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Synthesis and characterization of multimeric salicylaldimine thiosemicarbazones and their Pd(II) and Pt(II) complexes

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ABSTRACT

A series of di- and trithiosemicarbazone ligands as well as their Pd(II) and Pt(II) 1,3,5-triaza-7-phosphaadamantane (PTA) complexes have been synthesised using templated reactions between various substituted salicylaldimine thiosemicarbazone ligands and metal precursors of the general formula *cis*-$[M(PTA)_2Cl_2]$, where M = Pd or Pt. Characterization of these complexes was achieved using various analytical and spectroscopic techniques: elemental analysis, ESI-MS, FT-IR, and NMR (^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$) spectroscopy. The data revealed tridentate (O–N–S) coordination of the thiosemicarbazone moieties via the imine nitrogen, thiolato sulfur and phenolic oxygen to each metal center. *In vitro* biological evaluation of selected compounds was conducted against WHCO1 oesophageal cancer cells. Some of the multimeric compounds display some promising biological activity.

1. Introduction

Transition metal complexes of thiosemicarbazones have received considerable attention mainly due to their broad spectrum of pharmacological properties [1]. There are three main types of thiosemicarbazones that have been reported in literature namely mono-, di- and bis(thiosemicarbazones). Monothiosemicarbazones as their name suggests constitute one thiosemicarbazone moiety, while di- and bis(thiosemicarbazones) each possess two thiosemicarbazone moieties. Dithiosemicarbazones consist of the two moieties linked via their amino nitrogen atoms to a hydrocarbon spacer, while bis(thiosemicarbazones) have their moieties linked via their imine nitrogen atoms to an organic spacer [2]. Thiosemicarbazones are able to coordinate to metal ions in various ways due to their vast number of donor atoms. Thiosemicarbazones usually bind to metal ions by means of dissociation of the hydrazinic proton giving rise to bidentate (N, S) coordination, forming a five-membered chelate ring [3]. In the event that a third donor site is incorporated, tridentate coordination is often observed. This is usually observed for thiosemicarbazones derived from salicylaldehydes [4–6]. Although the chemistry of platinum and palladium complexes of many monothiosemicarbazones has been explored [4,6–10], there are very few reports on the preparation of multimeric thiosemicarbazones and their transition metal complexes [2,11–16]. Previously, we have reported the preparation of dithiosemicarbazones and their palladium triphenylphosphine complexes; however, the poor solubility of the complexes in many solvents including water has hindered their biological evaluation [17]. This study is therefore an extension of the afore-mentioned work as well as a study conducted in our group wherein similar monothiosemicarbazone derivatives were prepared (Fig. 1) and evaluated for their activity against the T1 strain of *Trichomonas vaginalis*. These compounds displayed very promising activity [18]. Herein we report the synthesis and characterization of Pd(II) and Pt(II) salicylaldimine dithiosemicarbazones as well as complexes of a new type of thiosemicarbazone system which we have coined "trithiosemicarbazones". The synthetic preparation, characterization and some preliminary biological data of these compounds are reported in this paper.

2. Experimental

2.1. Materials and methods

All reagents and solvents were purchased from commercial sources (Sigma–Aldrich, Fluka, Merck, Kimix) and used as received. Palladium dichloride and potassium tetrachloroplatinate was received as a donation from Anglo Platinum. Ethane-1,2-dithiosemicarbazide [15], *cis*-$[Pd(PTA)_2Cl_2]$ [19], *cis*-$[Pt(PTA)_2Cl_2]$ [20], dithiosemicarbazone ligands (**1**–**3**) [17] and complexes **M1**–**M4** [18] (Fig. 1) were prepared following reported literature procedures.

2.2. Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded using a Varian Mercury 300 MHz spectrometer, a Varian Unity

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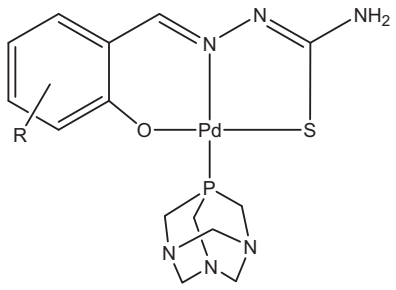


*R = H (**M1**), 3-OMe (**M2**), 3-^{t}Bu (**M3**), 5-Cl (**M4**)*

Fig. 1. Monothiosemicarbazone complexes showing promising antiparasitic activity [18].

400 MHz spectrometer or a Bruker 400 MHz FT spectrometer. Infrared (IR) spectra were determined using a Perkin Elmer Spectrum One FT-IR spectrometer and was carried out in the solid state using KBr pellets unless stated otherwise. Elemental analyses of these compounds were performed using a Thermo Flash 1112 Series CHNS-O Analyser. ESI mass spectrometry determinations were carried out using a Waters API Quattro instrument in either the positive or negative mode. Melting points are corrected and were determined on a Reichert Thermovar hot stage microscope.

*2.3. Synthesis of 5-chlorosalicylaldimine dithiosemicarbazone (**4**), tris(2-aminoethyl) thiosemicarbazide (**5**) and the salicylaldimine trithiosemicarbazone ligands (**6**–**9**)*

5-Chlorosalicylaldimine dithiosemicarbazone (**4**) was prepared using ethane-1,2-dithiosemicarbazide (0.218 g, 1.04 mmol) and 5-chlorosalicylaldehyde (0.330 g, 2.11 mmol). The reactants were stirred in DMF (20 ml) at 120 °C for 5 h. The product was obtained by precipitation with water. The precipitate was filtered on a Büchner funnel, washed with water and dried at 110 °C. The product was isolated as a yellow powder. Yield 0.507 g (90%). M.p. 237–243 °C. *Anal.* Calc. for $C_{18}H_{18}N_6S_2O_2Cl_2$: C, 44.54; H, 3.74; N, 17.32; S, 13.21. Found: C, 44.31; H, 3.73; N, 16.97; S, 13.58%. ν_{max}/cm^{-1} 826 (C═S); 1616 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 3.88 (4H, s, NH-CH_2), 6.89 (2H, d, J = 8.76, Ar–H), 7.23 (2H, dd, J = 2.65, J = 8.75, Ar–H), 8.05 (2H, s, Ar–H), 8.36 (2H, s, CH═N), 8.74 (2H, s, NH–CH$_2$), 10.27 (2H, s, OH), 11.56 (2H, s, N–NH) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 44.28, 118.39, 122.96, 124.08, 126.02, 131.08, 138.34, 155.85, 178.11 ppm. MS ESI: m/z 485 (100%, [M]$^+$).

Tris(2-aminoethyl) thiosemicarbazide (**5**) was prepared from tris(2-aminoethyl)amine (1.87 ml). This was added to a solution of NaOH (1.502 g, 0.037 mol) in water (25 ml). To this solution, CS_2 (2.27 ml) was added and the mixture stirred for 4 h giving rise to an orange solution. Sodium chloroacetate (4.375 g, 0.037 mol) was added to the solution and stirred for 16 h. The solution was then acidified with 2 M HCl (12 ml) to form a yellow precipitate. To this mixture, $NH_2NH_2{\cdot}H_2O$ (10 ml) was added and the solution stirred at 90 °C for 2 h. The solution was then removed from the heat and stirred overnight yielding an oily off-white substance. The product was dried at 115 °C and upon cooling a pale yellow solid is obtained. Yield 1.059 g (23%). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 2.68 (6H, m, N–CH_2), 3.56 (6H, m, NH–CH_2), 4.43 (6H, s, NH_2), 7.87 (3H, s, NH–CH$_2$), 8.60 (3H, s, NH$_2$–NH) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 41.73, 53.57, 181.76 ppm. MS ESI: m/z 369 (100%, [M+H]$^+$).

General procedure for ligands **6**–**9**: Tris(2-aminoethyl) thiosemicarbazide (**5**) (1 equiv) was added to hot ethanol (30 ml). To this mixture, the appropriate salicylaldehyde (3 equiv) was added and the mixture refluxed for 8–16 h resulting in clear yellow solutions. The volume of the yellow solution was reduced and water added to precipitate the desired products for compounds **6**, **7** and **9**. The products were collected using a Büchner funnel and washed with water. Compound **8** was isolated as a yellow oil. The oil was dissolved in DCM and the extract washed with water. The product was obtained after evaporation of the DCM.

Compound **6** was obtained from tris(2-aminoethyl) thiosemicarbazide (**5**) (0.146 g, 0.40 mmol) and salicylaldehyde (0.13 ml, 1.22 mmol). Compound **6** was isolated as a yellow powder. Yield 0.207 g (77%). M.p. 133–137 °C. *Anal.* Calc. for $C_{30}H_{36}N_{10}S_3O_3$: C, 52.92; H, 5.33; N, 20.57; S, 14.12. Found: C, 52.86; H, 5.43; N, 19.72; S, 12.77%. ν_{max}/cm^{-1} 803 (C═S); 1620 (C═N). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.85 (6H, m, N–CH$_2$), 3.72 (6H, m, NH–CH_2), 6.85 (6H, t, J = 8.82, Ar–H), 7.20 (3H, t, J = 8.82, Ar–H), 7.84 (3H, dd, J = 1.62, 7.79, Ar–H), 8.33 (3H, m, NH–CH$_2$), 8.38 (3H, s, CH═N), 9.79 (3H, s, OH), 11.34 (3H, s, N–NH) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 42.60, 53.42, 116.83, 120.07, 121.09, 127.27, 131.77, 140.00, 157.15, 177.64 ppm. MS ESI: m/z 681 (100%, [M]$^+$).

Compound **7** was obtained from tris(2-aminoethyl) thiosemicarbazide (**5**) (0.060g, 0.16 mmol) and 3-methoxy salicylaldehyde (0.076 g, 0.50 mmol). The product was isolated as a yellow amorphous solid. Yield 0.078 g (62%). M.p. 154–157 °C. *Anal.* Calc. for $C_{33}H_{42}N_{10}S_3O_6$: C, 51.41; H, 5.49; N, 18.17; S, 12.47. Found: C, 50.33; H, 5.61; N, 20.93; S, 13.42%. ν_{max}/cm^{-1} 883 (C═S); 1605 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 2.71 (6H, m, N–CH$_2$), 3.63 (6H, m, NH–CH_2), 3.71 (9H, s, OCH$_3$), 6.70 (3H, t, J = 8.04, Ar–H), 6.86 (3H, d, J = 7.88, Ar–H), 7.40 (3H, d, J = 7.82, Ar–H), 8.26 (3H, s, NH–CH$_2$), 8.32 (3H, s, CH═N), 9.04 (3H, s, OH), 11.33 (3H, s, N–NH) ppm. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C): δ = 41.57, 52.50, 55.82, 112.85, 117.86, 118.89, 120.73, 139.16, 145.87, 147.85, 176.88 ppm. MS ESI: m/z 771 (100%, [M]$^+$).

Compound **8** was obtained from tris(2-aminoethyl) thiosemicarbazide (**5**) (0.269g, 0.73 mmol) and 3-tert-butyl salicylaldehyde (0.36 ml, 2.10 mmol). The product was obtained as a yellow oil. Yield 0.521 g (84%). *Anal.* Calc. for $C_{42}H_{60}N_{10}O_3S_3{\cdot}CH_2Cl_2$: C, 55.29; H, 6.27; N, 15.00; S, 10.30. Found: C, 55.92; H, 6.30; N, 17.68; S, 11.84%. ν_{max}/cm^{-1} 854 (C═S); 1646 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.36 (27H, m, ^{t}Bu), 2.86 (6H, m, N–CH$_2$), 3.72 (6H, m, NH–CH_2), 6.84 (3H, t, $^3J_{H-H}$ = 7.65, Ar–H), 7.24 (6H, m, Ar–H), 8.25 (3H, s, NH–CH$_2$), 8.27 (3H, s, CH═N), 10.14 (3H, s, OH), 11.39 (3H, s, N–NH) ppm. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ = 25.46, 34.91, 42.52, 52.83, 119.16, 119.83, 128.90, 129.72, 137.24, 147.19, 155.86, 177.28 ppm. MS ESI: m/z 849 (100%, [M]$^+$).

Compound **9** was obtained from tris(2-aminoethyl) thiosemicarbazide (**5**) (0.122 g, 0.33 mmol) and 5-chlorosalicylaldehyde (0.155 g, 0.99 mmol). The product was obtained as a yellow powder. Yield 0.226 g (87%). M.p. 141–145 °C. *Anal.* Calc. for $C_{30}H_{33}N_{10}S_3O_3Cl_3$: C, 45.95; H, 4.24; N, 17.86; S, 12.26. Found: C, 45.28; H, 4.42; N, 17.29; S, 12.27%. ν_{max}/cm^{-1} 821 (C═S); 1618 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 2.87 (6H, m, N–CH$_2$), 3.75 (6H, m, NH–CH_2), 6.91 (3H, d, J = 8.72, Ar–H), 7.24 (3H, dd, J = 2.66, 8.73; Ar–H), 7.98 (3H, d, J = 2.62, Ar–H), 8.35 (3H, s, CH═N), 8.57 (3H, m, NH–CH$_2$), 10.22 (3H, s, OH), 11.50 (3H, s, N–NH) ppm. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C): δ = 41.58, 52.56, 117.63, 122.20, 123.26, 124.98, 130.11, 137.28, 154.98, 177.02 ppm. MS ESI: m/z 785 (100%, [M+H]$^+$).

Synthesis of Pd(II) and Pt(II) thiosemicarbazone complexes

General procedure: A heated mixture of the ligand (di- or tri-) in ethanol or methanol (30 ml) was stirred and to the mixture 2 equiv (for the dithiosemicarbazones) or 3 equiv (for the trithiosemicarbazones) of triethylamine was added. Upon dissolution of the thiosemicarbazone, 2 or 3 equiv of [M(PTA)$_2$Cl$_2$] (M = Pd or Pt) was added accordingly, resulting in a yellow or orange reaction

mixture. The reaction mixtures were refluxed for 8–48 h and then cooled to room temperature. The resulting precipitate was filtered, washed with the appropriate cold alcohol, diethyl ether and dried *in vacuo*. The reactions were carried out at room temperature in the case of compounds **3a**, **3b**, **8a** and **8b**.

2.4. Synthesis of binuclear Pd(II) (1a–4a) and Pt(II) (1b–4b) thiosemicarbazone complexes

2.4.1. Compound *1a*

Compound **1a** was obtained from compound **1** (0.039 g, 0.093 mmol), triethylamine (0.02 ml) and *cis*-[Pd(PTA)$_2$Cl$_2$] (0.086 g, 0.17 mmol). The product obtained was a yellow powder. Yield 0.067 g (82%). M.p. 250–254 °C. *Anal.* Calc. for $C_{30}H_{40}N_{12}S_2P_2O_2Pd_2{\cdot}2H_2O$: C, 36.93; H, 4.54; N, 17.23; S, 6.57. Found: C, 36.96; H, 4.63; N, 18.30; S, 6.03%. ν_{max}/cm^{-1} 1598 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 3.40 (4H, s, NH–CH_2), 4.31 (12H, s, P–CH$_2$ (PTA)), 4.42 (6H, d, J = 13.19, N–CH$_{ax}$–N (PTA)), 4.57 (6H, d, J = 12.85, N–CH$_{eq}$–N (PTA)), 6.56 (2H, t, J = 7.88, Ar–H), 6.89 (2H, d, J = 8.15, Ar–H), 7.07 (2H, s, NH), 7.23 (2H, t, J = 8.55, Ar–H), 7.38 (2H, dd, J = 1.75, 7.98, Ar–H), 8.31 (2H, d, J = 13.15, CH=N) ppm. ^{31}P{^{1}H} NMR (121 MHz, DMSO-d_6, 25 °C): δ = −40.55 (2P, s, PTA) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 45.86, 50.65, 72.59, 115.12, 118.66, 121.42, 133.23, 134.92, 149.08, 162.44, 170.83 ppm. MS ESI: m/z 247 (30%, [M+2H+2Na]$^{4+}$), 941 (50%, [M+H]$^+$).

2.4.2. Compound *2a*

Compound **2a** was obtained from compound **2** (0.051 g, 0.11 mmol), triethylamine (0.02 ml) and *cis*-[Pd(PTA)$_2$Cl$_2$] (0.103 g, 0.21 mmol). The precipitate was obtained as a yellow-orange powder. Yield 0.083 g (79%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{32}H_{44}N_{12}S_2P_2O_4Pd_2{\cdot}2H_2O$: C, 37.11; H, 4.67; N, 16.23; S, 6.19. Found: C, 37.35; H, 4.72; N, 14.95; S, 5.59%. ν_{max}/cm^{-1} 1598 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 3.41 (4H, s, NH–CH_2), 3.77 (6H, s, OCH$_3$), 4.33 (12H, s, P–CH$_2$ (PTA)), 4.43 (6H, d, J = 13.22, N–CH$_{ax}$–N (PTA)), 4.56 (6H, d, J = 12.85, N–CH$_{eq}$–N (PTA)), 6.49 (2H, t, J = 7.69, Ar–H), 6.89 (2H, dd, J = 1.60, 7.68, Ar–H), 7.03 (4H, m, NH, Ar–H), 8.29 (2H, d, J = 13.17, CH=N) ppm. ^{31}P{^{1}H} NMR (121 MHz, DMSO-d_6, 25 °C): δ = −39.22 (2P, s, PTA) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 45.15, 50.10, 56.28, 71.93, 113.42, 114.40, 117.77, 126.04, 148.07, 150.95, 153.12, 170.15 ppm. MS ESI: m/z 1001 (100%, [M+H]$^+$).

2.4.3. Compound *3a*

Compound **3a** was obtained from compound **3** (0.057 g, 0.11 mmol), triethylamine (0.03 ml) and *cis*-[Pd(PTA)$_2$Cl$_2$] (0.105 g, 0.21 mmol). The product obtained was a yellow-orange powder. Yield 0.075 g (82%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{38}H_{56}N_{12}S_2P_2O_2Pd_2$: C, 43.39; H, 5.37; N, 15.98; S, 6.09. Found: C, 44.17; H, 5.46; N, 18.08; S, 5.98%. ν_{max}/cm^{-1} 1594 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 1.46 (18H, s, CH$_3$ (^{t}Bu)), 3.52 (4H, s, NH–CH_2), 4.37 (12H, s, P–CH$_2$ (PTA)), 4.47 (6H, d, J = 13.85, N–CH$_{ax}$–N (PTA)), 4.55 (6H, d, J = 12.70, N–CH$_{eq}$–N (PTA)), 6.54 (2H, t, J = 7.58, Ar–H), 7.09 (2H, s, NH), 7.30 (4H, m, Ar–H), 8.33 (2H, d, J = 13.47, CH=N) ppm. ^{31}P{^{1}H} NMR (121 MHz, DMSO-d_6, 25 °C): δ = −40.28 (2P, s, PTA) ppm. MS ESI: m/z 365 (100%, [M+H+2Na]$^{3+}$); 1052 (10%, [M]$^+$).

2.4.4. Compound *4a*

Compound **4a** was obtained from compound **4** (0.045 g, 0.09 mmol), triethylamine (0.02 ml) and *cis*-[Pd(PTA)$_2$Cl$_2$] (0.090 g, 0.18 mmol). The product obtained was a yellow powder. Yield 0.077 g (83%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{30}H_{38}N_{12}S_2P_2O_2Cl_2Pd_2$: C, 35.73; H, 3.79; N, 16.67; S, 6.36. Found: C, 34.64; H, 4.01; N, 15.11; S, 6.01%. ν_{max}/cm^{-1} 1595 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 3.42 (4H, s, NH–CH_2), 4.30 (12H, s, P–CH$_2$ (PTA)), 4.42 (6H, d, J = 13.12, N–CH$_{ax}$–N (PTA)), 4.57 (6H, d, J = 12.93, N–CH$_{eq}$–N (PTA)), 6.90 (2H, d, J = 9.04, Ar–H), 7.20 (4H, m, NH, Ar–H), 7.47 (2H, d, J = 2.83, Ar–H), 8.31 (2H, d, J = 12.95, CH=N) ppm. ^{31}P{^{1}H} NMR (121 MHz, DMSO-d_6, 25 °C): δ = −39.92 (2P, s, PTA) ppm. ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C): δ = 45.02, 49.90, 71.82, 117.10, 119.05, 122.38, 131.75, 132.00, 147.12, 160.36, 170.88 ppm. MS ESI: m/z 1009 (5%, [M+H]$^+$).

2.4.5. Compound *1b*

Compound **1b** was obtained from compound **1** (0.070 g, 0.167 mmol), triethylamine (0.04 ml) and *cis*-[Pt(PTA)$_2$Cl$_2$] (0.191 g, 0.329 mmol). The product obtained was a yellow powder. Yield 0.141 g (83%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{30}H_{40}N_{12}O_2S_2Pt_2P_2{\cdot}3H_2O$: C, 30.77; H, 3.96; N, 14.36; S, 5.47. Found: C, 30.50; H, 3.71; N, 14.93; S, 5.22%. ν_{max}/cm^{-1} 1599 (C=N), 1635 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 3.52 (4H, s, NH–CH_2), 4.29 (12H, s, P–CH$_2$ (PTA)), 4.48 (6H, d, J = 13.06, N–CH$_{ax}$–N (PTA)), 4.57 (6H, d, J = 12.78, N–CH$_{eq}$–N (PTA)), 6.69 (2H, t, J = 7.25, Ar–H), 7.04 (2H, d, J = 8.50, Ar–H), 7.29 (2H, s, NH), 7.38 (2H, t, J = 7.62, Ar–H), 7.57 (2H, d, J = 7.85, Ar–H), 8.67 (2H, d, J = 11.19, CH=N) ppm. ^{31}P{^{1}H} NMR (161 MHz, DMSO-d_6, 25 °C): δ = −61.47 (2P, s, PTA) ppm, J = 3329.69. ^{13}C{^{1}H} NMR (100.577 MHz, DMSO-d_6, 25 °C): δ = 45.97, 50.27, 72.84, 116.09, 119.01, 121.64, 133.15, 134.71, 147.46, 160.58, 172.45 ppm. MS ESI: m/z 1117 (100%, [M]$^+$).

2.4.6. Compound *2b*

Compound **2b** was obtained from compound **2** (0.081 g, 0.171 mmol), triethylamine (0.05 ml) and *cis*-[Pt(PTA)$_2$Cl$_2$] (0.196 g, 0.338 mmol). The product was obtained as a yellow powder. Yield 0.175 g (95%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{32}H_{44}N_{12}O_4Pt_2P_2S_2$: C, 32.65; H, 3.77; N, 14.28; S, 5.45. Found: C, 31.44; H, 3.98; N, 13.13; S, 4.90%. ν_{max}/cm^{-1} 1596 (C=N), 1619 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 3.52 (4H, s, NH–CH_2), 3.84 (6H, s, OCH$_3$), 4.31 (12H, s, P–CH$_2$ (PTA)), 4.50 (6H, d, J = 13.02, N–CH$_{ax}$–N (PTA)), 4.57 (6H, d, J = 12.72, N–CH$_{eq}$–N (PTA)), 6.62 (2H, t, J = 7.83, Ar–H), 7.02 (2H, d, J = 7.78, Ar–H), 7.19 (2H, d, J = 8.16, Ar–H), 7.29 (2H, s, NH), 8.65 (2H, d, J = 11.18, CH=N) ppm. ^{31}P{^{1}H} NMR (161 MHz, DMSO-d_6, 25 °C): δ = −60.18 (2P, s, PTA) ppm, J = 3321.44. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C): δ = 45.16, 49.40, 56.23, 72.07, 113.56, 114.37, 118.047, 125.58, 146.35, 150.93, 151.07, 171.63 ppm. MS ESI: m/z 1177 (100%, [M]$^+$).

2.4.7. Compound *3b*

Compound **3b** was obtained from compound **3** (0.090 g, 0.170 mmol), triethylamine (0.05 ml) and *cis*-[Pt(PTA)$_2$Cl$_2$] (0.196 g, 0.338 mmol). The product obtained was a yellow amorphous solid. Yield 0.166 g (86%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{38}H_{56}N_{12}S_2P_2O_2Pt_2$: C, 37.13; H, 4.59; N, 13.68; S, 5.22. Found: C, 38.04; H, 4.61; N, 13.76; S, 4.99%. ν_{max}/cm^{-1} 1594 cm^{-1} (C=N).

2.4.8. Compound *4b*

Compound **4b** was obtained from compound **4** (0.086 g, 0.177 mmol), triethylamine (0.05 ml) and *cis*-[Pt(PTA)$_2$Cl$_2$] (0.206 g, 0.355 mmol). The product obtained was a yellow powder. Yield 0.167 g (79%). M.p. no melting < 300 °C. *Anal.* Calc. for $C_{30}H_{38}N_{12}O_2S_2Cl_2Pt_2P_2{\cdot}6H_2O$: C, 27.85; H, 3.89; N, 12.99; S, 4.95. Found: C, 27.47; H, 3.18; N, 13.14; S, 4.21%. ν_{max}/cm^{-1} 1595 (C=N), 1631 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 3.55 (4H, s, NH–CH_2), 4.31 (12H, s, P–CH$_2$ (PTA)), 4.50 (6H, d, J = 13.82, N–CH$_{ax}$–N (PTA)), 4.58 (6H, d, J = 12.69, N–CH$_{eq}$–N (PTA)), 7.07 (2H, d, J = 9.09, Ar–H), 7.26 (2H, s, NH), 7.35 (2H, dd, J = 2.70, 8.91, Ar–H), 7.64 (2H, d, J = 2.84, Ar–H), 8.64 (2H, d, J = 10.99,

CH=N) ppm. $^{31}P\{^1H\}$ NMR (161 MHz, DMSO-d_6, 25 °C): δ = −61.60 (2P, s, PTA) ppm, J = 3343.30. MS ESI: m/z 1117 (100%, $[M-Cl]^+$); 1187 (30%, $[M+H]^+$).

2.5. Synthesis of trinuclear Pd(II) (**6a**–**9a**) and Pt(II) (**6b**–**9b**) thiosemicarbazone complexes

2.5.1. Compound **6a**

Compound **6a** was obtained from compound **6** (0.044 g, 0.06 mmol), triethylamine (0.03 ml) and *cis*-$[Pd(PTA)_2Cl_2]$ (0.0951 g, 0.19 mmol). The product was obtained as a yellow powder. Yield 0.083 g (87%). M.p. 245–247 °C (with decomposition). *Anal.* Calc. for $C_{48}H_{66}N_{19}S_3O_3Pd_3P_3{\cdot}8H_2O$: C, 35.81; H, 5.13; N, 16.54; S, 5.97. Found: C, 35.58; H, 4.77; N, 16.67; S, 4.70%. ν_{max}/cm^{-1} 1598 (C=N). ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 2.72 (6H, m, N–CH_2), 3.33 (6H, m, NH–CH_2), 4.28 (18H, s, P–CH_2 (PTA)), 4.41 (9H, d, J = 13.27, N–CH_{ax}–N (PTA)), 4.55 (9H, d, J = 12.69, N–CH_{eq}–N (PTA)), 6.55 (3H, t, J = 6.84, Ar–H), 6.92 (3H, d, J = 8.27, Ar–H), 7.04 (3H, s, NH), 7.26 (3H, t, J = 7.94, Ar–H), 7.39 (3H, d, J = 7.91, Ar–H), 8.31 (3H, d, J = 12.99, CH=N) ppm. $^{31}P\{^1H\}$ NMR (161 MHz, DMSO-d_6, 25 °C): δ = −40.55 (3P, s, PTA) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 44.48, 50.67, 54.08, 72.66, 115.17, 118.80, 121.51, 133.30, 135.05, 149.09, 162.52, 171.15 ppm. MS ESI: m/z 1466 (25%, $[M+H]^+$).

2.5.2. Compound **7a**

Compound **7a** was obtained from compound **7** (0.041 g, 0.05 mmol), triethylamine (0.03 ml) and *cis*-$[Pd(PTA)_2Cl_2]$ (0.0782 g, 0.16 mmol). The product was obtained as an orange powder. Yield 0.046 g (57%). M.p. 234–239 °C (with decomposition). *Anal.* Calc. for $C_{51}H_{72}N_{19}S_3O_6Pd_3P_3{\cdot}4H_2O$: C, 37.63; H, 4.95; N, 16.35; S, 5.90. Found: C, 37.31; H, 4.80; N, 16.15; S, 6.53%. ν_{max}/cm^{-1} 1595 (C=N), 1621 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.72 (6H, m, N–CH_2), 3.36 (6H, m, NH–CH_2), 3.78 (9H, s, OCH_3), 4.31 (18H, s, P–CH_2 (PTA)), 4.44 (9H, d, J = 13.15, N–CH_{ax}–N (PTA)), 4.55 (9H, d, J = 12.65, N–CH_{eq}–N (PTA)), 6.46 (3H, m, Ar–H), 6.95 (9H, m, NH, Ar–H), 8.33 (3H, d, J = 13.18, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −36.00 (3P, s, PTA) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 44.91, 50.83, 53.74, 56.98, 72.72, 114.18, 114.87, 118.57, 126.85, 148.79 151.69, 153.73, 170.82 ppm. MS ESI: m/z 1556 (100%, $[M]^+$); 778 (20%, $[M+2H]^{2+}$).

2.5.3. Compound **8a**

Compound **8a** was obtained from compound **8** (0.082 g, 0.965 mmol), triethylamine (0.04 ml) and *cis*-$[Pd(PTA)_2Cl_2]$ (0.142 g, 0.289 mmol). The product was obtained as a yellow powder. Yield 0.099 g (63%). M.p. decomposes at 274 °C. ν_{max}/cm^{-1} 1594 (C=N), 1624 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 1.43 (27H, s, ^{t}Bu), 2.75 (6H, m, N–CH_2), 3.41 (6H, m, NH–CH_2), 4.33–4.54 (36H, m, CH_2 (PTA)), 6.46 (3H, t, J = 7.54, Ar–H), 7.21 (9H, m, NH, Ar–H), 8.26 (3H, d, J = 13.44, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −40.11 (3P, s, PTA) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 29.82, 35.66, 44.73, 51.48, 53.85, 72.31, 114.39, 118.60, 130.06, 133.76, 139.17, 149.95, 161.14, 169.41 ppm. MS ESI: m/z 1634 (30%, $[M]^+$); 818 (70%, $[M+2H]^{2+}$).

2.5.4. Compound **9a**

Compound **9a** was obtained from compound **9** (0.097 g, 0.124 mmol), sodium acetate (0.030 g, 0.362 mmol) and *cis*-$[Pd(PTA)_2Cl_2]$ (0.178 g, 0.362 mmol). The product obtained was a yellow powder. Yield 0.164 g (84%). M.p. 241–246 °C (with decomposition). *Anal.* Calc. for $C_{48}H_{63}N_6O_3S_3Pd_3P_3Cl_3$: C, 36.75; H, 4.05; N, 16.97; S, 6.13. Found: C, 35.12; H, 4.03; N, 16.00; S, 5.40%. ν_{max}/cm^{-1} 1597 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.78 (6H, m, N–CH_2), 3.38 (6H, m, NH–CH_2), 4.27 (18H, s, P–CH_2 (PTA)), 4.41 (9H, d, J = 12.81, N–CH_{ax}–N (PTA)), 4.55 (9H, d, J = 12.32, N–CH_{eq}–N (PTA)), 6.89 (3H, d, J = 8.95, Ar–H), 7.20 (6H, m, NH, Ar–H), 7.39 (3H, d, J = 2.74, Ar–H), 8.19 (3H, d, J = 12.92, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −36.32 (3P, s, PTA) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 43.93, 49.90, 52.80, 71.82, 117.08, 119.02, 122.35, 131.73, 131.99, 147.16, 160.35, 170.69 ppm. MS ESI: m/z 1569 (10%, $[M]^+$); 785 (90%, $[M+2H]^{2+}$).

2.5.5. Compound **6b**

Compound **6b** was obtained from compound **6** (0.074 g, 0.109 mmol), triethylamine (0.05 ml) and *cis*-$[Pt(PTA)_2Cl_2]$ (0.185 g, 0.319 mmol). The product was obtained as a yellow-orange amorphous solid. Yield 0.078 g (41%). M.p. 231–233 °C. *Anal.* Calc. for $C_{48}H_{66}N_{19}S_3O_3Pt_3P_3$: C, 33.29; H, 3.84; N, 15.37; S, 5.55. Found: C, 33.07; H, 4.07; N, 15.35; S, 4.69%. ν_{max}/cm^{-1} 1599 (C=N). ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 2.70 (6H, m, N–CH_2), 3.33 (6H, m, NH–CH_2), 4.15 (18H, s, P–CH_2 (PTA)), 4.36 (9H, d, J = 13.11, N–CH_{ax}–N (PTA)), 4.44 (9H, d, J = 12.78, N–CH_{eq}–N (PTA)), 6.60 (3H, t, J = 7.25, Ar–H), 6.98 (3H, d, J = 8.49, Ar–H), 7.10 (3H, s, NH), 7.32 (3H, t, J = 7.22, Ar–H), 7.46 (3H, d, J = 8.31, Ar–H), 8.57 (3H, d, J = 11.20, CH=N) ppm. $^{31}P\{^1H\}$ NMR (161 MHz, DMSO-d_6, 25 °C): δ = −61.49 (3P, s, PTA) ppm, J = 3348.80. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 44.80, 50.19, 53.92, 72.79, 115.66, 118.77, 121.29, 132.68, 134.29, 147.06, 160.58, 172.32 ppm. MS ESI: m/z 1731 (50%, $[M]^+$).

2.5.6. Compound **7b**

Compound **7b** was obtained from compound **7** (0.164 g, 0.213 mmol), triethylamine (0.10 ml) and *cis*-$[Pt(PTA)_2Cl_2]$ (0.368 g, 0.633 mmol). The product obtained was a yellow powder. Yield 0.054 g (14%). M.p. 237–241 °C (with decomposition). *Anal.* Calc. for $C_{51}H_{72}N_{19}O_6S_3Pt_3P_3$: C, 33.63; H, 3.98; N, 14.61; S, 5.28. Found: C, 32.03; H, 4.05; N, 13.79; S, 4.65%. ν_{max}/cm^{-1} 1592 (C=N), 1631 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.72 (6H, t, J = 6.37, N–CH_2), 3.42 (6H, m, NH–CH_2), 3.80 (9H, s, OCH_3), 4.24 (18H, s, P–CH_2 (PTA)), 4.48 (18H, s, N–CH_2 (PTA)), 6.50 (3H, t, J = 7.79, Ar–H), 6.86 (3H, s, NH), 6.95 (3H, dd, J = 1.50, 7.65, Ar–H), 7.07 (3H, dd, J = 1.55, 8.24, Ar–H), 8.51 (3H, d, J = 11.22, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −56.90 (3P, s, PTA) ppm, J = 3333.81. $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6, 25 °C): δ = 44.09, 49.52, 53.13, 56.23, 72.01, 113.67, 114.14, 118.04, 125.55, 146.09, 150.98, 154.49, 171.51 ppm. MS ESI: m/z 1821 (44%, $[M]^+$); 912 (10%, $[M+2H]^{2+}$).

2.5.7. Compound **8b**

Compound **8b** was obtained from compound **8** (0.085 g, 0.010 mmol), triethylamine (0.04 ml) and *cis*-$[Pt(PTA)_2Cl_2]$ (0.167 g, 0.289 mmol). The product was isolated as a yellow powder. Yield 0.069 g (38%). M.p. 259–264 °C (with decomposition). *Anal.* Calc. for $C_{60}H_{90}N_{19}O_3S_3Pt_3P_3{\cdot}4CH_2Cl_2$: C, 34.32; H, 4.41; N, 11.88; S, 4.29. Found: C, 34.28; H, 5.23; N, 16.25; S, 4.82%. ν_{max}/cm^{-1} 1594 (C=N), 1628 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 1.45 (27H, s, ^{t}Bu), 2.71 (6H, m, N–CH_2), 3.40 (6H, m, NH–CH_2), 4.27 (18H, s, P–CH_2 (PTA)), 4.44 (18H, m, N–CH_2 (PTA)), 6.53 (3H, t, J = 7.58, Ar–H), 7.07 (3H, s, NH), 7.30 (6H, d, J = 7.75, Ar–H), 8.58 (3H, d, J = 11.35, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −60.76 (3P, s, PTA) ppm, J = 3340.49. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C): δ = 30.02, 35.95, 44.70, 51.27, 53.88, 72.64, 115.47, 119.13, 130.09, 133.74, 139.51, 148.21, 159.25, 171.31 ppm. MS ESI: m/z 1900 (60%, $[M]^+$); 951 (100%, $[M+2H]^{2+}$).

*2.5.8. Compound **9b***

Compound **9b** was obtained from compound **9** (0.158 g, 0.202 mmol), triethylamine (0.100 ml) and *cis*-[$Pt(PTA)_2Cl_2$] (0.347 g, 0.598 mmol). The product obtained was a dark yellow powder. Yield 0.196 g (54%). M.p. 250–254 °C. *Anal.* Calc. for $C_{48}H_{63}N_{19}O_3S_3Pt_3P_3Cl_3$: C, 31.42; H, 3.46; N, 14.51; S, 5.24. Found: C, 30.19; H, 3.95; N, 13.65; S, 4.94%. ν_{max}/cm^{-1} 1596 (C=N), 1628 (C=N). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.71 (6H, t, J = 6.10, N–CH_2), 3.39 (6H, m, NH–CH_2), 4.23 (18H, s, P–CH_2 (PTA)), 4.43 (9H, d, J = 13.48, N–CH_{ax}–N (PTA)), 4.51 (9H, d, J = 12.75, N–CH_{eq}–N (PTA)), 6.99 (3H, d, J = 9.07, Ar–H), 7.12 (3H, m, NH), 7.27 (3H, dd, J = 2.80, 9.02, Ar–H), 7.52 (3H, d, J = 2.79, Ar–H), 8.53 (3H, d, J = 11.04, CH=N) ppm. $^{31}P\{^1H\}$ NMR (121 MHz, DMSO-d_6, 25 °C): δ = −58.19 (3P, s, PTA) ppm, J = 3341.09. $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6, 25°C): δ = 43.95, 49.27, 53.06, 71.93, 118.07, 119.20, 122.50, 131.49, 131.62, 145.28, 158.27, 172.36 ppm. MS ESI: m/z 1835 (30%, $[M]^+$); 918 (55%, $[M+2H]^{2+}$).

2.6. Cytotoxic assay

Selected thiosemicarbazones and their complexes were evaluated for their *in vitro* anticancer activity against the WHCO1 oesophageal cancer cell line, derived from biopsies of primary oesophageal squamous cell carcinomas [21] and kindly provided by Professor Rob Veale (University of Witwatersrand, South Africa). IC_{50} determinations were carried out using the MTT assay. Briefly, 3000 cells were seeded per well in 96-well plates. Cells were incubated at 37 °C under 5% CO_2 (24 h), after which aqueous DMSO solutions of each compound (10 μL, with a constant final concentration of DMSO = 0.2%) were plated at various concentrations. After a 48 h incubation, observations were made, and MTT (10 μL) solution added to each well. After 4 h incubation, solubilization solution (100 μL) was added to each well, and plates were incubated overnight. Plates were read at 595 nm on a BioTek microplate reader.

3. Results and discussion

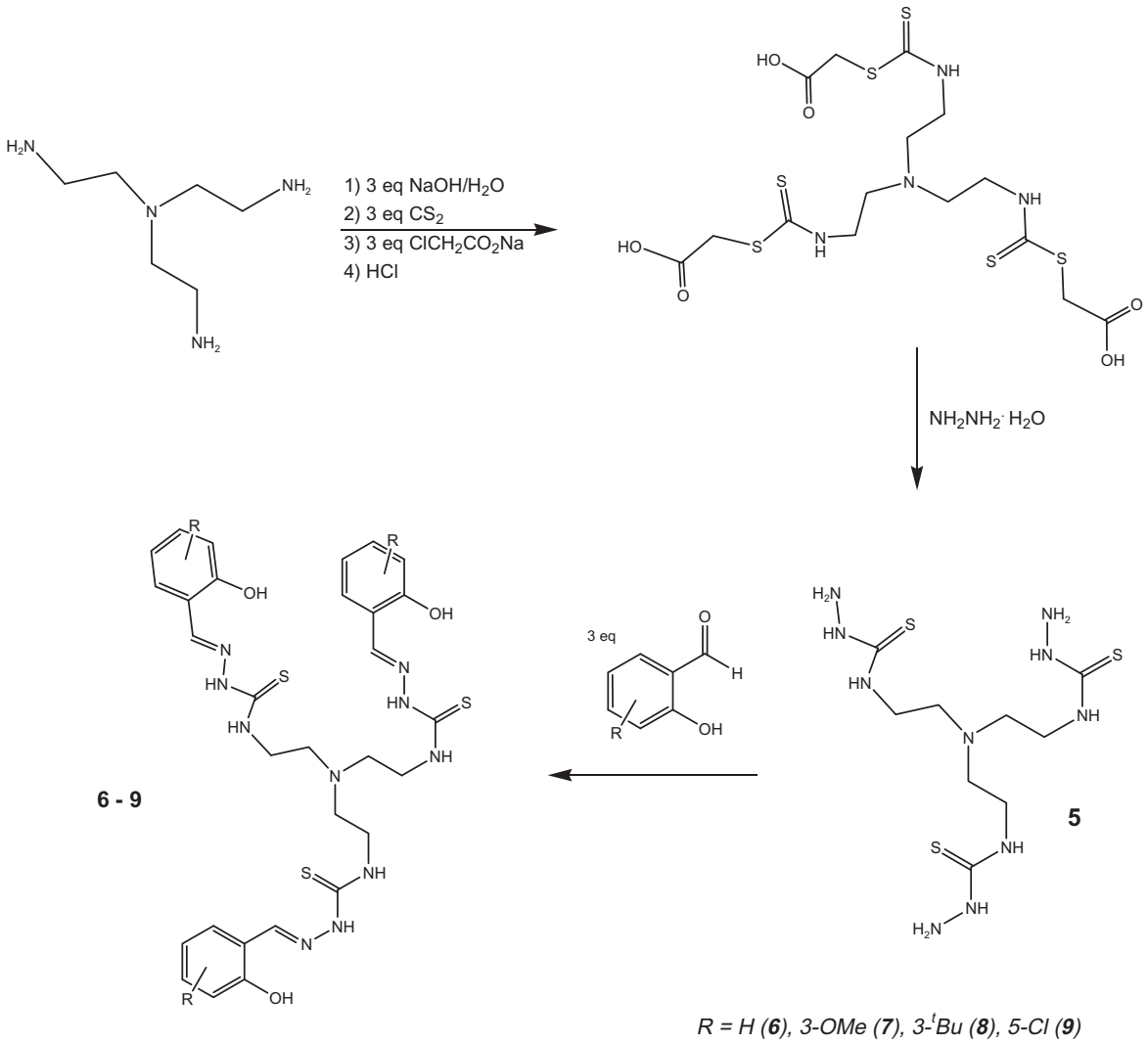
*3.1. Synthesis and characterization of multimeric thiosemicarbazone ligands (**4**–**9**)*

A series of multimeric thiosemicarbazone ligands have been prepared including a 5-chlorosalicylaldimine dithiosemicarbazone (**4**) and four new trithiosemicarbazones (**6**–**9**). Ligand **4** was obtained using the method previously reported by our group [17] whereby ethane-1,2-dithiosemicarbazide was condensed with 5-chlorosalicylaldehyde in DMF, followed by precipitation of the desired product with water. The trithiosemicarbazones (**6**–**9**) were obtained by condensation of tris(2-aminoethyl) thiosemicarbazide (**5**) and various salicylaldehydes. These trithiosemicarbazones possess three thiosemicarbazone moieties linked to a nitrogen core via ethyl linkers. Compound **5** was obtained by slight variation of the method previously described by Dilworth and co-workers [15]. A solution of the tris(2-aminoethyl)amine in water was treated with carbon disulfide, sodium chloroacetate and HCl, presumably affording a triacid precursor *in situ*, which is further reacted with hydrazine hydrate to deliver the desired product. Condensation of **5** with salicylaldehyde, 2-hydroxy-3-methoxy benzaldehyde, 3-*tert*-butyl salicylaldehyde and 5-chlorosalicylaldehyde gave rise to ligands **6**, **7** and **9** as pale yellow amorphous solids, while **8** was obtained as a yellow oil (Scheme 1). The structures of these ligands were confirmed using ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, elemental analysis as well as ESI mass spectrometry. Two-dimensional NMR experiments such as COSY and HSQC also aided in the assignment of the spectra. The proton NMR spectrum of compound **4** revealed a twofold symmetry about the ethane bridge. The imine signal appears at 8.36 ppm, while a singlet attributed to the aliphatic protons of the ethylene bridge appear at 3.88 ppm. A peak for the amino protons adjacent to the ethylene spacer appear as a singlet at 8.74 ppm and the signal attributed to the hydrazinic protons appear downfield at 11.56 ppm. These shifts are consistent with those observed for the other members of this series, thus confirming the integrity of this compound [17].

The proton NMR spectra of the trithiosemicarbazones (**6**–**9**) bear great similarity to the spectra of their dithiosemicarbazone counterparts. Signals for the imine protons are found between 8.35 and 8.57 ppm. Signals attributed to the hydrazinic protons appear in the range of 11.34–11.50 ppm. The methylene protons of the alkyl bridges are found at approximately 2.85 and 3.75 ppm, respectively. The carbon-13 NMR spectra of these compounds further support their structures. Signals for the thione carbon atoms of compounds **6**–**9** appear in the region of 176.88–177.64 ppm, while the imine signals are found between 137.28 and 140.00 ppm. Absorption bands for the imine stretching frequencies are observed in the region between 1605 and 1650 cm^{-1} in the IR spectra of these ligands. This confirms formation of imine bonds as a result of condensation of the thiosemicarbazides with the various salicylaldehydes. Mass spectrometry data also supports the attainment of these compounds. Compound **5** displayed a base peak at m/z 369 corresponding to the $[M+H]^+$ ion. Compounds **6**, **7**, **8** and **9** all displayed base peaks corresponding to their molecular ions at m/z 681, 771, 849 and 785, respectively.

*3.2. Synthesis and characterization of binuclear Pd(II) (**1a**–**4a**), binuclear Pt(II) (**1b**–**4b**), trinuclear Pd(II) (**6a**–**9a**) and trinuclear Pt(II) (**6b**–**9b**) thiosemicarbazone complexes*

Reaction of the thiosemicarbazones has been carried out with metal precursors containing a water soluble phosphine, namely 1,3,5-triaza-7-phosphaadamantane (PTA) to afford an interesting series of multimeric thiosemicarbazone compounds with potential biological properties. Polynuclear thiosemicarbazone palladium and platinum complexes were then prepared from the afore-mentioned ligands using two PTA precursors namely; [$Pd(PTA)_2Cl_2$] and [$Pt(PTA)_2Cl_2$] [19,20]. Binuclear complexes (**1a**–**4a** and **1b**–**4b**) were prepared by reaction of the dithiosemicarbazone ligands and the respective platinum group metal precursor in the presence of triethylamine in a 1:2:2 molar ratio, respectively. The trinuclear complexes (**6a**–**9a** and **6b**–**9b**) were obtained in a similar manner, however, a 1:3:3 (ligand:metal precursor:base) molar ratio was used. The method used to prepare these complexes is outlined in Scheme 2. These complexes were obtained as yellow or orange solids in various yields. The trinuclear complexes are sparingly soluble in polar solvents whereas the dithiosemicarbazone complexes have poor solubility even in DMSO. The complexes do not exhibit good solubility in water despite incorporation of the water-soluble phosphine ligand. The insoluble nature of complex **3b** in most deuterated solvents (including DMSO-d_6) did not allow for any NMR spectroscopic data to be obtained for this complex. The ^1H NMR data obtained for the rest of the complexes revealed that complexation of each thiosemicarbazone moiety occurs in a dianionic manner through the thiolate sulfur and phenolic oxygen. This is supported by the absence of signals accounting for the phenolic and hydrazinic protons. Two types of methylene protons are present in the PTA co-ligand. One type is assigned to the *P*–CH_2–*N* protons, which occur as a singlet in the region of 4.40 ppm. Signals for the protons of the *N*–CH_2–*N* moiety possess an AB spin system and appear as two doublets. One doublet corresponds to the three N–CH_{axial}–N protons, while the other is observed for the three N–$CH_{equatorial}$–N protons. This is consistent with other PTA

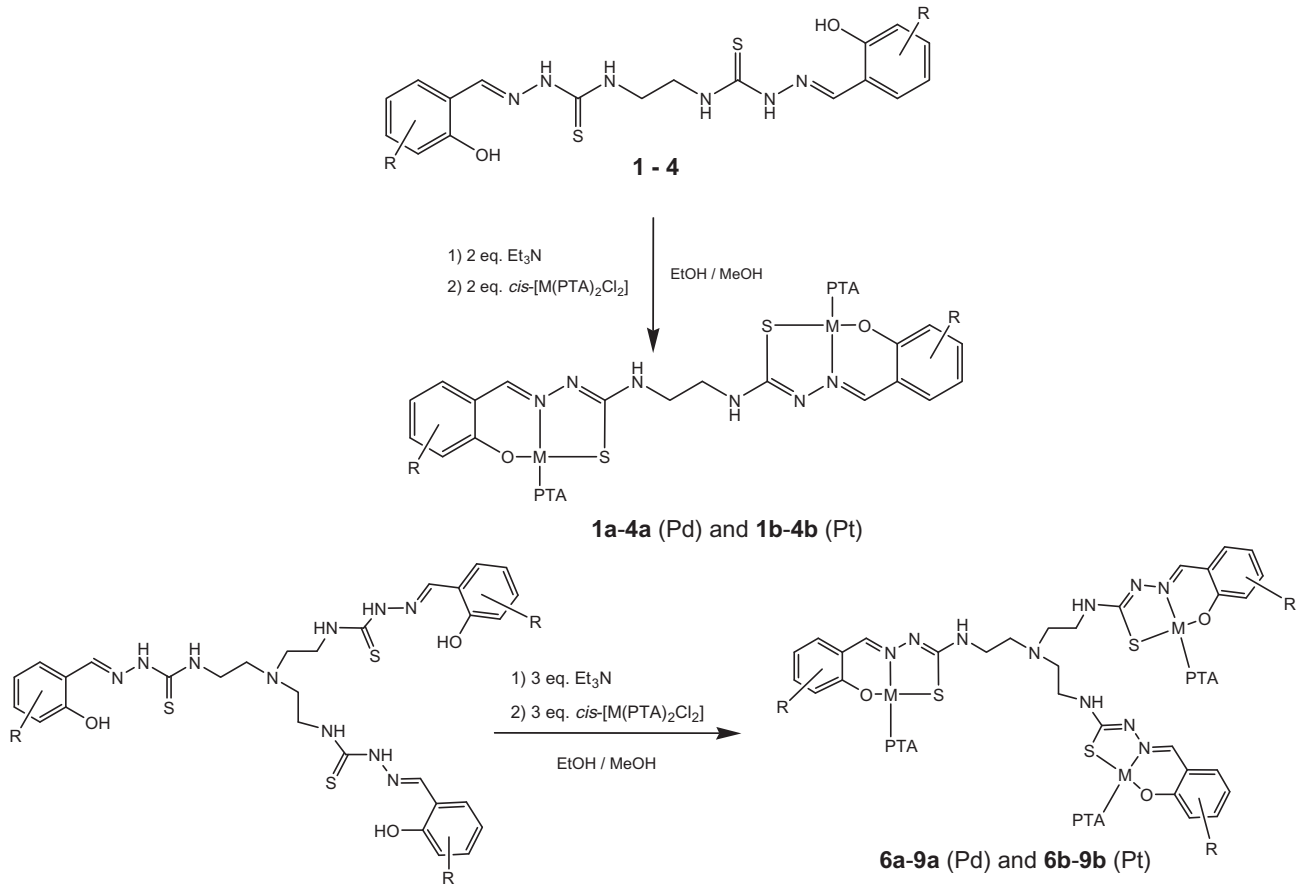


Scheme 1. Preparation of trithiosemicarbazone ligands.

transition metal complexes [22–24]. In both the Pd and Pt complexes, the signal for the imine proton is observed as a doublet. Coupling constants of approximately 13 Hz are observed for the Pd complexes and 11 Hz for the Pt derivatives. This is expected as the metal center coordinates to the azomethine nitrogen as well, supporting coordination in a tridentate manner. The appearance of the imine proton signal as a doublet is documented in literature for similar triphenylphosphine complexes [4–6,17]. $^{31}P\{^{1}H\}$ NMR spectroscopy was used to further confirm complexation of the ligand. Each Pd complex displays a singlet at approximately −40.00 ppm for the phosphorus nuclei of the PTA ligands, while each corresponding Pt derivative displays typical resonances at approximately −60.00 ppm. Infrared spectroscopy confirms coordination of ligands in the thiolate form as two absorption bands corresponding to the C═N bonds are found in each spectrum of most of the compounds. Bands of higher frequency are observed between 1619 and 1635 cm^{-1}, while bands of lower frequency are observed between 1592 and 1599 cm^{-1}. Upon complexation, a new band is observed due to formation of a second C═N bond upon deprotonation of the hydrazinic nitrogen. Mass spectrometry data also supports the integrity of these complexes. Due to the poor solubility of complex **3b** in most solvents, mass spectrometry could not be conducted. In the case of complexes **1a**, **2a**, **4a** and **6a**, the spectra displayed peaks corresponding to the $[M+H]^+$ ion. Peaks corresponding to the $[M]^+$ fragment are observed in the case of compounds **1b**, **2b**, **3a**, **6b**, **7a**, and **7b**. Peaks of the form $[M+2H]^+$ are seen for complexes **8a**, **8b**, **9a** and **9b**. For complex **4b**, a base peak corresponding to the $[M-Cl]^+$ fragment is also observed.

3.3. Preliminary biological data

Investigation of the biological activity of larger TSC molecules is limited in literature. This therefore prompted our investigation into the design and synthesis of larger thiosemicarbazone systems for biological evaluation. The preparation of trithiosemicarbazone compounds as potential anticancer agents stemmed from the phenomenon that macromolecules are able to accumulate more efficiently in tumor cells in comparison to healthy cells [25]. This phenomenon is referred to as the Enhanced Permeability and Retention (EPR) effect. Tumor cells display increased vascular permeability due to an increased porosity of surrounding blood vessels. This aids in diffusion of macromolecules into cancerous cells. Once inside these cells, the molecules are retained due to poor lymphatic drainage of the cell [25]. This supports the use of larger compounds for selective targeting of abnormal cells. Although the systems investigated in this study are not considered to be macromolecules, it is worthwhile investigating the effect of varying size and metal nuclearity on biological activity. Herein



*R = H; M = Pd (**1a**,**6a**),M = Pt (**1b**,**6b**)*

*R = 3-OMe; M = Pd (**2a**,**7a**),M = Pt (**2b**,**7b**)*

*R = 3-^{t}Bu; M = Pd (**3a**,**8a**), M = Pt (**3b**,**8b**)*

*R = 5-Cl; M = Pd (**4a**,**9a**),M = Pt (**4b**,**9b**)*

Scheme 2. Preparation of multimeric thiosemicarbazone complexes.

we discuss some preliminary results obtained from the biological evaluation of selected thiosemicarbazone ligands and complexes against the oesophageal cancer WHCO1 cell-line. The IC_{50} values are represented in Table 1. The synthesis of complexes **M1**–**M3** (Fig. 1) has been reported by our group [18].

Trithiosemicarbazone ligand **7** displays moderate activity (IC_{50} = 32.98 μM), while the 5-chloro derivative (**9**) displays increased activity with an IC_{50} value of 4.42 μM. The activity of this ligand is very similar to that of the analogous dithiosemicarbazone (IC_{50} = 4.43 μM). In this case, increasing the number of thiosemicarbazone moieties does not lead to an appreciable increase in the activity of the compound. The mononuclear palladium complexes (**M1**–**M3**) display good activity in the low micromolar range. It appears as though the nature of the R-group does not play a significant role on activity in this series. The biological evaluation of similar mononuclear salicylaldimine triphenylphosphine complexes was previously reported against the same cell-line [6]. Comparison of the results revealed that the PTA derivatives display enhanced activity in comparison to their PPh_3 counterparts. This may be attributed to slightly enhanced aqueous solubility of these compounds due to the PTA ligand. The dithiosemicarbazone complexes proved problematic during the biological evaluation due to the poor solubility of these compounds in the aqueous testing medium despite the presence of the water-soluble phosphine, therefore no reproducible data could be obtained for these complexes. The low water-solubility is mainly attributed to the thiosemicarbazone moiety, as the solubility of these compounds did not improve substantially despite the use of a water soluble co-ligand. There has also been a report of self-aggregation of thiosemicarbazone systems, which may contribute to their water-insoluble nature [26]. Complex **9b** showed good activity against this particular cell-line, but its activity is comparable to the activity of the free ligand (**9**). Overall, some of the selected compounds display promising anticancer activity, but further structure–activity studies are required in order to improve on the efficacy of these types of compounds.

4. Conclusions

A series of multimeric salicylaldimine thiosemicarbazones (**4**, **6**–**9**) and their corresponding palladium and platinum complexes

Table 1
IC_{50} values (μM) obtained for selected compounds in WHCO1 cells.

Compound	R	Type	M	IC_{50}[a,b] (μM)
M1	H	mono	Pd	1.37
M2	3-OMe	mono	Pd	1.04
M3	3-^{t}Bu	mono	Pd	1.05
4	5-Cl	di	–	4.43
6	H	tri	–	4.85
7	3-OMe	tri	–	32.98
7a	3-OMe	tri	Pd	inactive
7b	3-OMe	tri	Pt	0.13
9	5-Cl	tri	–	4.42
9b	5-Cl	tri	Pt	3.14

[a] Drug concentration required for 50% inhibition of cell viability.
[b] Standard error ±7 μM.

(**1a**/**b**–**4a**/**b** and **6a**/**b**–**9a**/**b**) were synthesized. Specifically, salicylaldimine dithiosemicarbazone and new trithiosemicarbazone complexes have been prepared efficiently using templated procedures. The salicylaldimine ligands were complexed using two metal precursors of the general formula *cis*-$[M(PTA)_2Cl_2]$, where M = Pd and Pt. Spectroscopic and analytical data supports tridentate coordination of each thiosemicarbazone moiety to the imine nitrogen, thiolate sulfur and phenolic oxygen atoms (O–N–S) giving rise to neutral complexes. The thiosemicarbazone complexes display very low water-solubility despite incorporation of a water-soluble phosphine, this low aqueous solubility seems to be elevated in the dithiosemicarbazone compounds. Despite this, selected compounds were screened for anticancer activity *in vitro* against WHCO1 oesophageal cancer cells and some of the complexes, particularly the mononuclear derivatives, show promising activity.

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References

[1] (a) S. Padhye, R.C. Chikate, P.B. Sonawane, A. Kumbhar, R. Yerande, D.X. West, A. Liberta, Coord. Chem. Rev. 123 (1993) 49;
(b) A.E. Liberta, D.X. West, Biometals 5 (1992) 121;
(c) J.G. Cory, A.H. Cory, G. Rappa, A. Lorico, M.C. Liu, T.-S. Lin, A.C. Sartorelli, Biochem. Pharmacol. 48 (1994) 335;
(d) M.J.M. Campbell, Coord. Chem. Rev. 15 (1975) 279;
(e) S.B. Padhye, G.B. Kaffman, Coord. Chem. Rev. 63 (1985) 127;
(f) I. Haiduc, C. Silvestru, Coord. Chem. Rev. 99 (1990) 253;
(g) D.X. West, S.B. Padhye, P.B. Sonawane, Struct. Bond. 76 (1992) 1;
(h) D.X. West, A.E. Liberta, S.B. Padhye, R.C. Chikate, P.B. Sonawane, A.S. Kumbhar, R.G. Yerande, Coord. Chem. Rev. 123 (1993) 49;
(i) A.G. Quiroga, C.N. Raninger, Coord. Chem. Rev. 248 (2004) 119;
(j) J.P. Scovill, D.L. Klayman, C.F. Franchino, J. Med. Chem. 25 (1982) 1261;
(k) D. Kovala-Demertzi, A. Domopoulou, M.A. Demertzis, C.P. Raptopoulou, A. Terzis, Polyhedron 13 (1994) 1917;
(l) A. Papageorgiou, Z. Iakovidou, D. Mourelatos, E. Mioglou, L. Boutis, A. Kotsis, D. Kovala-Demertzi, A. Domopoulou, D.X. West, M.A. Demertzis, Anticancer Res. 17 (1997) 247;
(m) D. Kovala-Demertzi, J.R. Miller, N. Kourkoumelis, S.K. Hadjikakou, M.A. Demertzis, Polyhedron 18 (1999) 1005;
(n) A.R. Cowly, J.R. Dilworth, P.S. Donnely, E. Labisbal, A. Sousa, J. Am. Chem. Soc. 124 (2002) 5270;
(o) S. Padhye, Z. Afrasiabi, E. Sinn, J. Fok, K. Mehta, N. Rath, Inorg. Chem. 44 (2005) 1154.
[2] J.K. Swearingen, D.X. West, Transition Met. Chem. 25 (2000) 241.
[3] Y.P. Tion, C.Y. Duan, Z.L. Lu, X.Z. You, H.K. Fun, S. Kandasamy, Polyhedron 15 (1996) 2263.
[4] S. Halder, S.M. Peng, G.H. Lee, T. Chatterjee, A. Mukherjee, S. Dutta, U. Sanyal, S. Bhattacharya, New J. Chem. 32 (2008) 105.
[5] S. Halder, R.J. Butcher, S. Bhattacharya, Polyhedron 26 (2007) 2741.
[6] P. Chellan, N. Shunmoogam-Gounden, D.T. Hendricks, J. Gut, P.J. Rosenthal, C. Lategan, P.J. Smith, K. Chibale, G.S. Smith, Eur. J. Inorg. Chem. 22 (2010) 3520.
[7] A.P. Rebolledo, M. Vietes, D. Gambino, O.E. Piro, E.E. Castellano, C.L. Zani, E.M. Souza–Fagundes, L.R. Teixeira, A.A. Batista, H. Beraldo, J. Inorg. Biochem. 99 (2005) 698.
[8] D. Kovala-Demertzi, A. Domopoulou, M.A. Demertzis, G. Valle, A. Papageorgiou, J. Inorg. Biochem. 68 (1997) 147.
[9] Z. Iakovidou, A. Papageorgiou, M.A. Demertzis, E. Mioglou, D. Mourelatos, A. Kotsis, P. Nath Yadav, D. Kovala-Demertzi, Anti-Cancer Drugs 12 (2001) 65.
[10] D. Kovala-Demertzi, M.A. Demertzis, J.R. Miller, C. Papadopoulou, C. Dodorou, G. Filousis, J. Inorg. Biochem. 86 (2001) 555.
[11] A.I. Matesanz, P. Souza, J. Inorg. Biochem. 101 (2007) 1354.
[12] A.I. Matesanz, P. Souza, J. Inorg. Biochem. 101 (2007) 245.
[13] D.M. Wiles, B.A. Gingras, T. Suprunchuk, Can. J. Chem. 45 (1967) 1735.
[14] O.P. Pandey, S.K. Sengupta, M.K. Mishra, C.M. Tripathi, Bioinorg. Chem. Appl. 1 (2003) 35.
[15] M. Christlieb, H.S.R. Struthers, P.D. Bonnitcha, A.R. Cowley, J.R. Dilworth, Dalton Trans. (2007) 5043.
[16] S. Tripathi, S.K. Sengupta, O.P. Pandey, Russ. J. Coord. Chem. 33 (2007) 704.
[17] T. Stringer, P. Chellan, B. Therrien, N. Shunmoogam-Gounden, D.T. Hendricks, G.S. Smith, Polyhedron 28 (2009) 2839.
[18] P. Chellan, T. Stringer, A. Shokar, P.J. Dornbush, G. Vazquez-Anaya, K.M. Land, K. Chibale, G.S. Smith, J. Inorg. Biochem. 105 (2011) 1562.
[19] A.M.M. Meij, S. Otto, A. Roodt, Inorg. Chim. Acta 358 (2005) 1005.
[20] D.J. Darensbourg, T.J. Decuir, N.W. Stafford, J.B. Robertson, J.D. Draper, J.H. Reibenspies, Inorg. Chem. 36 (1997) 4218.
[21] R.B. Veale, A.L. Thornley, S. Afr. J. Sci. 85 (1989) 375.
[22] R. Schibli, K.V. Katti, W.A. Volkert, C.L. Barnes, Inorg. Chem. 37 (1998) 5306.
[23] P. Smolenski, C. Dinoi, M. Fatima, C. Guedes da Silva, A.J.L. Pombeiro, J. Organomet. Chem. 693 (2008) 2338.
[24] P. Smolenski, A.J.L. Pombeiro, Dalton Trans. 1 (2008) 87.
[25] D.F. Baban, L.W. Seymour, Adv. Drug Deliv. Rev. 34 (1998) 109.
[26] R.J. Glisoni, D.A. Chiappetta, L.M. Finkielsztein, A.G. Moglioni, A. Sosnik, New J. Chem. 34 (2010) 2047.