European Journal of Medicinal Chemistry 45 (2010) 883–889

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Synthesis, characterization and biocidal activity of new organotin complexes of 2-(3-oxocyclohex-1-enyl)benzoic acid

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ARTICLE INFO

*Article history:*
Received 16 March 2009
Received in revised form
3 November 2009
Accepted 12 November 2009
Available online 18 November 2009

*Keywords:*
Antifungal activity
*C. Albicans*
*C. Neoformans*
Organotin carboxylates

ABSTRACT

The reaction of 1,3-cyclohexadione with 2-aminobenzoic acid has produced the 2-(3-oxocyclohex-1-enyl)benzoic acid (HOBz). Subsequent reactions of the ligand with organotin chlorides led to $[Me_2Sn(OBz)O]_2$ (**1**), $[Bu_2Sn(OBz)O]_2$ (**2**), $[Ph_2Sn(OBz)O]_2$ (**3**), $[Me_3Sn(OBz)]$ (**4**), $[Bu_3Sn(OBz)]$ (**5**) and $[Ph_3Sn(OBz)]$ (**6**). All complexes have been fully characterized. In addition the structure of complexes **(2)** and **(4)** have been authenticated by X-ray crystallography. The biological activity of all derivatives has been screened against *Cryptococcus neoformans* and *Candida albicans*. In addition we have performed toxicological testes employing human kidney cell. The complexes **(3)**, **(5)** and **(6)** displayed the best values of inhibition of the fungus growing, superior to ketoconazole. Compound **(5)** presented promising results in view of the antifungal and cytotoxicity assays.



## 1. Introduction

Tributyltin oxide (TBTO) was one of the first organotin compound to be used as biocide agent [1] in anti-fouling paints for ships [2,3]. However, important environmental problems have forced some nations to prohibit the use of such materials [4–7]. In spite of the drawbacks, organotin are among the most widely used organometallic compounds [8] and other potential applications have been observed. In the 1970s the growing of malignant tumours in mice were retarded by organotin species (acetates, oxides, hydroxides and alkoxides) [9–11]. Complexes with general formula $SnR_2X_2L_2$ ($L_2$ = bidentate ligand with oxygen and/nitrogen donor atoms) has been tested against P388 lymphatic leukaemia in mice [12,13]. Organotin complexes with aminoacids [14,15], thiols [16], o-phenanthroline, bipyridyl and histidine, carboxylates, have been found effective against a variety of tumours. Today, a number of interesting biologic applications have been found for organotin complexes. For example, $Bu_2SnCl_2$ or $Ph_3SnCl$ can inhibit oedemas in mice as effectively as hydrocortisones [17,18]. Complexes with ligands derived from aminoquinolines have schizonticidal and as antimalarial activities [19]. Those derivatives with some Schiff bases have potential use as amoebicidal agents [20]. Some 2-alkylindole derivatives have been tested against *Bacillus subtilis*, *Bacillus pumilus*, *Staphylococcus aureus* and *Micrococcus luteus* [21]. Activity against leishmaniasis in mice and helminthes in cats has been found for dioctyltin maleate [22,23].

Organotin(IV) carboxylates comprises the class of tin complexes which has attracted particular attention due to the potential biocide activity and cytotoxicity as well as their industrial and agricultural applications [24–28].

Our recent efforts have focused on mechanistic aspects of biological activity of organotin compounds using fungus cultures as models [29–32]. We have found that organotin complexes derived of some carboxylic acids seem to share mechanistic similarities to azole drugs such as ketoconazole or fluconazole [32].

Herein we report the synthesis, characterization and some biocide results involving new organotin carboxylate derivatives.

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doi:10.1016/j.ejmech.2009.11.026

## 2. Results and discussions

### 2.1. Chemistry

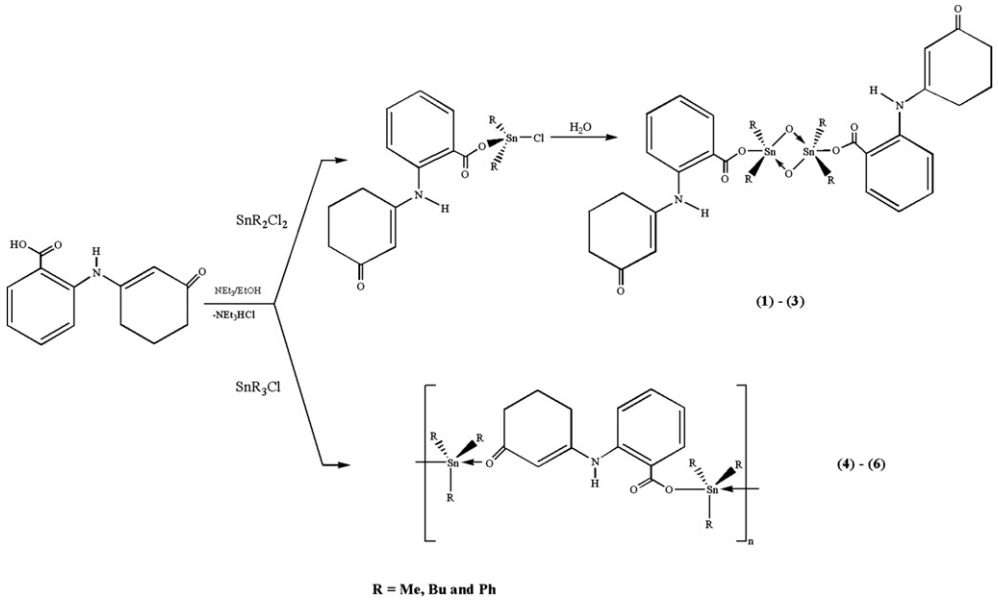
The preparation of 2-[(3-oxocyclohex-1-enyl)amino]benzoic acid, (HOBz), has been mentioned in the literature in a condensation reaction of isopropylidenemalonate [33], where HOBz was obtained in 37% yield while. We have managed to prepare HOBz in 75% yield by reacting 1,3-cyclohexadione with 2-aminobenzoic acid [34].

The 2-(3-oxocyclohex-1-enyl)benzoic acid has been employed in reactions with organotin halides, Scheme 1.

All complexes have been obtained as air stable and crystalline products with sharp melting points. Complexes **(1)–(3)** were expected as monochlorine–organotin compounds as products. However, the water employed in the final stage of the synthetic method, in order to remove $NEt_3HCl$ (secondary product of the reaction), promoted the hydrolysis of the expected product yielding a stannoxane derivatives as major product, Scheme 1. On the other hand complexes **(4)–(6)** were obtained as polymers. Such assemblies are not uncommon for organotin carboxylates [35].

The main bands in the infrared spectra of the ligand (HOBz) were observed at 1685 $cm^{-1}$ ($\nu_{CO}$) (sharp signal); 1655 $cm^{-1}$ ($\nu_{COO}$) (strong absorption with two small satellites at 1675, 1668 and); 1376 $cm^{-1}$ ($\nu_{C-N}$) (week vibration). The strong signals corresponding to the COO group indicates the presence of intermolecular hydrogen interactions –C═O···HOOC–, which is quite common in carboxylic acids in the solid state [36]. Upon coordination these vibrations have disappeared generating new bands in 1630–1590 $cm^{-1}$ and 1492–1360 $cm^{-1}$ regions, for complexes **(1)–(6)**, corresponding to the COO asymmetric and symmetric vibrations. Information about $\Delta\nu_{COO}$ ($\nu_{as}$–$\nu_s$) values has proved to be important in providing further details on the Sn-carboxyl bonding scheme [37–39]. We could not detect $\nu_s$ in the IR spectrum of the protonated ligand (HOBz). However, we have found for the potassium salt of the ligand, $\Delta\nu_{COO}$ at 163 $cm^{-1}$ ($\nu_{as}$ = 1583 $cm^{-1}$;$\nu_s$ = 1420 $cm^{-1}$) which is smaller than those encountered for the complexes, which varies from 221 $cm^{-1}$–252 $cm^{-1}$, **(1)** 1625, 1373 $cm^{-1}$, **(2)** 1615, 1376 $cm^{-1}$, **(3)** 1621, 1377 $cm^{-1}$, **(4)** 1598, 1366 $cm^{-1}$, **(5)** 1595, 1365 $cm^{-1}$ and **(6)** 1602, 1376 $cm^{-1}$. It indicates a monodentate coordination mode [36,40], in accordance with the X-ray results for complexes **(2)** and **(4)**. In addition it was observed for complexes **(1)–(6)** two bands ($\nu_{(Sn-C)as}$ and $\nu_{(Sn-C)s}$) {657 and 511 $cm^{-1}$ **(1)** 649 and 509 $cm^{-1}$ **(2)**, 279 and 228 $cm^{-1}$ **(3)**, 639 and 502 $cm^{-1}$ **(4)**, 642 and 511 $cm^{-1}$ **(5)**, 285 and 232 $cm^{-1}$ **(6)**}. According to literature it is a consequence of a bent C–Sn–C moiety in the complexes [41]. It also detected the presence of Sn–O bond due to the strong bands in the region of 480–440 $cm^{-1}$. The CO bond remains almost unchanged in the stannoxane complexes **(1)–(3)**, because of the stretching frequency displayed respectively at 1685, 1684 and 1681 $cm^{-1}$. On the other hand in complexes **(4)–(6)** it has moved to lower frequency, 1658, 1652 and 1658 $cm^{-1}$ due to –C═O ···Sn intermolecular interaction in order to outline the polymeric chain arrangement adopted by these compounds.

The signals of the –C═O and –COOH groups for the ligand were observed in NMR experiments at $\delta$ 170.38 and $\delta$ 201.89, respectively. No significant changes were detected in the $^{13}C$ NMR signals for complexes **(1)–(3)** upon coordination. In complexes **(4)–(6)** the CO carbon resonance shifted to up field at $\delta$ 173, which might be explained considering that the ligand coordinates to the tin fragment in the enolate form. The conjugated system involving the N–H group and C(12) would increase the electronic density at C(11), providing the necessary requirements for the formation of the enol form and therefore causing such variation in the $^{13}C$ chemical shift. On the other hand, the carboxylic signal remained almost unchanged at $\delta$ 200. The $^{119}Sn$ NMR signals were observed for complexes **(1)–(6)** at $\delta$ 97, −161, −193, −36, −82 and 69, respectively. The coordination number (NC) of the tin centre is one of the interferences in the $^{119}Sn$ chemical shift. It is suggested in the literature ranges for it, as follows: NC = 6 {$\delta$ − 300 and −550}; NC = 5 {$\delta$ − 150 and −250}; and NC = 4 {higher to $\delta$ − 150}, [42]. However, it must be carefully analysed since tin resonance is strongly dependent upon other factors, such as electronegativity of the ligands, temperature and concentration employed in the experiments. In our case, an increase in the coordination number of the tin atom has effected changes in $^{119}Sn$ $\delta$ values in contrast to the starting materials. $^{13}C$ NMR results can be used to estimate the C–Sn–C angle, by employing methods encountered in the literature, which correlate this angle with the first order $^{119}Sn$–$^{13}C$ coupling constant, in solution [43,44]. The empirical relationship, $|^1J(^{119}Sn–^{13}C)| = 11.4(\theta) – 875$, have provided the C–Sn–C angle for compounds **(1)–(3)** ranging from 146 to 158°. Complex **(2)** has been studied by X-ray




**Scheme 1.** Pathways of the reactions of 2-(3-oxocyclohex-1-enyl)benzoic acid with organotin halides.

**Table 1**
Crystallographic data of the complexes *bis*-[2-(3-oxocyclohex-1-enyl)benzoate-dibutylstannoxane] **(2)** and *catena*-Poly[[trimethyltin(IV)]-μ-2-[(3-oxocyclohex-1-enyl)amino]benzoato-$\kappa^2$O:O′] **(4).**

| Compound | (2) | (4) |
|---|---|---|
| Empirical formula | $C_{21}H_{30}NO_4Sn$ | $C_{32}H_{42}N_2O_6Sn_2$ |
| Molecular weight | 479.15 | 788.06 |
| Temperature | 293(2) K | 273(2) K |
| Wavelength | 0.71073 Å | 0.71073 Å |
| Crystal system | Monoclinic | Orthorhombic |
| Space group | P 21/N | Fdd2 |
| United cell dimensions | $a = 15.007(2)$ Å, $b = 10.2490(10)$ Å, $c = 16.2130(10)$ Å $\alpha = 90°$, $\beta = 116.290(10)°$, $\gamma = 90°$ | $a = 30.626(5)$ Å, $b = 12.981(2)$ Å, $c = 17.164(2)$ Å $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$. |
| Volume | 2235.7(4) Å$^3$ | 6823.6(19) Å$^3$ |
| Z | 4 | 16 |
| Density (calculated) | 1.424 Mg m$^3$ | 1.534 Mg m$^3$ |
| Absorption coefficient | 1.166 mm$^{-1}$ | 1.506 mm$^{-1}$ |
| F(000) | 980 | 3168 |
| Crystal size | 0.2 (max), 0.2 (mid), 0.2 (min) | 0.2 (max), 0.2 (mid), 0.2 (min) |
| Theta range for data collection | 5.36–11.74° | 11.757–12.501° |
| Reflections collected | 5702 | 7560 |
| Independent reflections | 3888 [R(int) = 0.0324] | 7303 [R(int) = 0.0183] |
| Refinement method | Full-matrix least-squares on F$^2$ | Full-matrix least-squares on F$^2$ |
| Data/restraints/parameters | 3888/3/225 | 7303/3/575 |
| Goodness-of-fit on F$^2$ | 0.971 | 0.893 |
| Final R indices [I > 2sigma(I)] | $R1 = 0.0479$, wR2 = 0.1296 | $R1 = 0.0321$, wR2 = 0.0981 |
| R indices (all data) | $R1 = 0.0748$, wR2 = 0.1485 | $R1 = 0.0391$, wR2 = 0.1100 |

crystallography and the angle C(14)–Sn–C(18) was found as 140.8(3)°. It is not very different from the value obtained by the empirical method. Based on that, one can conclude that the structures of the compounds **(1)–(3)** are very close to each other, both in solution and in the solid state. The same methodology was employed to complexes **(4)–(6)** provided C–Sn–C angle in solution from 202 to 232°, not comparable to the experimental data in the solid state for complex **(4)**, 120°. However it is a good indication that the polymeric chain, held by –C═O intermolecular contacts, collapse in monomers in solution with similar structural features for **(4)–(6)**.

The $^{119}$Sn-Mössbauer experiments were performed in order to determine the differences in the Sn nuclei on going from organotin starting materials to the complexes. The isomer shift parameters ($\delta$/mm s$^{-1}$) indicates the presence of *s* electron density at the tin nuclei, therefore it is a good indication of the hybridization scheme at the tin atom in the complexes. The isomer shift signals for complexes **(1)–(6)** were observed at 1.27, 1.25, 1.29, 1.45, 1.42, 1.40 mm s−1, respectively, indicates the presence of Sn(IV) and a pseudo *dsp*$^3$ hybridization at the tin centre. The non-zero value of the quadrupolar splitting parameters ($\Delta$/mm s$^{-1}$) indicates deviation from a spherical distribution of charge at the metal atom. For complexes **(1)–(3)** we have obtained ($\Delta$/mm s$^{-1}$) at 4.19, 3.16 and 3.08 that is compatible with expected five-coordinate distorted trigonal-bipyramidal tin. The values of $\Delta$/mm s$^{-1}$ 3.52, 3.57 and 3.16 are typical for a polymeric structure with intermolecular C═0···Sn bonds and two oxygen atoms in a trans configuration, with values ranging from 3.0 to 4.1 mm s−1 agree with a pseudo trigonal-bipyramidal geometry at the tin centre [45,46].

The structure of complexes **(2)** and **(4)** were determined by X-ray diffraction experiment, Table 1.

For complex **(2)** the X-ray study, Fig. 1, comprises a centrosymmetric four-membered $Sn_2O_2$ ring, where each tin atom adopts a five-coordinate distorted trigonal-bipyramidal geometry with two butyl group and three asymmetrically coordinated oxygen atoms.

In each monomer the Sn(IV) lies at the centre of the trigonal-bipyramid, where the equatorial positions are occupied by two butyl groups and an oxygen atom, Sn–O 2.029 Å. One of the axial position is occupied by a monodentate carboxylic group, Sn–O 2.177(4) and the fifth coordination is accomplished by a long intermolecular Sn–O interaction, 2.234(4)Å, through the axial corner. The sum of the angles at the equatorial position, O(4)– Sn–C(14) 107.1(3)°, C(14)–Sn–C(18) 140.8(3)° and O(4)–Sn–C(18) 111.6(3)° is almost 360° and the angle O(2)–Sn–O(4) described by the two oxygen atoms at the axial position, is smaller than 180°, Table 2 This assembly is not uncommon for organotin carboxylic containing complexes. Examples have been previously prepared, however employing different synthetic strategy [47].

The X-ray crystallographic study of complex **(4)** revealed that it crystallises forming an infinity double-polymeric chain structure, where the anionic ligand bridges two tin centre *via* the monodentate carboxylic moiety and the –C═O fragment, Fig. 2. Each chain possesses a tin atom surrounded by three methyl groups and two oxygen atoms, describing an almost perfect trigonal bypyramid geometry. The equatorial corners are occupied by the methyl groups and the axial positions by the oxygen atoms. The Sn–O–CO–R bond {Sn–O(1) 2.174(6) Å; is shorter than the Sn–O═C–R {Sn–O(3) 2.504(7) Å. The angles C–Sn–C and O–Sn–O are all close to 120° and 180° as expected for a trigonal-bipyramidal geometry, Table 3 [48].

## 2.2. Pharmacology

Fungal infections have increased in the last years affecting mainly those patients immuno-compromised [49]. *Candida*

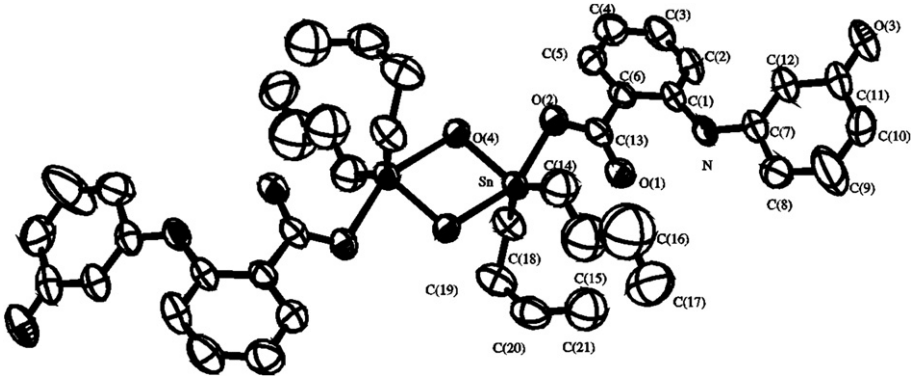



**Fig. 1.** The molecular structure of *bis*-[2-(3-oxocyclohex-1-enyl)benzoate-dibutylstannoxane].

**Table 2**
Selected bond distances (Å) and angles (°) for *bis*-[2-(3-oxocyclohex-1-enyl)benzoate-dibutylstannoxane].

| | | | |
|---|---|---|---|
| C(11) – O (3) | 1.233(7) | O(2)–Sn | 2.177(4) |
| C(13)–O(1) | 1.244(8) | O(4) Sn | 2.029(4) |
| C(13)–O(2) | 1.284(8) | O(4)–Sn | 2.234(4) |
| O(4)–Sn–C(14) | 107.1(3) | O(4)–Sn–C(18) | 111.6(3) |
| C(14)–Sn–C(18) | 140.8(3) | O(2)–Sn–O(4) | 155.03(16) |

**Table 3**
Selected bond distances (Å) and angles (°) for *catena*-Poly[[trimethyltin(IV)]-μ-2-[(3-oxocyclohex-1-enyl)amino]benzoato-$\kappa^2$O:O′].

| | | | |
|---|---|---|---|
| C(11) – O(3) | 1.237(6) | Sn – O(1) | 2.174(4) |
| C(13) – O(1) | 1.296(5) | Sn(1) – O(3) | 2.496(4) |
| C(13) – O(2) | 1.227(6) | | |
| O(1) – Sn – O(3) | 174.13(13) | C(14) – Sn – C(15) | 120.1(3) |
| C(14) – Sn – C(16) | 125.5(3) | C(15) – Sn – C(16) | 112.5(3) |

*albicans*, can infect the oral and vaginal cavities, skin, while *Cryptococcus neoformans* infections sometimes can be fatal to humans [50]. Both can seriously affect essential organs [51,52].

Antifungal therapies include two main classes of compounds: polyene [53] and azole drugs [54]. The former class comprises nystatin and amphotericin that act in the membrane of the fungal cell linking to ergosterol. These drugs interfere with the permeability of the membrane, causing losses of macromolecules and ions essentials to the survival of the fungal cell. The antifungal activity of azole arises from interaction with the sterol-14α-demthyllase (CYP51), involved in the biosynthesis of ergosterol. Such interactions results in a decreased availability of ergosterol and an accumulation of 14-methylsterols. Changes in ergosterol levels and sterol structure influence the membrane permeability and the activity of several metabolic pathways [55]. Metal-based compounds might represent an alternative therapeutic route since most of the clinical used drugs normally present problems with resistance and toxicity [56].

The antifungal activity of organotin complexes have been investigated for quite a long time [57]. A number of mechanisms for the biological action of organotin derivatives have been proposed. However, a complete understanding has still to be found [58–60]. The crossing of the cytoplasmatic membrane by organotin derivatives might be a consequence of lipid-solubility [61] effected by weak interactions with the aminoacids, proteins [62], nucleosides, carbohydrates and steroids [63], present in the cell membrane.

Complexes **(1)**–**(6)** have been tested against *C. Albicans* and *C. Neoformans*. Complexes **(3)**, **(5)** and **(6)** displayed good biocide activity against both the microorganism, in comparison to the organotin halide employed in the synthesis or to ketoconazol, used as standard, Table 4.

The cytotoxicity of complexes **(1)**–**(6)** has been screened in order to verify how toxic they are to human kidney cells (HEK293). Complexes **(3)** and **(5)** displayed low cytotoxicity in view of the high $IC_{50}$ values, in comparison with the other complexes, the organotin halide and ketoconazol, Table 5. It means that it is necessary high dosage of complexes **(3)** and **(5)** to produce a toxic effect in samples of human kidney cells. If these results are compared to the antifungal assays, compound **(5)** can be pointed out as a promising substance to be subject of further investigations, since it comprises high MIC values and low cytotoxicity results.

The results obtained indicate the order of the fungicidal activity as: $Bu_3SnOBz > Ph_3SnOBz > Ph_2SnOBz_2 >$ organotin halides. Which agrees with other previous work [27,52,64]. It is well established that the biological activity of related compounds depends upon the (i) structure, (ii) the type and (iii) number of organic groups attached to the organotin moiety. It is not a surprise that the tributyltin containing complex, is the more active, since studies have suggested that toxicity of organotin complexes correlates with total molecule surface (TSA) and hence *n*-propyl, *n*-butyl, *n*-pentyl, etc, should be more toxic for microorganisms than ethyl, methyltin based complexes. It seems that in this case the biological activity might occur by an intracellular mechanism by transport through cell membrane, as pointed out by us previously [27,28]. Therefore the order of biological activity suggests a close correlation between activity and lipophilicity [57,65].

### 2.3. Conclusions

Complexes **(1)**–**(6)** were prepared and fully characterized by a series of spectroscopic methods. Complexes **(3)**, **(5)** and **(6)** displayed good biocidal activity against *C. Albicans* and *C. Neoformans*. In addition complexes **(3)** and **(5)** displayed low cytotoxicity towards human kidney cells. Complex **(5)** showed promising results in our investigation. In spite of all controversy around the toxicity of organotin towards superior species it is possible that some of their complexes are not as hazardous as organotin halides. Therefore, complex **(5)** might represent a new class of drug to be employed alone or in combination with others in current use as new formulations for fungal diseases to overcome resistance.

## 3. Experimental

### 3.1. Chemistry

#### 3.1.1. Materials and methods

All starting materials were purchased from Aldrich, Merck or Synth and used as received. NMR spectra were recorded at 400 MHz using a Bruker DPX-400 spectrometer equipped with an 89 mm wide-bore magnet. $^1H$ and $^{13}C$ shifts are reported relative to $SiMe_4$

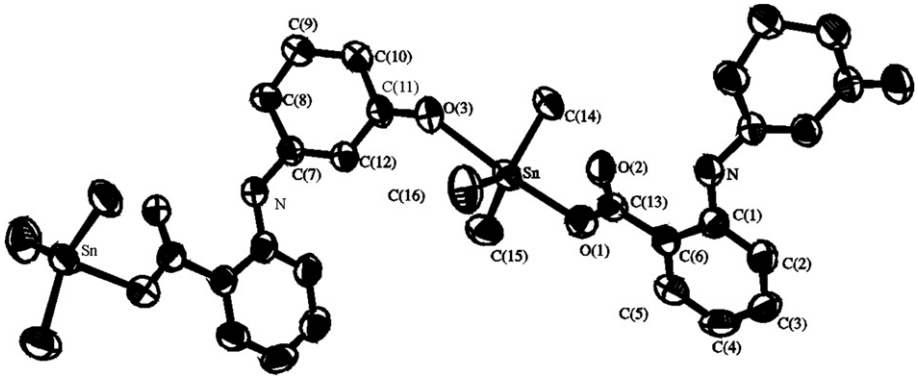



**Fig. 2.** The molecular structure of *catena*-Poly[[trimethyltin(IV)]-μ-2-[(3-oxocyclohex-1-enyl)amino]benzoato-$\kappa^2$O:O′].

**Table 4**
Minimal inhibitory concentrations (MIC) for organotin complexes **(1)**–**(6)** and starting materials towards *C. albicans* and *C. neoformans*.

| Compounds | *C. albicans*/MIC ($10^{-4}$ mmol $L^{-1}$) | *C. neoformans*/MIC ($10^{-6}$ mmol $L^{-1}$) |
|---|---|---|
| **(1)** | 100 | – |
| **(2)** | 150 | – |
| **(3)** | 3.0 | 6.0 |
| **(4)** | – | – |
| **(5)** | 0.1 | 0.5 |
| **(6)** | 0.9 | 2.0 |
| $SnMe_2Cl_2$ | 68.5 | 80 |
| $SnBu_2Cl_2$ | 45.1 | 70 |
| $SnPh_2Cl_2$ | 58.2 | 90 |
| $SnMe_3Cl$ | 5.6 | 200 |
| $SnBu_3Cl$ | 3.8 | 100 |
| $SnPh_3Cl$ | 6.5 | 800 |
| Ketoconazol | 2.4 | 600 |
| Ligand | – | – |

and $^{119}Sn$ shifts relative to $SnMe_4$. The infrared spectra were recorded with samples pressed as KBr pellets on a Perkin–Elmer 283B spectrometer in the range of 4000–400 $cm^{-1}$. Carbon, hydrogen and nitrogen analysis were performed on a Perkin–Elmer PE-2400 CHN-analysis using tin sample-tubes. $^{119}Sn$-Mössbauer spectra were run in standard equipment at liquid nitrogen temperature using a $BaSnO_3$ source kept at room temperature. Intensity data for the X-ray study were collected at 293(2) K on a Siemens XSCANS, using a Kα Mo radiation ($\lambda = 0.71073$ Å). The cell refinement was performed using an XSCANS program and the structure was solved employing the SHELXS97 software (Sheldrick, 1997) [66,67]. Further details are given in Table 1. All non-H atoms were refined anisotropic. The carbon H atoms were positioned stereochemically and were refined with fixed individual displacement parameters [Uiso (H)Z1.2 Ueq (C)] using the SHELXL riding model.

### 3.1.2. Synthesis of [2-(3-oxocyclohex-1-enyl)benzoic acid]

To a round-bottom-flask charged with 2-aminobenzoic acid (2.74 g, 0.02 mol) dissolved in methanol (20 mL) was slowly dropped an alcoholic solution of 1,3-cyclohexadione (2.24 g, 0.02 mol in 20 mL of methanol). The mixture was refluxed and stirred for 4 h and then it was observed a colour change from colourless to yellow. The solution was cooled to room temperature and the solvent was removed in vacuum and the yellow solid washed with ethyl ether. X-ray quality crystals were obtained after a slow evaporation of a methanol/water solution. Yield 75%. Mp. 183.7–185.5 °C. IV (ν/$cm^{-1}$): 1685 ($\nu_{CO}$), 1655 ($\nu_{COO}$)$_{as}$, 1492 ($\nu_{COO}$)$_s$, 1376 ($\nu_{C-N}$). $^1H$ NMR ($CDCl_3$, 400.13 MHz), δ 7.97–7.92 d ($C_6H_4$), 7.4 m ($C_6H_4$), 7.09 t ($C_6H_4$), 5.58 s (N*H*), 3.20 s ($C_6H_7$) 2.51–2.48 m ($C_6H_7$), 2.26–2.27 m ($C_6H_7$), 1.95–1.92 m ($C_6H_7$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.61 MHz), δ 201. 89 (*C*OO), 170.38 (*C*O), 165.43 ($C_6H_7$), 141.93 ($C_6H_4$), 134.64 ($C_6H_4$), 133.26 ($C_6H_4$), 125.35 ($C_6H_4$), 124.64 ($C_6H_4$), 122.58 ($C_6H_4$), 100.94 ($C_6H_7$), 37.12 ($C_6H_7$), 31.07 ($C_6H_7$), 22.92 ($C_6H_7$). Elemental Analysis for $C_{13}H_{13}NO_3$ found (calc.): C 67.21 (67.52), H 5.43 (5.66), N 5.96 (6.05).

**Table 5**
Cytotoxicity activity ($IC_{50}$) for organotin complexes **(1)**–**(6)**, and some reference compounds towards human embryonic kidney cells (HEK293).

| Compounds | IC50 ($10^{-4}$ mmol $L^{-1}$) | Compounds | IC50 ($10^{-4}$ mmol $L^{-1}$) |
|---|---|---|---|
| **(1)** | 27 | $Me_2SnCl_2$ | 0.1 |
| **(2)** | 21 | $Bu_2SnCl_2$ | 0.3 |
| **(3)** | 48 | $Ph_2SnCl_2$ | 0.5 |
| **(4)** | 17 | $Me_3SnCl$ | 0.08 |
| **(5)** | 52 | $Bu_3SnCl$ | 0.4 |
| **(6)** | 8 | $Ph_3SnCl$ | 0.1 |
| Ketoconazol | 0.6 | | |
| Ligand | 120 | | |

### 3.1.3. Synthesis of [dimethylstannoxane-2-[(3-oxocyclohex-1-enyl)amino]benzoato] **(1)**

To a round-bottom-flask containing [2-(3-oxocyclohex-1-enyl)benzoic acid] (1.0 g, 4.32 mmol) and triethylamine (0.6 mL, 4.3 mmol) dissolved in methanol, it was slowly added $SnMe_2Cl_2$ (0.48 g, 2.2 mmol) also in methanol (30 mL). After 4 h of reflux the solvent was removed in *vacuo* and washed with hot water, yielding a yellow solid. X-ray quality crystals were obtained from a methanol/water solution (3:1). Yield 70%. Mp 140.0–142.0 °C. IV (ν/$cm^{-1}$), 1684 ($\nu_{CO}$), 1625 ($\nu_{COO}$)$_{as}$, 1373 ($\nu_{COO}$)$_s$, 1320 ($\nu_{C-N}$), 657 ($\nu_{Sn-C}$)$_{as}$, 511 ($\nu_{Sn-C}$)$_s$, 447 ($\nu_{Sn-O}$). $^1H$ NMR (DMSO-$d_6$, 400.13 MHz), (δ): 8.63 m ($C_6H_4$), 8.06 m ($C_6H_4$), 7.72 m ($C_6H_4$), 6.23 s (N*H*), 3.05–3.03 m ($C_6H_7$) 2.81–2.78 m ($C_6H_7$), 2.47–2.44 m ($C_6H_7$), 3.82 s ($C_6H_7$), 1.58 s (*C*$H_3$). $^{13}C\{^1H\}$ NMR (DMSO-$d_6$, 100.61 MHz), δ 199.50 (COO), 170.44 (CO), 162.62 ($C_6H_4$), 141.84 ($C_6H_4$), 133.95 ($C_6H_4$), 133.59 ($C_6H_4$), 124.37 ($C_6H_4$), 124.21 (*C*$_6H_4$), 101.58 ($C_6H_7$), 101.56 ($C_6H_7$), 37.57 ($C_6H_7$), 31.19 ($C_6H_7$), 22.83 ($C_6H_7$), 11.69 ($^1J^{13}$ C–$^{119}$Sn = 825 Hz) (*C*$H_3$). $^{119}Sn\{^1H\}$ NMR (DMSO-$d_6$, 149.21 MHz), **δ** − 36 ($^1J^{119}$Sn–$^{13}$C = 825 Hz). $^{119}$Sn-Mössbauer(mm $s^{-1}$), δ 1.27, Δ 4.19. Elemental analysis for $C_{30}H_{36}N_2O_8Sn_2$ (%): found (calc.): C 45.27 (45.61), H 4.39 (4.59), N 3.49 (3.55).

### 3.1.4. Synthesis of [2-[(3-oxocyclohex-1-enyl)amino]benzoate-dibutylstannoxane] **(2)**

Prepared accordingly using [2-(3-oxocyclohex-1-enyl)benzoic acid] (1.0 g, 4.32 mmol), triethylamine (0.6 mL, 4.32 mmol) and SnBu2Cl2 (1.31 g, 4.32 mmol). Mp. 125.0–130.0 °C. IV (ν/$cm^{-1}$), 1685 ($\nu_{CO}$), 1615 ($\nu_{COO}$)$_{as}$, 1376 ($\nu_{COO}$)$_s$, 1331 ($\nu_{C-N}$), 649 ($\nu_{Sn-C}$)$_{as}$, 509 ($\nu_{Sn-C}$)$_s$, 472 ($\nu_{Sn-O}$). $^1H$ NMR ($CDCl_3$, 400.13 MHz),7.96–7.92 d ($C_6H_4$), 7.5 m ($C_6H_4$), 7.10 t ($C_6H_4$), 5.61 s (N*H*), 3.50–3.40 m ($C_6H_7$) 2.74 m ($C_6H_7$), 2.49–2.20 m ($C_6H_7$), 1.86 s ($C_6H_7$), 1.59 m ($C_4H_7$), 1.41 m ($C_4H_7$), 0.78 m ($C_4H_7$), 0.75 t ($C_4H_7$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.61 MHz), δ 201.14 (COO), 170.51 (*C*O), 168.10 ($C_6H_4$), 137.90 ($C_6H_4$), 132.59 ($C_6H_4$), 131.26 ($C_6H_4$), 127.99 ($C_6H_4$), 126.93 ($C_6H_4$), 126.02 ($C_6H_7$), 96.59 ($C_6H_7$), 36.96 ($C_6H_7$), 28.01 ($C_6H_7$), 27.69 ($C_6H_7$), 26.93($^1J^{13}$ C– $^{119}Sn$ = 799 Hz) ($C_4H_7$), 20.89 ($C_4H_7$), 17.43 ($C_4H_7$), 13.63 ($C_4H_7$). $^{119}Sn\{^1H\}$ NMR ($CDCl_3$, 149.21 MHz), δ − 82 ($^1J^{119}$Sn–$^{13}C$ = 799 Hz). $^{119}$Sn-Mössbauer (mm $s^{-1}$), δ 1.25, Δ 3.16. Analysis for $C_{42}H_{60}N_2O_8Sn_2$, found (calc.): C 52.55 (52.66), H 6.21 (6.27), N 2.82 (2.92).

### 3.1.5. Synthesis of [diphenylstannoxane-2-[(3-oxocyclohex-1-enyl)amino]benzoato] **(3)**

Similarly prepared employing [2-(3-oxocyclohex-1-enyl)benzoic acid] (1.0 g, 4.32 mmol), triethylamine (0.6 mL, 4.3 mmol) and $SnPh_2Cl_2$ (0.8 g, 2.2 mmol) in methanol (30 mL). Yield 65%. Mp 131–133.0 °C. IV (ν/$cm^{-1}$), 1683 ($\nu_{CO}$), 1621 ($\nu_{COO}$)$_{as}$, 1377 ($\nu_{COO}$)$_s$, 1330 ($\nu_{C-N}$), 279 ($\nu_{Sn-C}$)$_{as}$, 228 ($\nu_{Sn-C}$)$_s$, 453 ($\nu_{Sn-O}$). $^1H$ NMR (DMSO-$d_6$, 400.13 MHz), (δ): 10.72–10.44 m ($C_6H_4$), 10.14–10.05 m ($C_6H_4$), 10.00–9.72 m ($C_6H_4$), 5.8 s (N*H*), 3.96–3.89 m ($C_6H_7$) 2.47–2.35 m ($C_6H_7$), 2.07–2.04 m ($C_6H_7$), 1.91 s ($C_6H_7$), 5.26–5.18 m ($C_6H_5$), 5.08–4.93 m ($C_6H_5$), 4.80–4.60 m ($C_6H_5$). $^{13}C\{^1H\}$ NMR (DMSO-$d_6$, 100.61 MHz), δ 201.3 (COO), 169.55 (CO), 166.25 ($C_6H_4$), 140.76 ($C_6H_4$), 133.25 ($C_6H_4$), 131.94 ($C_6H_4$), 129.33 ($C_6H_4$), 123.03 ($C_6H_4$), 121.64 ($C_6H_7$), 101.94 ($C_6H_7$), 35.68 ($C_6H_7$), 31.88 ($C_6H_7$), 21.25 ($C_6H_7$), 162.12 ($C_6H_5$), ($^1J^{13}C$–$^{119}$Sn = 929 Hz) 135.87 ($C_6H_5$), 129.13 ($C_6H_5$), 116.55($C_6H_5$). $^{119}Sn\{^1H\}$ NMR (DMSO-$d_6$, 149.21 MHz), δ 69 ($^1J^{119}$Sn–$^{13}C$ = 933 Hz). $^{119}$Sn-Mössbauer(mm $s^{-1}$), δ 1.29, Δ 3.08. Elemental analysis for $C_{30}H_{36}N_2O_8Sn_2$ (%): found (calc.): C 57.48 (57.84), H 4.17 (4.27), N 2.59 (2.70).

*3.1.6. Synthesis of [{trimethyltin(IV)}-2-[(3-oxocyclohex-1-enyl)amino]benzoato]* ***(4)***

To a round-bottom-flask charged with [2-(3-oxocyclohex-1-enyl)-benzoic acid] (1.0 g, 4.32 mmol) and triethylamine (0.6 mL, 4.32 mmol) dissolved in methanol(20 mL) it was slowly added $SnMe_3Cl$ (0.86 g, 4.32 mmol). Within 4 h of reflux the solvent was removed in *vacuo* and the resultant solid material was washed with hot water, yielding a pale-yellow solid. X-ray quality crystals were obtained from a methanol/water solution (3:1). Yield 72%. Mp. 167–170. °C. IV ($\nu$/cm$^{-1}$), 1658 ($\nu_{CO}$), 1598 ($\nu_{COO}$)$_{as}$, 1366 ($\nu_{COO}$)$_s$, 1350 ($\nu_{C-N}$), 639 ($\nu_{Sn-C}$)$_{as}$, 502 ($\nu_{Sn-C}$)$_s$, 473 ($\nu_{Sn-O}$). $^1$H NMR (DMSO-$d_6$, 400.13 MHz), $\delta$ 9.31–9.27 m ($C_6H_4$), 8.7–8.65 m ($C_6H_4$), 8.5–8.2 m ($C_6H_4$), 5.7 s (N*H*), 3.7–3.6 m ($C_6H_7$), 3.25 m ($C_6H_7$), 2.4–2.0 m ($C_6H_7$), 2.44 s ($C_6H_7$), 1.86 s ($CH_3$). $^{13}$C{$^1$H} NMR (DMSO-$d_6$, 100.61 MHz), $\delta$ 199.73 (COO), 173.47 (CO), 160.72 ($C_6H_4$), 141.56 ($C_6H_4$), 133.13 ($C_6H_4$), 132.52 ($C_6H_4$), 122.41 ($C_6H_4$), 120.95 ($C_6H_4$), 119.45 ($C_6H_7$), 101.90 ($C_6H_7$), 58.37 ($C_6H_7$), 36.27 ($C_6H_7$), 21.38 ($C_6H_7$), 18.32 ($CH_3$) ($^1J^{13}C$–$^{119}Sn$ = 1590 Hz). $^{119}$Sn{$^1$H} NMR (DMSO-$d_6$, 149.21 MHz), $\delta$ 97 ($^1J^{119}Sn$–$^{13}C$ = 1588 Hz). $^{119}$Sn-Mössbauer (mm s$^{-1}$), $\delta$ 1.45, $\Delta$3.52. Analysis for $C_{16}H_{21}NO_3Sn$ found (calc.): C 48.41 (48.76), H 5.37 (5.38), N 3.46 (3.55).

*3.1.7. Synthesis of [{tributyltin(IV)}-2-[(3-oxocyclohex-1-enyl)amino]benzoato]* ***(5)***

Prepared in the same manner reacting [2-(3-oxocyclohex-1-enyl)benzoic acid] (1.0 g, 4.32 mmol), triethylamine (0.6 mL, 4.3 mmol) and $SnBu_3Cl$ (1.4 g, 4.3 mmol) in methanol (35 mL). Yield 74%. Mp 179–181 °C. IV ($\nu$/cm$^{-1}$), 1652 ($\nu_{CO}$), 1595 ($\nu_{COO}$)$_{as}$, 1365 ($\nu_{COO}$)$_s$, 1331 ($\nu_{C-N}$), 647 ($\nu_{Sn-C}$)$_{as}$, 511 ($\nu_{Sn-C}$)$_s$, 471 ($\nu_{Sn-O}$). Mp. 125.0–130.0 °C. IV ($\nu$/cm$^{-1}$): 471 ($\nu_{Sn-O}$). $^1$H NMR ($C_6D_6$, 400.13 MHz), $\delta$ 8.2–8.07 m ($C_6H_4$), 7.58–7.50 m ($C_6H_4$), 7.10 m ($C_6H_4$), 6.12 s (N*H*), 3.74 m ($C_6H_7$), 3.39 m ($C_6H_7$), 2.4–2.0 m ($C_6H_7$), 1.81 s ($C_6H_7$), 1.64 m ($C_4H_7$), 1.41 m ($C_4H_7$), 1.29 m ($C_4H_7$), 0.92 t ($C_4H_7$). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100.61 MHz), $\delta$ 201.78 (COO), 173.88 (CO), 164.88 ($C_6H_4$), 140.99 ($C_6H_4$), 132.67 ($C_6H_4$), 132.16 ($C_6H_4$), 124.39 ($C_6H_4$), 122.50 ($C_6H_4$), 126.02 ($C_6H_7$), 96.62 ($C_6H_7$), 31.47 ($C_6H_7$), 29.28 ($C_6H_7$), 28.01 ($C_6H_7$), 22.94 ($^1J^{13}C$– $^{119}Sn$ = 1427 Hz) ($C_4H_7$), 20.21 ($C_4H_7$), 14.10 ($C_4H_7$), 9.27 ($C_4H_7$). $^{119}$Sn{$^1$H} NMR (DMSO-$d_6$, 149.21 MHz), $\delta$ – 161 ($^1J^{119}Sn$–$^{13}C$ = 1428 Hz). $^{119}$Sn-Mössbauer (mm s$^{-1}$), $\delta$ 1.42, $\Delta$3.57. Elemental analysis for $C_{25}H_{39}NO_3Sn$ (%), found (calc.): C 57.69 (57.72), H 7.48 (7.56), N 2.54 (2.69).

*3.1.8. Synthesis of [{triphenyltin(IV)}-2-[(3-oxocyclohex-1-enyl)amino]benzoato]* ***(6)***

Prepared accordingly by reacting [2-(3-oxocyclohex-1-enyl)benzoic acid] (1.0 g, 4.32 mmol), triethylamine (0.6 mL, 4.3 mmol) and SnPh3Cl (1.7 g, 4.3 mmol) in methanol (30 mL). Yield 68%. Mp 122–124 °C. IV ($\nu$/cm$^{-1}$), 1658 ($\nu_{CO}$), 1602 ($\nu_{COO}$)$_{as}$, 1376 ($\nu_{COO}$)$_s$, 1344 ($\nu_{C-N}$), 285 ($\nu_{Sn-C}$)$_{as}$, 232 ($\nu_{Sn-C}$)$_s$, 453 ($\nu_{Sn-O}$). $^1$H NMR (DMSO-$d_6$, 400.13 MHz), $\delta$ 8.11–7.92 m ($C_6H_4$), 7.41–7.24 m ($C_6H_4$), 7.07–7.0 m ($C_6H_4$), 5.64 s (N*H*), 3.7 m ($C_6H_7$) 2.25–2.15 m ($C_6H_7$), 2.06–2.04 m ($C_6H_7$), 1.85 s ($C_6H_7$), 5.35–5.27 m ($C_6H_5$), 5.02–4.97 m ($C_6H_5$), 4.67–4.45 m ($C_6H_5$). $^{13}$C{$^1$H} NMR (DMSO-$d_6$, 100.61 MHz), $\delta$ 199.23 (COO), 173.13 (CO), 162.38 ($C_6H_4$), 142.83 ($C_6H_4$), 134.02 ($C_6H_4$), 133.67 ($C_6H_4$), 125.30 ($C_6H_4$), 124.02 ($C_6H_4$), 122.57 ($C_6H_7$), 102.56 ($C_6H_7$), 48.31 ($C_6H_7$), 38.18 ($C_6H_7$), 23.46 ($C_6H_7$), 138.83 ($C_6H_5$) ($^1J^{13}C$-$^{119}Sn$ = 1771 Hz), 130.88 ($C_6H_5$), 130.10 ($C_6H_5$), 129.43 ($C_6H_5$). $^{119}$Sn{$^1$H} NMR (DMSO-$d_6$, 149.21 MHz), $\delta$ – 193 ($^1J^{119}Sn$–$^{13}C$ = 1771 Hz). $^{119}$Sn-Mössbauer (mm s$^{-1}$), $\delta$ 1.40, $\Delta$ 3.16. Elemental analysis for $C_{31}H_{27}NO_3Sn$ (%): found (calc.): C 64.22 (64.18), H 4.54 (4.69), N 2.29 (2.41).

*3.2. Pharmacology*

*3.2.1. Antifungal activity of organotin compounds*

The antifungal activity of organotin compounds towards *C. albicans* (ATCC18804) and *C. neoformans* (ATCC24067D2) was assayed by the minimal inhibitory concentration (MIC) in liquid media according to the NCCLS M27-A protocol (2002). Fungi cells were obtained from cultures of *C. albicans* and *C. neoformans* grown on Sabouraud medium for 24 and 48 h, respectively. The minimal concentration of organotin able to inhibit the growth of the yeasts on RPMI 1640 medium was assayed on a 96 well plate. To each well 100 μl of an organotin solution was added and the plate was incubated at 37 °C for 48 h. Ketoconazol and DMSO 1 and 2% in RPMI were also tested and used as positive and negative controls. The experiments were performed in triplicate and according to the NCCLS M27 protocol. The endpoints were determined visually by comparison with the drug-free growth control well. MICs were defined as the lowest compound concentration for which the well was optically clear, and were expressed in mm L$^{-1}$.

*3.2.2. Cytotoxicity assay for organotin complexes towards human kidney cells (HEK293)*

Cytotoxicity assays for organotin derivatives **(1)**–**(6)** was performed. Human embryonic kidney cells (HEK293) were cultured in Dulbecco's minimal essential medium (DMEM) supplemented with 5% fetal calf serum (Cultilab), an antibiotic (gentamycin), and were incubated at 37 °C in a 5% $CO_2$ atmosphere for 24 h until formation of a confluent monolayer. Subsequently, 100 μl solutions of the test drugs, organotin or ketoconazole, were added in concentrations ranging from $6 \times 10^{-4}$ to $1 \times 10^{-6}$ mmol L$^{-1}$. The culture was further incubated for 24 h and 20 μl of 3-(4,5-dimetylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT-Sigma) solution (5 mg/ml) in phosphate-buffered saline, pH 7.4, were added to each well and re-incubated at 37 °C for 4 h. Supernatants were removed and 200 μl of a solution of HCl (0.04 mol L$^{-1}$) in isopropanol were added to the plates to dissolve MTT precipitates. Absorbance at 540 nm was then measured using the microplate spectrophotometer system SpectraMax 190 (Molecular Devices). The assay was performed in triplicates and results analysed by ANOVA and Student-Newman–Kewls tests ($P < 0.05$). The $IC_{50}$ for each complexes was determined in mmol L$^{-1}$.

## 4. Supplementary data

Crystallographic data are available on request from: (i) IUCr reference GW2023 for complex **(4)** respectively, and complex **(2)** at Cambridge Crystallographic Data Centre on quoting the deposition numbers CCDC 698568.

## Acknowledgements

This work was supported by CNPq and FAPEMIG – Brazil.

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