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Platinum(II) and palladium(II) complexes with (N,N′) and (C,N,N′)$^-$ ligands derived from pyrazole as anticancer and antimalarial agents: Synthesis, characterization and in vitro activities

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ABSTRACT

The study of the reactivity of three 1-(2-dimethylaminoethyl)-1*H*-pyrazole derivatives of general formula [1-$(CH_2)_2NMe_2$}-3,5-R_2-pzol] {where pzol represents pyrazole and R═H (**1a**), Me (**1b**) or Ph (**1c**)} with [$MCl_2(DMSO)_2$] (M═Pt or Pd) under different experimental conditions allowed us to isolate and characterize *cis*-[M{κ^2-*N*,*N*′-{[1-$(CH_2)_2NMe_2$}-3,5-R_2-pzol]}Cl_2] {MM═PtPt (**2a**–**2c**) or Pd (**3a**–**3c**)} and two cyclometallated complexes [M{κ^3-*C*,*N*,*N*′-{[1-$(CH_2)_2NMe_2$}-3-(C_5H_4)-5-Ph-pzol]}Cl] {M═Pt(II) (**4c**) or Pd(II) (**5c**)}. Compounds **4c** and **5c** arise from the orthometallation of the 3-phenyl ring of ligand **1c**. Complex **2a** has been further characterized by X-ray crystallography. Ligands and complexes were evaluated for their in vitro antimalarial against *Plasmodium falciparum* and cytotoxic activities against lung (A549) and breast (MDA MB231 and MCF7) cancer cellular lines. Complexes **2a**–**2c** and **5c** exhibited only moderate antimalarial activities against two *P. falciparum* strains (3D7 and W2). Interestingly, cytotoxicity assays revealed that the platinacycle **4c** exhibits a higher toxicity than cisplatin in the three human cell lines and that the complex **2a** presents a remarkable cytotoxicity and selectivity in lung (IC_{50} = 3 μM) versus breast cancer cell lines (IC_{50} > 20 μM). Thus, complexes **2c** and **4c** appear to be promising leads, creating a novel family of anticancer agents. Electrophoretic DNA migration studies in presence of the synthesized compounds have been performed, in order to get further insights into their mechanism of action.

1. Introduction

Platinum drugs have played a key role among the metal-based anticancer agents [1]. The discovery of the antitumor properties of *cis*-[$PtCl_2(NH_3)_2$] *cisplatin* [2] (Fig. 1) in 1965 was rapidly followed by clinical trials and finally in 1978, FDA granted approval. Platinum(II) complexes such as cisplatin and carboplatin (Fig. 1) are widely used to treat cancers such as testicular, ovarian, urinary bladder, melanoma, etc. The cytotoxicity of Pt-based drugs is mainly attributed to their ability to bind DNA and to induce DNA damage leading then to apoptosis [3–5].

Unfortunately, the use of cisplatin is restricted due to dose-limiting toxicity, including nephrotoxicity, neurotoxicity and ototoxicity [6,7]. Additional side effects such as blood pressure increase, severe nausea, vomiting and diarrhea have also been reported. Moreover, the biochemical resistance mode limits the clinical utility of the Pt-based drugs in current use [1].

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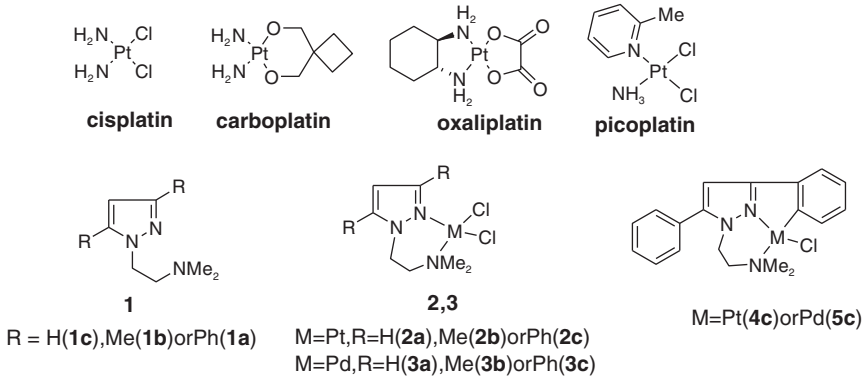

Fig. 1. Chemical structure of some platinum(II) based anticancer agents and compounds used in this study.

In the search of new metallodrugs avoiding toxicity and resistance, special attention has been paid to the replacement of one or both NH_3 ligands of *cisplatin* by other *N*-donor ligand(s). This strategy gave rise to oxaliplatin and picoplatin [8] (Fig. 1). In oxaliplatin, which is active in patients with colorectal cancer, both NH_3 units have been replaced by (1*R*,2*R*)-cyclohexane-1,2-diamine (*R*,*R*-dach); while picoplatin, that is in clinical development for the treatment of patients with solid tumors, contains a 2-methylpyridine instead of one NH_3 ligand.

The search of novel *N*-donor ligands (i.e. amines, oximes, imines or azoles) for the synthesis of optimized platinum(II) and palladium(II) drugs is still in progress [9,10]. In addition, it is well-known that azoles are valuable reagents in coordination chemistry and that their binding to a transition metal ion affects their properties and activities. Few complexes with pyrazole ligands showing an antitumor activity similar to that of cisplatin have been reported [11–20], but the effect produced by the substituents on the heterocycle has not been clarified so far. Within this therapeutic context, and in order to clarify this point and to elucidate the influence of mode of binding of this family of ligands in the biological activity of the complexes, we decided to synthesize the new pyrazole derivatives **1a**–**1c** (Fig. 1) and to study their reactivity with Pt(II) and Pd(II). Due to the relative disposition of the two nitrogen atoms, compounds **1a**–**1c** may bind to the M(II) center as a neutral (*N*) or (*N*,*N*′) ligand. Moreover, for **1c**, the presence of the phenyl ring on position 3 of the heterocycle may also allow the formation of metallacycles containing **1c** as a *mer*-terdentate $(C,N,N')^-$ ligand.

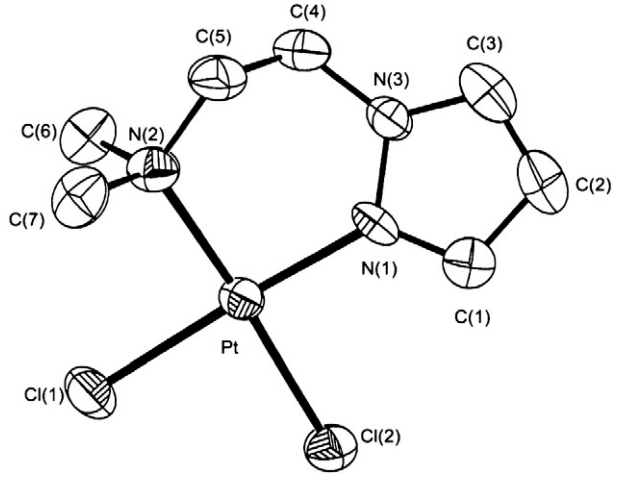

Fig. 2. ORTEP plot of complex **2a**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (in Å) and angles (in deg.) for **2a**: Pt–N(1), 2.010(3); Pt–N(3), 2.091(4); Pt–Cl(1), 2.3056(13); Pt–Cl(2), 2.3058(13); N(1)–C(1),1.339(6); N(1)–N(2), 1.370(6); N(3)–C(7), 1.499(5); N(3)–C(6), 1.499(7); N(3)–C(8), 1.506(6); C(1)–C(2), 1.409(8); C(2)–C(3), 1.367(10); C(3)–N(2), 1.349(7); N(2)–C(5), 1.453(7); C(5)–C(6), 1.483(7); N(1)–Pt–N(3), 93.57(15); N(1)–Pt–Cl(1), 176.60(11), N(3)–Pt–Cl(1), 89.61(12); N(1)–Pt–Cl(2), 89.32(12); N(3)–Pt–Cl(2), 177.03(12); Cl(1)–Pt–Cl(2), 87.52(5); C(1)–N(1)–N(2), 105.3(4); C(1)–N(1)–Pt, 129.5(3); N(2)–N(1)–Pt, 125.2(3); C(7)–N(3)–C(6), 108.2(4); C(7)–N(3)–C(8), 108.3(4); C(6)–N(3)–C(8), 106.6(4); C(7)–N(3)–Pt, 109.7(3); C(6)–N(3)–Pt, 113.5(3); C(8)–N(3)–Pt, 110.4(3); N(1)–C(1)–C(2), 111.0(5); C(3)–C(2)–C(1), 104.7(5); N(2)–C(3)–C(2), 108.5(6); C(3)–N(2)–N(1), 110.6(4); C(3)–N(2)–C(5), 129.1(5); N(1)–N(2)–C(5), 120.1(4); N(2)–C(5)–C(6), 111.5(4) and C(5)–C(6)–N(3), 113.8(4).

Cyclometallated complexes derived from *N*-donor ligands have attracted great interest during the last decade due to their properties and applications in a wide variety of fields [10,20–36] and compounds of this kind containing Pd(II), Pt(II), Ru(II), Ir(III) Rh(III) and Au have shown promising cytotoxic activities [10,20,27–36]. Few cyclopalladated complexes derived from pyrazole are known [37–41] and, to the best of our knowledge, their cytotoxicity has only been reported once [41]. On the other hand despite the interest for Pt(II) complexes, platinacycles with pyrazolyl ligands are scarce and studies on their biological activity have not been performed so far.

In this work, we present the study of the reactivity of ligands **1a**–**1c** with syntheses of *cis*-$[MCl_2(DMSO)_2]$, the new compounds **2a**–**2c** and **3a**–**3c** and the cyclometallated complexes **4c** and **5c**, together with a comparative study of their antineoplastic activity against lung (A549) and breast (MDA MB231 and MCF7) human cancer cell lines. As our interests lie also in the area of antiparasitic drugs [42,43] and since a few Pt(II) [44] and Pd(II) based complexes [45] with antimalarial activity (in the micromolar range) have been reported, we also tested the potential of the free ligands (**1a**–**1c**) and the complexes **2a**–**5c** against the chloroquine-susceptible strain (3D7) and the chloroquine-resistant strain (W2) of *Plasmodium falciparum*.

2. Experimental

2.1. Chemistry

2.1.1. Materials and methods

Reagents were obtained from commercial sources and used as received. *Cis*-$[MCl_2(DMSO)_2]$ (M═Pd or Pt) were prepared according to literature protocols [46,47]. All reactions were carried out with dry and freshly distilled solvents. Column chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh) or Al_2O_3 (neutral alumina, 63–200 μm). Analytical TLC was performed on SiO_2 (Merck silica gel 60 F_{254}) plates. Elemental analyses were carried out at the Serveis Cientifico-Tècnics (*Universitat Barcelona*). Mass spectra (electrospray ionization, ESI^+) were performed at the Servei d'Espectrometria de Masses (*Universitat de Barcelona*). Infrared spectra were obtained with a Nicolet 400FTIR instrument using KBr pellets. Only noteworthy IR absorptions are listed. Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 298 K with a Mercury-400 MHz. ^1H and ^{13}C chemical shifts (δ) are reported in ppm downfield and referred to $SiMe_4$ and to the resonance of $CDCl_3$, respectively and coupling constants (*J*) are given in Hz. All NMR assignments were