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Synthesis and characterization of a new bioactive mono (thiosemicarbazone) ligand based on 3,5-diacetyl-1,2,4-triazol diketone and its palladium and platinum complexes

A.I. Matesanz *, P. Albacete, P. Souza

Departamento de Química Inorgánica (Módulo 07), Facultad de Ciencias, c/ Francisco Tomás y Valiente n° 7, Universidad Autónoma de Madrid, 28049 Madrid, Spain

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ABSTRACT

Preparation and characterization of a new ^{4}*N*-*p*-chlorophenyl substituted thiosemicarbazone ligand, H_3L^2, and its derived palladium(II) and platinum(II) complexes, $[Pt(HL^2)(PPh_3)]$ and $[Pd(HL^2)(PPh_3)]$, is described. The molecular structures of the two new metal complexes have been determined by single crystal X-ray diffraction. In both complexes the metal ion is four-coordinated with a $[N_2SP]$ donor environment, *via* one triazole nitrogen atom, the azomethine nitrogen and thione sulfur atoms of the thiosemicarbazone moiety and a phosphorous atom from the triphenylphosphine coligand. The biological activity of the new compounds synthesized was initially explored by determining their antiproliferative activity *in vitro* against T-47D, A2780 and A2780*cis*R human cancer cell lines. The cytotoxicity data suggest that these compounds may be endowed with important antitumor properties, especially H_3L^2 since is capable not only to circumvent cisplatin resistance in A2780*cis*R cells but also to exhibit high antiproliferative activity in breast cancer T-47D cells.

1. Introduction

Thiosemicarbazones (TSCs) constitute a class of nitrogen–sulfur donor ligands especially attractive because of their structural, electronic and biological properties. They are mainly obtained by the condensation of a suitable carbonyl compound, aldehyde or ketone, with a thiosemicarbazide derivative. From appropriated dicarbonyl compounds and controlling the ratio of reactants and reaction conditions it is possible to synthesize two different series of compounds, collectively known as mono- and bis(thiosemicarbazones) [1–3].

General chemical structure of TSCs, R_1R_2-C=N-NH-C(S)-N-R_3R_4, can be modified in multiple ways and in some cases, small modifications have resulted in dramatic changes to the biological activity. Specifically, TSCs functionalized with a nitrogen containing heterocycle in a position α to the thiosemicarbazide side chain, namely α-N-heterocyclic thiosemicarbazones, have demonstrated significant antitumor activity. It has been reported that the activity strongly dependent upon the nature of the N-heterocyclic ring [4–8].

1,2,4-Triazoles are well known aromatic five-membered heterocycles which, containing three nitrogen and one hydrogen atoms, present some important features like aromaticity and tautomerism. In addition they are very strong N-donors towards d-metal ions and can also be readily deprotonated [9–11].

Keeping in view the above observations and as part of our systematic investigation on the coordination chemistry of thiosemicarbazone derivatives we recently reported palladium(II) and platinum(II) binuclear complexes derived of 3,5-diacetyl-1,2,4-triazol bis(^{4}*N*-*p*-chlorophenylthiosemicarbazone), Fig. 1. The *in vitro* antiproliferative experiments have shown that both the free ligand and the platinum(II) complex exhibit important cytotoxic activity in various human cell lines derived from different types of solid tumors [12]. These results encouraged us to synthesize new derivatives, specifically was planned to synthesize the mono (thiosemicarbazone) analog, Fig. 1.

Therefore here we describe the synthesis and chemical characterization of the new {(E)-2-[1-(3-acetyl-1H-1,2,4-triazol-5-yl) ethylidene]-N-(4-chlorophenyl)hydrazidecarbothioamide}, H_3L^2, together with the palladium(II) and platinum(II) complexes, $[Pd(HL^2)(PPh_3)]$ and $[Pt(HL^2)(PPh_3)]$. The cytotoxic activity of the new compounds synthesized and cisplatin, assumed as the reference antitumor drug, has been studied against three human cancer cell lines: T-47D (breast cancer), A2780 and A2780*cis*R (epithelial ovarian cancer).

* Corresponding author.
E-mail address: ana.matesanz@uam.es (A.I. Matesanz).

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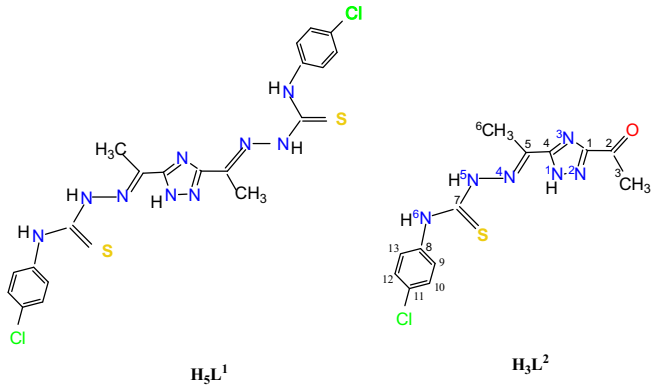

H_5L^1 H_3L^2

Fig. 1. Chemical structure of 3,5-diacetyl-1,2,4-triazole based bis- and monothiosemicarbazone ligands, H_5L^1 and H_3L^2.

2. Experimental

2.1. Measurements

Elemental analyses were performed on a LECO CHNS-932 microanalyzer. Fast atom bombardment (FAB) mass spectrum (MS) was performed on a VG AutoSpec spectrometer and Electrospray Ionization (ESI) mass spectra were carried out on a QSTAR mass spectrometer. Nuclear Magnetic Resonance (NMR) spectra were recorded on a BRUKER AMX-300 spectrometer. All cited physical measurements were obtained out by the Servicio Interdepartamental de Investigación (SIdI) of the Universidad Autónoma de Madrid.

Melting points were determined with a Stuart Scientific SMP3 apparatus. The pH measurements were carried out with a Crison BASIC 20+ pH-meter equipped with a combined Crison glass electrode. Infrared spectra were recorded on a Jasco FT/IR-410 spectrophotometer. Electronic spectra were recorded on a Thermo Scientific Evolution 260 Bio UV–visible (UV–Vis) spectrophotometer.

2.2. Materials

Solvents were purified and dried according to standard procedures. Ultrapure Milli Q water was used for all biological experiments. Hydrazine hydrate, L-lactic acid, *p*-chlorophenyl isothiocyanate, palladium(II) chloride, lithium chloride and potassium tetrachloridoplatinate(II) were commercially available.

2.3. Synthesis of compounds

The starting materials, *p*-chlorophenylthiosemicarbazide and 3,5-diacetyl-1,2,4-triazol, were prepared as described in the literature [13,14].

2.3.1. {(E)-2-[1-(3-acetyl-1H-1,2,4-triazol-5-yl)ethylidene]-N-(4-chlorophenyl)hydrazidecarbothioamide}, H_3L^2

0.153 g (1 mmol) of 3,5-diacetyl-1,2,4-triazol was dissolved in 20 ml of water and added slowly to a methanolic solution (20 mL) of the *p*-chlorophenylthiosemicarbazide (0.20 g, 1 mmol) with some drops of conc. HCl and cooled to 0 °C. The mixture was stirred at 0 °C for 1 h and then the white solid formed was filtered, washed with cold methanol and diethyl ether and dried *in vacuo*. Yield (80%), mp 177 °C. Elemental analysis found, C, 43.75; H, 4.00; N, 23.55; S, 9.35; $C_{13}H_{13}N_6ClOS{\cdot}H_2O$ requires C, 44.00; H, 4.25, N, 23.70; S, 9.05%. MS (FAB^+ with *m*NBA: nitrobenzyl alcohol matrix) *m*/*z* 337 for $[C_{13}H_{13}N_6OSCl+H]^+$. IR (KBr pellet): ν/cm^{-1} 3326 (s, ^{1}NH), 3149 (s, ^{5}NH and ^{6}NH), 1691 (s, CO), 1586 (m, CN); 755 (w, CS-thioamide IV band). ^{1}H NMR (DMSO-d_6): δ (ppm) 15.13 (s, ^{1}NH, 1H), 13.06 (s, ^{5}NH, 1H), 10.42 (s, ^{6}NH, 1H), 7.77–7.31 (m, Cl-Ph, 4H); 2.66 (s, $^6CH_3$, 3H); 2.05 (s, $^3CH_3$, 3H). UV–Vis (DMSO): λ/nm 256, 317.

2.3.2. Metal complexes

Were obtained by reaction of the corresponding $MCl_2(PPh_3)_2$ metallic salt (M = Pd, Pt) with H_3L^2 ligand in ethanol, in the presence of two equivalents of $LiOH{\cdot}H_2O$, in 1:1 molar ratios. The reaction mixture was stirred for 2 h at room temperature and then, the solid formed was filtered, washed with ethanol and diethyl ether and finally dried *in vacuo*.

2.3.3. [Pt(HL^2)(PPh$_3$)]

Yield (79%), mp 196 °C (descomposes). Elemental analysis found, C, 46.40; H, 3.50; N, 11.10; S, 4.45; $C_{31}H_{26}ClN_6OPPtS$ requires C, 47.00; H, 3.65; N, 10.60; S, 4.05%. MS (FAB^+ with mNBA: nitrobenzyl alcohol matrix) *m*/*z* 792 for $[C_{31}H_{26}ClN_6OPPtS]^+$. IR (KBr pellets): ν/cm^{-1} 3286 (s, NH); 1681 (s, CO); 1585 (w, CN); 1097 (s, PC); 748 (m, CS-thioamide IV band). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.18 (s, ^{6}NH, 1H); 7.71–7.37 (m, aromatic protons); 2.61 (s, $^6CH_3$, 3H); 2.16 (s, $^3CH_3$, 3H). UV–Vis (DMSO): λ/nm 260, 367, 454.

Crystallization in DMSO allowed us to isolate single crystals, which were studied by X-ray diffraction techniques.

2.3.4. [Pd(HL^2)(PPh$_3$)]

Yield (46%), mp 189 °C (descomposes). Elemental analysis found, C, 53.00; H, 3.80; N, 11.95; S, 4.05; $C_{31}H_{26}ClN_6OPPdS$ requires C, 52.90; H, 3.70; N, 11.95; S, 4.55%. MS (ESI+ with MeOH): *m*/*z* 705 for $[C_{31}H_{26}N_6OPPdS+H]^+$. IR (KBr pellets): ν/cm^{-1} 3153 (s, NH); 1693 (s, CO); 1587 (w, CN); 1095 (s, PC); 744 (m, CS-thioamide IV band). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.08 (s, ^{6}NH, 1H); 7.67–7.37 (m, aromatic protons); 2.62 (s, $^6CH_3$, 3H); 2.23 (s, $^3CH_3$, 3H). UV–Vis (DMSO): λ/nm 259, 362, 461.

Crystallization in DMSO allowed us to isolate single crystals, which were studied by X-ray diffraction techniques.

2.4. Crystallography

Data were collected on a Bruker Kappa Apex II diffractometer. Crystallographic data are listed in Table 1. The software package SHELXTL was used for space group determination, structure solution, and refinement [15]. The structures were solved by direct methods, completed with difference Fourier syntheses, and refined with anisotropic displacement parameters.

2.5. DMSO/Tris-buffer stability assays

The stability of the compounds in Tris buffer–DMSO (99:1) was analyzed using UV spectrophotometry. To this end, the compounds were first dissolved in DMSO to obtain 10^{-4} and 10^{-2} M stock solutions which were diluted in Tris-buffer (NaCl 50 mM, Tris–HCl 5 mM, pH was adjusted to 7.2 with NaOH 0.5 M) to 1 and 100 μM final concentrations, thus giving homogeneous solutions with the DMSO content of 1% (the maximum DMSO concentration usually tolerated by cell monolayers *in vitro* is 2%).

The absorbance, at the corresponding λ_{max} established for each compound, was measured over 24 h.

2.6. In vitro antiproliferative activity

The human cancer cells: A2780 and A2780*cis*R (epithelial ovarian cancer) and T-47D (breast cancer); were grown in RPMI-1640