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Anticancer activity and X-ray structure determination of gold(I) complexes of 2-(diphenylphosphanyl)-1-aminocyclohexane

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ABSTRACT

Phosphane gold(I) complexes, [Au(ACP)Cl] (**1**) and [Au(ACP)(S_2CNR_2)] (**2**–**4**) where ACP = 2-(diphenylphosphanyl)-1-aminocyclohexane or (2-aminocyclohexyl)diphenylphosphane, and R = methyl, ethyl, benzyl, were synthesized and characterized by elemental analysis, FTIR and multinuclear NMR spectroscopy. The molecular structure of one of the compounds, [Au(ACP)Cl] (**1**), was determined by single crystal X-ray diffraction analysis, which revealed a linear geometry around the Au(I) center. The crystal structure is stabilized by N–H···Cl hydrogen bonding interactions. The *in vitro* cytotoxicity of the complexes was evaluated against three cancer cells, A549 (human lung cancer), HeLa (human cervical cancer) and HepG2 (human liver cancer) cell lines. Three of the four complexes showed excellent *in vitro* cytotoxicity; their inhibition effect is much greater than that of cisplatin.

1. Introduction

Gold(I) compounds have played an important role in the treatment of rheumatoid arthritis for many years [1–5]. As time evolved, it was noticed that the receivers of chrysotherapy for arthritis exhibited lower evidence of malignancy rates and thus it was thought that gold compounds might have anti-cancer properties [6,7]. Later, the orally active anti-arthritic drug auranofin [8–10] and tetrahedral gold(I) complexes containing disphosphane ligands [11–13], particularly [Au(dppe)$_2$]Cl [11] (dppe = 1,2-bis (diphenylphosphano)ethane), were found to exhibit potent antitumor activity against a range of tumor models in mice, including ovarian cancer cells and a cisplatin-resistant subline of 388 leukemia. The outcomes of such studies inspired significant interest in the investigation of the cytotoxic properties of gold(I) complexes of phosphane and thiolate ligands [14–30]. Structural studies of these complexes support the strong tendency of gold(I) ions to form stable complexes with polarizable soft donor atoms, such as phosphorus and sulfur [20–22,27–30].

Phosphanogold(I) dithiocarbamate complexes have been considered as a novel class of potential anticancer agents because of their remarkable cytotoxicity and tumor specificity [20,26–29]. Keter et al. [20] reported the anticancer properties of a series of phosphanogold(I) complexes of dithiocarbamates (L), namely [AuL(PPh_3)] and [Au_2L_2(diphosphanes)]. The stability of these complexes depends on the nature of the phosphane ligand used. Triphenylphosphane and diphenylphosphanoalkyl ligands with alkyl chains longer than ethyl produced stable gold dithiocarbamates in solution, but the (diphenylphosphano)ethanegold(I) complexes, being unstable, were found to transform into an Au_{18} cluster. The complexes, which were stable in solution displayed activity against HeLa cancer cells, suggesting the importance of the P–Au–S moiety in conferring activity to the compounds [9,16,20]. These investigations were motivated by the desire to tailor the lipophilicity of the gold(I) complexes so as to target mitochondria [5,26,31].

It has been established that gold compounds, such as auranofin, act against cancer cells *via* mitochondria by inhibiting its enzyme thioredoxin reductase (TrxR) with high potency and specificity [10,26,31,32]. The inhibition of TrxR activity demonstrated for gold

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compounds is evidently based on the covalent binding of the gold center to a selenocysteine residue in the active site of the enzyme [4,5,31].

Recently, our group has reported the structural elucidation and anticancer activity of several gold(I) dithiocarbamate complexes [28–30,33]. In these complexes the gold(I) atom possesses a linear geometry and most of the complexes displayed significantly superior *in vitro* cytotoxic effects against A549, HeLa or HepG2 cell lines, as compared to cisplatin. To further improve our knowledge on the coordination chemistry and cytotoxicity of such complexes, we report here the synthesis, spectroscopic characterization and antiproliferative properties of four novel gold(I) complexes derived from a phosphane, 2-(diphenylphosphanyl)-1-aminocyclohexane (ACP), and three dithiocarbamate ligands. The X-ray structure of one of the compounds, [Au(ACP)Cl] (**1**), is also presented. The possible structures of the other complexes and the resonance assignments are shown in Scheme 1.

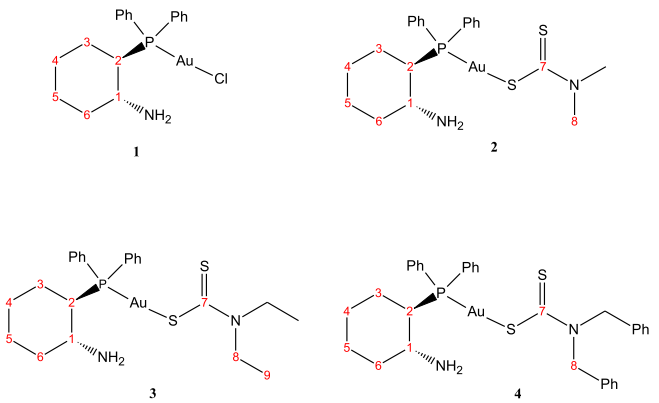
2. Experimental

2.1. Materials

Sodium tetrachloridoaurate(III) dihydrate ($NaAuCl_4{\cdot}2H_2O$), sodium salts of dimethyldithiocarbamate dihydrate, diethyldithiocarbamate and dibenzyldithiocarbamate, ethanol, acetone and dichloromethane were purchased from Sigma Aldrich, Co., United States. (R_1,R_2)-2-(diphenylphosphanyl)-1-aminocyclohexane (ACP) was purchased from Strem Chemicals Inc., Massachusetts, United States, while dimethylsulfide was purchased from Fluka AG, St. Gallen, Switzerland. All solvents were of analytical grade and were used without further purification.

2.2. Instrumentation

Elemental analysis was carried out on a Perkin Elmer Series 11 (CHNS/O) Analyzer 2400. The solid-state FTIR spectra of the free ligands and their gold(I) complexes were recorded on a Perkin Elmer FTIR 180 spectrophotometer over the range 4000–400 cm^{-1} at a resolution of 4.0 cm^{-1}. The ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a JEOL-LA 500 NMR spectrophotometer, operating at 500.0, 125.65 and 200.0 MHz respectively, corresponding to a magnetic field of 11.74 T. The ^{13}C NMR spectra were obtained using ^1H broadband decoupling with the following spectral conditions: 32 k data points, 1 s acquisition time, 2.5 s pulse delay, and 5.12 μs pulse width. All spectra were recorded at 297 K in $CDCl_3$. For the ^1H and ^{13}C NMR spectra, tetramethylsilane (TMS) was used as an internal standard, while the ^{31}P NMR chemical shifts were measured relative to an external reference (H_3PO_4 in D_2O) at δ 0.00 ppm.



Scheme 1. The structures of the prepared gold(I) complexes along with the resonance assignments.

2.3. Synthesis of the complexes

The parent compound, $(CH_3)_2S$-AuCl, was prepared by the previously reported method [34]. The white product was washed twice with ethanol (5.0 mL) and three times with diethyl ether (10 mL), then dried in the dark and stored in a fridge. Yield = 91%. Calc. for C_2H_6AuClS (294.55 g/mol): C, 8.35; H 2.13. Found: C, 8.12; H, 1.83%. ^1H NMR ($CDCl_3$, ppm) δ: 2.75 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm) δ: 25.3 [34].

Complex **1** was synthesized by adding 0.5 mmol of 2-(diphenylphosphanyl)-1-aminocyclohexane (ACP) in 10 mL dichloromethane dropwise to a solution of 0.5 mmol $(CH_3)_2S$-AuCl in 5.0 mL of dichloromethane. Mixing resulted in a colorless solution that was stirred for 30 min. The solution was then concentrated by slow evaporation at room temperature. The product, obtained as a white solid, was recrystallized from a dichloromethane/ethanol mixture and dried overnight in a vacuum. Yield = 87%.

Calc. for **1**, $C_{18}H_{22}NPAuCl$ (515.77 g/mol): C, 41.91; H, 4.30; N, 2.72. Found: C, 41.17; H, 3.85; N, 2.34%. IR (cm^{-1}): ν(N–H) 3461, 3324; $\nu(CH_2)$ 2935_{asym}, 2850_{sym}, ν(C–H) 1315_{bend}, δ(N–H) 1572, ν(P–C) 1242. ^1H NMR ($CDCl_3$, ppm) δ: 1.97 (s, NH), 2.54 (m, C(1)H), 3.15 (m, C(2)H), 1.74 (m, C(3)H), 1.33 (m, C(4)H), 1.22 (m, C(5)H), 1.42 (m, C(6)H), 7.47–7.94 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm) δ: 43.54 C(1), 56.01 C(2), 37.65 C(3), 25.65 C(4), 24.73 C(5), 28.10 C(6), 128.96–134.84 C(C_6H_5). ^{31}P NMR ($CDCl_3$, ppm) δ: 41.84.

For compounds **2**–**4**, to a 1:1 stirred solution of $(CH_3)_2S$-AuCl and phosphane (ACP) in 15 mL dichloromethane, the corresponding sodium dithiocarbamate ligand (0.5 mmol) in 10 mL ethanol was added at room temperature with continuous stirring for 2 h. The mixture was filtered, and the clear colored solution was kept at room temperature for slow evaporation. The yellow or orange solids obtained were recrystallized from acetone/dichloromethane and dried overnight in a vacuum. Yield = 85–88%.

2.3.1. Analysis

Calc. for **2**, $C_{20}H_{28}AuN_2PS_2$ (600.53 g/mol): C, 42.00; H, 4.69; N, 4.66; S, 10.67. Found: C, 41.64; H, 4.77; N, 4.40; S, 10.40%. IR (cm^{-1}): ν(N–H) 3461, 3334; $\nu(CH_2)$ 2927_{asym}, 2851_{sym}, ν(C–H) 1246_{bend}, δ(N–H) 1615, ν(C–N) 1486, ν(C=S) and ν(P–C) 1134, 1099. ^1H NMR ($CDCl_3$, ppm) δ: 1.92 (s, NH), 3.35 (m, C(1)H), 3.38 (m, C(2)H), 1.87 (m, C(3)H), 1.30 (m, C(4)H), 1.29 (m, C(5)H), 1.45 (m, C(6)H), 3.52 (m, C(8)H), 7.47–8.06 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm) δ: 45.29 C(1), 54.55 C(2), 40.96 C(3), 25.18 C(4), 24.04 C(5), 30.92 C(6), 207.51 C = S(7), 50.53 C(8), 128.97–134.05 C(C_6H_5). ^{31}P NMR ($CDCl_3$, ppm) δ: 41.68.

Calc. for **3**, $C_{23}H_{32}AuN_2PCS_2$ (640.59 g/mol): C, 44.99; H, 5.03; N, 4.37; S, 10.01. Found: C, 44.64; H, 4.77; N, 4.40; S, 10.40%. IR (cm^{-1}): ν(N–H) 3461, 3334; $\nu(CH_2)$ 2927_{asym}, 2851_{sym}, ν(C–H) 1264_{bend}, δ(N–H) 1610, ν(C–N) 1496, ν(C=S) and ν(P–C) 1068, 984. ^1H NMR ($CDCl_3$, ppm) δ: 1.93 (s, NH), 2.93 (m, C(1)H), 3.46 (m, C(2)H), 2.32 (m, C(3)H), 1.35 (m, C(4)H), 1.41 (m, C(5)H), 1.83 (m, C(6)H), 3.54 (s, C(8)H), 1.33 (s, C(9)H) 7.46–8.12 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm) δ: 44.12 C(1), 54.87 C(2), 39.55 C(3), 25.11 C(4), 24.15 C(5), 29.65 C(6), 204.16 C = S(7), 52.25 C(8), 12.1 C(9), 128.38–134.65 C(C_6H_5). ^{31}P NMR ($CDCl_3$, ppm) δ: 40.15.

Calc. for **4**, $C_{33}H_{36}AuN_2PS_2$ (752.72 g/mol): C, 52.65; H, 4.82; N, 3.72; S, 8.51. Found: C, 52.04; H, 4.25; N, 3.81; S, 8.06%. IR (cm^{-1}): ν(N–H) 3461, 3334; $\nu(CH_2)$ 2923_{asym}, 2852_{sym}, ν(C–H) 1210_{bend}, δ(N–H) 1600, ν(C–N) 1437, ν(C=S) and ν(P–C) 1099, 973. ^1H NMR

($CDCl_3$, ppm) δ: 1.7 (s, NH), 3.25 (m, C(1)H), 3.88 (m, C(2)H), 2.02 (m, C(3)H), 0.88 (m, C(4)H), 1.46 (m, C(5)H), 1.84 (m, C(6)H), 4.71, 5.11 (d, C(8)H), 7.48–8.11 (m, 20H, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm) δ: 43.65 C(1), 55.88 C(2), 37.06 C(3), 25.74 C(4), 24.45 C(5), 27.89 C(6), 210.17 C = S(7), 58.40 C(8), 127.82–135.92 C(C_6H_5). ^{31}P NMR ($CDCl_3$, ppm) δ: 39.18.

2.4. Single crystal structure determination

Suitable crystals of complex **1** were obtained as colorless rods from a dichloromethane/ethanol mixture. The X-ray data were collected at 173 K on a Stoe IPSD 2 Image Plate Diffraction System [35] connected with a two-circle goniometer and using a MoKα graphite monochromator (λ = 0.71073 Å). The structure was solved by the SHELXS-2014 program [36]. The refinement and further calculations were carried out with SHELXL-2014 [36]. A semi-empirical absorption correction was applied using the MUL scan ABS routine in PLATON [37]. The crystal structure and crystal packing were drawn using Mercury software [38]. The crystal data and refinement details are given in Table S1 (Supporting Information).

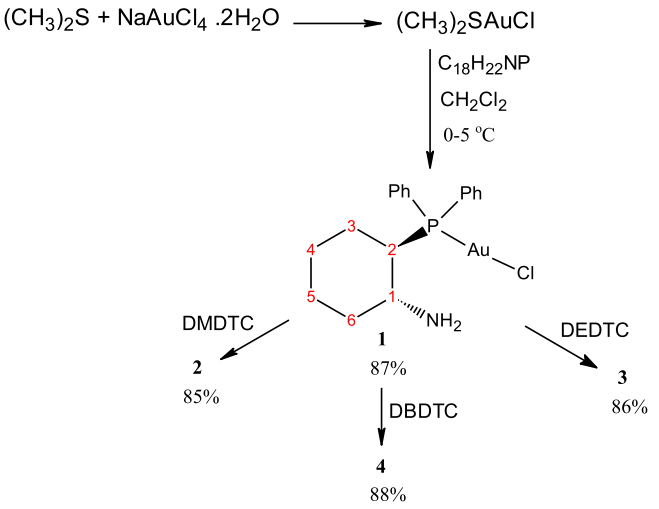
2.5. Antiproliferative study

The cell growth inhibition effects of complexes **1**–**4** and cisplatin were measured by a Cell Titer-Glo® luminescence-based assay against the A549 (human lung carcinoma), HeLa (human cervical cancer) and HepG2 (human liver cancer) cell lines according the manufacture's protocol. Briefly, cell suspensions were added to each well of a 384-w plate at a suitable density (total volume 40 μL). The margin wells of the plate were filled with PBS buffer. The gold compounds were added at various concentrations in triplicate (added 10 μL compound solutions to the plate) then the plate was incubated for 72 h in a 5% CO_2 incubator at 37 °C. After that, the Cell Titer reagent was added to each tested well and stirred for 2 min on an orbital shaker. The plate was shortly centrifuged for 30 s and incubated at room temperature for an additional 10 min to stabilize the luminescent signal. Luminescence signals were detected on PHERAstar Plus. Data acquisition and analysis were performed using the Microsoft Excel (version 2003) program and GraphPad Prism 6. The potential effect of the testing compounds on cell growth inhibition, expressed as IC_{50} values, was calculated by the formula below: Cell growth inhibition % = 100–100 * (Luminescence $_{Compound}$)/(Luminescence $_{DMSO}$). Cell viability % = 100 * (Luminescence $_{Compound}$)/(Luminescence $_{DMSO}$).

3. Results and discussion

The reaction of 2-(diphenylphosphanyl)-1-aminocyclohexane (ACP) with $(CH_3)_2$S-AuCl in a 1:1 M ratio yielded the complex [Au(ACP)Cl] (**1**) as colorless crystals. The mixed ligand complexes **2**–**4** were prepared by addition of one equivalent of a dithiocarbamate ligand to a 1:1 mixture of $(CH_3)_2$S-AuCl and the phosphane. The collected products have the composition [Au(phosphane)(dithiocarbamate)], as indicated by elemental analysis. The structure of complex **1** was established by single crystal X-ray diffraction, while complexes **2**–**4** are assumed to be mononuclear molecules possessing a linear geometry at the gold center [20,26–29]. The procedure for the synthesis of the complexes is explained in Scheme 2.

Selected IR frequencies of the synthesized gold(I) complexes are given in the experimental section. In IR spectra of all the complexes (**1**–**4**), the N–H stretching bands of the amino group of the phosphanes were observed around 3400 and 3340 cm^{-1}. The NH_2 bending vibrations were detected at about 1600 cm^{-1}. The ν(P–C) band of ACP [39] and the band due to the –C═S moiety of the



Scheme 2. Synthetic summary of the gold(I) complexes **1**–**4**.

dithiocarbamate ligands [39] are overlapped and appear as a single peak around 1100 cm^{-1}. The C–N stretching vibration of the dithiocarbamate (N–CSS^-) group is observed near 1500 cm^{-1} [28–30]. This value defines a carbon–nitrogen bond order that is intermediate between a single bond (ν = 1350–1250 cm^{-1}) and a double bond (ν = 1690–1640 cm^{-1}) [40]. The aromatic and aliphatic C–H stretching bands of medium intensity are observed in the regions of 3000 and 2900 cm^{-1} respectively.

In ^{1}H NMR spectra of the complexes, the C–H hydrogens of ACP attached to the nitrogen and phosphorus atoms resonate around 2.5–3 and 3 ppm respectively. The benzylic methylene protons in **4**, being diastereotopic, give two signals at δ = 4.7 and 5.1 ppm. The other aliphatic protons appear as multiplets between 1 and 2 ppm. The aromatic hydrogens are observed between 7 and 8 ppm. In ^{13}C NMR spectra of complexes, the carbon atoms attached to the phosphorus atom appeared as doublets due to coupling with the ^{31}P nuclei. The C═S resonances of the dithiocarbamate ligands were observed at the most downfield position, above 200 ppm. The appearance of this peak indicates the complexation of the dithiocarbamates to the gold(I) center. The next upfield resonances are for the alkyl carbon atoms attached to the dithiocarbamate moiety. The remaining methyl or methylene moieties are detected between 10 and 30 ppm. The aromatic signals of the ACP phosphane and dibenzyl groups were observed in the region of 120–135 ppm. The ^{31}P NMR chemical shifts for complexes **1**–**4** are observed near 40 ppm.

3.1. X-ray structure of complex *1*

The molecular structure of complex **1** is depicted in Fig. 1. Selected bond lengths and bond angles are given in Table 1. The asymmetric unit of the complex consists of two independent mononuclear molecules. The stereochemistry of the two independent molecules is the same and the structure is pseudo centrosymmetric with the space group $P2_1$. In each complex molecule ([Au($C_{18}H_{22}$NP)Cl]), the Au(I) atom is almost linearly coordinated to the phosphorus atom of a phosphane molecule and a Cl^- ion, with a ∠P1-Au-Cl1 angle of 176.93(17)°. The single crystal structure analysis of a Cy_3P (Cy = cyclohexyl) complex, [Cy_3P-Au(thiourea)]Cl [41] revealed that the geometry at gold(I) ion deviated significantly from linearity, with a P-Au-S bond angle of 168.54(9)°. The deviation from linearity was ascribed to an intramolecular Au···NH_2(thiourea) contact with a distance of 3.418(3) Å. No such contact of the Au(I) ion with the NH_2 group was observed in the case of complex **1**. The phosphane ligand binds

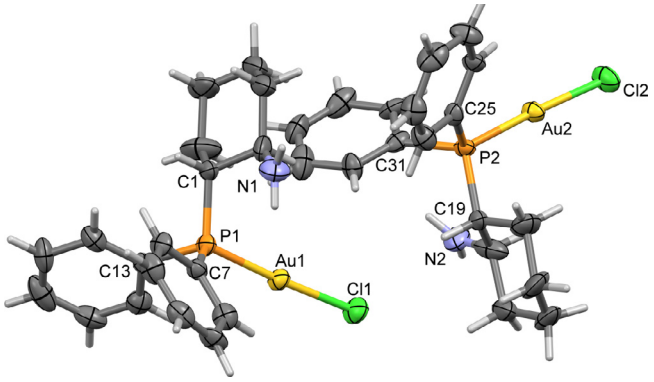


Fig. 1. ORTEP diagram of complex **1** with the partial atomic labelling scheme, showing 30% probability ellipsoids.

Table 1
Selected bond lengths and bond angles for complex **1**.

Bond Lengths (Å)		Bond Angles (°)	
Au1–Cl1	2.297(5)	P1–Au1–Cl1	176.93(17)
Au1–P1	2.243(4)	Au1–P1–C1	110.5(5)
P1–C1	1.825(16)	Au1–P1–C7	114.0(5)
P1–C7	1.817(13)	Au1–P1–C13	113.2(5)
P1–C13	1.812(12)	C1–P1–C7	109.6(7)
C2–N1	1.413(17)	C1–P1–C13	106.0(6)
		C7–P1–C13	103.0(6)

only through the phosphorus atom, while the NH_2 group remains uncoordinated. The amino cyclohexane group adopts a chair conformation. The tertiary phosphine has a common propeller-type arrangement, characteristic for this type of ligand [42]. The phosphorus atom in the complex has the usual tetrahedral environment. The Au1–P1 and Au1–Cl1 bond distances are 2.243(4) and 2.297(5) Å respectively, and fall in the range of other chloridophosphanegold(I) complexes [43,44], such as Ph_3P–AuCl (2.235(3) and 2.279(3) Å) [43]. However, the Au–P bond is particularly short when compared with some other phosphanegold(I) complexes [42,45–48]. For example, it is: 2.2542(13) Å in [Ph_3P-Au-SCN] [42], 2.278 Å in [Ph_3P-Au-CN] [46], 2.287(3) Å in [Cy_3P-Au-CN] [47], 2.2533(6) Å in [Ph_3P-Au-(indazolyldithiocarbamate)] [20], 2.2623(9) Å in [Ph_3P-Au-(thiosaccharinate)] [48] and 2.274(2) Å in [Cy_3P-Au-(thiourea)]Cl [41]. The shorter distance reflects the greater donation of electron density by the phosphane due to the presence of an amino group. However, in [TPA-Au-(2-pyridylbenzimidazolate)] (TPA = 1,3,5-triaza-7-phosphaadamantane), where the phosphane contains three nitrogen atoms, the Au–P distance is even shorter (2.205(4) Å) [21]. The structure of complex **1** can be compared with the quite similar of phosphanegold(I)-chloride complexes [44].

Intermolecular hydrogen bonds in **1** are observed between the NH_2 group of the phosphane and Cl^- ions of neighboring molecular species. No Au···Au (aurophilic) interaction was detected in the crystal packing of compound **1**. As shown in Fig. S1 (Supporting Information), the Au···Au distance between the neighboring gold centers ranges from 7.668 to 9.778 Å, which is much longer than 3.5 Å, the minimum distance required for the existence of an attractive aurophilic interaction in compound **1** [49]. A closer gold-gold contact is probably hindered by the steric bulk of the phosphane ligands. This observation is consistent with some of our previous studies on such a type of gold(I) complex [28–30]. However, in two cases ([{$Au(CEP)_2$}{$Au(CN)_2$}] [50] and [Me_3P-Au-Seu]$_2Cl_2$ [51] where CEP = tris(2-cyanoethyl)phosphane and Seu = selenourea), we found that the aurophilic interactions led to the formation of dinuclear complexes.

3.2. Cytotoxic activity of the complexes

The gold(I) complexes **1**–**4** and cisplatin were examined for their cell growth inhibition effects against A549, HeLa and HepG2 human cancer cell lines using a Cell Titer-Glo® luminescence-based assay. The dose-dependent inhibition of cell proliferation was obtained by specific increases of the complex concentrations against a fixed number of three cell lines, as shown in Fig. 2. The IC_{50} values (Table 2) were obtained from the plot of the complex concentrations against the percentage of cell viability. The IC_{50} values of the complexes were in the range 2.2–>100 μM, compared to that of the cisplatin IC_{50} values of 13.75, 21.39 and 9.6 μM for A549, HeLa and HepG2 cell lines, respectively. The data clearly show that the complexes **1, 2** and **4** show excellent inhibition of cell proliferation; complex **2** having the best. Their IC_{50} values are several fold better than that of cisplatin. Specifically, the effectiveness of **1** is greater for HeLa cells, while **2** and **4** are more effective towards HepG2 cell lines. Complex **3** showed less activity with respect to cisplatin. The higher potency of the inhibition of cell proliferation of the investigated compounds can be related to the presence of the labile phosphane and dithiocarbamate ligands around the gold(I) ion, which enhances the activity and selectivity of the complexes [23].

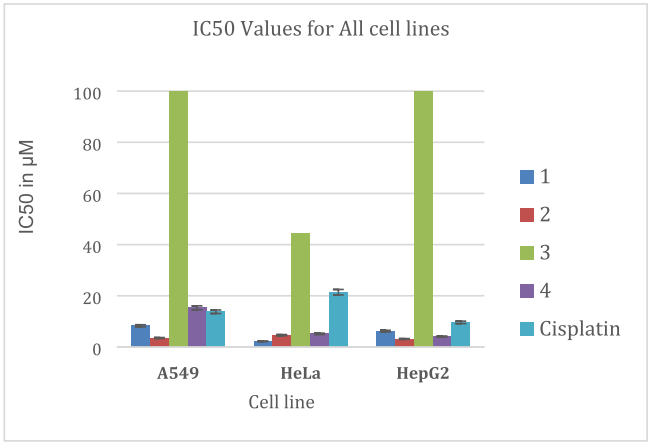


Fig. 2. Effect of the concentration of the gold(I) complexes **1**–**4** and cisplatin on the percentage viability of A549, HeLa and HepG2 cancer cell lines.

Table 2
Half-maximal inhibitory concentrations (IC_{50}) values (μM) of gold(I) complexes and cisplatin against A549, HeLa and HepG2 cell lines. The values of cisplatin are different for each group.

Compound	A549	HeLa	HepG2
1	8.26 ± 0.52	2.21 ± 0.25	6.19 ± 0.15
2	3.50 ± 0.53	4.6 ± 0.20	3.11 ± 0.13
3	>100	44.50 ± 0.27	>100
4	15.30 ± 0.40	5.14 ± 0.11	4.06 ± 0.08
Cisplatin	13.75 ± 0.40	21.39 ± 0.72	9.60 ± 0.90
1a*	6.79	–	5.76
2a	4.87	–	7.41
3a	6.58	–	6.90
4a	6.64	–	8.35
5a	7.06	–	6.21
Cisplatin	29.76	–	30.53
1b*	14.30 ± 0.81	16.03 ± 1.01	–
2b	26.90 ± 1.04	2.11 ± 0.43	–
3b	19.40 ± 0.64	3.18 ± 0.54	–
Cisplatin	41.60 ± 3.00	19.40 ± 1.85	–

*The values of the complexes marked with '**a**' are taken from Ref. [29], while those marked with '**b**' are from Ref. [28].

The cytotoxicity profile of the complexes is comparable to the related alkylphosphanegold(I) dithiocarbamates [28,29]. We have previously investigated the anticancer properties of analogous alkylphosphanegold(I) dithiocarbamate complexes against A549 and HepG2 cancer cells [29]. The studied complexes, [Au(PMe_3)(S_2-$CNMe_2$)] (**1a**), [Au(PMe_3)(S_2CNEt_2)] (**2a**), [Au(PEt_3)(S_2CNMe_2)] (**3a**), [Au(PEt_3)(S_2CNEt_2)] (**4a**) and [Au{P(*i*-Pr)$_3$}(S_2CNMe_2)] (**5a**), were found to be more active against the tested tumor cell lines as compared to cisplatin (Table 2). Complexes with (*ter*-Bu)$_3$P ([Au{P(*ter*-But)$_3$}Cl] (**1b**), [Au{P(*ter*-But)$_3$}(S_2CNMe_2)] (**2b**) and [Au{P(*ter*-But)$_3$}(S_2CNEt_2)] (**3b**)) were tested towards A549 and HeLa cell lines [28]. The cytotoxicity of the gold(I) complexes **2b** and **3b** against HeLa cells is six to eight times better than cisplatin (Table 2). Auranofin is also highly effective (IC_{50} = 1.67 ± 0.03 μM) against A549 cells [52]. The greater cytotoxic effect of the above complexes could be related to the presence of labile phosphane ligands and non-ionic nature of the complexes. The better activities of the complexes than cisplatin supports the conception that a P–Au–S motif enhances the anticancer effect of phosphine gold(I) compounds [15,26,53].

Gold(I) complexes containing PPh_3 and dithiocarbamates {L_1 = pyrazolyldithiocarbamate, L_2 = 3,5-dimethylpyrazolyldithiocarbamate, L_3 = indazolyldithiocarbamate} displayed somewhat poor antitumor activity as compared to cisplatin against the HeLa cells, but still they are very effective [20]. The complexes ([Au(PPh_3)(L_1)], [Au(PPh_3)(L_2)], [Au(PPh_3)(L_3)] and cisplatin) showed IC_{50} values of 2.56 ± 0.12, 2.63 ± 0.10, 2.56 ± 0.17 and 0.45 ± 0.09 μM respectively.

Regarding the mechanism of action, it has been proposed on the basis of substantial volume of experimental evidence that mitochondria, in particular the enzyme thioredoxin reductase (TrxR), represent the most relevant target for anticancer gold(I) compounds [10,14,31,54–56]. Mitochondrial and cytosolic isoforms of thioredoxin reductase play an important role in regulating cellular events, such as cell signalling, apoptosis and cell proliferation [10]. In addition, the thioredoxin system is markedly expressed in tumor cell lines [57]. The inhibition of thioredoxin reductase can shift the redox balance towards a more oxidized state and appears as the initiating event leading to apoptosis. The oxidized TrxR can act on several different membrane targets leading to increased permeability of the mitochondrial membranes, release of cytochrome *c* and eventually cell death [10,54,55,58].

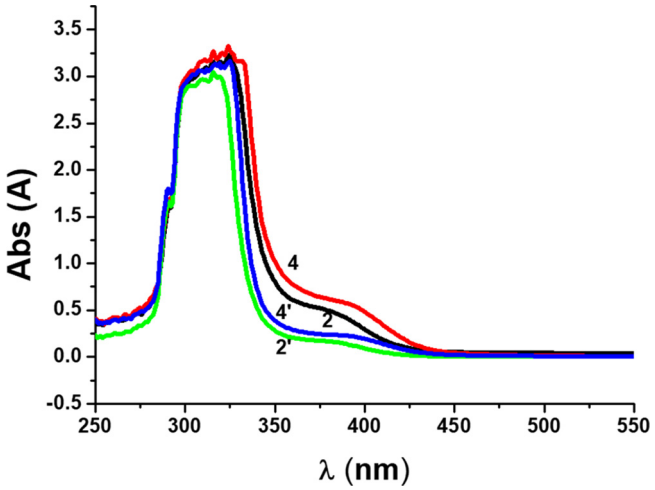


Fig. 3. UV–Vis spectra of 0.1 M gold(I) complexes **2** and **4** at the initial time and after 24 h (**2′** and **4′**) in a DMSO solution (10 mL) at 25 °C.

3.3. Stability of complexes *2* and *4*

The stability of gold(I) complexes **2** and **4** was studied by UV–Vis spectrophotometry using their 0.1 M solutions in DMSO (10 mL) at room temperature for 24 h. The complexes did not undergo decomposition or a reaction with some other species, indicating their high stability in DMSO solution. The spectra are shown in Fig. 3.

4. Conclusions

The present paper describes the synthesis and spectral characterization of four gold(I) complexes of 2-(diphenylphosphanyl)-1-aminocyclohexane (ACP) and dithiocarbamates, as well as their anticancer activity against A549, HeLa and HepG2 human cancer cell lines. The crystal structure of complex **1** was determined by X-ray crystallography, which reveals that the complex is mononuclear, exhibiting a linear geometry at the gold center. We have observed that these gold compounds are extremely effective in inhibiting the growth of all three types of cell lines. The significant cytotoxicity of the complexes recommends their further exploration in order to develop suitable anticancer agents.

CRediT authorship contribution statement

Adam A.Sulaiman: Investigation, Methodology, Formal analysis, Writing - original draft. **Ali Alhoshani:** Methodology, Formal analysis. **Homood M. As Sobeai:** Methodology, Formal analysis. **Meshal Alghanem:** Methodology, Formal analysis. **Ahmed K. Abogosh:** Methodology, Formal analysis. **Saeed Ahmad:** Investigation, Methodology, Formal analysis, Writing - original draft. **Muhammad Altaf:** Formal analysis. **Muhammad Monim-ul-Mehboob:** Investigation, Methodology, Formal analysis, Writing - original draft. **Helen Stoeckli-Evans:** Formal analysis. **Anvarhusein A. Isab:** Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Crystallographic data of complex **1** have been deposited with the Cambridge Crystallographic Data Center via the CCDC Number 1960931. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk. Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2020.114532.

References

[1] L. Messori, G. Marcon, Met. Ions Biol. Syst. 41 (2004) 279–304.
[2] C.F. Shaw III, Chem. Rev. 99 (1999) 2589–2600.
[3] L.R.A. James, Z.-Q. Xu, R. Sluyter, E.L. Hawksworth, C. Kelso, B. Lai, D.J. Paterson, M.D. de Jonge, N.E. Dixon, J.L. Beck, S.F. Ralph, C.T. Dillon, J. Inorg. Biochem. 142 (2015) 28–38.
[4] I. Ott, Coord. Chem. Rev. 253 (2009) 1670–1681.
[5] S.J. Berners-Price, A. Filipovska, Metallomics 3 (2011) 863–873.

[6] J.F. Fries, D. Bloch, P. Spitz, D.M. Mitchell, Am. J. Med. 78 (1985) 56–59.
[7] J.R. Ward, Am. J. Med. 85 (1988) 39–44.
[8] T.M. Simon, D.H. Kunishima, G.J. Vibert, A. Lorber, Cancer Res. 41 (1981) 94.
[9] C.K. Mirabelli, R.K. Johnson, C.M. Sung, L. Faucette, K. Muirhead, S.T. Crooke, Cancer Res. 45 (1985) 32–39.
[10] C. Marzano, V. Gandin, A. Folda, G. Scutari, A. Bindoli, M.P. Rigobello, Free Radic. Biol. Med. 42 (2007) 872–881.
[11] S.J. Berners-Price, C.K. Mirabelli, R.K. Johnson, M.R. Mattern, F.L. McCabe, L.F. Faucette, C.-M. Sung, S.-M. Mong, P.J. Sadler, S.T. Crooke, Cancer Res. 46 (1986) 5486.
[12] P.C. Healy, Bradley T. Loughrey, Michael L. Williams, Peter G. Parsons, J. Inorg. Biochem. 104 (2010) 625–631.
[13] G. Lupidi, L. Avenali, M. Bramucci, L. Quassinti, R. Pettinari, H.K. Khalife, H. Gali-Muhtasib, F. Marchetti, C. Pettinari, J. Inorg. Biochem. 124 (2013) 78–87.
[14] S. Nobili, E. Mini, I. Landini, C. Gabbiani, A. Casini, L. Messori, Med. Res. Rev. 105 (2010) 550–580.
[15] E.R.T. Tiekink, Inflammopharmacology 16 (2008) 138.
[16] E.R.T. Tiekink, Bioinorg. Chem. Appl. 1 (2003) 53.
[17] C.K. Mirabelli, R.K. Johnson, D.T. Hill, L.F. Faucette, G.R. Girard, G.Y. Kuo, C.M. Sung, S.T. Crooke, J. Med. Chem. 29 (1986) 218–223.
[18] T. Marzo, D. Cirri, C. Gabbiani, T. Gamberi, F. Magherini, A. Pratesi, A. Guerri, T. Biver, F. Binacchi, M. Stefanini, A. Arcangeli, ACS Med. Chem. Lett. 8 (2017) 997–1001.
[19] T. Marzo, L. Massai, A. Pratesi, M. Stefanini, D. Cirri, F. Magherini, M. Becatti, I. Landini, S. Nobili, E. Mini, O. Crociani, A. Arcangeli, S. Pillozzi, T. Gamberi, L. Messori, ACS Med. Chem. Lett. 10 (2019) 656–660.
[20] F.K. Keter, I.A. Guzei, M. Nell, W.E. van Zyl, J. Darkwa, Inorg. Chem. 53 (2014) 2058–2067.
[21] M. Serratrice, M.A. Cinellu, L. Maiore, M. Pilo, A. Zucca, C. Gabbiani, A. Guerri, I. Landini, S. Nobili, E. Mini, L. Messori, Inorg. Chem. 51 (2012) 3161–3171.
[22] J.D.S. Chaves, F. Neumann, T.M. Francisco, C.C. Corrêa, M.T.P. Lopes, H. Silva, A. P.S. Fontes, M.V. de Almeida, Inorg. Chim. Acta 414 (2014) 85–90.
[23] K.K. Ooi, C.I. Yeo, K.-P. Ang, A.M. Akim, Y.-K. Cheah, S.N.A. Halim, H.-L. Seng, E. R.T. Tiekink, J. Biol. Inorg. Chem. 20 (2015) 855–873.
[24] M.P. Chrysouli, C.N. Banti, N. Kourkoumelis, N. Panayiotou, G.S. Markopoulos, A.J. Tasiopoulos, S.K. Hadjikakou, J. Inorg. Biochem. 179 (2018) 107–120.
[25] C.K. Adokoh, J. Darkwa, H.H. Kinfe, Polyhedron 138 (2017) 57–67.
[26] V. Gandin, A.P. Fernandes, M.P. Rigobello, B. Dani, F. Sorrentino, F. Tisato, M. Bjornstedt, A. Bindoli, A. Sturaro, R. Rella, C. Marzano, Biochem. Pharmacol. 79 (2010) 90–101.
[27] D. de Vos, S.Y. Ho, E.R.T. Tiekink, Bioinorg. Chem. Appl. 2 (2004) 141–154.
[28] M. Altaf, M. Monim-ul-Mehboob, A.A.A. Seliman, M. Sohail, M.I.M. Wazeer, A.A. Isab, L. Li, V. Dhuna, G. Bhatia, K. Dhuna, Eur. J. Med. Chem. 95 (2015) 464–472.
[29] S.S. Al-Jaroudi, M. Altaf, A.A. Seliman, S. Yadav, F. Arjmand, A. Alhoshani, H.M. Korashy, S. Ahmad, A.A. Isab, Inorg. Chim. Acta 464 (2017) 37–48.
[30] A.A.A. Sulaiman, M. Altaf, A.A. Isab, A. Alawad, S. Altuwaijri, S. Ahmad, Z. Anorg. Allg. Chem. 642 (2016) 1454–1459.
[31] M.J. McKeage, L. Maharaj, S.J. Berners-Price, Coord. Chem. Rev. 232 (2002) 127–135.
[32] W. Fiskus, N. Saba, M. Shen, M. Ghias, J. Liu, S.D. Gupta, L. Chauhan, R. Rao, S. Gunewardena, K. Schorno, C.P. Austin, K. Maddocks, J. Byrd, A. Melnick, P. Huang, A. Wiestner, K.N. Bhalla, Cancer Res. 74 (2014) 2520–2532.
[33] M. Altaf, M. Monim-ul-mehboob, A.A. Seliman, A.A. Isab, V. Dhuna, G. Bhatia, K. Dhuna, J. Organomet. Chem. 765 (2014) 68–79.
[34] S. Ahmad, M.N. Akhtar, A.A. Isab, A.R. Al-Arfaj, M.S. Hussain, J. Coord. Chem. 51 (2000) 225–234.
[35] Stoe & Cie, X-Area X-RED32, Stoe Cie GmbH, Darmstadt, Germany, 2009.
[36] G.M. Sheldrick, Acta Crystallogr. A 64 (2008) 112–122.
[37] A.L. Spek, Acta Crystallogr. D 65 (2009) 148–155.
[38] J. van de Streek, P.A.W.C.F. Macrae, I.J. Bruno, J.A. Chisholm, P.R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. Appl. Crystallogr. 41 (2008) 466–470.
[39] A.A. Isab, S. Nawaz, M. Saleem, M. Altaf, M. Monim-ul-Mehboob, S. Ahmad, H. Stoeckli-Evans, Polyhedron 29 (2010) 1251.
[40] M. Sarwar, S. Ahmad, S. Ahmed, S. Ali, S.A. Awan, Transit. Met. Chem. 32 (2007) 199–203.
[41] A.A. Isab, M.B. Fettouhi, S. Ahmad, L. Ouahab, Polyhedron 22 (2003) 1349–1354.
[42] D. Schneider, S. Nogai, A. Schier, H. Schmidbaur, Inorg. Chim. Acta 352 (2003) 179–187.
[43] N.C. Baenziger, W.E. Bennett, D.M. Soborofe, Acta Crystallogr. B 32 (1976) 962.
[44] K. Angermaier, E. Zeller, H. Schmidbaur, J. Organomet. Chem. 472 (1994) 371–376.
[45] S. Ahmad, Coord. Chem. Rev. 248 (2004) 231–243.
[46] P.G. Jones, J. Launter, Acta Crystallogr. C 44 (1988) 2091.
[47] A.R. Al-Arfaj, J.H. Reibenspies, M.S. Hussain, M.Y. Darensbourg, N. Akhtar, A.A. Isab, Acta Crystallogr. C 53 (1997) 1553.
[48] M. Dennehy, O.V. Quinzani, R.M. Ferullo, A. Granados, R.A. Burrow, Inorg. Chim. Acta 377 (2011) 77–83.
[49] H. Schmidbaur, A. Schier, Chem. Soc. Rev. 41 (2012) 370.
[50] M.S. Hussain, A.R. Al-Arfaj, M.N. Akhtar, A.A. Isab, Polyhedron 16 (1996) 2781.
[51] M. Fettouhi, M.I.M. Wazeer, S. Ahmad, A.A. Isab, Polyhedron 23 (2004) 1.
[52] J.F. Arambula, R. McCall, K.J. Sidoran, D. Magda, N.A. Mitchell, C.W. Bielawski, V.M. Lynch, J.L. Sessler, K. Arumugam, Chem. Sci. 7 (2016) 1245–1256.
[53] J.S. Casas, E.E. Castellano, M.D. Couce, J. Ellena, A. Sanchez, J. Sordo, C. Taboada, J. Inorg. Biochem. 100 (2006) 1858.
[54] A. Bindoli, M.P. Rigobello, G. Scutari, C. Gabbiani, A. Casini, L. Messori, Coord. Chem. Rev. 253 (2009) 1692–1707.
[55] C. Schmidt, B. Karge, R. Misgeld, A. Prokop, M. Brönstrup, I. Ott, Med. Chem. Commun. 8 (2017) 1681.
[56] R. Rubbiani, I. Kitanovic, H. Alborzinia, S. Can, A. Kitanovic, L.A. Onambele, M. Stefanopoulou, Y. Geldmacher, W.S. Sheldrick, G. Wolber, A. Prokop, S. Wolfl, I. Ott, J. Med. Chem. 53 (2010) 8608–8618.
[57] D.T. Lincoln, E.M. Ali Emadi, K.F. Tonissen, F.M. Clarke, Anticancer Res. 23 (2003) 2425–2433.
[58] M.P. Rigobello, G. Scutari, A. Folda, A. Bindoli, Biochem. Pharmacol. 67 (2004) 689–696.