Journal of Organometallic Chemistry 695 (2010) 1189–1199

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

New pentacoordinated Schiff-base diorganotin(IV) complexes derived from nonpolar side chain α-amino acids

Nikoloz Kobakhidze [a], Norberto Farfán [a,*], Margarita Romero [a], J. Manuel Méndez-Stivalet [a], M. Gabriela Ballinas-López [a], Héctor García-Ortega [a], Oscar Domínguez [b], Rosa Santillan [b], Francisco Sánchez-Bartéz [c], Isabel Gracia-Mora [d]

[a] Facultad de Química, Departamento de Química Orgánica, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, D.F., Mexico
[b] Departamento de Química, Centro de Investigación y de Estudios Avanzados del IPN, Apdo. Postal 14-740, 07000, México D.F., Mexico
[c] Facultad de Química, Departamento de Farmacia, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, D.F., Mexico
[d] Facultad de Química, Departamento de Química Inorgánica y Nuclear, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, D.F., Mexico

A R T I C L E I N F O

Article history:
Received 24 June 2009
Received in revised form 21 January 2010
Accepted 21 January 2010
Available online 29 January 2010

Keywords:
Schiff-bases
^{119}Sn NMR
Organotin compounds
Amino acids
Cancer cell lines
Crystal structure

A B S T R A C T

In this work we report the synthesis and spectroscopic characterization of twenty new pentacoordinated diorganotin(IV) compounds. These compounds have been prepared in good yields by multicomponent reactions (MCRs) of α-amino acids (isoleucine, leucine, methionine, phenylalanine and aminophenylacetic acid), 2,4-dihydroxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde and either di-*n*-butyltin(IV) oxide or diphenyltin(IV) oxide. All compounds were characterized by IR spectroscopy, ^{1}H, ^{119}Sn and ^{13}C NMR spectroscopy and mass spectrometry. Each compound has a coordinative N→Sn bond and shows the expected ^{119}Sn NMR chemical shift indicative of a pentacoordinated or hexacoordinated tin atom in $CDCl_3$ and DMSO-d_6, respectively. These compounds were also tested in tumoral cell lines, HeLa, HCT-15 and MCF-7, in order to evaluate the antiproliferative activity and to obtain the medial inhibitory concentrations (IC_{50}) values.

1. Introduction

During the past few decades, research about new organotin compounds has increased dramatically, most likely due to their diverse biological applications [1]. A huge interest on metal complexes of Schiff-bases derived from amino acids and salicylaldehyde has emerged due to their structural, magnetic and electrochemical properties, as well as their potential use as models for a number of important biological systems [2–4] and for the research of pyridoxal reaction pathways [5–7]. Among their several biological functions, they show antimicrobial [8], antimalarial [9], antiproliferative [10], chemotherapeutic [11], radiopharmaceutical [12], insulin-mimetic [13] and fungicidal [14] properties. One of the most important bioinorganic chemistry research areas in organotin compounds is the investigation of their cytotoxic and antineoplastic (antiproliferative) activities [15]. Moreover, tin(IV) complexes characterized by the presence of one or more carbon–tin bonds have proved to be cytotoxic against the breast adenocarcinoma tumor MCF-7 and the colon carcinoma WiDr [16]. In general, the toxicity of organotin compounds seems to increase with the chain length of the organic alkyl groups, which are often more active than aryl ones. More recent results indicate that for the design of new antitumor tin compounds it is necessary to balance some factors such as solubility and lipophilicity features in order to achieve efficacy [17]. The importance of tuning electronic properties of organotins has been discussed in the context of the role they could play in biological interactions [18,19].

Recently, we synthesized and characterized Schiff-base diorganotin(IV) complexes by a one-step procedure [20–22]. This route involves the equimolecular reaction of an α-amino acid with salicylaldehyde and either di-*n*-butyltin(IV)- or diphenyltin(IV)-oxide leading to exclusive formation of one product in good yields, therefore, the present compounds were prepared using this methodology. As a continuation of these studies we report the results of the synthesis, characterization and antiproliferative activity of a series of Schiff-base diorganotin(IV) complexes derived from amino acids. All the chemical structures were established by ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy, IR spectroscopy as well as mass spectrometry. The Schiff-bases act as tridentate ligands where the nitrogen atom of the imine forms a coordinative N→Sn bond that stabilizes the tin compounds forming a pentacoordinated tin atom,

* Corresponding author. Tel.: +52 55 56 22 37 31; fax +52 55 56 22 37 22.
E-mail address: norberto.farfan@gmail.com (N. Farfán).

0022-328X/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2010.01.024

as described in previous papers [23–25]. In continuation of a study on tin chemistry, we now report the synthesis and spectroscopic characterization of twenty new Schiff-base diorganotin(IV) complexes obtained by reaction of α-amino acids such as isoleucine, leucine, methionine, phenylalanine and aminophenylacetic acid with 2,4-dihydroxybenzaldehyde and 2-hydroxy-4-methoxybenzaldehyde as a strategy to modify the physicochemical and electronic properties and improve the cytotoxic activity of these molecules by introducing an amino acid fragment.

2. Results and discussion

The compounds **1a**–**d** to **5a**–**d** were prepared by MCRs from the reaction of the hydroxybenzaldehydes, amino acids and phenyl or butyl tin oxide in methanol to give the tin complexes in good yield (Scheme 1).

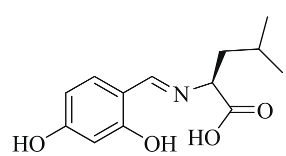
In compounds **1a–5d** the tin atoms are pentacoordinated and bound covalently to two carbon and two oxygen atoms (Scheme 1), one from the carboxylic acid and the other is of phenolic nature. The intramolecular N→Sn interaction is formed with the participation of the imine nitrogen atom, giving a trigonal bipyramid geometry for the tin atom.

In the IR spectra, these complexes did not show, or decrease, the ν(OH) band, indicating the deprotonation of the phenolic and carboxylic oxygens of the ligand due to the formation of the oxygen tin bond. The C=N stretching vibrations for these diorganotin complexes are in the range from 1680 to 1636 cm^{-1} (Table 1). The intensity observed for the symmetric Sn–$^{\alpha}CH_2$ stretching vibration at ~1440 cm^{-1}, indicates a bent C–Sn–C moiety for the *n*-dibutyltin complexes **1a,b**–**5a,b**, while the corresponding Sn-C*i* band appears at ~1075 cm^{-1} for the diphenyl derivatives **1c,d**–**5c,d**. All the compounds show the characteristic Sn–O band at about 700 cm^{-1} [26]. This data is consistent with a trigonal bipyramidal configuration for the tin atom.

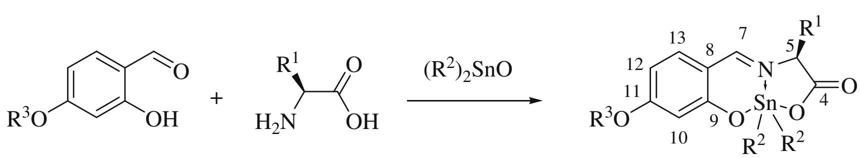
The characteristic ^{1}H, ^{13}C and ^{119}Sn NMR data for **1a,d**–**5a,d** are shown in Tables 2a and 2b. The ^{1}H NMR spectra of the complexes show that the signal assigned to the azomethine proton CH=N (H-7) appears in the range from 8.0 to 8.6 ppm for almost all com-

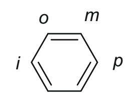
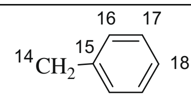
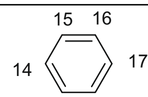
Table 1
IR data for compounds **1**, **1a**–**1d**, **2a**–**2d**, **3a**–**3d**, **4a**–**4d**, **5a**–**d**.

Compound	IR (ν, cm^{-1})			
	C=N	C=O	Sn–C	Sn–O
1	1618	1506	–	–
1a	1642	1597	1438	706
1b	1671	1613	1440	688
1c	1650	1598	1074	696
1d	1679	1607	1075	698
2a	1639	1595	1438	702
2b	1670	1606	1442	701
2c	1644	1595	1074	697
2d	1678	1600	1074	698
3a	1638	1594	1437	682
3b	1671	1607	1441	683
3c	1644	1594	1075	696
3d	1678	1602	1076	697
4a	1636	1595	1438	700
4b	1666	1606	1442	702
4c	1647	1595	1075	697
4d	1680	1600	1074	698
5a	1641	1594	1438	700
5b	1678	1596	1440	700
5c	1650	1592	1074	696
5d	1680	1598	1074	698



1



Compound	R1	R2	R3	
1a-1d	$^{14}CH_2{}^{15}CH\ (^{16,17}\ CH_3)_2$	$^{\alpha}CH_2{}^{\beta}CH_2{}^{\gamma}CH_2{}^{\delta}CH_3$	H	a
2a-2d	$^{14}CH(^{17}CH_3)\ ^{15}CH_2{}^{16}CH_3$		CH3	b
3a-3d	$^{14}CH_2{}^{15}CH_2S^{17}CH_3$		H	c
4a-4d			CH3	d
5a-5d				

Scheme 1.

Table 2a
Selected chemical shifts (ppm) and coupling constants (Hz) obtained from NMR spectra of compounds **1. 1,1a–1b**, **2a–2b**, **3a–3b**, **4a–4b**, **5a–5b**.

Compound	H-5	H-7	C-4	C-5	C-7	C-α,α′ or C-*i*,*i*′		Sn	θ (C–Sn–C)
(Solvent)	($^3J^{119/117}$Sn)		($^2J^{119/117}$Sn)	($^3J^{119/117}$Sn)		$J^{119/117}$Sn, ^{13}C			(°)
1 (DMSO-d$_6$)	4.02	8.40	173.1	67.6	165.9	–	–	–	
1a (CDCl$_3$)	4.05	8.00	174.9	66.6	169.5	21.6	21.2	−194	136.9–133.5
	(33.4)	(49.1)	(20.9)	(17.2)		622/593[a]	616/588[a]		
2a (CDCl$_3$)	3.88	8.01	175.4	72.8	170.3	22.2	20.9	−195	138.2–131.8
	(34.5)	(51.1)	(20.9)	(–)		635/607	597/571		
3a (CDCl$_3$)	4.24	8.14	174.3	66.0	170.4	21.8	21.3	−193	137.1–133.1
	(32.4)	(49.9)	(20.2)	(16.5)		624/595[a]	612/58[a]		
4a (CDCl$_3$)	4.13	7.32	174.7	68.9	170.3	21.3	21.2	−192	136.9–132.5
	(38.4)	(50.5)	(23.2)	(15.0)		622/597[a]	604/578[a]		
5a (DMSO-d$_6$)	5.26	8.47	171.9	70.0	173.0	22.9	22.5	−220	144.2–134.8
	(29.4)	(50.3)	(22.4)	(16.5)		695/639	658/601		
1b (CDCl$_3$)	3.99	8.01	174.4	67.1	169.6	21.9	21.4	−197	136.5–133.2
	(36.9)	(49.9)	(22.1)	(17.2)		618/590	611/585		
2b (CDCl$_3$)	3.85	8.06	173.2	73.0	170.3	22.3	20.8	−197	138.3–131.7
	(35.2)	(51.0)	(22.1)	(14.6)		635/607	597/571		
3b (CDCl$_3$)	4.19	8.18	173.8	66.2	170.6	22.0	21.5	−196	136.7–132.9
	(40.2)	(49.6)	(22.4)	(16.5)		620/593	609/582		
4b (CDCl$_3$)	4.18	7.38	173.6	69.3	170.4	21.5	21.5	−196	136.1–133.4
	(36.8)	(51.2)	(22.1)	(16.1)		614/587	614/587		
5b (CDCl$_3$)	5.14	8.14	172.3	70.7	171.7	22.3	21.8	−197	136.7–133.0
	(28.5)	(50.4)	(24.3)	(18.0)		619/592	610/583		

[a] The compounds were measured in 1 mL of CDCl$_3$ with 20 μL of DMSO-d$_6$.

Table 2b
Selected chemical shifts (ppm) and coupling constants (Hz) obtained from NMR spectra of compounds **1c–1d**, **2c–2d**, **3c–3d**, **4c–4d**, **5c–5d**.

Compound	H-5	H-7	C-4	C-5	C-7	C-α,α′ or C-*i*,*i*′		Sn	(C–Sn–C)
(Solvent)	($^3J^{119/117}$Sn)		($^2J^{119/117}$Sn)	($^3J^{119/117}$Sn)		($J^{119/117}$Sn,^{13}C)			(°)
1c (CDCl$_3$)	4.15	8.01	176.7	66.8	169.6	137.8	137.6	−337	126.8–123.6
	(41.7)	(62.4)	(12.0)	(15.7)		1005/929	1015/971		
2c (DMSO-d$_6$)	4.12	8.58	172.3	70.7	172.8	140.3	139.9	−352	127.4–124.8
	(42.4)	(72.3)	(10.5)	(14.2)		1006/961	1031/984		
3c (DMSO-d$_6$)	4.26	8.53	173.1	65.7	171.6	142.5	142.4	−384	127.6–125.7
	(38.5)	(69.5)	(11.2)	(16.8)		1031/987	1037/990		
4c (DMSO-d$_6$)	4.43	7.93	172.9	67.6	171.6	142.1	141.7	−376	127.8–125.3
	(40.5)	(70.0)	(11.2)	(16.8)		1023/977	1043/999		
5c (DMSO-d$_6$)	5.35	8.36	171.9	69.4	172.4	143.0	142.6	−384	128.0–125.8
	(31.4)	(68.6)	(12.7)	(17.5)		1031/988	1048/1000		
1d (CDCl$_3$)	4.11	8.08	174.1	67.1	169.6	138.0	137.8	−339	126.8–124.8
	(39.6)	(62.8)	(13.8)	(16.8)		1008/963	1017/972		
2d (CDCl$_3$)	4.02	8.13	173.3	72.8	170.8	138.5	138.2	−337	127.7–124.0
	(40.4)	(64.2)	(13.7)	(13.9)		984/940	1040/996		
3d (CDCl$_3$)	4.30	8.20	173.5	66.2	170.5	138.1	137.8	−340	127.1–124.7
	(38.8)	(62.8)	(13.8)	(16.8)		1006/960	1022/976		
4d (CDCl$_3$)	4.19	7.14	173.4	69.9	170.1	138.2	137.7	−340	126.9–125.0
	(48.5)	(63.2)	(14.2)	(17.2)		1011/966	1017/972		
5d (CDCl$_3$)	5.13	8.06	172.5	70.8	172.4	138.5	138.3	−338	127.0–125.0
	(30.0)	(62.3)	(–)	(17.6)		1013/968	1021/976		

pounds, except for **4a–4d** where this signal shifts to lower frequencies (7.1–7.9 ppm) due to the shielding effect of the CH_2-phenyl group on H-7. The signals in the range from 3.8 to 5.4 ppm were assigned to H-5. The tin nuclei are *trans* to the azomethine proton showing a spin–spin coupling between the azomethine ^3J(Sn–N=C^{7}H) in agreement with previous reports [27]. Also spin coupling of the methine ^3J(Sn–N–C^{5}H) protons with the tin nucleus is observed in all complexes. The values of the coupling constant are ~50 and 62–70 Hz for ^3J(Sn–N=C^{7}H), and 28–40 and 40–50 Hz for ^3J(Sn–N–C^{5}H) for compounds **1a**,**b**–**5a**,**b** and **1c**,**d**–**5c**,**d**, respectively. All these values are in agreement with the values reported for the diphenyltin dichloride complexes of a series of Schiff-bases obtained from substituted salicylaldehydes and *o*-aminophenols [27a], and thus confirm the presence of N→Sn coordination in all the complexes.

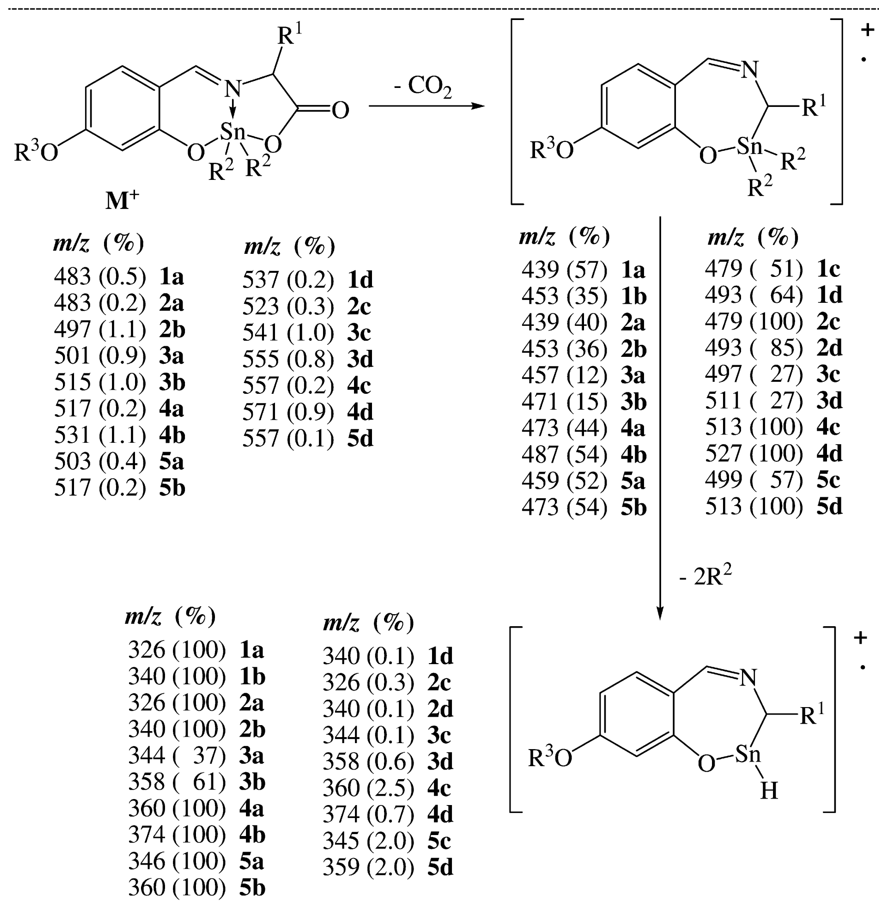
The ^{13}C NMR data for all compounds show that the signal of the carboxyl carbon (C-4) appears in the range from 171 to 177 ppm, in agreement with the data reported for analogous esters [16,20,28]. The signal of the imine carbon (C-7) appears in the range from 169 to 173 ppm, showing in some cases a marked deshielding with respect to an imine group due to N→Sn coordination, which induces N=C polarization. The C-5 signals appear in the range from 66 to 73 ppm, depending on the nature of the R^1 substituent. In all cases two signals for Cα, or C*i*, are observed due to the diastereotopic nature (*n*-butyl or phenyl) owing to the presence of a stereogenic center (C-5). The ^{119}Sn NMR chemical shifts show that the compounds in CDCl$_3$ (non-coordinating solvent) and in DMSO-d$_6$ (coordinate solvent) have characteristic of pentacoordinated and hexacoordinated tin atoms, respectively [15,29].

Compounds **1a**,**b**–**5a**,**b** show ^1J($^{119/117}$Sn,^{13}C$^{\alpha}$) values in the range from 587 to 695 Hz, while compounds **1c**,**d**–**5c**,**d** have ^1J($^{119/117}$Sn,^{13}C*i*) values of 929–1031 Hz (Tables 2a–b). The ^1J($^{119/117}$Sn,^{13}C$^{\alpha}$) values allow the calculation of the bond angle for the C–Sn–C fragment, which is in the order of 126° and 138°, respectively, suggesting that the tin atom has a slightly distorted trigonal bipyramidal geometry (TBP) geometry, this behavior is in agreement with the values reported for pentacoodinated tin compounds [16, 20, 28].

In general, the molecular ion is not an important fragment in mass spectra. However, the decarboxylation of the amino acid fragment and losses of butyl or phenyl substituent are common fragmentations (Scheme 2), which are in agreement with our previous reports [20–24].

2.1. X-ray analysis

It has been reported that organotin carboxylates frequently have dimeric or polymeric structures resulting from intermolecu-



Scheme 2.

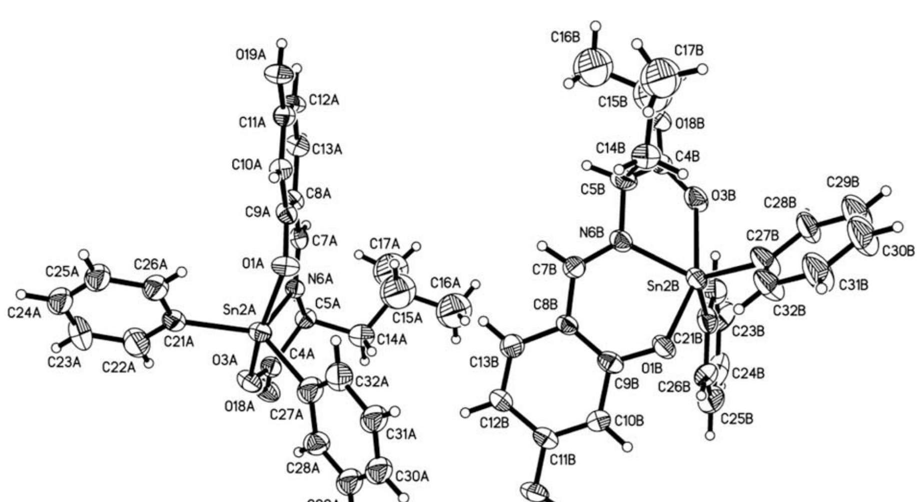


Fig. 1. Molecular structure of **1c**. Displacement ellipsoids are drawn at the 30% probability level and the H atoms are shown as spheres of arbitrary radii. Compound **1c** crystallized with one disordered chloroform molecule which has been omitted for clarity.

lar bridging by carboxyl oxygen atoms. In contrast, di-*n*-butyl and diphenyl-substituted organotin compounds with rigid tridentate ligands tend to exist as monomeric species [20,30]. In this study, suitable crystals of **1c** and **2d** allowed to determine their structure by single crystal X-ray diffraction analyses. In **1c** (Fig. 1), there are two independent molecules in the asymmetric unit, which are labeled as molecules **1A** and **1B**, respectively. The molecular structure of **2d** is shown in Fig. 2. Most relevant crystallographic data for these compounds are summarized in Tables 3 and 4. In the solid state, the metal coordination geometry is best described as slightly distorted TBP geometry and forms five- and six-membered chelate rings with the tridentate organic ligand. The axial sites are occupied by the phenolic atom O(1) and carboxylic atom O(3), while the two phenyl carbon atoms [C(21) and C(27)] and the imine nitrogen atom N(6) are equatorially oriented defining the trigonal plane.

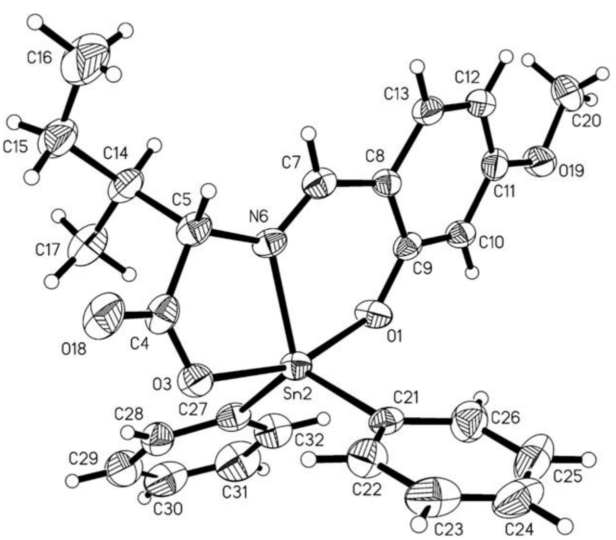


Fig. 2. Molecular structure of **2d** showing the atom-numbering scheme. Displacements ellipsoids are drawn at the 50% probability level and the H atoms are shown as spheres of arbitrary radii.

The slight distortion in the TBP geometry can be attributed to the rigidity of the organic ligand and the strong steric effect between the phenyl rings and the oxygen atoms around the metal, these contributions are responsible for the envelope conformations in the newly formed five- and six-membered rings. Thus, while the geometries in these rings are nearly planar in compound **2d**, in **1c** are well defined envelope conformations. The five-membered rings formed by the N(6A)–C(5A)–C(4A)–O(3A)–Sn(2A) fragment in complex **1c** and the N(6B)–C(5B)–C(4B)–O(3B)–Sn(2B) fragment in complex **1c**′ have the nitrogen atoms out of the mean planes by 0.137(4)° and −0.206 (5)°, respectively. With respect to the six-membered rings defined by the N(6A)–C(7A)–C(8A)–C(9A)–O(1A)–Sn(2A) and N(6B)–C(7B)–C(8B)–C(9B)–O(1B)–Sn(2B) fragments, the maximum deviations from the mean planes correspond to the oxygen atoms by 0.234(4)° and 0.320(5)°, respectively.

The distorted trigonal geometry in both compounds may be corroborated by observation of C(21)–Sn(2)–C(27), C(21)–Sn(2)–N(6) and C(27)–Sn(2)–N(6) angles which show values of 128.8(2), 110.5(2) and 120.6(2)° in **2d**; 125.8(3), 115.8(2) and 118.1(3)° in **1c**; 121.7(3), 124.4(3) and 113.6(3)° in **1c**′ (Table 4). This distorted geometry is also observed in the axial plane defined by the O(1)–Sn(2)–O(3) angle, whose values are very close to 160° (Table 4), indicating that the hardly deformable ligands avoid the complete *anti* disposition of the O(1) and O(3) atoms. Furthermore, the newly formed bonds between the oxygen atoms of the ligands and the metal, O(1)–Sn(2) and O(3)–Sn(2) (Table 4) are in the range of covalent bonds characteristic of phenolic TBP compounds possessing diphenyl substituents [23] and analogous carboxylic derivatives [20,22,31], respectively. On the other hand, the N(6)–Sn(2) bond distances are in accordance with the values previously reported for coordinative bonds in pentacoordinated tin atom containing diphenyl fragments [15c,32].

2.2. Antiproliferative activity

A screening was performed with 17 compounds plus ligands, in a panel of 3 different cancer cell lines: MCF-7 (breast adenocarcinoma), HCT-15 (colon adenocarcinoma) and HeLa (cervical uterine adenocarcinoma). The percentage of survival versus compound concentration (0–10 μg/mL) was tested, and the medial inhibitory concentration (IC_{50}) was determined by Probit analysis (Table 5).

Table 3
Crystallographic data for compounds **1c** and **2d**.

	1c	**2d**
Empirical formula	$C_{51}H_{51}Cl_3N_2O_8Sn_2 \cdot CHCl_3$	$C_{26}H_{27}NO_4Sn$
Formula weight	1163.67	536.18
Crystal size (mm)	0.25 × 0.25 × 0.13	0.35 × 0.25 × 0.15
T (K)	293	293
Crystal system	orthorhombic	orthorhombic
Space group	$P\,2_12_12_1$	$P\,2_12_12_1$
Unit cell dimensions		
a (Å)	16.025(3)	9.7688(2)
b (Å)	34.010(7)	14.1550(3)
c (Å)	9.805(2)	17.5469(5)
$\alpha = \beta = \gamma$ (°)	90	90
V ($Å^3$)	5343.8(19)	2426.34(10)
Z	4	4
D_{calc} (g/cm^3)	1.447	1.468
Absorption coefficient (mm^{-1})	1.136	1.084
Collected reflections	29252	15855
Independent reflections	11556	5507
Parameters	468	292
Final *R* indices [$I > 2\sigma(I)$]	0.0614	0.0487
R indices (all data)	0.1183	0.0969
Goodness-of-fit	1.007	0.992

Table 4
Selected bond distances (Å) and angles (°) for compounds **1c** and **2d**.

	1c	1c′	2d
Bond distances (Å)			
C(7)–N(6)	1.293(9)	1.301(9)	1.295(6)
C(5)–N(6)	1.457(8)	1.477(10)	1.481(6)
O(1)–Sn(2)	2.057(5)	2.088(5)	2.084(3)
O(3)–Sn(2)	2.149(6)	2.172(6)	2.131(4)
N(6)–Sn(2)	2.144(6)	2.114(7)	2.146(4)
C(21)–Sn(2)	2.128(4)	2.114(5)	2.110(5)
C(27)–Sn(2)	2.122(9)	2.115(4)	2.128(5)
Bond angles (°)			
C(21)–Sn(2)–C(27)	125.8(3)	121.7(3)	128.8(2)
C(21)–Sn(2)–N(6)	115.8(2)	124.4(3)	110.5(2)
C(27)–Sn(2)–N(6)	118.1(3)	113.6(3)	120.6(2)
O(1)–Sn(2)–N(6)	84.1(2)	83.1(2)	85.0(2)
O(3)–Sn(2)–N(6)	75.4(3)	73.6(3)	76.1(2)
O(1)–Sn(2)–O(3)	159.4(2)	156.6(2)	160.50(13)
Torsion angles (°)			
C(7)–C(8)–C(9)–O(1)	2.9(11)	4.9(11)	−6.5(8)
C(9)–O(1)–Sn(2)–O(3)	39.6(10)	38.1(10)	35.8(7)
C(5)–C(4)–O(3)–Sn(2)	3.5(9)	3.4(10)	9.2(7)
C(8)–C(7)–N(6)–C(5)	−174.5(7)	−178.8(7)	−175.5(5)
C(4)–O(3)–Sn(2)–C(27)	−110.9(6)	−100.9(7)	−122.0(4)
C(9)–O(1)–Sn(2)–C(21)	−79.6(6)	−79.3(6)	−87.9(4)

Table 5
Antiproliferative activities (IC_{50}).

Compound	HeLa (μg/mL)	HeLa (μM)	HCT-15 μg/mL	HCT-15 μM	MCF-7 μ(g/mL)	MCF-7 μM
1a	0.3550	0.7300	0.4291	0.8820	0.2434	0.5010
1b	0.6582	1.3260	0.6632	1.3360	0.2537	0.5110
1c	0.3123	0.5980	29.5692	56.626	0.3625	0.6940
1d	0.6660	1.2420	0.6236	1.1630	0.4862	0.9070
2a	0.7600	1.5630	0.6226	1.2800	0.1782	0.3660
2b	4.9800	10.036	13.976	28.165	0.5677	1.1440
2c	0.0475	0.0950	0.9561	1.9190	ND	ND
2d	0.1208	0.2360	2.9160	5.6930	ND	ND
3a	ND	ND	0.7133	1.4260	0.0382	0.0760
3d	6.7280	12.139	1.2305	2.2200	0.4611	0.8320
4a	17.1723	33.264	0.6337	1.2280	0.0517	0.1000
4b	0.8505	1.604	1.2792	2.412	0.0700	0.1320
4c	1.5849	2.8500	5.5523	9.9830	0.4795	0.8620
4d	1.4820	2.599	4.0928	7.1770	0.0512	0.0900
5a	ND	ND	9.4127	18.7430	0.2268	0.4520
5c	1.0248	1.8900	ND	ND	ND	ND
5d	ND	ND	4.1699	7.4970	0.2773	0.4990
CisPt	1.56	5.20	1.38	4.60	1.68	5.60

ND: not determinated.

All compounds tested exhibit a high activity in all cell lines. In particular, compounds **4a**, **4b** and **4d** showed excellent antiproliferative activities against MCF-7, whereas compound **4a** was not active against HeLa in the same scale. Compound **2c** shows the highest activity over HeLa cells, while compound **1c** had the lowest over HCT-15.

3. Conclusion

A series of tin complexes were prepared in good yields by multicomponent reactions. As has been reported, organotin compounds have high antineoplastic activity and compounds presented here are not the exception. All compounds show a high antineoplastic activity disregarding the cell line type, the IC_{50} is reached at micromolar concentrations mainly below IC_{50} reported for CisPt. Selectivity is observed in the activities of some compounds over particular cell lines, which is very important for the future medicinal applications in order to avoid the side effects, so we can conclude that the compounds synthesized and tested look very promising.

4. Experimental section

4.1. Instrumentation

All starting materials were commercially available. Solvents were used without further purification. Melting points were recorded on a Mel-Temp® Electrothermal apparatus and were corrected. Infrared spectra were measured on a FT–IR Perkin–Elmer Spectrum GSX spectrophotometer using KBr pellets. ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on Bruker Avance DPX-300, Jeol GSX 270 and Jeol Eclipse +400 Varian Unity Inova-300, Varian MR-400 and Varian VNMRS-400 spectrometers. All experiments were made with concentrations between 80 and 100 mg/mL at 25 °C. Chemical shifts (ppm) are relative to $Si(CH_3)_4$ for ^{1}H and ^{13}C, and $Sn(CH_3)_4$ for ^{119}Sn. Mass spectra were recorded on a Hewlett Packard 5989A spectrometer. The single crystal X-ray diffraction analysis was realized on a KAPPA CCD diffractometer, $\lambda_{(Mo\ K\alpha)}$ = 0.71073 Å, graphite monochromator, T = 293 K. The structures were solved by direct methods, SHELXS-86 [33]. All nonhydrogen atoms were refined anisotropically using SHELXL-97 [34] software package by full matrix less squares and the hydrogen atoms were placed in geometrically calculated positions using a riding model with isotropic parameters tied to the parent atom.

4.2. General procedure

The reaction flask was first charged with a mixture of the α-amino acid (2 mmol), 2,4-dihydroxybenzaldehyde or 2-hydroxy-4-methoxybenzaldehyde (2 mmol) and either di-*n*-butyltin(IV) oxide (2 mmol) or diphenyltin(IV) oxide (2 mmol) and 50 mL of methanol as a solvent. The reaction mixture was stirred and heated under reflux using a Dean-Stark trap, during 5 h in the case of the reactions with di-*n*-butyltin(IV) oxide or overnight in the case of diphenyltin(IV) oxide. The solution was allowed to cool to room temperature and concentrated to dryness using a vacuum pump. The product was redissolved in chloroform and filtered through a column (2 × 4 cm) packed with silica using the same solvent as eluent. Attempts to crystallize them only produced amorphous samples that were unsuitable for single crystal X-ray diffraction, except for compounds **1c** and **2d**.

4.2.1. (2S)-2-(2,4-Dihydroxybenzylideneimino)-4-methylpentanoic acid (*1*)

Orange solid, 50% yield; m.p. 194 °C (decomposes). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.12 (O–H), 8.40 (s, 1H; H-7), 7.22 (d, J = 8.4 Hz, 1H; H-13), 6.30 (d, J = 8.4 Hz, 1H; H-12), 6.20 (s, 1H; H-10), 4.02 (t, J = 6.6, 1H; H-5), 1.69 (t, J = 6.6 2H; H-14), 1.52 (m, 1H; H-15), 0.90 and 0.88 (d each J = 6.8 6H; H-16, H-17) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.1 (C-4), 165.9 (C-7), 164.0 (C-9), 162.0 (C-11), 133.6 (C-13), 111.2 (C-8), 107.1 (C-12), 102.5 (C-10), 67.6 (C-5), 41.9 (C-14), 24.3 (C-15), 22.9, 21.4 (C-16, C-17) ppm. TOF^{+}-HRMS calc. m/z for $C_{13}H_{17}NO_4 + H^{+}$: 252.1230, found: 252.1236, error 2.24 ppm. Elemental Anal. Calc. C, 62.14; H, 6.82; N, 5.57. Found: C, 62.29; H, 6.93; N, 5.77%.

4.2.2. (5S)-6-Aza-2,2-di-n-butyl-11-hydroxy-5-isobutyl-1,3-dioxa-2-stannabenzocyclo nonen-4-one (*1a*)

Yellow solid, 95% yield; m.p. 196 °C (decomposes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.16 (br s, 1H; O–H), 8.00 (s, 1H; H-7), 7.01 (d, J = 8.7 Hz, 1H; H-13), 6.42 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H; H-12), 6.30 (d, J = 2.2 Hz, 1H; H-10), 4.05 (dd, J = 8.6 Hz, J = 5.3 Hz, 1H; H-5), 1.94–1.86 (m, 1H; H-14), 1.82–1.70, 1.56–1.20 (m, 12H; H-α, H-α′, H-β, H-β′, H-γ, H-γ′), 1.68–1.58 (m, 2H; H-14, H-15), 1.01 and 1.00 (d each J = 6.4 Hz, 6H; H-16, H-17), 0.93, 0.82 (t, t, J = 7.3 Hz, 6H; H-δ, H-δ′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-DMSO-d_6): δ = 174.9 (C-4), 171.5 ($^{2}J^{119/117}Sn$ = 28.1 Hz, C-9), 169.5 (C-7), 166.9 (C-11), 137.5 (C-13), 111.2 ($^{3}J^{119/117}Sn$ = 28.4 Hz, C-8), 108.6 (C-12), 106.4 (C-10), 66.6 (C-5), 45.4 (C-14), 26.9 ($^{2}J^{119/117}Sn$ = 29.2 Hz, C-β), 26.7 (C-β′), 26.5 ($^{3}J^{119/117}Sn$ = 92.0 Hz, C-γ), 26.4 ($^{3}J^{119/117}Sn$ = 87.5 Hz, C-γ′), 23.8 (C-15), 22.9, 22.0 (C16, C-17), 21.6 (C-α), 21.2 (C-α′), 13.5, 13.4 (C-δ, C-δ′) ppm. MS-EI (m/z, %): 483 (M^{+}, 0.5), 439 (57), 400 (15), 397 (17), 396 (87), 395 (33), 394 (64), 393 (27), 330 (16), 328 (17), 326 (100), 325 (39), 324 (85), 323 (33), 322 (51), 243 (34), 241 (28), 239 (16). TOF^{+}-HRMS calc. m/z for $C_{21}H_{33}NO_4Sn + H^{+}$: 484.1504, found: 484.1517, error 2.61 ppm. Elemental Anal. calc. C, 52.31; H, 6.90; N, 2.90. Found: C, 52.63; H, 7.08; N, 2.69%.

4.2.3. (5S)-6-Aza-2,2-di-n-butyl-5-isobutyl-11-methoxy-1,3-dioxa-2-stannabenzocyclo nonen-4-one (*1b*)

Yellow solid, 90% yield; m.p. 74–76 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.01 (s, 1H; H-7), 6.70 (d, J = 8.8 Hz, 1H; H-13), 6.31 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H; H-12), 6.19 (d, J = 2.4 Hz, 1H; H-10), 3.99 (dd, J = 8.2 Hz, J = 5.5 Hz, 1H; H-5), 3.78 (s, 3H; O–CH_3), 2.00–1.20 (m, 15H; H-α, H-α′, H-β, H-β′, H-γ, H-γ′, H-14, H-15), 0.95 (d, J = 6.3 Hz, 6H; H-16, H-17), 0.90 and 0.78 (t each J = 7.1 Hz, 6H; H-δ, H-δ′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 174.4 (C-4), 171.9 ($^{2}J^{119/117}$Sn = 26.9 Hz, C-9), 169.6 (C-7), 167.9 (C-11), 136.8 (C-13), 111.6 ($^{3}J^{119/117}$Sn = 26.2 Hz, C-8), 108.2 (C-12), 103.7 (C-10), 67.1 (C-5), 55.5 (O–CH_3), 45.5 (C-14), 27.0 ($^{2}J^{119/117}$Sn = 29.2 Hz, C-β), 26.9 ($^{2}J^{119/117}$Sn = 34.4 Hz, C-β′), 26.6 ($^{3}J^{119/117}$Sn = 94.3 Hz, C-γ), 26.5 ($^{3}J^{119/117}$Sn = 89.4 Hz, C-γ′), 24.0 (C-15), 22.9, 22.0 (C16, C-17), 21.9 (C-α), 21.4 (C-α′), 13.5, 13.5 (C-δ, C-δ′) ppm. MS-EI (*m/z*, %): 453 (35), 452 (15), 451 (26), 410 (63), 409 (25), 408 (47), 407 (19), 406 (26), 344 (17), 342 (16), 341 (15), 340 (100), 339 (38), 338 (81), 337 (32), 336 (47), 257 (30), 255 (23), 121 (49). TOF$^+$-HRMS calcd. m/z for $C_{22}H_{35}NO_4Sn$ + H^+: 498.1660, found: 498.1662, error 0.23 ppm. Elemental Anal. calc. C, 53.25; H, 7.11; N, 2.82. Found: C, 53.27; H, 7.31; N, 2.50%.

4.2.4. (5S)-6-Aza-11-hydroxy-5-isobutyl-1,3-dioxa-2,2,-diphenyl-2-stannabenzocyclo nonen-4-one (**1c**)

Yellow solid, 89% yield; m.p. 236–238 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.80 (br s, 1H; OH), 8.01 (s, 1H; H-7), 7.96–7.88 and 7.83–7.74 (m each $^{3}J^{119/117}$Sn = 81.6 Hz, *J* = 5.8 Hz, 4H; H-*o*, H-*o*′), 7.45–7.33, 7.29–7.22 (m, m, $J^{119/117}$Sn = 32.3 Hz, 3H; H-*m*, H-*m*′, H-*p*, H-*p*′), 7.02 (d, *J* = 9.3 Hz, 1H; H-13), 6.72 (d, *J* = 2.3 Hz, 1H; H-10), 6.53 (dd, *J* = 9.3 Hz, *J* = 2.3 Hz, 1H; H-12), 4.15 (dd, *J* = 8.3 Hz, *J* = 5.2 Hz, 1H; H-5), 1.84–1.63 (m, 2H; H-14, H-15), 1.52 (ddd, *J* = 13.3 Hz, *J* = 8.3 Hz, *J* = 5.2 Hz, 1H; H-14), 0.89 (d, *J* = 6.2 Hz, 3H; H-16), 0.82 (d, *J* = 6.2 Hz, 3H; H-17) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7 (C-4), 171.8 ($^{2}J^{119/117}$Sn = 27.7 Hz, C-9), 169.6 (C-7), 167.6 (C-11), 137.9 (C-13), 137.8 (C-*i*), 137.6 (C-*i*′), 136.5 ($^{2}J^{119/117}$Sn = 55.3 Hz, C-*o*), 136.2 ($^{2}J^{119/117}$Sn = 57.6 Hz, C-*o*′), 130.8 ($^{4}J^{119/117}$Sn = 17.2 Hz, C-*p*), 130.7 ($^{4}J^{119/117}$Sn = 17.2 Hz, C-*p*′), 129.0 ($^{3}J^{119/117}$Sn = 84.5 Hz, C-*m*), 129.0 ($^{3}J^{119/117}$Sn = 82.3 Hz, C-*m*′), 111.4 ($^{3}J^{119/117}$Sn = 32.9 Hz, C-8), 109.7 (C-12), 107.4 (C-10), 66.8 (C-5), 45.0 (C-14), 23.9 (C-15), 22.9, 22.0 (C16, C-17) ppm. MS-EI (*m/z*, %): 524 (M^+, 0.001), 479 (51), 478 (23), 477 (38), 476 (17), 475 (21), 437 (22), 436 (100), 435 (40), 434 (71), 433 (30), 432 (40), 183 (16), 78 (44). TOF$^+$-HRMS calc. *m/z* for $C_{25}H_{25}NO_4Sn$ + H^+: 524.0878, found: 524.0883, error 0.89 ppm. Elemental Anal. Calc. C, 57.50; H, 4.83; N, 2.68. Found: C, 57.27; H, 4.62; N, 2.36%.

4.2.5. (5S)-6-Aza-5-isobutyl-11-methoxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzocyclo nonen-4-one (**1d**)

Beige solid, 92% yield; m.p. 212 °C (decomposes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1H; H-7), 7.99–7.96 and 7.84–7.82 (dd each *J* = 7.4 Hz, *J* = 4.1 Hz, 4H; H-*o*, H-*o*′), 7.50–7.36 (m, 6H; H-*m*, H-*m*′, H-*p*, H-*p*′), 7.07 (d, *J* = 8.8 Hz, 1H; H-13), 6.57 (d, *J* = 2.4 Hz, 1H; H-10), 6.39 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H; H-12), 4.11 (dd, *J* = 5.6 Hz, *J* = 8.3 Hz, 1H; H-5), 3.90 (s, 3H; O–CH_3), 1.82–1.75 (m, 1H; H-14a), 1.70–1.64 (m, 1H; H-15), 1.53–1.46 (m, 1H; H-14b), 0.88 and 0.82 (d each *J* = 6.6 Hz, 6H; H-16, H-17) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C-4), 172.0 ($^{2}J^{119/117}$Sn = 27.7 Hz, C-9), 169.6 (C-7), 168.3 (C-11), 138.0 (C-*i*), 137.8 (C-*i*′), 137.1 (C-13), 136.6 ($^{2}J^{119/117}$Sn = 57.6 Hz, C-*o*), 136.3 ($^{2}J^{119/117}$Sn = 55.4 Hz, C-*o*′), 130.8 ($^{4}J^{119/117}$Sn = 17.6 Hz, C-*p*), 130.6 ($^{4}J^{119/117}$Sn = 18.0 Hz, C-*p*′), 129.0 ($^{3}J^{119/117}$Sn = 87.9 Hz, C-*m*), 128.9 ($^{3}J^{119/117}$Sn = 88.3 Hz, C-*m*′), 111.8 ($^{3}J^{119/117}$Sn = 31.8 Hz, C-8), 108.6 (C-12), 104.3 (C-10), 67.1 (C-5), 55.7 (O–CH_3), 45.0 (C-14), 23.9 (C-15), 22.8, 22.1 (C16, C-17) ppm. MS-EI (*m/z*, %): 538 (M^+, 0.2), 494 (18), 493 (64), 492 (28), 491 (45), 490 (20), 489 (24), 454 (17), 452 (16), 451 (24), 450 (100), 449 (42), 448 (70), 447 (31), 446 (37), 344 (17), 197 (25). TOF$^+$-HRMS calc. *m/z* for $C_{26}H_{27}NO_4Sn$ + H^+: 538.1037, found: 538.1034, error 0.40 ppm. Elemental Anal. Calc. C, 58.24; H, 5.08; N, 2.61. Found: C, 57.82; H, 4.87; N, 2.51%.

4.2.6. (5S)-6-Aza-2,2-di-n-butyl-5-[(2′S)-but-2′-yl]-11-hydroxy-1,3-dioxa-2-stanna benzocyclononen-4-one (**2a**)

Yellow solid, 93% yield; m.p. 150–152 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.98 (br s, 1H; OH), 8.01 (s, 1H; H-7), 6.97 (d, *J* = 8.9 Hz, 1H; H-13), 6.42 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H; H-12), 6.29 (d, *J* = 2.2 Hz, 1H; H-10), 3.88 (d, *J* = 4.2 Hz, 1H; H-5), 2.00-1.85 (m, *J* = 4.2 Hz, *J* = 6.8 Hz, 1H; H-14), 1.78–1.15 (m, 14H; H-α, H-α′, H-β, H-β′, H-γ, H-γ′, H-15), 1.02 (d, *J* = 6.8 Hz, 3H; H-17), 0.94 and 0.90 (t each *J* = 7.3 Hz, 6H; H-δ, H-δ′), 0.78 (t, *J* = 7.3 Hz, 3H; H-16) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4 (C-4), 171.8 ($^{2}J^{119/117}$Sn = 26.2 Hz, C-9), 170.3 (C-7), 167.3 (C-11), 137.7 (C-13), 111.4 ($^{3}J^{119/117}$Sn = 26.6 Hz, C-8), 109.3 (C-12), 106.9 (C-10), 72.8 (C-5), 42.0 (C-14), 26.9 ($^{2}J^{119/117}$Sn = 22.4 Hz, C-β), 26.9 ($^{2}J^{119/117}$Sn = 32.9 Hz, C-β′), 26.6 ($^{3}J^{119/117}$Sn = 98.0 Hz, C-γ), 26.5 ($^{3}J^{119/117}$Sn = 91.3 Hz, C-γ′), 25.3 (C-15), 22.2 (C-α), 20.9 (C-α′), 15.3 (C-17), 13.6, 13.5, 11.9 (C-16, C-δ, C-δ′) ppm. MS-EI (*m/z*, %): 483 (M^+, 0.2), 439 (40), 426 (16), 424 (15), 410 (23), 408 (18), 370 (15), 330 (17), 328 (16), 326 (100), 325 (38), 324 (80), 323 (32), 322 (47), 243 (33), 241 (27), 239 (16). TOF$^+$-HRMS calc. *m/z* for $C_{21}H_{33}NO_4Sn$ + H^+: 484.1504, found: 484.1515, error 2.20 ppm. Elemental Anal. Calc. C, 52.31; H, 6.90; N, 2.90. Found: C, 51.98; H, 6.68; N, 2.71%.

4.2.7. (5S)-6-Aza-2,2-di-n-butyl-5-[(2′S)-but-2′-yl]-11-methoxy-1,3-dioxa-2-stannabenzocyclononen-4-one (**2b**)

Yellow solid, 94% yield; m.p. 82–84 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.06 (s, 1H; H-7), 7.02 (d, *J* = 8.8 Hz, 1H; H-13), 6.31 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H; H-12), 6.20 (d, *J* = 2.4 Hz, 1H; H-10), 3.85 (d, *J* = 4.4 Hz, 1H; H-5), 3.79 (s, 3H; O–CH_3), 2.01–1.84 (m, 1H; H-14), 1.80–1.73 (m, 2H; H-α′), 1.71–1.64 (m, 2H; H-β′), 1.63–1.53 (m, 2H; H-γ′), 1.49–1.43 (m, 2H; H-α), 1.40–1.29 (m, 4H; H-β, H-γ), 1.26–1.11 (m, 2H; H-15), 1.00 (d, *J* = 7.2 Hz, 3H; H-17), 0.93 (t, *J* = 7.2 Hz, 3H; H-δ′), 0.91 (t, *J* = 7.2 Hz, 3H; H-δ), 0.77 (t, *J* = 7.7 Hz, 3H; H-16) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (C-4), 172.1 ($^{2}J^{119/117}$Sn = 26.9 Hz, C-9), 170.3 (C-7), 167.9 (C-11), 137.0 (C-13), 111.8 ($^{3}J^{119/117}$Sn = 26.6 Hz, C-8), 108.3 (C-12), 103.7 (C-10), 73.0 (C-5), 55.6 (O–CH_3), 42.1 (C-14), 27.0 ($^{2}J^{119/117}$Sn = 23.9 Hz, C-β), 27.0 ($^{2}J^{119/117}$Sn = 31.4 Hz, C-β′), 26.7 ($^{3}J^{119/117}$Sn = 95.7 Hz, C-γ), 26.5 ($^{3}J^{119/117}$Sn = 89.8 Hz, C-γ′), 25.4 (C-15), 22.3 (C-α), 20.8 (C-α′), 15.2 (C-17), 13.6, 13.5, 11.9 (C-16, C-δ, C-δ′) ppm. MS-EI (*m/z*, %): 497 (M^+, 4), 493 (26), 464 (38), 463 (16), 462 (28), 340 (100), 257 (43), 121 (79). TOF$^+$ -HRMS calc. m/z for $C_{22}H_{35}NO_4Sn$ + H^+: 498.1660, found: 498.1663, error 0.43 ppm. Elemental Anal. Calc. C, 53.25; H, 7.11; N, 2.82. Found: C, 53.47; H, 7.41; N, 2.96%.

4.2.8. (5S)-6-Aza-5-[(2′S)-but-2′-yl]-11-hydroxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzo cyclononen-4-one (**2c**)

Yellow solid, 91% yield; m.p. 222–224 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.78 (br s, 1H; OH), 8.58 (s, 1H; H-7), 7.83 and 7.62 (dd each $^{3}J^{119/117}$Sn = 83.9 Hz, *J* = 6.8 Hz, *J* = 2.2 Hz, 4H; H-*o*, H-*o*′), 7.52-7.43 and 7.42-7.38 (m each, 3H; H-*m*, H-*m*′, H-*p*, H-*p*′), 7.28 (d, *J* = 8.6 Hz, 1H; H-13), 6.38 (d, *J* = 2.4 Hz, 1H; H-10), 6.34 (dd, *J* = 8.6 Hz, *J* = 2.4 Hz, 1H; H-12), 4.12 (d, *J* = 4.2 Hz, 1H; H-5), 1.80–1.70 (m, 1H; H-14), 1.53–1.43 (m, 1H; H-15a), 1.20–1.07 (m, 1H; H-15b), 0.77 (t, *J* = 7.4 Hz, 3H; H-16), 0.70 (d, *J* = 6.8 Hz, 3H; H-17) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8 (C-7), 172.3 (C-4), 171.3 ($^{2}J^{119/117}$Sn = 26.9 Hz, C-9), 167.1 (C-11), 140.3 (C-*i*), 139.9 (C-*i*′), 139.1 (C-13), 136.4 ($^{2}J^{119/117}$Sn = 53.1 Hz, C-*o*), 136.1 ($^{2}J^{119/117}$Sn = 54.6 Hz, C-*o*′), 130.8 ($^{4}J^{119/117}$Sn = 15.7 Hz, C-*p*), 130.7 ($^{4}J^{119/117}$Sn = 15.7 Hz, C-*p*′), 129.3 ($^{3}J^{119/117}$Sn = 84.2 Hz, C-*m*), 129.3 ($^{3}J^{119/117}$Sn = 84.2 Hz, C-*m*′), 111.9 ($^{3}J^{119/117}$Sn = 36.3 Hz, C-8), 108.9 (C-12), 106.6 (C-10), 70.7 (C-5), 42.0 (C-14), 26.2 (C-15), 15.2 (C-17), 12.1 (C-16) ppm. MS-EI (*m/z*, %): 523 (M^+, 0.4), 483 (19), 481 (18), 480 (27), 479 (100), 478 (46), 477 (73), 476 (33), 475 (40), 464 (17), 454 (16), 450 (96), 449 (41), 448 (69), 447 (30), 446 (39), 319 (22), 317 (18), 183 (23), 78 (40). TOF$^+$-HRMS calc. *m/z* for $C_{25}H_{25}NO_4Sn$ + H^+: 524.0878, found: 524.0884, error 1.08 ppm. Elemental Anal. Calc. C, 57.50; H, 4.83; N, 2.68. Found: C, 57.68; H, 4.68; N, 2.44%.

*4.2.9. (5S)-6-Aza-5-[(2′S)-but-2′-yl]-11-methoxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzo cyclononen-4-one (**2d**)*

Yellow solid, 86% yield; m.p. 184–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1H; H-7), 8.05–8.02 and 7.80–7.77 (dd each $^3J^{119/117}$Sn = 76.2 Hz, J = 8.8 Hz, J = 5.8 Hz, 4H; H-*o*, H-*o′*), 7.49–7.43 and 7.40–7.32 (m each 6H; H-*m*, H-*m′*, H-*p*, H-*p′*), 7.09 (d, J = 9.0 Hz, 1H; H-13), 6.59 (d, J = 2.4 Hz, 1H; H-10), 6.42 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H; H-12), 4.02 (d, J = 4.2 Hz, 1H; H-5), 3.94 (s, 3H; O–CH_3), 1.97–1.82 (m, 1H; H-14), 1.61 (dqd, J = 5.3 Hz, J = 7.3 Hz, J = 13.5 Hz, 1H; H-15′), 1.20 (dqd, 1H; J = 5.3 Hz, J = 7.3 Hz, J = 11.2 Hz, H-15), 0.89 (d, J = 6.9 Hz, 3H; H-17), 0.82 (t, J = 7.2 Hz, 3H; H-16) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (C-4), 172.5 ($^2J^{119/117}$Sn = 27.8 Hz, C-9), 170.8 (C-7), 168.5 (C-11), 138.5 (C-*i*), 138.2 (C-*i′*), 137.5 (C-13), 136.8 ($^2J^{119/117}$Sn = 55.7 Hz, C-*o*), 136.7 (^{2}J119/117Sn = 55.6 Hz, C-*o′*), 130.9 ($^4J^{119/117}$Sn = 16.2 Hz, C-*p*), 130.8 ($^4J^{119/117}$Sn = 17.5 Hz, C-*p′*), 129.1 ($^3J^{119/117}$Sn = 84.5 Hz, C-*m*), 129.1 ($^3J^{119/117}$Sn = 89.0 Hz, C-*m′*), 112.1 ($^3J^{119/117}$Sn = 32.5 Hz, C-8), 108.9 (C-12), 104.5 (C-10), 72.8 (C-5), 56.0 (O–CH_3), 42.9 (C-14), 26.0 (C-15), 15.5 (C-17), 12.1 (C-16) ppm. MS-EI (*m/z*, %): 497 (14), 495 (15), 494 (23), 493 (85), 492 (40), 491 (63), 490 (30), 489 (34), 478 (18), 468 (17), 465 (26), 464 (100), 463 (46), 462 (75), 333 (27). TOF$^+$ - HRMS calc. *m/z* for $C_{26}H_{27}NO_4Sn$ + H^+: 538.1050, found: 538.1034, error 2.82 ppm. Elemental Anal. Calc. C, 58.24; H, 5.08; N, 2.61. Found: C, 58.29; H, 5.01; N, 2.39%.

*4.2.10. (5S)-6-Aza-2,2-di-n-butyl-5-(2-methylsulfanylethyl)-11-hydroxy-1,3-dioxa-2-stannabenzocyclononen-4-one (**3a**)*

Yellow solid, 79% yield; m.p. 188–190 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.18 (br s, 1H; OH), 8.14 (s, 1H; H-7), 6.98 (d, J = 8.8 Hz, 1H; H-13), 6.39 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H; H-12), 6.26 (d, J = 2.2 Hz, 1H; H-10), 4.24 (dd, J = 7.7 Hz, J = 5.2 Hz, 1H; H-5), 2.74–2.64 (m, 1H; H-15), 2.56–2.46 (m, 1H; H-15), 2.38–2.25 (m, 1H; H-14), 2.09 (s, 3H; S–CH_3), 2.09–1.96 (m, 1H; H-14), 1.77–1.18 (m, 12H; H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.90, 0.80 (t, t, J = 6.9 Hz, 6H; H-δ, H-δ') ppm. ^{13}C NMR (100 MHz, $CDCl_3$ – DMSO-d_6): δ = 174.3 (C-4), 171.9 ($^2J^{119/117}$Sn = 25.8 Hz, C-9), 170.4 (C-7), 167.3 (C-11), 137.8 (C-13), 111.4 ($^3J^{119/117}$Sn = 28.4 Hz, C-8), 108.9 (C-12), 106.5 (C-10), 66.0 (C-5), 35.1 (C-14), 29.5 (C-15), 27.0 ($^2J^{119/117}$Sn = 28.4 Hz, C-β), 26.8 (C-β'), 26.6 ($^3J^{119/117}$Sn = 94.2 Hz, C-γ), 26.5 ($^3J^{119/117}$Sn = 88.3 Hz, C-γ'), 21.8 (C-α), 21.3 (C-α'), 15.2 (C-17), 13.6, 13.5 (C-δ, C-δ') ppm. MS-EI (*m/z*, %): 501 (M^+, 0.9), 448 (18), 446 (21), 445 (21), 444 (100), 443 (40), 442 (72), 441 (30), 440 (41), 400 (23), 396 (82), 394 (58), 344 (37), 282 (16). TOF$^+$-HRMS calc. *m/z* for $C_{20}H_{31}NO_4SSn$ + H^+: 502.1068, found: 502.1073, error 0.88 ppm. Elemental Anal. Calc. C, 48.02; H, 6.25; N, 2.80; S, 6.41. Found: C, 48.42; H, 6.36; N, 2.68; S, 6.82%.

*4.2.11. (5S)-6-Aza-2,2-di-n-butyl-5-(2-methylsulfanylethyl)-11-methoxy-1,3-dioxa-2-stannabenzocyclononen-4-one (**3b**)*

Yellow solid, 93% yield; m.p. 62–64 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.18 (s, 1H; H-7), 7.02 (d, J = 9.0 Hz, 1H; H-13), 6.33 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H; H-12), 6.19 (d, J = 2.4 Hz, 1H; H-10), 4.19 (t, J = 7.6 Hz, 1H; H-5), 3.79 (s, 3H; O–CH_3), 2.75–2.61 (m, 1H; H-14a), 2.58–2.43 (m, 1H; H-14b), 2.38–2.22 (m, 1H; H-15a), 2.08 (s, 3H; H-17), 2.08–1.92 (m, 1H; H-15b), 1.79–1.18 (m, 12H, H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.90, 0.79 (t, t, J = 7.13 Hz, 6H; H-δ, H-δ') ppm.. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (C-4), 172.1 ($^2J^{119/117}$Sn = 26.9 Hz, C-9), 170.6 (C-7), 168.1 (C-11), 137.0 (C-13), 111.7 ($^3J^{119/117}$Sn = 26.6 Hz, C-8), 108.3 (C-12), 103.7 (C-10), 66.2 (C-5), 55.5 (O–CH_3), 35.1 (C-14), 29.6 (C-15), 27.0 ($^2J^{119/117}$Sn = 28.4 Hz, C-β), 26.8 ($^2J^{119/117}$Sn = 34.4 Hz, C-β'), 26.6 ($^3J^{119/117}$Sn = 94.2 Hz, C-γ), 26.5 ($^3J^{119/117}$Sn = 89.0 Hz, C-γ'), 22.0 (C-α), 21.5 (C-α'), 15.2 (C-17), 13.5, 13.5 (C-δ, C-δ') ppm. MS-EI (*m/z*, %): 515 (M^+, 1), 471 (15), 460 (16), 459 (17), 458 (77), 457 (32), 456 (60), 455 (23), 454 (33), 414 (28), 412 (24), 411 (22), 410 (100), 409 (38), 408 (73), 407 (30), 406 (42), 402 (17), 358 (61), 357 (26), 356 (49), 355 (22), 354 (35), 328 (29), 310 (22), 308 (20), 296 (49), 295 (17), 294 (37), 292 (22), 257 (21), 255 (26), 253 (18), 121 (41). TOF$^+$-HRMS calc. *m/z* for $C_{21}H_{33}NO_4SSn$ + H^+: 516.1225, found: 516.1222, error −0.59 ppm. Elemental Anal. Calc. C, 49.01; H, 6.47; N, 2.72; S, 6.24. Found: C, 49.34; H, 6.62; N, 2.73; S, 6.03%.

*4.2.12. (5S)-6-Aza-5-(2-methylsulfanylethyl)-11-hydroxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzocyclononen-4-one (**3c**)*

Yellow solid, 47% yield; m.p. 214–216 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.69 (s, 1H; OH), 8.53 (s, 1H; H-7), 7.80–7.70 and 7.70–7.60 (m each $^3J^{119/117}$Sn = 75.9 Hz, 4H; H-*o*, H-*o′*), 7.50-7.31 (m, 6H; H-*m*, H-*m′*, H-*p*, H-*p′*), 7.25 (d, J = 8.4 Hz, 1H; H-13), 6.34 (d, J = 2.1 Hz, 1H; H-10), 6.32 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H; H-12), 4.26 (t, J = 8.7 Hz, 1H; H-5), 2.27 (t, J = 7.7 Hz, 2H; H-15), 2.10-1.85 (m, 2H; H-14), 1.79 (s, 3H; S-CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.1 (C-4), 171.6 (C-7), 171.1 ($^2J^{119/117}$Sn = 29.2 Hz, C-9), 166.8 (C-11), 142.5 (C-*i*), 142.4 (C-*i′*), 139.0 (C-13), 136.0 ($^2J^{119/117}$Sn = 54.6 Hz, C-*o*), 135.9 ($^2J^{119/117}$Sn = 54.6 Hz, C-*o′*), 130.4 ($^4J^{119/117}$Sn = 15.7 Hz, C-*p*), 130.3 ($^4J^{119/117}$Sn = 16.5 Hz, C-*p′*), 129.1 ($^3J^{119/117}$Sn = 83.0 Hz, C-*m*), 129.1 ($^3J^{119/117}$Sn = 86.0 Hz, C-*m′*), 112.1 ($^3J^{119/117}$Sn = 36.3 Hz, C-8), 108.5 (C-12), 106.7 (C-10), 65.7 (C-5), 34.9 (C-14), 29.3 (C-15), 15.0 (C-17) ppm. MS-EI (*m/z*, %): 541 (M^+, 1), 497 (27), 495 (20), 467 (22), 465 (18), 440 (18), 438 (17), 437 (23), 436 (100), 435 (41), 434 (74), 433 (31), 432 (41), 78 (94), 77 (16). TOF$^+$-HRMS calc. *m/z* for $C_{24}H_{23}NO_4SSn$ + H^+: 542.0442, found: 542.0446, error: 0.63 ppm. Elemental Anal. Calc. C, 53.36; H, 4.29; N, 2.59; S, 5.94. Found: C, 53.16; H, 4.16; N, 2.62; S, 6.10%.

*4.2.13. (5S)-6-Aza-5-(2-methylsulfanylethyl)-11-methoxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzocyclononen-4-one (**3d**)*

Yellow solid, 80% yield; m.p. 192–194 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.20 (s, 1H; H-7), 8.00–7.91, 7.85–7.76 (m, m, 4H; H-*o*, H-*o′*), 7.52–7.30 (m, 6H; H-*m*, H-*m′*, H-*p*, H-*p′*), 7.06 (d, J = 8.9 Hz, 1H; H-13), 6.55 (d, J = 2.3 Hz, 1H; H-10), 6.39 (dd, J = 8.9 Hz, J = 2.3 Hz, 1H; H-12), 4.30 (t, J = 6.3 Hz, 1H; H-5), 3.90 (s, 3H; O–CH_3), 2.53-2.43 (m, 1H; H-14a), 2.37–2.26 (m, 1H; H-14b), 2.25–1.95 (m, 2H; H-15), 1.87 (s, 3H; S-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5 (C-4), 172.2 ($^2J^{119/117}$Sn = 28.4 Hz, C-9), 170.5 (C-7), 168.5 (C-11), 138.1 (C-*i*), 137.8 (C-*i′*), 137.3 (C-13), 136.5 ($^2J^{119/117}$Sn = 56.5 Hz, C-*o*), 136.3 ($^2J^{119/117}$Sn = 56.1 Hz, C-*o′*), 130.8 ($^4J^{119/117}$Sn = 18.0 Hz, C-*p*), 130.7 ($^4J^{119/117}$Sn = 17.6 Hz, C-*p′*), 129.0 ($^3J^{119/117}$Sn = 87.7 Hz, C-*m*), 128.9 ($^3J^{119/117}$Sn = 87.5 Hz, C-*m′*), 111.9 ($^3J^{119/117}$Sn = 32.2 Hz, C-8), 108.8 (C-12), 104.2 (C-10), 66.2 (C-5), 55.8 (O–CH_3), 34.8 (C-14), 29.4 (C-15), 15.2 (C-17) ppm. MS-EI (*m/z*, %): 555 (M^+, 0.8), 511 (27), 509 (20), 454 (17), 452 (16), 451 (24), 450 (100), 449 (43), 448 (73), 447 (32), 446 (41). TOF$^+$-HRMS calc. *m/z* for $C_{25}H_{25}NO_4SSn$ + H^+: 556.0599, found: 556.0606, error 1.25 ppm. Elemental Anal. Calc. C, 54.18; H, 4.55; N, 2.53; S, 5.79. Found: C, 53.92; H, 4.68; N, 2.40; S, 5.60%.

*4.2.14. (5S)-6-Aza-5-benzyl-2,2-di-n-butyl-11-hydroxy-1,3-dioxa-2-stannabenzocyclo nonen-4-one (**4a**)*

Yellow solid, 90% yield; m.p. 84–86 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 9.58 (br s, 1H; OH), 7.32 (s, 1H; H-7), 7.24–7.13 (m, 3H; H-16, H-18), 7.12–7.03 (m, 2H; H-17), 6.62 (d, J = 8.6 Hz, 1H; H-13), 6.33 (dd, J = 8.6 Hz, J = 1.7 Hz, 1H; H-12), 6.27 (d, J = 1.7 Hz, 1H; H-10), 4.13 (dd, J = 8.2 Hz, J = 3.7 Hz, 1H; H-5), 3.42 (dd, J = 13.6 Hz, J = 3.7 Hz, 1H; H-14a), 3.03 (dd, J = 13.6 Hz, J = 8.7 Hz, 1H; H-14b), 1.68-1.12 (m, 12H, H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.88 and 0.77 (t each, J = 7.2 Hz, 6H, H-δ, H-δ') ppm. ^{13}C NMR (100 MHz, $CDCl_3$ – DMSO-d_6): δ = 174.7 (C-4), 171.7 ($^2J^{119/117}$Sn = 25.4 Hz, C-9), 170.3 (C-7), 166.9 (C-11), 137.7 (C-13), 135.2 (C-15), 130.2 (C-16), 128.8 (C-18), 127.3 (C-17), 111.1 ($^3J^{119/117}$Sn = 25.8 Hz, C-8), 108.7 (C-12), 106.5 (C-10), 68.9 (C-5), 41.8 (C-14), 27.0 ($^2J^{119/117}$Sn = 26.9 Hz, C-β), 26.7 ($^2J^{119/117}$Sn = 34.0 Hz, C-β'), 26.5 ($^3J^{119/117}$Sn = 98.0 Hz, C-γ), 26.4 ($^3J^{119/117}$Sn = 89.8 Hz, C-γ'), 21.3 (C-α), 21.2 (C-α'), 13.4, 13.4 (C-δ, C-δ') ppm. MS-EI (*m/z*, %): 517 (M^+, 0.2), 473 (44), 472 (19), 471 (32), 470 (15), 469 (18), 458 (86), 400 (57), 364 (17), 362 (16), 361 (17), 360 (100), 356 (43), 312 (28), 297 (22), 256 (67), 148 (33), 137 (30), 107 (25). TOF$^+$-HRMS calc. *m/z* for $C_{24}H_{31}NO_4Sn$ + H^+: 518.1347, found: 518.1352, error 0.80 ppm. Elemental Anal. Calc. C, 55.84; H, 6.05; N, 2.71. Found: C, 55.88; H, 6.13; N, 2.47%.

4.2.15. (5S)-6-Aza-5-benzyl-2,2-di-n-butyl-11-methoxy-1,3-dioxa-2-stannabenzocyclo nonen-4-one (**4b**)

Yellow oil, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H; H-7), 7.30–7.20 (m, 3H, H-17, H-18), 7.17–7.08 (m, 2H; H-16), 6.65 (d, *J* = 8.7 Hz, 1H; H-13), 6.24 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H; H-12), 6.18 (d, *J* = 2.4 Hz, 1H; H-10), 4.18 (dd, *J* = 7.9 Hz, *J* = 3.2 Hz, 1H; H-5), 3.80 (s, 3H; O-CH_3), 3.46 (dd, *J* = 13.7 Hz, *J* = 4.0 Hz, 1H; H-14a), 3.06 (dd, *J* = 13.7 Hz, *J* = 8.4 Hz, 1H; H-14b), 1.70-1.18 (m, 12H; H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.92 and 0.80 (t each, *J* = 7.1 Hz, 6H; H-δ, H-δ') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (C-4), 172.0 ($^2J^{119/117}$Sn = 26.9 Hz, C-9), 170.4 (C-7), 167.9 (C-11), 136.9 (C-13), 135.4 (C-15), 130.3 (C-16), 128.9 (C-18), 127.4 (C-17), 111.3 ($^3J^{119/117}$Sn = 26.6 Hz, C-8), 108.1 (C-12), 103.5 (C-10), 69.3 (C-5), 55.5 (O-CH_3), 42.0 (C-14), 27.1 ($^2J^{119/117}$Sn = 27.7 Hz, C-β), 26.8 ($^2J^{119/117}$Sn = 32.9 Hz, C-β'), 26.6 ($^3J^{119/117}$Sn = 96.5 Hz, C-γ), 26.5 ($^3J^{119/117}$Sn = 90.5 Hz, C-γ'), 21.5 (C-α, C-α'), 13.6, 13.5 (C-δ, C-δ') ppm. MS-EI (m/z,%): 531 (M^+, 1.1), (19), 483 (21), 378 (18), 376 (17), 375 (19), 374 (100), 373 (44), 372 (80), 371 (35), 370 (47), 121 (27). TOF$^+$-HRMS calcd. m/z for $C_{25}H_{33}NO_4Sn$ + H^+: 532.1504, found: 532.1513, error 1.63 ppm. Elemental Anal. Calc. C 56.63%, H 6.27%, N 2.64%, found: C 56.84%, H 6.44%, N 2.76%.

4.2.16. (5S)-6-Aza-5-benzyl-11-hydroxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzo cyclononen-4-one (4c)

Beige solid, 92% yield; m.p. 146–148 °C (decomposes). ^{1}H NMR (270 MHz, DMSO-d_6): δ = 10.67 (br s, 1H; O-H), 7.93 (s, 1H; H-7), 7.70–7.60 (m, 4H; H-*o*, H-*o'*), 7.50–7.34 (m, 6H, H-*m*, H-*m'*, H-*p*, H-*p'*), 7.10–6.91 (m, 3H; H-16, H-18), 6.94 (d, *J* = 8.2 Hz, 1H; H-13), 6.93 (d, *J* = 8.4 Hz, 2H; H-17), 6.34 (d, *J* = 2.2 Hz, 1H; H-10), 6.26 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H; H-12), 4.43 (dd, *J* = 8.0 Hz, *J* = 4.5 Hz, 1H; H-5), 3.26 (dd, *J* = 13.7 Hz, *J* = 4.5 Hz, 1H; H-14a), 2.79 (dd, *J* = 13.7 Hz, *J* = 8.0 Hz, 1H; H-14b) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.9 (C-4), 171.6 (C-7), 171.0 ($^2J^{119/117}$Sn = 28.4 Hz, C-9), 166.8 (C-11), 142.1 (C-*i*), 141.7 (C-*i'*), 138.7 (C-13), 136.0 ($^2J^{119/117}$Sn = 54.2 Hz, C-*o*), 135.9 ($^2J^{119/117}$Sn = 53.1 Hz, C-*o'*), 135.8 (C-15), 130.3 ($^4J^{119/117}$Sn = 17.2 Hz, C-*p*), 130.3 ($^4J^{119/117}$Sn = 18.7 Hz, C-*p'*), 130.1 (C-16), 129.1 ($^3J^{119/117}$Sn = 86.0 Hz, C-*m*), 129.0 ($^3J^{119/117}$Sn = 84.5 Hz, C-*m'*), 128.7 (C-18), 127.2 (C-17), 111.6 ($^3J^{119/117}$Sn = 35.5 Hz, C-8), 108.5 (C-12), 106.6 (C-10), 67.6 (C-5), 55.4 (C-14) ppm. MS-EI (*m/z*, %): 557 (M^+, 0.2), 517 (17), 515 (18), 514 (30), 513 (100), 512 (45), 511 (74), 510 (33), 509 (40), 436 (18), 409 (33), 408 (17), 407 (26), 319 (34), 317 (28), 315 (17) 183 (19), 78 (39). FAB$^+$-HRMS calc. *m/z* for $C_{28}H_{23}NO_4Sn$ + H^+: 558.0721, found: 558.0723, error 0.21 ppm. Elemental Anal. Calc. C, 60.46; H, 4.17; N, 2.52. Found: C, 55.61; H, 3.68; N, 1.88% ($C_{28}H_{23}NO_4Sn$ 0.5$CHCl_3$).

4.2.17. (5S)-6-Aza-5-benzyl-11-methoxy-1,3-dioxa-2,2,-diphenyl-2-stannabenzocyclo nonen-4-one (**4d**)

Yellow solid, 84% yield; m.p. 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.95 and 7.85–7.82 (dd each, $^3J^{119/117}$Sn = 80.8 Hz, 4H; H-*o*, H-*o'*), 7.51–7.48, 7.40–7.38 (m, m, 6H; H-*m*, H-*m'*, H-*p*, H-*p'*), 7.14 (s, 1H; H-7), 7.17–7.07 (m, 3H; H-17, H-18), 6.97–6.94 (m, 2H; H-16), 6.59 (d, *J* = 8.8 Hz, 1H; H-13), 6.55 (d, *J* = 2.3 Hz, 1H; H-10), 6.29 (dd, *J* = 8.8 Hz, *J* = 2.3 Hz, 1H; H-12), 4.19 (dd, *J* = 10.3 Hz, *J* = 3.3 Hz, 1H; H-5), 3.92 (s, 3H; O-CH_3), 3.49 (dd, *J* = 13.7 Hz, *J* = 3.2 Hz, 1H; H-14a), 2.74 (dd, *J* = 13.7 Hz, *J* = 10.3 Hz, 1H; H-14b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (C-4), 171.9 ($^2J^{119/117}$Sn = 28.4 Hz, C-9), 170.1 (C-7), 168.2 (C-11), 138.2 (C-*i*), 137.7 (C-*i'*), 137.1 (C-13), 136.5 ($^2J^{119/117}$Sn = 55.7 Hz, C-*o*), 136.3 ($^2J^{119/117}$Sn = 55.7 Hz, C-*o'*), 135.2 (C-15), 130.7 ($^4J^{119/117}$Sn = 17.2 Hz, C-*p*), 130.6 ($^4J^{119/117}$Sn = 18.0 Hz, C-*p'*), 130.1 (C-16), 129.0 ($^3J^{119/117}$Sn = 87.9 Hz, C-*m*), 128.9 ($^3J^{119/117}$Sn = 87.5 Hz, C-*m'*), 128.8 (C-18), 127.3 (C-17), 111.3 ($^3J^{119/117}$Sn = 31.4 Hz, C-8), 108.4 (C-12), 104.1 (C-10), 69.9 (C-5), 55.7 (O-CH_3), 41.8 (C-14) ppm. MS-EI (*m/z*, %): 572 (M^+, 1.8), 531 (17), 529 (18), 528 (31), 527 (100), 526 (51), 525 (74), 524 (36), 523 (39), 450 (16), 423 (31), 422 (20), 421 (26), 420 (15), 333 (34), 332 (16), 331 (29), 329 (17), 197 (30). TOF$^+$-HRMS calc. *m/z* for $C_{29}H_{25}NO_4Sn$ + H^+: 572.0878, found: 572.0880, error 0.29 ppm. Elemental Anal. Calc. C, 61.08; H, 4.42; N, 2.46. Found: C, 61.13; H, 4.33; N, 2.58%.

4.2.18. (5S)-6-Aza-2,2-di-n-butyl-11-hydroxy-1,3-dioxa-5-phenyl-2-stannabenzocyclo nonen-4-one (**5a**)

Yellow solid, 87% yield; m.p. 196–198 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ = 10.58 (br s, 1H; OH), 8.47 (s, 1H; H-7), 7.45–7.27 (m, 5H; H-15, H-16, H-17), 7.11 (d, *J* = 8.8 Hz, 1H; H-13), 6.20 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 1H; H-12), 6.04 (d, *J* = 2.2 Hz, 1H; H-10), 5.26 (s, 1H; H-5), 1.67-1.20 (m, 12H; H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.82 and 0.81 (t each, *J* = 7.2 Hz, 6H; H-δ, H-δ') ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.0 (C-7), 171.9 (C-4), 171.6 ($^2J^{119/117}$Sn = 26.9 Hz, C-9), 167.1 (C-11), 140.0 (C-14), 138.8 (C-13), 129.3 (C-15), 128.4 (C-17), 127.6 (C-16), 112.0 ($^3J^{119/117}$Sn = 24.7 Hz, C-8), 108.3 (C-12), 106.0 (C-10), 70.0 (C-5), 27.1 ($^2J^{119/117}$Sn = 32.2 Hz, C-β), 27.0 ($^2J^{119/117}$Sn = 33.7 Hz, C-β'), 26.4 ($^3J^{119/117}$Sn = 95.7 Hz, C-γ), 26.3 ($^3J^{119/117}$Sn = 92.8 Hz, C-γ'), 22.9 (C-α), 22.5 (C-α'), 13.9, 13.9 (C-δ, C-δ') ppm. MS-EI (*m/z*, %): 503 (M^+, 0.4), 459 (52), 458 (22), 457 (39), 456 (17), 455 (21), 350 (17), 348 (16), 347 (17), 346 (100), 345 (45), 344 (75), 343 (35), 342 (43), 243 (23), 241 (23), 239 (14), 227 (53), 91 (30). FAB$^+$-HRMS calc. *m/z* for $C_{23}H_{29}NO_4Sn$ + H^+: 504.1191, found: 504.1196, error 0.92 ppm. Elemental Anal. Calc. C, 55.01; H, 5.82; N, 2.79. Found: C, 55.32; H, 5.91; N, 2.51%.

4.2.19. (5S)-6-Aza-2,2-di-n-butyl-11-methoxy-1,3-dioxa-5-phenyl-2-stannabenzocyclo nonen-4-one (**5b**)

Yellow solid, 92% yield; m.p. 46–48 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.14 (s, 1H; H-7), 7.42–7.30 (m, 5H; H-15, H-16, H-17), 6.94 (d, *J* = 8.7 Hz, 1H; H-13), 6.29 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H; H-12), 6.23 (d, *J* = 2.4 Hz, 1H; H-10), 5.14 (s, 1H; H-5), 3.80 (s, 3H; O–CH_3), 1.74–1.28 (m, 12H; H-α, H-α', H-β, H-β', H-γ, H-γ'), 0.88 (dt, *J* = 6.5 Hz, 6H; H-δ, H-δ') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C-4, $^2J^{119/117}$Sn = 27.7 Hz, C-9), 171.7 (C-7), 168.3 (C-11), 138.4 (C-14), 137.2 (C-13), 129.1 (C-15), 128.5 (C-17), 127.3 (C-16), 111.9 ($^3J^{119/117}$Sn = 25.1 Hz, C-8), 108.4 (C-12), 103.5 (C-10), 70.7 (C-5), 55.6 (O-CH_3), 26.9 ($^2J^{119/117}$Sn = 34.4 Hz, C-β), 26.9 ($^2J^{119/117}$Sn = 28.4 Hz, C-β'), 26.6 ($^3J^{119/117}$Sn = 96.5 Hz, C-γ), 26.6 ($^3J^{119/117}$Sn = 88.3 Hz, C-γ'), 22.3 (C-α), 21.8 (C-α'), 13.6, 13.5 (C-δ, C-δ') ppm. MS-EI (m/z,%): 517 (M^+, 0.1), 474 (18), 473 (67), 471 (48), 469 (26), 364 (18), 362 (16), 361 (19), 360 (100), 359 (51), 358 (76), 357 (39), 356 (44), 257 (20), 255 (21), 121 (25). TOF$^+$-HRMS calc. m/z for $C_{24}H_{31}NO_4Sn$ + H^+: 518.1347, found: 518.1345, error −0.55 ppm. Elemental Anal. Calc. C, 55.84; H, 6.05; N, 2.71. Found: C, 56.16; H, 6.06; N, 2.49%.

4.2.20. (5S)-6-Aza-11-hydroxy-1,3-dioxa-2,2,5-triphenyl-2-stannabenzocyclononen-4-one (**5c**)

Beige solid, 26% yield; m.p. 300 °C (decomposes). ^{1}H NMR (270 MHz, DMSO-d_6): δ = 10.81 (s, 1H; OH), 8.36 (s, 1H; H-7), 7.80–7.67 (m, $^{3}J^{119/117}$Sn = 76.2 Hz, 4H, H-*o*, H-*o*′), 7.52–7.37 (m, 6H; H-*m*, H-*m*′, H-*p*, H-*p*′), 7.25–7.10 (m, 6H; H-13, H-15, H-16, H-17), 6.35 (d, *J* = 2.4 Hz, 1H; H-10), 6.27 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H; H-12), 5.35 (s, 1H; H-5) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4 (C-7), 171.9 (C-4), 171.2 ($^{2}J^{119/117}$Sn = 29.6 Hz, C-9), 167.1 (C-11), 143.0 (C-*i*), 142.6 (C-*i*′), 139.9 (C-14), 139.1 (C-13), 136.1 ($^{2}J^{119/117}$Sn = 52.5 Hz, C-*o*), 135.9 ($^{2}J^{119/117}$Sn = 55.5 Hz, C-*o*′), 130.4 ($^{4}J^{119/117}$Sn = 15.2 Hz, C-*p*), 130.3 ($^{4}J^{119/117}$Sn = 16.3 Hz, C-*p*′), 129.2 ($^{3}J^{119/117}$Sn = 82.4 Hz, C-*m*), 129.1 ($^{3}J^{119/117}$Sn = 82.2 Hz, C-*m*′), 129.0 (C-15), 128.3 (C-17), 128.3 (C-16), 112.1 ($^{3}J^{119/117}$Sn = 35.7 Hz, C-8), 108.7 (C-12), 106.6 (C-10), 69.4 (C-5) ppm. MS-EI (*m/z*, %): 499 (57), 497 (42), 495 (23), 319 (24), 317 (19), 241 (18), 227 (48), 183 (88), 78 (100). TOF^{+}-HRMS calc. *m/z* for $C_{27}H_{21}NO_4Sn + H^+$: 544.0565, found: 544.0566, error 0.12 ppm. Elemental Anal. Calc. C, 59.81; H, 3.90; N, 2.58. Found: C, 59.65; H, 3.50; N, 2.53%.

*4.2.21. (5S)-6-Aza-11-methoxy-1,3-dioxa-2,2,5-triphenyl-2-stannabenzocyclononen-4-one (**5d**)*

Yellow solid, 86% yield; m.p. 108–110 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.06 (s, 1H; H-7), 8.00–7.91 (m, 4H; H-*o*, H-*o*′), 7.43–7.30 (m, 6H; H-*m*, H-*m*′, H-*p*, H-*p*′), 7.17 (m, 5H; H-15, H-16, H-17), 6.92 (d, *J* = 8.9 Hz, 1H; H-13), 6.55 (d, *J* = 2.5 Hz, 1H; H-10), 6.33 (dd, *J* = 8.9 Hz, *J* = 2.5 Hz, 1H; H-12), 5.13 (s, 1H; H-5), 3.90 (s, 3H, O-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 ($^{2}J^{119/117}$Sn = 29.2 Hz, C-9), 172.5 (C-4), 172.4 (C-7), 169.0 (C-11), 138.8 (C-14), 138.5 (C-*i*), 138.3 (C-*i*′), 137.9 (C-13), 136.9 ($^{2}J^{119/117}$Sn = 53.4 Hz, C-*o*), 136.8 ($^{2}J^{119/117}$Sn = 54.4 Hz, C-*o*′), 131.1 ($^{4}J^{119/117}$Sn = 17.6 Hz, C-*p*), 131.0 ($^{4}J^{119/117}$Sn = 17.5 Hz, C-*p*′), 129.4 (C-15), 129.3 ($^{3}J^{119/117}$Sn = 87.6 Hz, C-*m*), 129.3 ($^{3}J^{119/117}$Sn = 88.1 Hz, C-*m*′), 128.8 (C-17), 128.1 (C-16), 112.3 ($^{3}J^{119/117}$Sn = 31.2 Hz, C-8), 109.1 (C-12), 104.3 (C-10), 70.8 (C-5), 56.1 (O-CH_3) ppm. MS-EI (*m/z*, %): 517 (18), 515 (19), 514 (30), 513 (100), 512 (45), 511 (72), 510 (33), 509 (38), 333 (51), 332 (19), 331 (39), 330 (15), 329 (23), 197 (36). TOF^{+}-HRMS calc. *m/z* for $C_{28}H_{23}NO_4Sn + H^+$: 558.0721, found: 558.0719, error −0.51 ppm. Elemental Anal. Calc. C, 60.46; H, 4.17; N, 2.52. Found: C, 60.68; H, 3.96; N, 2.26%.

4.2.21.1. In vitro experiments. Measurements of cell growth inhibition. Cell lines, MCF-7 (breast), HCT-15 (colon) and HeLa (cervic-uterine) were acquired from ATCC (American Tissue Culture Collection) and maintained in incubation at 37 °C and 5% CO_2 with D-MEM (GIBCO®, Invitrogen corporation) supplemented with 10% BFS (GIBCO®, Invitrogen corporation). The cells were cultured to confluence and after that 2∗104 cells/well were plated in 96 well (costar®) microplate and allowed to incubate for 24 h. At the end of the incubation time the medium was vacuumed and replaced with 90 µL of fresh supplemented medium and different concentrations (0, 0.01, 0.1, 1, 10 µg/mL) added in 10 µL of sterile water and no more than 0.1% of DMSO and cells were exposed to drugs in at the conditions mentioned above for 24 h by triplicate. Cell growth inhibition was determined according to the sulforhodamine B (SIGMA®) assay, described by Skehan [35,36]. Absorbance was measured at 564 nm (Microplate reader BIO-RAD 550) and% cells growth for each concentration of drug were calculated as:% growth = 100∗[*T*/*C*]; where *T* is the absorbance of treated wells and *C* is the absorbance of untreated wells. The medial inhibitory concentration was calculated using a Probit analysis (StatPlus, 2007) for those compounds where it was reached [35–37].

Acknowledgements

Financial support from CONACyT and UNAM (PAPIIT IN-214010 and PAPIIT IN-202708) is acknowledged. N. Kobakhidze thanks DGEP, UNAM for a scholarship. The authors thank MSc. Nuria Esturau Escofet and MSc. María Eugenia Ochoa Becerra for running the ^{13}C NMR spectra.

Appendix A. Supplementary material

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC Nos. 713862 (**1d**) and 719202 (**2c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail:deposit@ccdc.cam.ac.uk).

References

[1] S.J. Blunden, P.A. Cusack, R. Hill, The Industrial Uses of Tin Chemicals, The Royal Society of Chemistry, London, 1985;
A.G. Davies, M. Gielen, K.H. Pannell, E.R.T. Tiekink (Eds.), Tin Chemistry: Fundamentals, Frontiers and Applications, John Wiley & Sons, United Kingdom, 2008.
[2] G. Eng, E.J. Tierney, J.M. Bellama, F.E. Brinckman, Appl. Organomet. Chem. 2 (2) (1988) 171–175.
[3] V. Valla, M. Bakola-Christianopoulou, Synth. React. Inorg., Met.-Org., Nano-Met. Chem. 37 (7) (2007) 507–525.
[4] D. Point, W. Davis, C. Clay, J. Steven, M.B. Ellisor, R.S. Pugh, P.R. Becker, O.F.X. Donard, B.J. Porter, S.A. Wise, Anal. Bioanal. Chem. 387 (7) (2007) 2343–2355.
[5] V.M. Doctor, J. Oró, Biochem. J. 112 (1969) 691–697.
[6] A.E. Martell, Acc. Chem. Res. 22 (4) (1989) 115–124.
[7] J. Krätsmar-Šmogrovič, M. Blahová, V. Kettmann, Chirality 3 (6) (1991) 503–505.
[8] G. Plesch, C. Friebel, O. Svajlenova, J. Kratsmar-Smogrovic, D. Mlynarcik, Inorg. Chim. Acta 151 (2) (1988) 139–143.
[9] D.E. Goldberg, V. Sharma, A. Oksman, I.Y. Gluzman, T.E. Wellems, D. Piwnica-Worms, J. Biol. Chem. 272 (10) (1997) 6567–6572.
[10] P. Köpf-Maier, H. Köpf, Chem. Rev. 87 (5) (1987) 1137–1152.
[11] M.Z. Wang, Z. Meng, B. Liu, G. Cai, C. Zhang, X. Wang, Inorg. Chem. Commun. 8 (4) (2005) 368–371.
[12] M.Z. Wang, Z. Meng, J. Fu, Appl. Radiat. Isot. 64 (2) (2006) 235–240.
[13] J.C. Pessoa, I. Covaco, I. Correia, M.T. Duarte, R. D, Gillard, R.T. Henriques, F.J. Higes, C. Madeira, I. Tomaz, Inorg. Chim. Acta 293 (1) (1999) 1–11.
[14] G. Eng, D. Whalen, Y.Z. Zhang, A. Kirksey, M. Otieno, L.E. Khoo, B.D. James, Appl. Organomet. Chem. 10 (7) (1996) 501–503.
[15] (a) C. Camacho-Camacho, I. Rojas-Oviedo, M.A. Paz-Sandoval, J. Cárdenas, A. Toscano, M. Gielen, L. Barrón, F. Sánchez, I. Gracia-Mora, Appl. Organomet. Chem. 22 (3) (2008) 171–173;
(b) L. Tian, Z. Shang, X. Zheng, Y. Sun, Y. Yu, B. Qian, X. Liu, Appl. Organomet. Chem. 20 (1) (2006) 74–80;
(c) L. Tian, B. Qian, Y. Sun, X. Zheng, M. Yang, H. Li, X. Liu, Appl. Organomet. Chem. 19 (8) (2005) 980–987;
(d) L. Tian, Y. Sun, B. Qian, G. Yang, Y. Yu, Z. Shang, X. Zheng, Appl. Organomet. Chem. 19 (10) (2005) 1127–1131;
(e) N. Ogwuru, L.E. Khoo, G. Eng, Appl. Organomet. Chem. 12 (6) (1998) 409–417;
(f) M. Nath, R. Yadav, M. Gielen, H. Dalil, D. de Vos, G. Eng, Appl. Organomet. Chem. 11 (9) (1997) 727–736;
(g) H.I. Beltrán, C. Damian-Zea, S. Hernández-Ortega, A. Nieto-Camacho, M.T. Ramírez-Apan, J. Inorg. Biochem. 101 (7) (2007) 1070–1085.
[16] M. Gielen, Coord. Chem. Rev. 151 (1996) 41–51.
[17] D. de Vos, R. Willem, M. Gielen, K.E. van Wingerden, K.K. Nooter, Met.-Based Drugs 5 (4) (1998) 179–188.
[18] D. Schönfelder, U. Thust, in: F. Darvas (Ed.), Chemical Structure-Biological Activity Relationships: Quantitative Approaches, Pergamon Press, New York, 1980.
[19] J. Chen, S. Wang, X. Quan, S. Chen, D. Xue, Y. Zhao, J. Dalian Univ. Tech. 40 (3) (2000) 305–308.
[20] (a) H.I. Beltrán, L.S. Zamudio-Rivera, T. Mancilla, R. Santillan, N. Farfán, Chem. Eur. J. 9 (2003) 2291–2306;
(b) J. Holeček, M. Nádvorník, K. Handlír, J. Organomet. Chem. 315 (3) (1986) 299–308.
[21] H. Reyes, C. García, N. Farfán, R. Santillan, P.G. Lacroix, C. Lepetit, K. Nakatani, J. Organomet. Chem. 689 (14) (2004) 2303–2310.
[22] J.M. Rivera, H. Reyes, A. Cortés, R. Santillan, P.G. Lacroix, C. Lepetit, K. Nakatani, N. Farfán, Chem. Mater. 18 (5) (2006) 1174–1183.
[23] J.M. Rivera, D. Guzmán, M. Rodríguez, J.F. Lamère, K. Nakatani, R. Santillan, P.G. Lacroix, N. Farfán, J. Organomet. Chem. 691 (8) (2006) 1722–1732.
[24] H. Reyes, R. Santillan, M.E. Ochoa, M. Romero, N. Farfán, J. Mex. Chem. Soc. 51 (1) (2007) 39–44.
[25] C.E. Holloway, M. Melnick, Main Group Met. Chem. 23 (1–2) (2000) 1–147.
[26] F.E. Smith, R.C. Hynes, T.T. Ang, L.E. Khoo, G. Eng, Can. J. Chem. 70 (4) (1992) 1114–1120.
[27] (a) K. Kawkami, T. Tanaka, J. Organomet. Chem. 49 (2) (1973) 409–415;
G. Matsubayashi, T. Tanaka, S. Nisbigaki, N. Nakatsu, J. Chem. Soc., Dalton Trans. (1979) 501–505.

[28] M. Nath, S. Pokharia, R. Yadav, Coord. Chem. Rev. 215 (1) (2001) 99–149.
[29] B. Wrackmeyer, NMR spectroscopy of tin chemistry, in: A.G. Davies, M. Gielen, K.H. Pannell, E.R.T. Tiekink (Eds.), Tin Chemistry: Fundamentals, Frontiers and Applications, John Wiley & Sons, United Kingdom, 2008.
[30] (a) F.E. Smith, L.E. Khoo, N.K. Goh, R.C. Hynes, G. Eng, Can. J. Chem. 74 (11) (1996) 2041–2047;
(b) S. Knoll, F. Tschwatschal, T. Gelbrich, T. Ristau, R. Borsdorf, Z. Anorg. Allg. Chem. 642 (6) (1998) 1015–1020.
[31] D. Dakternieks, T.S.B. Baul, S. Dutta, E.R.T. Tiekink, Organometallics 17 (14) (1998) 3058–3062.
[32] Y. Dong, Acta Crystallogr., Sect. E 63 (2007) m2689.
[33] G.M. Sheldrick, SHELXS-86–Program for Crystal Structure Solution, University of Göttingen, Germany, 1986.
[34] G.M. Sheldrick, SHELXL-97–A Program for the Refinement of Crystal Structure, University of Göttingen, Germany, 1997.
[35] P. Skehan, R. Storeng, D.A. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bockesch, S. Kenney, M.R. Boyd, J. Natl. Can. Inst. 82 (13) (1990) 1107–1112.
[36] L.V. Rubinstein, R.H. Shoemaker, K.D. Paull, R.M. Simon, S. Tosini, P. Skehan, D.A. Scudiero, A. Monks, M.R. Boyd, J. Natl Cancer Inst. 82 (13) (1990) 1113–1118.
[37] M.C. Alley, D.A. Scudiero, A. Monks, M.L. Hursey, M.J. Czerwinski, D.L. Fine, B.J. Abbott, J.G. Mayo, R.H. Shoemaker, M.R. Boyd, Cancer Res. 48 (3) (1988) 589–601.