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Synthesis, characterization and cytotoxicity of new gold(III) complexes with 1,2-diaminocyclohexane: Influence of stereochemistry on antitumor activity

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ABSTRACT

Gold(III) complexes of the type $[(DACH)AuCl_2]Cl$, derived from sodium tetrachloroaurate(III) dihydrate $NaAuCl_4{\cdot}2H_2O$, where DACH is diaminocyclohexane, have been synthesized. These potential metallodrug compounds were characterized using various spectroscopic and analytical techniques, including elemental analysis, UV–Vis, infrared spectroscopy, solution as well as solid NMR spectroscopy and X-ray crystallography. The potential of the synthesized gold(III) complexes as anti-cancer agents was investigated by measuring some relevant physicochemical and biochemical properties, such as the stability of the Au–N bonds by vibrational stretching from far-IR as well as cytotoxicity and the stomach cancer cell inhibiting effect. The solid-state ^{13}C NMR chemical shift shows that the ligand is strongly bound to the gold(III) center via N atoms. An X-ray crystallography study of the complexes shows that the cyclohexyl ring adopts a chair conformation and the gold coordination sphere adopts a distorted square planar geometry. The *cis* isomer in solution showed higher activity towards the inhibitory effect of human cancer cell lines such as prostate cancer (PC-3) and gastric carcinoma (SGC-7901) than that of the *trans* isomer. The cytotoxicity of the *cis* isomer complex has also been estimated in PC-3 and SGC-7901 cells.

1. Introduction

The serendipitous discovery of cisplatin by Rosenberg in 1965 heralded a new area of anticancer drug research based on metallopharmaceuticals [1]. Cisplatin has been one of the most successful chemotherapies in the last 30 years and has been used to treat numerous types of cancers, including testicular, ovarian, head–neck and bladder tumors. Despite having great utility as a chemotherapeutic agent, cisplatin does have drawbacks; tumors often develop resistance to the drug and patients routinely experience severe side effects throughout the course of the treatment [2]. Subsequently, researchers are continually looking for therapeutic alternatives that might alleviate these limitations. Unfortunately, they have several major drawbacks. Common problems include cumulative toxicities of nephrotoxicity and cytotoxicity [3–6]. In addition to the serious side effects, the therapeutic efficacy is also limited by inherent or treatment-induced resistant tumor cells. These drawbacks have provided the motivation for alternative chemotherapeutic strategies. To circumvent the problem of drug-resistance in cisplatin-resistant cells, gold(III)-based complexes have been designed as potential alternatives to cisplatin [7–11].

Gold(III) compounds have greatly attracted researchers' attention in the last decade for their outstanding cytotoxic actions. It is a metal ion which typically adopts a four-coordinate, square-planar geometry and is therefore expected to mimic the structural and electronic properties of platinum(II). Recent studies have shown that several gold(III) complexes are highly cytotoxic against different tumor cells [12–14], including some which are active even against the cisplatin-resistant cell lines [8,15–17]. Several lines of evidence suggest that gold(III) compounds produce their antiproliferative effects through innovative and non-conventional modes of action. For instance, the hypothesis that their biological effects are mediated by an antimitochondrial mechanism rather than by direct DNA damage, as it is the case for cisplatin and its analogs, has gained much credit during the last few years [10].

The strict relationship to platinum(II) compounds makes gold (III) complexes good candidates for development and testing as anticancer drugs, although the relatively high kinetic liability and the usually high redox potentials have largely hindered such investigations. These problems can possibly be circumvented by forming gold(III) compounds with one or more multidentate nitrogen-donor ligands to enhance the stability of the gold(III) complexes [18–20]. Some recent studies reporting that novel

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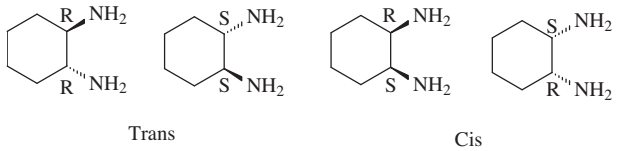
gold(III) compounds show favorable antitumor properties both *in vitro* and *in vivo* have raised new interest in this research area [21–23].

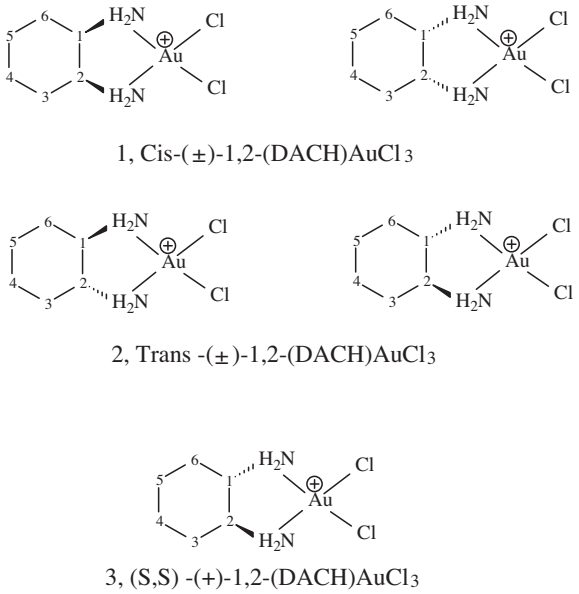
Although, there are a multitude of structural analogs of the antitumor agent cis-diamine dichloroplatinum(II) (cisplatin) [24], only a few are presently used in clinical practice [25], including *trans*-1,2-diaminocyclohexane (DACH) dichloroplatinum(II) [26]. Since the molecule is chiral, the relevance of stereochemical issues has been addressed by a number of investigators [27].The ligand DACH has three isomeric forms: the enantiomers (IR,2R-DACH) (*trans*-l-DACH), (lS,2S-DACH) (*trans*-DACH) and the diastereoisomer Pt(1R,2S-DACH) (*cis*-DACH). In spite of conflicting views [28–32], the consensus is that the (R,R) isomer is generally more active than the (S,S) isomer [33,34], although activity has also been demonstrated with the (R,S) isomer [35]. With regard to the stereochemistry of the complexes, the DACH platinum compounds, Pt(IR,2R-DACH) and Pt(lS,2S-DACH), have a higher antitumor activity than the Pt(IR,2S-DACH) complex [36–38].

In the early 1990s, a few gold compounds were prepared and characterized for their antitumor activity with positive results [39,40] Recently, the use of various Au(III) complexes with novel functionality has elicited more interest due to their distinct physical and chemical properties, stability under physiological conditions and outstanding cytotoxic effects [41,42]. *Cis*-diaminedichloroplatinum(II) (cisplatin) is one of the most widely used anticancer drugs today. However, platinum compounds possessing the 1,2-diaminocyclohexane (DACH) carrier ligand offer advantages over cisplatin with regard to bioavailability, activity and decreased renal toxicity [43]. Furthermore, the success of oxaliplatin, which incorporates the 1R,2R-DACH carrier ligand as a Pt(II) complex, raised considerable research interest over the past three decades in platinum–DACH complexes.

Over the past several years, significant effort has been devoted to the study of the antitumor activity of platinum–DACH complexes, whereas gold–DACH complexes [44] have received relatively little attention, although, Au(III) has a fairly rich biological chemistry. For instance, it is redox active, can be coordinated by amino acids and proteins, is able to deprotonate and bind to the amide N of peptides and it is capable of cross-linking histidine imidazole rings [45]. As in the case of the parent cisplatin, the antitumor activity of platinum–DACH is accompanied by some toxicity. The emergence of resistance and low water solubility, that can affect the pharmacokinetics, are additional features that must be improved in the quest for a more effective analog [46]. As a continuation of our intrinsic interest in the synthesis of gold(III) complexes and to better understand the chemical and physical behavior of biologically relevant mono-(DACH) gold(III) complexes, the chiral isomers [*cis*-(±)-1,2-(DACH)$AuCl_2$]Cl (**1**), [*trans*-(±)-1,2-(DACH)$AuCl_2$]Cl (**2**) and [(1S,2S)-(+)-1,2-(DACH)$AuCl_2$]Cl (**3**) have been synthesized and fully characterized by IR, NMR, elemental analysis and UV–Vis. Scheme 1 illustrates the structures of the ligands and Scheme 2 shows the structures of the complexes. Their cytotoxicity has been tested *in vitro* in human gastric carcinoma cell line SGC-7901 and prostate cancer cell line PC-3. In this study, the influence of the relative stereochemistry of (DACH) gold(III) complexes on their antitumor activities was addressed. These compounds are sparingly water soluble.



Scheme 1. Isomerization structures of diaminocyclohexane (DACH).



Scheme 2. Chemical structures of the synthesized gold(III) complexes.

2. Experimental

2.1. General procedures

All commercial reagents were purchased from Aldrich and used as received unless otherwise stated. The ^1H and ^{13}C NMR experiments were performed on a Bruker Advance 400 or Jeol JNM-LA 500 spectrometer. ^1H and ^{13}C NMR chemical shifts were given as values with reference to tetramethylsilane (TMS) as an internal standard.

2.2. Synthesis of the Au(III) complexes

Gold complexes of *cis*-(±)-1,2-diaminocyclohexane (**1**), *trans*-(±)-1,2-diaminocyclohexane (**2**) and the purely optical active isomer of (S,S)-(+)-1,2-diaminocyclohexane (**3**) were synthesized by a general method described in literature for similar compounds [47], by dissolving of 199 mg (0.50 mmol) sodium tetrachloroaurate(III) dihydrate ($NaAuCl_4{\cdot}2H_2O$) in a minimum amount of absolute ethanol at ambient temperature. In a separate beaker, a solution of 57 mg (0.50 mmol) of the diaminocyclohexane in the least amount of absolute ethanol was prepared, both solutions were mixed (total of 40 ml) and stirred for around 30 min until a clear solution was obtained, which was filtered and concentrated to 10 ml solvent then left for crystallization in the refrigerator. The produced solid was dried under vacuum. The product was obtained in a yield of 91–98%. The complexes prepared in the present study were characterized by their physical properties, NMR, IR, elemental analysis and X-ray crystallography. All the data support the formation of the desired DACH complexes. Melting points and elemental analyses for the complexes are presented in Table 1 (See Supplementary data for Tables 1–7).

2.3. Electronic spectra

Electronic spectra were obtained for the diaminocyclohexane gold(III) complexes using a Lambda 200, Perkin-Elmer UV–Vis spectrometer. The resulting absorption data are shown in Table 2.