Journal of Molecular Structure 1048 (2013) 88–97

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Trans- and *cis*-2-phenylindole platinum(II) complexes as cytotoxic agents against human breast adenocarcinoma cell lines

Maria Tomé [a], Concepción López [a,*], Asensio González [b], Bahadir Ozay [b,1], Josefina Quirante [b], Mercè Font-Bardía [c], Teresa Calvet [d], Carme Calvis [e], Ramon Messeguer [e], Laura Baldomá [f], Josefa Badía [f]

[a] Departament de Química Inorgànica, Facultat de Química, Universitat de Barcelona, Martí i Franqués 1-11, E-08028 Barcelona, Spain
[b] Laboratori de Química Orgànica, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XXIII s/n, E-08028 Barcelona, Spain
[c] Unitat de Difracció de Raigs-X, Centre Científic i Tecnològic de la Universitat de Barcelona, Universitat de Barcelona, Solé i Sabaris 1-3, E-08028 Barcelona, Spain
[d] Department de Cristal·lografia, Mineralogia i Dipòsits Minerals, Facultat de Geologia, Universitat de Barcelona, Martí i Franqués s/n, E-08028 Barcelona, Spain
[e] Biomed Division, Leitat Tecnological Center, Parc Científic de Barcelona, Edifici Hèlix, c/Baldiri Reixach 15-21, E-08028 Barcelona, Spain
[f] Departament de Bioquímica i Biología Molecular, Facultat de Farmàcia, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Avda Joan XXIII s/n, 08028 Barcelona, Spain

HIGHLIGHTS

- *Trans*- and *cis*-isomers of [Pt(L)Cl_2(DMSO)] complexes with a new 3-methoxyimino-2-phenyl-3*H*-indole ligand have been prepared and characterized by X-ray diffraction.
- Conclusive proofs of the key role of the DMSO ligand and its location in the coordination sphere of the Pt(II) and on the crystal architecture are presented.
- The study of the antitumoral activity of *cis*- and *trans*- [Pt(L)Cl_2(DMSO)] shows that most of them are potent cytotoxic agents.
- The influence of the relative disposition of the Cl^- ligands in the *cis*- and *trans*-isomers on their cytotoxic activities is discussed.
- Compounds 4b and 5a are more cytotoxic than cisplatin in MDA-MB231 and MCF-7 breast cancer lines.

ARTICLE INFO

Article history:
Received 14 February 2013
Received in revised form 29 April 2013
Accepted 30 April 2013
Available online 28 May 2013

Keywords:
Platinum(II) complexes
2-Phenylindole
Cis- and *trans*-complexes
Cytotoxicity
Cancer

ABSTRACT

The synthesis and characterization of the new 2-phenylindole derivative: C_8H_3N-2-C_6H_5-3NOMe-5OMe (**3c**) and the *trans*- and *cis*-isomers of [Pt(**3c**)Cl_2(DMSO)] complexes (**4c** and **5c**, respectively) are described. The crystal structures of **4c**·CH_2Cl_2 and **5c** confirm: (a) the existence of a Pt-N_{indole} bond, (b) the relative arrangement of the Cl^- ligands [*trans*- (in **4c**) or *cis*- (in **5c**)] and (c) the *anti*-(*E*) configuration of the oxime. The cytotoxic assessment of C_8H_3N-2-(C_6H_4-4′R^1)-3NOMe-5R^2 [with $R^1 = R^2 = H$ (**3a**); R^1 = Cl, R^2 = H (**3b**) and R^1 = H, R^2 = OMe (**3c**)] and the geometrical isomers of [Pt(L)Cl_2(DMSO)] with L = **3a**–**3c** [*trans*- (**4a**–**4c**) and *cis*- (**5a**–**5c**), respectively] against human breast adenocarcinoma cell lines (MDA-MB231 and MCF-7) is also reported and reveals that all the platinum(II) complexes (except **4a**) are more cytotoxic than *cisplatin* in front of the MCF7 cell line. Electrophoretic DNA migration studies of the synthesized compounds in the absence and in the presence of topoisomerase-I have been performed, in order to get further insights into their mechanism of action.

1. Introduction

Heterocycles have important applications as fine and bulk chemicals, agrochemicals and participate in the structure of many pharmaceutical agents and biomolecules [1]. They are also valuable ligands in coordination and organometallic chemistry [2,3], in which the nature of the transition metal, its oxidation state, the electronic and/or steric features of heterocyclic ligands and their relative disposition modify their physical and chemical properties and have direct implications on their applications in chemistry, medicine, biology and materials science [1–3].

Moreover, the interest in novel *cis*- and *trans*-isomers of [Pt(L^1)(L^2)Cl_2] with L^1 or L^2 = heterocycles with N donor atoms has increased considerably in recent years mainly due to their potential use in cancer therapy and biomedicine [4–11]. Platinum(II) complexes [Pt(L^1)(L^2)Cl_2] or [Pt(L^1)$_2Cl_2$] with L^1 derived from pyrazole, imidazole, benzimidazole or purine and pyrimidine bases of DNA have been reported [8–10].

* Corresponding author. Tel.: +34 403 91 34; fax: +34 490 77 25.
E-mail address: conchi.lopez@qi.ub.es (C. López).
[1] Current address: Faculty of Pharmacy, Ege University, Izmir, Turkiye.

0022-2860/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2013.04.071

On the other hand, 2-phenylindole derivatives have attracted great interest since their introduction by von Angerer in 1983 [12]. The 2-phenylindole-3-carboxaldehydes (**1**) (Fig. 1) proved to exert an antimitotic activity in human breast cancer cells by inhibition of tubulin polymerization [13]. Related derivatives containing oximes, methylamines, propanedinitriles and hydrazones [14] or the ferrocenylmethyl unit (**2** in Fig. 1) on position **3** have been also investigated [15].

Despite the interest of exploring the potential synergic effect induced by the presence of phenylindole ligands in *cis*- or *trans*-isomers of $[Pt(L^1)(L^2)Cl_2]$, platinum(II) complexes with indolyl frameworks are extremely scarce [16]. Quite recently we have developed synthetic procedures to achieve the two 3-methoxyimino-2-phenyl-3*H*-indoles: C_8H_4N-2-(C_6H_4-4′R^1)-3NOMe with R^1 = H (**3a**) or Cl (**3b**) (Fig. 1) [17] and the *trans*- (**4a** or **4b**) and *cis*- (**5a** and **5c**) isomers of compounds $[Pt(L^3)Cl_2(DMSO)]$ (with L^3 = **3a** or **3b**, Fig. 1) [18]. In this paper we report the new 2-phenylindole derivative, C_8H_3N-2-(C_6H_4-4′R^1)-3NOMe-5R^2 with R^1 = H, R^2 = OMe (**3c**) (Fig. 1 and Scheme 1) and the two geometrical isomers of $[Pt(\mathbf{3c})Cl_2(DMSO)]$. A comparative study of the cytotoxic activity of the free ligands (**3a**–**3c**) and the *trans*- (**4a**–**4c**) and *cis*- (**5a**–**5c**) isomers of the Pt(II) complexes in two human breast adenocarcinoma cell lines (MDA-MB231 and MCF-7) is also reported, together with a study of their effect on the electrophoretic mobility of pBluescript SK$^+$ DNA and their behavior in solution.

2. Experimental

2.1. Materials and methods

Cis-$[PtCl_2(DMSO)_2]$, the 3-hydroxyimino-5-methoxy-2-phenyl-3*H*-indole, ligands **3a**, **3b** and complexes **4a**, **4b**, **5a** and **5b**, were prepared as reported previously [17–19]; 2-phenylindole and cetyltrimethylammonium bromide (CTAB) were obtained from commercial sources and used as received. Solvents were dried and distilled using the standard procedures [20]; except methanol which was of HPLC grade [21]. Elemental analyses were carried out at the *Serveis Científico-Tècnics* (Universitat de Barcelona). Mass spectra (ESI^+) were performed at the *Servei d'Espectrometria de Masses* (Universitat de Barcelona), using a VG-Quatro instrument. Infrared spectra were obtained with a Nicolet 400FTIR, Nicolet 520 or 5700 instrument using KBr pellets; while far IR-spectra of **4c** and **5c** (in the range 200–400 cm^{-1}) were registered with a Bomen-DA3 instrument using polyethylene discs. The ultraviolet–visible (UV–vis) spectra of **3c**–**5c** in CH_2Cl_2 were recorded at 298 K with a Varian Cary 100 spectrophotometer. Routine ^1H and $^{13}C\{^1H\}$ NMR spectra were registered with a Mercury-400 MHz instrument. High resolution ^1H NMR spectra and the two dimensional [$\{^1H—^1H\}$-NOESY, COSY and $\{^1H—^{13}C\}$ HSQC and HMBC] experiments were registered with a Varian Inova 500 and Bruker DMX-500 MHz instruments at 298 K. The $^{195}Pt\{^1H\}$ NMR spectra of **4c** and **5c** were obtained with a Bruker DRX-250 MHz instrument. The chemical shifts (δ) are given in ppm, the coupling constants (J) in Hz and the labeling of the atoms corresponds to the pattern shown in Scheme 1. The splitting of proton resonances in the reported ^1H NMR spectra is defined as s = singlet, d = doublet, dd = doublet of doublet, m = multiplet. Except where quoted, the solvent used for the NMR experiments was $CDCl_3$ (99.9%) and the references were $SiMe_4$ [for ^1H and $^{13}C\}$ and $H_2[PtCl_6]$ for $^{195}Pt\{^1H\}$ NMR.

2.2. Preparation of the compounds

2.2.1. Synthesis of C_8H_3N-2-C_6H_5-3-NOMe-5-OMe (**3c**)

To a solution containing 3-hydroxyimino-5-methoxy-2-phenyl-3H-indole (666 mg, 3.0×10^{-3} mol), CTAB (690 mg, 1.9×10^{-3} mol) and NaOH (12 mL of a 40% solution) in CH_2Cl_2 (125 mL), methyl iodide (2.28 g, 1 mL, 16×10^{-3} mol) was added. The reaction mixture was stirred at room temperature for 24 h. After this period water (75 mL) was added and the resulting solution was transferred to a separating funnel. The organic layer was separated

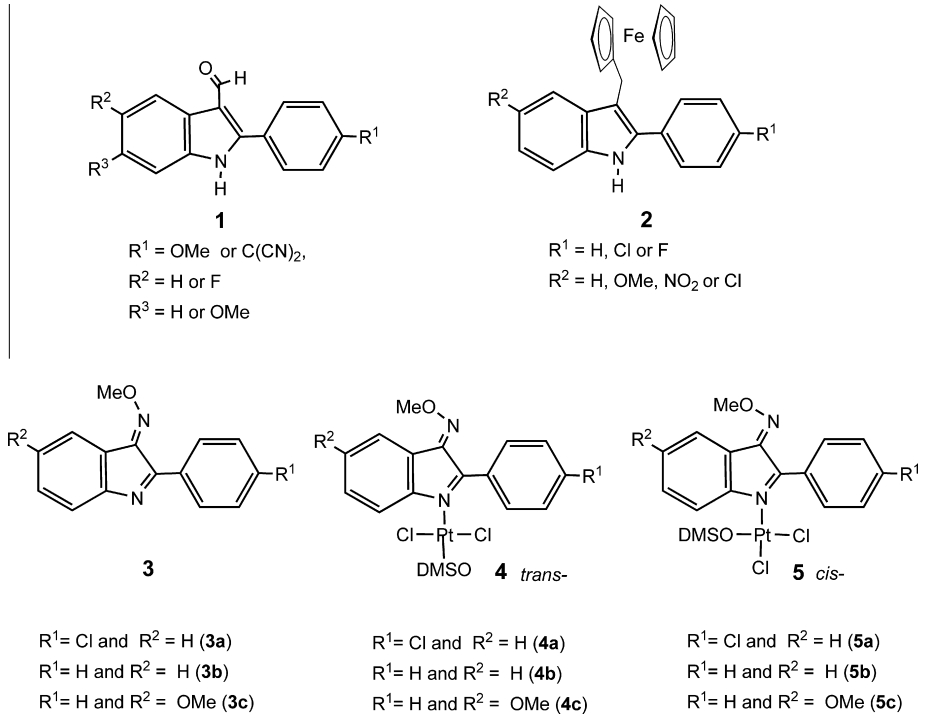

Fig. 1. General formulae of different types of 2-phenylindole derivatives with antitumoral activity (**1** and **2**) [12–15], the functionalized compounds **3a** and **3b** and their platinum(II) complexes (**4a**, **4b**, **5a**, **5b**) reported recently [18].