European Journal of Medicinal Chemistry 46 (2011) 5616–5624

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Novel platinum(II) and palladium(II) complexes of thiosemicarbazones derived from 5-substitutedthiophene-2-carboxaldehydes and their antiviral and cytotoxic activities

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ARTICLE INFO

Article history:
Received 26 May 2011
Received in revised form
16 September 2011
Accepted 20 September 2011
Available online 1 October 2011

Keywords:
Thiosemicarbazones
Platinum(II) complexes
Palladium(II) complexes
Cytotoxic activity
Antiviral activity

ABSTRACT

A series of thiosemicarbazones and their platinum(II) and palladium(II) complexes have been synthesized. The chemical structures of ligands and their complexes were characterized by UV–Vis, IR, ^{1}H NMR, ^{13}C NMR, MS spectra, elemental analysis and TGA. The antiviral and cytotoxic activities of all compounds have been tested. Results of broad antiviral evaluation showed that none of the compounds evaluated endowed with anti-DNA or -RNA virus activity at subtoxic concentrations except for the palladium complex **1b.** This compound exhibited slightly selective inhibition against cytomegalovirus. The platinum complex **4a** exhibited the best cytostatic activities against human cervix carcinoma. Ligands **2, 4** and **5** showed cytostatic potential. The palladium complexes were in general less cytostatic than the corresponding platinum complexes or unliganded congeners.

1. Introduction

Since the discovery of the importance of metal containing compounds used in cancer treatment, reports on the use of metals are increasing [1–5]. In recent years new metal complexes have been identified as a very promising class of anticancer active compounds [6–8]. Metals bound to atoms such as N, O and S can form a chelate ring that binds the metal more tightly when compared to the non-chelate form. Large biological molecules (proteins, enzymes, DNA etc.) are electron-rich but metal ions are electron-deficient. Therefore, interactions occur between metal ions and many important biological molecules. This event has led to the use of metals or metal-containing agents to modulate biological systems [9]. Organometallic compounds have gained importance as enzyme inhibitors due to the capability of binding large biological molecules more strongly than metal-free organic compounds [10].

Metal complexes can inhibit metalloenzymes by chelate substitution and also inhibit non-metalloenzymes by coordinating to their active site. The other property of metals is to catalyze the formation of reactive oxygen species [11]. The anticancer potential of metal containing agents, from main group elements to early transition metals, have been evaluated [12–14]. Especially organoplatinum compounds such as cisplatin, carboplatin and oxaliplatin are metal-based drugs that are among the most active and widely used clinical drugs in cancer chemotherapy [15–17]. These platinum complexes react *in vivo*, binding to and causing crosslinking of DNA which finally activates programmed cell death [18]. However, the clinical utility of these drugs is limited to a relatively narrow range of tumors (sarcomas, small cell lung cancer, ovarian cancer, lymphomas and germ cell tumors) because of primary resistance and the development of resistance secondary to the initial treatment [19,20]. Therefore, unconventional platinum complexes, that could be used in cisplatin-resistant tumors are made by different research groups [21–24].

Lipophilicity that controls the rate of entry into the cell is altered by metal-coordination and some side-effects can be reduced by complexation. Moreover, metal complexes can exhibit biological activities more than free ligand [6]. Recently, thiosemicarbazones and their metal complexes have achieved importance due to their application in pharmaceutical chemistry and proved to be chemotherapeutic agents potentially useful for inhibiting the activities of cancer cells [25,26]. For example, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine®; Vion Pharmaceuticals Inc. New Haven, CT) inhibit the biosynthesis of DNA in leukemia L1210 cells by blocking

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doi:10.1016/j.ejmech.2011.09.031

activity of ribonucleotide reductase [27]. Many heterocyclic thiosemicarbazone derivatives and their platinum and palladium complexes have a wide range of pharmacological activities, such as antituberculosis [28], antibacterial [29], antitumor [30], antiprotozoal [31], antimalarial [32], antimicrobial [33], antiviral [34], antifungal [35], anticonvulsant [36] and anti-trypanosomal [37] activities.

In our present work, the synthesis and characterization of thiosemicarbazones derived from 5-substitutedthiophene-2-carboxaldehydes and their platinum(II) and palladium(II) complexes are reported. The results of *in vitro* antiviral and cytostatic/toxic activities of ligands and their platinum and palladium complexes have been evaluated.

2. Chemistry

The precursors phenyl isothiocyanate and 4-nitrophenyl isothiocyanate were synthesized from aniline and 4-nitroaniline according to the method described in the literature [38]. *N*-phenylhydrazinecarbothioamide and *N*-(4-nitrophenyl)hydrazinecarbothioamide were prepared by stirring isothiocyanates with hydrazine monohydrate in diethyl ether at room temperature according to Ref. [39]. The ligands **1**–**5** used in this work were obtained by refluxing in methanol (20–30 mL) an equimolar amount of 5-substituted-2-thiophene carboxaldehydes with thiosemicarbazides according to Refs. [35,40–42]. The chemical structures of the ligands are given in Scheme 1. All thiosemicarbazone derivatives synthesized were characterized by UV–Vis, IR, ^{1}H NMR, ^{13}C NMR, MS spectral data and elemental analysis.

The platinum(II) and palladium(II) complexes of thiosemicarbazone derivatives **1a**–**5a** and **1b**–**5b** were prepared by exposing a solution of the K_2PtCl_4 or K_2PdCl_4 in water to a solution of the appropriate ligand in ethanol in a 1:1 M:L molar ratio [43]. The structures of Pt(II) and Pd(II) complexes were confirmed by elemental analysis, UV–Vis, IR, ^{1}H NMR, MS spectroscopies, elemental analyses and TGA thermogram and are given in Fig. 1. The elemental analysis data of the ligands and their Pt(II) and Pd(II) complexes are presented in Table 1.

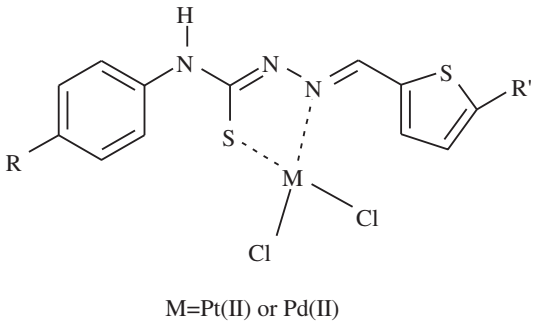


Fig. 1. The structures of Pt(II) and Pd(II) complexes (**1a**–**5a** and **1b**–**5b**).

3. Results and discussion

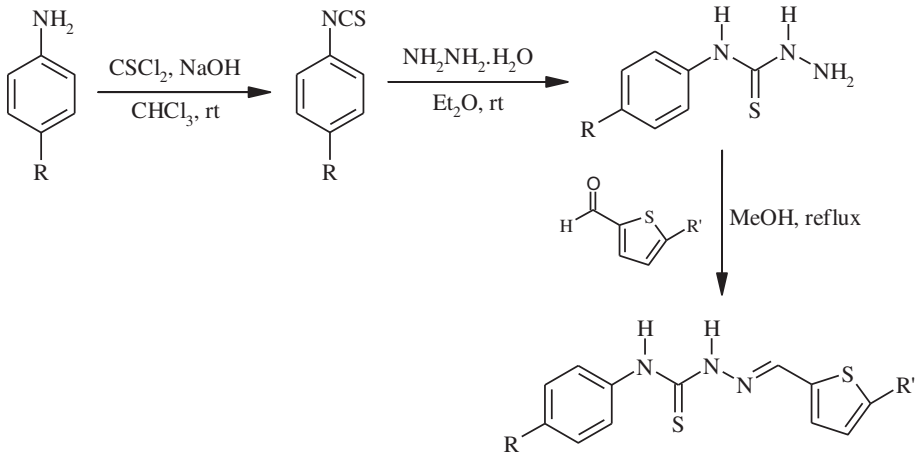
3.1. Synthesis

All of the newly synthesized metal complexes **1a-5a** and **1b-5b** are solids and decomposed above ca. 200 °C. They are insoluble in organic solvents such as acetone, chloroform and methanol but soluble in DMF and DMSO. The elemental analyses data of the thiosemicarbazones and their platinum and palladium complexes (Table 1) were compatible with the structures of the ligands shown in Scheme 1. and the formulas of the complexes are shown in Fig. 1.

3.2. Spectral studies

3.2.1. Electronic spectral studies

The study of the electronic spectra in the ultraviolet and visible (UV–Vis) ranges for the ligand and metal complexes was carried out in DMF. Solid-state electronic spectra of all thiosemicarbazone derivatives reveal similar patterns, exhibiting two bands in the 433–344 nm and 28–258 nm regions. An intense band at ca. 433–344 nm is attributed to the $n \rightarrow \pi^*$ transitions of C=S group, C=N group and thiophene ring, which are overlapped. The $\pi \rightarrow \pi^*$



Scheme 1. General synthesis of thiosemicarbazones (**1**–**5**).