



Cite this: *INEOS OPEN*,
2025, 8 (1–3), XX–XX
DOI: 10.32931/ioXXXXx

Received XX Month 20XX

Accepted 25 January 2025

<http://ineosopen.org>

SYNTHESIS AND CYTOTOXIC ACTIVITY OF NEW ORGANOTIN COMPLEXES

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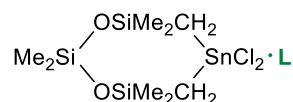
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Abstract

A number of new organotin complexes based on 1,1-dichloro-1-stanna-3,3,5,5,7,7-hexamethyl-3,5,7-trisilyl-4,6-dioxacyclooctane and mono- and bidentate ligands were synthesized. The *in vitro* anticancer activity of the complexes obtained was studied on a number of human cancer cell lines.

Key words: synthesis, heterocyclic silylmethyldichlorostannane, complexes, *N*-donor ligands, cytotoxicity, cancer cells.



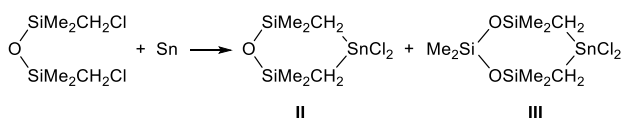
L = Bipy, Phen, 1-methylimidazole,
1-vinylimidazole, 1-allylimidazole

Introduction

Earlier we reported the synthesis of a number of complexes based on bis(trimethylsilylmethyl)tin dichloride (**I**) and 1,1-dichloro-1-stanna-3,3,5,5-tetramethyl-3,5-disila-4-oxa-cyclohexane (**II**) using mono- or bidentate ligands (**L**), namely, 2,2'-bipyridine (Bipy), 1,10-phenanthroline (Phen) and 1-methyl-, 1-vinyl- and 1-allylimidazoles (Me-Im, Vin-Im, All-Im), taken in a 1:1 molar ratio, and their *in vitro* anticancer activity against different human cancer cell lines [1]. In continuation of these studies, we synthesized a series of new complexes based on eight-membered heterocyclic compound—1,1-dichloro-1-stanna-3,3,5,5,7,7-hexamethyl-3,5,7-trisila-4,6-dioxacyclooctane (**III**), using the same mono- and bidentate ligands.

Results and discussion

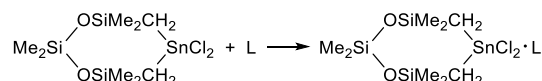
The original eight-membered heterocyclic compound, silylmethyltin dichloride **III**, was obtained as a by-product during the direct synthesis of the six-membered heterocyclic compound, namely, silylmethyltin dichloride **II** (Scheme 1) [2, 3].



Scheme 1. Direct synthesis of heterocycles **II** and **III**.

Complexes **III**:Bipy, **III**:Phen, **III**:Me-Im, **III**:Vin-Im, and **III**:All-Im were obtained by the reaction of heterocyclic compound **III** with the corresponding mono- or bidentate

ligands (**L**), taken in a 1:1 molar ratio in benzene upon heating or without it (Scheme 2).



Scheme 2. Synthesis of complexes **III**:Bipy, **III**:Phen, **III**:Me-Im, **III**:All-Im.

All complexes were isolated in high yields (80–99%), their properties and elemental analyses are presented in Table 1. The discussion of the NMR spectroscopic and X-ray diffraction data will be presented later in an extended report.

The cytotoxicity of the resulting complexes was evaluated on different human cancer cell lines, including prostate cancer (PC3), breast cancer (MCF7), and colorectal cancer (HCT 116), as well as pseudonormal (non-cancerous) human embryonic kidney cells (HEK 293). The values of half-maximal inhibitory concentrations (IC₅₀) are presented in Table 2.

The results obtained indicate that the efficiency of all the complexes explored (except for **III**:All-Im) was higher than that of the well-known anticancer drug cisplatin: the values of IC₅₀ ranged within 1.7–8.0 and 13.0–21.0 μM, respectively.

A comparative assessment of the complexes of six-membered (**II**) [1] and eight-membered (**III**) heterocycles with the same ligands did not reveal significant differences in their cytotoxic activities on the tested cells. A certain difference in the values of IC₅₀ were observed for complexes **II**:All-Im (3.5–5.2 mmol) [1] and **III**:All-Im (10.0–16.0 mmol).

Experimental section

All reactions were carried out in a dry nitrogen atmosphere. The solvents were purified and dried prior to use. 1,1-Dichloro-1-stanna-3,3,5,5,7,7-hexamethyl-3,5,7-trisila-4,6-

dioxacyclooctane (**III**) was synthesized by the published procedure [2, 3].

Table 1. Yields, properties, and elemental analyses of the resulting complexes

Compound	Yield, %	Mp, °C	Anal. found (calcd), %				
			C	H	N	Sn	Cl
III·Bipy	86	50–53	36.85 (37.25)	4.98 (5.21)	5.57 (4.83)	21.06 (20.46)	12.79 (12.22)
III·Phen	81	146–149	40.26 (39.75)	5.40 (5.00)	5.09 (4.64)	20.11 (19.64)	11.79 (11.75)
III·Me-Im	88	101–105	28.78 (28.47)	5.70 (5.53)	5.44 (5.58)	23.24 (23.45)	14.44 (14.01)
III·Vin-Im	99	85–87	30.71 (30.13)	5.40 (5.45)	5.13 (5.41)	23.23 (22.91)	13.56 (13.68)
III·All-Im	79	–	31.30 (31.59)	5.90 (5.68)	5.39 (5.26)	22.76 (22.30)	14.50 (13.82)

Cisplatin 20.0±2.0 21.0±3.0 14.0±4.0 13.0±1.0

General procedure for the synthesis of the complexes with bidentate ligands Bipy and Phen. A solution of Bipy or Phen (0.01 mol) in benzene was added to a stirred solution of compound **III** (4.24 g, 0.01 mol) in 10 mL of benzene. The resulting amorphous precipitate was filtered off and recrystallized from hexane to give the target complexes. The yields and elemental analyses are presented in Table 1. **III·Bipy**: ¹H NMR (CDCl₃) δ 8.67 (m, 2H, bipy), 8.39 (m, 2H, bipy), 7.80 (m, 2H, bipy), 7.29 (m, 2H, bipy), 1.03 (s, 4H, CH₂), 0.25 (s, 12H, SiMe₂), 0.08 (s, 6H, Si-Me) ppm. **III·Phen**: ¹H NMR (CDCl₃) δ 9.20 (m, 2H, phen), 8.26 (m, 2H, phen), 7.78 (m, 2H, phen), 7.64 (m, 2H, phen), 1.03 (s, 4H, CH₂), 0.24 (s, 12H, SiMe₂), 0.07 (s, 6H, Si-Me) ppm.

General procedure for the synthesis of the complexes with 1-substituted imidazoles Me-Im, Vin-Im and All-Im. A solution of Me-Im, Vin-Im, or All-Im (0.01 mol) in 5 mL of benzene was added to a stirred solution of compound **III** (4.24 g, 0.01 mol) in 5 mL of benzene. The stirred reaction mixture was refluxed for 4 h. The solvent was removed under vacuum to give the target complexes as white or slightly colored crystalline powders (**III·Me-Im**, **III·Vin-Im**) or a viscous yellow substance (**III·All-Im**). The yields and elemental analyses are presented in Table 1. **III·Me-Im**: ¹H NMR (CDCl₃) δ 8.36 (s, 1H, Me-Im), 7.52 (s, 1H, Me-Im), 7.01 (s, 1H, Me-Im), 3.78 (s, 3H, Me-Im), 1.12 (s, 4H, CH₂), 0.19 (s, 12H, SiMe₂), 0.07 (s, 6H, Si-Me) ppm. **III·Vin-Im**: ¹H NMR (CDCl₃) δ 8.1 (s, 1H, Vin-Im), 7.35 (s, 1H, Vin-Im), 7.22 (s, 1H, Vin-Im), 6.93 (m, 1H, Vin-Im), 5.39 (m, 1H, Vin-Im), 5.04 (m, 1H, Vin-Im), 1.09 (s, 4H, CH₂), 0.25 (s, 12H, SiMe₂), 0.10 (s, 6H, Si-Me) ppm. **III·All-Im**: ¹H NMR (CDCl₃) δ 8.25 (s, 1H, All-Im), 7.45 (s, 1H, All-Im), 7.01 (s, 1H, All-Im), 5.82 (m, 1H, All-Im), 5.22 (m, 1H, All-Im), 4.55 (m, 1H, All-Im), 4.69 (m, 2H, All-Im), 1.03 (s, 4H, CH₂), 0.11 (s, 12H, SiMe₂), –0.02 (6H, Si-Me) ppm.

Conclusions

A series of new organotin complexes were obtained based on 1,1-dichloro-1-stanna-3,3,5,5,7,7-hexamethyl-3,5,7-trisyl-4,6-dioxacyclooctane using mono- or bidentate ligands, including 1,1'-bipyridine, 1,10-phenanthroline, and *N*-substituted imidazoles, taken in a 1:1 molar ratio. A comparative evaluation of the cytotoxic activity of the complexes with six-membered (**II**) and eight-membered heterocycles (**III**) with the same ligands against several cancer cell lines did not reveal a clear correlation between the ring size and cytotoxicity.

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Table 2. Cytotoxic activity of the compounds explored

Compound	IC ₅₀ , μM			
	PC3	MCF7	HCT116	HEK293
II·Bipy	3.6±1.4	4.6±1.4	2.8±1.4	3.3±0.8
II·Phen	2.8±0.3	4.0±1.5	3.2±0.05	4.0±1.3
II·Me-Im	3.2±1.2	4.4±1.2	2.7±0.1	3.3±0.6
II·Vin-Im	3.7±1.7	4.0±0.5	4.0±0.6	3.5±0.8
II·All-Im	4.0±2.0	5.2±2.0	4.2±1.2	3.5±1.0
III·Bipy	4.2±0.2	3.5±1.5	2.8±1.0	4.6±0.8
III·Phen	3.5±0.5	3.5±0.8	2.6±0.2	2.0±0.3
III·Me-Im	5.2±2.5	6.4±0.6	4.8±1.2	5.5±2.0
III·Vin-Im	6.0±0.2	4.3±0.5	6.6±1.4	4.2±1.8
III·All-Im	16.0±4.0	10.5±2.5	14.5±1.5	10.0±2.0