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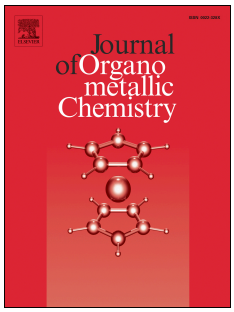

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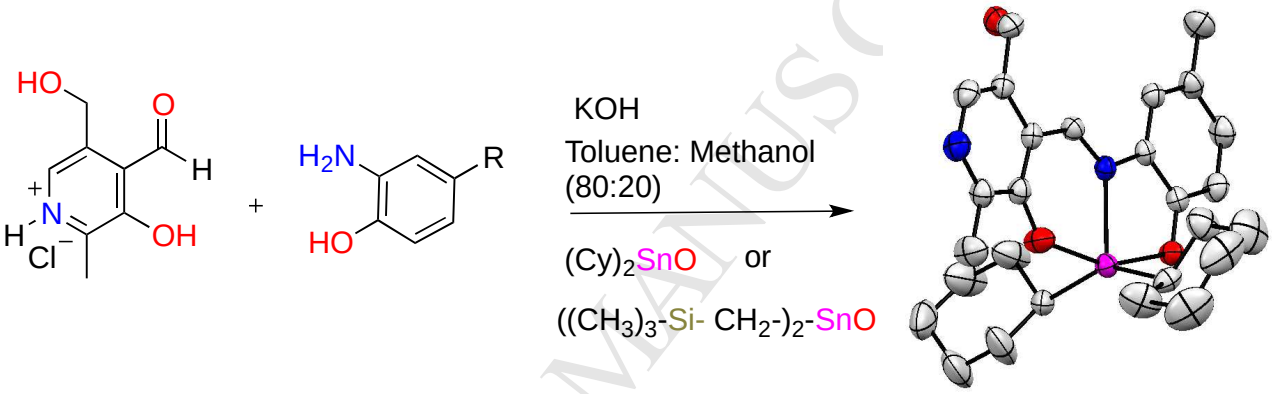

Schiff base Sn(IV) complexes as cytotoxic agents: synthesis, structure, isosteric and bioisosteric replacement

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ABSTRACT

The preparation and characterization of two series of organotin(IV) complexes are reported, each series differing in the nature of the substituent bonded to the tin atom (cyclohexyl or bis(trimethyl)silylmethyl). The isosteric and bioisosteric approach was used as the strategy of molecular design. The ligand was 5-hydroxymethyl-4-[(2-hydroxyphenyl)iminomethyl]-2-methylpyridin-3-ol substituted at position 5 by methyl, halogeno (F, Cl), methoxy, nitro and *tert*-butylsilyl; the synthesis of the organotin(IV) complexes was performed by a multi-component strategy in reasonable to high yields depending on the nature of the ligand. All new complexes were fully characterized by IR, MS, X-ray determinations and NMR (^{1}H, ^{13}C, ^{119}Sn). Crystallographic data of complexes showed the geometries adopted around the metal tin center varied between square pyramidal in **2c** and a trigonal bipyramidal in **3b-3d** with the alkyl groups in the trigonal plane and the two oxygen atoms in the equatorial plane. Additionally, the in vitro cytotoxicity tests of the complexes towards six types of human cancerous cell lines U-251 (glioblastoma), K-562 (chronic myelogenous leukemia), HCT-15 (human colorectal), MCF-7 (human breast), MB-231(human breast) and SKLU-1 *(*non-small cell lung) showed the superior activity of the organotin complexes compared to the corresponding cisplatin used as positive control. The complexes containing fluorine exhibited excellent IC_{50} data indicating that both the bioisosteric replacement and the cyclohexyl ring bonded to the tin atom increased the potency of the cytotoxic activity towards the cancer cell lines tested.

KEYWORDS

Cytotoxicity, Organotin (IV), Schiff base, NMR spectroscopy, X-ray crystallography

1 INTRODUCTION

Since the development of metal complexes with anticancer activity, medicinal inorganic chemistry has encouraged investigators to search for new metal complexes and organometallic compounds with growing importance in medicine, particularly in oncology.[1-4] It is known that more than 99% of currently approved clinical drugs are organic compounds. In contrast, the percentage of metal-containing drugs (metallodrugs) is low.[5] Metal-based compounds offer versatility and the possibility for designing therapeutic agents not seen in organic compounds in terms of the ability to vary coordination number, geometry, and redox states.[4, 6, 7] Additionally, metals provide a positive effect in the pharmacological properties, forming complexes with a variety of ligands. The metal is usually a key feature in the mechanism action, however; a fragment of the complex, or the metal, or the ligand may also be responsible for the biological activity.[8] Although cisplatin has showed significant clinical benefit for the treatment of several types of solid tumors, toxic side effects and tumor resistance leads to the occurrence of secondary malignancies;[9] however, the discovery and use of cisplatin have encouraged investigators to search for and develop novel non platinum-containing metal species with superior anti-cancer activity and low side effects. Organotin derivatives have attracted much attention due to their potential biological activities, including antimicrobial, antituberculosis, cardiovascular, antiviral, anti-parasitic, antihypertensive biocidal, antifungal, bactericidal, anti-inflammatory, antioxidant, and cytotoxic properties.[10-14]

The biological activity of organotin(IV) complexes has been associated with the molecular structure, coordination number and the nature of the organic groups bonded to the tin atom.[10, 15, 16] In many cases, it is known that metal complexes of ligands with biological activity are more active than the free ligands.[17, 18]

Schiff bases have often been used as chelating ligands in the field of coordination chemistry, and their metal complexes have been of great interest. Their biological activity is usually increased by complexation; consequently it is essential to understand the properties of both ligands and metal for the synthesis of highly active compounds.[19] The complexes of vitamin B6 have been studied with the purpose of knowing about the electronic and structural properties that are implicated in several important model reactions. The Schiff base complexes derived from vitamin B6 (VB6) are important compounds due to their tumor-targeting properties.[20] VB6 is known to be taken up by cells through a VB6 transporting membrane carrier (VTC)-mediated diffusion pathway. As cancer cells have high demand for VB6, compounds having this moiety could achieve VTC-mediated entry into the tumor cells in preference to normal ones.[21]

Schiff base ligands having a vitamin B6 moiety are selected for their tumor-targeting properties. VB6 is known to be taken up in cells by facilitated diffusion through VB6 transporting membrane carriers.[20, 22] Moreover, serine hydroxymethyltransferase isoforms (SHMTs), are vitamin VB6-dependent enzymes, and are implicated in DNA biosynthesis.[23] SHMTs have been correlated with the increased demand for nucleotide biosynthesis in tumors and their activity is known to be high in proliferative and tumor cells.[24] VB6 has an enormous potential as a biologically active reagent; it is known that organotin complexes incorporating pyridoxal moieties show biological activity. The organotin derivatives from pyridoxine have shown activity against P388, L1210, P815 leukemias. We recently described a series of organotin(IV) complexes containing pyridoxamine Schiff base skeletons. The complexes were tested across a panel of human cell lines, namely, U-251 (glioblastoma), PC-3 (prostate), K-562 (chronic myelogenous leukemia), HCT- 15 (human colorectal), MCF-7 (human breast), SKLU-1 (non-small cell lung), and MDA-MB-231 (human breast), to establish their activity. The bioisosteric replacement of a methyl group with iodine caused an increase in cytotoxicity. [25] More recently a series of pentacoordinated diorganotin complexes derived from pyridoxal hydrochloride and 4- or 5-R-substituted *ortho*-aminophenols were described by our group. In this case the position of the

substitution on the aromatic ring and the electronic character of the substituents were associated with the cytotoxic activity.[26] The antimicrobial activity has also been explored for pyridoxal organotin complexes containing methyl, butyl or phenyl substituents bonded to the tin atom.[27-29] Although a wide range or organotin complexes with a diversity of biological activities are known, the effect on the biological response of sterically-hindered substituents such as cyclohexyl or bis(trimethyl)silylmethyl bonded to the tin atom has scarcely been explored, despite these moieties forming molecules with potent cytotoxic activity against human tumor cell lines, which make them promising agents in cancer therapy.[30-35]

In the present paper, we report on the synthesis and characterization of diorganotin complexes containing cyclohexyl and bis(trimethyl)silylmethyl moieties with various aminophenols. The X-ray crystal structures of four complexes are described herein. The in vitro anti-tumor activity of the complexes against human breast adenocarcinoma (MCF-7, MB-231) U-251 (glioblastoma), K-562 (chronic myelogenous leukemia), HCT-15 (human colorectal), and SKLU-1 *(*non-small cell lung) tumor cell lines are also studied.

2. EXPERIMENTAL

2.1 **Materials**

All reagents and solvents were obtained from commercial suppliers and used without further purification. The dicyclohexyl and bis[(trimethylsilyl)methyl] tin(IV) oxides were obtained following the methodology described by Kong *et al*.[36]

2.2 **Physical measurements**

Meting points of the complexes were measured with a Fischer-Johns MEL-TEMP II apparatus and are not corrected. Infrared (IR) spectra of ligands and complexes were recorded with BRUKER TENSOR 27 spectrometer using KBr or CsI. Molar conductivity measurements were recorded with a Metrohm 644 using anhydrous methanol as solvent. The UV-vis absorption spectra were obtained with a Shimadzu UV-160U spectometer in methanol at 2.4530×10^{-5} M for all complexes.

^{1}H, ^{13}C and ^{119}Sn spectra were recorded with a Bruker Advance III spectrometer at 300.0, 75.4 and 111.8 MHz, in chloroform-*d* or DMSO-d_6. COSY, HSQC and HMBC experiments were used to completely assign the ^{1}H and ^{13}C signals. The FAB (fast atom bombardment) mass spectra were recorded with a JEOL-JMS-X103 spectrometeter and for exact mass spectra, poly(ethylene glycol) 600 was used as matrix. Single crystals of complexes **2d** and **3b**-**3d** suitable for X-ray diffraction studies were grown from their solution in chloroform/heptane, choroform or methanol. The crystals of each compound were mounted on a glass fiber at room temperature for **3b**-**3d**, and at 150 (2) K for **2d**, and then placed in a Bruker Smart Apex CCD diffractometer, equipped with a Mo radiation ($\lambda_{Mo\ K\alpha}$ = 0.71073 Å) and graphite monochromator at 293 K; decay was negligible in all cases. Systematic absences and intensity statistics were used in space group determination. The structure was solved using the direct methods SHELXS-2014 program. Anisotropic structure refinements were achieved using a full matrix, least-squares technique on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times (for –CH) and 1.5 times (for $–CH_3$) the value of the attached atom. Structure solutions and refinements were performed using SHELXL-2014 software.[37] Crystallographic data of **2d**, **3c**, **3d** and **3e** have been deposited with the Cambridge Crystallographic Data Centre CCDC 1554835-1554838 numbers.

2.3 General procedure for the synthesis of the Schiff bases 1b and 1e

To a solution of potassium hydroxide in 50 mL of toluene/methanol (60:40) mixture, pyridoxal hydrochloride and the corresponding ortho-aminophenol-5-R-substituted in a stoichiometric ratio were added. The reaction mixture was stirried over 4 days at room temperature, and the solvent removed under reduced pressure to give light brown and orange solids.

The synthesis of the Schiff bases **1a**, **1c–d** have been reported previously, using sodium methanolate as base and methanol as solvent. [27, 38]

5-Hydroxymethyl-4-[(2-hydroxy-5-fluorophenyl)iminomethyl]-2-methylpyridin-3-ol (**1b**).

Compound **1b** was prepared from 0.0450 g (0.8034 mmol) of potassium hydroxide, 0.1636 g of pyridoxal hydrochloride (0.8034 mmol) and 0.1021 g of 2-amino-4-fluorophenol (0.8034 mmol), affording 0.1559 g (70%) of a light brown solid; m.p. 265–267 ^{o}C (dec.); Molar conductance, Λ_M (1 × 10^{-3} M, methanol): 5.0 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1}cm^{-1})]: 205 (20383) π–π* (aromatic), 285 (5340) π–π* (C=N), 385 (2935) n–π* (C=N); IR (KBr) cm^{-1}: 3073 ν(OH$_{Alcohol}$), 1597 ν(C=N), 1259 ν(C–O$_{Arom}$), 1146 ν(C–F), 1016 ν(C–O$_{Prim}$); ^{1}H NMR (300.52 MHz, DMSO-d_6) δ: 2.45 (3H, s, H-14), 4.80 (2H, s, H-15), 5.47 (1H, s, H-16), 7.07 (2H, d, J = 5.71 Hz, H-9, H-7), 7.50 (1H, d, J = 9.52 Hz, H-10), 7.99 (1H, s, H-3), 9.23 (1H, s, H-5), 10.13 (1H, s, H-13), 14.52 (1H, s, H-11); MS: (FAB$^+$) [*m/z*] (%): [M$^+$+1, 277] (7); HR-MS (FAB$^+$) *m/z*: 277.0988 (Calc. for $C_{14}H_{14}N_2O_3F$), observed: 277.0992.

5-Hydroxymethyl-4-[(2-hydroxy-5-methoxyphenyl)iminomethyl]-2-methylpyridin-3-ol (**1e**).

This compound was synthesized from 0.0450 g (0.8034 mmol) of potassium hydroxide, 0.1636 g pyridoxal hydrochloride (0.0450 mmol), 0.1118 g of 2-amino-4-methoxyphenol (0.8034 mmol). Compound **1e** was obtained as a dark orange solid (0.1962 g, 85%); m.p. 223–225^{o}C (dec.); Molar conductance, Λ_M (1 × 10^{-3} M, methanol): 75.0 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 205 (21647), π–π* (aromatic), 276 (6400) π–π* (C=N), 394 (3342) n–π* (C=N); IR (KBr) cm^{-1}: 3063 ν(OH$_{Alcohol}$), 1613 ν(C=N), 1194 ν(C–O$_{Arom}$), 1151 ν(C–OCH$_3$), 1016 ν(C–O$_{Prim}$); ^{1}H NMR (300.52 MHz, DMSO-d_6) δ: 2.45 (3H, s, H-14), 3.76 (3H, s, H-17), 4.81 (2H, s, H-15), 5.61 (1H, s, H-16), 6.85 (1H, dd, J = 1.53 Hz, J = 8.72 Hz, H-9), 6.98 (1H, d, J = 8.72 Hz, H-10), 7.17 (1H, d, J = 1.80 Hz, H-7), 7.95 (1H, s, H-3), 9.24 (1H, s, H-5), 9.77 (1H, s, H-13), 15.09 (1H, s, H-11); ^{13}C NMR (75.57 MHz, DMSO-d_6)δ: 158.5 (C-5), 155.0 (C-13a), 153.2 (C-10a), 148.6 (C-4), 146.3 (C-8), 136.6 (C-3), 134.4 (C-4a), 133.8 (C-6a), 120.7 (C-1), 117.7 (C-

10), 115.8 (C-9), 105.1 (C-7), 58.7 (C-17), 56.2 (C-15), 18.8 (C-14); MS: (FAB^+) [*m/z*] (%): [M^++1, 289] (12); HR-MS (FAB^+) *m/z*: 289.1188 (Calc. for $C_{15}H_{17}N_2O_4$), observed: 289.1191.

2.4 General procedure for the synthesis of the complexes

To a solution of potassium hydroxide in 50 mL of toluene/methanol (60:40) mixture, pyridoxal hydrochloride, the corresponding ortho-aminophenol-5-R-substituted and the corresponding diorganotin(IV) oxide in a stoichiometric ratio were added. The reaction mixtured was refluxed for 8h for bis(trimethylsilyl)methyl tin(IV) oxide and 48 h for dicyclohexyltin(IV) oxide. It was then filtered to remove the potassium chloride and the solvent removed under reduced pressure to afford the resultant compound as a solid. All complexes had intense color and were soluble in most common organic solvents. They were purified by crystallization from chlorform or methanol solutions.

12,12-Dicyclohexyl-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2a**).

Compound **2a** was prepared from 0.0372 g of potassium hydroxide (0.6644 mmol), 0.1352 g pyridoxal hydrochloride (0.6644 mmol), 0.0725 g of 2-aminophenol (0.6644 mmol) and 0.2 g of dicyclohexyl tin(IV) oxide (0.6644 mmol), affording 0.2596 g (72%) of a dark red solid; m.p. 168–170 ^oC (dec.); Molar conductance, Λ_M (1 × 10^{-3} M, methanol): 6.5 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (39625) π–π* (aromatic), 317 (6604) π–π* (C=N), 472 (10966) n–π* (C=N); IR (KBr) cm^{-1}: 3153 ν($OH_{Alcohol}$), 1589 ν(C=N), 1180 ν(C–O_{Arom}), 1021 ν(C–O_{Prim}), 592 ν(Sn-C), 527 ν(Sn–O), 408 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.26–2.13 (22H, m, H-α, β, γ, δ), 2.41 (3H, s, H-14), 4.75 (2H, s, H-15), 5.61 (1H, s, H-16), 6.67 (1H, t, *J* = 7.51 Hz, H-9), 6.86 (1H, d, *J* = 8.41 Hz, H-10), 7.19 (1H, t, *J* = 7.51 Hz, H-8), 7.39 (1H, d, *J* = 8.71 Hz, H-7), 7.43 (1H, s, H-3), 9.46 (1H, s, $^3J(^1H\text{-}^{119/117}Sn)$ = 42 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 162.2

(C-13a), 160.5 (C-10a), 158.8 (C-5), 156.3 (C-4), 133.4 (C-3), 132.8 (C-4a), 132.2 (C-6a), 131.2 (C-8), 119.0 (C-10), 118.1 (C-1), 116.8 (C-9), 115.7 (C-7), 60.9 (C-15), 40.5 (C-α), 30.04, 29.99 (C-β, $^{2}J(^{119}Sn\text{-}^{13}C)$ = 26 Hz), 28.61, 28.57 (C-γ, $^{3}J(^{119}Sn\text{-}^{13}C)$ = 86 Hz), 26.6 (C-δ), 19.4 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -252; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -268; MS: (FAB^+) [*m/z*] (%): [M^++1, 543] (100), [M^+-2Cy, 377] (37), [M^+-CH_2OH, 346] (8); HR-MS (FAB^+) m/z: 543.1670 (Calc. for $C_{26}H_{35}N_2O_3Sn$), observed: 543.1681.

12,12-Dicyclohexyl-8-fluoro-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazaestanonine (**2b**).

Compound **2b** was synthesized from 0.0372 g of potassium hydroxide (0.6644 mmol), 0.1352 g of pyridoxal hydrochloride (0.6644 mmol), 0.0844 g of 2-amino-4-fluorophenol (0.6644 mmol) and 0.2 g of dicyclohexyltin(IV) oxide (0.6644 mmol), to give 0.2871 g (77%) of a dark red solid; m.p. 162–164 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 7.3 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (43253) π–π* (aromatic), 287 (9335) π–π* (C=N), 482 (12597) n–π* (C=N); IR (KBr) cm^{-1}: 3158 $\nu(OH_{Alcohol})$, 1594 ν(C=N), 1253 ν(C-F), 1187 $\nu(C\text{–}O_{Arom})$, 1023 $\nu(C\text{–}O_{Prim})$, 619 ν(Sn–C), 541 ν(Sn–O), 409 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.28–2.17 (22H, m, H-α, β, γ, δ), 2.46 (3H, s, H-14), 3.99 (1H, s, H-16), 4.80 (2H, s, H-15), 6.83 (1H, dd, *J* = 5.40 Hz, *J* = 9.01 Hz, H-10), 6.96 (1H, td, *J* = 2.40 Hz, *J* = 8.56 Hz, H-7), 7.13 (1H, dd, *J* = 2.40 Hz, *J* = 9.31 Hz, H-9), 7.54 (1H, s, H-3), 9.33 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn)$ = 40 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 162.4 (C-13a), 159.3 (C-5), 156.4 (C-4), 156.9 (C-10a), 154.5 (d, $^{1}J(^{13}C\text{-}^{19}F)$ = 237 Hz, C-8), 133.6 (C-3), 132.8 (C-4a), 131.5 (d, $^{3}J(^{13}C\text{-}^{19}F)$ = 8.84 Hz, C-6a), 119.3 (d, $^{3}J(^{13}C\text{-}^{19}F)$ = 7.86 Hz, C-10), 118.3 (C-1), 118.2 (d, ^{2}J = 22.59 Hz, C-7), 102.3 (d, $^{2}J(^{13}C\text{-}^{19}F)$ = 24.93 Hz, C-9), 60.9 (C-15), 40.7 (C-α), 30.00, 29.96 (C-β, $^{2}J(^{119}Sn\text{-}^{13}C)$ = 26 Hz), 28.59, 28.55 (C-γ, $^{3}J(^{119}Sn\text{-}^{13}C)$ = 81 Hz), 26.5 (C-δ), 19.4 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -246; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -268; MS: (FAB^+) [*m/z*] (%): [M^++1, 561] (100), [M^+-2Cy, 395] (5); HR-MS (FAB^+) *m/z*: 561.1575 (Calc. for $C_{26}H_{34}N_2O_3SnF$), observed: 561.1576.

12,12-Dicyclohexyl-8-chloro-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2c**).

Compound **2c** was obtained from 0.0372 g potassium hydroxide (0.6644 mmol), 0.1352 g of pyridoxal hydrochloride (0.6644 mmol), 0.0953 g of 2-amino-4-chlorophenol (0.6644 mmol) and 0.2 g of dicyclohexyltin (IV) oxide (0.6644 mmol), affording 0.3266 g (85%) of a dark brown solid; m.p. 175–177 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 3.9 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (40155), π–π* (aromatic), 287 (8439), π–π* (C=N), 479 (10885) n–π* (C=N); IR (KBr) cm^{-1}: 3177 ν(OH$_{Alcohol}$), 1588 ν(C=N), 1179 ν(C–O$_{Arom}$), 1070 ν(C–Cl), 1040 ν(C–O$_{Prim}$), 536 ν(Sn–C), 517 ν(Sn–O), 406 ν(Sn–N); ^{1}H NMR (300.52 MHz, CDCl$_3$) δ: 1.26–2.15 (22H, m, H-α, β, γ, δ), 2.42 (3H, s, H-14), 4.77 (2H, s, H-15), 6.79 (1H, d, J = 8.72 Hz, H-10), 7.14 (1H, d, J = 8.72 Hz, H-9), 7.34 (1H, s, H-7), 7.48 (1H, s, H-3), 9.35 (1H, s, ^3J(^{1}H-$^{119/117}$Sn) = 40 Hz, H-5); ^{13}C NMR (75.57 MHz, CDCl$_3$) δ: 162.4 (C-13a), 159.6 (C-5), 159.2 (C-10a), 156.4 (C-4), 133.9 (C-3), 132.9 (C-4a), 132.7 (C-6a), 130.9 (C-9), 121.4 (C-8), 120.0 (C-10), 117.9 (C-1), 115.7 (C-7), 60.7 (C-15), 40.7 (C-α, ^1J(^{119}Sn-^{13}C) = 576 Hz), 30.00, 29.97 (C-β), 28.60, 28.57 (C-γ, ^3J(^{119}Sn-^{13}C) = 80 Hz), 26.5 (C-δ), 19.4 (C-14); ^{119}Sn NMR (112.07 MHz, CDCl$_3$) δ: -248; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -273; MS: (FAB$^+$) [*m/z*] (%): [M$^+$+1, 577] (80), [M$^+$-2Cy, 411] (22), [M$^+$-*CH$_2$OH*, 380] (12); HR-MS (FAB$^+$) *m/z*: 577.1280 (Calc. for $C_{26}H_{34}N_2O_3SnCl$), observed: 577.1276.

12,12-Dicyclohexyl-4-hydroxymethyl-1,8-dimethylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2d**).

Compound **2d** was prepared from 0.0372 g of potassium hydroxide(0.6644 mmol), 0.1352 g of pyridoxal hydrochloride (0.6644 mmol), 0.0818 g of 2-amino-4-methylphenol (0.6644 mmol) and 0.2 g of dicyclohexyltin (IV) oxide (0.6644 mmol), to give 0.3132 g (85%) of a dark red solid; m.p. 200–202 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 5.7 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (49776), 285 (8357) π–π* (aromatic), 320

(8724) π–π* (C=N), 483 (13494) n–π* (C=N); IR (KBr) cm^{-1}: 3197 $\nu(OH_{Alcohol})$, 1589 ν(C=N), 1182 $\nu(C–O_{Arom})$, 1069 $\nu(C–O_{Prim})$, 540 ν(Sn–C), 518 ν(Sn–O), 477 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.25–2.15 (22H, m, H-α, β, γ, δ), 2.30 (3H, s, H-17), 2.43 (3H, s, H-14), 4.77 (2H, s, H-15), 5.30 (1H, s, H-16), 6.78 (1H, d, *J*=8.41 Hz, H-10), 7.04 (1H, d, *J*=8.11 Hz, H-9), 7.17 (1H, s, H-7), 7.50 (1H, s, H-3), 9.35 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn) = 42$ Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 162.0 (C-13a), 158.4 (C-10a), 158.2 (C-5), 156.0 (C-4), 133.7 (C-3), 132.9 (C-4a), 132.3 (C-9), 131.7 (C-6a), 126.2 (C-8), 118.7 (C-10), 118.3 (C-1), 115.7 (C-7), 60.9 (C-15), 40.3 (C-α), 30.05, 30.00 (C-β), 28.61, 28.57 (C-γ), 26.6 (C-δ), 20.9 (C-17), 19.3 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$)δ: -251; ^{119}Sn NMR (112.07 MHz, DMSO-d_6)δ: -485; MS: (FAB^+) [*m/z*] (%): [M^++1, 557] (100), [M^+-2Cy, 391] (36), [M^+-CH_2OH, 360] (5); HR-MS (FAB^+) [*m/z*] (%): 557.1826 (Calc. for $C_{27}H_{37}N_2O_3Sn$), observed: 557.1840.

12,12-Dicyclohexyl-4-hydroxymethyl-8-methoxy-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2e**).

Compound **2e** was obtained from 0.0372 g of potassium hydroxide(0.6644 mmol), 0.1352 g of pyridoxal (0.6644 mmol), 0.0924 g of 2-amino-4-methoxyphenol (0.6644 mmol) and 0.2 g of dicyclohexyltin (IV) oxide (0.6644 mmol), affording 0.3211 g (93%) of a dark purple solid; m.p. 179–181 ^{o}C (dec.); Molar conductance, Λ_M ($1X10^{-3}$ M, methanol): 5.9 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (31798) π–π* (aromatic), 293 (6645) π–π* (C=N), 498 (7419) n–π* (C=N); IR (KBr) cm^{-1}: 3190 $\nu(OH_{Alcohol})$, 1595 ν(C=N), 1221 $\nu(C–O_{Arom})$, 1149 $\nu(C–OCH_3)$, 1026 $\nu(C–O_{Prim})$, 549 ν(Sn–C), 512 ν(Sn–O), 420 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.26-2.12 (22H, m, H-α, β, γ, δ), 2.43 (3H, s, H-14), 3.79 (3H, s, H-17), 4.77 (2H, s, H-15), 6.82 (1H, d, *J*=8.72 Hz, H-10), 6.87 (1H, d, *J* = 2.40 Hz, H-7), 6.91 (1H, dd, *J* = 2.40 Hz, *J* = 8.72 Hz, H-9), 7.54 (1H, s, H-3), 9.31 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn) = 41$ Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 162.2 (C-13a), 158.3 (C-5), 156.5 (C-4), 155.2 (C-10a), 151.1 (C-8), 134.0 (C-3), 132.3 (C-4a), 131.6 (C-6a), 119.3 (C-10), 118.2 (C-7), 118.0 (C-1), 100.7 (C-9), 61.1 (C-15), 56.2 (C-17), 40.4 (C-α), 30.04, 29.99 (C-β, $^{2}J(^{119}Sn\text{-}^{13}C) = 27$ Hz), 28.62, 28.57

(C-γ, $^{3}J(^{119}Sn\text{-}^{13}C) = 80$ Hz), 26.6 (C-δ), 19.6 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -248; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -475; MS: (FAB^+) [*m/z*] (%): [M^++1, 573] (17), [M^+-2Cy, 407] (9); HR-MS (FAB^+) *m/z*: 573.1775 (Calc. for $C_{27}H_{37}N_2O_4Sn$), observed: 573.1784.

12,12-Dicyclohexyl-4-hydroxymethyl-1-methyl-8-nitrobenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2f**).

Compound **2f** was synthesized 0.0372 g (0.6644 mmol) of potassium hydroxide, 0.1352 g of pyridoxal (0.6644 mmol), 0.1024 g of 2-amino-4-nitrophenol (0.6644 mmol) and 0.2 g of dicyclohexyltin(IV) oxide (0.6644 mmol), to give 0.2894 g (74%) of a light red solid; m.p. 240–242°C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 4.1 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 206 (26253) π–π* (aromatic), 340 (11415) π–π* (C=N), 434 (10395) n–π* (C=N); IR (KBr) cm^{-1}: 3093 *ν*($OH_{Alcohol}$), 1589 *ν*(C=N), 1305 *ν*(NO_2), 1265 *ν*(C–O_{Arom}), 1042 *ν*(C–O_{Prim}), 542 *ν*(Sn–C), 504 *ν*(Sn–O), 415 *ν*(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.26–2.25 (22H, m, H-α, β, γ, δ), 2.45 (3H, s, H-14), 4.88 (2H, s, H-15), 6.85 (1H, d, *J* = 9.32 Hz, H-10), 7.64 (1H, s, H-3), 8.12 (1H, dd, *J* = 2.40 Hz, *J* = 9.02 Hz, H-9), 8.34 (1H, d, *J* = 2.40 Hz, H-7), 9.56 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn) = 38$ Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 166.8 (C-10a), 162.7 (C-13a), 162.1 (C-5), 156.6 (C-4), 137.3 (C-8), 134.2 (C-3), 133.0 (C-4a), 131.8 (C-6a), 126.8 (C-9), 118.5 (C-10), 117.7 (C-1), 112.8 (C-7), 60.6 (C-15), 41.3 (C-α), 29.93, 29.91 (C-β), 28.57, 28.54 (C-γ, $^{3}J(^{119}Sn\text{-}^{13}C) = 84$ Hz), 26.4 (C-δ), 19.4 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -244; ^{119}Sn NMR (112.07 MHz, DMSO-d_6)δ: -290; MS: (FAB^+) [*m/z*] (%): [M^++1, 588] (57), [M^+-2Cy, 422] (12), [M^+-CH_2OH, 391] (7); HR-MS (FAB^+) *m/z*: 588.1520 (Calc. for $C_{26}H_{34}N_3O_5Sn$), observed: 588.1514.

12,12-Dicyclohexyl-8-*t*-butyl-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**2g**).

Compound **2g** was prepared from 0.0372 g of potassium hydroxide (0.6644 mmol), 0.1352 g of pyridoxal hydrochloride (0.6644 mmol), 0.1097 g of 2-amino-4-*tert*-

butylphenol (0.6644 mmol) and 0.2 g of dicyclohexyltin(IV) oxide (0.6644 mmol), affording 0.3143 g (79%) of a light red solid; m.p. 75–77 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 57.0 ohm^{-1} cm^{2} mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (34244), 281 (5789) π–π* (aromatic), 318 (5422) π–π* (C=N), 481 (8316) n–π* (C=N); IR (KBr) cm^{-1}: 3222 ν(OH$_{Alcohol}$), 1595 ν(C=N), 1263 ν(C–O$_{Arom}$), 1024 ν(C–O$_{Prim}$), 548 ν(Sn–C), 516 ν(Sn–O), 456 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 1.32 (9H, s, H-18), 1.54–2.12 (22H, m, H-α, β, γ, δ), 2.43 (3H, s, H-14), 4.78 (2H, s, H-15), 6.82 (1H, d, J = 8.41 Hz, H-10), 7.29 (1H, dd, J = 1.80 Hz, J = 8.71 Hz, H-9), 7.38 (1H, d, J = 1.80 Hz, H-7), 7.46 (1H, s, H-3), 9.47 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn)$ = 43 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 162.1 (C-13a), 158.4 (C-10a), 158.0 (C-5), 155.7 (C-4), 139.8 (C-4a), 133.3 (C-3), 133.2 (C-8), 131.1 (C-6a), 128.9 (C-9), 118.6 (C-1), 118.5 (C-10), 111.9 (C-7), 60.9 (C-15), 40.4 (C-α), 34.3 (C-17), 31.5 (C-18), 30.05, 29.99 (C-β, $^{2}J(^{119}Sn\text{-}^{13}C)$ = 26 Hz), 28.63, 28.58 (C-γ), 26.6 (C-δ), 19.2 (C-14); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -251; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -263; MS: (FAB^{+}) [*m/z*] (%): [M^{+}+1, 599] (36), [M^{+}-2Cy, 433] (10); HR-MS (FAB^{+}) *m/z*: 599.2296 (Calc. for $C_{30}H_{43}N_2O_3Sn$), observed: 599.2301.

12,12-Bis[(trimethylsilyl)methyl]-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3a**).

Compound **3a** was synthesized from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0706 g of 2-aminophenol (0.6469 mmol) and 0.2 g of bis(trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), affording 0.2605 g (73%) of a light red solid; m.p. 134–136 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 11.0 ohm^{-1} cm^{2} mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 206 (21891) π–π* (aromatic), 324 (4117) π–π* (C=N), 469 (6971) n–π* (C=N); IR (KBr) cm^{-1}: 3129 ν(OH$_{Alcohol}$), 1590 ν(C=N), 1186 ν(C–O$_{Arom}$), 1020 ν(C–O$_{Prim}$), 828 ν(Si–CH$_3$), 532 ν(Sn–C), 515 ν(Sn–O), 407 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si(C$\underline{H}$)$_3$), 0.45 (4H, s, $\underline{CH_2}$-Si(CH)$_3$), 2.51 (3H, s, H-14), 4.86 (2H, s, H-15), 6.72 (1H, t, J = 7.51 Hz, H-9), 6.81 (1H, d, J = 7.81 Hz, H-10), 7.24 (1H, t, J = 7.51 Hz, H-

8), 7.46 (1H, d, J = 8.11 Hz, H-7), 7.69 (1H, s, H-3), 9.39 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn)$ = 41 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 159.9 (C-13a), 158.2 (C-10a), 157.2 (C-5), 154.8 (C-4), 132.1 (C-3), 131.8 (C-4a), 130.5 (C-8), 130.1 (C-6a), 118.1 (C-10), 117.2 (C-1), 116.0 (C-9), 114.5 (C-7), 59.7 (C-15), 18.1 (C-14), 7.0 ($\underline{CH_2}$-Si$(CH)_3$), 0.0 (CH_2-Si$(\underline{CH})_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -149; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -161; MS: (FAB$^+$) [m/z] (%): [M$^+$+1, 551] (100), [M$^+$-(CH_2-Si$(CH_3)_3)_2$, 377] (37), [M$^+$-*CH_2OH*, 346] (8); HR-MS (FAB$^+$) m/z: 551.1208 (Calc. for $C_{22}H_{35}N_2O_3Si_2Sn$), observed: 551.1198.

12,12-Bis[(trimethylsilyl)methyl]-8-fluoro-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3b**).

Compound **3b** was obtained from 0.0362 g of potassium hydroxide(0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0822 g of 2-amino-4-fluorophenol (0.6469 mmol) and 0.2 g of bis(trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), to give 0.2756 g (75%) of a dark red solid; m.p. 140–142 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 11.0 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (41378) π–π* (aromatic), 284 (10273) π–π* (C=N), 482 (15124) n–π* (C=N); IR (CsI) cm^{-1}: 3130 ν($OH_{Alcohol}$), 1597 ν(C=N), 1248 ν(C–F), 1188 ν(C–O_{Arom}), 1015 ν(C–O_{Prim}), 832 ν(Si–CH_3), 616 ν(Sn–C), 538 ν(Sn–O), 415 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si$(\underline{CH})_3$), 0.43 (4H, s, $\underline{CH_2}$-Si$(CH)_3$), 2.42 (3H, s, H-14), 4.00 (1H, s, H-16), 4.80 (2H, s, H-15), 6.77 (1H, dd, J = 4.81 Hz, J = 8.41 Hz, H-10), 6.96 (1H, dd, J = 6.31 Hz, J = 8.11 Hz, H-9), 7.16 (1H, d, J = 6.61 Hz, H-7), 7.55 (1H, s, H-3), 9.33 (1H, s, $^{3}J(^{1}H\text{-}^{119/117}Sn)$ = 45 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 160.1 (C-13a), 158.2 (C-5), 155.0 (C-10a), 154.5 (C-4), 153.4 (d, $^{1}J(^{13}C\text{-}^{19}F)$ = 236.84 Hz, C-8), 132.3 (C-3), 131.9 (C-4a), 129.5 (d, $^{3}J(^{13}C\text{-}^{19}F)$ = 8.99 Hz, C-6a), 118.4 (d, $^{3}J(^{13}C\text{-}^{19}F)$ = 7.48 Hz, C-10), 117.4 (d, $^{2}J(^{13}C\text{-}^{19}F)$ = 23.12 Hz, C-9), 117.0 (C-1), 101.1 (d, $^{2}J(^{13}C\text{-}^{19}F)$ = 25.77 Hz, C-7), 59.6 (C-15), 18.2 (C-14), 7.2 ($\underline{CH_2}$-Si$(CH)_3$), 0.0 (CH_2-Si$(\underline{CH})_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -142; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -157; MS: (FAB$^+$) [m/z] (%): [M$^+$+1, 569] (100), [M$^+$-(CH_2-

$Si(CH_3)_3)_2$, 395] (5); HR-MS (FAB^+) *m/z*: 569.1114 (Calc. for $C_{22}H_{34}N_2O_3Si_2SnF$), observed: 569.1115.

12,12-Bis[(trimethylsilyl)methyl]-8-chloro-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3c**).

Compound **3c** was prepared from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0928 g of 2-amino-4-chlorophenol (0.6469 mmol) and 0.2 g of bis(trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), affording 0.2866 g (76%) of a light red solid; m.p. 145–147 ^oC (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 50.0 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (30045) π–π* (aromatic), 283 (6807), 314 (5789) π–π* (C=N), 478 (9499) n–π*(C=N); IR (CsI) cm^{-1}: 3150 $\nu(OH_{Alcohol})$, 1600 ν(C=N), 1251 $\nu(C–O_{Arom})$, 1077 $\nu(C–O_{Prim})$, 1025 ν(C–Cl), 837 $\nu(Si–CH_3)$, 678 ν(Sn–C), 541 ν(Sn–O), 413 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si($\underline{CH}$)$_3$), 0.44 (4H, s, $\underline{CH_2}$-Si(CH)$_3$), 2.43 (3H, s, H-14), 4.81 (2H, s, H-15), 6.75 (1H, d, J = 9.02 Hz, H-10), 7.16 (1H, d, J = 8.72 Hz, H-9), 7.39 (1H, s, H-7), 7.58 (1H, s, H-3), 9.34 (1H, s, $^3J(^1H$-$^{119/117}Sn)$ = 46 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 160.1 (C-13a), 157.9 (C-5), 156.9 (C-10a), 153.9 (C-4), 133.2 (C-4a), 130.9 (C-3), 130.5 (C-9), 127.8 (C-6a), 120.7 (C-8), 119.1 (C-10), 117.9 (C-1), 114.7 (C-7), 59.0 (C-15), 17.4 (C-14), 7.3 ($\underline{CH_2}$-Si(CH)$_3$), 0.0 (CH_2-Si($\underline{CH}$)$_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -143, ($^1J(^{119}Sn$-$^{13}C)$ = 503 Hz; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -159; MS: (FAB^+) [*m/z*] (%): [M^++1, 585] (100), [M^+- $(CH_2$-$Si(CH_3)_3)_2$, 411] (15), [M^+-CH_2OH, 380] (5); HR-MS (FAB^+) *m/z*: 585.0819 (Calc. for $C_{22}H_{34}N_2O_3Si_2SnCl$), observed: 585.0818.

12,12-Bis[(trimethylsilyl)methyl]-4-hydroxymethyl-1,8-dimethylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3d**).

Compound **3d** was synthesized from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0796 g of 2-amino-4-methylphenol (0.6469 mmol) and 0.2 g of bis(trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), to give 0.2099 g (58%) of a dark red solid; m.p. 168–170 ^oC (dec.);

Molar conductance, Λ_M (1×10^{-3} M, methanol): 4.3 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (33143) π–π* (aromatic), 324 (5911) π–π* (C=N), 482 (10395) n–π* (C=N); IR (CsI) cm^{-1}: 3128 $\nu(OH_{Alcohol})$, 1594 ν(C=N), 1250 $\nu(C–O_{Arom})$, 1018 $\nu(C–O_{Prim})$, 830 $\nu(Si–CH_3)$, 544 ν(Sn–C), 481 ν(Sn–O), 407 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si(CH)$_3$), 0.42 (4H, s, CH_2-Si(CH)$_3$), 2.31 (3H, s, H-17), 2.42 (3H, s, H-14), 4.80 (2H, s, H-15), 6.73 (1H, d, J = 8.41 Hz, H-10), 7.05 (1H, d, J = 8.41 Hz, H-9), 7.20 (1H, s, H-7), 7.54 (1H, s, H-3), 9.36 (1H, s, $^3J(^1H-^{119/117}Sn)$ = 48 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 159.7 (C-13a), 156.9 (C-5), 156.0 (C-10a), 155.2 (C-4), 132.9 (C-3), 131.4 (C-9), 131.3 (C-4a), 129.5 (C-6a), 125.2 (C-8), 117.7 (C-10), 116.9 (C-1), 114.3 (C-7), 59.8 (C-15), 19.7 (C-14), 18.4 (C-17), 6.9 (CH_2-Si(CH)$_3$), 0.0 (CH_2-Si(CH)$_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -149; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -159; MS: (FAB$^+$) [*m/z*] (%): [M^++1, 565] (100), [M^+-(CH_2-$Si(CH_3)_3)_2$, 391] (10), [M^+-CH_2OH, 360] (5); HR-MS (FAB$^+$) [*m/z*] (%): 565.1365 (Calc. for $C_{23}H_{37}N_2O_3Si_2Sn$), observed: 565.1363.

12,12-Bis[(trimethylsilyl)methyl]-4-hydroxymethyl-8-methoxy-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3e**).

Compound **3e** was obtained from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0900 g of 2-amino-4-methoxyphenol (0.6469 mmol) and 0.2 g of bis (trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), affording 0.3298 g (88%) of a dark purple solid; m.p. 120–121 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 4.1 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 206 (29759), 293 (5544) π–π* (aromatic), 323 (4892) π–π* (C=N), 504 (7583) n–π* (C=N); IR (CsI) cm^{-1}: 3165 $\nu(OH_{Alcohol})$, 1596 ν(C=N), 1250 $\nu(C–O_{Arom})$, 1146 $\nu(C–OCH_3)$, 1032 $\nu(C–O_{Prim})$, 828 $\nu(Si–CH_3)$, 608 ν(Sn–C), 517 ν(Sn–O), 412 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si(CH)$_3$), 0.42 (4H, s, CH_2-Si(CH)$_3$), 2.42 (3H, s, H-14), 3.80 (3H, s, H-17), 4.80 (2H, s, H-15), 6.77 (1H, d, J = 9.02 Hz, H-10), 6.89 (1H, dd, J = 2.40 Hz, J = 9.01 Hz, H-9), 6.94 (1H, s, H-7), 7.58 (1H, s, H-3), 9.31 (1H, s, $^3J(^1H-^{119/117}Sn)$ = 47 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 159.7 (C-13a),

157.2 (C-5), 155.6 (C-10a), 152.8 (C-4), 150.0 (C-8), 133.3 (C-3), 130.9 (C-4a), 129.5 (C-6a), 118.3 (C-10), 117.3 (C-9), 116.6 (C-1), 99.3 (C-7), 59.9 (C-15), 54.9 (C-17), 18.7 (C-14), 6.9 ($\underline{CH_2}$-Si$(CH)_3$), 0.0 (CH_2-Si$(\underline{CH})_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -146; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -157; MS: (FAB$^+$) [*m/z*] (%): [M$^+$+1, 581] (100), [M$^+$-(CH_2-Si$(CH_3)_3)_2$, 407] (10); HR-MS (FAB$^+$) *m/z*: 581.1314 (Calc. for $C_{23}H_{37}N_2O_4Si_2Sn$), observed: 581.1306.

12,12-Bis[(trimethylsilyl)methyl]-4-hydroxymethyl-1-methyl-8-nitrobenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3f**).

Compound **3f** was prepared from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g of pyridoxal hydrochloride (0.6469 mmol), 0.0997 g of 2-amino-4-nitrophenol (0.6469 mmol) and 0.2 g of bis (trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), giving 0.2960 g (77%) of a dark yellow solid; m.p. 183–185 ^oC (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 7.1 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 206 (28740) π–π* (aromatic), 348 (13983) π–π* (C=N), 463 (12108) n–π* (C=N); IR (CsI) cm^{-1}: 3185 ν($OH_{Alcohol}$), 1603 ν(C=N), 1305 ν(NO_2), 1243 ν(C–O_{Arom}), 1013 ν(C–O_{Prim}), 830 ν(Si–CH_3), 533 ν(Sn–C), 504 ν(Sn–O), 419 ν(Sn–N); ^{1}H NMR (300.52 MHz, $CDCl_3$) δ: 0.00 (18H, s, CH_2-Si$(\underline{CH})_3$), 0.49 (4H, s, $\underline{CH_2}$-Si$(CH)_3$), 2.45 (3H, s, H-14), 4.90 (2H, s, H-15), 6.81 (1H, d, *J* = 8.41 Hz, H-10), 7.72 (1H, s, H-3), 8.13 (1H, d, *J* = 8.41 Hz, H-9), 8.38 (1H, s, H-7), 9.54 (1H, s, ^3J(^{1}H-$^{119/117}$Sn) = 43 Hz, H-5); ^{13}C NMR (75.57 MHz, $CDCl_3$) δ: 164.2 (C-10a), 160.8 (C-5), 160.5 (C-13a), 155.1 (C-4), 136.5 (C-8), 132.4 (C-4a), 132.3 (C-3), 129.7(C-6a), 126.0 (C-9), 117.6 (C-10), 117.1 (C-1), 111.7 (C-7), 59.4 (C-15), 18.0 (C-14), 7.4 ($\underline{CH_2}$-Si$(CH)_3$), 0.0 (CH_2-Si$(\underline{CH})_3$); ^{119}Sn NMR (112.07 MHz, $CDCl_3$) δ: -138; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -163; MS: (FAB$^+$) [*m/z*] (%): [M$^+$+1, 596] (100), [M$^+$-(CH_2-Si$(CH_3)_3)_2$, 422] (7); HR-MS (FAB$^+$) *m/z*: 596.1059 (Calc. for $C_{22}H_{34}N_3O_5Si_2Sn$), observed: 596.1076.

12,12-Bis[(trimethylsilyl)methyl]-8-*t*-butyl-4-hydroxymethyl-1-methylbenzo[d]-pyrido[4,3-h]-11,13,2,6-dioxazastannonine (**3g**).

Compound **3g** was synthetized from 0.0362 g of potassium hydroxide (0.6469 mmol), 0.1317 g pyridoxal hydrochloride (0.6469 mmol), 0.1068 g of 2-amino-4-*tert*-butylphenol (0.6469 mmol) and 0.2 g of bis (trimethylsilyl)methyl tin(IV) oxide (0.6469 mmol), affording 0.2784 g (71%) of a dark red solid; m.p. 103–105 ^{o}C (dec.); Molar conductance, Λ_M (1×10^{-3} M, methanol): 3.7 ohm^{-1} cm^2 mol^{-1} (non-electrolyte); UV-vis [methanol, λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 207 (33020) π–π* (aromatic), 282 (8031) π–π* (C=N), 478 (4729) n–π* (C=N); IR (CsI) cm^{-1}: 2952 ν(OH$_{Alcohol}$), 1575 ν(C=N), 1247 ν(C–O$_{Arom}$), 1019 ν(C–O$_{Prim}$), 831 ν(Si–CH$_3$), 539 ν(Sn–C), 513 ν(Sn–O), 409 ν(Sn–N); ^{1}H NMR (300.52 MHz, CDCl$_3$) δ: 0.00 (18H, s, CH$_2$-Si(CH)$_3$), 0.43 (4H, s, CH$_2$-Si(CH)$_3$), 1.31 (9H, s, H-18), 2.41 (3H, s, H-14), 4.81 (2H, s, H-15), 6.77 (1H, d, J = 8.72 Hz, H-10), 7.28 (1H, d, J = 9.61 Hz, H-9), 7.37 (1H, s, H-7), 7.58 (1H, s, H-3), 9.42 (1H, s, ^3J(^{1}H-$^{119/117}$Sn) = 48 Hz, H-5); ^{13}C NMR (75.57 MHz, CDCl$_3$) δ: 159.6 (C-13a), 156.8 (C-5), 155.9 (C-10a), 155.2 (C-4), 138.9 (C-8), 132.9 (C-3), 131.2 (C-4a), 129.1 (C-6a), 127.9 (C-9), 117.4 (C-10), 116.9 (C-1), 110.5 (C-7), 59.9 (C-15), 33.1 (C-17), 30.3 (C-18), 18.5 (C-14), 6.8 (CH$_2$-Si(CH)$_3$), 0.0 (CH$_2$-Si(CH)$_3$); ^{119}Sn NMR (112.07 MHz, CDCl$_3$) δ: -149; ^{119}Sn NMR (112.07 MHz, DMSO-d_6) δ: -158; MS: (FAB$^+$) [*m/z*] (%): [M$^+$+1, 607] (30), [M$^+$-(CH$_2$-Si(CH$_3$)$_3$)$_2$, 432] (10), [M$^+$-*CH$_2$OH*, 401] (8); HR-MS (FAB$^+$) *m/z*: 607.1834 (Calc. for $C_{26}H_{43}N_2O_3Si_2Sn$), observed: 607.1846.

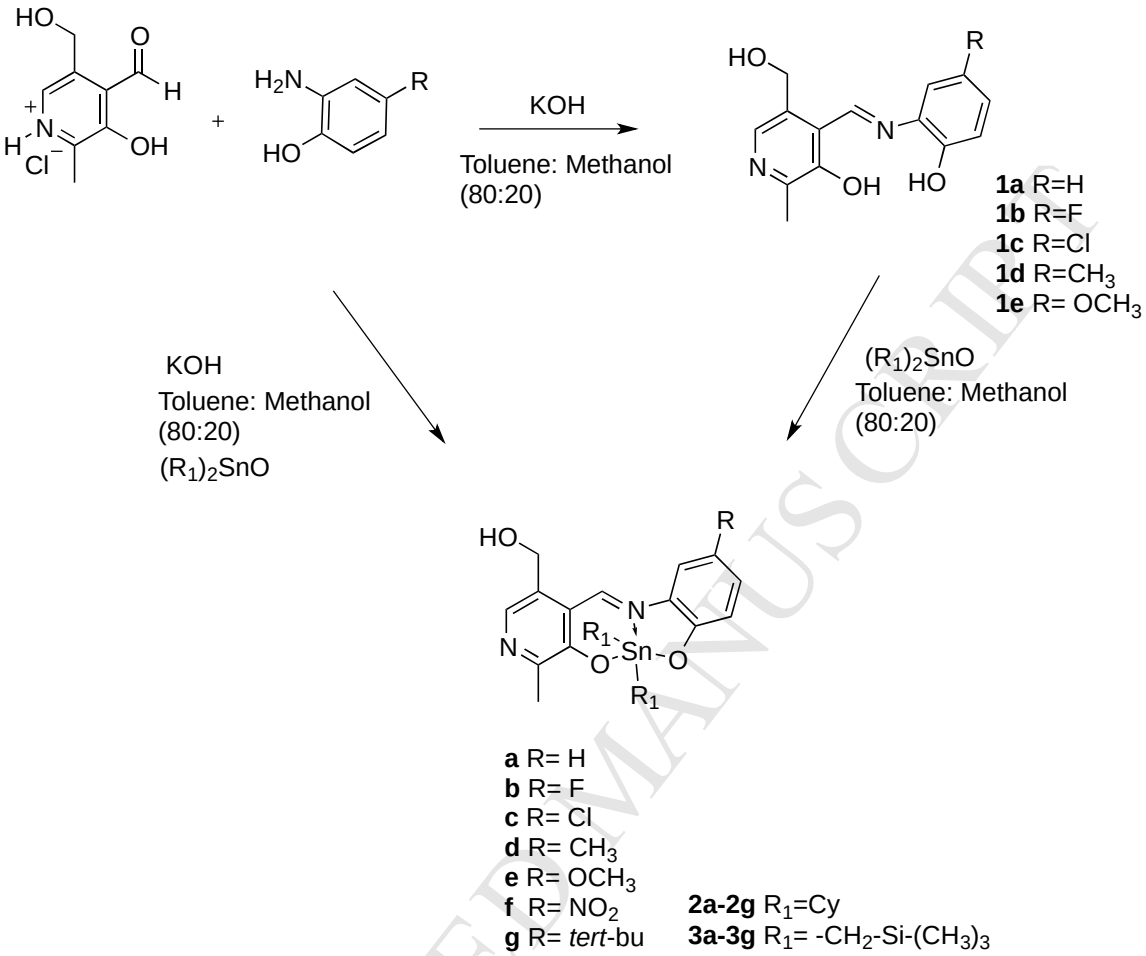
2.5 Cytotoxic Activity Assay

The cytotoxic activity was evaluated by sulforhodamine B assay,[39] using the human cancerous cell lines: U-251 (glioblastoma), K-562 (chronic myelogenous leukemia), HCT-15 (human colorectal), MCF-7 (human breast), MB-231(human breast), SKLU-1 (non-small cell lung) and cisplatin as reference.

3. Results and discussion

3.1 Synthesis

The synthetic route to the ligands and complexes is described in Scheme 1. The Schiff-base ligands **1a–e** were obtained by reaction of pyridoxal hydrochloride and the corresponding 2-amino-5-R-phenol (R=H, F, Cl, CH_3, OCH_3) in the presence of potassium hydroxide. The compounds **1a**, **1c–d** have been reported previously, using sodium methanolate as base and methanol as solvent;[27, 38] however, the methodology used by our group gives higher yields. The ligands were reacted with dicyclohexyl and bis(trimethylsilyl)methyl tin(IV) oxides, under reflux, using a toluene/methanol mixture as solvent. The expected complexes were isolated in yields of 60–65%. Attempts to isolate ligands containing $–NO_2$ and *tert*-bu substituents failed, as the pure compounds could not be isolated. Keeping this in mind and based on our previous results, we decided to use the multicomponent strategy; in this case, the yields were improved with respect to the two-step synthesis from the isolated ligands (71–93%). The obtained complexes were solids, soluble in most organic solvents, with molar conductance values from 3.7 to 57.0 Λ (ohm^{-1} cm^2 $mol^{-1)}$ indicating the non-electrolytic nature of these complexes (The electronic data are given in S1Table 1 supporting material).



Scheme 1

3.2 Electronic Absorption Spectra

The electronic spectral data for ligands **1a**–**1e**, show three main absorption bands: the first one at 206–207 nm (ε_{max} = 20628–23441 M^{-1} cm^{-1}) is due to π–π* transition of the aromatic ring; the second, at 76–287 nm (ε_{max} =5177–6400) was assigned to π–π* transition within the azomethine (C=N); and the band at 375–394 nm (ε_{max} 2935–5422) to the n–π* transition (C=N). For the metal complexes **2a–2g** and **3a–3g** the electronic spectra show the absorption bands similar to those of the ligands for transition π–π* of the aromatic ring and (C=N); however, the band due to the transition n–π* (C=N) 434–504 nm (4729–13494) is shifted lower on coordination, because of the coordination of the nitrogen atom of the azomethine (Conductivity

values are summarized in Table S1 supporting information). This shift can be attributed to overlapping of the central-metal d-orbital with the p-orbital of the donor atom.[25, 40-42] The complexes **2d**, **2g**, **3c** and **3e** also showed a band at 229–293 nm (ε_{max} = 4933–13333) associated with the charge transfer band, since it is known that metalloids and metals form dπ–pπ bonds with ligands containing nitrogen and oxygen as donor atoms. Additionally, the change of the substituent cyclohexyl to bis(oftrimethylsilyl)methyl group results in a lower molar extinction coefficient.

3.3 IR Spectra

The IR spectra of complexes **2a–g** and **3a–g** show vibrational bands in the range of 3034 to 3335 cm^{-1} which are assigned to ν(OH). The corresponding vibrational bands ν(O–H) of the free ligands appear at 2952–3222 cm^{-1}, revealing the non-participation of the hydroxyl group from the pyridoxal ring in the coordination with the metal.

The vibration bands ν(C=N) for complexes **2a–g** and **3a–g** were observed in the region of 1575–1603 cm^{-1}; a comparative analysis of complexes **2a–e** and **3a–e** with respect to the free ligands showed a shift of the stretching frequencies $\Delta\nu$(C=N) of 18 to 26 cm^{-1}. Further evidence of the bonding is given by the observation of new bands in the spectra of the metal complexes of medium or weak intensity at the region 467–435 cm^{-1} due to ν(Sn—N) stretching vibrations supporting the involvement of the nitrogen atom of the azomethine group via coordination to the tin center. Two new bands at 532–619 and 481–541 cm^{-1} are characteristic of Sn–C and Sn–O absorptions respectively, indicating the deprotonation of the phenolic hydroxyl. All these values are consistent with those detected in pyridoxamine and pyridoxal organotin compounds described previously. [25, 26, 43] For complexes **3a–g** an additional vibration band at 828–837 cm^{-1} for ν(Si-CH_3) was observed (Vibrational bands for all complexes are given in Table S2 supporting information).

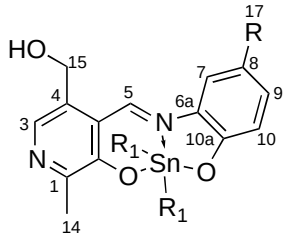
3.4 ^{1}H NMR spectra

The use of one and two-dimensional (COSY, HSQC and HMBC) NMR experiments in $CDCl_3$ allowed us to assign proton and carbon chemical shifts of the complexes in solution. The chemical shifts were in accordance with the structures depicted in Scheme 1, and the chemical shifts of complexes are summarized Table 1. A common feature upon complexation to tin was the disappearance of the phenolic hydroxyl protons at positions 11 and 13. The signal of the azomethine (CH=N) around 9.35–9.56 ppm showed the expected satellite signals due to coupling to the tin atom $^{3}J(^{119/117}Sn–^{1}H)$ with values of 38 to 48 Hz, corroborating the formation of the Sn–N coordination bond as a consequence of the complex formation.[44] All complexes showed the expected single signal at 7.43 to 7.72 ppm for the H-3 proton of the pyridoxal ring, and the well-defined signals for the aromatic ring. The protons of the methylene and hydroxyl of CH_2OH, as well as the methyl group attached to the pyridoxal ring, did not showed significant changes in the chemical shift as a consequence of the complexation, as was observed previously for pyridoxine, pyridoxamine and pyridoxal tin derivatives,[25, 26, 43] which suggest that the hydroxyl groups do not participate in the coordination with the tin. For complexes **2a–2g** multiplet signals were observed in the aliphatic region in the range 1.25–2.25 ppm for the cyclohexyl group, and for **3a**–**3g** two singlet signals were observed at 0.0–0.49 ppm for the moiety bis(trimethylsilyl)methyl bonded to the tin atom.

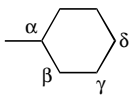
Table 1. ^{1}H NMR ($CDCl_3$, 300 MHz) data for complexes **2a**-**g**.

Compound	2a	2b	2c	2d	2e	2f	2g
H-3	7.43 (s)	7.54 (s)	7.48 (s)	7.50 (s)	7.54 (s)	7.64 (s)	7.46 (s)
H-5 (^{3}J ($^{1}H^{119/117}Sn$))	9.46 (42)	9.33 (40)	9.35 (40)	9.35 (42)	9.31 (41)	9.56 (38)	9.47 (43)
H-7	7.39 (d, *J*=8.7 Hz)	6.96 (td, *J*=2.4, 8.6 Hz)	7.34 (s)	7.17 (s)	6.87 (d, *J*=2.4 Hz)	8.34 (d, *J*=2.4 Hz)	7.38 (d, *J*=1.8 Hz)
H-8	7.19 (t, *J*=7.5 Hz)						
H-9	6.67 (t, *J*=7.5 Hz)	7.13 (dd, *J*=2.4, 9.3 Hz)	7.14 (d, *J*=8.7 Hz)	7.04 (d, *J*=8.1 Hz)	6.91 (dd, *J*=2.4, 8.7 Hz)	8.12 (dd, *J*=2.4, 9.02 Hz)	7.29 (dd, *J*=1.8, 8.7 Hz)
H-10	6.86(d, *J*=8.4 Hz)	6.83 (dd, *J*=5.4, 9.0 Hz)	6.79 (d, *J*=8.7 Hz)	6.78 (d, *J*=8.4 Hz)	6.82 (d, *J*=8.7 Hz)	6.85 (d, *J*=9.3 Hz)	6.82 (d *J*=8.4 Hz)
H-14	2.41 (s)	2.46 (s)	2.42(s)	2.43 (s)	2.43 (s)	2.45 (s)	2.43 (s)
	4.75 (s)	4.80 (s)	4.77 (s)	4.77 (s)	4.77 (s)	4.88 (s)	4.78 (s)
H-16	5.61 (s)	3.99 (s)		3.75 (s)			
H-17	5.61 (s)	3.99 (s)		3.75 (s)			
H-18				2.30 (s)	3.79 (s)		
H- Cy (α, β, γ, δ)	1.26-2.13 (m)	1.28-2.17 (m)	1.26-2.15 (m)	1.25-2.15 (m)	1.26-2.12 (m)	1.26-2.25 (m)	1.54-2.12 (m)

	3a	3b	3c	3d	3e	3f	3g
H-3	7.69(s)	7.55 (s)	7.58 (s)	7.54 (s)	7.58 (s)	7.72 (s)	7.58 (s)
H-5 (^{3}J ($^{1}H^{119/117}Sn$))	9.39 (41)	9.33 (45)	9.34 (46)	9.36 (48)	9.31 (47)	9.54 (43)	9.42 (48)
H-7	7.46 (d, *J*=8.1 Hz)	7.16 (d,*J*=6.61 Hz)	7.39 (s)	7.20 (s)	6.94 (s)	8.38 (s)	7.37 (s)
	7.24 (t. *J*=7.5 Hz)						
H-9	6.72 (t, *J*=7.5 Hz)	6.96 (dd, *J*=6.3, 8.1 Hz)	7.16 (d, *J*=8.7 Hz)	7.05 (d, *J*=8.4 Hz)	6.89 (dd, *J*=2.4, 9.0 Hz)	8.13 (d, *J*=8.4 Hz)	7.28 (d, *J*=9.6 Hz)
H-10	6.81 (d, *J*=7.8 Hz)	6.77 (dd, *J*=4.8, 8.4 Hz)	6.75 (d, *J*=9.0 Hz)	6.73 (d, *J*=8.4 Hz)	6.77 (d *J*=9.0 Hz)	6.81 (d, *J*=8.4 Hz)	6.77 (d, *J*=8.7 Hz)
H-14	2.51 (s)	2.42 (s)	2.43 (s)	2.42 (s)	2.42 (s)	2.45 (s)	2.41 (s)
H-15	4.86 (s)	4.80 (s)	4.81 (s)	4.80 (s)	4.80 (s)	4.90 (s)	4.81 (s)
H-16		4.00 (s)					
H-17				2.31 (s)	3.80(s)		
H-18							1.31 (s)
$Si(\underline{CH_3})_3$	0.00 (s)	0.00 (s)	0.00 (s)	0.00 (s)	0.00 (s)	0.00 (s)	0.00 (s)
$-\underline{CH_2}-Si(CH_3)_3$	0.45 (s)	0.43 (s)	0.44 (s)	0.42 (s)	0.42 (s)	0.49 (s)	0.43 (s)



a R= H
b R= F
c R= Cl
d R= CH_3
e R= OCH_3
f R= NO_2
g R= *tert*-bu

2a-2g R_1= 

3a-3g R_1= $-CH_2-Si(CH_3)_3$

3.5 ^{13}C NMR Spectra

The ^{13}C NMR of organotin complexes showed signals in the aliphatic region from 26.4 to 41.3 for the cyclohexyl derivatives **2a**–**2g**; for complexes **3a–g** two signals were detected: one at 0.0 ppm and the other at 6.8–7.3 ppm for the methylene and methyl groups of the bis(trimethylsilyl)methyl fragment (^{13}C NMR data for all complexes are summarized in Table S3 supplementary material) . The azomethine carbon C-5 appeared at 158.0–162.1 ppm; smaller up- and downfield effects were observed for all the carbon atoms as a consequence of the coordination both of the nitrogen atom from the azomethine, and of the phenolic groups to the tin atom. For complexes **2a–b** and **2g** it was possible to observe the coupling constants $^{2}J(^{119}\text{Sn}–^{13}\text{C})$; **2a–c** and **2e** also showed the coupling constant $^{3}J(^{119}\text{Sn}–^{13}\text{C})$. For the cyclohexyl groups attached to the tin, the obtained values are similar to those described in the literature.[32-34] The C–Sn–C bond angle of 127.3º for **2c** was calculated using the value of the coupling constant $J(^{119}\text{Sn}–^{13}\text{C})$ = 576 Hz and the Lockhart-Manders equation.[45] For complexes **3a–3g** the satellite signals due to $^{13}\text{C}–^{119}\text{Sn}$ coupling in the ^{13}C spectra were not observed.

3.6 ^{119}Sn NMR

Evidence of formation of the newly pentacoordinated heterocycle ring species was provided by ^{119}Sn NMR. It is well known that the chemical shifts of tin complexes depend not only on the coordination number but are also sensitive to the type of donor atoms bonded to the tin atom. So, the chemical shifts are an indicator of the coordination number of organotin complexes. In this case, all complexes showed a sharp singlet, revealing the formation of a single tin species. The ^{119}Sn chemical shifts for **2a**–**2g** were found in the range of –244 to –252 ppm in a non-coordinated solvent ($CDCl_3$), suggesting that the tin atom is pentacoordinated. The complexes **2a–c** and **2f–g** exhibited chemical shifts in coordinated solvent DMSO-d_6 at –263

and –290 ppm, indicative of pentacoordinate tin species (Table 2) . In contrast, the chemical shifts for complexes **2d–e** bearing $–CH_3$ and $–OCH_3$ substituents on the aromatic ring were found at –485 and –475 ppm which evidenced the formation of hexacoordinated species, due to the coordination of DMSO to the metallic center.

For complexes **3a–g,** chemical shifts in $CDCl_3$ were found at –138 and –149 ppm;– in this case non significative differences were observed when DMSO-d_6 was used as solvent the values were in the range of 157 to –163 ppm, indicating a coordination number of five. The comparative analysis of the chemical shifts for **2a–2g** and **3a–g** derivatives evidenced that the cyclohexyl group is a better sigma donor than its counterpart bis(trimethylsilyl)methyl, as has been described for pyrazolone organotin derivatives.[46]

For complex **3c** it was possible to observe the coupling constant $J(^{119}Sn–^{13}C)$ = 503 Hz; using the Lockhard-Manders equation the C–Sn–C bond angle of 120.9º was calculated.[45] Meanwhile, an angle of 125.0º was calculated using the Holeček equation (IV).[47] This value reveals a pentacoordinate geometry in solution.

Table 2. ^{119}Sn NMR data for complexes **2a-g** and **3a-g**

	$CDCl_3$	**DMSO-d_6**
2a	-252	-268
2b	-246	-268
2c	-248	-273
2d	-251	-485
2e	-248	-475
2f	-244	-290
2g	-251	-263
3a	-149	-161
3b	-142	-157
3c	-143	-159
3d	-149	-159
3e	-146	-157
3f	-138	-163
3g	-149	-158

3.7 Mass Spectra

The monomeric structure of all complexes was established by mass spectrometry, which showed the molecular ions in all cases. Fragment ions [M^+–R_1] and [M^+–CH_2OH] were also detected. The fragmentation pattern analysis showed the characteristic natural isotopic profile, in which the ^{120}Sn was the most abundant isotope.

3.8 X-Ray Crystallography

Complexes **2d** and **3b**–**3d** were crystallized from a solution of chloroform (**2d**), chloroform/heptane (**3b**, **3c**), and methanol (**3d**). The crystals belonged to the monoclinic crystal system. Selected crystallographic parameters are given in Table 3. An ORTEP view of the molecules is shown in Figure 1. Selected bond distances and angles are given in Table 4. The structure showed a distorted pentacoordinated geometry $SnO_2N(R_1)_2$ with the ligand coordinating to the metal in the equatorial mode, although the geometry is best described as intermediate between trigonal bypyramidal (TB) and square pyramidal (SP). The pyridoxal Schiff base coordinated through two phenolic oxygen atoms and a nitrogen atom. The Sn(12)–O(11) and Sn(12)–O(13) bond distances were from 2.073(2) to 2.114(2) and from 2.087(1) to 2.134(2) Å, respectively. In this case, the Sn–O bond length for complexes bonded to bis(trimethylsilyl)methyl group (**3b**–**3d)** are shorter than in the cyclohexyl derivative **2b**. The Sn–N bond distances varied from 2.225(2) to 2.258(2) Å. The Sn(12)–N(6) of **2b** is longer compared to the Sn(12)–N(6) in complexes **3b**–**3d**.

The C–Sn–C bond angles are in the range of 156.6(7)º to 115.2(9)º. The characterization of the two possible limiting pentacoordinated geometries is well established by the parameter τ, which adopts a value of zero for pure SP geometry and $\tau = 1$ for TB geometry.[48] For the complexes, the τ parameter spanned a relatively large range, with the lower value ($\tau = 0.16$) found for **2d** and the largest (τ=0.46) for **3d.** Complexes **3b** and **3c** exhibited similar values ($\tau = 0.38$ and 0.39 respectively). This indicates that the use of dicyclohexyl tin oxide in preparing **2b**

results in a pentacoordinate complex with geometry close to SP, as has been described for tin complexes derivatives from amino acids and naphthoylhydrazide.[32-35] In the crystalline system, the hydrogen bonds between the hydroxyl from the pyridoxal ring and the nitrogen atom of the neighboring rings stabilize a supramolecular dimer though a week intermolecular hydrogen bond O(16)–H(16)... N(2); the donor acceptor distance is in the range 2.26(3) to 1.96(2) Å (S1 Figure 1 Supporting Information).

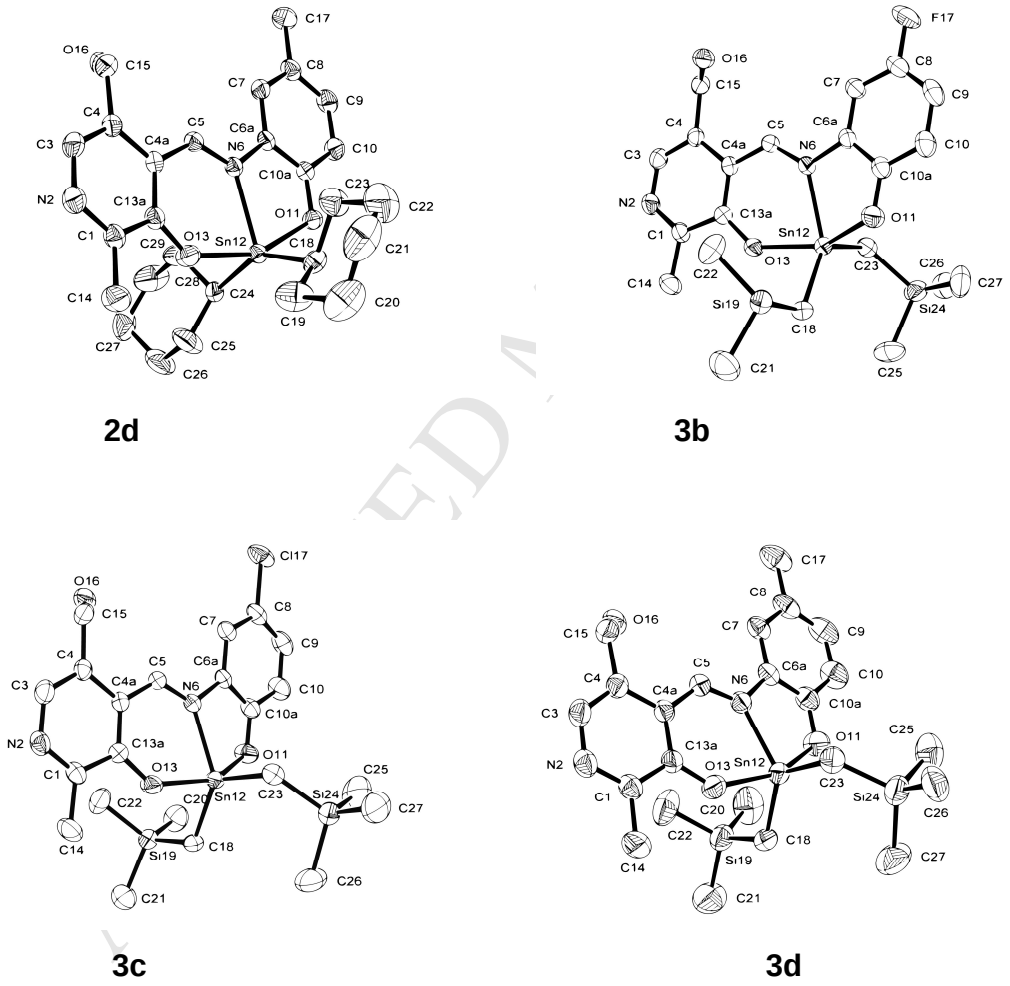


Figure 1 Crystal structures of complexes **2d**, **3b**–**3c**, all hydrogen atoms were omitted for clarity. Thermal ellipsoids at 30% level probability.

Table 3. Crystal data and structure refinement for complexes **2d** and **3b–d**.

	2d	**3b**	**3c**	**3d**
Formula	$C_{27}H_{38}N_2O_3Sn$	$C_{22}H_{33}N_2O_3Si_2SnF$	$C_{22}H_{33}N_2O_3Si_2SnCl$	$C_{23}H_{36}N_2O_3Si_2Sn$
Molecular Weight	557.28	517.22	583.82	563.41
Temperature (K)	150	296	298	296
Crystal size	0.26 × 0.10 × 0.09	0.22 × 0.14 × 0.06	0.35 × 0.22 × 0.14	0.22 × 0.21 × 0.12
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P-2_1/C	P-2_1/C	C2/c	C2/c
a (Å)	11.712(3)	32.759(13)	33.172(10)	33.357(12)
b (Å)	21.931(6)	8.069(3)	8.182(2)	8.658(3)
c (Å)	10.212(3)	22.041(8)	22.022(7)	21.591(8)
α (^{o})	90	90	90	90
β (^{o})	104.29 (1)	114.30(1)	113.51(1)	113.74(1)
γ (^{o})	90	90	90	90
V (Å^3)	2541.99(12)	5310.3(3)	5481.0(3)	5707.7(4)
Z	4	8	8	8
ρ (g/cm^3)	1.456	1.419	1.415	1.311
Absorption coefficient (mm^{-1})	1.036	1.083	1.141	1.003
F (000)	1152	2320	2384	2320
θ Range of collection data	2.26 to 25.38	2.62 to 25.40	1.93 to 25.40	2.45 to 25.40
Reflections collected	29588	50955	30972	33050
Independent reflections (R_{int})	4649 (0.0782)	4887 (0.0368)	5013 (0.0424)	5245 (0.1119)
Max. and Min. Transmission	0.9321and 0.8382	0.7452 and 0.6932	0.8939 and 0.8009	0.9068 and 0.8435
Data/restraints/parameters	4649/0/303	4887/72/310	5013/0/285	5245/73/316
Goodness-of-fit on F^2	1.058	1.060	1.026	1.084
Final R indices [I > 2σ (I)]	R_1 = 0.0276	R_1 = 0.0213	R_1= 0.0236	R_1 = 0.0316
	wR_2 = 0.0665	wR_2 = 0.0494	wR_2 = 0.0551	wR_2 = 0.0773
R indices (all data)	R_1 = 0.0325	R_1 = 0.0263	R_1 = 0.0320	R_1 = 0.0361
	wR_2 = 0.0693	wR_2 = 0.0518	wR_2 = 0.0582	wR_2 = 0.0811
$\Delta\rho_{max}$ / $\Delta\rho_{min}$ (e Å^{-3})	0.52 and –0.45	0.31 and –0.35	0.42 and –0.39	0.68 and –0.38

Table 4. Selected bond lengths (Å) and bond angles for complexes **2c** and **3b–d**.

	2c		**3b**	**3c**	**3d**
Bond lengths					
Sn(12)-N(6)	2.258(2)	Sn(12)-N(6)	2.247(2)	2.243(2)	2.225(2)
Sn(12)-C(18)	2.143(3)	Sn(12)-C(18)	2.120(2)	2.122(2)	2.123(3)
Sn(12)-C(24)	2.150(2)	Sn(12)-C(23)	2.116(2)	2.117(2)	2.122(3)
Sn(12)-O(11)	2.114(2)	Sn(12)-O(11)	2.075(1)	2.075(2)	2.073(2)
Sn(12)-O(13)	2.134(2)	Sn(12)-O(13)	2.090(1)	2.087(1)	2.097(2)
C(6a)-N(6)	1.428(3)	C(6a)-N(6)	1.418(2)	1.417(2)	1.424(3)
C(5)-N(6)	1.303(3)	C(5)-N(6)	1.294(2)	1.299(3)	1.297(3)
C(13a)-O(13)	1.302(3)	C(13a)-O(13)	1.308(2)	1.311(2)	1.301(3)
C(13a)-C(4a)	1.403(3)	C(13a)-C(4a)	1.407(3)	1.403(3)	1.406(4)
C(6a)-C(10a)	1.409(3)	C(6a)-C(10a)	1.405(3)	1.403(3)	1.404(4)
C(4a)-C(5)	1.439(3)	C(4a)-C(5)	1.440(3)	1.439(3)	1.434(4)
C(10a)-O(11)	1.327(3)	C(10a)-O(11)	1.331(3)	1.311(2)	1.328(3)
Bond angles					
C(18)-Sn(12)-C(24)	147.1(1)	C(18)-Sn(12)-C(23)	124.9(8)	124.3(9)	127.4(1)
O(11)-Sn(12)-C(18)	94.8(9)	O(11)-Sn(12)-C(18)	95.3(7)	94.8(4)	94.2(1)
O(11)-Sn(12)-C(24)	95.9(9)	O(11)-Sn(12)-C(23)	101.5(8)	101.8(8)	99.6(1)
O(13)-Sn(12)-C(18)	91.7(9)	O(13)-Sn(12)-C(18)	86.9(7)	87.2(7)	89.0(1)
O(13)-Sn(12)-C(24)	90.6(9)	O(13)-Sn(12)-C(23)	103.5(7)	103.3(8)	97.9(1)
O(11)-Sn(12)-O(13)	156.6(7)	O(11)-Sn(12)-O(13)	147.7(6)	147.9(7)	155.2(9)
N(6)-Sn(12)-C(18)	106.8(9)	N(6)-Sn(12)-C(18)	136.5(7)	136.5(7)	127.3(9)
N(6)-Sn(12)-C(24)	105.9(8)	N(6)-Sn(12)-C(23)	98.6(7)	99.2(8)	105.3(1)
N(6)-Sn(12)-O(11)	75.9(6)	N(6)-Sn(12)-O(11)	75.8(6)	75.7(6)	76.7(8)
N(6)-Sn(12)-O(13)	80.7(7)	N(6)-Sn(12)-O(13)	80.6(5)	80.9(6)	81.8(7)
C(4a)-C(5)-N(6)	128.1(2)	C(4a)-C(5)-N(6)	126.7(2)	126.8(2)	127.7(2)
C(13a)-C(4a)-C(5)	123.1(2)	C(13a)-C(4a)-C(5)	122.4(2)	122.5(2)	122.9(2)
C(10a)-C(6a)-O(11)	120.7(2)	C(10a)-C(6a)-O(11)	120.2(2)	119.9(2)	120.6(2)
C(4a)-C(13a)-O(13)	123.8(2)	C(4a)-C(13a)-O(13)	124.6(2)	124.6(2)	124.2(2)

3.9 Solubility and stability

The complexes were soluble in methanol, ethanol, dichloromethane, chloroform, N,N-dimethylformamide and dimethyl sulfoxide. To examine the biological activity of the complexes the stability of the complexes under physiological conditions a solution DMSO–DPBS (1:1 v/v) was used, after 72 h the UV–vis spectra do not show significant shift of the absorption bands or appearance of any new peaks. The intensity of the bands also remained essentially similar, which exclude the possibility of any degradation of the complexes in physiological conditions. In the ^{1}H and ^{119}Sn NMR after 72 h in DMSO no-decomposed products or changes in the coordination number were observed.

3.10 Cytotoxicity and Structure activity relationship

The cytotoxicity of complexes **2a**–**2g** and **3a**–**3g** was examined in different cell lines: U-251 (human glioblastoma), K-562 (human myelogenous leukemia), HCT-15 (human colorectal adenocarcinoma), MCF-7 (human breast adenocarcinoma), SKLU-1 (human lung adenocarcinoma) and MDA-MB-231 (human breast adenocarcinoma). The ligands were not evaluated due to their instability in DMSO. The IC_{50} values are listed in Table 5; cisplatin was used as positive control. The cells were incubated for 48 h at different concentrations using the protein-binding dye sulforhodamine B in a micro-culture assay to measure cell growth. The complexes were remarkably more active than cisplatin. All tested complexes share common structural characteristics; the main differences are the substitution of the aromatic ring and the substituent attached to the tin atom (cyclohexyl or bis(trimethylsilyl)methyl). In general, the bioisosteric replacement of hydrogen by fluorine resulted in a greater cytotoxic effect. A closer inspection of the IC_{50} values for the series **2a**–**2g** showed that for U-251, K562, HCT-15 and SKLU-1 cell lines the complex **2b** (fluorine substituted) was the most cytotoxic, with IC_{50} values

ranging from 0.04 to 0.14 μM. However, for MCF-7 and MDA-MB-231 cell lines complex **2d** showed the highest cytotoxic effect.

For the series **3a**–**3g,** the increase in cytotoxic activity due to the bioisosteric replacement of H (**3a**) by F (**3b**) was evident only for HCT-15 (IC_{50} = 0.23μM) and MCF-7 (IC_{50} = 0.11 μM). Under identical experimental conditions in U-252, K-562, HCT-15, MCF-7, SKLU-1, MDA-MB-231 cell lines, **3b** was rather less cytotoxic, with IC_{50} values > 0.14μM. In addition, the isosteric replacement of F by Cl (complex **3c** chlorine-substituted) resulted in a higher cytotoxic effect for SKLU-1 and MDA-MB-231 cell lines.

Additionally, for dicyclohexyltin(IV) complexes **2a**–**2g,** a selective cytotoxicity against breast cell line MDA-MB-231 was observed compared to breast cell line MCF-7, and the opposite effect was observed for bis(trimethylsilyl)methyl tin(IV) derivatives **3a–3g**, which showed a higher cytotoxicity towards MCF-7, suggesting that substituents bonded to the tin atom could be involved in the cytotoxicity mechanism.

In general, the complexes displayed higher cytotoxic potency that the pyridoxamine and pyridoxal butyl tin(IV) derivatives previously described.[25, 26]

Table 5. Inhibitory Concentration IC_{50} (μM) for complexes **2a–g** and **3a–g**

Complex	U-251	K-562	HCT-15	MCF-7	SKLU-1	MDA-MB-231
2a	0.19 ± 0.01	0.047 ± 0.03	0.52 ± 0.05	0.21 ± 0.01	0.16 ± 0.02	0.15 ± 0.01
2b	0.14 ± 0.01	0.040 ± 0.01	0.24 ± 0.01	0.16 ± 0.01	0.11 ± 0.01	0.12 ± 0.01
2c	0.24 ± 0.01	0.087 ± 0.01	0.55 ± 0.01	0.25 ± 0.01	0.19 ± 0.01	0.11 ± 0.01
2d	0.24 ± 0.01	0.075 ± 0.01	0.52 ± 0.04	0.16 ± 0.01	0.23 ± 0.01	0.10 ± 0.004
2e	0.22 ± 0.01	0.099 ± 0.01	0.47 ± 0.02	0.28 ± 0.03	0.19 ± 0.01	0.25 ± 0.01
2f	0.28 ± 0.01	0.130 ± 0.01	0.50 ± 0.05	0.21 ± 0.02	0. 31 ± 0.03	0.44 ± 0.02
2g	0.19 ± 0.01	0.080 ± 0.002	0.63 ± 0.01	0.17 ± 0.03	0 .21 ± 0.01	0.35 ± 0.02
3a	0.13 ± 0.01	0.08 ± 0.01	0.64 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.29 ± 0.02
3b	0.14 ± 0.01	0.17 ± 0.33	0.23 ± 0.01	0.11 ± 0.01	0.16 ± 0.01	0.20 ± 0.01
3c	0.33 ± 0.03	0.18 ± 0.01	0.27 ± 0.01	0.16 ± 0.01	0.12 ± 0.011	0.14 ± 0.01
3d	0.12 ± 0.01	0.08 ± 0.01	0.19 ± 0.001	0.17 ± 0.01	0.16 ± 0.01	0.32 ± 0.02
3e	0.32 ± 0.01	0.20 ± 0.01	0.49 ± 0.001	0.20 ± 0.01	0.34 ± 0.03	0.35 ± 0.02
3f	0.29 ± 0.02	0.15 ± 0.01	0.36 ± 0.02	0.22 ± 0.004	0. 21 ± 0.01	0.22 ± 0.01
3g	0.32 ± 0.01	0.22 ± 0.003	0.40 ± 0.04	0.31 ± 0.01	0. 29 ± 0.005	0.27 ± 0.01
cis-platin	9.09 ± 0.80	15.20 ± 1.400	13.83 ± 0.70	13.03 ± 1.30	7.13 ± 0.20	13.03 ± 1.30

The present data are the three or four times averaged independent values ± standard error on the mean (x ± SE)

4. Conclusions

In summary, we designed and synthesized a series of novel dicyclohexyl and bis(trimethylsilyl)methyl tin(IV) Schiff-base complexes from piridoxal and *o*-aminophenols. Their molecular structures were determined by physicochemical and spectroscopic studies. The ^{119}Sn NMR indicates pentacoordinated geometries for all complexes in solution. The X-ray diffraction of four complexes evidenced that the geometry of these compounds in the solid state can be described as intermediate between square pyramidal and trigonal bipyramidal. These pentacoordinated dicyclohexyl and bis(trimethylsilyl)methyl tin(IV) complexes were screened for their cytotoxic activity. Both the isosteric F by Cl and bioisosteric H by F replacements were used as a strategy to design molecules with a higher degree of selectivity. It was generally observed that the presence of a fluorine substituent in the molecule (**2b**) increased the cytotoxicity towards all cell lines tested, being more cytotoxic towards MDA-MB-231 than MCF-7. However, for **3b** the presence of fluorine in the molecule improved the cytotoxic activity for HCT-15 and MCF-7, while the isosteric replacement of fluorine by chlorine in complex **3c** showed a potent inhibitory activity against SKLU-1 lung cancer and MDA-MB-231 breast cancer cell lines. An interesting observation is that Schiff-base complexes bearing a cyclohexyl moiety showed potent antiproliferative activities in vitro, especially against MDA-MB-231, while the bis(trimethylsilyl)methyl moiety exhibited major potency towards MCF-7. The complexes were found to be more active than the cisplatin and pyridoxamine or pyridoxal butyl analogs. The development of these organotin molecules can confer a higher degree of selectivity and could be efficient anticancer agents.

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Highlights

Schiff base Sn(IV) complexes as cytotoxic agents.

Organotin(IV) complexes were successfully obtained by multi-component synthesis.

Isosteric and bioisosteric approach was used as the strategy of molecular design.