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Synthesis, characterization, cytotoxic and antitubercular activities of new gold(I) and gold(III) complexes containing ligands derived from carbohydrates

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Abstract Novel gold(I) and gold(III) complexes containing derivatives of D-galactose, D-ribose and D-glucono-1,5-lactone as ligands were synthesized and characterized by IR, ^{1}H, and ^{13}C NMR, high resolution mass spectra and cyclic voltammetry. The compounds were evaluated in vitro for their cytotoxicity against three types of tumor cells: cervical carcinoma (HeLa) breast adenocarcinoma (MCF-7) and glioblastoma (MO59J) and one non-tumor cell line: human lung fibroblasts (GM07492A). Their antitubercular activity was evaluated as well expressed as the minimum inhibitory concentration (MIC_{90}) in μg/mL. In general, the gold(I) complexes were more active than gold(III) complexes, for example, the gold(I) complex (**1**) was about 8.8 times and 7.6 times more cytotoxic than gold(III) complex (**8**) in MO59J and MCF-7 cells, respectively. Ribose and alkyl phosphine derivative complexes were more active than galactose and aryl phosphine complexes. The presence of a thiazolidine ring did not improve the cytotoxicity. The study of the cytotoxic activity revealed effective antitumor activities for the gold(I) complexes, being more active than cisplatin in all the tested tumor cell lines. Gold(I) compounds (**1**), (**2**), (**3**), (**4**) and (**6**) exhibited relevant antitubercular activity even when compared with first line drugs such as rifampicin.

Keywords Gold complexes · Carbohydrates · Cytotoxic activity · Antitubercular activity

Abbreviations

IR	Infrared
NMR	Nuclear magnetic resonance
TMS	Tetramethylsilane
Isop	Isopropylidene
DMF	Dimethyl formamide
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid, *N*-(2-hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid)
HMRS(ESI)	High-resolution mass spectra (eletrospray ionization)
HAM-F10	Nutrient mixture F-10
DMEM	Dulbecco's modified Eagle's medium
XTT	2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide

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DMSO	Dimethylsulfoxide
PBS	Phosphate buffer saline

Introduction

Chrysotherapy, the use of gold compounds in medicine, refers to the fact that gold compounds, usually gold thiolates, are used clinically to alleviate of the symptoms associated with rheumatoid arthritis. Auranofin (triethylphosphine-(2,3,4,6-tetra-*O*-acetyl-β-1-D-thiopyranosato-S)gold(I)) and solganol (gold(I) thioglucose) (Fig. 1) are gold(I) complexes that exhibit thiosugars as ligand and have been used in the treatment of rheumatoid arthritis for more than 50 years (Yoshida et al. 1999; Eisler 2003; Shoeib et al. 2010).

Auranofin is efficacious and well tolerated, to treat rheumatoid arthritis (Shi et al. 1997) and it has also been found to be highly cytotoxic to tumor cells (Simon et al. 1981) and active against P388 leukemia (Mirabelli et al. 1985). The use of auranofin and other gold complexes as anticancer agents represent an exciting new possible therapeutic application for these compounds.

There are other potencial applications for gold complexes in medicine. Studies have shown that auranofin is a candidate drug for treating HIV infection, showing the potential to hit crucial therapeutic targets that are not accessible to the antirretroviral drugs currently in use (Chirullo et al. 2013). Recently, Debnath has described auranofin as a promising drug in the treatment of amebiasis (Debnath et al. 2012).

Previous structure–activity relationship studies have shown the importance of the phosphine ligand for the activity of gold(I) compounds. Gold complexes containing tertiary phosphines with a linear S–Au–P arrangement have been found to be more active than similar compounds with no phosphinic substituents (Ott et al. 2009). In the course of our studies on the gold(I) compounds, we have synthesized gold(I) complexes with a linear S–Au–P arrangement, which have been shown to be potential antitumor candidates (Chaves et al. 2014).

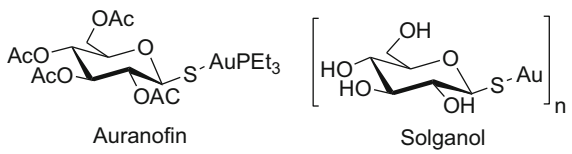


Fig. 1 Chemical structures of auranofin and solganol

In fact, several gold compounds containing triphenylphosphine and triethylphosphine have been reported in the literature to exhibit anticancer activity (Simon et al. 1979, 1981; Sadler et al. 1984; Mirabelli et al. 1985; Ott 2009). Other biological activities for these compounds have also been reported. For instance, antiinflammatory (Trávnicek et al. 2012) and antiparasitic activities (Navarro 2009).

Gold(III) compounds have also attracted much attention for their outstanding cytotoxic activity, structural and electronic similarity (square planar, d^8) to platinum(II) complexes, (Gabbiani et al. 2007; Lessa et al. 2012; Maiore et al. 2012). One of the main obstacles for their use in medicine is their low stability in physiological conditions which can be increased by coordination of multidentate ligands. However, the extra stability can result in loss of biological activity (Messori et al. 2000). Gold(III) complexes having diamine ligands have displayed significant cytotoxic properties (Bruni et al. 1999; Messori et al. 2000). For instance, ethylenediamine gold(III) complexes have shown to be as effective, or even more effective against certain tumor cell lines than cisplatin (Messori and Marcon 2004). The mechanisms of action of cytotoxic gold(III) complexes seem to be innovative and substantially different from that of cisplatin (Gabbiani et al. 2007; Al-Maythalony et al. 2009). The cytotoxic action of a range of gold(I) and gold(III) complexes seems to be related to the inhibition of mitochondrial thioredoxin reductase and mitochondrial function (Rigobello et al. 2004; Barnard and Berners-Price 2007; Hickey et al. 2008; Navarro 2009) rather than covalent binding to DNA such as cisplatin and its analogues.

Synthesis of compounds derived from carbohydrates has also become increasingly important in medicinal chemistry, highlighting the wide range of biological activity, and the low toxicity of such compounds. Many anti-cancer substances that have sugar residue, (e.g. bleomycin, adriamycin, and many antibiotics) have been widely used clinically (Tsubomura et al. 1986). More specifically, gold compounds containing carbohydrates have been investigated for their antitumor activity. For instance, Mirabelli et al. have reported the cytotoxic and antitumor activity of

several gold complexes containing different carbohydrates. They have found that in vivo antitumor activity is generally optimized binding Au(I) to a substituted phosphine and a thiosugar (Mirabelli et al. 1986).

On the other hand, compounds containing the thiazolidine ring stand out because they are able to interact with a variety of biological targets (Brown 1961). The synthesis and pharmacology of the thiazolodinones containing sugar moieties have been published (Al-Thebeiti 1999; Rauter et al. 2005; Chen et al. 2008). The use of different types of organic ligands can modify the biological activity of the complexes and, for this reason, the use of different carbohydrates is very promising. Our research group has also described the synthesis of sugar derivatives and their platinum complexes (Almeida et al. 2000).

Considering that diamine gold(III) complexes have shown antitumor activity and that gold(I) compounds containing tertiary phosphine and thiolates are among the most promising agents for the treatment of cancer, we have developed gold complexes containing a thiosugar or aminosugar, PPh_3, PEt_3 and Cl.

Since the antitumor activity can be influenced by the nature of the ligands the novel gold(I) complexes described herein are auranofin analogues, however the thiolate is linked to C5 and C6 positions of the carbohydrate derivatives D-galactose and D-ribose. We have also prepared gold(III) complexes containing carbohydrate derivatives that present aliphatic side chains with the aim to study the structure and biological activity relationships.

On the other hand, gold complexes have been reported to present antimicrobial activity as well. For instance, complexes such as sodium bis(thiosulfato-S)aurate(I) (sanocrysin) have shown considerable promise as antimicrobial treatments for *M. tuberculosis* (Eiter et al. 2009; Benedek 2004). Recently, it was reported that auranofin is very active against staphylococcus and present potential to be used in the treatment of severe staphylococcal infections (Cassetta et al. 2014).

Despite the efforts done up to now, the potential use of gold derivatives as antimicrobial drugs is still little explored. Considering that the compounds described herein could have the potential to act as antibacterial agents and the necessity to develop new therapeutic agents, their activity against *M. Tuberculosis* was also evaluated.

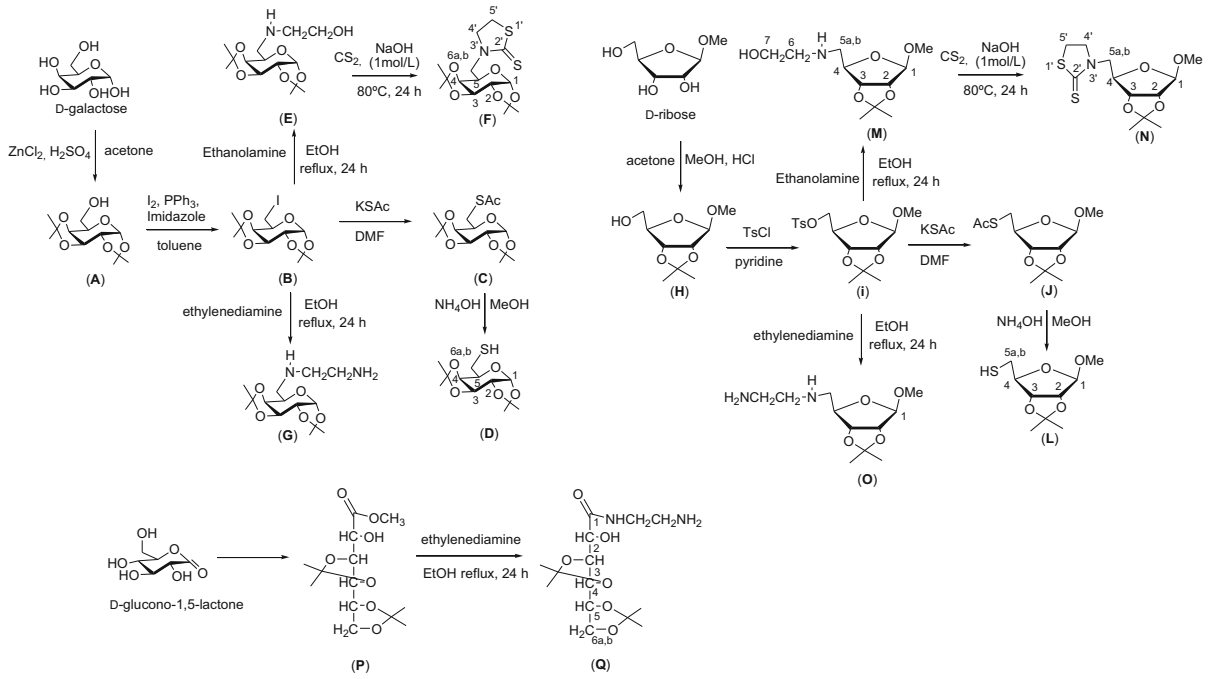
Materials and methods

All reagents and solvents were reagent grade and were used without prior purification. $Au(PEt_3)Cl$ is commercially available and $Au(PPh_3)Cl$ was synthesized from $K[AuCl_4]$ according to the literature (Baenziger et al. 1976). The progress of all reactions was monitored by thin-layer chromatography which was performed on 2.0 × 6.0 cm aluminium sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. Infrared (IR) spectra were recorded on a Bomem FTIR MB-102 spectrometer in the region of 4000–300 cm^{-1} as a KBr pellet, with 4 cm^{-1} of spectral resolution, and average of 64 scans. Only significant peaks were recorded. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded as solutions in $CDCl_3$ and CD_3OD on a Bruker spectrometer. The chemical shifts were expressed as δ (in ppm) with respect to a standard internal TMS reference (^1H NMR). Raman spectra were obtained using a Bruker RFS 100 FT-Raman instrument equipped with a germanium detector refrigerated by liquid nitrogen, with excitation at 1064 nm from a Nd: YAG laser, power between 103 mW for sample in solid phase, in the range between 4000 and 50 cm^{-1}, and with a spectral resolution of 4 cm^{-1}, and an average of 500 scans. The high-resolution mass spectra were recorded on a Micromass LCT spectrometer, with electrospray ionization, at the Institut de Chimie des Substances Naturelles at Gif-sur-Yvette, France.

Cyclic voltammograms were obtained on a μAutolab Type III potentiostat (Eco Chemie, Netherlands) with GPES version 4.9 software. The voltammetric measurements were made using a glassy carbon electrode as working electrode, a platinum wire and a $Ag/AgCl_{(s)}$, $KCl_{(sat)}$ as auxiliary and reference electrodes respectively. Cyclic voltammograms were made between −1.50 and 1.70 V at 100 mV s^{-1}. Solutions of compounds (1×10^{-3} mol L^{-1}) were recorded with $NaClO_4$ (0.1 mol L^{-1}) (supporting electrolyte) dissolved in DMF.

Synthesis of ligands (Scheme 1)

Ligand (**D**) was prepared from D-galactose and ligand (**L**) from D-ribose in four steps as previously described (Sout et al. 1975; Garegg 1984; Amarante 2005) and (Gyepes et al. 2008), respectively. The novel ligands



Scheme 1 Synthesis of ligands (**D**), (**F**), (**L**), (**N**) and (**Q**)

(**F**) and (**N**) were prepared from classical carbohydrate chemistry methods (Garegg 1984; Delaunay et al. 1995) by reaction of ethanolamine with 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**B**) or methyl 5-*O*-tosyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**I**), in ethanol at reflux for 24 h obtaining the aminoalcohols (**E**) and (**M**). The treatment of these aminoalcohols with excess of carbon disulfide under basic conditions provided the ligands (**F**) and (**N**) (Scheme 1). The ligands (**R**) e (**S**) were prepared from D-galactose and D-ribose according to the experimental procedure previously described (De Almeida et al. 2000). The ligand (**Q**) was obtained by the reaction of ethylenediamine with methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (**P**) initially obtained from the D-glucono-1,5-lactone by following the procedure described in reference (Releling et al. 1987).

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-mercapto-α-D-galactose (**D**)

yield, (50 %) as a oil, lit. (Sout et al. 1975) IR ν_{max} KBr (cm^{-1}): 2987; 2935; 2574; 1071; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33; 1.35; 1.44 and 1.54 (4s, 12H, 4 CH_3-isop); 1.61–1.68 (m, 1H, SH); 2.62–2.82 (m, 2H, H6a, H6b); 3.78 (td, 1H, $J_{5,6a} = 7.0$ Hz, $J_{5,6b} = 7.0$ Hz, $J_{5,4} = 1.8$ Hz, H5); 4.31 (dd, 1H, $J_{2,1} = 5.0$ Hz, $J_{2,3} = 2.4$ Hz, H2); 4.34 (dd, 1H, $J_{4,3} = 7.8$ Hz, $J_{4,5} = 1.8$ Hz, H4); 4,62 (dd, 1H, $J_{3,4} = 7.8$ Hz, $J_{3,2} = 2.4$ Hz, H3); 5.53 (d, 1H, $J_{1,2} = 5.0$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.6; 24.6; 25.1 and 26.2 (CH_3-isop); 26.1 (C6); 70.1 (C2); 70.7 (C3); 71.1(C4); 71.5 (C5); 96.8 (C1); 108.8, 109.5 [$C(CH_3)_2$].

Methyl 5-deoxy-2,3-*O*-isopropylidene-5-mercapto-β-D-ribofuranoside (**L**)

Yield, (14 %) as a solid, m.p. 64–66 °C, lit. (Ingles and Whistler 1962) m.p. 67 °C. IR ν_{max} KBr (cm^{-1}): 2991; 2935; 2565; 1105; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25; 1.32; 1.48 (3s, 7H, $2CH_3$-isop, SH); 2.52–2.60 (m, 1H, H5a); 2.74–2.83 (m, 1H, H5b); 3.35 (s, 3H, OCH_3); 4.17 (t, 1H, $J_{4,5a} = 7.5$ Hz, H4); 4.60 (d, 1H, $J_{2,3} = 5.9$ Hz, H2); 4.69 (d, 1H, $J_{3,2} = 5.9$ Hz, H3); 4.97 (s, 1H, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1 and 26.6 (CH_3-isop); 29.9 (C5); 55.3 (OCH_3); 83.1 (C4); 85.4 (C3); 88.9 (C2); 109.7 (C1); 112.7 [$C(CH_3)_2$].

6-Deoxy-6-(3-thiazolydyl-2-thione)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**F**)

yield, (42 %) as a solid, m.p. 119–121 °C. IR ν_{max} KBr (cm^{-1}): 2987; 2936; 2891; 1497; 1244; 1068; 757. Raman ν_{max}: 2991; 2938; 2896; 1461; 1244; 1068; 757; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30; 1.33; 1.45 and 1.49 (4s, 12H, $4CH_3$-isop); 3.22–3.31 (m, 2H, H5a′, H5b′); 3.49 (dd, 1H, $J_{6a,6b} = 14.7$ Hz, $J_{6,5} = 9.6$ Hz, H6a); 4.06–4.14 (m, 1H, H4b′); 4.23–4.44 (m, 5H, H4a′, H4, H2; H5, H6b); 4.60 (dd, 1H, $J_{3,4} = 2.4$ Hz, $J_{3,2} = 7.8$ Hz, H3); 5.48 (d, 1H, $J_{1,2} = 4.8$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.5, 25.2; 26.1 and 26.2 (CH_3-isop); 28.1 (C5′); 50.3 (C6); 59.4 (C4'); 66.6 (C2); 70.7 (C3); 71.0 (C4); 71.9 (C5); 96.5 (C1); 109.5, 109.7 [$C(CH_3)_2$]; 196.9 (C2'); HRMS(ESI): *m/z* cal. for $C_{15}H_{23}O_5NS_2$ $[M+H]^+$ 362.1096, found 362.1107.

Methyl 5-deoxy-5-(2-hydroxy-ethylamino)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**M**)

Yield, 66 % as a oil, IR ν_{max} KBr (cm^{-1}): 3401; 3186; 2987; 2936; 1103; ^{1}H NMR(300 MHz, CD_3OD) δ: 1.26; 1.42 (2s, 6H, $2CH_3$-isop); 2.62 (s, 2H, NH; OH); 2.67(s, 1H, H5a); 2.69 (s, 1H, H5b); 2.74 (t, 2H, $J_{6,7} = 5.1$ Hz, H6); 3.29 (s, 3H, OCH_3); 3.60 (t, 1H, $J_{7,6} = 5.1$ Hz, H7); 4.24 (t, 1H, $J_{4,5a} = 7.2$ Hz, H4); 4.51–4.58 (m, 2H, H3, H2); 4.91 (s, 1H, H1); ^{13}C NMR (75 MHz, CD_3OD) δ: 25.1; 26.6 (CH_3-isop); 51.2 (C5); 52.7 (C6); 55.3 (OCH_3); 60.9 (C7); 82.8 (C4); 85.5 (C2); 86.2 (C3); 109.9 (C1); 112.5 [$C(CH_3)_2$].

Methyl 5-deoxy-5-(3-thiazolydyl-2-thione)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**N**)

Yield, (64 %) as a solid, m.p. 135–136 °C. IR ν_{max} KBr (cm^{-1}): 2984; 2924; 1495; 1218; 1062; Raman ν_{max}: 2942; 2841; 1449; 1232; 1037; 711; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 and 1.43 (2s, 6H, $2CH_3$-isop); 3.28 (t, 2H, $J_{5',4a'} = J_{5',4b'} = 7.8$ Hz, H5′); 3.34 (s, 3H, OCH_3); 3.43 (dd, 1H, $J_{5a,5b} = 13.2$ Hz, $J_{5a,4} = 6.6$ Hz, H5a), 4.00–4.10 (m, 1H, H4a′); 4.24–4.37 (m, 2H, H4b′, H5b); 4.41–4.44 (m, 1H, H4); 4.61 (d, 1H, $J_{2,3} = 5.8$ Hz, H2); 4.75 (d, 1H, $J_{3,2} = 5.8$ Hz, H3); 4.96 (s, 1H, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1 and 26.6 (CH_3-isop); 27.8 (C5′); 52.2 (C5); 55.8 (OCH_3); 57.4 (C-4′); 82.4 (C2); 84.5 (C3); 85.2 (C4); 110.4 (C1); 112.9 [$C(CH_3)_2$]; 197.9 (C2′); HRMS(ESI): *m/z* cal. for $C_{12}H_{19}O_4NS_2$ $[M+H]^+$ 306.0834, found 306.0834.

6-Deoxy-6-[*N*-(2'-amino-ethylamino)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**R**)

yield, (54 %) as a oil, lit. (Almeida et al. 2000). IR ν_{max} KBr (cm^{-1}): 3443; 2989; 2926; 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30; 1.42 and 1.58 (3s, 12H, $4CH_3$-isop); 2.89–3.04 (m, 2H, H6a, H6b); 3.14–3.15 (m, 2H, H8); 3.26–3.28 (m, 2H, H7); 3.99 (d, 1H, $J_{5,6a} = 6.4$ Hz, H5); 4.23 (d, 1H, $J_{4,3} = 7.9$ Hz, H4); 4.29–4.30 (m,1H, H2); 4.58 (d, 1H, $J_{3,4} = 7.9$ Hz, H3); 5.42 (s, 3H, NH, NH_2); 5.65 (d, 1H, $J_{1,2} = 5.0$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.5; 25.0; 26.2 and 26.7 (CH_3-isop); 38.5 (C8); 46.3 (C6); 48.6 (C7); 66.2 (C5); 70.4 (C2); 70.8 (C3); 71.7 (C4); 96.4 (C1); 109.2 and 109.6 112.9 [$C(CH_3)_2$].

Methyl 5-deoxy-5-[*N*-(2′-amino-ethylamino)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**S**)

Yield, (44 %) as a oil. IR ν_{max} KBr (cm^{-1}): 3434; 2995; 2939; 1108; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.34 and 1.47 (2s, 6H, $2CH_3$-isop); 2.72–2.87 (m, 6H, H6, H7, H5a, H5b); 3.38 (s, 3H, OCH_3); 4.27 (t, 1H, $J_{4,5a} = 7.4$ Hz, H4); 4.62 (d, 1H, $J_{3,2} = 6.0$ Hz, H3); 4.71 (d, 1H, $J_{2,3} = 6.0$ Hz, H_2); 4.87 (s, 3H, NH and NH_2); 4.95 (s, 1H, H1); ^{13}C NMR (75 MHz, CD_3OD) δ: 25.2 and 26.8 (CH_3-isop); 41.4 (C7); 51.1 (C5); 53.8 (C6); 55.6 (OCH_3); 84.0 (C4); 86.7 (C2); 87.4 (C3); 111.2 (C1); 113.5 [$C(CH_3)_2$].

3,4:5,6-Di-*O*-isopropylidene-*N*-(2′-aminoethyl)-D-gluconamide (**Q**)

Yield, (63 %) as a solid, m.p. 136–140 °C. IR ν_{max} KBr (cm^{-1}): 3396; 3327; 2919;1662; 1061; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24; 1.32; 1.36; 1.40 (4s, 12H, $4CH_3$-isop); 2.91(s, 2H, NH_2); 3.20 (s, 2H, H8); 3.41 (s, 2H, H7, $C\underline{H}_2NH$); 3.96 (s, 2H, H6a, H6b); 4.11(s, 2H, H4, H5); 4.25 (s, 1H, H3); 4,42 (d, 1H, $J_{2,3} = 9.0$ Hz, H2); 7.26 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.4; 26.9; 27.1; 27.3; (CH_3-isop); 41.5 (C7); 41.8 (C8); 67.9 (C6); 70.5 (C2); 76.6 (C5); 77.2 (C3); 80.3 (C4); 109.9 and 110.0 [$C(CH_3)_2$]; 172.3 (CO); HRMS(ESI): *m/z* cal. for $C_{14}H_{26}O_6N_2$ $[M+H]^+$ 319.1869, found 319.1853.

Synthesis of gold(I) complexes (**1**), (**2**) and (**3**)

The ligand (**D**) (0.11 g, 0.4 mmol) or (**L**) (0.09 g, 0.4 mmol) was dissolved in ethanol (5 mL) and K_2CO_3 (0.08 g, 0.6 mmol) was added. After 1 h in the dark at room temperature a solution of Au(PEt_3)Cl (0.198 g, 0.4 mmol) or Au(PPh_3)Cl (0.140 g, 0.4 mmol) in (1:1) ethanol/dichloromethane (4 mL) was slowly added. The reaction mixture was stirred for 24 h the product was extracted with dichloromethane/water. The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to furnish a white residue which was purified by chromatography on silica gel (eluent: hexane/dichloromethane) to give the desired compounds (**1**), (**2**) and (**3**).

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-mercapto-α-D-galactose)(triethylphosphine) gold(I) **(1)**

Yield, (52 %) as a white semi-solid. IR ν_{max} KBr (cm^{-1}): 2965; 2923; 2850; 1395; 1087; 319; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07–1.18 (m, 9H, CH_3); 1.25; 1.28; 1.37; 1.49 (4s, 12H, 4CH_3-isop); 1.71–1.82 (m, 6H, CH_2); 3.06 (dd, 1H, $J_{6b–5} = 5.5$ Hz, $J_{6b–6a} = 12.1$ Hz, H6b); 3.17 (dd, 1H, $J_{6a–5} = 8.1$ Hz, $J_{6a–6b} = 12.1$ Hz, H6a); 3.74–3.78 (m, 1H, H5); 4.21 (dd, 1H, $J_{2–3} = 2.2$ Hz, $J_{2–1} = 5.0$ Hz, H2); 4.52 (dd, 1H, $J_{3–2} = 2.2$ Hz, $J_{3–4} = 8.0$ Hz, H3); 4.65 (d, 1H, $J_{4–3} = 8.0$ Hz, H4); 5.45 (d, 1H, $J_{1–2} = 5.0$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.2 (CH_3Et); 18.2 (d, CH_2Et, $J_{CH2\text{-}P} = 35.0$ Hz); 24.6; 25.2; 26.2; 26.6 (CH_3-isop); 27.8; (C6); 70.9 (C2); 71.0 (C3); 71.1 (C4); 72.3 (C5); 96.9 (C1); 108.5 and 109.0 [$C(CH_3)_2$]; HRMS(ESI): *m/z* calc. for $C_{18}H_{34}O_5PSAu$ $[M+Na]^+$ 613.1428, found 613.1435.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-mercapto-α-D-galactose(triphenylphosfine) gold(I) (**2**)

Yield, (52 %) as a white solid, m.p. 189–195 °C. IR ν_{max} KBr (cm^{-1}): 3134; 2989; 2931; 1435; 1066; 331; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23; 1.25; 1.31; 1.42 (4s, 12H, 4CH_3-isop); 3.20 (dd, 1H, $J_{6b–5} = 5.1$ Hz, $J_{6b–6a} = 12.3$ Hz, H6b); 3.31 (dd, 1H, $J_{6a–5} = 9.4$ Hz, $J_{6a–6b} = 12.3$ Hz, H6a); 3.89–3.94 (m, 1H, H5); 4.23 (dd, 1H, $J_{2–3} = 2.2$ Hz, $J_{2–1} = 5.0$ Hz, H2); 4.58 (dd, 1H, $J_{3–2} = 2.2$ Hz, $J_{3–4} = 8.0$ Hz, H3); 4.85 (d, 1H, $J_{4–3} = 8.0$ Hz, H4); 5.47 (d, 1H, $J_{1–2} = 5.0$ Hz, H1); 7.44–7.56 (m, 15H, Ar-PPh_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.5; 25.1; 26.2; 26.3 (CH_3-isop); 27.7 (C6); 70.7 (C2); 71.0 (C3); 71.1 (C4); 72.5 (C5); 96.9 (C1); 108.4 and 108.9 [$C(CH_3)_2$]; 129.2 (d, C3′, C5′, $J_{3'–P} = J_{5'–P} = 11.6$ Hz); 129.9 (d, C1′ $J_{1'–P} = 55.4$ Hz), 131.7 (d, C4′, $J_{4'–P} = 2.3$); 134.4 (d, C2′, C6′, $J_{2'–P} = J_{6'–P} = 13.4$ Hz); HRMS(ESI): *m/z* calc. for $C_{30}H_{34}O_5PSAu$ $[M+AuPPh_3]^+$ 1193.2107, found 1193.2.

(Methyl 2,3-*O*-isopropylidene-5-deoxy-5-mercapto-β-D-ribofuranoside) (triphenylphosphine)gold(I) **(3)**

Yield, (32 %) as a white solid, m.p. 145 °C. IR ν_{max} KBr (cm^{-1}): 3058; 2920; 1096; 327; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 and 1.43 (2s, 6H, 2CH_3-isop); 3.06 (t, 1H, $J_{5b–5a} = 12.5$ Hz, H5b); 3.23–3.29 (m, 4H, H5a, OCH_3); 4.37 (dd, 1H, $J_{4–3} = 4.8$ Hz, $J_{4\text{-}5a} = 11.2$ Hz, H4); 4.55 (d, 1H, $J_{2\text{-}1} = 6.0$ Hz, H2); 4.92 (s, 1H, H3); 5.11 (d, 1H, $J_{1–2} = 5.0$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0; 26.6 (CH_3-isop); 31.9 (C5); 54.7(OCH_3); 83.3 (C2); 85.4 (C3); 92.0 (C4); 109.4 (C1); 112.0 [$C(CH_3)_2$]; 129.3 (d, C1′, $J_{1'–P} = 58.8$ Hz); 129.4 (d, C3′, C5′, $J_{3'–P} = J_{5'–P} = 11.7$ Hz); 131. 9 (d, C4′, $J_{4'–P} = 2.4$ Hz); 134.4 (d, C2′, C6′, $J_{2'–P} = J_{6'–P} = 13.4$ Hz); HRMS(ESI): *m/z* calc. for $C_{27}H_{30}O_4PSAu$ $[M+Na]^+$ 701.1166, found 701.1157.

Synthesis of gold(I) complexes (**4**), (**5**), (**6**) and (**7**)

To a solution of Au(PPh_3)Cl (0.198 g, 0.4 mmol) or Au(PEt_3)Cl (0.140 g, 0.4 mmol) in dichloromethane (3 mL), ligand (**F**) or (**N**) (0.4 mmol) dissolved in dichloromethane (4 mL) was slowly added during 3 h. After 6 h at room temperature in the dark, the solvent was removed under reduced pressure to furnish a white residue which was purified by preparative chromatography (eluent: dichloromethane) to give the desired compounds (**4**), (**5**), (**6**) and (**7**).

6-Deoxy-6-(3-thiazolydyl-2-thione)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (triethylphosphine)gold(I) **(4)**

Yield, (50 %) as a white solid, m.p. 66–67 °C. IR ν_{max} KBr (cm^{-1}): 2979; 2962; 2890; 1497; 1246; 1068; 755;

Raman ν_{max}: 2992; 2944; 2914; 1457; 1182; 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13–1.25 (m, 9H, CH_3); 1.31; 1.33; 1.46 and 1.50 (4s, 12H, $4CH_3$-isop); 1.78–1.89 (m, 6H, CH_2); 3.23–3.31 (m, 2H, H5a', H5b′); 3.50 (dd, 1H, $J_{6a,6b} = 14.7$ Hz, $J_{6a,5} = 9.6$ Hz, H6a); 4.10 (ddd, 1H, $J_{4b',4a'} = 11.7$ Hz, $J_{4b',5a'} = 6.5$ Hz, $J_{4b',5b'} = 6.3$ Hz; H4b′); 4.23–4.44 (m, 5H, H4a′, H4, H2; H5, H6b); 4.60 (dd,1H, $J_{3,4} = 2.4$ Hz, $J_{3,2} = 7.5$ Hz, H3); 5.47 (d, 1H, $J_{1,2} = 4.8$ Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.2 (CH_3); 18.3 (d, $J_{CH2,P} = 36.5$ Hz); 24.5, 25.3; 26.2 and 26.3 (CH_3-isop); 28.2 (C5′); 50.3 (C6); 59.4 (C4′); 66.6 (C2); 70.7 (C3); 71.0 (C4); 71.9 (C5); 96.5 (C1); 109.3 and 109.7 [$C(CH_3)_2$]; 197.0 (C2'); HMRS(ESI): *m/z* Calc. for $[C_{21}H_{38}O_5NPS_2Au]Cl$ $[M^+]$ 676.1595, found 676.1613, $[M+H]^+$ Calc. 677.1673, found 677.1635.

6-Deoxy-6-(3-thiazolydyl-2-thione)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (triphenylphosfine)gold(I) **(5)**

Yield, (43 %) as a white solid, m.p. 159–161 °C. IR ν_{max} KBr (cm^{-1}): 3071; 2980; 2935; 2891; 1496; 1245; 1068; 713; Raman ν_{max}: 3060; 2991; 2939; 2896; 1460; 1184; 756; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30; 1.33; 1.46; 1.50 (4 s, 12H, $4CH_3$-isop); 3.23–3.31 (m, 2H, H5a′, H5b′); 3.50 (dd, 1H, $J_{6a,6b} = 14.4$ Hz, $J_{6a,5} = 9.3$ Hz, H6a); 4.10 (ddd, 1H, $J_{4b',4a'} = 11.4$ -Hz, $J_{4b',5a'} = 6.6$ Hz, $J_{4b',5b'} = 6.3$ Hz; H4b′); 4.23–4.41 (m, 5H, H4a′, H4, H2; H5, H6b); 4.60 (dd,1H, $J_{3,4} = 2.4$ Hz, $J_{3,2} = 7.8$ Hz, H3); 5.47 (d, 1H, $J_{1,2} = 4.8$ Hz, H-1); 7.45–7.55 (m, 15H, Ar-PPh_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.5, 25.3; 26.1 and 26.3 (CH_3-isop); 28.1 (C5′); 50.3 (C6); 59.3 (C4′); 66.6 (C2); 70.7 (C3); 71.0 (C4); 71.9 (C5); 96.5 (C1); 109.3 and 109.7 [$C(CH_3)_2$]; 128.5 (C1′′); 129.4 (d, C3′′, C5′′, $J_{3'',P} = J_{5''-P} = 12.0$ Hz); 132.2 (C4′′); 134.3 (d, C2′′, C6′′, $J_{2'',P} = J_{6'',P} = 13.7$ Hz); 196.9 (C2′); HMRS(ESI): *m/z* Calc. for $[C_{33}H_{38}O_5NPS_2Au]Cl$ $[M^+]$ 820.1595, found 820.1627, $[M+H]^+$ Calc. 821.1673, found: 821.1684.

Methyl 5-deoxy-5-(3-thiazolydyl-2-thione)-2,3-*O*-isopropylidene-β-D-ribofuranoside(triethylphosphine)gold(I) (**6**)

Yield, (49 %) as a white solid, m.p. 68–69 °C. IR ν_{max} KBr (cm^{-1}): 2965; 2928; 2875; 1494; 1218; 1061; 780; Raman ν_{max}: 2940; 1450; 1233; 1038; 713; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41-1.26 (m, 9H, CH_3); 1.31 and 1.50 (2s, 6H, $2CH_3$-isop); 1.79–1.90 (m, 6H, CH_2); 3.32 (t, 2H, $J_{5',4a'} = J_{5',4b'} = 7.8$ Hz, H5′); 3.38 (s, 3H, OCH_3); 3.46 (dd, 1H, $J_{5a,5b} = 12.9$ Hz, $J_{5a,4} = 6.3$ Hz, H5a), 4.04–4.13 (m, 1H, H4a′); 4.27–4.48 (m, 3H, H4, H5b, H4b′); 4.64 (d, 1H, $J_{2,3} = 6.0$ Hz, H2); 4.79 (d, 1H, $J_{3,2} = 6.0$ Hz, H3); 4.99 (s, 1H, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.2 (CH_3); 18.2 (d, CH_2, $J_{CH2-P} = 36.5$ Hz); 25.1 and 26.7 (CH_3-isop); 27.8 (C5′); 52.2 (C5); 55.8 (OCH_3); 57.5 (C4′); 82.4 (C2); 84.5 (C3); 85.2 (C4); 110.5 (C1); 112.9 [$C(CH_3)_2$]; 198.0 (C2′); HMRS(ESI): *m/z* Calc. for $[C_{18}H_{34}O_4NPS_2Au]Cl$ $[M^+]$ 620.1332, found 620.1354, $[M+H]^+$ Calc. 621.1411, found 621.1378.

Methyl 5-deoxy-5-(3-thiazolydyl-2-thione)-2,3-*O*-isopropylidene-β-D-ribofuranoside(triphenylphosfine)gold(I) (**7**)

Yield, (40 %) as a white solid, m.p. 136 °C. IR ν_{max} KBr (cm^{-1}): 3056; 2982; 2928; 1486; 1219; 1062; 777; Raman ν_{max}: 3060; 2942; 2840; 1448; 1234; 1027; 716; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 and 1.47 (2 s, 6H, $2CH_3$-isop); 3.31 (t, 2H, $J_{5',4a'} = -J_{5',4b'} = 7.8$ Hz, H5′); 3.37 (s, 3H, OCH_3); 3.47 (dd, 1H, $J_{5a,5b} = 13.2$ Hz, $J_{5a,4} = 6.6$ Hz, H5a), 4.04–4.13 (m, 1H, H4a′); 4.27–4.50 (m, 3H, H4, H5b, H4b′); 4.64 (dd, 1H, $J_{2,3} = 6.0$ Hz, $J_{2,1} = 1.8$ Hz, H2); 4.79 (d, 1H, $J_{3,2} = 6.0$ Hz, H3); 4.99 (d, 1H, $J_{1,2} = 1.8$ Hz, H1); 7.43–7.55 (m, 15H, Ar-PPh_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.1 and 26.7 (CH_3-isop); 27.8 (C5′); 52.2 (C5); 55.8 (OCH_3); 57.5 (C4′); 82.4 (C2); 84.5 (C3); 85.2 (C4); 110.5 (C1); 112.8 [$C(CH_3)_2$]; 128.5 (C1′′); 129.4 (d, C3′′, C5′′, $J_{3''-P} = J_{5''-P} = 11.8$ Hz); 132.2 (C4′); 134.3 (d, C2′, C6′, $J_{2''-P} = J_{6''-P}$ 13.4 Hz); 198.0 (C2′); HMRS(ESI): *m/z* Calc. for $[C_{30}H_{34}O_4NPS_2Au]Cl$ $[M^+]$ 764.1332, found 764.1354, $[M+H]^+$ Calc. 765.1411, found 765.1395.

Synthesis of gold(III) complexes (**8**), (**9**) and (**10**)

To a solution of $K[AuCl_4]$ (0.151 g, 0.4 mmol) in methanol or ethanol (5 mL), ligand (**R**) or ligand (**S**) (0.4 mmol) dissolved in methanol (4 mL) or ligand (**Q**) (0.4 mmol) dissolved in ethanol was slowly added during 4 h. The reaction mixture was stirred at 0 °C in the dark. After 4 h, the products were extracted

with dichloromethane/water. The organic phase was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give of yellow solids, complexes (**8**), (**9**) and (**10**).

Chloride dichloro {6-deoxy-6-[*N*-(2′-amino-ethylamino)]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose}gold(III) **(8)**

Yield, (76 %) as a yellow solid, m.p. 146–158 °C. IR ν_{max} KBr (cm^{-1}): 3453; 2990; 2925; 1066; 516; 357; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35; 1.47 and 1.62 (3 s, 12H, $4CH_3$-isop); 3.16 (s, 1H, NH); 3.53–3.74 (m, 6H, H6a, H6b, H7, H8); 4.23–4.37 (m, 3H, H2, H4, H5); 4.64 (d, 1H, $J_{3,4} = 4.8$ Hz, H3); 5.64 (d, 1H, $J_{1,2} = 4.5$ Hz, H1); 7.56, 7.63 and 8.21 (3s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.4; 25.1; 26.4 and 26.6 (CH_3-isop); 37.7 (C8); 46.3 (C6); 49.6 (C7); 63.9 (C5); 70.5 (C2); 70.7 (C3); 71.4 (C4); 96.1 (C1); 109.9 and 110.5 [$C(CH_3)_2$]; HMRS(ESI): *m/z* Calc. for $[C_{14}H_{26}N_2O_5AuCl_2]Cl$ $[M]^+$ 569.0884, found 569.0891 $[M+H]^+$ Calc. 570.0963, found 570.0909.

Chloride dichloro {methyl 5-deoxy-5-[(*N*-2′-amino-ethylamino)]-2,3-*O*-isopropylidene-β-D-ribofuranoside}gold(III) (**9**)

Yield, (78 %) as a yellow solid, m.p. 116–117 °C. IR ν_{max} KBr (cm^{-1}): 3429; 2987; 2941; 1110; 516; 354; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 and 1.49 (2s, 6H, $2CH_3$-isop); 3.24-3.80 (m, 10H, H5a, H5b, OCH_3, H8, H7, NH), 4.65–4.73 (m, 3H, H2, H3, H4); 5.05 (s, 1H, H1), 7.58 e 8.12 (2s, 2H, NH_2); HRMS(ESI): *m/z* Calc. for $[C_{11}H_{22}O_4N_2AuCl_2]Cl$ $[M]^+$ 513.0622, found 513.0643 $[M+H]^+$ Calc. 514.0700, found 514.2986.

Trichloro[3,4:5,6-di-*O*-isopropylidene-*N*-2-aminoethyl-D-gluconamide]gold(III) (**10**)

Yield, (64 %) as a yellow solid, m.p. 120–124 °C. IR ν_{max} KBr (cm^{-1}): 3426; 2989; 2933; 1659; 1068; 514; 362; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24; 1.34; 1.38; 1.42 (4s, 12H, $4CH_3$-isop); 2.90 (s, 2H, NH_2); 3.43 (s, 2H, H8); 3.71 (s, 2H, H7); 3.97 (s, 2H, H6a, H6b); 4.13 (s, 2H, H4, H5); 4.36 (s, 2H, H2, H3); 7.66 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.5; 27.0; 27.5; (CH_3-isop); 39.8 (C8); 53.6 (C7); 67.7 (C6); 70.7 (C2); 76.8 (C3); 77.1 (C5); 80.2 (C4); 110.3 and 110.7 [$C(CH_3)_2$]; 174.7 (CO); HMRS(ESI): *m/z* Calc. for $C_{14}H_{26}O_6N_2AuCl_3$ $[M-H]^-$ 619.0440, found 619.0433.

Cytotoxicity assay

XTT-based cytotoxicity assay

The cytotoxicity was measured using the in vitro Toxicology Colorimetric Assay Kit (XTT; Roche Diagnostics) according to manufactureŕs instructions. For the evaluation of the cytotoxicity were used four cell lines: a normal human lung fibroblasts (GM07492A), and three cancer cell lines, breast adenocarcinoma (MCF-7), cervical carcinoma (HeLa) and glioblastoma (MO59 J). The cell lines were cultured in HAM-F10 (Sigma-Aldrich) and DMEM (Sigma-Aldrich) (1:1) culture medium supplemented with 10 % fetal bovine serum (Nutricell), antibiotics (0.01 mg/mL streptomycin and 0.005 mg/mL penicillin; Sigma-Aldrich), and 2.38 mg/mL Hepes (Sigma-Aldrich) at 37 °C with 5 % CO_2. For these experiments, the cells (10^4 cells/well) were plated onto 96-well microplates, each well received 100 µL HAM F10/DEMEN medium containing the obtained gold complexes (**1**–**10**), precursors $Au(PEt_3)Cl$, $Au(PPh_3)$, $K[AuCl_4]$ at concentrations ranging from 12.5 to 1600 µM, and cisplatin at concentrations ranging from 3.12 to 400 µM, dissolved in 0.2 % DMSO. Negative (without treatment), solvent (0.2 % DMSO) and positive (25 % DMSO) controls were included. After incubation at 37 °C for 24 h, the medium was removed; cells were washed twice with 100 µL PBS (phosphate buffer saline) and exposed to 100 µL of HAM-F10 medium without phenol red. Then, 25 µL of XTT were added to each well. The microplates were covered and incubated at 37 °C for 17 h. The absorbance of sample was determined by a multi-plate reader (ELISA–Asys–UVM 340/Microwin 2000) at a test wavelength of 450 nm and a reference wavelength of 620 nm. Cell viability was expressed as a percentage of untreated cells, which served as the negative control group and was designated as 100 %. The experiments were performed in triplicate.

Anti-Mycobacterium tuberculosis activity assay

The antimycobacterial activities of ligands, gold complexes and gold salts were assessed against *M. tuberculosis* $H_{37}Rv$ ATCC 27294 (Canetti et al. 1963)

using the micro plate Alamar Blue assay (MABA) (Franzblau et al. 1998). This methodology is nontoxic, uses thermally-stable reagents and shows good correlation with proportional and BACTEC radiometric methods (Vanitta and Paramasivan 2004; Reis et al. 2004). Briefly, two hundred microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96 well plates (Falcon, 3072: Becton–Dickinson, Lincoln Park NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 μL of the Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) and a serial dilution of the compounds was made directly on the plate. The final drug concentrations tested were 0.01–10.0 μL/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for 5 days. After this time, 25 μL of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake Ohio) reagent and 10 % Tween 80 were added to the plate and incubated for 24 h. A blue color in the well was interpreted as absence of bacterial growth and a pink color was scored as growth. The MIC was defined as the lowest drug concentration to give 90 % inhibition of bacterial growth, which prevented a color change from blue to pink.

Results and discussion

The novel ligands (**F**) and (**N**) were prepared by reaction of the corresponding aminoalcohols and excess of carbon disulfide under basic conditions, and were isolated by simple filtration. Ligand (**Q**) was synthesized by reaction of ethylenediamine and ester (**P**) and isolated by column chromatography. Gold(I) complexes (Scheme 2) were synthesized by reaction of the corresponding ligands with $Au(PEt_3)Cl$ or $Au(PPh_3)Cl$. Gold(III) complexes (Scheme 3) were obtained by addition of the corresponding ligands to $K[AuCl_4]$.

The compounds were characterized using a combination of several methods that included ^{1}H NMR, ^{13}C NMR, infrared, Raman, high-resolution mass spectra and cyclic voltammetry.

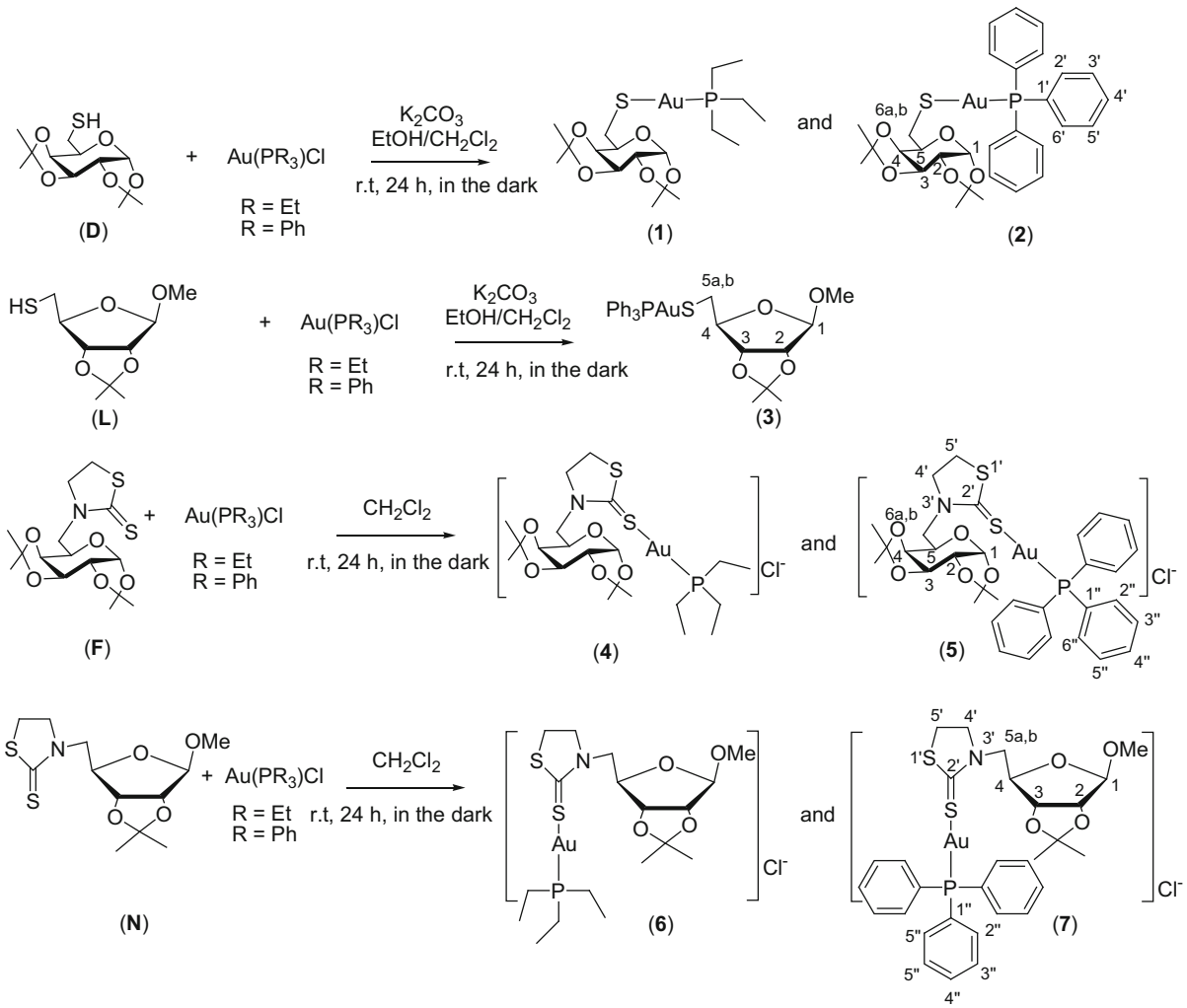
The absorption corresponding to *v*SH, at approximately 2565–2574 cm^{-1} was not observed in the infrared spectra of gold(I) complexes (**1**), (**2**) and (**3**) indicating that the ligands (**D**) and (**L**) are attached to the metal center in the form of thiolates. Weak bands corresponding to gold-to-ligand stretching modes were also identified in the low wave number region in the spectra of these complexes (319, 331, 327, *v*(Au–S) cm^{-1}). Significant changes in the absorption corresponding to $vC = S$ was not observed in the IR and Raman spectra of complexes (**4**), (**5**), (**6**) and (**7**) in comparison to the spectra of ligand (**F**) and ligand (**N**). The presence of absorptions around 354–363 and 561–514 cm^{-1} attributed to *v*Au–S and to *v*Au–N, respectively, were observed in the IR spectra of gold(III) complexes suggest the formation of these compounds.

The ^{1}H NMR and ^{13}C NMR spectra of complexes (**1**–**2**) were analyzed and compared to the spectra of the free ligands. Table 1 shows the ^{1}H and ^{13}C chemical shifts (δ) of the ligands (**D**) and (**L**) and their complexes (**1**), (**2**) and (**3**). No changes were observed in the ^{1}H NMR spectra of compounds (**4**-**7**) after coordination. In the ^{13}C NMR spectra, the signal corresponding to the thione group showed a small chemical shift, on the order of δ 0.2 ppm.

In the ^{1}H NMR spectra of complexes (**1**), (**4**) and (**6**) two signals were observed in the following regions: δ 1.78–1.90 ppm (CH_2) and δ 1.13–1.25 ppm (CH_3) corresponding to hydrogens of the PEt_3 group. For complexes (**2**), (**3**), (**5**), and (**7**) signals were observed in the δ 7.41–7.55 ppm region corresponding to aromatic hydrogens of the PPh_3 group.

In the ^{1}H NMR spectra of the ligand (**Q**) signals were observed at δ 3.41 (H7) and δ 3.20 (H8) ppm, whereas in the spectrum of complex (**10**) the corresponding signals appeared at δ 3.71 (H7) and δ 3.43 (H8) ppm, showing a chemical shift to higher frequency due to the presence of the metal.

Results of the high-resolution mass spectra and NMR suggested that the obtained complexes were in the 1:1 metal/ligand ratio. NMR and infrared spectra showed that in complexes (**1**–**3**) the ligands are in the thiolate form. The high-resolution mass spectrum of gold(III) complexes (**8**) and (**9**) clearly revealed peaks corresponding to the $[Au(ligand)Cl_2]^+$ species (*m/z* 569.0891) and (*m/z* 513.0643), respectively. Data obtained for complex (**10**) suggested that this compound exhibits a neutral structure with three chlorides and a nitrogen atom of the NH_2 group from the amide moiety coordinated to the gold(III) center. Similar gold(III) complexes with 3 Cl coordinated to the metal center have been previously reported in the literature (Bruni et al. 1999).



Scheme 2 Synthesis of gold(I) complexes **1**–**7**

The complexes are insoluble in water and soluble in dichloromethane and DMSO. Several attempts to obtain crystals of complexes (**1**), (**2**), and (**3**) were performed and showed that the complex had a tendency to decompose when dissolved in organic solvents, releasing ligand, $Au(PEt_3)Cl$ or $Au(PPh_3)Cl$ and a yellow precipitate. According to the literature (Coates et al. 1966) it could be characterized as an insoluble polymer of gold(I) mercaptide. Stability of the complex is related to the chemical structure of the sulfur ligands attached to the gold atom. Complex (**10**) was highly unstable to moisture and light and showed a tendency to form metallic gold when in solution for an extended period of time.

The electrochemical behavior of gold(I) complexes (**4**–**7**) and gold(III) complexes (**8**–**10**) were studied in DMF solutions, using cyclic voltammetry and compared to that of $KAuCl_4$. In the cyclic voltammograms of gold(III) complexes one cathodic peak centered at −0.02, 0.06 and 0.04 V versus $Ag/AgCl_{(s)},KCl_{(sat)}$ respectively, related to gold(II) → gold(I) reduction, which is absent in the ligand's cyclic voltammograms but present in $KAuCl_4$, was observed. The observation of a gold(II) → gold(I) process indicates that Au(III) was present. Thus, the results suggested the presence of Au(III) as the central ion in the obtained complexes. The cyclic voltammograms of complexes (**10**), Ligand (**Q**) and $KAuCl_4$ are shown in Fig. 2. The redox potentials of these complexes are summarized in Table 2.

The cyclic voltammograms of complexes (**4**), (**5**), (**6**) and (**7**) were compared to that of $KAuCl_4$ and similarities were not found. In addition, one cathodic

Scheme 3 Synthesis of gold(III) complexes **8–10**

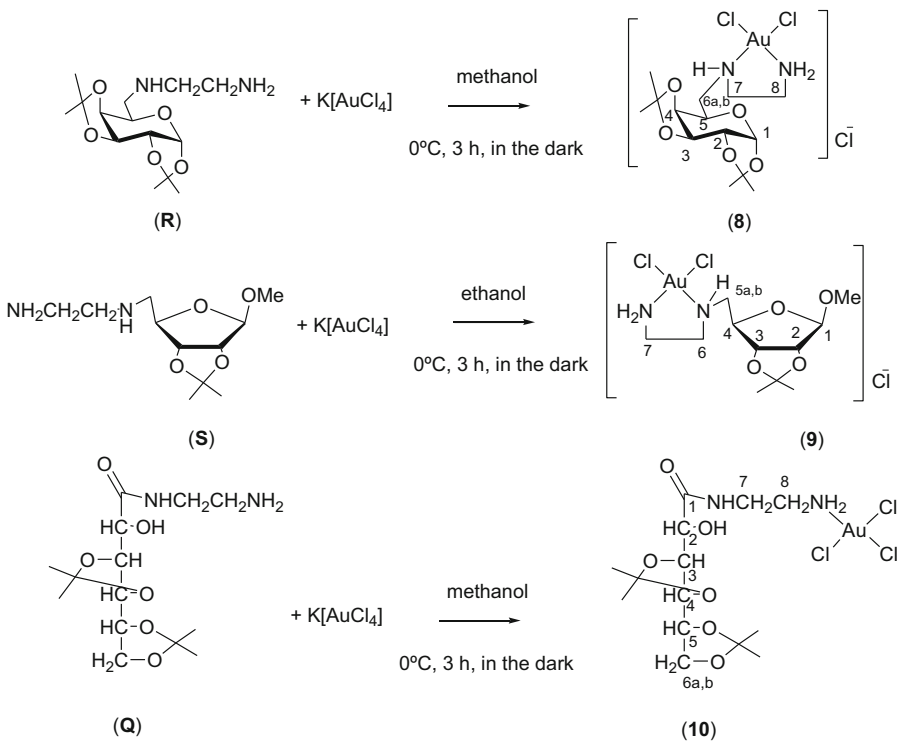


Table 1 ^{13}C and ^{1}H NMR chemical shifts for compounds (**D**), (**L**), (**1**), (**2**) and (**3**)

Compound	Chemical shifts (ppm)					
	H5a	H5b	H6a	H6b	C5	C6
(A) ligand	–	–	2.61–2.81	2.61–2.81	–	25.1
(**1**) complex	–	–	3.11	3.21	–	27.8
(**2**) complex	–	–	3.19	3.30	–	27.7
(**B**) ligand	2.73–2.82	2.48–2.59	–	–	29.9	–
(**3**) complex	3.23–3.26	3.01–3.10	–	–	31.9	–

peak centered at −1.30 V versus $Ag/AgCl_{(s)},KCl_{(sat)}$ was observed to the complexes (**4**), (**5**), (**6**) and (**7**), which may be attributed to gold(I) → gold(0). Thus, the results suggested the presence of Au(I) in the structure of these complexes. The cyclic voltammograms of complex (**5**), Ligand (**F**) and $Au(PPh_3)Cl$ are shown in Fig. 3.

Biological testes

Cytotoxic activity

Messori et al. and Bruni et al. have studied the cytotoxic properties of some selected gold(III) compounds with bidentate ligands containing diamines, namely $[Au(en)_2]Cl_3$, $[Au(dien)Cl]Cl_2$. In 2014, Al-Jaroudi et al. described the cytotoxic properties of gold(III) complexes of type $[(DACH)Au(en)]Cl_3$. All of the mentioned gold(III) complexes exhibited good potential for the treatment of cancer.

A variety of auranofin analogues and phosphine gold(I) compounds containing S-donor ligands has been developed and shown to possess potent cytotoxic activities (Tienkink 2002; Sun and Che 2009). In this study, a new series gold(I) (**1–7**) and gold(III) complexes (**8–10**) containing carbohydrates ligands were subjected to in vitro cytotoxic evaluation against HeLa, MCF-7, MO59J cancer cell lines.

To ascertain the cytotoxicity of the compounds we performed XTT assays in GM07492-A, HeLa,

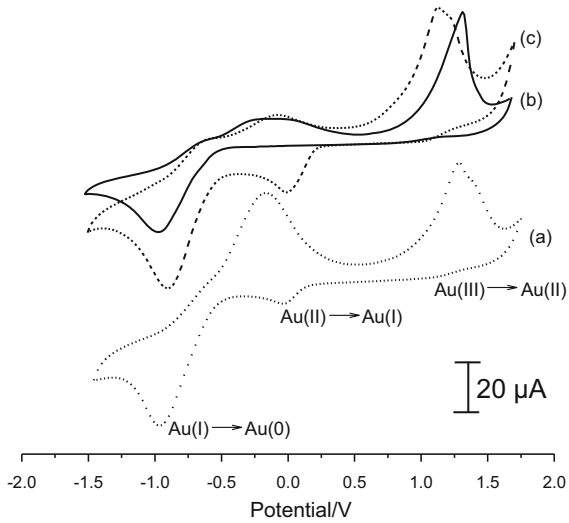


Fig. 2 Cyclic voltammograms of 1×10^{-3} mol L^{-1} $KAuCl_4$ (**a**), ligand (**Q**) (**b**) and complex (**10**) (**c**). Experimental conditions: working electrode—glass carbon, 100 mmol L^{-1} $NaClO_4$, reference electrode—$Ag/AgCl_{(s)}$,$KCl_{(sat)}$ and scan rate 100 mV s^{-1}

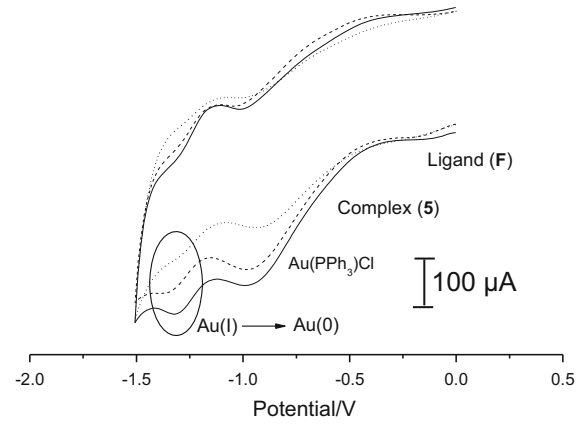


Fig. 3 Cyclic voltammograms of 1.10^{-3} mol L^{-1} ligand (**F**) and complex (**5**). Experimental conditions: working electrode—glass carbon, 100 mmol L^{-1} $NaClO_4$, reference electrode—$Ag/AgCl_{(s)}$, $KCl_{(sat)}$ and scan rate 100 mV s^{-1}

MCF-7, MO59J cell lines. The cultures received the gold complexes (**1**–**10**), $Au(PPh_3)Cl$, $Au(PPh_3)Cl$, $K[AuCl_4]$ precursors and cisplatin treatment for 24 h. The viability of the cells was determined, establishing a relationship between the absorbance obtained in the treated and untreated (negative control) groups. IC_{50} values, calculated from the cell viability dose are shown in Table 3.

In general, compounds showed cytotoxic effects against the studied tumor cell lines. All the gold(I) complexes were more cytotoxic than cisplatin in the tumor cell lines, except complex (**3**) against (MO59 J) cells.

The alkyl phosphine complexes (**1**), (**4**) and (**6**) were more cytotoxic compared to aryl phosphine complexes (**2**), (**5**) and (**7**). Complex (**4**) was about 6.6 times more cytotoxic than complex (**5**) in MO59 J cells. Comparing gold(I) complexes and gold(III) complexes, the prior were more cytotoxic showing IC_{50} values from 2 to 10 times greater than the values for gold(III) complexes. In addition, it is possible to notice in Table 3 that the precursor gold salts already have this difference in cytotoxicity.

Different organic moieties can modify the biological activity of the complexes but the presence of a thiazolidine ring in this case does not improve the antitumor cytotoxic activity as showed in Table 3 for complexes (**1**), (**2**) and (**3**) compared to respective thiazolidine related complexes (**4**), (**5**) and (**7**).

The presence of carbohydrate ligands showed a structure–activity relationship. Comparing complexes (**2**), (**4**) and (**5**) which carry ligands derived from D-galactose and the respective complexes (**3**), (**6**) and (**7**) which carry ligands derived from D-ribose we can

Table 2 Cyclic voltammetry data of ligands (**R**), (**S**), (**Q**) and gold(III) complexes

E (V)	Ligand (R)	Complex (8)	Ligand (S)	Complex (9)	Ligand (Q)	Complex (10)	$K[AuCl_4]$
E_{pa}	−0.614	−0.644	−0.675	−0.614	−0.644	−0.600	−0.695
	−0.107	−0.097	−0.178	−0.327	0.056	−0.208	−0.208
	1.335	1.131	1.123	1.304	1.263	1.254	1.243
E_{pc}	−0.958	1.049	−0.838	0.992	−0.867	1.096	1.012
		−0.020		0.040		0.060	−0.076
		−0.908		−0.776		−0.756	−0.999
				−1.172			

Table 3 Cytotoxic activities against cell line [IC_{50} (μM)]

Compounds	Non-tumor cells IC_{50} (μM)	Tumor cells IC_{50} (μM)		
	GM07492A	HeLa	MCF-7	MO59J
(**1**)	13.1	<12.5	<12.5	<12.5
(**2**)	39.0	35.7	15.2	38.3
(**3**)	13.8	15.0	19.9	17.3
(**4**)	13.5	14.2	<12.5	12.5
(**5**)	253.4	56.8	68.9	82.7
(**6**)	<12.5	14.6	<12.5	<12.5
(**7**)	24.7	48.4	58.1	36.9
(**8**)	117.6	99.7	94.7	110.4
(**9**)	115.0	98.7	57.9	80.4
(**10**)	>1600.0	>1600.0	>1600.0	>1600.0
$Au(PPh_3)Cl$	113.8	117.3	136.6	112.0
$Au(PEt_3)Cl$	15.4	13.0	13.1	<12.5
$K[AuCl_4]$	89.0	128.8	107.3	77.5
Cisplatin	69.0	77.7	111.3	80.1

observe that the ribose derivative complexes are more active in all cell lines used in this study.

Among all the studied compounds, complex (**1**) was one of the most cytotoxic.

Antitubercular activity

Considering that auranofin, a gold complex containing carbohydrate, is a promising agent that might be repurposed for the treatment of bacterial infections (Casseta et al. 2014), the compounds described herein were tested for their antitubercular activity.

All the tested gold complexes and gold salts exhibited activity against *M. tuberculosis* (Table 4). Gold(I) compounds (**1**), (**2**) and (**3**) displayed the best antiproliferative activity with MIC_{90} of 2.5, 3.12, and 5.0 μg/mL, respectively. Triethylphosphine complexes (**4**) and (**6**) were more active than their triphenylphosphine analogues (**5**) and (**7**). However, the same relationship was not observed for complexes (**1**) and (**2**) being compound (**2**) which is a triphenylphosphine derivative, more active than its triethylphosphine analogue (**1**). Eiter et al. showed in their studies that the gold(I) complex analogue of triethylphosphine was active in relation to the triphenylphosphine derivative.

There are examples in the literature showing thiolates compounds presenting high antitubercular activity (Cuin et al. 2011). As a matter of fact, we have

Table 4 The in vitro activity of ligands (**D**, **F**, **G**, **L**, **N**, **O**, **Q**), complexes (**1–10**) and $Au(PPh_3)Cl$, $Au(PEt_3)Cl$ e $K[AuCl_4]$ against *M. tuberculosis* H37Rv strain (ATCC 27294, susceptible to rifampicin)

Compounds	MIC_{90} (μg/mL)
(**D**) Ligand	Resistant
(**1**) Gold(I) complex	3.12
(**2**) Gold(I) complex	2.50
(**L**) Ligand	Resistant
(**3**) Gold(I) complex	5.00
(**F**) Ligand	Resistant
(**4**) Gold(I) complex	12.50
(**5**) Gold(I) complex	50.00
(**N**) Ligand	Resistant
(**6**) Gold(I) complex	6.25
(**7**) gold(I) complex	100.00
(**G**) Ligand	Resistant
(**8**) Gold(III) complex	100.00
(**O**) Ligand	Resistant
(**9**) Gold(III) complex	25.00
(**Q**) Ligand	Resistant
(**10**) Gold(III) complex	100.00
$K[AuCl_4]$	50.00
$Au(PPh_3)Cl$	25.00
$Au(PEt_3)Cl$	6.25
Rifampicin	1.00

found that the thiolate compounds (**1**–**3**) exhibited the best antitubercular activity. In general, gold(I) compounds showed higher activity than gold(III) compounds. It was observed that complexation favored antibacterial activity, since the complexes were more active than their salts in most of the cases and none of the free ligands showed biological activity.

Conclusions

The compounds obtained in this work were characterized by different techniques. Spectroscopic data for the gold(I) complexes containing thiosugars or thiazolidines derived from carbohydrates and a phosphine unit indicate that the structures present an S–Au–P arrangement.

The gold(III) compounds were highly unstable. Spectroscopic evidences suggested that complexes (**8**) and (**9**) present the general formula $[(\text{ligand})AuX_2]^+$, where the ligand is coordinated to gold in the bidentate fashion while complex (**10**) occurred in the neutral form and present three chloride ions in the coordination sphere in addition to the carbohydrate ligand.

Concerning the cytotoxicity, a structure–activity relationship was determined considering that gold(I) complexes showed a higher activity than gold(III) complexes. Ribose and alkyl phosphine complexes were more cytotoxic than their galactose and aryl phosphine analogues. Gold(I) complexes were more active than cisplatin in all the tested tumor cell lines.

In general, gold(I) alkyl phosphine complexes were also more active against *M. tuberculosis*. The presence of thiazolidine ring did not improve the cytotoxicity or the antitubercular activity. Several of the investigated complexes exhibited antitubercular activity. The coordination was effective on improving the activity since the complexes were more active than the free ligands and the original gold salts.

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