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Synthesis and in vitro antimalarial and antitubercular activity of gold(III) complexes containing thiosemicarbazone ligands

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ABSTRACT

Gold(III) thiosemicarbazone complexes derived from [Au(damp-C^1,N)Cl_2] (**2**), where damp = dimethylaminoethylphenyl, have been synthesized. The compounds were characterised using various spectroscopic and analytical techniques, including NMR spectroscopy, mass spectrometry, infrared spectroscopy and elemental analysis. The gold complexes were screened for in vitro antimalarial and antitubercular activity. Although incorporation of the gold(III) centre into thiosemicarbazone scaffolds enhanced their efficacy against the malaria parasite *Plasmodium falciparum*, this trend was not observed for the antitubercular activity of selected thiosemicarbazones against the *Mycobacterium tuberculosis* virulent strain H_{37}Rv.

1. Introduction

The greatest challenge confronting malaria and tuberculosis chemotherapies is the growing incidence of drug resistance against clinically established drugs [1,2]. The causative agents of these diseases, *Plasmodium falciparum* and *Mycobacterium tuberculosis*, are a major global problem with millions of deaths being reported every year. This combined with the emergence of drug resistance necessitated increased efforts to search for new chemical compounds with novel modes of action [3]. Similarly, the diminishing efficacy of currently used anti-TB drugs coupled with the emergence of resistant strains compliment the need to discover novel drugs [4]. Recently, there has been greater interest in transition metal complexes based on thiosemicarbazones as potential antimalarial and antitubercular agents [5,6,7]. Some studies have shown that coordination of metal ions such as gold(I) and platinum(II) with thiosemicarbazones enhanced antimalarial and antibacterial activity [8,9].

Thiosemicarbazones possess a wide spectrum of pharmacological properties including both antimalarial [10] and antitubercular [11,12] biological activities and their use as potential chemotherapeutics is an active area of research. In addition, thiosemicarbazones are well known metal chelates possessing N and S donor atoms, and their chemistry with transition metals has been extensively reviewed [13]. These compounds have also been attractive ligands in coordination chemistry of gold [13]. In 1998, Ortner and Abram reported crystal structures of the square-planar gold(III) thiosemicarbazone complex **1** (Fig. 1) including a NNS tridentate coordinate gold(III) complex [14]. Although the reaction leading to gold(III) thiosemicarbazone derivatives is often carried out in MeOH, very recently we observed in our ligand systems, that using similar reaction conditions reported by Ortner and Abram, reduction of the gold(III) complex **2**, [Au(damp-C^1,N)Cl_2] [15], occurred to form gold(I) thiosemicarbazone derivatives [17]. Castiñeiras et al. [16] demonstrated that by carrying out the reaction involving **2** and thiosemicarbazone ligands in acetone instead of MeOH appeared to suppress the reduction of gold(III) to gold(I).

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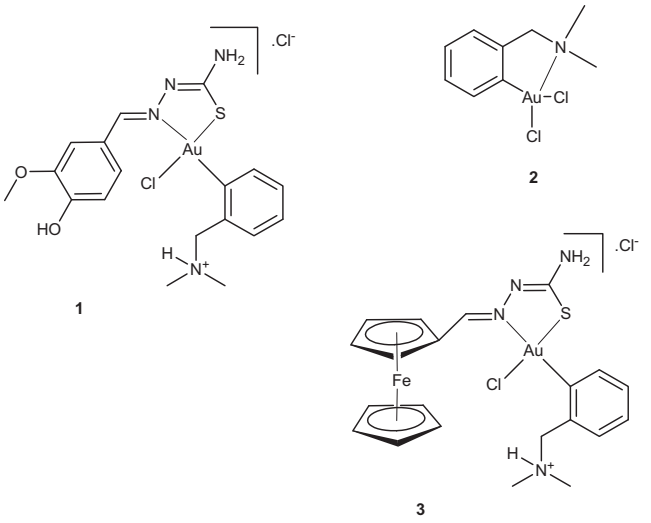


Fig. 1. Cyclometallated gold (III) and derived gold(III) thiosemicarbazone complexes [14].

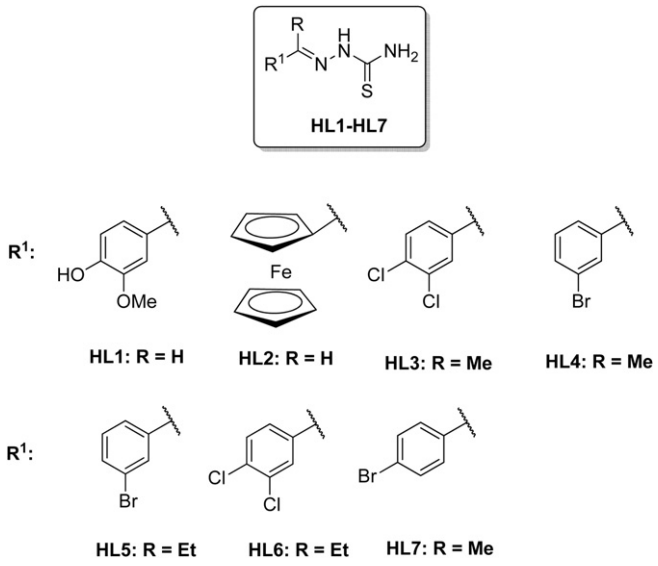


Fig. 2. Structures of thiosemicarbazones HL1–HL7.

The preliminary antitumour activity of gold(III) thiosemicarbazone complexes against human MCF-7 breast cancer cell line reported by Abram et al. [18] inspired Casas et al. [19] to develop analogous complexes (e.g. compound **3**) based on ferrocenyl thiosemicarbazone ligands. Although the solubility of the compounds was a challenge, compound **3** and its derivatives display comparable cell growth inhibitory properties as Cisplatin®, an anticancer metal-based drug, against the HeLa-229 human cervix carcinoma cell line [19]. However, to the best of our knowledge, no information has been reported on the antimalarial and antituberculosis properties of gold(III) thiosemicarbazone complexes. Given our ongoing investigations into the biological applications of thiosemicarbazones and their metal complexes [5,6,8,10], we herein report the synthesis and evaluation of the biological activity of gold(III) complexes of thiosemicarbazones against W2 (chloroquine-resistant) and $H_{37}Rv$ strains of *P. falciparum* and *M. tuberculosis*, respectively.

2. Results and discussion

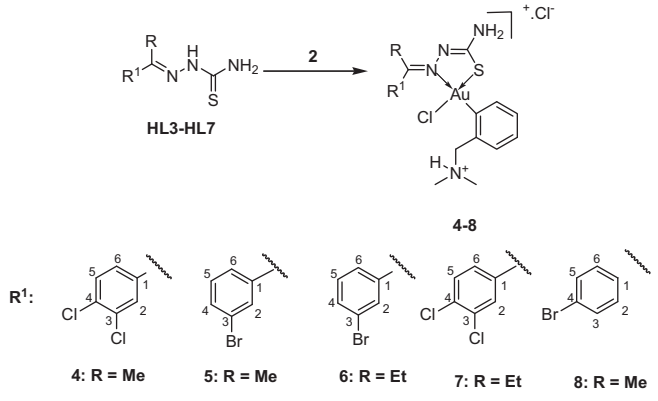
2.1. Synthesis and characterization of gold(III) thiosemicarbazone complexes

Thiosemicarbazones **HL1**–**HL7** [20,21,22] (Fig. 2), the precursor gold(III) complex **2** [15], as well as gold(III) thiosemicarbazone complexes **1** [14] and **3** [19] (Fig. 1), were synthesised as described in the literature. Initially, the reaction of **2** with **HL3**–**HL7** in refluxing MeOH for 2 h resulted in a mixture of gold(I) and gold(III) thiosemicarbazone complexes. Analysis of the mass spectrometry data of resulting solids revealed the presence of gold(I) complexes and the desired gold(III) thiosemicarbazone complexes as a mixture of products. The isolation of crystals of gold(I) thiosemicarbazone complexes consistent with the general structure $[TSC\text{-}Au^{I}\text{-}TSC]^{+}.Cl^{-}$ supported the fact that gold(III) complex **2** was reduced to gold(I) under these reaction conditions [7]. However, mass spectral analysis of the aforementioned solids did not reveal the nature of possible gold(III) complexes remaining in solution.

It was later established that in order to avoid the reduction of gold(III) to gold(I), the reactions should be conducted in polar aprotic solvents such as acetone, since MeOH appeared to influence the redox behaviour of gold(III), thus, favouring its reduction to gold(I) [16]. Thus, subsequent reactions of the starting gold(III) complex **2** with **HL3**–**HL7** in acetone resulted in the isolation of the target gold(III) thiosemicarbazone complexes **4**–**8** as yellow to orange–yellow solids in good yields (90–98%) (Scheme 1). In each case, ESI-MS data showed no evidence of the formation of the competing gold(I) complexes of the form $[TSC\text{-}Au^{I}\text{-}TSC]^{+}.Cl^{-}$. The complexes are soluble in DMSO and sparingly soluble in common organic solvents.

The ^{1}H NMR spectra of **4**–**8** showed chemical shifts in the range δ 10.35–10.83 ppm, assigned to the protonated tertiary amine (NH^{+}) group of the damp ligand [14]. Coordination of the damp ligand is also supported by the appearance of chemical resonance peaks in the regions δ 4.30–5.40 ppm and δ 2.65–3.20 ppm, which are attributed to the CH_2 and $N(CH_3)_2$ groups, respectively. The absence of chemical shifts due to –NH protons suggest coordination of **HL3**–**HL7** with the gold(III) centre in the thiol form [19].

Characteristic weak absorption bands are observed in the infrared spectra for the complexes **4**, **6**, and **7,** in the region 2664–2683 cm^{-1} for the NH^{+} stretches, following cleavage of the Au–N bond in **2** and protonation of the tertiary amine moiety of the damp ligand. Previously, similar NH^{+} bands have been observed for compounds **1** and **3** [14,19]. Absorption bands associated with the ν(C=S) stretch appear at lower wavenumbers. This suggests participation of the sulphur donor atom in gold(III) coordination. The absorption bands due to the imine moiety ν(C=



Scheme 1. (a) **HL3**–**HL7**, acetone, reflux 1 h, r.t. 5 h.