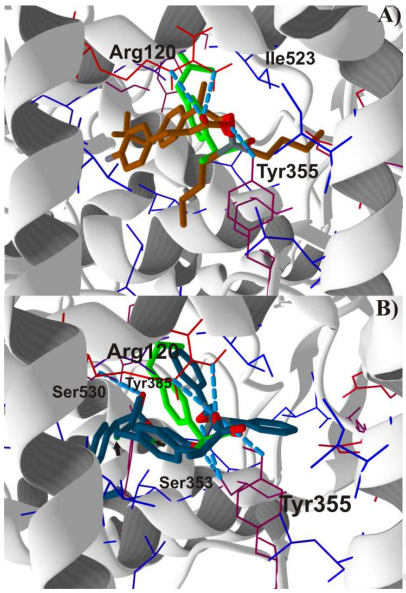


Figure 10. Comparison of the binding modes of compounds **7** *S* (A) and **12** *SS* (B) to ibuprofen (green). Legend: black arrows point the regions where steric clashes are observed. The blue dashed lines represent the HB.

Docking results suggest that stannoxanes may bind to COX isoforms; thus, they may be screened as COX inhibitors *in vitro*. The interaction energies of compounds **7** and **12** are suggestive of a theoretical selectivity towards COX-2, in part due to the differences between COX isoforms' active sites [51, 52]. Namely, (i) COX-2 active site is larger than that of COX-1, which may allow it to "accept" larger inhibitors that may favorably accommodate and interact with the lipophilic pocket (Val523). (ii) The active site of COX-2 is more hydrophobic than COX-1, which may also favor the binding of hydrophobic inhibitors, as is the case of Sn-derivatives. (iii) The COX-2 active site can use esters of arachidonic acid as substrates [45, 53], which implies that the presence of an ester bond within tin derivatives increase their selectivity and favor their binding to COX-2. The reported anti-inflammatory activity of a variety of organotin(IV) derivatives is straightforward [54, 55]. However, the results reported in this section should be framed in a theoretical context and be validated experimentally through an *in vitro* model.

3. Conclusions

The organotin compounds discussed in this work displayed interesting behavior regarding their coordination. Most of them (**1**-**9**) were hexacoordinated in chloroform. However, molecules **1**-**4** and **7**-**9** could add a solvent's molecule to their coordination sphere when dissolved in DMSO, effectively bringing them to an heptacoordination. This was concluded through the analysis and concordance of the NMR and FT-IR data, while further supported by DFT calculations. In addition, the resulting energies from the docking calculations suggested all compounds interact with COXs. Furthermore, all the systems

were theoretically more selective towards COX-2 than the ibuprofen. Ligands with glycol spacers and diphenyltin showed the best binding energies towards COX-2 due to forming steric interactions in constriction channel and lipophilic pocket. The spacer group increases the flexibility and favors the arrangement of the ligand in the active site.

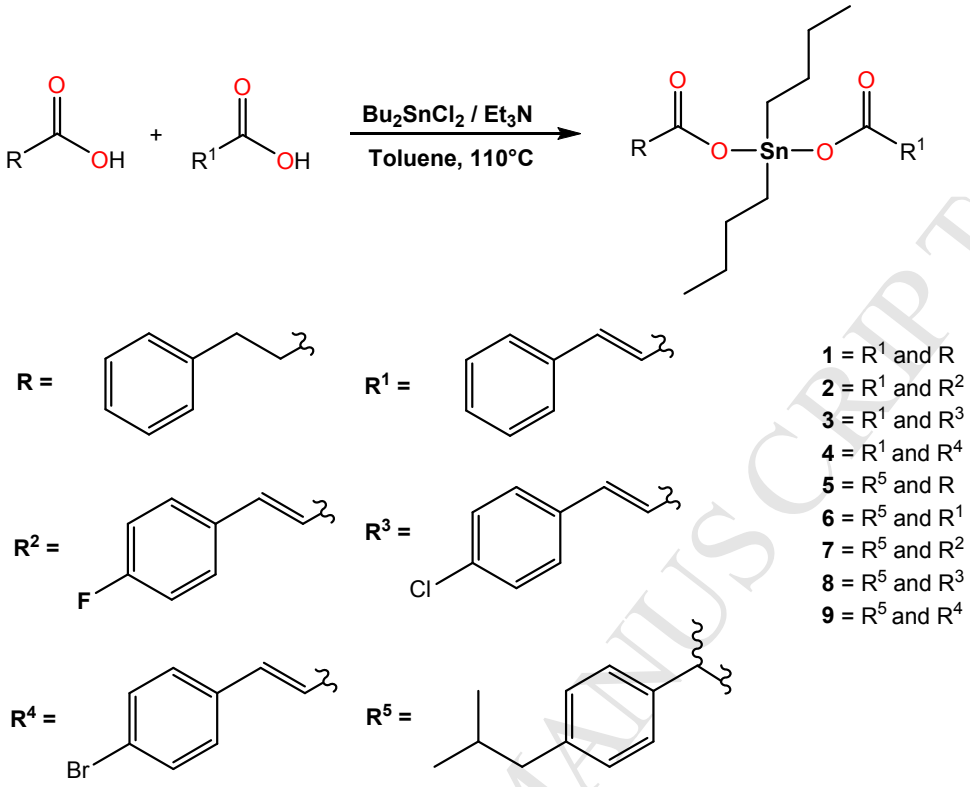
4. Experimental

4.1. Materials and instruments

Hydrocinnamic acid, *trans*-cinnamic acid, 4-fluoro-*trans*-cinnamic acid, 4-*trans*-chlorocinnamic acid, 4-bromo-*trans*-cinnamic acid, dimethylaminopyridine (DMAP), dicyclohexylcarbodiimide (DCC), organotin(IV) monochlorides and dichlorides were purchased from Sigma-Aldrich and were used without further purification. Ibuprofen was supplied by the Alfadelta S. A. de C. V. as racemic mixture and was not further purified. The NMR spectra of compounds were obtained in two deuterated solvents ($CDCl_3$ and DMSO-d_6) and were analyzed with a Bruker 400 MHz NMR spectrometer for ^{1}H (400.13247 MHz), ^{13}C (100.62282 MHz), ^{19}F (376. 46071 MHz) and ^{119}Sn (149.16624 MHz). Chemical shifts (δ) are reported in ppm and coupling constants in Hz. The infrared spectra were recorded on a Varian Excalibur 3100 FT-IR spectrophotometer using KBr pellets. Elemental analysis was performed on Truspec Micro elemental analyzers. Melting points were obtained with a Melt-Temp II apparatus and were not corrected.

*4.2. General procedure for the synthesis of stannoxanes (**1-9**) ibuprofen, 3-phenylpropanoic acid and cinnamic acid derivatives*

The nine stannoxanes were obtained by reacting two equivalents of the corresponding carboxylic acid with dibutyltin dichloride in a mixture of boiling toluene and triethylamine like base. This mixture was kept under reflux for 6 hours and then cooled to room temperature and stirred vigorously for 12 hours (Scheme 1).



Scheme 1. Synthesis and sequence enumeration of stannoxanes derived from the combination of carboxylic acids.

*Dibutyl(3-phenylpropanoyl) oxystannyl cinnamate (**1**).* In a dry flask, the hydrocinnamic acid (246 mg, 1.638 mmol) and the *trans*-cinnamic acid (242 mg, 1.633 mmol) were dissolved in 100 ml of dry toluene, next 0.874 ml of triethylamine (660 mg, 6.581 mmol) was added, the mixture was stirred until its complete dissolution. On the reaction mixture at 80°C is added dropwise the dibutyltin dichloride (500 mg, 1.645 mmol) previously dissolved in 50 ml of toluene. Then, the mixture was heated to 110 °C for 6 h, after that, the heating was removed and kept for 12 h under continue stirring. The precipitated triethylamine hydrochloride was eliminated by filtration and the toluene was evaporated under reduced pressure. The final product was washed three times with CH_2Cl_2 and H_2O to remove any remaining triethylamine. The organic phase was treated with $MgSO_4$ to remove any residual water. Finally, the product was recovered by evaporation after removal of the hydrated $MgSO_4$ by filtration. Compound **1** was obtained as a yellow liquid. Yield: 0.863 g (99%). Analyses (%): calcd for $C_{26}H_{34}O_4Sn$, C 59.00, H 6.48, O 12.09, Sn 22.43; found, C 59.27, H 6.83. FT-IR (cm^{-1}): ν_1(O=C) 1639; ν_2(O=C) 1580; ν_{asym}(COO) 1589; ν_{sym}(COO) 1499; ν(O-C) 1371; ν(Sn-C) 593; ν(Sn-O) 422. ^{1}H NMR ($CDCl_3$) δ: 7.81 (d, ^3J = 16.0 Hz, 1H, H7), 7.55 (m, 1H, H2), 7.55 (m, 1H, H6), 7.42 (m, 1H, H2'), 7.42 (m, 1H, H6'), 7.34 (d, ^3J = 7.3 Hz, 1H, H3), 7.34 (d, ^3J = 7.3 Hz, 1H, H5), 7.29 (m,1H, H4), 7.28 (d, ^3J = 7.2 Hz, 1H, H3'), 7.28 (d, ^3J = 7.2 Hz, 1H, H5'), 7.25 (m, 1H, H4'), 6.52 (d, ^3J = 16.0 Hz, 1H,

H8), 3.03 (t, ^{3}J = 7.7 Hz, 2H, H7'), 2.82 (t, ^{3}J = 7.8 Hz, 2H, H8'), 1.70 (m, 2H, H10), 1.70 (m, 2H, H12), 1.34 (sext, ^{3}J = 7.2 Hz, 2H, H11), 0.94 (d, ^{3}J = 7.3 Hz, 3H, H13). NMR ^{13}C ($CDCl_3$) δ: 182.9 (C9'), 176.2 (C9), 146.3 (C7), 140.5 (C1'), 134.4 (C1), 130.3 (C4), 129.3 (C3),129.3 (C5), 128.9 (C3'), 128.9 (C5'), 128.3(C2),128.3 (C6), 128.1 (C2'), 128.1 (C6'), 126.2 (C4'), 117.7 (C8), 35.6 (C8'), 31.1 (C7'), 26.3 (J (C11-^{119}Sn) = 95.5 Hz), 26.6 (J (C12-^{119}Sn) = 35.2 Hz), 25.2 (J (C10-^{119}Sn) = 569.5 Hz; J (C10-^{117}Sn) = 562.4), 13.6 (C13). ^{119}Sn NMR ($CDCl_3$) δ: –146.9.

*Dibutyl(((E,Z)-3-(4-fluorophenyl)acryloyl)oxy)stannyl cinnamate (**2**).* Following the same procedure that for compound **1**, a mixture of 4-fluoro-*trans*-cinnamic acid (272 mg, 1.637 mmol), *trans*-cinnamic acid (242 mg, 1.633 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and the dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. The residual solution was dried under low pressure to get compound **2** as a white solid. Yield: 0.887 g (98%). M.p. 70-72 °C. Analyses (%): calcd for $C_{26}H_{31}FO_4Sn$, C 57.27, H 5.73, F 3.48, O 11.74, Sn 21.77; found, C 56.94, H 6.12. FT-IR (cm^{-1}): ν_1(O=C) 1683; ν_2(O=C) 1639; ν_{asym}(COO) 1547; ν_{sym}(COO) 1491; ν(O-C) 1223; ν(Sn-C) 593; ν(Sn-O) 470. ^{1}H NMR ($CDCl_3$) δ: 7.79 (d, ^{3}J = 18.0 Hz, 1H, H7'), 7.79 (d, ^{3}J = 16.2 Hz, 1H, H7), 7.57 (m, 1H, H4), 7.56 (m, 1H, H3'), 7.56 (m, 1H, H5'), 7.41 (m, 1H, H2), 7.41 (m, 1H, H6), 7.11 (d, ^{3}J = 8.6 Hz,1H, H2'), 7.11 (d, ^{3}J = 8.6 Hz, 1H, H6'), 7.09 (d, ^{3}J = 8.6 Hz, 1H, H3), 7.09 (d, ^{3}J = 8.6 Hz, 1H, H5), 6.54 (d, ^{3}J = 16.0 Hz, 1H, H8'), 6.45 (d, ^{3}J = 16.0 Hz, 1H, H8), 1.74 (m, 2H, H10), 1.74 (m, 2H, H12), 1.44 (sext, ^{3}J = 8.0 Hz, 2H, H11), 0.95 (t, ^{3}J = 7.3 Hz, 3H, H13). ^{13}C NMR ($CDCl_3$) δ: 176.3 (C9'), 176.1 (C9), 165.2 (J (C4'-^{19}F) = 251.5 Hz), 146.3 (C7'), 144.9 (C7), 134.4 (C4'), 130.7 (C1), 130.7 (C2'), 130.7 (C6'), 130.5 (C2), 130.5 (C6), 128.2 (C3), 128.8 (C4), 128.2 (C5), 117.5 (C8), 117.7 (C8'), 116.1 (C3'), 116.1 (C5'), 26.4 (J (C11-^{119}Sn) = 97.6 Hz), 26.6 (J (C12-^{119}Sn) = 34.5 Hz), 25.4 (J (C10-^{119}Sn) = 586.8 Hz; J (C10-^{117}Sn) = 560.5 Hz), 13.6 (C13). ^{119}Sn NMR ($CDCl_3$) δ: –147.4.

*Dibutyl(((E,Z)-3-(4-chlorophenyl)acryloyl)oxy)stannyl cinnamate (**3**).* Following the same procedure that for compound **1**, a mixture of 4-chloro-*trans*-cinnamic acid (299 mg, 1.64 mmol), *trans*-cinnamic acid (242 mg, 1.633 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. The residual solution was dried under low pressure to get compound **3** as a yellow crystalline solid. Yield: 0.861 g (93%). M.p. 87-89 ºC. Analyses (%): calcd for $C_{26}H_{31}ClO_4Sn$, C 55.60, H 5.56, Cl 6.31, O 11.39, Sn 21.13; found, C 55.95, H 5.73. FT-IR (cm^{-1}): ν(O=C) 1637; ν_{asym} (COO) 1534; ν_{sym} (COO) 1449; ν(O-C) 1356; ν(Sn-C) 589; ν(Sn-O) 465. ^{1}H NMR ($CDCl_3$) δ: 7.90 (d, ^{3}J = 16.0 Hz, 1H, H7), 7.75 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.57 (m, 1H, H2'), 7.57 (m, 1H, H6'), 7.41 (m, 1H, H2), 7.41 (m, 1H, H6), 7.40 (d, ^{3}J = 8.4 Hz, 1H, H3'), 7.40 (d, ^{3}J = 8.4 Hz, 1H, H5'), 7.37 (d, ^{3}J = 8.5 Hz, 1H, H3), 7.37(d, ^{3}J = 8.5 Hz, 1H, H5), 7.28 (m, 1H, H4), 6.52 (d, ^{3}J = 15.7 Hz, 1H, H8'), 6.48 (d, ^{3}J = 15.4 Hz, 1H, H8), 1.74 (sext, ^{3}J = 7.5 Hz, 2H, H11), 1.44 (m, 2H, H10), 1.44 (m, 2H, H12), 0.95 (t, ^{3}J = 7.4 Hz, 3H, H13). ^{13}C NMR ($CDCl_3$) δ: 176.3 (C9), 175.9 (C9'). 146.3 (C7'), 144.7 (C7), 136.3 (C4'), 134.4

(C1), 132.9 (C1'), 130.4 (C4), 129.3 (C2'), 129.3 (C6'), 129.2 (C2), 129.2 (C6), 128.9 (C3'), 1sta28.9 (C5'), 128.1 (C3), 128.1 (C5), 118.5 (C8'), 117.8 (C8), 26.7 (*J* (C12-^{119}Sn) = 35.2 Hz), 26.4 (*J* (C11-^{119}Sn) = 98.6 Hz), 25.8 (*J* (C10-^{119}Sn) = 585.6 Hz; *J* (C10-^{117}Sn) = 561.5 Hz), 13.6 (C13). ^{119}Sn NMR ($CDCl_3$) δ: –147.8.

*(((E,Z)-3-(4-bromophenyl)acryloyl)oxy)dibutylstannyl cinnamate (**4**).* Following the same procedure that for compound **1**, a mixture of 4-bromo-*trans*-cinnamic acid (372 mg, 1.638 mmol), *trans*-cinnamic acid (242 mg, 1.633 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. The residual solution was dried under low pressure to get compound **4** as a yellow crystalline solid. Yield: 0.886 g (88%). M.p. 74-76 ºC. Analyses (%): calcd for $C_{26}H_{31}BrO_4Sn$-H_2O, C 50.03, H 5.33, Br 12.80, O 12.82, Sn 19.02; found, C 49.95, H, 5.53. FT-IR (cm^{-1}): ν_1(O=C) 1685; ν_2(O=C) 1626; ν_{asym}(COO) 1535; ν_{sym}(COO) 1451; ν(O-C) 1334; ν(Sn-C) 593; ν(Sn-O) 445. ^{1}H RMN ($CDCl_3$) δ: 7.81 (d, ^3J = 16.7 Hz, 1H, H7'), 7.71 (d, ^3J = 15.9 Hz, 1H, H7), 7.56 (m, 1H, H2'), 7.56 (m, 1H, H6'), 7.53 (m, 1H, H2), 7.53 (m, 1H, H6), 7.42 (m, 1H, H3), 7.42 (m, 1H, H5), 7.41 (m, 1H, H3'), 7.41 (m, 1H, H5'), 7.28 (m, 1H, H4), 6.54 (d, ^3J = 8.9 Hz, 1H, H8'), 6.50 (d, ^3J = 8.9 Hz, 1H, H8), 1.74 (m, 1H, H10), 1.74 (m, 1H, H12), 1.44 (sext, ^3J = 7.2 Hz, 2H, H11), 0.95 (t, ^3J = 7.4 Hz, H1, H13). ^{13}C RMN ($CDCl_3$) δ: 176.3 (C9'),176.0 (C9), 146.3 (C7'), 144.7 (C7), 134.4 (C4'), 134.3 (C1), 132.1 (C1'), 130.4 (C4), 129.5 (C2'), 129.5 (C6'),128.9 (C2), 128.9 (C6), 128.2 (C3'), 128.2 (C5'), 124.6 (C3), 124.6 (C5), 117.7 (C8), 117.7 (C8'), 26.9 (*J* (C12-^{119}Sn) = 35.2 Hz), 26.5 (*J* (C11-^{119}Sn) = 99.6 Hz), 25.8 (*J* (C10-^{119}Sn) = 584.6 Hz; *J* (C10-^{117}Sn) = 559.4 Hz), 13.6 (C13). ^{119}Sn RMN ($CDCl_3$) δ: –149.6.

*Dibutyl((2-(4-isobutylphenyl)propanoyl)oxy)stannyl 3-phenylpropanoate (**5**).* Following the same procedure that for compound **1**, a mixture of hydrocinnamic acid (246 mg, 1.638 mmol), ibuprofen (338 mg, 1.638 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. Compound **5** was obtained as a yellow liquid. Yield: 0.920 g (95%). Analyses (%): calcd for $C_{26}H_{31}BrO_4Sn$, C 58.59, H 7.61, O 12.59, Sn 18.68; found, C 58.77, H 8.04. FT-IR (cm^{-1}): ν_1(O=C) 1639; ν_2(O=C) 1565; ν_{asym}(COO) 1512; ν_{sym} (COO) 1383; ν(O-C) 1376; ν(Sn-C) 594; ν(Sn-O) 435. ^{1}H NMR ($CDCl_3$) δ: 7.26 (d, ^3J = 8.0 Hz, 1H, H2'), 7.26 (d, ^3J = 8.0 Hz, 1H, H6'), 7.24 (m, H4'), 7.23 (d, ^3J = 8.0 Hz, 1H, H2), 7.23 (d, ^3J = 8.0 Hz, 1H, H6), 7.19 (d, ^3J = 8.0 Hz, 1H, H3'), 7.19 (d, ^3J = 8.0 Hz, 1H, H5'), 7.11 (d, ^3J = 8.0 Hz, 1H, H3), 7.11 (d, ^3J = 8.0 Hz, 1H, H5), 3.79 (q, ^3J = 7.0 Hz, 1H, H7), 3.00 (t, ^3J = 8.0 Hz, 2H, H7'), 2.72 (t, ^3J = 8.0 Hz, 2H, H8'), 2.45 (d, ^3J = 7.5 Hz, 3H, H9), 1.86 (m, 1H, H10), 1.64 (m, 2H, H13), 1.55 (d, ^3J = 7.2 Hz, 3H, H8), 1.54 (m, H14), 1.53 (d, ^3J = 6.6 Hz, 3H, H11), 1.27 (sext, ^3J = 7.7 Hz, 2H, H15), 0.85 (m, 2H, H16). ^{13}C NMR ($CDCl_3$) δ: 186.0 (C9'), 185.0 (C12), 140.5 (C1), 140.4 (C1'), 137.9 (C4), 129.2 (C2), 128.4 (C2'), 128.4 (C6'), 128.3 (C3'), 128.3 (C5'), 127.1 (C3), 127.1 (C5), 129.2 (C6), 126.2 (C4'), 45.1 (C10), 45.0 (C7), 35.6 (C8'),

31.4 (C7'), 30.2 (C8), 26.2 (C14), 25.6 (C15), 25.0 (C13), 22.3 (C9), 18.7 (C11), 13.5 (C16). ^{119}Sn NMR ($CDCl_3$) δ: –145.9.

*Dibutyl((2-(4-isobutylphenyl)propanoyl)oxy)stannyl cinnamate (**6**).* Following the same procedure that for compound **1,** a mixture of ibuprofen (338 mg, 1.638 mmol), *trans*-cinnamic acid (242 mg, 1.633 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. Compound **6** was obtained as a yellow liquid. Yield: 0.930 g (96%). Analyses (%): calcd for $C_{30}H_{42}O_4Sn$, C 61.56, H 7.23, O 10.93, Sn 20.28; found, C 61.47, H 7.64. FT-IR (cm^{-1}): ν_1(O=C) 1639; ν_2(O=C) 1639; ν_{asym}(COO) 1514; ν_{sym}(COO) 1372; ν(O-C) 1365; ν(Sn-C) 593; ν(Sn-O) 448. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, ^3J = 16.0 Hz, 1H, H7'), 7.55 (m, 1H, H2'), 7.55 (m, 1H, H6'), 7.42 (m, 1H, H4'), 7.41 (m, 1H, H3'), 7.41 (m, 1H, H5'), 7.29 (d, ^3J = 8.0 Hz, 1H, H2), 7.29 (d, ^3J = 8.0 Hz, 1H, H6), 7.11 (d, ^3J = 8.1 Hz, 1H, H3), 7.11 (d, ^3J = 8.1 Hz, 1H, H5), 6.52 (d, ^3J = 16.0 Hz, 1H, H8'), 3.81 (q, ^3J = 7.1 Hz, 1H, H7), 2.46 (d, ^3J = 7.2 Hz, 2H, H9), 1.86 (hept, ^3J = 6.7 Hz, 1H, H10), 1.68 (m, 2H, H14), 1.61 (m, 2H, H13), 1.49 (d, ^3J = 7.2 Hz, 3H, H8), 1.33 (sext, ^3J = 7.4 Hz, 2H, H15), 0.91 (d, ^3J = 6.6 Hz, 3H, H11), 0.85 (t, ^3J = 7.3 Hz, 1H, H16). ^{13}C NMR ($CDCl_3$) δ: 184.7 (C12), 176.1 (C9'), 146.3 (C7'), 140.5 (C4), 137.9 (C1), 134.4 (C1'), 130.4 (C4'), 129.2 (C2), 129.2 (C6), 128.9 (C2'), 128.9 (C6'), 128.4 (C3'), 128.4 (C5'),127.2 (C3), 127.2 (C5), 117.7 (C8'), 45.1 (C9), 45.0 (C7), 30.1 (C10), 26.5 (*J* (C13-^{119}Sn) = 583.6 Hz; *J* (C13-^{117}Sn) = 557.5 Hz), 26.2 (*J* (C14-^{117}Sn) = 97.6 Hz), 25.1 (*J* (C15-^{117}Sn) = 36.2 Hz), 22.3 (C11), 18.7 (C8), 13.5 (C16). ^{119}Sn NMR ($CDCl_3$) δ: –150.1.

*(E,Z)-dibutyl((2-(4-isobutylphenyl)propanoyl)oxy)stannyl 3-(4-fluorophenyl)acrylate (**7**).* Following the same procedure that for compound **1**, a mixture of ibuprofen (338 mg, 1.638 mmol), 4-fluoro-*trans*-cinnamic acid (272 mg, 1.633 mmol) 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. The residual solution was dried under low pressure to get compound **7** as a white solid. Yield: 0.976 g (98%). M.p. 46-48 ºC. Analyses (%): calcd for $C_{30}H_{41}FO_4Sn$, C 59.72, H 6.85, F 3.15, O 10.61, Sn 19.68; found, C 60.33, H 6.81. FT-IR (cm^{-1}): ν_1(O=C) 1626; ν_2(O=C) 1565; ν_{asym}(COO) 1508; ν_{sym}(COO) 1387; ν(O-C) 1340; ν(Sn-C) 626; ν(Sn-O) 468. ^{1}H NMR ($CDCl_3$) δ: 7.74 (d, ^3J = 16.0 Hz, 1H, H7'), 7.53 (d, ^3J = 5.6 Hz, 1H, H2'), 7.53 (d, ^3J = 5.6 Hz, 1H, H6'), 7.28 (d, ^3J = 5.8 Hz, 1H, H3'), 7.28 (d, ^3J = 5.8 Hz, 1H, H5'), 7.11 (d, ^3J = 7.8 Hz, 1H, H2), 7.11 (d, ^3J = 7.8 Hz, 1H, H6), 7.09 (d, ^3J = 7.8 Hz, 1H, H3), 7.09 (d, ^3J = 7.8 Hz, 1H, H5), 6.43 (d, ^3J = 16.8 Hz, 1H, H8'), 3.80 (q, ^3J = 7.0 Hz, 1H, H7), 2.45 (d, ^3J = 7.0 Hz, 2H, H9), 1.86 (hept, ^3J = 6.6 Hz, 1H, H10), 1.75 (m, 2H, H13), 1.65 (m, 2H, H14), 1.53 (d, ^3J = 7.1 Hz, 3H, H8), 1.33 (sext,^3J = 7.3 Hz, 1H, H15), 0.90 (d, ^3J = 6.6 Hz, 3H, H11), 0.86 (t, ^3J = 7.2 Hz, 3H, H16). ^{13}C NMR ($CDCl_3$) δ: 185.0 (C12), 176.0 (C9'), 162.2 (*J* (C4'-^{19}F) = 251.6 Hz), 144.9 (C7'), 140.4 (C4), 137.9 (C1), 130.6 (C1'), 130.0 (C3'), 130.0 (C5'), 129.0 (C2), 129.0 (C6), 127.1 (C3), 127.1 (C5), 117.5 (C8'), 115.9 (C2'), 115.9 (C6'), 45.1 (C9), 45.0 (C7), 30.1 (C10), 26.2 (*J* (C13-^{119}Sn) =

584.6 Hz; *J* (C13-^{117}Sn) = 559.5 Hz), 26.0 (*J* (C14-^{119}Sn) = 98.6 Hz C14), 25.1 (*J* (C15-^{119}Sn) = 36.2 Hz C15), 22.3 (C11), 18.7 (C8), 13.5 (C16). ^{119}Sn NMR ($CDCl_3$) δ: –149.5.

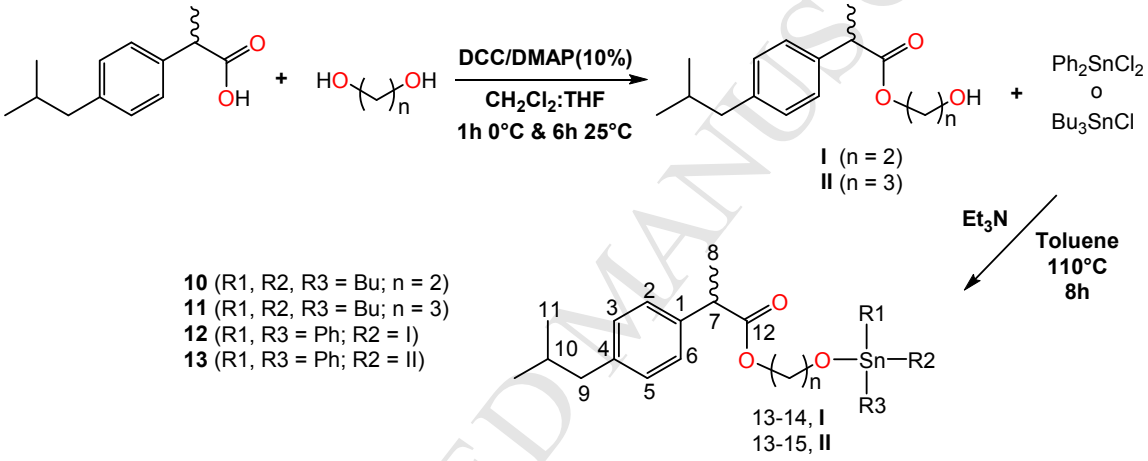
*(E,Z)-dibutyl((2-(4-isobutylphenyl)propanoyl)oxy)stannyl 3-(4-chlorophenyl)acrylate (**8**).* Following the same procedure that for compound **1,** a mixture of ibuprofen (338 mg, 1.638 mmol), 4-chloro-*trans*-cinnamic acid (299 mg, 1.653 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) was reacted. The residual solution was dried under low pressure to get compound **8** as a yellow crystalline solid. Yield: 0.990 g (98%). M.p. 83-85 ºC. Analyses (%): calcd for $(C_{30}H_{41}ClO_4Sn)_2$-H_2O, C 57.30, H 6.73, Cl 5.72, O 10.33, Sn 19.15; found, C 57.08, H 6.75. FT-IR (cm^{-1}): ν_1(O=C) 1687; ν_2(O=C) 1627; ν_{asym}(COO) 1510; ν_{sym}(COO) 1386; ν(O-C) 1334; ν(Sn-C) 637; ν(Sn-O) 452. ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, ^3J = 16.3 Hz, 1H, H7'), 7.53 (d, ^3J = 7.9 Hz, 1H, H2'), 7.53 (d, ^3J = 7.9 Hz, 1H, H6'), 7.39 (d, ^3J = 7.9 Hz, 1H, H3'), 7.39 (d, ^3J = 7.9 Hz, 1H, H5'), 7.27 (d, ^3J = 7.6 Hz, 1H, H2), 7.27 (d, ^3J = 7.6 Hz, 1H, H6), 7.09 (d, ^3J = 7.4 Hz, 1H, H3), 7.09 (d, ^3J = 7.4 Hz, 1H, H5), 6.48 (d, ^3J = 15.9 Hz, 1H,H8'), 3.79 (q, ^3J = 6.8 Hz, 1H, H7), 2.44 (d, ^3J = 6.9 Hz, 2H, H9), 1.86 (hept, ^3J = 6.8 Hz, 1H, H10), 1.71 (m, 1H, H13), 1.65 (m, 1H, H14), 1.53 (d, ^3J = 7.8 Hz, 3H,H8), 1.31 (sext, ^3J = 7.5 Hz, 2H, H15), 0.88 (d, ^3J = 6.4 Hz, 3H, H11), 0.84 (t, ^3J = 7.3 Hz, 3H, H16). ^{13}C NMR ($CDCl_3$) δ: 185.0 (C12), 175.9 (C9'), 144.7 (C7'), 140.4 (C4), 132.1 (C2'), 137.9 (C1), 133.3 (C4'), 132.1 (C6') 129.5 (C3), 129.5 (C5), 129.2 (C2), 129.2 (C6), 127.1 (C3'), 127.1 (C5'), 124.6 (C1'), 118.5 (C8'), 45.1 (C9), 45.0 (C7), 30.1 (C10), 26.3 (*J* (C13-^{119}Sn) = 568.5 Hz; *J* (C13-^{117}Sn) = 555.5 Hz), 26.2 (*J* (C14-^{119}Sn) = 97.6 Hz), 25.1 (*J* (C15-^{119}Sn) = 37.2 Hz), 22.3 (C11), 18.7 (C8), 13.5 (C16). ^{119}Sn NMR ($CDCl_3$) δ: –149.4.

*(E,Z)-dibutyl((2-(4-isobutylphenyl)propanoyl)oxy)stannyl 3-(4-bromophenyl)acrylate (**9**).* Following the same procedure that for compound **1**, a mixture of ibuprofen (338 mg, 1.638 mmol), 4-bromocinnamic acid (372 mg, 1.638 mmol), 0.874 ml of triethylamine (660 mg, 6.581 mmol) and dibutyltin dichloride (500 mg, 1.645 mmol) were reacted. The residual solution was dried under low pressure to get compound **9** as a yellow crystalline solid. Yield: 1.006 g (97%). M.p. 60-62 ºC. Analyses (%): calcd for $(C_{30}H_{41}ClO_4Sn)_2$-H_2O, C 54.24, H 6.22, Br 12.03, O 9.63, Sn 17.87; found, C 5.74, H 9.90. FT-IR (cm^{-1}): ν_1(O=C) 1626; ν_2(O=C) 1566; ν_{asym}(COO) 1513; ν_{sym}(COO) 1384; ν(O-C) 1338; ν(Sn-C) 583; ν(Sn-O) 433. ^{1}H NMR ($CDCl_3$) δ: 7.71 (d, ^3J = 16.0 Hz, 1H, H7'), 7.46 (d, ^3J = 8.4 Hz, 1H, H3'), 7.46 (d, ^3J = 8.4 Hz, 1H, H5'), 7.36 (d, ^3J = 8.4 Hz, 1H, H6'), 7.36 (d, ^3J = 8.4 Hz, 1H, H2'), 7.26 (d, ^3J = 8.0 Hz, 1H, H2), 7.26 (d, ^3J = 8.0 Hz, 1H, H6), 7.09 (d, ^3J = 8.4 Hz, 1H, H3), 7.09 (d, ^3J = 8.4 Hz, 1H, H5), 6.47 (d, ^3J = 16.0 Hz, 1H, H8'), 3.79 (q, ^3J = 7.1 Hz, 1H, H7), 2.46 (d, ^3J = 7.2 Hz, 2H, H9), 1.84 (hept, ^3J = 6.7 Hz, 1H, H10), 1.72 (m, 2H, H13), 1.64 (m, 1H, H14), 1.53 (d, ^3J = 7.2 Hz, 3H, H8), 1.32 (sext, ^3J = 7.3 Hz, 2H, H15), 0.88 (d, ^3J = 6.6 Hz, 3H, H11), 0.85 (t, ^3J = 7.3 Hz, 3H, H16). ^{13}C NMR ($CDCl_3$) δ: 184.9 (C12), 175.8 (C9') 140.4 (C4), 144.7 (C7'), 137.9 (C1), 132.9 (C1'), 129.5 (C3'), 129.5 (C5'), 129.3 (C2), 129.2 (C6), 129.2 (C2'), 129.2 (C4'), 129.2 (C6'), 127.1 (C3),

127.1 (C5), 118.3 (C8'), 45.1 (C9), 45.0 (C7), 30.1 (C10), 26.3 (*J* (C13-^{119}Sn) = 571.5 Hz; *J* (C13-^{117}Sn) = 558.2 Hz), 26.2 (*J* (C14-^{119}Sn) = 96.5 Hz), 25.1 (*J* (C15-^{119}Sn) = 36.2 Hz), 22.3 (C11), 18.7 (C8), 13.5 (C16). ^{119}Sn NMR ($CDCl_3$) δ: –149.3.

*4.3. General procedure for the synthesis of stannoxanes ibuprofen derivatives using glycol spacers (**10-13**)*

As a first step for the synthesis of compounds, the coupling between ibuprofen and the diols (i.e., the spacer group) was performed (Scheme 2: **I**, **II**). After purification, the free alcohol in this structure acts as nucleophile against organotin(IV) halides to form the stannoxanes **10-13** (Scheme 2).



Scheme 2. Synthesis and sequence enumeration of stannoxanes ibuprofen derivatives with spacers groups.

*2-hydroxyethyl 2-(4-isobutylphenyl)propanoate (**I**) and 3-hydroxypropyl 2-(4-isobutylphenyl)propanoate (**II**).* In a dry flask, the ibuprofen (1000 mg, 4.85 mmol), dimethylaminopyridine (60 mg, 0.48 mmol) and ethylene or propylene glycol (14.56 mmol) were added in dry tetrahydrofuran (THF) and dichloromethane (DCM) (1:1), this mixture was stirred and the dicyclohexylcarbodiimide (1000 mg, 4.84 mmol) was added dropwise over 30 min in anhydrous dichloromethane solution, the reaction mixture was stirred at 0 °C for 2 h and then kept overnight at room temperature. The dicyclohexylurea (DCU) was separated by filtration and washed with HCl (0.05 N, 30 ml), 5% potassium bicarbonate and water, respectively, the mixture was dried over anhydrous $MgSO_4$, the solvent was evaporated and the products **I** and **II** were obtained as yellow liquids with yields of 92% and 90%, respectively [56].

*2-((tributylstannyl)oxy)ethyl 2-(4-isobutylphenyl)propanoate (**10**).* For stannoxanes **10-15**, the same procedure was used. For compound **10**, in a flask ball was added the hydroxy ester

(**I**) (1000 mg, 3.99 mmol), triethylamine (0.56 ml, 3.99 mmol) in dry toluene, then, tributyltin chloride (1.07 ml, 3.99 mmol) was slowly added and the reaction was allowed 8h at 110 °C. Then the solvent was evaporated at low pressure, the hydrochloride triethylamine (Et_3N: HCl) was precipitated and filtered in cold pentane, at once the solvent was evaporated under reduced pressure. Compound **10** was obtained as a yellow liquid. Yield: 1.68 g (78%). Analyses (%): calcd for $C_{27}H_{48}O_3Sn$-$(H_2O)_3$, C 54.65, H 9.17, O 16.18, Sn 20.00; found, C 54.26, H 9.65. FT-IR (cm^{-1}): ν(O=C) 1737; ν(O-C) 1163; ν(Sn-C) 507; ν(Sn-O) 466. ^{1}H NMR ($CDCl_3$) δ: 7.14 (d, ^3J = 8.0 Hz, 1H, H2), 7.14 (d, ^3J = 8.0 Hz, 1H, H6), 7.01 (d, ^3J = 8.0 Hz, 1H, H3), 7.01 (d, ^3J = 8.0 Hz, 1H, H5), 4.12 (w, 2H, H13), 3.67 (w, 1H, H7), 3.67 (w, 2H, H14), 2.38 (d, ^3J = 7.2 Hz, 2H, H9), 1.78 (hept, d, ^3J = 7.2 Hz, 1H, H10), 1.55 (w, 2H, H15), 1.43 (d, ^3J = 7.2 Hz, 3H, H8),1.28 (sext, ^3J = 7.6 Hz, 2H, H17), 1.23 (sext, ^3J = 7.6 Hz, 2H, H16), 0.85 (t, ^3J = 7.2 Hz, 3H, H18), 0.81 (d, ^3J = 6.8 Hz, 3H, H11). ^{13}C NMR ($CDCl_3$) δ: 175.1 (12), 140.7 (4), 137.7 (1), 129.4 (2), 129.4 (6), 127.2 (3), 127.2 (5), 66.3 (13), 62.3 (14), 45.1 (7), 45.1 (9), 30.2 (10), 27.9 (*J* (C17-^{119}Sn) = 22.1 Hz), 26.9 (*J* (C16-^{119}Sn) = 63.4 Hz), 22.4 (11), 19.2 (8), 17.6 (*J* (C15-^{119}Sn) = 336.1 Hz; *J* (C15-^{117}Sn) = 332.0 Hz), 13.6 (18). ^{119}Sn NMR ($CDCl_3$) δ: + 156.4.

*3-((tributylstannyl)oxy)propyl 2-(4-isobutylphenyl)propanoate (**11**).* Following the same procedure that for compound **10**, a mixture of compound **II** (1000 mg, 3.78 mmol), triethylamine (0.53 ml, 3.78 mmol) and tributyltin chloride (1.02 ml, 3.78 mmol) was reacted. Compound **11** was obtained as a yellow liquid. Yield: 1.72 g (82%). Analyses (%): calcd for $C_{28}H_{50}O_3Sn$-$(H_2O)_2$, C 57.06, H 9.23, O 13.57, Sn 20.14; found, C 56.28, H 9.42. FT-IR (cm^{-1}): ν(O=C) 1734; ν(O-C) 1166; ν(Sn-C) 536; ν(Sn-O) 462. ^{1}H NMR ($CDCl_3$) δ: 7.21 (d, ^3J = 8.0 Hz, 1H, H2), 7.21 (d, ^3J = 8.0 Hz, 1H, H6), 7.12 (d, ^3J = 8.0 Hz, 1H, H3), 7.12 (d, ^3J = 8.0 Hz, 1H, H5), 4.25 (oct, ^3J = 6.0 Hz, 2H, H13), 3.73 (q, ^3J = 7.2 Hz, 1H, H7), 3.55 (t, ^3J = 6.8 Hz, 2H, H15), 2.47 (d, ^3J = 7.2 Hz, 2H, H9), 1.86 (hept, ^3J = 6.8 Hz, 1H, H10), 1.83 (sext, ^3J = 6.4 Hz, 2H, H14), 1.68 (m, ^3J = 7.2 Hz, 2H, H16), 1.52 (d, ^3J = 7.2 Hz, 3H, H8), 1.41 (m, ^3J = 7.2 Hz, 2H, H17), 1.33 (m, ^3J = 7.6 Hz, 2H, H18), 0.94 (t, ^3J = 7.2 Hz, 3H, H19), 0.91 (d, ^3J = 6.8 Hz, 3H, H11). ^{13}C NMR ($CDCl_3$) δ: 175.2 (12), 140.5 (4), 137.7 (1), 129.9 (2), 129.9 (6), 126.3 (3), 126.3 (5), 61.7 (13), 58.8 (15), 45.1 (7), 45.1 (9), 31.7 (14), 30.1 (10), 27.8 (*J* (C18-^{119}Sn) = 22.1 Hz), 26.8 (*J* (C17-^{119}Sn) = 64.4 Hz), 22.3 (11), 18.4 (8), 18.3 (*J* (C16-^{119}Sn) = 337.1 Hz; *J* (C16-^{117}Sn) = 332.0 Hz), 13.6 (19). ^{119}Sn NMR ($CDCl_3$) δ: + 156.2.

*((diphenylstannanediyl)bis(oxy)) bis(ethane-2,1-diyl)bis(2-(4-isobutylphenyl) propanoate) (**12**)).* Following the same procedure that for compound **10**, a mixture of compound **I** (1000 mg, 3.99 mmol), triethylamine (0.56 ml, 3.99 mmol) and diphenyltin dichloride (0.68 mg, 1.99 mmol) was reacted. Compound **12** was obtained as a yellow liquid. Yield: 2.56 g (83%). Analyses (%): calcd for $C_{42}H_{52}O_6Sn$-$CHCl_3$, C 57.97, H 6.00, O 10.77, Sn 13.32; found, C 58.95, H 6.32. FT-IR (cm^{-1}): ν(O=C) 1735; ν(O-C) 1162; ν(Sn-C) 517; ν(Sn-O) 462. ^{1}H NMR ($CDCl_3$) δ: 7.68 (w, 1H, H16), 7.46 (W, 1H, H17), 7.46 (w, 1H, H18), 7.16

(d, ^{3}J = 8.0 Hz, 1H, H2), 7.16 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.02 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.02 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.19 (w, 2H, H13), 3.75 (w, 1H, H7), 3.75 (w, 1H, H14), 2.45 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.86 (hept, ^{3}J = 6.8 Hz, 1H, H10), 1.41 (d, ^{3}J = 6.8 Hz, 3H, H8), 0.88 (d, ^{3}J = 6.8 Hz, 3H, H11). ^{13}C NMR ($CDCl_3$) δ: 175.1 (12), 141.1 (4), 137.4 (1), 137.4 (*J* (C15-^{119}Sn) = 619.8 Hz), 136.2 (*J* (C17-^{119}Sn) = 48.2 Hz), 130.5 (*J* (C18-^{119}Sn) = 14.1 Hz), 129.8 (2), 129.8 (6), 129.2 (*J* (C16-^{119}Sn) = 58.3 Hz), 127.0 (3), 127.0 (5), 66.3 (13), 61.2 (14), 45.2 (7), 45.0 (9), 30.2 (10), 22.3 (11), 18.4 (8). ^{119}Sn NMR ($CDCl_3$) δ: -46.6.

*((diphenylstannanediyl)bis(oxy))bis(propane-3,1-diyl) bis(2-(4-isobutylphenyl)propanoate) (**13**)*. Following the same procedure that for compound **10**, a mixture of compound **II** (1000 mg, 3.78 mmol), triethylamine (0.53 ml, 3.78 mmol) and diphenyltin dichloride (0.65 mg, 1.89 mmol) was reacted. Compound **13** was obtained as a yellow liquid. Yield: 2.60 g (86%). Analyses (%): calcd for $C_{44}H_{56}O_6Sn$-$CHCl_3$, C 58.81, H 6.25, O 10.45, Sn 12.92; found, C 58.36, H 6.47. FT-IR (cm^{-1}): ν(O=C) 1732; ν(O-C) 1165; ν(Sn-C) 514; ν(Sn-O) 455. ^{1}H RMN ($CDCl_3$) δ: 7.67 (w, 1H, H17), 7.46 (w, 1H, H18), 7.46 (w, 1H, H19), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.18 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.18 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.22 (m, 2H, H13), 3.69 (q, ^{3}J = 7.2 Hz, 1H, H7), 3.53 (t, ^{3}J = 7.2 Hz, 1H, H15), 2.45 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.85 (hept, ^{3}J = 6.8 Hz, 1H, H10), 1.49 (d, ^{3}J = 7.2 Hz, 3H, H8), 0.88 (d, ^{3}J = 6.7 Hz, 3H, H11). ^{13}C RMN ($CDCl_3$) δ:175.3 (12), 140.6 (4), 137.9 (1), 137.4 (*J* (C16-^{119}Sn) = 631.9 Hz), 136.1 (*J* (C18-^{119}Sn) = 49.3 Hz), 130.5 (*J* (C19-^{119}Sn) = 14.1 Hz), 130.3 (9) 129.5 (2), 129.5 (6), 129.2 (*J* (C17-^{119}Sn) = 63.4 Hz) 127.0 (3), 127.0 (5), 61.7 (13), 59.1 (15), 45.2 (7), 45.1 (9), 31.9 (14), 30.2 (10), 22.4 (11), 18.3 (8). ^{119}Sn RMN ($CDCl_3$) δ: -46.23.

*3.4. Compounds (**1a-13a**) were analyzing directly in the NMR tube by adding DMSO-d_6, and were not isolated*

(1a). ^{1}H NMR (DMSO-d_6) δ: 7.67 (w, 1H, H7), 7.57 (w,1H, H4), 7.53 (m, 1H, H4'), 7.40 (w, 1H, H2), 7.40 (w, 1H, H6), 7.25 (w, 1H, H2'), 7.25 (w, 1H, H6'), 7.25 (w, 1H, H3'), 7.25 (w, 1H, H5'), 7.17 (w, 1H, H3), 7.17 (w, 1H, H5), 6.55 (d, ^{3}J = 16.0 Hz, 1H, H8), 2.83 (t, ^{3}J = 7.0 Hz, 2H, H7'), 2.83 (t, ^{3}J = 7.0 Hz, 2H, H8'), 1.44 (w, 2H, H10), 1.35 (w, 2H, H12), 1.25 (sext, ^{3}J = 7.2 Hz, 2H,H11), 0.80 (d, ^{3}J = 7.2 Hz, 3H, H13). ^{13}C NMR (DMSO-d_6) δ: 180.0 (C9'), 173.0 (C9), 143.6 (C7), 141.6 (C1'), 135.1 (C1), 130.3 (C4), 129.3 (C2'), 129.3 (C6'), 128.6 (C2),128.6 (C6), 128.6 (C3),128.6 (C5), 128.4 (C3'), 128.4 (C5'), 126.3 (C4'), 117.8 (C8), 37.1 (C8'), 36.3 (C7'), 29.9 (*J* (C10-^{119}Sn) = 855.2 Hz; *J* (C10-^{117}Sn) = 827.1 Hz), 27.2 (*J* (C12-^{119}Sn) = 50.3 Hz), 26.2 (*J* (C11-^{119}Sn) = 138.8 Hz), 13.9 (C13). ^{119}Sn NMR (DMSO-d_6) δ: –204.6.

(2a). ^{1}H RMN (DMSO-d_6) δ: 7.76 (w, 1H, H2'), 7.76 (w, 1H, H6'), 7.68 (w, 1H, H3'), 7.68 (w, 1H, H5'), 7.56 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.56 (d, ^{3}J = 16.0 Hz, 1H, H7), 7.39 (w, 1H, H4), 7.39 (w, 1H, H2), 7.39 (w, 1H, H6), 7.23 (d, ^{3}J = 8.7 Hz, 1H, H3), 7.23 (d, ^{3}J = 87 Hz, 1H, H5), 6.58 (d, ^{3}J = 16.0 Hz, 1H, H8'), 6.54 (d, ^{3}J = 16.0 Hz, 1H, H8), 1.56 (w, 2H,

H10), 1.45 (w, 2H, H12), 1.28 (sext, ^{3}J = 7.2 Hz, 2H, H11), 0.95 (t, ^{3}J = 7.3 Hz, 3H, H13). ^{13}C RMN (DMSO-d_6) δ: 173.8 (C9'), 173.8 (C9), 163.4 (*J* (C4'-^{19}F) = 248.0 Hz), 143.5 (C7), 142.2 (C7'), 135.0 (C1), 131.7 (C1'), 130.8 (C4), 130.7 (C2'), 130.7 (C6'), 129.3 (C2), 129.3 (C6), 128.5 (C3), 128.5 (C5), 121.4 (C8), 121.2 (C8'), 116.3 (C3'), 116.3 (C5'), 30.0 (*J* (C10-^{119}Sn) = 835.1 Hz; *J* (C10-^{117}Sn) = 820.0 Hz), 27.3 (*J* (C12-^{119}Sn) = 62.3 Hz), 26.2 (*J* (C11-^{119}Sn) = 137.8 Hz), 13.6 (C13). ^{119}Sn RMN (DMSO-d_6) δ: –193.4.

(3a). ^{1}H NMR (DMSO-d_6) δ: 7.73 (d, ^{3}J = 8.1 Hz, 1H, H2'), 7.73 (d, ^{3}J = 8.1 Hz, 1H, H6'), 7.67 (w, 1H, H3'), 7.67 (w, 1H, H5'), 7.60 (d, ^{3}J = 15.8 Hz, 1H, H7'), 7.55 (d, ^{3}J = 15.8 Hz, 1H, H7), 7.43 (d, ^{3}J = 8.6 Hz, 1H, H2), 7.43 (d, ^{3}J = 8.6 Hz, 1H, H6), 7.39 (d, ^{3}J = 8.5 Hz, 1H, H3), 7.39 (d, ^{3}J = 8.5 Hz, 1H, H5), 7.39 (w, 1H, H4), 6.61 (d, ^{3}J = 15.8 Hz, 1H, H8'), 6.57 (d, ^{3}J = 15.8 Hz, 1H, H8), 1.53 (w, 2H, H10), 1.43 (w, 2H, H12), 1.27 (sext, ^{3}J = 7.0 Hz, 2H, H11), 0.95 (t, ^{3}J = 7.4 Hz, 3H, H13). ^{13}C NMR (DMSO-d_6) δ: 174.1 (C9'), 173.3 (C9), 143.6 (C7), 142.2 (C7'), 135.0 (C4'), 134.9 (C1'), 130.4 (C4), 130.4 (C1), 130.1 (C3'), 130.2 (C5'), 129.3 (C3), 129.3 (C5), 128.1 (C2'), 128.1 (C6'), 128.1 (C2), 128.1 (C6), 120.9 (C8'), 120.9 (C8), 30.0 (*J* (C10-^{119}Sn) = 851.2 Hz; *J* (C10-^{117}Sn) = 814.0 Hz), 27.2 (*J* (C12-^{119}Sn) = 57.3 Hz), 26.1 (*J* (C11-^{119}Sn) = 137.8 Hz), 14.0 (C13). ^{119}Sn NMR (DMSO-d_6) δ: –205.8.

(4a). ^{1}H NMR (DMSO-d_6) δ: 7.67 (d, ^{3}J = 16.0 Hz, 1H, H7), 7.66 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.63 (m, 1H, H2'), 7.63 (m, 1H, H6'), 7.60 (m, 1H, H2), 7.60 (m, 1H, H6), 7.58 (m, 1H, H3'), 7.58 (m, 1H, H5'), 7.53 (m, 1H, H3), 7.53 (m, 1H, H5), 7.40 (m, 1H, H4), 6.59 (d, ^{3}J = 8.4 Hz, 1H, H8'), 6.55 (d, ^{3}J = 8.5 Hz, 1H, H8), 1.58 (m, 1H, H10), 1.43 (m, 1H, H12), 1.24 (sext, ^{3}J = 7.1 Hz, 2H, H11), 0.81 (t, ^{3}J = 7.2 Hz, H1, H13). ^{13}C NMR (DMSO-d_6) δ: 172.6 (C9'),172.6 (C9), 143.4 (C7), 141.9 (C7'), 135.0 (C4'), 134.4 (C1'), 132.3 (C4), 130.3 (C1), 130.4 (C2'), 130.4 (C6'), 129.3 (C3'), 129.3 (C5'), 129.3 (C3), 129.3 (C5), 128.4 (C2), 128.4 (C6),122.3 (C8'), 121.3 (C8), 29.3 (*J* (C10-^{119}Sn) = 855.2 Hz; *J* (C10-^{117}Sn) = 854.2 Hz), 27.2 (*J* (C12-^{119}Sn) = 72.4 Hz), 26.2 (*J* (C11-^{119}Sn) = 139.8 Hz), 13.9 (C13). ^{119}Sn NMR (DMSO-d_6) δ: –198.4.

(5a). ^{1}H NMR (DMSO-d_6) δ: 7.23 (w, 1H, H2'), 7.23 (w, 1H, H6'), 7.25 (w, 1H, H4), 7.20 (d, ^{3}J = 7.9 Hz, 1H, H2), 7.23 (d, ^{3}J = 7.9 Hz, 1H, H6), 7.21 (w, 1H, H3'), 7.21 (w, 1H, H5'), 7.01 (d, ^{3}J = 7.8 Hz, 1H, H3), 7.01 (d, ^{3}J = 78 Hz, 1H, H5), 3.58 (q, ^{3}J = 7.0 Hz, 1H, H7), 2.84 (d, ^{3}J = 7.5 Hz, 2H, H7'), 2.50 (d, ^{3}J = 7.5. Hz, 2H, H8'), 2.39 (d, ^{3}J = 7.1 Hz, 2H, H9), 1.86 (hept, ^{3}J = 6.6 Hz, 1H, H10), 1.64 (H13), 1.54 (H14), 1.34 (d, ^{3}J = 7.1 Hz, 2H, H8), 1.30 (w, 2H, H13), 1.22 (w, 2H, H14), 1.13 (sext, ^{3}J = 7.1 Hz, 2H, H15) 0.84 (d, ^{3}J = 6.8 Hz, 3H, H11), 0.72 (t, ^{3}J = 7.9 Hz, 3H, H16). ^{13}C NMR (DMSO-d_6) δ: 181.6 (C12), 179.4 (C9'), 141.6 (C4), 139.6 (C1'), 139.6 (C1), 129.2 (C2), 129.2 (C6), 128.9 (C3), 128.9 (C4'), 128.9 (C5), 126.5 (C3'), 126.5 (C5'), 126.3 (C2'), 126.3 (C6'), 45.1 (C9), 45.0 (C7), 36.2 (C8'), 31.4 (C7'), 30.3 (*J* (C13-^{119}Sn) = 867.3 Hz; *J* (C13-^{117}Sn) = 847.2 Hz), 30.1 (C10), 27.8 (*J* (C15-^{119}Sn) = 41.6 Hz), 26.1 (*J* (C14-^{119}Sn) = 142.8 Hz), 22.6 (C11), 19.4 (C8), 14.0 (C16). ^{119}Sn NMR (DMSO-d_6) δ: –167.4.

(6a). ^{1}H NMR (DMSO-d_6) δ: 7.64 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.45 (m, 1H, H4'), 7.40 (m, 1H, H2'), 7.40 (m, 1H, H6'), 7.38 (m, 1H, H3'), 7.38 (m, 1H, H5'), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.05 (d, ^{3}J = 7.9 Hz, 1H, H3), 7.05 (d, ^{3}J = 7.9 Hz, 1H, H5), 6.52 (d, ^{3}J = 16.0 Hz, 1H, H8'), 3.52 (q, ^{3}J = 7.4 Hz, 1H, H7), 2.39 (d, ^{3}J = 7.1 Hz, 2H, H9), 1.85 (hept, ^{3}J = 6.6 Hz, 1H, H10), 1.44 (d, ^{3}J = 7.9 Hz, 3H, H8), 1.33 (m, 2H, H13), 1.30 (m, 2H, H14), 1.17 (sext, ^{3}J = 7.5 Hz, 2H, H15), 0.84 (d, ^{3}J = 6.9 Hz, 3H, H11), 0.75 (t, ^{3}J = 7.1 Hz, 1H, H16). ^{13}C NMR (DMSO-d_6) δ: 181.0 (C12), 172.5 (C9'), 143.8 (C7'), 139.7 (C4), 135.0 (C1), 134.9 (C1'), 130.4 (C4'), 129.3 (C2), 129.3 (C6), 129.2 (C3'), 129.2 (C5'), 128.5 (C2'), 128.5 (C6'),127.6 (C3), 127.6 (C5), 120.6 (C8'), 44.7 (C9), 43.3 (C7), 29.9 (C10), 30.3 (J (C13-^{119}Sn) = 856.3 Hz; J (C13-^{117}Sn) = 839.1 Hz), 27.3 (J (C15-^{117}Sn), 26.2 (J (C14-^{117}Sn) = 144.8 Hz), = 34.1 Hz), 22.6 (C11), 19.3(C8), 14.0 (C16). ^{119}Sn NMR (DMSO-d_6) δ: –172.1.

(7a). ^{1}H NMR (DMSO-d_6) δ: 7.71 (d, ^{3}J = 8.6 Hz, 1H, H2'), 7.71 (d, ^{3}J = 8.6 Hz, 1H, H6'), 7.54 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.45 (d, ^{3}J = 8.5 Hz, 1H, H3'), 7.45 (d, ^{3}J = 8.5 Hz, 1H, H5'), 7.21 (d, ^{3}J = 7.8 Hz, 1H, H2), 7.21 (d, ^{3}J = 7.8 Hz, 1H, H6), 7.02 (d, ^{3}J = 8.1 Hz, 1H, H3), 7.02 (d, ^{3}J = 8.1 Hz, 1H, H5), 6.56 (d, ^{3}J = 16.0 Hz, 1H, H8'), 3.59 (q, ^{3}J = 7.1 Hz, 1H, H7), 2.38 (d, ^{3}J = 7.1 Hz, 2H, H9), 1.78 (hept, ^{3}J = 6.6 Hz, 1H, H10), 1.45 (m, 2H, H13), 1.38 (m, 2H, H14), 1.35 (d, ^{3}J = 7.1 Hz, 3H, H8), 1.21(sext,^{3}J = 7.2 Hz, 1H, H15), 0.83 (d, ^{3}J = 6.6 Hz, 3H, H11), 0.78 (t, ^{3}J = 7.3 Hz, 3H, H16). ^{13}C NMR (DMSO-d_6) δ: 172.3 (C12), 172.3 (C9'), 164.4 (J (C4'-^{19}F) = 248.0 Hz), 144.4 (C7'), 139.7 (C4), 135.9 (C1), 131.6 (C1'), 130.8 (C2'), 130.8 (C6'), 130.2 (C2), 130.2 (C6), 127.6 (C3), 127.6 (C5), 120.7 (C8'), 116.3 (C3'), 116.3 (C5'), 45.4 (C9), 44.7 (C7), 31.3 (C10), 30.2 (J (C13-^{119}Sn) = 857.3 Hz; J (C13-^{117}Sn) = 813.0 Hz), 27.4 (J (C14-^{119}Sn) = 140.8 Hz C14), 26.2 (J (C15-^{119}Sn) = 35.1 Hz C15), 22.6 (C11), 19.4 (C8), 14.0 (C16). ^{119}Sn NMR (DMSO-d_6) δ: –149.5.

(8a). ^{1}H NMR (DMSO-d_6) δ: 7.64 (d, ^{3}J = 8.6 Hz, 1H, H2'), 7.64 (d, ^{3}J = 8.6 Hz, 1H, H6'), 7.59 (d, ^{3}J = 8.6 Hz, 1H, H3'), 7.59 (d, ^{3}J = 8.6 Hz, 1H, H5'), 7.52 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.21 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.01 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.01 (d, ^{3}J = 8.0 Hz, 1H, H5), 6.58 (d, ^{3}J = 16.0 Hz, 1H, H8'), 3.60 (q, ^{3}J = 7.1 Hz, 1H, H7), 2.44 (d, ^{3}J = 7.1 Hz, 2H, H9), 1.78 (hept, ^{3}J = 6.8 Hz, 1H, H10), 1.43 (m, 1H, H13), 1.43 (m, 1H, H14), 1.53 (d, ^{3}J = 7.1 Hz, 3H, H8), 1.31 (sext, ^{3}J = 7.1 Hz, 2H, H15), 0.82 (d, ^{3}J = 6.6 Hz, 3H, H11), 0.77 (t, ^{3}J = 7.3 Hz, 3H, H16). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C12), 172.7 (C9'), 142.2 (C7'), 142.2 (C4'), 139.7 (C4), 134.4 (C1), 132.2 (C2'), 132.2 (C6') 127.6 (C3), 127.6 (C5), 130.4 (C2), 130.4 (C6), 129.2 (C3'), 129.2 (C5'), 134.4 (C1'), 116.3 (C8'), 44.7 (C9), 45.4 (C7), 30.1 (C10), 30.3 (J (C13-^{119}Sn) = 850.2 Hz; J (C13-^{117}Sn) = 825.1 Hz), 26.1 (J (C14-^{119}Sn) = 139.8 Hz), 27.5 (J (C15-^{119}Sn) = 38.2 Hz), 22.6 (C11), 20.0 (C8), 14.0 (C16). ^{119}Sn NMR (DMSO-d_6) δ: –149.4.

(9a). ^{1}H NMR (DMSO-d_6) δ: 7.71 (d, ^{3}J = 16.0 Hz, 1H, H7'), 7.46 (d, ^{3}J = 8.4 Hz, 1H, H2'), 7.46 (d, ^{3}J = 8.4 Hz, 1H, H6'), 7.36 (d, ^{3}J = 8.4 Hz, 1H, H2'), 7.36 (d, ^{3}J = 8.4 Hz,

1H, H6'), 7.26 (d, ^{3}J = 8.0 Hz, 1H, H3'), 7.26 (d, ^{3}J = 8.0 Hz, 1H, H5'), 7.09 (d, ^{3}J = 8.4 Hz, 1H, H3), 7.09 (d, ^{3}J = 8.4 Hz, 1H, H5), 6.47 (d, ^{3}J = 16.0 Hz, 1H, H8'), 3.79 (q, ^{3}J = 7.1 Hz, 1H, H7), 2.46 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.84 (hept, ^{3}J = 6.7 Hz, 1H, H10), 1.72 (m, 2H, H13), 1.64 (m, 1H, H14), 1.53 (d, ^{3}J = 7.2 Hz, 3H, H8), 1.32 (sext, ^{3}J = 7.3 Hz, 2H, H15), 0.88 (d, ^{3}J = 6.6 Hz, 3H, H11), 0.85 (t, ^{3}J = 7.3 Hz, 3H, H16). ^{13}C NMR (DMSO-d_6) δ: 184.9 (C12), 175.8 (C9') 140.4 (C4), 144.7 (C7'), 137.9 (C1), 132.9 (C4'), 129.5 (C3'), 129.5 (C5'), 129.3 (C2), 129.2 (C6), 129.2 (C2'), 129.2 (C1'), 129.2 (C6'), 127.1 (C3), 127.1 (C5), 118.3 (C8'), 45.1 (C9), 45.0 (C7), 30.1 (C10), 26.3 (J (C13-^{119}Sn) = 571.5 Hz; J (C13-^{117}Sn) = 558.2 Hz), 26.2 (J (C14-^{119}Sn) = 96.5 Hz), 25.1 (J (C15-^{119}Sn) = 36.2 Hz), 22.3 (C11), 18.7 (C8), 13.5 (C16). ^{119}Sn NMR (DMSO-d_6) δ: –149.3.

(10a). ^{1}H NMR (DMSO-d_6) δ: 7.13 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.13 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.01 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.01 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.12 (m, 2H, H13), 3.64 (w, 1H, H7), 3.64 (w, 2H, H14), 2.38 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.77 (hept, d, ^{3}J = 6.8 Hz, 1H, H10), 1.57 (w, 2H, H15), 1.41 (d, ^{3}J = 7.2 Hz, 3H, H8),1.29 (sext, ^{3}J = 7.6 Hz, 2H, H17), 1.22 (sext, ^{3}J = 8.0 Hz, 2H, H16), 0.85 (t, ^{3}J = 7.6 Hz, 3H, H18), 0.81 (d, ^{3}J = 6.8 Hz, 3H, H11). ^{13}C NMR (DMSO-d_6) δ: 175.0 (12), 140.7 (4), 137.7 (1), 129.5 (2), 129.5 (6), 127.1 (3), 127.1 (5), 66.2 (13), 60.8 (14), 45.0 (7), 45.0 (9), 30.1 (10), 27.8 (J (C17-^{119}Sn) = 23.1 Hz), 26.8 (J (C16-^{119}Sn) = 64.3 Hz), 22.3 (11), 19.4 (8), 17.7 (J (C15-^{119}Sn) = 343.2 Hz; J (C15-^{117}Sn) = 327.0 Hz), 13.5 (18). ^{119}Sn NMR (DMSO-d_6) δ: + 148.9.

(11a). ^{1}H NMR (DMSO-d_6) δ: 7.16 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.16 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.05 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.05 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.18 (w, 2H, H13), 3.65 (q, ^{3}J = 6.0 Hz, 1H, H7), 3.49 (w, 2H, H15), 2.40 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.74 (w, 1H, H10), 1.74 (w, 2H, H14), 1.60 (m, 2H, H16), 1.45 (d, ^{3}J = 7.2 Hz, 3H, H8), 1.33 (m, 2H, H18), 1.29 (m, ^{3}J = 7.2 Hz, 2H, H17), 0.90 (t, ^{3}J = 7.6 Hz, 3H, H19), 0.84 (d, ^{3}J = 6.6 Hz, 3H, H11). ^{13}C NMR (DMSO-d_6) δ: 175.0 (12), 140.5 (4), 137.7 (1), 129.3 (2), 129.3 (6), 127.1 (3), 127.1 (5), 61.7 (13), 58.8 (15), 4501 (7), 45.0 (9), 31.7 (14), 30.1 (10), 27.8 (J (C18-^{119}Sn) = 23.1 Hz), 26.8 (J (C17-^{119}Sn) = 64.4 Hz), 22.3 (11), 18.4 (8), 17.9 (J (C16-^{119}Sn) = 339.1 Hz), 13.1 (19). ^{119}Sn NMR (DMSO-d_6) δ: + 143.8.

(12a). ^{1}H NMR (DMSO-d_6) δ: 7.72 (w, 1H, H16), 7.49 (w, 1H, H17), 7.49 (w, 1H, H18), 7.22 (d, ^{3}J = 8.0 Hz, 1H, H2), 7.22 (d, ^{3}J = 8.0 Hz, 1H, H6), 7.10 (d, ^{3}J = 8.0 Hz, 1H, H3), 7.10 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.23 (m, 2H, H13), 3.79 (w, 1H, H7), 3.79 (w, 1H, H14), 2.44 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.88 (hetp, ^{3}J = 6.8 Hz, 1H, H10), 1.49 (d, ^{3}J = 7.2 Hz, 3H, H8), 0.91 (d, ^{3}J = 6.4 Hz, 3H, H11). ^{13}C NMR (DMSO-d_6) δ: 175.1 (12), 140.7 (4), 137.7 (1), 137.5 (J (C15-^{119}Sn) = 619.8 Hz), 136.1 (J (C17-^{119}Sn) = 42.3 Hz), 130.5 (C18), 129.3 (2), 129.3 (6), 129.1 (J (C16-^{119}Sn) = 62.4 Hz), 127.1 (3), 127.1 (5), 66.3 (13), 61.2 (14), 45.1 (7), 45.0 (9), 30.2 (10), 22.4 (11), 18.4 (8). ^{119}Sn NMR (DMSO-d_6) δ: -63.7.

(13a). ^{1}H NMR (DMSO-d_6) δ: 7.75 (w, 1H, H17), 7.46 (w, 1H, H18), 7.46 (w, 1H, H19), 7.21 (d, ^{3}J = 8.4 Hz, 1H, H2), 7.21 (d, ^{3}J = 8.4 Hz, 1H, H6), 7.09 (d, ^{3}J = 8.0 Hz, 1H, H3),

7.09 (d, ^{3}J = 8.0 Hz, 1H, H5), 4.23 (t, ^{3}J = 6.4 Hz, 2H, H13), 3.72 (q, ^{3}J = 7.2 Hz, 1H, H7), 3.52 (t, ^{3}J = 6.0 Hz, 1H, H15), 2.47 (d, ^{3}J = 7.2 Hz, 2H, H9), 1.85 (hept, ^{3}J = 6.8 Hz, 1H, H10), 1.51 (d, ^{3}J = 7.2 Hz, 3H, H8), 0.91 (d, ^{3}J = 6.8 Hz, 3H, H11). ^{13}C NMR (DMSO-d_6) δ:175.1 (12), 140.6 (4), 137.7 (1), 138.8 (C16), 136.2 (*J* (C18-^{119}Sn) = 49.3 Hz), 130.1 (*J* (C19-^{119}Sn) = 13.1 Hz), 130.3 (2), 130.3 (6), 129.1 (*J* (C17-^{119}Sn) = 63.4 Hz) 127.0 (3), 127.0 (5), 61.7 (13), 59.0 (15), 45.1 (7), 45.0 (9), 32.7 (14), 30.5 (10), 22.4 (11), 18.4 (8). ^{119}Sn NMR (DMSO-d_6) δ: -73.6.

4.5. Computational details

Full structure optimizations, without symmetry constraints, were performed with the hybrid exchange–correlation functional, B3LYP [57-60]. To confirm the optimized minima on the potential energy surface, a frequency analysis was performed. All electrons were treated explicitly using the triple zeta valence plus polarization (def2-TZVP) [61, 62] basis set for all atoms as they are implemented in the Gaussian 09 code [63].

4.5.1 Molecular docking

Molecular dockings were carried out on Molegro Virtual Docker (MVD) 6 [64], employing the crystal structure (retrieved from the Protein Data Bank) of COX-1 [PDB: 1EQG] [65] and COX-2 [PDB: 4PH9] [66], complex with ibuprofen. Both, rigid and flexible docking approaches were performed. The potential binding sites (defined as cavities) of both: COX-1 and COX-2 were detected by the expanded Van der Waals spheres method.

The cavities found for COX-1 (61.44 Å^3) and COX-2 (56.32Å^3), where all the binding calculations were performed, corresponded to the active site of each isoform. All water molecules were removed from the crystal.

For the flexible approach, a total of 47 residues were set as flexible for COX-2 and 46 for COX-1. Partial charges were set according to MVD´s 6.0 internal charge scheme. All the residues bearing four or more free rotating bonds were assigned as a zero strength factor. For those whose number of free rotating bonds was less than four, a one strength factor was set. The search function MolDock SE (Simplex Evolution) was employed for COX-1 and MolDock Optimizer for COX-2, both functions used genetic algorithm technique for searching the best binding site of a given enzyme. The scoring function Moldock Score [GRID] was used to calculate the binding energy. A value of 2000 minimization steps for each flexible residue and the ligand, and 2000 steps of global minimization per run were set. For the scoring function, the GRID partition was of 0.2 Å

and the search sphere was fixed with a 10 Å radius. For the energetic analysis of the ligand: the electrostatic internal interactions, the internal H-bond and the sp^2-sp^2 torsions were used. For the MolDock SE function a total of 15 runs with a maximum of 1500 iterations using a population of 50 individuals per run were set. For Moldock SE optimizer the same number of runs was set with a maximum of 2000 iterations and a population of 100 individuals per run.

Rather than looking for overall binding energies, the interactions with residues that are considered key to selectively binding to each isoform were analyzed and compared among stannoxanes and reference compounds following the reported method [48, 67].

The method was validated by reproducing the experimental binding mode of the reference inhibitor, with a root mean square deviation (RMSD) value of 0.38 Å for COX-1 and 0.56 Å for COX-2 (see supporting information).

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Highlights

- The NMR data of stannoxanes in $CDCl_3$ revealed several hexacoordinated compounds with octahedral geometry.
- In DMSO-d_6 some complexes switched to heptacoordination with a pentagonal-bipyramidal geometry due to the inclusion of a solvent's molecule.
- The structural results were supported by Density Functional Theory (DFT) computational calculations.
- Docking results showed that the systems were theoretically more selective towards COX-2 than the ibuprofen.