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Triphenylphosphane Pt(II) complexes containing biologically active natural polyphenols: Synthesis, crystal structure, molecular modeling and cytotoxic studies

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ABSTRACT

Platinum complexes bearing phosphane ligands in *cis* configuration with deprotonated flavonoids (3-hydroxyflavone, quercetin) and deprotonated ethyl gallate were synthesized starting from *cis*-[$PtCl_2(PPh_3)_2$]. In all cases, *O,O′* chelate structures were obtained. While quercetin and ethyl gallate complexes are quite stable in solution, the 3-hydroxyflavonate complex undergoes a slow aerobic photodegradation in solution with formation of salicylic and benzoic acids. The X-ray diffraction structures of quercetin and ethyl gallate complexes are reported. Cell cycle studies (in the dark) of the complexes in two human cell lines revealed that the cytotoxic activity of the complex bearing 3-hydroxyflavonate is higher than those exhibited by 3-hydroxyflavone or by *cis*-[$PtCl_2(PPh_3)_2$] alone. Density functional theory studies on the hydrolysis pathway for the 3-hydroxyflavone and ethyl gallate complexes explained the different cytotoxic activity observed for the two compounds on the basis of the different intermediates formed during hydrolysis (relatively inert hydroxy Pt complexes for ethyl gallate and monoaqua complexes for 3-hydroxyflavone).

1. Introduction

The discovery of antiproliferative activity of cisplatin by Rosenberg et al. [1] in 1965 contributed to the development of cancer chemotherapy. Today cisplatin is a widely used drug in chemotherapy, but its applicability has many disadvantages, as it causes many severe side effects including: nephrotoxicity, neurotoxicity, myelotoxicity, hematological toxicity and gastrointestinal reactions [2–4]. In addition, some tumors have acquired resistance to cisplatin, while others develop resistance after the initial treatment. In view of these limitations, research has been extended to other platinum complexes. A large number of platinum analogs have been tested during the last 30 years [5]. Unfortunately, the vast majority of these compounds were rejected in preclinical or early clinical stages of testing (only carboplatin and oxaliplatin, Scheme 1, are in world-wide clinical use) and the discovery of a new platinum drug more selective and less toxic than cisplatin is still highly desirable.

Recently, the antitumor activity of dietary flavonoids (flavus = yellow), which are primarily benzo-γ-pyrone (phenylchromone) derivatives (Scheme 2), comprising a massive group of polyphenolic compounds [6–7] universally distributed in the plant kingdom, has been reviewed [8]. The pharmacological effects of flavonoids include induction of apoptosis, suppression of protein tyrosine kinase activity, antiproliferation, antimetastatic and antiinvasive effects, and antiangiogenesis [8].

Because of structural differences, flavonoids are divided into eight different groups, flavonols being one of them. 3-Hydroxyflavone (Scheme 3a) is the backbone of all flavonols [9], while quercetin (Scheme 3b) is another very important flavonol with well-known anticancer activity [10]. Due to their polyphenolic structure, flavonols are effective metal ion chelators, playing a key role in the initiation of free radical and antioxidant processes [11]. Moreover flavonols can intercalate into deoxyribonucleic acid (DNA) as well as covalently bind to DNA and proteins [12–13]. As a result of these characteristics, flavonols have complex biological interactions and in some therapies they are combined with cisplatin increasing efficacy over individual treatments [14] and reducing side effects associated with cisplatin [15]. However, combinations of flavonols with platinum are poorly understood, although multiple theories currently exist trying to explain the interactions between cisplatin and flavonols [16].

Like flavonols, also plant phenols, such as ethyl gallate (Scheme 3c), have antitumor activity [17–20] and can effectively bind metal ions.

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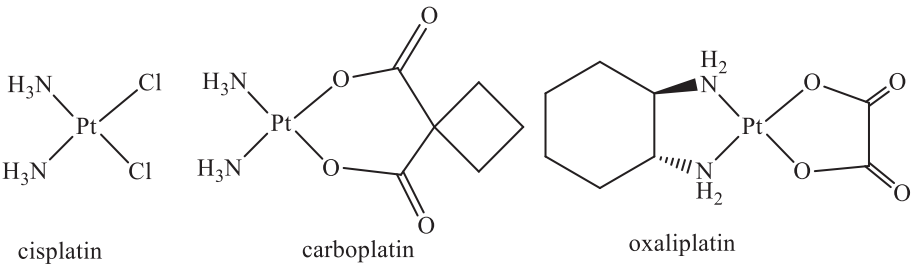
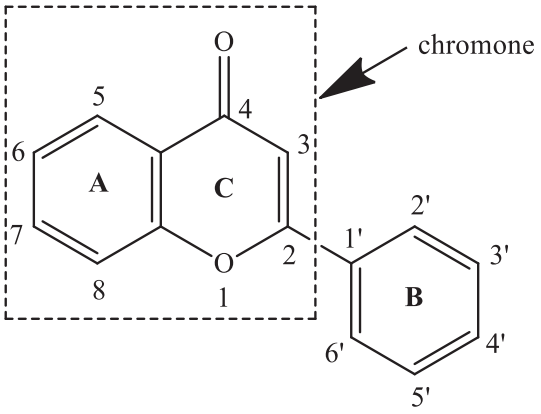


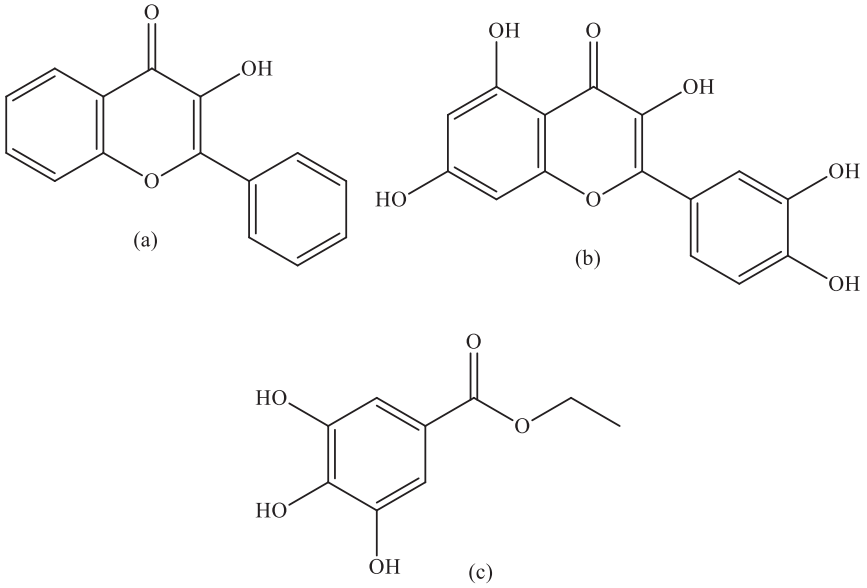
Scheme 1. Platinum based anticancer drugs used in clinical therapies.



Scheme 2. Flavone backbone.

All these considerations prompted us to check whether platinum complexes of natural polyphenols would exhibit synergic cytotoxic activity. Although since the early 1980s scientists have investigated more than 40 metal–flavonoid complexes [21–22], to the best of our knowledge Pt(II) complexes with 3-hydroxyflavone and ethyl gallate as ligands have never been synthesized. On the contrary, the synthesis of a platinum(II) complex with quercetin has already been reported [23]. Its formula is *cis*-[$Pt(NH_3)_2$(que)] (que = dianion of quercetin) and a complexation of platinum(II) to the ligand through oxygen atoms at $C^{3'}$ and $C^{4'}$ was hypothesized, although neither XRD (X-ray diffraction) nor citotoxicity studies were carried out.

Phosphane ligands with hydrophobic character have been shown to increase in some cases the cytotoxicity of their platinum complexes, possibly by enhancing the cellular membrane transfer process [24]. In previous works [25–26], interesting results were obtained by synthetizing platinum compounds bearing two mutually *cis* triphenylphosphanes with bioactive ligands. In these studies, it has been reported that Pt(II) complexes containing PPh_3 and the N7-coordinated anionic ligand 8-MTT (8-(methylthio)theophyllinate) have a remarkable cytotoxic activity on some cancer cell lines. This antiproliferative activity on both cisplatin-sensitive T2 and cisplatin-resistant SKOV3 cell lines decreased when PPh_3 was substituted by the more hydrophilic 1,3,5-triaza-7-phosphaadamantane (PTA) ligand. Although the total replacement of the usually employed amine carrier ligands (Scheme 1) for air and water stable triarylphosphanes may exhibit some disadvantages (the major of them being that a tertiary phosphane cannot establish any hydrogen bond with the DNA backbone), however it has been found that triarylphosphane ligands may stabilize DNA-Pt adducts through π-π interactions occurring between the phosphane phenyl groups and the nucleobases [27]. For this reason, recently a series of platinum compounds where the two ammonia ligands of cisplatin and cisplatin analogs were replaced by phosphanes have been prepared and biologically characterized [28–29]. In some cases promising interactions between DNA (or cell proteins) and platinum complexes bearing two phosphane groups in mutually *cis* position have been found and studied [30–34], in spite of the poor antiproliferative activity of *cis*-[$PtCl_2(PPh_3)_2$] [35]. Moreover, PR_3 ligand has a kinetic *trans* effect stronger than NH_3, which can facilitate the leaving group displacement by H_2O in the human cell. The ligand release by hydrolysis is a key-step for the DNA-adduct formation and attracted numerous



Scheme 3. (a) 3-Hydroxyflavone; (b) quercetin; (c) ethyl gallate.

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