European Journal of Medicinal Chemistry 76 (2014) 360–368

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Evaluation of novel *trans*-sulfonamide platinum complexes against tumor cell lines

Carlos Pérez [a,b], C. Vanesa Díaz-García [a,b], Alba Agudo-López [a,b], Virginia del Solar [c], Silvia Cabrera [c], M. Teresa Agulló-Ortuño [a,b], Carmen Navarro-Ranninger [c], José Alemán [d,*], José A. López-Martín [a,b,**]

[a] Medical Oncology Service, Hospital Universitario 12 de Octubre, Avda de Córdoba S/N, 28041 Madrid, Spain
[b] Instituto de Investigación Hospital 12 de Octubre, Avda de Córdoba S/N, 28041 Madrid, Spain
[c] Inorganic Chemistry Department (Módulo 7), Universidad Autónoma de Madrid, C/Fco Tomás y Valiente, 5, Cantoblanco, 28049 Madrid, Spain
[d] Organic Chemistry Department (Módulo 1), Universidad Autónoma de Madrid, C/Fco Tomás y Valiente, 5, Cantoblanco, 28049 Madrid, Spain

ARTICLE INFO

Article history:
Received 5 December 2013
Received in revised form
30 January 2014
Accepted 8 February 2014
Available online 11 February 2014

Keywords:
trans-platinum complexes
Sulfonamides
Cytotoxicity profiles
Cell cycle analyses

ABSTRACT

Platinum-based drugs, mainly cisplatin, are employed for the treatment of solid malignancies. However, cisplatin treatment often results in the development of chemoresistance, leading to therapeutic failure. Here, the antitumor activity of different *trans*-sulfonamide platinum complexes in a panel of human cell lines is presented. The cytotoxicity profiles and cell cycle analyses of these platinum sulfonamide complexes were different from those of cisplatin. These studies showed that complex **2b** with cyclohexyldiamine and dansyl moieties had the best antitumoral activities.

1. Introduction

Cisplatin (CDDP) is the most known platinum antitumor complex and, as well, one of the most effective antitumor agents used against a variety of cancers [1,2]. Despite the therapeutic success of platinum anticancer drugs, their severe toxicities and the drug resistance limit their clinical use [3,4]. In view of these limitations, research has been extended to new platinum analogues with the aim of overcoming these adverse effects. On the other hand, *N*-sulfonamides have been used extensively in medicinal chemistry as antibacterial activity, anticonvulsant (sultiame), inhibitors of the carbonic anhydrase, inhibitors of histone deacetylases, and inhibitors of microtubule polymerization among others [5–11]. Besides these large number of publications concerning to the use of sulfonamides, the synthesis of platinum compounds containing in their structure sulfonamides have been scarce. Based on our experience in *trans*-platinum complexes [12,13], and the use of sulfur donor ligands (as DMSO) in platinum complexes [14], we have recently published the synthesis of a series of *trans*-sulfonamide platinum complexes [13]. Thus, we conducted preliminary *in vitro* cytotoxicity tests and have identified quite active complexes with the *trans*-1,2-cyclohexyldiamine moiety. However, only a limited number of cancer cell lines were tested and therefore further biological data are needed.

In the present work, new biological effects of *trans*-sulfonamide platinum complexes on cellular proliferation and DNA damage response will be presented. The *in vitro* activity of the compounds is evaluated and also compared to that of cisplatin.

2. Results and discussion

2.1. Synthesis and characterization

We initially studied five different compounds (Fig. 1), two of them with dansyl moiety and the other three with the tolyl and mesityl groups (**2a**–**e**). First, we synthesized the sulfonamide ligands from commercially available sulfonyl chlorides and the corresponding amines (**1a**–**e**). Then, complexes **2a**–**e** were formed with good yield, starting from *cis*-[$PtCl_2(DMSO)_2$] (**2f**) and

* Corresponding author.
** Corresponding author. Organic Chemistry Department (Módulo 1), Universidad Autónoma de Madrid, C/Fco Tomás y Valiente, 5, Cantoblanco, 28049 Madrid, Spain.
E-mail addresses: jose.aleman@uam.es (J. Alemán), jlmartin@salud.madrid.org (J.A. López-Martín).

http://dx.doi.org/10.1016/j.ejmech.2014.02.022
0223-5234/

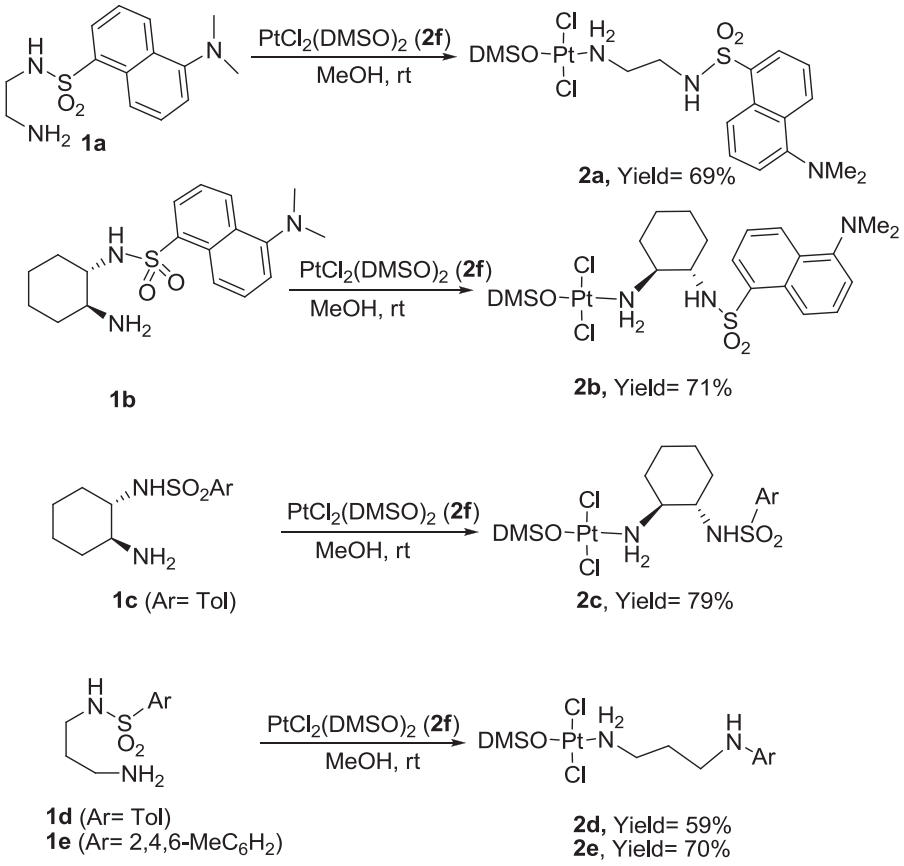

Fig. 1. Complexes studied in the present publication. Racemic mixture of *trans*-cyclohexyl-1,2-diamine was used (only one isomer is shown).

monosulfonamide ligands **1**. Complexes **2a**–**e** were determined with *trans* geometry by X-ray analysis of complex **2e** (see Fig. 2) and by comparison of NMR data and mass spectrometry of the rest of complexes. All the complexes (**2a**–**e**) showed a clear peak in mass spectrometry and matched elemental analyses which are in accordance with the proposal structures (see Section 4 and S.I.).

2.2. Solubility and stability studies

Next, we focused our attention in the solubility and stability of these complexes. Two important drawbacks in platinum complexes are related to their administration as drugs, their low solubility and the limited stability of these complexes in aqueous solution [15–18]. Thus, we studied the stability of complex **2b** because it was one of the most active complexes (see above) in saline solution (0.9% NaCl solution) at 37 °C (corporal human temperature), which is one of the pharmaceutical dosage forms for platinum complexes. In a 100 μM saline solution, slightly more than 50% of complex **2b** remained unaltered after 24 h of incubation (Fig. 3). Additionally, the solubility of complex **2b** was determined to be 0.826 $mg \cdot mL^{-1}$ in a saturated saline solution after 3 h of incubation which is comparable with the solubility of cisplatin in the same solution (1.0 $mg * mL^{-1}$).

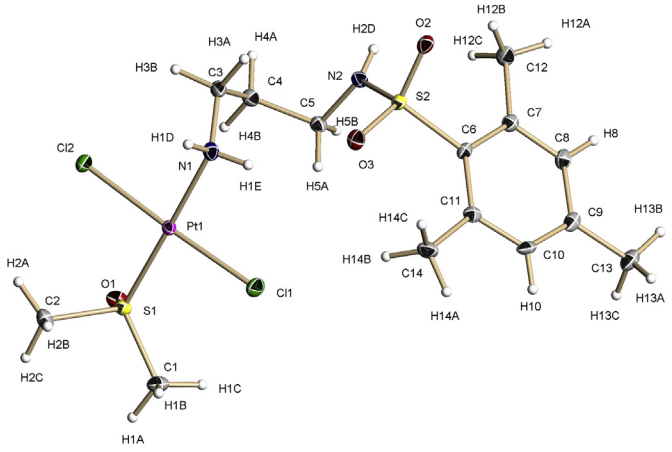

Fig. 2. X-ray analysis ORTEP of compound **2e**. Ellipsoids displayed at 30% probability.

2.3. In vitro cytotoxic activity

We initially studied all these complexes (**2a**–**e**) in two representative tumor cell lines, HeLa (cervix adenocarcinoma) and T-47D (ductal breast epithelial tumor cell line), in order to find which the optimal structural features are (Fig. 4). From this data, it can be concluded that compounds **2a**, **2d** and **2e** with linear alkyl chains in their structures, are less active than compounds **2b**–**c** with the *trans*-cyclohexyl-1,2-diamine moiety.

With these preliminary data, we decided to focus on the more active complexes **2b**–**c** with the *trans*-cyclohexyl-1,2-diamine moiety and its comparison with one linear alkyl complex derivative (**2a**), and to perform a large screening in 12 different human tumor cell lines of different tissue origins (see Table 1 and Fig. 5). The most sensitive cell lines are SK-MEL-5 (melanoma), DLD-1 (colorectal adenocarcinoma), MCF-7 (luminal breast adenocarcinoma), Tera-2 (testicular embryonal carcinoma) and, HeLa (cervix adenocarcinoma). We carried out parallel experiments with