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Vanadium(V) complexes with salicylaldehyde semicarbazone derivatives bearing in vitro anti-tumor activity toward kidney tumor cells (TK-10): crystal structure of $[V^{V}O_2$(5-bromosalicylaldehyde semicarbazone)]

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Abstract

As a contribution to the development of novel vanadium complexes with pharmacologically interesting moieties, new dioxovanadium(V) semicarbazone complexes with the formula *cis*-VO_2L, where L = 5-bromosalicylaldehyde semicarbazone and 2-hydroxynaphtalen-1-carboxaldehyde semicarbazone have been synthesized. and characterized by ^{1}H and ^{13}C NMR, Raman and FTIR spectroscopies. Results were compared with those previously reported for other three analogous complexes of this series. The five complexes were tested in three different human tumor cell lines for bioactivity as potential anti-tumor agents, showing selective cytotoxicity on TK-10 cell line. Results showed that structural modifications on the semicarbazone moiety could have a significant effect on the anti-tumor activity of the vanadium complexes. In addition, the electrochemical behavior of all the complexes was studied. No apparent correlation could be demonstrated between reduction potentials of the complexes and their anti-tumor activities. The molecular structure of the novel $[V^{V}O_2$(5-bromosalicylaldehyde semicarbazone)] complex was solved by X-ray diffraction methods. The vanadium atom shows a distorted square pyramidal coordination sphere. The $(VO_2)^{+}$ cation is coordinated to a nearly planar $(L)^{-}$ anion acting as a tridentate ligand through both oxygen and one nitrogen atoms.

Keywords: Vanadium; Semicarbazones as ligands; Tridentate ligands; N,O,O ligands; Anti-tumor activity

1. Introduction

The pharmacological activity of different vanadium compounds is well known [1–4]. Medicinal applications

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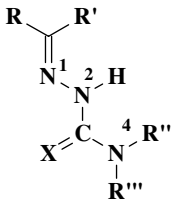
of vanadium compounds have focused on their in vitro and in vivo activity in the treatment of diabetes. Therefore, in recent years the insulin-mimetic effects of vanadium compounds have been especially investigated [1,5–7, and references therein]. Different approaches have been attempted for the development of more potent and orally active vanadium-containing insulin enhancing agents [8–10]. Besides insulin enhancing effects, other pharmacological activities of vanadium compounds include tumor growth inhibition and prophylaxis against carcinogenesis. So, concomitantly with the current growing interest in transition metal complexes as potential antineoplastic agents [11–14], the study on the interaction of simple vanadium species with drugs bearing anti-tumor activity, like bleomycin, and on the antitumor properties of vanadium compounds constitute a field of increasing research [1,2,15,16, and references therein]. In particular, various groups of vanadium compounds have shown anti-carcinogenic activity towards experimentally induced tumors, including organometallic vanadium(IV) compounds, inorganic vanadium salts and peroxovanadates. The main example may be vanadocenedichloride, that demonstrated an activity against certain animal tumors comparable to that of cisplatin [2,17].

Based on the previous considerations, we are currently interested in the investigation of the interaction of simple vanadium species with ligand groups bearing pharmacological activity, particularly those with antitumor and insulin mimetic properties.

Semicarbazones and thiosemicarbazones (Fig. 1) have demonstrated a wide range of biological activities [18–21]. Although some vanadium thiosemicarbazone complexes have been synthesized and characterized, only very few examples with the analogous semicarbazone ligands have been described [18,19].

As part of a program concerning the chelating behavior of semicarbazones bearing pharmacological interest [18,22–26], a more detailed physicochemical characterization of their vanadium complexes is being performed. In a recent paper we reported the synthesis, characterization and in vitro biological evaluation as potential insulin mimetic agents of a series of novel VO_2^+ semicarbazone complexes with the general formula *cis*-V^VO_2L [18]. Selected ligands L (Fig. 2) were salicylaldehyde semicarbazone derivatives bearing moieties with different lipophilicity: salicylaldehyde semicarbazone (L^1), salicylaldehyde N^4-*n*-butylsemicarbazone (L^2) and salicylaldehyde N^4-(2-naphtyl)semicarbazone (L^3). Lipophilicity has been well recognized as the responsible of adequate bio-response of drugs, further it has been related with their absorption, distribution, metabolism, elimination and toxicity [27]. In this paper other two new V(V) semicarbazone complexes with the formula V^VO_2L are synthesized and characterized, being L chemically related ligands: 5-bromosalicylaldehyde semicarbazone (L^4) and 2-hydroxynaphtalen-1-carboxaldehyde semicarbazone (L^5) (Fig. 2). In addition, some new aspects of the complete series are investigated. The electrochemical behavior of the five complexes is studied in comparison to that of the free ligands and further spectroscopical studies are performed. As part of the global research program, the five novel complexes are biologically tested as potential anti-tumor agents. Their in vitro cytotoxicity using three different kinds of mammalian tumor cells (mammary, kidney and colon) is evaluated.



R, R', R", R"' = H or alkyl or aryl group

Fig. 1. General formula of semicarbazones (X=O) and thiosemicarbazones (X=S).

2. Experimental

2.1. Materials

All common laboratory chemicals were purchased from commercial sources and used without further purification. N^4-*n*-butylsemicarbazide, N^4-(2-naphthyl)semicarbazide, 2-hydroxynaphtalen-1-carboxaldehyde and $V^{IV}O(acac)_2$ (where acac = acetylacetonate), were prepared according to well established literature procedures [28–31].

2.2. Syntheses of the ligands

All the reactions were carried out under a nitrogen atmosphere. L^1, L^2 and L^3 were synthesized as previously described [18]. L^4 and L^5 were synthesized by slow addition of 10.0 mL of an ethanolic solution containing

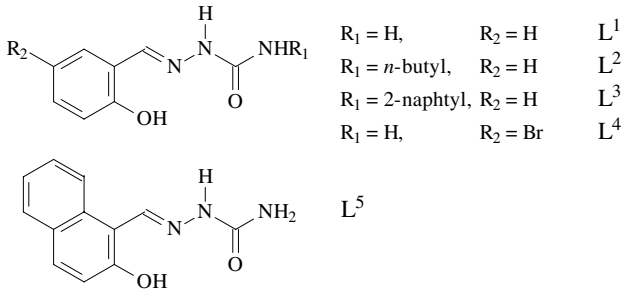


Fig. 2. Ligands: salicylaldehyde semicarbazone (L^1), salicylaldehyde N^4-*n*-butylsemicarbazone (L^2), salicylaldehyde N^4-(2-naphtyl)semicarbazone (L^3), 5-bromosalicylaldehyde semicarbazone (L^4), and 2-hydroxynaphtalen-1-carboxaldehyde semicarbazone (L^5).