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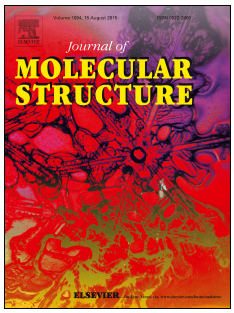

Homoleptic tin(IV) compounds containing tridentate ONS dithiocarbazate Schiff bases: Synthesis, X-ray crystallography, DFT and cytotoxicity studies

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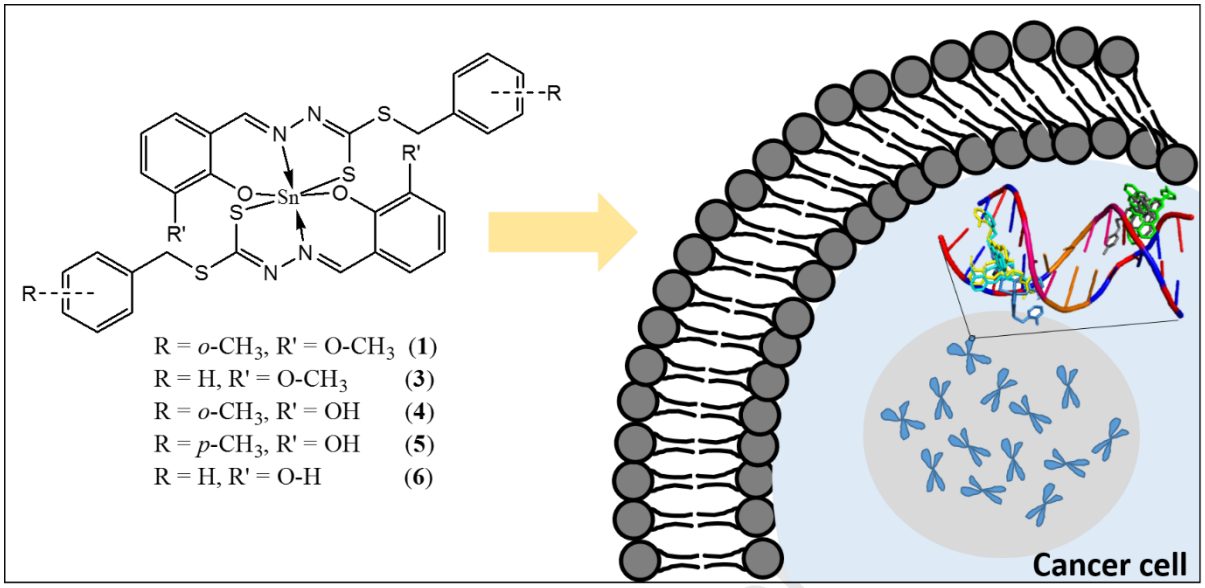
Graphical Abstract



Highlight

A series of octahedral homoleptic tin(IV) compounds were designed, synthesised and evaluated for their *in vitro* cytotoxicity against ten cancer cells.

Homoleptic tin(IV) compounds containing tridentate ONS dithiocarbazate Schiff bases: Synthesis, X-ray crystallography, DFT and cytotoxicity studies

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Abstract Six new tin(IV) compounds derived from tridentate dinegatively charged ONS dithiocarbazate Schiff bases derived from 2-hydroxy-3-methoxybenzaldehyde (H_2L1, H_2L2 and H_2L3) and 2,3-dihydroxybenzaldehyde (H_2L4, H_2L5 and H_2L6) (where H_2Ln = di-acids of Schiff base) are reported. The compounds were characterised by elemental analysis, FT-IR and multinuclear NMR (^1H, ^{13}C and ^{119}Sn) spectroscopy. The crystal structures of tin(IV) [*S*-4-methybenzyl-*β*-*N*-(2-hydroxy-3-methoxybenzylmethylene)dithiocarbazate] (**2**) and tin(IV) [*S*-benzyl-*β*-*N*-(2-hydroxy-3-methoxy benzylmethylene)dithiocarbazate] (**3**) were determined by X-ray single crystal diffraction analysis. X-ray crystallography showed the molecular geometries in homoleptic **2** and **3** to be quite similar in which the dinegative tridentate ligand coordinated the tin atoms via thiolate-S, phenoxide-O and imine-N atoms. The coordination geometries are based on an octahedron with like-atoms mutually trans. The

experimental findings were validated by density functional theory (DFT) calculations at the B3LYP/LanL2DZ/6-311G(d,p) level of theory. All the tin(IV) compounds, except the insoluble compound **2** were screened for their in vitro cytotoxicity against a panel ten of cancer cell lines and one normal breast cell line (MCF-10A) by MTT assay. Interestingly, the cytotoxicity of five tin(IV) compounds against HT29, MCF7 and MIA was higher than the reference drug, cisplatin.

Keywords tin complex; X-ray crystallography; cytotoxicity

1. Introduction

Metal ions play an important role in biological systems and are involved in various applications, such as cancer therapy and diagnosis of diseases [1]. Metal-based drugs including compounds of mercury, copper, gold and arsenic have been used since ancient Egyptian, Greek and Chinese societies to treat a broad spectrum of diseases including cancer [2–4]. For example, mercury sulphide (cinnabar) was used in the treatment of ailments and arsenic trioxide (ATO) for the treatment of rheumatoid diseases, syphilis and psoriasis. In the 18th century until early 20th century, ATO was among the first group of compounds used in the treatment of leukemia, before it was replaced by radiation and chemotherapeutic agents [4]. Targeting cancer with chemotherapy after the failure of other therapeutic treatments was a valid option due to the effectiveness and action of the chemotherapeutic drugs throughout the entire body [5]. In the 1960s, a platinum-based drug, cisplatin was discovered for cancer treatments [6] and following its success, the development of platinum drugs flourished, with some of them approved as chemotherapeutic drugs. However, platinum-based drugs suffer from ineffectiveness in the treatment of platinum-resistant cancers and also have severe side effects. Despite the wide use of platinum-based drugs, their biggest challenges - unclear therapeutic mechanisms and high toxicity - remain. Hence, the development of improved non-platinum-based anticancer drugs became one of the fundamental goals in medicinal chemistry.

There are many possible advantages in using non-platinum-based compounds, such as: (i) a variety of coordination sites, (ii) diversity of oxidation states and (iii) affinity and kinetics of the bound organic ligands [7–9]. Keeping this in view, tin(IV) compounds have shown a wide range of applications and were one of the most in-demand class of organometallic

compounds due to their biomedical effectiveness as antifouling, antimicrobial and antiviral agents. Saxena and Huber (1989) reported that tin-based compounds were known to localise in tumour tissues, hence explaining their effectiveness [10–12]. Since then, tin-based compounds have been in the pipeline as potential chemotherapeutic drugs to modulate toxicity effects. On top of reduced side effects, tin(IV) compounds exhibited no gametogenesis, as cisplatin did, and had increased solubility in water. Tin(IV) compounds also did not develop tumour drug resistance which was reported to be the major problem in chemotherapy for cisplatin and its analogues towards certain cancer cells [13–15]. Further, tin(IV) compounds had potential industrial applications, such as bactericides, fungicides and pesticides [16–20].

Ligand selectivity can be introduced into a system in order to determine their effectiveness in bioactivity, particularly in anticancer activity. Ligands not only modify the solubility in lipid permeable membranes, but also play a role in transporting and addressing the compound to their specific target site [21]. On this note, Schiff bases have long been studied as potential target ligands to enhance the bioactivity of chemotherapeutic drugs. Schiff bases can coordinate to the tin centre and form stable ligand-tin bonds. Therefore, any modification of the structure could modulate the structural diversity and activity of the entire compound [22]. A number of reports [23–31] on the complexation of dithiocarbazate Schiff bases have received much attention because of their special abilities, including (i) formation of an interesting series of ligands where the properties can be greatly modified by introducing different types of aldehyde or ketones and (ii) the interaction of donor atoms to the centre metal ions creating different geometries and properties, as well as their potential biological activities [32]. The number and diversity of applications of tin(IV) compounds, and the synthesis and characterisation of tin(IV) compounds containing O-, N-, S- donor Schiff bases have been a subject of interest for researchers in the inorganic field, where sulphur is of paramount importance in the metal-ligand linkage. The well elucidated structures of the Schiff base containing compounds showed interesting biological activities depending on their substituents and geometries [33–35].

In view of all these findings and in continuation of our previously reported research work [36] on the chemistry, therapeutic potential and structure-activity relationship of tin(IV) compounds coordinated with two dithiocarbazate Schiff bases, we report here the synthesis of six new octahedral tin(IV) compounds derived from 2-hydroxy-3-methoxybenzaldehyde and

2,3-dihydroxybenzaldehyde dithiocarbazate. The compounds were characterised by FT-IR, multinuclear NMR (^{1}H, ^{13}C and ^{119}Sn), mass spectroscopy, UV-vis and density functional theory (DFT) calculations. The *in vitro* cytotoxicity studies were explored and the compounds were found to have good activity against the tested cell lines.

2. Experimental Section

2.1. Materials and Instruments

All solvents and reagents were of analytical reagent grade and used without further purification. Chemicals: hydrazine hydrate, 80% (Fluka), benzylchloride, ≥ 99% (Merck), 2-methybenzyl chloride, 99% (ACROS), 4-methylbenzyl chloride (ACROS), potassium hydroxide (HmbG), carbon disulphide (Merck), 2-hydroxy-3-methoxybenzaldehyde (Merck), tin(II) dichloride, 97% (Merck), trimethylamine and > 99% (Sigma Aldrich). Solvents: acetonitrile (Baker), absolute ethanol, 99.8% (Scharlau), ethanol, 95% (J. Kollin Chemical), methanol (Fisher Scientific) and dimethylsulfoxide (Scharlau). Melting points were determined using an Electrothermal digital melting point apparatus. C, H and N elemental analyses were carried out using a LECO CHNS-932 instrument and Thermo Flash EA110 elemental analyser. FT-IR spectra were recorded using PerkinElmer Spectrum 100 with Universal ATR Polarization in the range of 4000–280 cm^{-1} at room temperature. Molar conductivities of 10^{-3} M solutions of the metal complexes in DMSO were measured at 27 °C using a Jenway 4310 conductivity meter and a dip-type cell with a platinized electrode. Electronic spectra were recorded on a Shimadzu UV-2501 PC recording spectrophotometer (1000–200 nm). Multinuclear (^{1}H and ^{13}C) Nuclear Magnetic Resonance (NMR) spectroscopic analyses were recorded using NMR JNM ECA400 spectrometer. ^{119}Sn NMR were measured using a Bruker BioSpin Avance III (600 MHz) spectrometer.

2.2. Synthesis

2.2.1. Synthesis of Schiff bases

Schiff bases were synthesised following references [37,36]. Dithiocarbazate (S-2-methylbenzyldithiocarbazate, S-4-methylbenzyldithiocarbazate or S-benzyldithiocarbazate) (10 mmol) was dissolved in hot acetonitrile or ethanol (100 cm^{3}) and added to an equimolar

amount of 2-hydroxy-3-methoxybenzaldehyde (1.52 g) or 2,3-dihydroxybenzaldehyde (1.38 g) in absolute ethanol (20 cm^3). The mixture was heated (80 °C) with continuous stirring for about 30 min and then allowed to stand overnight at room temperature. The resultant product was recrystallised from CH_3CN/EtOH (1:1) to give a light-yellow crystalline solid that was filtered and washed with cold absolute ethanol.

*2.2.2. Synthesis of tin(IV) compounds (**1-3**)*

The Schiff base (0.35 g (H_2L1, H_2L2); 0.33 g (H_2L3, H_2L4, H_2L5); 0.32g (H_2L6), 1 mmol) was dissolved in absolute ethanol (50 cm^3) and dichloromethane (20 cm^3) and was mixed with an ethanolic solution (2 mmol) of triethylamine. With continuous stirring, an ethanolic solution of $SnCl_2$ (0.20 g, 1 mmol) was added to the mixture. A cloudy solution formed which was filtered. The yellow filtrate was then heated under reflux for *ca* 6 h. The mixture was left overnight and the reduction of the volume of the reaction mixture resulted in an orange precipitate, which was filtered off. The precipitate was recrystallised in dry ether to remove the remaining triethylamine hydrochloride salt from the mixture.

*2.2.2.1. Tin(IV) [S-2-methylbenzyl-β-N-(2-hydroxy-3-methoxybenzylmethylene) dithiocarbazate] (**1**)*

Orange solid. Yield: 82%. Melting point: >300°C. Analysis calculated for $C_{34}H_{32}N_4O_4S_4Sn$: C, 50.56; H, 3.99; N, 6.94%. Found: C, 50.87; H, 3.58; N, 5.27%. FT-IR (ATR, cm^{-1}): 1587, *ν*(C=N); 1088, *ν*(N-N); 955, *ν*(C-S). ^{1}H NMR ($CDCl_3$) δ (ppm.): 8.81, 8.45 (s, 2H, CH), 6.77-7.32 (multiplet, 14H, Ar-H), 4.35, 4.47 (s, 4H, CH_2), 3.57, 3.85 (s, 6H, O-CH_3), 2.40, 2.36 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm.): 177.2, 171.0 (C-S), 165.4, 161.7 (C=N); 115.2, 117.2, 118.4, 119.0, 120.2, 121.9, 126.1, 126.2, 126.4, 126.7, 127.6, 128.0, 130.4, 130.4, 130.5, 130.6, 133.5, 134.5, 137.2, 137.3, 147.6, 150.4, 152.0, 156.7 (aromatic-C), 55.3, 56.9 (O-CH_3), 36.2, 34.0 (CH_2), 19.4 (CH_3),.^{119}Sn NMR ($CDCl_3$) δ (ppm.): -446.

*2.2.2.2. Tin(IV) [S-4-methybenzyl-β-N-(2-hydroxy-3-methoxybenzylmethylene) dithiocarbazate] (**2**)*

Orange crystals. Yield: 87%. Melting point: 211-214°C. Analysis calculated for $C_{34}H_{32}N_4O_4S_4Sn$: C, 51.56; H, 3.99; N, 6.94%. Found: C, 51.89; H, 4.22; N, 6.53%. FT-IR

(ATR, cm^{-1}): 1593, *v*(C=N); 1083, *v*(N-N); 958, *v*(C=S). ^{1}H NMR ($CDCl_3$) δ (ppm.): 8.77, (s, 2H, CH), 6.76-7.24 (multiplet, 14H, Ar-H), 4.36 (s, 4H, CH_2), 3.56 (s, 6H, O-CH_3), 2.33 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm.): 170.8 (C-S), 165.4 (C=N); 117.2, 118.4, 119.0, 126.7, 129.2, 129.4, 133.1, 137.3, 152.0, 156.7 (aromatic-C), 56.9 (O-CH_3), 35.5 (CH_2), 21.2 (CH_3). ^{119}Sn NMR ($CDCl_3$) δ (ppm.): -446.

*2.2.2.3. Tin(IV) [S-benzyl-β-N-(2-hydroxy-3-methoxybenzylmethylene)dithiocarbazate] (**3**)*

Orange crystals. Yield: 53%. Melting point: >300°C. Analysis calculated for $C_{32}H_{28}N_4O_4S_4Sn$: C, 49.30; H, 3.62; N, 7.19%. Found: C, 49.26; H, 3.26; N, 6.02 %. FT-IR (ATR, cm^{-1}): 1582, *v*(C=N); 1031, *v*(N-N); 958, *v*(C-S). ^{1}H NMR ($CDCl_3$) δ (ppm.): 8.78 (s, 2H, CH), 6.76-7.36 (multiplet, 16H, Ar-H), 4.44 (s, 4H, CH_2), 3.55 (s, 6H, O-CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm.): 170.7 (C-S), 165.5 (C=N); 117.2, 118.4, 119.0, 126.7, 127.6, 128.7, 129.3, 136.3, 152.0, 156.9 (aromatic-C), 56.9 (CH_3), 35.7 (CH_2).^{119}Sn NMR ($CDCl_3$) δ (ppm.): -447.

*2.2.2.4. Tin(IV)[S-2-methylbenzyl-β-N-(2,3-dihydroxybenzylmethylene) dithiocarbazate] (**4**)*

Orange powder. Yield: 40%. Melting point: 188-192 °C. Analysis calculated for $C_{32}H_{28}N_4O_4S_4Sn$: C, 49.30; H, 3.62; N, 7.19%. Found: C, 49.14; H, 3.43; N, 7.50%. FT-IR (ATR, cm^{-1}): 1610, *v*(C=N); 1035, *v*(N-N); 964, *v*(C-S). ^{1}H NMR ($CDCl_3$) δ (ppm.) : 8.90 (s, 2H, CH), 6.02-7.34 (multiplet, 14H, Ar-H), 4.48 (s, 4H, CH_2), 2.42 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm.): 171.3 (C-S), 165.6 (C=N), 115.1, 119.0, 119.6, 125.4, 126.5, 128.3, 130.5, 130.8, 133.2, 137.4, 148.2, 152.1 (aromatic-C), 34.3 (CH_2), 19.5 (CH_3).^{119}Sn NMR (DMSO-d_6) δ (ppm.): -441.

*2.2.2.5. Tin(IV) [S-4-methybenzyl-β-N-(2,3-dihydroxybenzylmethylene) dithiocarbazate] (**5**)*

Orange powder. Yield: 83%. Melting point: 206-209 °C. Analysis calculated for $C_{32}H_{28}N_4O_4S_4Sn$: C, 49.30; H, 3.62; N, 7.19%. Found: C, 49.02; H, 3.16; N, 7.85%. FT-IR (ATR, cm^{-1}): 1620, *v*(C=N); 1006, *v*(N-N); 965, *v*(C-S). ^{1}H NMR (DMSO-d_6) δ (ppm.): 8.65, (s, 2H, CH), 6.50-7.35 (multiplet, 14H, Ar-H), 4.41 (s, 4H, CH_2), 2.29 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm.): 150.8 (C-S), 145.2 (C=N); 118.4, 129.5, 129.6, 134.2, 136.8 (aromatic-C), 21.2 (CH_3), 37.8 (CH_2).^{119}Sn NMR (DMSO-d_6) δ (ppm.): -443.

*2.2.2.6. Tin(IV) [S-benzyl-β-N-(2,3-dihydroxy-benzylmethylene)dithiocarbazate] (**6**)*

Orange powder. Yield: 67%. Melting point: 206-208 °C. Analysis calculated for $C_{30}H_{24}N_4O_4S_4Sn$: C, 47.95; H, 3.22; N, 6.46%. Found: C, 47.72; H, 2.93; N, 6.25%. FT-IR (ATR, cm^{-1}): 1612, *ν*(C=N); 1016, *ν*(N-N); 960, *ν*(C-S). ^{1}H NMR (DMSO-d_6) δ (ppm.): 8.60, (s, 2H, CH), 6.27-7.41 (multiplet, 16H, Ar-H), 4.44 (s, 4H, CH_2); ^{13}C NMR (DMSO-d_6) δ (ppm.): 155.9 (C-S), 153.4 (C=N); 111.6, 114.3, 115.9, 116.9, 127.5, 128.9, 129.7, 137.6, 146.9 (aromatic-C), 38.1 (CH_2).^{119}Sn NMR (DMSO-d_6) δ (ppm.): -462.

2.3 Single crystal X-ray structure determination

An Oxford Diffraction Gemini Eos CCD diffractometer fitted with Mo Kα radiation (λ = 0.71073 Å) was employed to measure intensity data for the orange crystals of **2** and **3** at T = 150 K. The data reduction and analytical absorption corrections were accomplished with CrysAlisPro [38]. The structures were solved by direct-methods [39] and refined (anisotropic displacement parameters, C-bound H atoms in the riding model approximation) on F^2 [40]. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$) was introduced in each case. In the final cycles of the refinement of **2**, a reflection, i.e. (-6 -4 8), was omitted owing to poor agreement. The molecular structure diagrams was generated with ORTEP for Windows [41] with 50% displacement ellipsoids and the packing diagrams were drawn with DIAMOND [42]. Additional data analysis was made with PLATON [43]. Crystal data and refinement details are given in Table 1.

2.4 Computational calculations

DFT calculations were performed as reported previously from our group [36].

2.5 In vitro cytotoxic activity

The cytotoxicity of tin(IV) compounds against HT29 (colon), U87 and SJ-G2 (glioblastoma), MCF-7 (breast), A2780 (ovarian), H460 (lung), A431 (skin), Du145 (prostate), BE2-C (neuroblastoma), MIA (pancreas) cell lines and one normal breast cell line, MCF-10A

(normal breast) were performed by MTT assay using the same method reported by Yusof *et al* [36].

Table 1

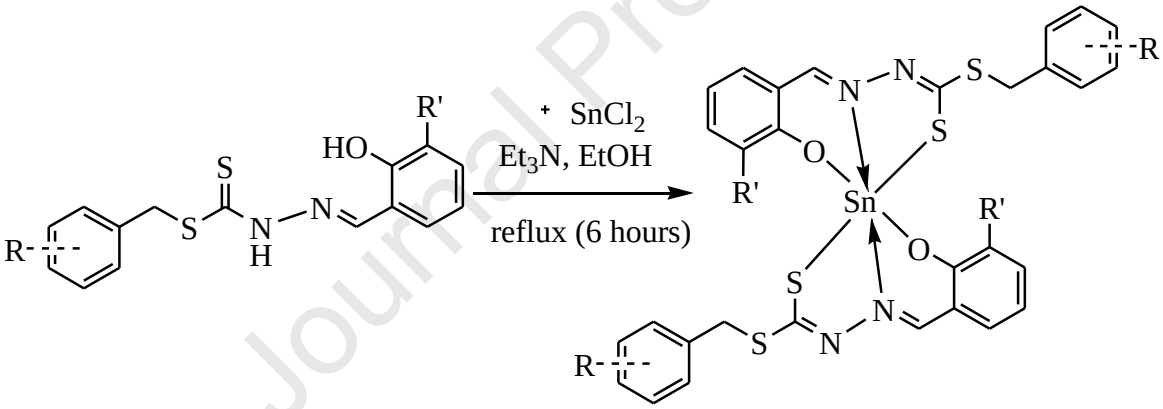
Crystal data and refinement details for complexes **2** and **3**.

Complex	**2**	**3**
Formula	$C_{34}H_{32}N_4O_4S_4Sn$	$C_{32}H_{28}N_4O_4S_4Sn$
Formula weight	807.56	779.51
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/Å	12.8540(2)	12.8656(3)
b/Å	19.4686(5)	8.4693(2)
c/Å	27.2466(6)	29.8639(7)
β/°	101.109(2)	96.634(2)
V/Å^3	6690.7(3)	3232.26(13)
Z	8	4
D_c/g cm^{-3}	1.603	1.602
F(000)	3280	1576
μ(Mo$K\alpha$)/mm^{-1}	1.059	1.093
Measured data	44247	36728
θ range/°	3.3 – 25.2	3.4 – 25.2
Unique data	15972	7934
Observed data ($I \geq 2.0\sigma(I)$)	10737	6324
No. parameters	855	408
R, obs. data; all data	0.041; 0.079	0.035; 0.072
a; b in weighting scheme	0.036; 1.389	0.032; 2.061
R_w, obs. data; all data	0.076; 0.093	0.052; 0.080
GoF	1.05	1.02
Range of residual electron density peaks/eÅ^{-3}	-0.75 – 0.91	-0.57 – 0.50

3. Results and discussion

3.1 Synthesis

Six new homoleptic tin(IV) compounds were synthesised by the condensation reaction of S-substituted dithiocarbazate Schiff bases of 2-hydroxy-3-methoxybenzaldehyde or 2,3-dihydroxybenzaldehyde with tin(II) chloride (Scheme 1), whereby the tin(II) precursor underwent oxidation to tin(IV) after reflux for 6 hours [44]. The tin(IV) compounds were stable at room temperature and soluble in most organic solvents, especially dimethylsulfoxide (DMSO) and dimethylformamide (DMF), except **2** which was not soluble in DMSO. Due to the insolubility of **2**, cytotoxic activity was not determined. The molar conductance of 10^{-3} M solutions of synthesised compounds in DMSO were in the range 1.12-6.07 Ω^{-1} cm^2 mol^{-1}, indicating their non-electrolytic nature [45].



Where: R = *o*-CH_3, R' = O-CH_3 (**1**)
R = *p*-CH_3, R' = O-CH_3 (**2**)
R = H, R' = O-CH_3 (**3**)
R = *o*-CH_3, R' = OH (**4**)
R = *p*-CH_3, R' = OH (**5**)
R = H, R' = O-H (**6**)

Scheme 1: Synthetic pathway for the synthesis of **1**-**6**.

3.2 Infrared spectra analysis

The infrared spectra of **1**-**6** were measured in the range of 4000 to 280 cm^{-1} and verified using frequencies predicted using DFT. Complete experimental and calculated IR data are provided in Supplementary Information, Table S1. In the experimental IR spectra of Schiff bases (H_2L1-6), the vibration bands of *ν*(*o*-O-H), *ν*(NH), *ν*(C=N), *ν*(N-N) and *ν*(C-S) were observed in the range of 3488-3501, 3084-3106, 1598-1608, 1114-1125 and 1012-1030 cm^{-1}, respectively. However, the *ν*(O-H) of H_2L1, H_2L2 and H_2L3 were not observed in the IR spectra due to the intra- and inter-molecular interactions between the molecules, which was similar to that reported in our previous work [36]. The disappearance of the *ν*(N-H) band for all Schiff bases and the *ν*(O-H) band for H_2L4, H_2L5 and H_2L6 indicate the deprotonation of N-H and O-H groups and its subsequent coordination to the central tin atom. The shifting of *ν*(C=N) band observed in the spectra of tin(IV) compounds proves that the complexation occurred through the azomethine nitrogen. The IR group assignments for the experimental and theoretical calculation in gas phase appeared in good agreement with experimental data, shown in Fig. S1.

3.3 Multinuclear (^{1}H, ^{13}C and ^{119}Sn) NMR spectral analysis

The important signals observed in the range of 9.51-9.61 ppm and 13.32-13.41 ppm were assigned to the proton of -OH and -NH in the Schiff base, respectively, which were reported in our previous publications [36]. Both of the signals disappeared in the ^{1}H NMR of the tin(IV) compounds indicating the deprotonation of the -OH and -NH groups upon complexation. This confirmed the coordination of the oxygen and nitrogen donor atom of Schiff bases to the tin ion. Moreover, the signal of the HC=N proton in the spectra of tin(IV) compounds shifted to the downfield region due to the coordination of –NH to tin atom, which was a result of the formation of the C=N-N=C conjugated systems [46]. The downfield shift of the HC=N signal in the ^{13}C NMR spectra, due to electron density transfer from the Schiff bases to the acceptor (Sn atom), was consistent with that observed in earlier reports [47,48]. Furthermore, the signal attributable to the C–S moiety in the ^{13}C NMR spectra of the tin(IV) compounds was shifted upfield compared to their Schiff bases, suggesting coordination of the sulphur atom to the tin centre. These observations supported the FTIR analysis noted above.

All the data obtained in the ^{1}H NMR and ^{13}C NMR spectra are listed in Tables S2 and S3, respectively.

The geometry of compounds **1**-**6** was verified further *via* ^{119}Sn NMR spectroscopy. A sharp signal was observed in the range δ -441 to -462 in the ^{119}Sn NMR spectra of compounds **1**-**6**, which strongly supported a six-coordinated, distorted octahedral geometry around tin, comparable to reported literature [49].

3.4 UV-vis absorption spectral analysis

The experimental UV-vis spectra of tin(IV) compounds in DMSO showed a prominent absorption peak in the range of 343-355 nm, which is attributed to the n→π* and π→π* transitions, and showed excellent correlation with the TD-DFT electronic excitations between 348-353 nm (gas phase). The other experimental absorption peak to take into account ranged from 415-427 nm, which indicated the presence of the S→Sn^{IV} LMCT band; TD-DFT predicted equivalent transitions between 428-438 nm. The HOMO in **1**-**6** was primarily located on the dithiocarbazate backbone, the phenyl ring of the aldehyde moiety, and the oxygen atom coordinated to central tin. The LUMO centred on the dithiocarbazate backbone and phenyl ring of aldehyde. Analysis of these frontier MO's (Fig. 1) supported the hypothesis that the n→π* transition occurred due to the presence of the electron lone-pairs in the azomethine nitrogen, thiolate sulphur and phenoxide oxygen atoms. The π→π* transition observed in all tin(IV) compounds corresponded to the electron delocalisation around the aromatic rings. Complete transitions are tabulated in Table S4.

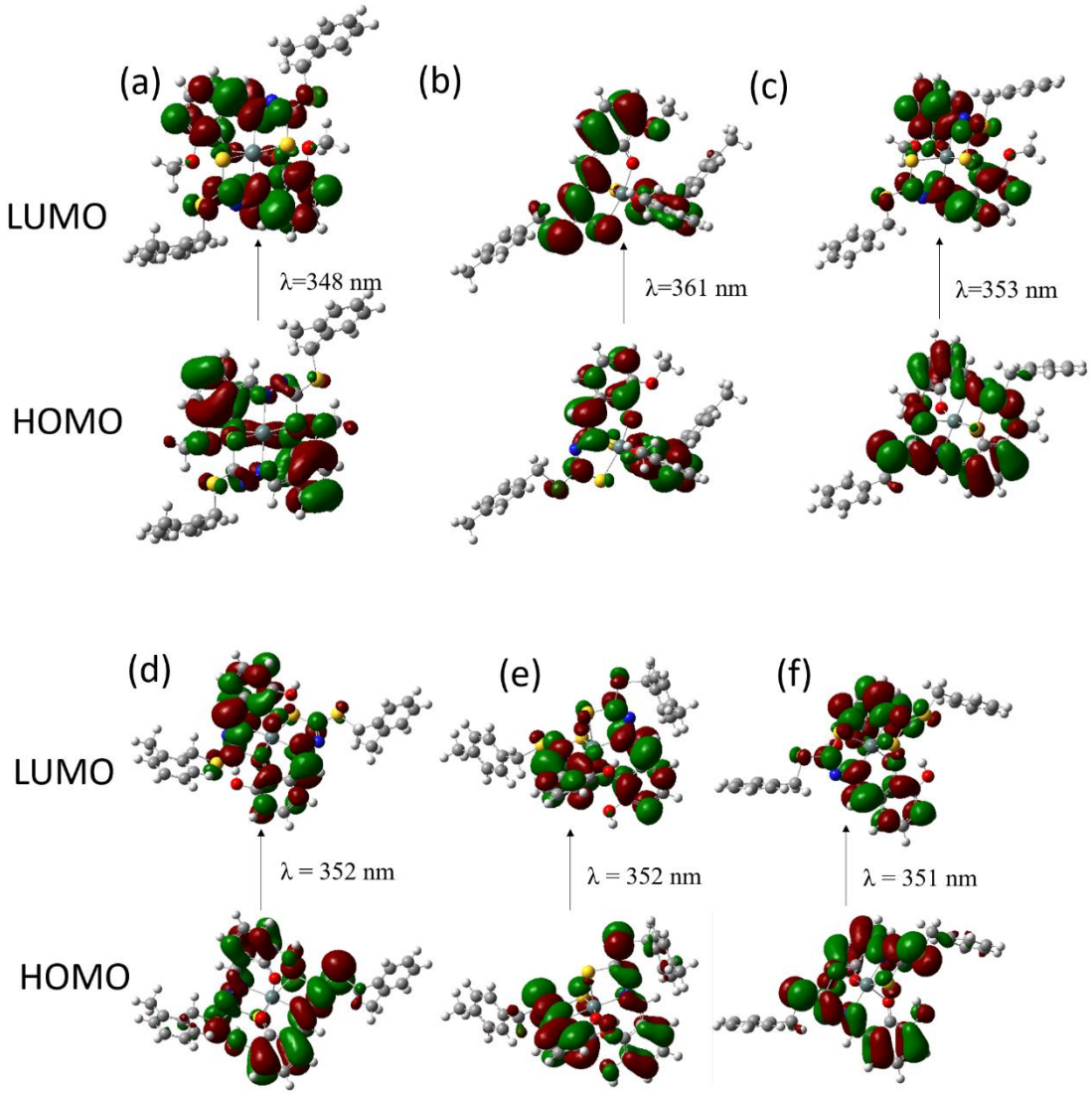


Fig. 1. Frontier MOs of (a) **1**, (b) **2**, (c) **3**, (d) **4**, (e) **5** and (f) **6**.

3.5 X-ray crystallography

Crystal structure determinations were achieved for each of the homoleptic compounds **2** and **3**; selected geometric parameters are collected in Table S5. The crystallographic asymmetric unit of **2** comprises two independent molecules with the first shown in Fig. 2(a) and the second molecule shown in Fig. S2. For **3**, one molecule comprises the asymmetric unit, Fig. 2(b). For the first independent molecule of **2**, the dinegative tridentate ligand coordinates the tin atom *via* thiolate-S, phenoxide-O and imine-N atoms to establish five-membered Sn,S,C,N_2 and six-membered Sn,O,C_3,N rings. Evidence for the presence of thiolate-sulphur

atoms is found in the elongation of the C1−S1 and C18−S3 bond lengths (Table S5) from 1.670(2) Å, which is found in the most closely related acid molecule for which a crystallographic analysis has been reported, i.e. the benzyl ester rather than the 4-tolylCH_2 ester [37]. Concomitantly, the C1−N1 and C18−N3 bond lengths (Table S5) have decreased considerably from 1.338(2) Å in the acid [37]. The conformation of the two tridentate ligands is such that all like atoms are mutually trans in a distorted octahedral environment. The major distortions from the ideal octahedral geometries are due to the acute chelate angles in the five-membered rings, i.e. 78.88(7)° for S1−Sn−N2 and 78.94(7)° for the S3−Sn−N4 angle.

The S1-five-membered chelate ring formed by the tridentate ligand is strictly planar with the RMSD of the fitted atoms being 0.0036 Å. However, the S3-ring is less planar with the RMSD being 0.0629 Å. A better description for the latter is an envelope in which the tin atom lies 0.308(4) Å out of the least-squares plane defined by the remaining four atoms (RMSD = 0.0060 Å). Envelope conformations also apply for the six-membered chelate rings. For the O1-ring, the tin atom lies 0.579(4) Å out the plane through the five remaining atoms. For the O3-ring the envelope is somewhat flattened with the tin atom 0.135(4) Å out of the plane (RMSD = 0.0234 Å), see Table S6. The dihedral angle between the five-membered chelate rings is 81.56(8)°.

As seen from the overlay diagram in Fig. 2(c), there are conformational differences between the independent molecules of **2**, at least with respect to the terminal thioester residues. The data in Table S5 and Table S6 confirm the close similarity between the independent molecules in terms of the tin-atom geometries.

The trends in the structure of **3** follow those established for **2**, with the most obvious difference relating to the coordination of the imine-N2 and N4 atoms. The angle they subtend at the tin atom is wider by *ca* 6-7°, and there is evidence to suggest the Sn–N2, N4 bond lengths are marginally shorter than the equivalent bonds in the molecules of **2**. Each of the chelate rings adopts an envelope conformation with data presented in Table S6. The dihedral angle between the five-membered chelate rings in **3** is 81.77(5)°, *i.e.* within experimental error of the value computed for **2**.

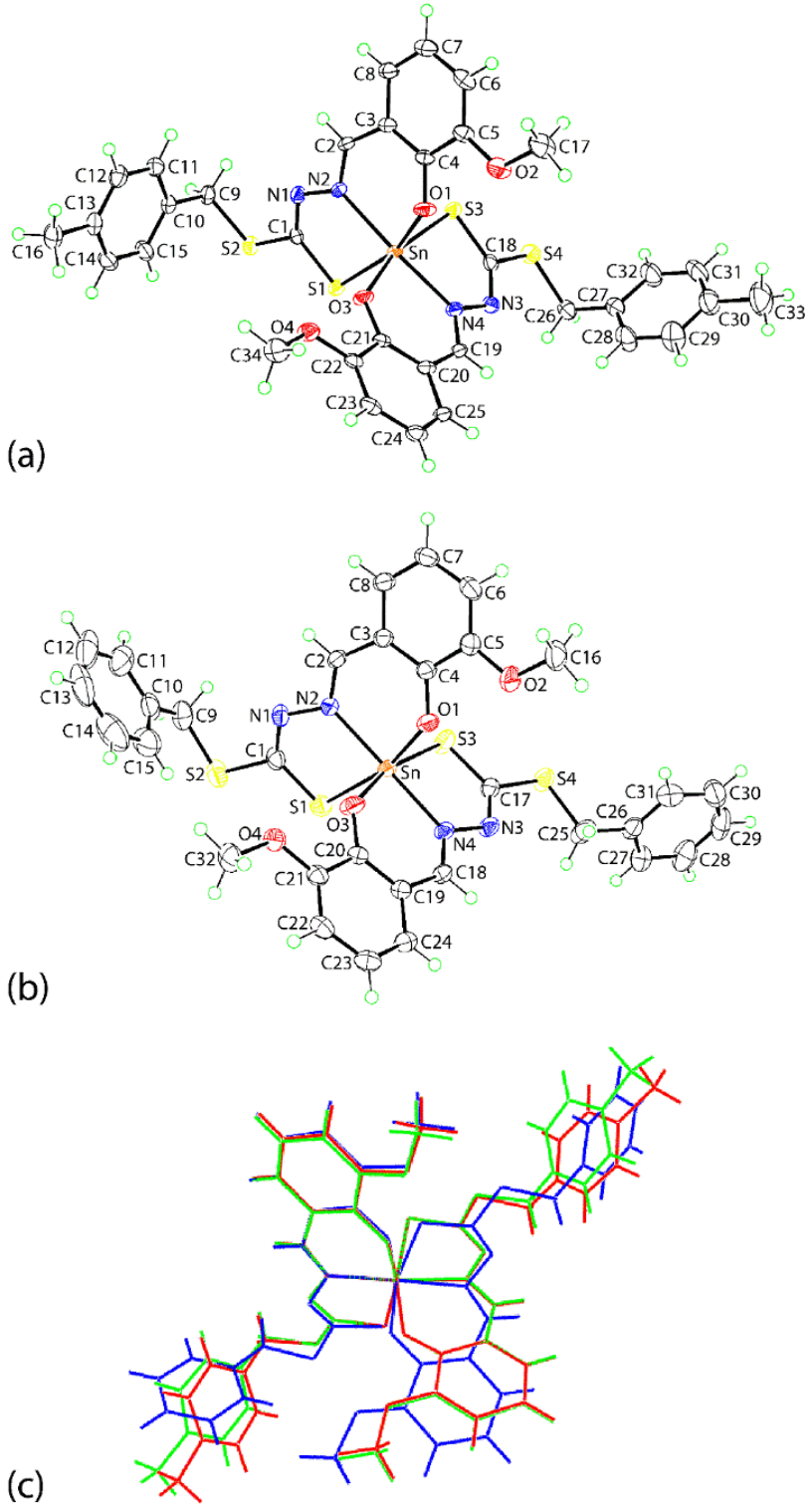


Fig. 2. Molecular structures of the molecules in (a) **2** (first independent molecule; the structure for the second independent molecule is shown in Fig. S2) and (b) **3**, showing atom labelling schemes and 50% displacement ellipsoids. (c) Overlay diagram of the molecules in

2 (red image for the first independent molecule), **2a** (green, inverted second molecule) and **3** (blue). Molecules have been overlapped so the Sn,S1,N2 chelate rings are coincident.

There are three related homoleptic tin(IV) compounds that have been structurally characterised in the literature, namely the ethyl thioester and unsubstituted phenoxide residue [50], benzyl thioester, unsubstituted phenoxide residue and methyl bound to the imine-carbon [51] and benzyl thioester with a ferrocenyl substituent adjacent to the alkoxide-oxygen atom [44]. The contrasting and curious feature of the literature structures is that the thiolate-sulphur atoms are mutually cis, as are the alkoxide-oxygen atoms. The reasons for the different conformations observed in **2** and **3**, and those in the literature remain unclear.

In the absence of conventional hydrogen bonding, the crystals of **2** and **3** are sustained by a variety of other non-covalent interactions; the geometric parameters characterising these are included in the captions to the respective figures in the Tables 2 and 3. In the molecular packing of **2**, each of the independent molecules form equivalent intermolecular contacts with the other independent molecule to sustain a supramolecular layer in the *ab*-plane. These are imine-C2-H···S3(thiolate), imine-C19-H···S1(thiolate), methoxybenzene-C7-H···O2(methoxy), methoxybenzene-C24-H···O4(methoxy) and π(C3-C8)···π(C20-C25). The connections between layers along the *c*-axis direction are of the type methyl-C16a-H···O2a, methyl-C16-H···π(C10-C15) and methoxy-C34-H···π(C10-C15). These occur between like-molecules and hence, differentiate the independent molecules comprising the asymmetric unit in terms of their supramolecular association. Images of the supramolecular association operating in the crystal of **2** are shown in Fig. S3.

As seen in Fig. S4, supramolecular layers in the *ab*-plane are also formed in the crystal of **3** *via* a combination of methoxybenzene-C7–H···O4(methoxy), methoxybenzene-C23–H···O2(methoxy), methylene-C25–H···S1(thiolate), methoxy-C16–H···π(C10-C15) and π(C3-C8)···π(C3…C8) interactions. Layers inter-digitate along the c-axis direction but, without directional interactions between them. Geometric parameters characterising intermolecular interactions in the crystal of **3** are given in Table 3.

Table 2

Geometric parameters (Å, °) characterising intermolecular interactions in the crystal of **2**.

A	H	B	H···B	A···B	A–H···B	Symmetry operation
C2	H2	S3a	2.81	3.721(3)	162	-1+x, y, z
C2A	H2a	S3	2.81	3.628(3)	145	1+x, y, z
C7	H7	O2a	2.49	3.421(4)	166	½-x, -½+y, ½-z
C7a	H7a	O2	2.49	3.267(4)	139	1½-x, ½+y, ½-z
C16a	H16f	O2a	2.56	3.425(4)	147	-1+x, y, z
C19	H19	S1a	2.72	3.564(3)	148	x, y, z
C19a	H19a	S1	2.77	3.699(3)	166	x, y, z
C24	H24	O4a	2.45	3.267(4)	144	1½-x, -½+y, ½-z
C24a	H24a	O4	2.53	3.464(3)	169	½-x, ½+y, ½-z
C16	H16b	Cg(C10-C15)	2.85	3.533(4)	127	-x, -y, -z
C34	H34b	Cg(C10-C15)	2.84	3.609(4)	136	-x, -y, -z
Cg(C3-C8)		Cg(C20a-C25a)		3.4564(19)		½-x, -½+y, ½-z
Cg(C20-C25)		Cg(C3a-C8a)		3.5716(19)		1½-x, -½+y, ½-z

Table 3

Geometric parameters (Å, °) characterising intermolecular interactions in the crystal of **3**.

A	H	B	H···B	A···B	A–H···B	Symmetry operation
C7	H7	O4	2.60	3.487(3)	156	1-x, -y, 2-z
C23	H23	O2	2.37	3.140(3)	138	2-x, -y, 2-z
C25	H25b	S1	2.79	3.645(3)	145	2-x, 1-y, 2-z
C16	H16a	Cg(C10-C15)	2.95	3.354(4)	106	1-x, -y, 2-z
Cg(C3-C8)		Cg(C3-C8)		3.5623(15)		1-x, -y, 2-z

3.6 In vitro cytotoxic activity

The cytotoxic assay of **1**, **3**, **4**, **5** and **6** were carried out against a panel ten of cancer cell lines and one normal cancer cell line. All the compounds, except compound **2** used in this work were insoluble in water. However, they were very soluble in DMSO, and the presence of 1% DMSO proved sufficient for their dissolution in aqueous media for cytotoxicity test. The stability of the compounds was analysed by monitoring the electronic spectra of the compounds in DMSO as well as DMSO-H_2O (1:99) over 72 h at room temperature, and an unchanged pattern in the spectra was indicative that the compounds were stable in both the solvent systems tested. We were unable to determine the cytotoxicity of **2** due to its insolubility in 100% DMSO at 1 mM. Cisplatin (standard drug) was used as a positive control and DMSO was used as the negative control. Table 4 shows that the cytotoxicity of the tin(IV) compounds and their respective Schiff bases. **1**, **3**, **4**, **5** and **6** exhibited moderate activity against all the tested cancer cell lines. The cytotoxicities of these compounds against HT29, MCF7 and MIA were higher than cisplatin. With respect to the cytotoxicity of the precursor Schiff bases, **1**, **2**, **5** and **6** were equipotent to their corresponding Schiff bases, with the exception of **4**. Compound **4** demonstrated higher potency than their corresponding Schiff bases against HT29, U87, MCF-7, A431 and Du145 cells. The mechanism of action of **4** is worthy of further in-depth investigation. In general, for compounds **1**, **2**, **5** and **6**, it can be inferred that the presence of tin does not influence cytotoxicity. This is possibly due to the bulkiness of the compound and only the coordinated Schiff bases playing a role in binding to macromolecules [52].

Table 4

Summary of the *in vitro* cytotoxicity of tin(IV) compounds in several cell lines, determined by the MTT assay and expressed as a GI_{50} value with standard error. GI_{50} is the concentration of tin(IV) compounds at which cell growth is inhibited at 50% over 72 hours.

Compounds	Growth inhibition concentration, GI_{50} (μM)										
	HT29	U87	MCF-7	A2780	H460	A431	Du145	BE2-C	SJ-G2	MIA	MCF10A
H_2L1	3.9 ± 0.71	4.3 ± 0.30	2.7 ± 0.21	3.2 ± 0.15	4.3 ± 0.12	3.8 ± 0.033	4.1 ± 0.09	3.1 ± 0.00	3.0 ± 0.09	4.9 ± 0.37	3.1 ± 0.07
1	3.9 ± 0.53	4.2 ± 0.03	2.9 ± 0.07	3.3 ± 0.10	4.0 ± 0.09	3.8 ± 0.15	4.6 ± 0.17	3.0 ± 0.13	2.9 ± 0.12	4.2 ± 0.27	3.2 ± 0.21
H_2L2	8.0 ± 3.5	3.9 ± 0.00	3.5 ± 0.00	3.1 ± 0.40	5.5 ± 0.73	4.2 ± 0.74	5.4 ± 0.23	3.6 ± 0.27	3.3 ± 0.87	11 ± 2.3	3.5 ± 0.23
2	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
H_2L3	2.2 ± 0.033	3.1 ± 0.26	2.5 ± 0.12	3.0 ± 0.06	3.3 ± 0.21	3.0 ± 0.15	3.4 ± 0.30	2.8 ± 0.20	2.4 ± 0.26	4.5 ± 0.25	3.0 ± 0.067
3	2.5 ± 0.30	3.1 ± 0.13	2.5 ± 0.23	2.6 ± 0.12	3.0 ± 0.12	2.5 ± 0.32	3.5 ± 0.26	2.1 ± 0.00	1.4 ± 0.36	2.7 ± 0.21	2.8 ± 0.19
H_2L4	10 ± 3.5	20 ± 5.2	10 ± 3.1	1.8 ± 1.2	8.7 ± 1.9	14 ± 1.5	23 ± 3.6	0.38 ± 0.07	6.4 ± 2.2	5.5 ± 1.1	3.7 ± 0.50
4	4.4 ± 0.83	9.3 ± 1.8	4.4 ± 1.9	2.7 ± 0.20	4.7 ± 0.23	3.7 ± 0.25	6.4 ± 1.4	1.7 ± 0.33	1.9 ± 0.36	4.6 ± 0.97	3.3 ± 0.19
H_2L5	2.8 ± 0.033	4.0 ± 0.43	2.8 ± 0.067	2.8 ± 0.20	3.7 ± 0.10	3.7 ± 0.20	4.2 ± 0.59	3.2 ± 0.30	3.3 ± 0.30	6.6 ± 1.7	2.9 ± 0.033
5	3.3 ± 0.26	4.8 ± 0.52	3.0 ± 0.15	3.3 ± 0.26	4.2 ± 0.12	3.7 ± 0.32	6.0 ± 0.58	2.7 ± 0.43	3.0 ± 0.27	11 ± 0.88	2.8 ± 0.33
H_2L6	2.1 ± 0.35	2.7 ± 0.47	2.3 ± 0.32	2.2 ± 0.25	2.6 ± 0.27	2.4 ± 0.26	2.8 ± 0.15	2.0 ± 0.23	2.2 ± 0.47	2.2 ± 0.64	2.9 ± 0.21
6	2.1 ± 0.44	3.3 ± 0.23	2.2 ± 0.20	2.4 ± 0.38	2.1 ± 0.28	2.8 ± 0.23	3.8 ± 0.52	2.1 ± 0.17	1.4 ± 0.23	2.5 ± 0.64	2.8 ± 0.088
$SnCl_2$	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25
Cisplatin	11.0 ± 2.0	4.0 ± 1.0	6.5 ± 0.8	1.0 ± 0.1	0.9 ± 0.2	2.4 ± 0.3	1.2 ± 0.1	1.9 ± 0.2	0.4 ± 0.1	8.0 ± 1.0	nd

GI_{50} (μM): (the colors indicate) = 0.1 – 0.99; = 1.0 – 9.9; = 10 - 100; = nd (not determined)

(The compounds H_2L1, H_2L2 and H_2L3 published as S2MoVaH, S4MoVaH, SBoVaH, respectively in ref [36])

4. Conclusions

Six octahedral tin(IV) compounds were synthesised by the condensation reaction of tin(II) chloride with dithiocarbazate Schiff bases. The oxidation of tin(II) to tin(IV) occurred in this work as two binegatively charged Schiff bases ONS-bonded to the tin centre with general formulae $[Sn(Ln)_2]$. X-ray crystallography indicated that the dinegative tridentate ligands of **2** and **3** coordinated to the tin atoms via thiolate-S, phenoxide-O and imine-N atoms, leading to octahedral geometries in which the like-atoms were mutually trans. The *in vitro* cytotoxicity against a panel of cancer cell lines viz., HT29, U87, SJ-G2, MCF-7, A2780, H460, A431, Du145, BE2-C and MIA cancer cell lines revealed that compounds **1**, **3**, **5** and **6** showed moderate cytotoxicity; similar to that of their respective Schiff bases. However, compound **4** exhibited a higher potency against HT29, U87, MCF-7, A431 and Du145 cells as compared to the precursor Schiff base.

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Supplementary data

Crystallographic data for **2** and **3** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication nos 1916354 (**2**) and 1916354 (**3**). These data can be obtained free of charge via

www.ccdc.cam.ac.uk/getstructures. Crystallographic diagrams and details of intermolecular interactions are given in Figures S2-S4, Tables S5-S6.

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Author contributions

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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