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New palladium(II) complexes of 3-methoxysalicylaldehyde-4(*N*)-substituted thiosemicarbazones: Synthesis, spectroscopy, X-ray crystallography and DNA/protein binding study

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ABSTRACT

A series of 4(*N*)-substituted 3-methoxysalicylaldehyde thiosemicarbazone (**H_2L1**–**H_2L4**) were reacted with equimolar amount of $[PdCl_2(AsPh_3)_2]$ in ethanol/dichloromethane medium. The new complexes have been characterized by various spectroscopic techniques. The structure determination of the complexes [Pd(H-Msal-mtsc)($AsPh_3$)](**2**), [Pd(H-Msal-etsc)($AsPh_3$)](**3**) and [Pd(Msal-ptsc)($AsPh_3$)](**4**) by X-ray crystallography showed that the ligands **H_2L2** and **H_2L3** are coordinated as monobasic bidentate NS donor in the complexes **2** and **3** by forming a five member chelate ring. However, in the complex **4**, the ligand **H_2L4** bound to palladium as dibasic tridentate ONS donor by forming six and five member chelate rings. The binding ability of the palladium(II) precursor $[PdCl_2(AsPh_3)_2]$, ligands (**H_2L1**–**H_2L4**) and their corresponding complexes (**1**–**4**) with calf-thymus DNA (CT DNA) has been examined by photophysical studies, which revealed that the complexes bound to DNA through intercalation mode. The protein binding studies have been monitored by quenching of tryptophan and tyrosine residues in the presence of compounds by taking bovine serum albumin (BSA) as a model protein and the mechanism of quenching was found as static. The binding study results showed that the new complexes **1**–**4** possess better binding affinity than the starting precursor and ligands (**H_2L1**–**H_2L4**).

1. Introduction

The chemistry of thiosemicarbazones has shown considerable interest being agents of diverse applications by exhibiting analytical, antimicrobial and antitumoral properties [1–3]. The presence of nitrogen and sulfur donor atoms in the ligand may be responsible for their potential biological activity. Nowadays metal based drugs have gained importance and become the burning topics in the experimental oncology [4]. Following the discovery of cisplatin *cis*-$[Pt(NH_3)Cl_2]$, interest on the discovery of new efficient antitumor complexes were increased. The clinical success of cisplatin is limited by significant side effects and acquired or intrinsic resistance. Therefore, much attention has been focused on designing more-efficacious, target-specific and less-toxic cytotoxic drugs. In general, platinum(II) complexes are thermodynamically and kinetically more stable than their analogs palladium(II) complexes. Palladium(II) complexes undergo aquation and ligand exchange reactions 10^5 times faster than the corresponding platinum(II) complexes [5]. A variety of palladium(II) complexes have been investigated as potential antitumor drugs [6–9] and some of the palladium(II) thiosemicarbazone complexes are tested and proved to be efficient compounds of pharmaceutical interest exerting cytotoxicity against the second most dangerous type of cancer called breast cancer, anti-mycobacterium tuberculosis activity [10], antimicrobial activity and antitrypanosomal activity [11–13]. Generally, the anti-cancer activity of the drugs is based on its interaction with the DNA of cancerous cell, which ultimately leads to programmed cell death. For the development of new metal-based therapeutics, detailed studies on their interactions with DNA in are anticipated [14,15]. In continuation with our investigation on palladium thiosemicarbazone complexes [16–20], herein we report the reactions of 3-methoxysalicylaldehyde-4(*N*)-substituted thiosemicarbazone (**H_2L1**–**H_2L4**) with palladium(II) complexes and their DNA/protein interactions.

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2. Experimental

2.1. Materials and instrumentation

The ligands [**H_2L1**–**H_2L4**] and the palladium complex [$PdCl_2(AsPh_3)_2$] were synthesized according to the standard literature procedures [21,22]. All the reagents used were analaR grade, were purified and dried according to the standard procedure [23]. The syntheses, analytical and spectral characterization of the ligands (**H_2L1**–**H_2L4**) were reported by our group earlier [17]. Melting points were determined with Lab India instrument. Elemental analysis of complexes was performed on Vario EL III Elementar elemental analyzer. Electronic absorption spectra of the compounds were recorded using JASCO 600 spectrophotometer and emission measurements were carried out by using a JASCO FP-6600 spectrofluorometer. Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm^{-1}) of the ligands and the complexes as KBr pellets. ^{1}H NMR spectra were recorded in DMSO at room temperature with a Bruker 400 MHz instrument, chemical shift relative to tetramethylsilane. The chemical shifts are expressed in parts per million (ppm). CT DNA, BSA and ethidium bromide (EB) were obtained from Sigma Aldrich.

2.2. Synthesis of new palladium(II) complexes

2.2.1. Synthesis of [Pd(Msal-tsc)($AsPh_3$)] (**1**)

An ethanolic (25 ml) solution of [$PdCl_2(AsPh_3)_2$] (0.200 g; 0.253 mmol) was slowly added to 3-methoxysalicylaldehydethiosemicarbazone [H_2-Msal-tsc] (0.058 g, 0.253 mmol) in dichloromethane (25 ml). The mixture was allowed to stand for 4 days at room temperature.

A yellowish orange solid formed was filtered, washed with petroleum ether (60–80 °C). Yield: 51%. M.p. 225 °C. *Anal.* Calc. for $C_{27}H_{24}N_3O_2SPdAs$: C, 51.00; H, 3.80; N, 6.61; S, 5.04. Found: C, 50.98; H, 3.77; N, 6.59; S, 5.01%. FT-IR (cm^{-1}) in KBr: 1584 ($\nu_{C=N}$), 1310 (ν_{C-O}), 753 (ν_{C-S}), 1436, 1066, 694 cm^{-1} (for $AsPh_3$); UV–Vis (CH_2Cl_2), λ_{max}: 262 (30778) (intra-ligand transition); 332 (22160), 357 (19960), 418 (10360) nm ($dm^3\ mol^{-1}\ cm^{-1}$) (LMCT s → d); ^{1}H NMR (DMSO-d6, ppm): 8.25 (d (J = 14.1 Hz), 1H, CH=N), 3.61 (s, 3H, OCH_3), 6.49–7.71 (m, aromatic).

The very similar method was followed to synthesize other complexes.

2.2.2. Synthesis of [Pd(H-Msal-mtsc)($AsPh_3$)](**2**)

The complex **2** was prepared by the procedure as used for (**1**) with 3-methoxysalicylaldehyde 4(*N*)-methylthiosemicarbazone [H_2-Msal-mtsc] (0.060 g; 0.253 mmol) and [$PdCl_2(AsPh_3)_2$] (0.200 g; 0.253 mmol). The resulting solution was allowed to stand for 4 days at room temperature. The orange color solid obtained was recrystallized from CH_2Cl_2 and CH_3CN to yield orange red crystals which was filtered, washed with n-hexane and dried. Yield: 57%. M.p. 126 °C. *Anal.* Calc. for $C_{28}H_{27}N_3O_2SClPdAs$: C, 49.01; H, 3.96; N, 6.12; S, 4.67. Found: C, 48.98; H, 3.92; N, 6.09; S, 4.65%. FT-IR (cm^{-1}) in KBr: 3327 (ν_{OH}), 1547 ($\nu_{C=N}$), 1241 (ν_{C-O}), 734 (ν_{C-S}), 1458, 1072, 688 cm^{-1} (for $AsPh_3$); UV–Vis (CH_2Cl_2), λ_{max}: 263 (34536) nm ($dm^3\ mol^{-1}\ cm^{-1}$) (intra-ligand transition); ^{1}H NMR (DMSO-d6, ppm): 11.28 (s, 1H, OH), 8.36 (s, 1H, CH=N), 8.40 (s, 1H, $NHCH_3$), 3.61 (s, 3H, OCH_3), 6.49–7.71 (m, aromatic), 2.73 (d (J = 4.82), 3H, CH_3).

2.2.3. Synthesis of [Pd(H-Msal-etsc)($AsPh_3$)] (**3**)

The complex **3** was prepared by the procedure as used for (**1**) with 3-methoxysalicylaldehyde 4(*N*)-ethylthiosemicarbazone [H_2-Msal-etsc] (0.064 g; 0.253 mmol) and [$PdCl_2(AsPh_3)_2$] (0.200 g; 0.253 mmol). The red solid obtained was recrystallized from DMF to yield dark red crystals which was filtered, washed with n-hexane and dried. Yield: 67%. M.p. 231 °C. *Anal.* Calc. for $C_{29}H_{29}N_3O_2SClPdAs$: C, 49.73; H, 4.17; N, 6.01; S, 4.58. Found: C, 49.71; H, 4.15; N, 5.98; S, 4.57%. FT-IR (cm^{-1}) in KBr: 3318(ν_{OH}), 1578 ($\nu_{C=N}$), 1239 (ν_{C-O}), 733 (ν_{C-S}), 1457, 1082, 687 cm^{-1} (for $AsPh_3$); UV–Vis (CH_2Cl_2), λ_{max}: 267 (27821) nm ($dm^3\ mol^{-1}\ cm^{-1}$) (intra-ligand transition); ^{1}H NMR (DMSO-d6, ppm): 11.31 (s, 1H, OH), 8.58 (d (J = 4.40), 1H, CH=N), 7.68 (br s, 1H, NHC_2H_5), 3.78 (s, 3H, OCH_3), 6.79–7.67 (m, aromatic), 3.12–3.15 (m, 2H, CH_2), 1.05 (t, 3H, CH_3).

2.2.4. Synthesis of [Pd(Msal-ptsc)($AsPh_3$)] (**4**)

The complex **4** was prepared by the procedure as has been used for (**1**) with 3-methoxy salicylaldehyde 4(*N*)-phenylthiosemicarbazone [H_2-Msal-ptsc] (0.076 g; 0.253 mmol) and [$PdCl_2(AsPh_3)_2$] (0.200 g; 0.253 mmol). Dark red crystals obtained were filtered and washed with n-hexane and dried. Yield: 71%. M.p. 242 °C. *Anal.* Calc. for $C_{33}H_{28}N_3O_2SPdAs$: C, 55.67; H, 3.96; N, 5.90; S, 4.50. Found: C, 55.65; H, 3.95; N, 5.88; S, 4.48%. FT-IR (cm^{-1}) in KBr: 1591 ($\nu_{C=N}$), 1312 (ν_{C-O}), 738 (ν_{C-S}), 1431, 1078, 689 cm^{-1} (for $AsPh_3$);UV–Vis (CH_2Cl_2), λ_{max}: 263 (34647) ($dm^3\ mol^{-1}\ cm^{-1}$) (intra-ligand transition); 353 (26070), 409 (17320) nm ($dm^3\ mol^{-1}\ cm^{-1}$) (LMCT s → d); ^{1}H NMR (DMSO-d6, ppm): 8.67 (d (J = 13.4), 1H, CH=N), 9.41 (s, 1H, NHPh), 3.65 (s, 3H, OCH_3), 6.54–7.74 (m, aromatic).

2.3. X- ray crystallography

Single crystal data collections and corrections for the new **Pd(II)** complexes **2**, **3** and **4** were done at 293 K with CCD Kappa Diffractometer using graphite mono chromated Mo Kα (λ = 0.71073 Å) radiation [24]. The structural solutions were done by using SHELXTL-97 [25] and refined by full matrix least square on F^2 using SHELXL-97 [26].

2.4. Binding studies

2.4.1. DNA binding study

All of the experiments involving the binding of the compounds with CT DNA were carried out in deionised water with tris(hydroxymethyl)-aminomethane (Tris, 5 mM) and sodium chloride (50 mM) and adjusted to pH 7.2 with hydrochloric acid at room temperature. Various concentrations of CT-DNA (0–50 μM) was added to the compounds (10 μM). Absorption spectra were recorded after equilibrium at 20 °C for 10 min. The intrinsic binding constant K_b was determined by using Stern–Volmer equation (1) [27,28].

$$([DNA]/[\varepsilon_a - \varepsilon_f]) = [DNA]/[\varepsilon_b - \varepsilon_f] + 1/K_b[\varepsilon_b - \varepsilon_f] \quad (1)$$

The absorption coefficients ε_a, ε_f, and ε_b correspond to A_{obsd}/[compound], the extinction coefficient for the free compound and the extinction coefficient for the compound in the fully bound form, respectively. The slope and the intercept of the linear fit of the plot of $[DNA]/[\varepsilon_a - \varepsilon_f]$ versus [DNA] give $1/[\varepsilon_a - \varepsilon_f]$ and $1/K_b[\varepsilon_b - \varepsilon_f]$, respectively. The intrinsic binding constant K_b can be obtained from the ratio of the slope to the intercept. It can be determined by monitoring the changes in the absorbance in the intra ligand band at the corresponding λ_{max} with increasing concentration of DNA and is given by the ratio of slope to the Y intercept in plots of $[DNA]/(\varepsilon_a - \varepsilon_f)$ versus [DNA].

2.4.2. Competitive binding with ethidium bromide

In order to know the mode of attachment of CT DNA to the complexes fluorescence quenching experiments of EB–DNA were carried out by adding 0–50 μM compounds containing 10 μM EB,