Journal of Organometallic Chemistry 814 (2016) 16–24

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Non-symmetric CNS-Pt(II) pincer complexes including thioether functionalized iminophosphoranes. Evaluation of their *in vitro* anticancer activity

Sandra Ramírez-Rave [a], María Teresa Ramírez-Apan [b], Hugo Tlahuext [c], David Morales-Morales [b, **], Rubén A. Toscano [b], Jean-Michel Grévy [c, *]

[a] Departamento de Química, Área de Catálisis, Grupo ECOCATAL, Universidad Autónoma Metropolitana-Iztapalapa, Avenida San Rafael Atlixco # 189, 09340, Ciudad de México, Mexico
[b] Instituto de Quimica, Universidad Nacional Autonoma de Mexico, Cd. Universitaria, Circuito Exterior, Coyoacan, 04510, Ciudad de México, Mexico
[c] Centro de Investigaciones Quimicas, Instituto de Investigación en Ciencias Básicas y Aplicadas, Universidad Autonoma del Estado de Morelos, Avenida Universidad # 1001, Chamilpa, CP 62209 Cuernavaca, Morelos, Mexico

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
17 April 2016
Accepted 18 April 2016
Available online 24 April 2016

Keywords:
Platinum compounds
Iminophosphorane
Anticancer compounds
Crystal structures
Non-symmetric pincer compounds

ABSTRACT

Iminophosphoranes of general formula $Ph_3P = NC_6H_4SR$ [R = 4-$C_6H_4NO_2$ (**3**) and $CH_2C_6H_5$ (**4**)], combining the iminophosphorane group with a thioether moiety were synthesized and fully characterized, including the unequivocal determination of the solid state structure of ligand (**3**) by single crystal X-ray diffraction techniques. These ligands and other related [R = CH_3 (**1**), C_6H_5 (**2**)] were further reacted with $[Pt(S(CH_3)_2)_2Cl_2]$ to produce, in all cases, the non-symmetric CNS-Pt(II) pincer complexes [PtCl{$C_6H_4(Ph_2P = NC_6H_4SR-\kappa^3-C,N,S)$}] [R = CH_3 (**5**), C_6H_5 (**6**), 4-$C_6H_4NO_2$ (**7**), $CH_2C_6H_5$ (**8**)]. All compounds were fully characterized using common analytical techniques and the solid state structures of (**5**), (**6**) and (**7**) were unequivocally determined by single crystal X-ray diffraction experiments. The *in vitro* antiproliferative activity of these new species was explored against a series of tumoral cell lines [U251 (human glioblastoma), PC-3 (human prostate cancer cell line), K562 (human leukemia), HCT-15 (human colorectal adenocarcinoma), MCF-7 (human breast adenocarcinoma), SKLU (human lung adenocarcinoma) and HeLa (epitheloid cervix carcinoma)] showing compounds **5** (R = CH_3) and **8** (R = $CH_2C_6H_5$) to have better cytotoxic activity than cisplatin against HeLa and K562 tumoral cell lines.

1. Introduction

While the use of inorganic compounds in medicine started more than 5000 years ago [1], it has been only recently that modern developments of these compounds have focused on the generation of new anticancer agents [2]. Cancer is caused by a genetic damage of cells producing their abnormal grow and lack of response to normal control of a specific tissue. Thus, the affected cells rapidly multiply and spread, forming tumors of various grades. Nowadays, a variety of treatments can be used [3] and during the past 40 years, platinum based drugs, particularly cisplatin and carboplatin have dominated the treatment of various types of cancers.

The successful development of cisplatin as antitumor drug is often seen as a historic event, as the number of patients who have been treated and cured with cisplatin is impressive. In addition, the fact that the exact mechanism of action of this compound continues unsolved, has generated a tremendous interest in understanding the behavior of the metal in the presence of DNA and consequently, the cisplatin chemistry has provided a fertile ground for the development of bioinorganic chemistry research. The key that explains the success of Pt in these processes is related to the kinetics of ligand exchange, as it is best when occurs slowly in order to modulate the arrival to the cellular DNA. For this reason, mentioning the *trans* effect is mandatory, because it is responsible for the kinetics of ligand exchange, and this effect is particularly pronounced in Pt(II) complexes. However, despite the success of cisplatin, it has been found that its lack of selectivity in cancerous tumors causes many side effects that are only partially reversible if therapy is interrupted. Thus, the scientific community has placed a

* Corresponding author.
** Corresponding author.
E-mail addresses: damor@unam.mx (D. Morales-Morales), jeanmichelg@gmail.com (J.-M. Grévy).

http://dx.doi.org/10.1016/j.jorganchem.2016.04.022
0022-328X/

lot of effort in the design of new platinum complexes with efficient anticancer activity and reduced side effects [4]. These efforts have produced several Pt complexes (second and third generation) (Scheme 1). However, with no significant advantages over cisplatin. Second generation drugs like Carboplatin and Oxaliplatin have shown fewer side effects due to their robustness, but this also make them less active than Cisplatin [5].

Notably, iminophosphorane group 10 transition metal complexes have been relevant in the design of new, potentially active and selective anticancer compounds. Thus, Contel et al. have recently synthesized a series of water-soluble Au(III), Pd(II) and Pt(II) compounds with iminophosphorane *N*,*N*'-chelating ligands, that were tested *in vitro* as potential anticancer agents towards DU-145 (human prostate cancer) and Jurkat-T (acute lymphoblastic leukemia) tumor cell lines. The study showed that these compounds indeed exhibit anticancer activity and, that the Au(III) and Pt(II) complexes were the more efficient against the above mentioned cancerous cell lines (Scheme 2), displaying lower IC_{50} values than cisplatin [6].

Additionally, in 2012 the same group examined the *in vitro* effect of cationic organogold(III) complexes containing *C*,*N*-chelating iminophosphorane ligands, against HeLa (human cervical carcinoma) and Jurkat-T (lymphoblastic leukemia) tumor cell lines (Scheme 2). The results indicated these Au(III) species to be more cytotoxic when coordinated to dithiocarbamato ligands, affording lower IC_{50} values than cisplatin. This cytotoxicity not being related to an interaction with DNA [7] as is the case for cisplatin.

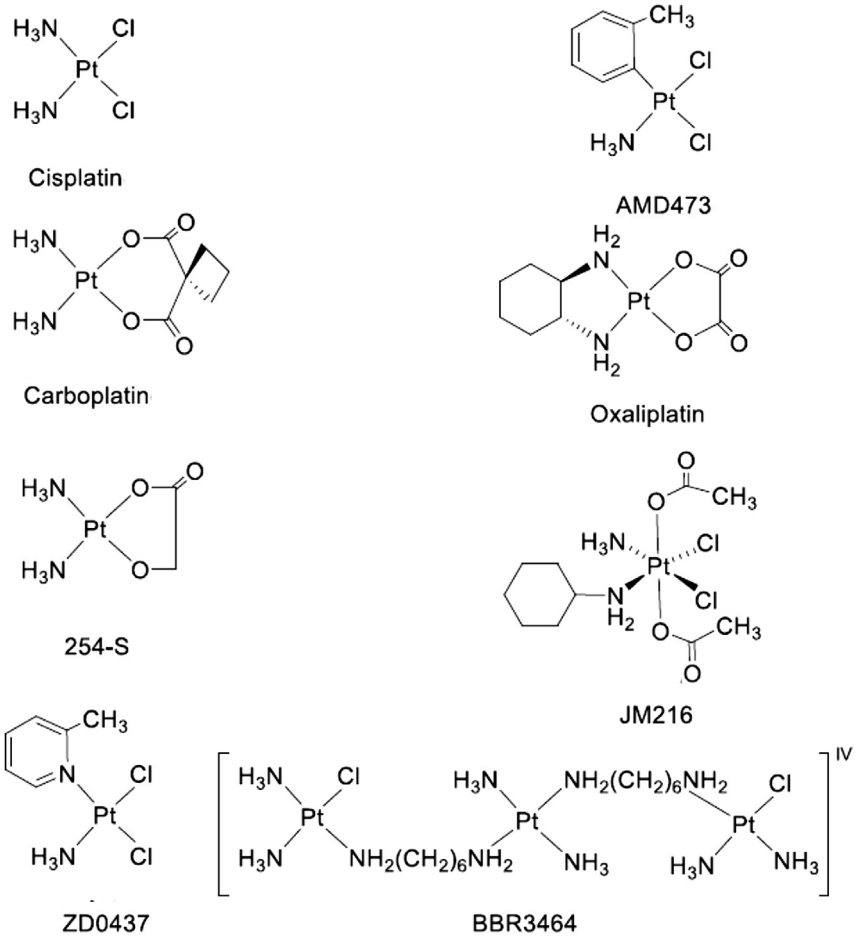
Other studies by the same research group reported the synthesis of a series of new cationic Pd(II) iminophosphorane complexes, were their hydrophilic/lipophilic ratios were varied and their cytotoxic activity towards different tumor cell lines *in vitro* studied. The results obtained, revealed these compounds not to be as efficient as their Au(III) and Pt(II) counterparts against cancerous cells and their cytotoxicity and selectivity was related to their degree of lipophilicity [8]. The same authors demonstrated that a series of water-soluble cationic iminophosphorane Ru(II) complexes, were in fact more cytotoxic *in vitro* to a number of human cancer cell lines than cisplatin [9]. Moreover, experiments *in vivo*, using the *exo* *N*,*O*-chelated complex [(η^6-*p*-cymene)Ru{(Ph_3P = N–CO–2–N–C_5H_4)–κ^2-N,O}Cl]Cl showed an impressive tumor reduction (56% after 28 days) on xenografted breast carcinoma MDA-MB-231 tumors with low systemic toxicity.

Thus, based on the above we rationalize that a combination of d^8 metals and iminophosphorane ligands, may produce good organometallic candidates for potentially efficient and selective, anticancer applications. Hence, in the present study we wish to report the synthesis and characterization of a series of new tertdentate non-symmetric iminophosphorane CNS-Pt(II) pincer complexes, and the results of their cytotoxic evaluation against different tumoral cell lines *in vitro*.

2. Experimental

2.1. Materials and methods

All reactions were carried out under nitrogen atmosphere using



Scheme 1. Pt complexes used in cancer treatment.