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Heteronuclear gold(I)–silver(I) sulfanylcarboxylates: Synthesis, structure and cytotoxic activity against cancer cell lines

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ABSTRACT

Heteronuclear complexes of the type $[AgAu(PPh_3)_2(\mathbf{x}spa)]$ [$H_2\mathbf{x}spa$ = 3-(aryl)-2-sulfanylpropenoic acids; (**x** = 3-phenyl-; 3-(2-chlorophenyl)-; 3-(*o*-methoxyphenyl)-; 3-(*p*-methoxyphenyl)-; 3-(*p*-hydroxyphenyl)-; 3-(2-furyl)-; 3-(2-thienyl)-; spa = 2-sulfanylpropenoate)] were prepared by reacting the appropriate $[Au(PPh_3)(H\mathbf{x}spa)]$ precursor with $Ag(PPh_3)NO_3$. The compounds were characterized by spectroscopic methods, (IR; ^1H, ^{13}C and ^{31}P NMR) and mass spectrometry and the structures of the phenyl and *p*-methoxyphenyl derivatives were determined by X-ray diffraction. The *in vitro* antitumor activity against the HeLa-229, A2780 and A2780*cis* cell lines was determined and compared with that of cisplatin and the equivalent homonuclear gold(I) complexes.

1. Introduction

Cisplatin and other platinum metallo-drugs are considerably effective for the treatment of cancer. However, side effects, the limited spectrum of tumors against which these drugs are active and the frequent development of drug resistance are negative and limiting factors for its clinical use [1–3].

At the same time as new platinum drugs and new delivery vehicles that are able to minimize these adverse effects are investigated, new alternatives based on other metals are defining a particularly interesting and active field [4]. Recent developments in cadmium [5], copper [6], palladium [7], ruthenium [8], silver [9], tin [10] or zinc [11] based drugs are significant examples of this activity.

In addition, gold [Au(III) and Au(I)]-based drugs have been extensively studied [12,13]. Due to its electronic and structural similarity with those of Pt(II), Au(III) compounds have received predictable and significant attention [13,14]. But, on the other hand, Au(I) complexes exhibit cytotoxic activity toward cells from several tumor cell lines, some of which are resistant to cisplatin [12,13] thus the effect on the enzyme thioredoxin reductase is increasingly considered as the origin of this activity [15–20].

Among these gold(I) complexes the thiolate derivatives containing the S–Au–P fragment – where the antiarthritic drug Auranofin, triethylphosphine (2,3,4,6-tetra-o-acetyl-β,1-D-thiopyranosato-S) gold(I), which also shows significant cytotoxic activity, is included – were widely studied [21] and the modulation of its biological activity was related to the replacement of the thiolate ligand [22,23].

In previous papers we have explored the interaction of gold(I) with 3(aryl)-2-sulfanylpropenoic acids, R–CH–C(SH)–COOH, $H_2\mathbf{x}spa$, a class of sulfanylcarboxylic acids which, once deprotonated, have, besides the S-donor atom, the O-atoms of the carboxylic group as potential donor atoms capable of reinforcing the gold–sulfur bond. As a result of this study, mononuclear compounds of the types R–CH–C($SAuPPh_3$)–COOH, $[Au(PPh_3)(H\mathbf{x}spa)]$ [24], [HQ][R–CH–C($SAuPPh_3$)–COO], [HQ] $[Au(PPh_3)(\mathbf{x}spa)]$, and [HP][R–CH–C($SAuPPh_3$)–COO], [HP][$Au(PPh_3)$ (**x**spa)] [25], (HQ = diisopropylammonium; HP = triethylammonium) and dinuclear compounds of the type {R–C[$S(AuPPh_3)_2$]–COO}, $[(AuPPh_3)_2(\mathbf{x}spa)]$ [26], were prepared and structurally characterized. All of these compounds but particularly the latter dinuclear ones showed promising activity against the cell lines of human cervix carcinoma HeLa-229 and human ovarian carcinoma A2780, and also with its cisplatin-resistant mutant A2780*cis*.

The presence of different metallic centers in heterodi- or polynuclear complexes can give rise to an improved biological activity with respect to the equivalent homonuclear compounds. This can be due to their ability to interact with multiple biological targets or to their favorable physicochemical properties [27,28]. Promising heteronuclear Ti–Ru [27], Ti–Au [28], Ti–Au_2 [29], Ag_2Au [30] and Co–Sn [31] compounds have been recently described.

In this line, we try to study the effect that the substitution of a gold(I) atom for a silver(I) atom would have on the structure and on the biological activity of the active homo-dinuclear $[(AuPPh_3)_2(\mathbf{x}spa)]$ complexes.

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In a first attempt we synthesized the complex [AgAu(PPh_3)$_2$(cpa)] (H_2cpa = 2-cyclopentilidene-2-sulfanylacetic acid) [32]. The structure of this compound proved to be dinuclear, resembling those of the [(AuPPh$_3$)$_2$(**x**spa)] complexes and containing S-bonded Ag(I) and Au(I) atoms placed at a short distance of 3.0463(10) Å, which can be compared to the Au–Au distance, 3.0338(10) Å, found in the equivalent dinuclear complex [(AuPPh$_3$)$_2$(cpa)]. The biological activity of this heteronuclear compound, even though better than that of cisplatin against the A2780 and A2780*cis* cell lines, was slightly worse than the equivalent homo-dinuclear [(AuPPh$_3$)$_2$(cpa)] compound. However, the situation could be different for complexes prepared from sulfanylcarboxylate ligands with a different R fragment due to their ability to modulate the hydro/lipophilicity of the compounds, a property of great importance for drug action [22,23,33]. This fact, together with the lack of biological data for similar heteronuclear compounds led us to select the H_2**x**spa sulfanylcarboxylic acids depicted in Scheme 1 and to prepare their derived heteronuclear [AgAu(PPh_3)$_2$(**x**spa)] complexes. The structural study of some of them revealed significant differences with the cpa derivative as the carboxylate group is now being involved in the formation of Ag – O bonds, which led to the formation of tetranuclear units, resembling those present in homonuclear silver(I) complexes previously described. This enables a comparative study on the structural changes caused by the replacement of silver(I) atoms for gold(I) atoms. The cytotoxic activity of these compounds against the HeLa-229, A2780 and A2780*cis* cell lines was investigated and compared with that of cisplatin and the equivalent homo-dinuclear [(AuPPh$_3$)$_2$(**x**spa)] complexes.

2. Experimental

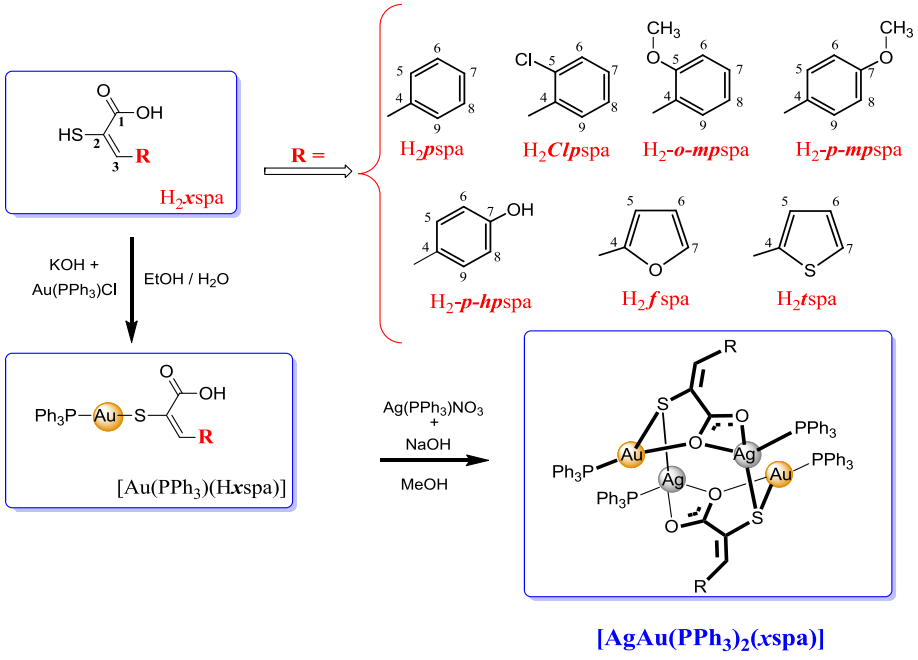
2.1. Materials and methods

Triphenylphosphine (from Riedel-de-Haën) and silver nitrate (from Prolabo) were used as supplied. Complexes of type [Au(PPh_3)(H**x**spa)] (**x** = p = 3-phenyl-; Clp = 3-(2-chlorophenyl)-; mp = 3-methoxyphenyl-; hp = 3-hydroxyphenyl-; f = 3-(2-furyl)-; t = 3-(2-thienyl)-; spa = 2-sulfanylpropenoate) were prepared by adding Au(PPh_3)Cl in 1:1 mole ratio to a solution of the appropriate sulfanylcarboxylic acid and KOH in ethanol [24]. Ag(PPh_3)NO_3 was prepared in accordance to the literature [34].

Elemental analyses were performed with a Fisons 1108 microanalyzer. Melting points were determined with a Büchi apparatus. Mass spectra (MS) were recorded on a Kratos MS50TC spectrometer connected to a DS90 system and operating in FAB (fast atom bombardment) mode (*m*-nitrobenzyl alcohol, Xe, 8 eV; *ca.* 1.28×10^{-15} J), and positive electrospray ionization (in methanol) on a Hewlett-Packard 1100 LC/MSD spectrometer. Ions were identified by DS90 software and the data characterizing the metallated peaks were calculated using the isotope ^{197}Au and assuming the Ag isotope to be ^{107}Ag. IR spectra (KBr pellets or Nujol mulls) were recorded on a Bruker IFS66V FT-IR spectrometer and are reported in the Synthesis section using the following abbreviations: vs = very strong, s = strong, and m = medium. Fluorescence spectra were recorded in a trace-element X-ray fluorescence spectrometer (XRF1) with a sealed tube of 2.2 kW with a molybdenum anode. ^{1}H and ^{13}C NMR spectra in solution were recorded in DMSO-d$_6$, at room temperature on a Bruker AMX 300 operating at 300.14 and 75.40 MHz, respectively, using 5 mm o.d. tubes; chemical shifts are reported relative to TMS (tetramethylsilane) using the solvent signal (δ^1H = 2.50 ppm; δ^{13}C = 39.50 ppm) as reference. The ^{1}H–^{1}H COSY (correlated spectroscopy) NMR spectra, ^{1}H–^{13}C HMBC (heteronuclear multiple bond correlation) and HMQC (heteronuclear multiple quantum coherence) experiments were measured using a Varian Inova 400 spectrometer. ^{31}P NMR spectra were recorded at 202.46 MHz on a Bruker AMX 500 spectrometer using 5 mm o.d. tubes and are reported relative to external H_3PO_4 (85%). NMR data were obtained from freshly prepared concentrated solutions. All the physical measurements were carried out by the RIAIDT services of the University of Santiago de Compostela.

2.2. Synthesis

Complexes were prepared by adding solid Ag(PPh_3)NO_3 in 1:1 molar ratio to a methanol solution of the corresponding [Au(PPh_3)(**x**spa)] complex, to which the appropriate amount of aqueous concentrated NaOH was previously added. After stirring the mixture in the



Scheme 1.