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Synthesis, characterization and theoretical calculations of (1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) chloride complexes: in vitro cytotoxic evaluations against human cancer cell lines

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Abstract The gold(III) complexes of the type (1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) chloride, [(DACH)Au(pn)]Cl_3, [where DACH = *cis*-, *trans*-1,2- and *S,S*-1,2-diaminocyclohexane and pn = 1,3-diaminopropane] have been synthesized and characterized using various spectroscopic and analytical techniques including elemental analysis, UV–Vis and FTIR spectroscopy; solution as well as solid-state NMR measurements. The solid-state ^{13}C NMR shows that 1,2-diaminocyclohexane (1,2-DACH) and 1,3-diaminopropane (pn) are strongly bound to the gold(III) center via N donor atoms. The stability of the mixed diamine ligand gold(III) was checked by UV–Vis spectroscopy and NMR measurements. The molecular structure of compound **1** (containing *cis*-1,2-DACH) was determined by X-ray diffraction analysis. The structure of **1** consists of $[(cis\text{-DACH})Au(pn)]^{3+}$ complex ion and chloride counter ions. Each gold atom in the complex ion adopts a distorted square-planar geometry. The structural details and relative stabilities of the four possible isomers of the complexes were also estimated at the B3LYP/LANL2DZ level of theoretical calculations. The computational study demonstrates that *trans*-conformations are slightly more stable than the *cis*-conformations. The antiproliferative effects and cytotoxic properties of the mixed ligand gold(III) complexes were evaluated in vitro on human gastric SGC7901 and prostate PC3 cancer cells using MTT assay. The antiproliferative study of the gold(III) complexes on PC3 and SGC7901 cells indicate that complex **3** (containing 1*S*,2*S*-(+)-1,2-(DACH)) is the most effective antiproliferative agent. The IC_{50} data reveal that the in vitro cytotoxicity of complex **3** against SGC7901 cancer cells manifested similar and very pronounced cytotoxic effects with respect to cisplatin. Moreover, the electrochemical behavior, and the interaction of complex **3** with two well-known model proteins, namely, hen egg white lysozyme and bovine serum albumin is also reported.

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Keywords Gold(III) complex · 1,2-Diaminocyclohexane · 1,3-Diaminopropane · Anticancer · Gastric carcinogenesis (SGC-7901) · Prostate cancer (PC-3)

Introduction

The development of new metal-based cancer therapeutics with a pharmacological activity different from platinum drugs is one of the major goals of modern bioinorganic and bio-organometallic chemistry research (Bertrand et al. 2015; Sadler and Sue 1994; Shaw 1999; Best and Sadler 1996; van Rijt and Sadler 2009; Panteli et al. 2015; Al-Jaroudi et al. 2013). Gold complexes have recently gained a considerable attention as a class of antitumor compounds with different pharmacodynamics and kinetic properties than cisplatin with strong cell growth inhibiting effects (Bertrand et al. 2015; Shaw 1999; Best and Sadler 1996).

The high effectiveness of cisplatin in the treatment of several types of tumors is severely hindered by some clinical problems such as normal tissue toxicity and the frequent occurrence of intrinsic and acquired resistance to the drug (Kelland 2007; Ahmad 2010; Thayer 2010; Sava et al. 2011a, b; Dhar and Lippard 2011; Wang and Guo 2011). To overcome this cross-resistance, the so-called third generation of platinum complexes was introduced and the most promising drug is oxaliplatin (Graham et al. 2004), which bears a 1,2-diaminocyclohexane (DACH) ligand and oxalate ion as a leaving group. The bulky chiral ligand, 1*R*,2*R*-diaminocyclohexane (1*R*,2*R*-DACH), contributes to high cytotoxicity against cisplatin-resistant cell lines, possibly due to the steric hindrance effect of the DACH-platinum–DNA adducts (Misset et al. 2000; Francesco et al. 2002; Raymond et al. 1998; Zdraveski et al. 2002). One of the earliest leads in the development of Pt complexes with activity in resistant tumor cells was a series of complexes with 1,2-diaminocyclohexane (DACH) carrier ligand (Burchenal et al. 1978; Burchenal et al. 1979). Consequently many substituted DACH complexes have been evaluated (Chaney 1995; Kidani 1991; Hoeschele et al. 1994) for their cytotoxicity and some of them have entered into preclinical and clinical trials (Yu et al. 2006; Liu et al. 2007; Rothenburger et al. 2006; Yu et al. 2008). Thus, it can be deduced that 1*R*,2*R*-DACH is an effective carrier group in designing DACH-type platinum derivatives. Moreover, in searching for better platinum compounds, a wide variety of carrying ligands and leaving groups have been screened. Vicinal diamines, and particularly DACH, appear to be useful carrying ligands (Monti et al. 2005; Berger et al. 2007; Bitha et al. 1989).

Gold(III) complexes, those are isoelectronic and isostructural to platinum(II) complexes, show promising antitumor activity (Sadler 1976; Ott 2009; Bindoli et al. 2009; Cutillas et al. 2013). Surprisingly, only a few reports exist in the literature describing the cytotoxic properties and the in vivo antitumor effects of gold(III) complexes (Buckley et al. 1996; Calamai et al. 1998; Cossu et al. 1994). The interests for the development of gold(III) complexes were further stimulated by the promising results of platinum(II) complexes against selected types of cancer. Currently, gold(III) complexes having the same square-planar geometries as cisplatin (Ronconi et al. 2006), become the subject of increased anti-cancer research and hold great potential to enter clinical trials since a few of them are highly cytotoxic to solid cancer tumors in vitro and in vivo while causing minimal systemic toxicity (Cattaruzza et al. 2011; Ronconi et al. 2010; Milacic et al. 2006; To et al. 2009; Sun and Che 2009). In general, gold(III) complexes are not very stable under physiological conditions due to their high reduction potential and fast hydrolysis rate (Messori et al. 2000). Therefore, selection of suitable ligands to enhance the stability is a big challenge in the design of gold(III) complexes. The Au(III) ion is best coordinated by at least two chelating nitrogen donors which lower the reduction potential of metal center and thereby stabilize the complex (Giovagnini et al. 2005; Che et al. 2003; Casini et al. 2008). The stability of the complexes facilitated extensive pharmacological investigations, both in vitro and in vivo (Tieking 2008; Casini et al. 2008, 2009; Ortiz et al. 2007).

Structurally, DACH ligand has two asymmetric carbon centers. Thus, it can exist as three isomeric forms that are the enantiomers (1*R*,2*R*-DACH) (*trans*-DACH), (l*S*,2*S*- DACH) (*trans*-DACH) and the diastereoisomer (1*R*,2*S*- DACH) (*cis*- DACH). Since DACH is chiral, the relevance of stereochemical issues has been addressed by some investigators (Kidani et al. 1977), which affect the cytotoxicity of complexes (Kemp et al. 2007). In spite of conflicting views

(Gulloti et al. 1984; Kidani et al. 1978; Noji et al. 1981; Kidani et al. 1980; Pasini et al. 1982), the consensus is that the (*R*,*R*) isomer is generally more active than the (*S*,*S*) isomer (Burchenal et al. 1977; Bruck et al. 1984). Although activity demonstrated by Pt(I*R*,2*R*- DACH) and Pt(l*S*,2*S*- DACH) complexes have a higher antitumor activity than Pt(1*R*,2*S*-DACH) complex (Johnson et al. 1989; Cleare et al. 1978; Al-Sarraf et al. 1987). The analogous gold(III) (1*R*,2*S*-DACH) complex (with *cis*-DACH ligand) has been reported with higher antitumor activity than gold(III) (1*R*,2*R*-DACH) complex (with *trans*-DACH ligand) and gold(III) (l*S*,2*S*- DACH) complex (with *trans*- DACH ligand) (Vollano et al. 1987).

Over the past several years, significant efforts have been devoted to studying the antitumor activity of platinum-DACH complexes, whereas, gold-DACH complexes (Arsenijevic et al. 2012) have relatively got little attention. As in the case of cisplatin, the antitumor activity of platinum-DACH is accompanied by some toxicity. The emergence of resistance, and low water solubility that can affect the pharmacokinetics are additional features that must be improved in the quest for a more efficient analog (Hanessian and Wang 1993). As a continuation of our intrinsic interest in the synthesis of gold(III) complexes and to better understand the chemical and physical behavior of biologically relevant gold(III)-diaminecomplexes (Ahmed et al. 2012; Al-Jaroudi et al. 2013, 2014), in this study, three chiral isomers [{*cis*-1,2-DACH}Au(pn)]Cl_3 (**1**), [{*trans*-(±)-1,2-DACH}Au(pn)]Cl_3 (**2**) and [{(1*S*,2*S*)-(+)-1,2-DACH}Au(pn)]Cl_3 (**3**), have been synthesized and fully characterized by Elemental Analysis, UV–Vis, FTIR and NMR spectroscopic techniques, and one of them by X-ray crystallography. Theoretical analysis of the complexes is also presented. Their cytotoxicity has been tested in vitro against human gastric SGC-7901 and prostate PC-3 cancer cell lines. In this study, the influence of relative stereochemistry of (DACH)(pn)gold(III) complexes on their antitumor activity is addressed. To the best of our knowledge, this is the first work of synthesizing gold(III) complexes based on mixed diamine ligands of 1,2-diaminocyclohexane and 1,3-diaminopropane. These new Au(III) complexes are highly water soluble and show high cytotoxic effects. Scheme 1 illustrates the structures of the ligands and Scheme 2 shows the structures of the complexes reported.

Experimental

Chemicals, cell lines and cell cultures

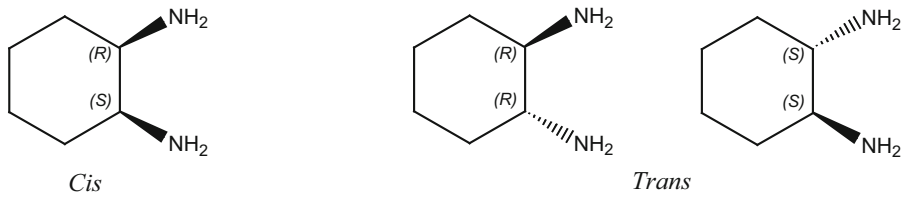
Sodium tetrachloridoaurate(III) dihydrate $NaAuCl_4{\cdot}2H_2O$, lysozyme, bovine albumin serum (BSA), phosphate buffer and 1,3-diaminopropane (pn) were purchased from Sigma-Aldrich. *cis*-1,2-diaminocyclohexane (*cis*-1,2-DACH), *trans*-(±)-1,2-diaminocyclohexane (*trans*-(±)-DACH) and *S,S*-(+)-diaminocyclohexane (*S,S*-(+)-1,2-DACH) were purchased from Aldrich. Absolute C_2H_5OH, CH_3OH, D_2O, and DMSO-d_6 were obtained from Fluka Chemicals Co. All other reagents as well as solvents were obtained from Aldrich Chemical Co., and used as received.

Human gastric SGC7901 and prostate PC3 cancer cell lines were provided by American Type Culture Collection (ATCC). Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % fetal calf serum (FCS), penicillin (100 kU L^{-1}) and streptomycin (0.1 g L^{-1}) at 37 °C in a 5 % CO_2–95 % air atmosphere. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazole) was purchased from Sigma Chemical Co, St. Louis, MO, USA.

Synthesis of Au(III) complexes

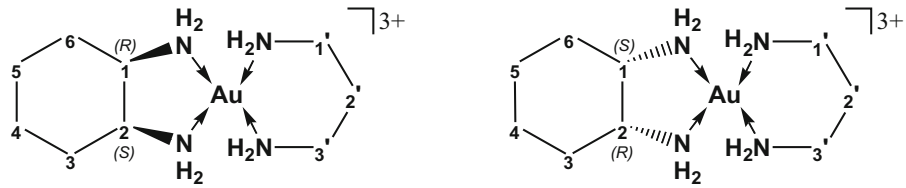
Mixed ligand gold(III) chloride compounds namely, (*cis*-1,2-diaminocyclohexane)(1,3-diaminopropane)-gold(III) chloride, [{*cis*-(1,2-DACH)Au(pn)}]Cl_3 (**1**); (*trans*-(±)-1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) chloride, [{(*trans*-(±)-(1,2-DACH)}Au(pn)]Cl_3 (**2**); and (*S,S*-(+)- 1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) chloride [{(*S,S*)-(+)-(1,2-DACH)}Au(pn)]Cl_3 (**3**); were synthesized by mixing one equivalent of sodium tetrachloridoaurate dihydrate, $NaAuCl_4{\cdot}2H_2O$ with one equivalent of 1,3-diaminopropane (pn) and one equivalent of *cis*-1,2-DACH or *trans*-(±)-1,2-DACH or *S,S*-(+)-1,2-DACH respectively similar to the procedure reported in the literature (Al-Jaroudi et al. 2014).

Sodium tetrachloridoaurate dihydrate $NaAuCl_4{\cdot}2H_2O$, 398 mg (1.0 mmol) was dissolved in minimum volume i.e. 10 mL of absolute ethanol at ambient temperature. To this solution, 114 mg (1.0 mmol) of 1,2-diaminocyclohexane (1,2-DACH), dissolved in 10 mL of absolute ethanol(separately for each isomer) was added dropwise and the mixture was stirred for



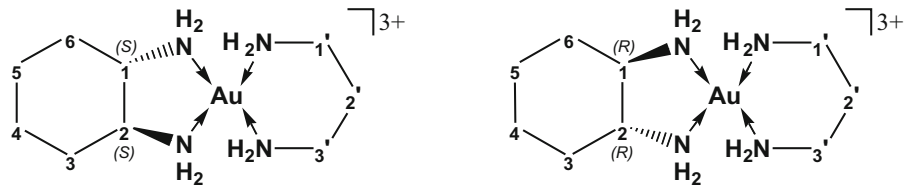
Scheme 1 Isomerization structure of diaminocyclohexane (DACH)

Scheme 2 Possible chemical structure of the synthesized (DACH)(pn)gold (III) complexes



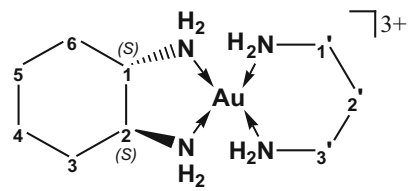
(a) **(b)**

1, [{*cis*-1,2-(DACH)}Au(pn)]Cl_3



(a) **(b)**

2, [{*trans*-(±)-1,2-(DACH)}Au(pn)]Cl_3



3, [{(1*S*,2*S*)-(+)-1,2-(DACH)}Au(pn)]Cl_3

half an hour. After which, a clear solution was obtained that was filtered. In a separate beaker, 1,3-diaminopropane (pn), 74 mg (1.0 mmol) was dissolved in 10 mL of absolute ethanol at ambient temperature. The pn solution was added dropwise to the above filtered solution. Upon stirring for overnight, the white precipitates of [(1,2-DACH)Au(pn)]Cl_3 were obtained. The product was isolated, dissolved in 2 mL of water and filtered through Celite pad to remove NaCl. On addition of 100 mL of cold CH_3OH to the filtrate, white precipitates were obtained, which were filtered and washed with cold CH_3OH. The solid product was dried under reduced pressure with P_2O_5. The yield of the compounds **1**, **2** and **3** was in the range of 70–73 %. Melting points and elemental analysis for complexes are presented in Table 1. The complexes prepared in the present study were characterized by their physical properties, NMR, IR, elemental analysis and X-ray crystallography. The density functional Theory (DFT) calculations based on hybrid B3LYP

were also performed to optimize the structures of gold(III) complexes. All the data support the formation of the desired [(1,2-DACH)Au(pn)]Cl_3 complexes.

Electronic spectra

Electronic spectra were obtained for the gold(III) complexes using Lambda 200, Perkin-Elmer UV–Vis spectrometer. UV–Vis spectroscopy was used to determine the stability of the complexes in a physiological buffer (40 mM phosphate, 4 mM NaCl, pH 7.4). Electronic spectra were recorded on freshly prepared solution of each complex in a buffer at room temperature. Then, their electronic spectra were monitored over 3 days at 37 °C. The resulting UV–Vis absorption data are shown in Table S1.

Mid and Far-IR studies

IR spectra of the ligands and their (1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) complexes were recorded on a Perkin-Elmer FT-IR 180 spectrophotometer using KBr pellets over the range 4000–400 cm^{-1}. The selected IR frequencies are given in Table 2. Far-infrared spectra were recorded for complexes **1**, **2** and **3** at 4 cm^{-1} resolution at room temperature as cesium chloride disks on a Nicolet 6700 FT-IR with Far-IR beam splitter. Far-IR data for the complexes studied are given in Table 3.

Solution NMR measurements

All NMR measurements were carried out on a Jeol JNM-LA 500 NMR spectrophotometer at 297 K. The ^{1}H NMR spectra were recorded at a frequency of 500.00 MHz. The ^{13}C NMR spectra were obtained at a frequency of 125.65 MHz with ^{1}H broadband decoupling and referenced relative to TMS. The spectral conditions were: 32 k data points, 0.967 s acquisition time, 1.00 s pulse delay and 45 pulse angle. The ^{1}H and ^{13}C NMR chemical shifts are given in Table 4 and Table 5, respectively, according to Scheme 2.

Solid state NMR studies

^{13}C solid-state NMR spectra were performed on a Bruker 400 MHz spectrometer at ambient temperature of 298 K. Samples were packed into 4 mm zirconium oxide rotors. Cross polarization and high power decoupling were employed. Pulse delay of 7.0 s and a contact time of 5.0 ms were used in the CPMAS experiments. The magic angle spinning rates were 4 and 8 kHz. Carbon chemical shifts were referenced to TMS by setting the high-frequency isotropic peak of solid adamantane to 38.56 ppm. The solid NMR data are given in Table 6.

X-ray diffraction analysis

The intensity data were collected at 173 K on a two circle (Stoe and Cie 2006) Stoe Image Plate diffraction system, using Mo-Kα graphite monochromated radiation. The structure was solved by direct methods, using the program SHELX-97 (Sheldrick 2008). The refinement and all further calculations were also carried out using SHELX-97 (Sheldrick 2008). The H-atoms were either located from Fourier difference maps and freely refined or included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. Empirical or multiscan absorption corrections were applied using and MULSCANABS routines in PLATON (Spek 2009). A summary of crystal data and refinement details for compound **1** are given in Table 7. Figures 1 and S1 were drawn using the programs PLATON and MERCURY (Macrae et al. 2006).Selected bond distances and bond angles are given in Table S2.

Table 1 Melting point (MP) and CHN analysis of gold(III) complexes **1**, **2** and **3**

Complex	Melting point (°C)	Found(Calc.) %		
		H	C	N
(1).3H_2O	161–163	5.57(5.54)	19.64(19.81)	10.25(10.27)
(2).3H_2O	171–173	5.59(5.54)	19.67(19.81)	10.21(10.27)
(3).3H_2O	173–175	5.52(5.54)	19.74(19.81)	10.24(10.27)

Table 2 IR frequencies, $\nu(cm^{-1})$ for cyclohexanediamine-Au(III)-propylenediamine complexes

Complex	ν(N–H)	ν_{shift}	ν(C–N)	ν_{shift}	Refs.
(pn)	3357 m, 3282 m		1093 w		[d]
(pn)$AuCl_3$	3447 br	127	1178 s	85	[d]
cis-1,2-(DACH)	3356 m, 3286 m		1092 s		[e]
[*cis*-1,2-(DACH)$AuCl_2$]Cl	3414 w	93	1183 s	91	[e]
1	3426 br, 3106 br	105[a], 107[b]	1163 w	71[a], 70[b]	[c]
trans-(±)-1,2-(DACH)	3348 m, 3271 m, 3183 m		1082 m		[e]
[*trans*-(±)-1,2-(DACH)$AuCl_2$]Cl	3485 w, 3420 w, 3384 w	137, 149, 201	1175 m	93	[e]
2	3452 br, 3112 br	131[a], 133[b]	1184 m	92[a], 91[b]	[c]
(*S*,*S*)-(+)-1,2-(DACH)	3340 m, 3252 m, 3167 m		1082 m		[e]
[(*S*,*S*)-(+)-1,2-(DACH)$AuCl_2$]Cl	3604 m, 3340 m, 3306 m, 3168 m	132, 27	1171 m	89	[e]
3	3444 br, 3118	123[a], 125[b]	1186 m	94[a], 93[b]	[c]

[a] With respect to (DACH)

[b] With respect to (pn)

[c] This work

[d] Al-Maythalony et al. (2009)

[e] Al-Jaroudi et al. (2013)

Table 3 Far-IR frequencies, $\nu(cm^{-1})$ for **1**, **2**, and **3** complexes

Species	Au–Cl	Au–N	Refs.
$NaAuCl_4$	365	–	[a]
[(pn)$AuCl_2$]Cl	–	391, 474	[b]
[{*cis*-1,2-(DACH)}$AuCl_3$]Cl	352, 367	437	[c]
1	–	331, 425	[a]
[{*trans*-(±)-1,2-(DACH)}$AuCl_2$]Cl	353, 365	437	[c]
2	–	392, 448	[a]
[{(1*S*,2*S*)-(+)-(DACH)}$AuCl_2$]Cl	353, 366	395, 436	[c]
3	–	383, 451	[a]

[a] This work

[b] Al-Maythalony et al. (2009)

[c] Al-Jaroudi et al. (2013)

Computational study

The structures of the $[(DACH)Au(pn)]^{3+}$ complex with four possible conformations (*cis*-SR, *cis*-RS, *trans*-SS and *trans*-RR) were optimized without any geometrical constraints using GAUSSIAN09 program (Frisch et al. 2009). The hybrid B3LYP density functional (the three-parameter Becke functional with correlation from the Lee–Yang–Parr functional) (Becke 1988; Lee et al. 1988) with theLos Alamos National Laboratory-2 double-ζ (LANL2DZ) basis set (Wadt and Hay1985a, b, c) was employed in this study. We reported results for some gold-based complexes at this level of calculations (Al-Jaroudi et al. 2014) giving decent results that are consistent with our experimental finding. Moreover, stationary points have been confirmed by frequency calculation. Calculated bond distances and angles are listed alongside with experimental values in Table S2 for compound **1**, while Table S3 compares the relative stabilities based on the calculated energies of the optimized minimum structures.

Stability of Gold(III) compounds

Compounds **1, 2** and **3** were tested for their stability in water as well as mixed solvents of DMSO/water (2/1 v/v ratio) solution by ^{13}C and ^{1}H NMR. The compounds are highly soluble in water but sparingly soluble in DMSO. The hygroscopic nature of DMSO

Table 4 ^{1}H NMR chemical shifts of free ligands and cyclohexanediamine -Au(III)-propylenediamine complexes in D_2O

Compound	^{1}H(δ in ppm)							
	H1,H2	H3,H6 (eq)	H3,H6 (ax)	H4,H5 (eq)	H4,H5 (ax)	H1′,H3′	H2′	Refs.
(pn)	–	–	–	–	–	2.98, t	1.94, *pt*	[a]
cis-1,2-(DACH)	2.23, *m*	1.85, *m*	1.69, *m*	1.28, *m*	1.12, *m*	–	–	[b]
trans-(±)-(DACH)	2.25, *m*	1.85, *m*	1.68, *m*	1.28, *m*	1.11, *m*	–	–	[b]
(1*S*,2*S*)-(+)-1,2-(DACH)	2.24, *m*	1.85, *m*	1.69, *m*	1.28, *m*	1.11, *m*	–	–	[b]
1	3.65, *m*	1.96, *m*	1.79, *m*	1.60, *m*	1.41, *m*	2.94, m	2.19, *m,* 1.96, *m*	[a]
2	3.07, *m*	2.11, *m*	1.56, *m*	1.47, *m*	1.10, *m*	2.91, m	2.12, *m*	[a]
3	3.08, *m*	2.11, *m*	1.56, *m*	1.47, *m*	1.11, *m*	2.91, m	2.13, *m*	[a]

[a] This work

[b] Al-Jaroudi SS (2013)

Table 5 ^{13}C NMR chemical shifts of free ligands and cyclohexanediamine-Au(III)-propylenediamine complexes in D_2O

Compound	^{13}C(δ in ppm)				
	C1,C2	C3,C6	C4,C5	C1′,C3′	C2′
(pn)	–	–	–	37.47	25.69
cis-1,2-(DACH)	58.20	35.26	26.36	–	
trans-(±)-1,2-(DACH)	58.46	35.55	26.63	–	
(1*S*,2*S*)-(+)-1,2-(DACH)	58.27	35.32	26.43	–	
1	61.98	26.92	20.73	40.95	26.92
2	64.47	32.88	23.91	40.90	26.90
3	64.50	32.90	23.94	40.92	26.92

Table 6 Solid ^{13}C NMR chemical shifts of free ligands and (DACH)-Au(III)-(pn) complexes

Compound	^{13}C(δ in ppm)					
	C1,C2	C3,C6	C4,C5	C1′,C3′	C2′	Refs.
[{*cis*-1,2-(DACH)}$AuCl_2$]Cl	66.20, 65.35	30.98	27.02, 22.12	–		[b]
1	64.03	29.31	21.74	44.57	28.01	[a]
[{*trans*-(±)-1,2-(DACH)}$AuCl_2$]Cl	69.60	37.37	27.99	–		[b]
2	66.80	37.35	28.09	45.76	28.09	[a]
[{(1*S*2*S*)-(+)-1,2-(DACH)}$AuCl_2$]Cl	70.21	37.86	29.16	–		[b]
3	67.31, 64.41	36.05, 34.10	27.92	45.65	27.92	[a]

[a] This work

[b] Al-Jaroudi SS (2013)

could, unfortunately, leads to stability issue (Ellson et al. 2005). To investigate the structural stability of the compounds, NMR spectra of the compounds dissolved in D_2O and mixed DMSO-d_6/D_2O (v/v: 2/1) solvents were obtained on immediate dissolution and later at 24 h and after 3 days 72 h at room temperature in mixed DMSO-d_6/D_2O and at 37 °C in D_2O. A minimum of 30 mg/mL of representative gold(III) compounds **1, 2** and **3** were subjected to ^{1}H and ^{13}C NMR spectra analysis followed by dissolution

Table 7 Crystallographic data for compound **1**

Compound	1
Emperical formula	$C_9H_{24}AuCl_3N_4$
Formula weight	491.64
Crystal size/mm	0.15 × 0.3 × 0.09
Wavelength/Å	0.71073
Temperature/K	173 (2)
Crystal symmetry	Monoclinic
Space group	P21/m
a/Å	10.139 (2)
b/Å	7.2586 (11)
c/Å	11.458 (4)
α/°	90
β/°	115.55 (2)
γ/°	90
V/Å^3	760.8 (3)
Z	4
D_c/Mg m^{-3}	2.146
μ(Mo-Kα)/mm^{-1}	6.92
F(000)	472
θ Limits/°	2.0–25.7
Collected reflections	5312è
Unique reflections (R_{int})	985 (0.269)
Observed eflections [$F_o > 2\sigma(F_o)$]	1565
Goodness of fit on F^2	1.05
$R_1(F)$, [a][$I > 2\sigma$ (*I*)]	0.158
wR_2 (F^2), [b][$I > 2\sigma(I)$]	0.407
Largest diff.peak, hole/e Å^{-3}	7.02, −2.72

in D_2O and DMSO-d_6/D_2O (v/v: 2/1, 1 mL). The duplicate samples were dissolved and immediately then stored at room temperature and 37 °C, respectively, and followed by determination of stability through NMR measurements for compounds **1**, **2** and **3** over time periods of 24 h and 72 h.

Electrochemical measurements

The cyclic voltammetric (CV) measurements were performed at room temperature using a potentiostat (CHI1232 A, CH Instruments, Austin, TX). All measurements were performed on solutions deaerated by bubbling ultra-pure argon for 5 min. The electrochemical cell contained a glassy carbon electrode (GCE; 3.0 mm diameter, Model CHI104, CH Instruments, Austin, TX) as a working electrode, Ag/AgCl

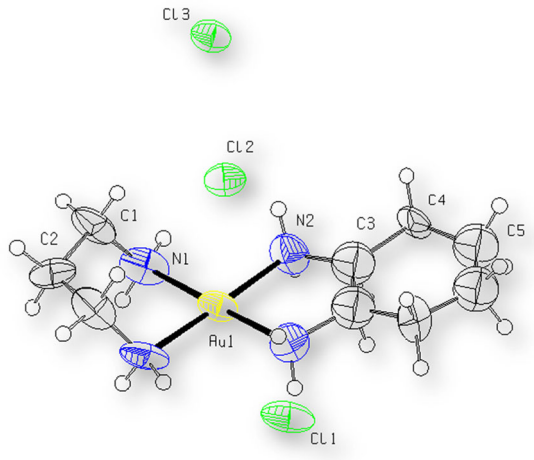


Fig. 1 A view of the molecular structure of mononuclear complex 1, with partial atom labelling scheme and displacement ellipsoids drawn at 50 % probability level

Sat. KCl reference electrode (Model CHI111, CH Instruments, Austin, TX), and a platinum wire counter electrode were inserted into a 2 mL glass cell through holes in its Teflon cover. Before each CV measurement, the GCE was polished with 3.0 and 0.05 μm alumina slurries and washed with double distilled water. Each CV measurement was performed at room temperature in a quiescent 0.1 M phosphate buffer (pH 7.0) aqueous solution, and with an initial potential of −0.5 V and final potential of +1.2 V. The values of potential reported here were measured against an Ag/AgCl Sat. KCl reference electrode. The cyclic voltammetry of the compounds **1, 2** and **3** were measured in absence and presence of model protein at a scan rate of 100 mV/s and a sample interval of 1 mV.

MTT assay for inhibitory effects of [{(1,2-DACH)}Au(pn)]Cl_3 compounds, **1–3** on PC3 and SCG7901 cancer cells

An MTT assay was used to obtain the number of living cells in the sample. Human gastric cancer SGC7901 and prostate cancer PC3 cells were seeded on 96-well plates at a predetermined optimal cell density, i.e. ca 6000 cells/100 μL per well in 96-well plates, to ensure exponential growth in the duration of the assay. After24 h pre-incubation, the growth medium was replaced with the experimental medium containing the appropriate drug, using one of 1,2-diaminocyclohexane (1,3-diaminopropane)gold (III) chloride compounds **1**,

2 and **3** or a control using water. Six duplicate wells were set up for each sample and cells untreated with drug served as a control. In one set of culture plates, human gastric cancer SGC7901 and human prostate PC3 cells were treated with 10 μM compounds **1**, **2** and **3** as the drug and the control (water) for 24, 48 and 72 h. In other sets, the compounds **1**, **2** and **3** with different concentration, i.e. 10, 20 and 30 μM, were employed to determine the growth inhibitory effect for both PC3 and SGC7901cells separately. After incubation, 10 μL MTT (6 g/L, Sigma) was added to each well and the incubation was continued for 4 h at 37 °C. After removal of the medium, MTT stabilization solution [dimethylsulfoxide (DMSO):ethanol = 1:1] was added to each well, and shaken for 10 min until all crystals were dissolved. Then, theoptical density was detected in a micro plate reader at 550 nm wavelength using an Enzyme-Linked Immuno-Sorbent Assay (ELISA) reader. After being treated with the (1,2-diaminocyclohexane)(1,3-diaminopropane)gold(III) chloride compounds, **1**, **2** and **3**,the cell viability was examined by MTT assay. Each assay was performed in triplicate. An MTT assay for the inhibitory effect has been used for compounds **1**, **2** and **3** against PC3 and SGC7901 cells. These cells were treated with various concentrations of compounds **1**, **2** and **3**for 24–72 h. The results are shown in Figs. 2, 3, 4 and S2, S3, S4 and S5.

In vitro cytotoxic assay for PC3 and SGC7901 cancer cells

Human prostate PC3 and gastric SGC7901 cells were used in this study. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % fetal calf serum (FCS), penicillin (100 kU L^{-1}) and streptomycin (0.1 g L^{-1}) at 37 °C in a 5 % CO_2–95 % air atmosphere. Human gastric SGC7901 cells and prostatePC3 were incubated with these compounds at fixed concentrations or with water as a control to assess the inhibitory effect on cell growth. The standard MTT assay has been used to assess the inhibitory effect on cell growth. The cell survival versus drug concentration is plotted. Cytotoxicity was evaluated in vitro with reference to the IC_{50} value. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound to inhibit biological or biochemical functions. According to the FDA, IC_{50} represents the concentration of a drug/compound/complex that is required for 50 % inhibition in vitro. It is evaluated from the survival curves as the concentration needed for a 50 % reduction of survival. IC_{50} values are expressed in μM. The IC_{50} values were calculated from dose–response curves obtained in replicate experiments, as shown in Table 8.

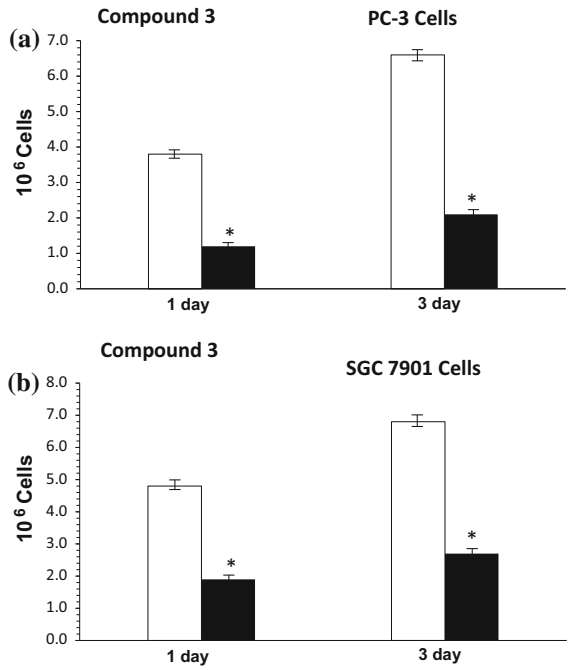


Fig. 2 Effect of (1*S*,2*S*)-(+)-1,2-(DACH)gold(III)(pn) complex on cell growth in **a** PC-3 and **b** SGC-7901 cells. The cells were treated with 10 μM of the compound (**3**) for 1 day and 3 days. The anti-proliferative effect was measured by MTT assay. Results were expressed as the mean, SD. *P < 0.05

Results and discussion

Electronic spectra

The λ_{max} values obtained from UV–Vis spectra for the complexes studied are shown in Table S1. The gold(III) complexes **1**, **2** and **3** exhibit, in a reference buffered phosphate solution, intense absorptions in the range 332–341 nm, which are assigned as ligand-to-metal charge-transfer (LMCT) transitions characteristically associated to the gold(III) center (Esumi et al. 1998). It is worth mentioning that these spectral features appear only at relatively high pH values (pH > 6–7) at which the deprotonation of the ligand has fully occurred. According to crystal field theory

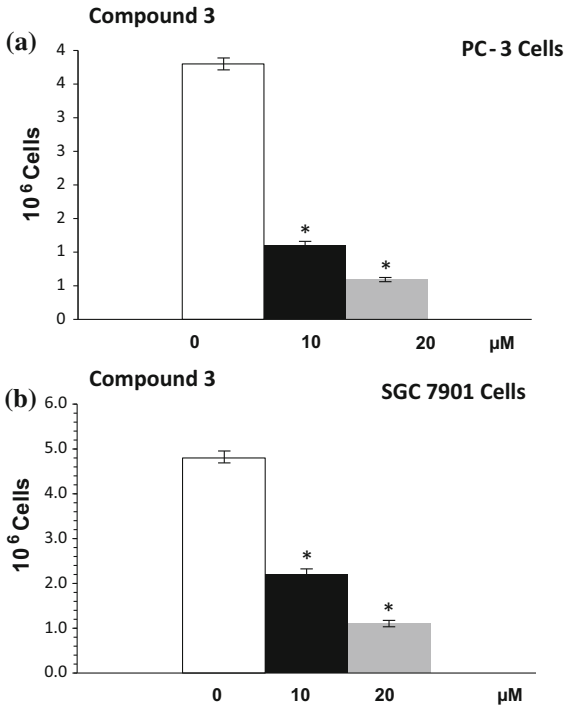


Fig. 3 Effect of (1*S*,2*S*)-(+)-1,2-(DACH)gold (III)(pn) complex on cell growth in **a** PC-3 and **b** SGC-7901 cells. The cells were treated with various concentrations of the compound (**3**) for 24 h. The anti-proliferative effect was measured by MTT assay. Results were expressed as the mean, SD. *P < 0.05

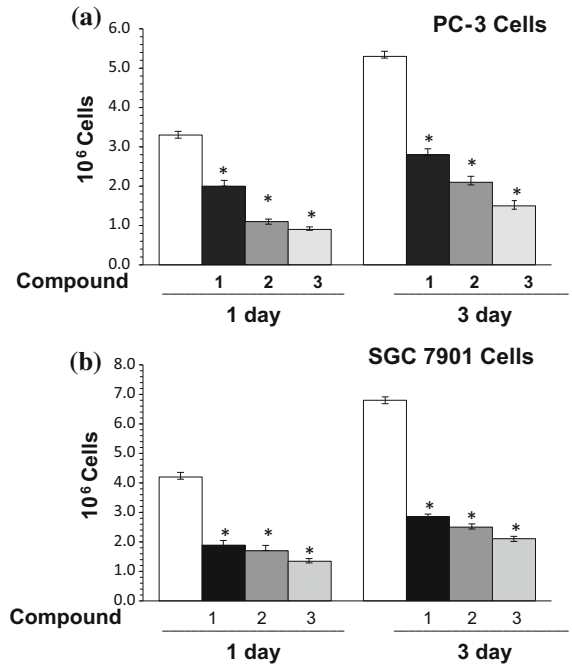


Fig. 4 Effect of compounds **1**–**3** on cell growth in **a** PC-3 and **b** SGC-7901 cells. The cells were treated with 10 μM of the compounds 1 and 2 for day 1, day2 and day 3. The anti-proliferative effect was measured by MTT assay. Results were expressed as the mean, SD. *P < 0.05

for d^8 complexes the lowest unoccupied molecular orbital (LUMO) orbital is $d_{x^2-y^2}$, so ligand to metal charge transfer could be due to $p_\sigma \rightarrow d_{x^2-y^2}$ transition (Haruko et al. 1967). Additionally, there was no absorption observed at around 293 nm (Al-Jaroudi et al. 2013), which corresponds to charge transfer of the counter ion, chloride to gold(III) indicating the absence of the dichlorido(1,2-DACH)gold(III) chloride complex.

The electronic spectra of compounds **1, 2** and **3** were monitored at 37 °C over 3 days after mixing in the buffer solution. The electronic spectra for compounds **1, 2** and **3** at just after mixing; and after 3 days are illustrated in Figure S6. It is apparently observed that the transitions remain relatively unmodified over a period of 3 days. Such observations show a substantial evidence for the stability of these compounds **1, 2** and **3** under the conditions of solution state. Nevertheless, a slight decrease in intensity of the characteristic bands was noticed with time without significant modifications in the shape of spectra. Further, such observation indicates that the gold center in these compounds remains in the +3 oxidation state. The minor spectral changes that are generally observed within the first few hours may be ascribed either to dissociation of the diamine ligands from the gold(III) complex or to partial reduction of gold(III) to metallic gold. In general, however, loss of spectral intensity is lower than 10 % of the original intensity within the

Table 8 In vitro cytotoxicity data of the complexes **1**, **2** and **3** after the exposure of 72 h towards human cancer SGC7901 and PC3 cell lines

IC_{50}^{a} (μM)		
Compounds	SGC7901	PC3
Cisplatin	7.3 ± 0.5	1.1 ± 0.1
1	10.8 ± 0.2	9.5 ± 0.2
2	10.9 ± 0.1	10.2 ± 0.1
3	10.1 ± 0.1	9.1 ± 0.1

[a] Concentration of sample required to reduce the cell growth of tumor cell line by 50 %

observation period of 3 days, which indicates the high stability of these compounds in the buffer.

It is a possible proposition that compounds **1, 2** and **3** would be stable enough in the physiological environment to undergo the necessary reactions/interactions required for bioactivity, without decomposition.

Mid and Far-IR spectroscopic studies

The most significant bands recorded in the FT-IR spectra of the ligands and [{(1,2-DACH)}Au(pn)]Cl_3 complexes are reported in Tables 2 and 3. It is observed that N–H stretching vibrations of complexes **1–3** exhibit, in the range 3426–3452 cm^{-1}, blue shifting compared with the amino group of the corresponding free ligands. This is most likely due to stronger H-bonding interactions in the free ligands as compared to two coordinated amino groups (–NH_2). The coordination of amino groups (–NH_2) with Au(III) center via nitrogen donor atoms and formation of Au–N bond can be supported by the presence of a ν(Au–N) band at 425-451 cm^{-1} in the Far-IR (Beck et al. 1967). The C–N stretching bands also showed a significant shift to higher wave number, indicating a shorter C–N bond in the compound than in the free ligand. Moreover, there was no signal observed at 352 and 367 cm^{-1} corresponding to the symmetric and asymmetric stretching of the Cl–Au-Cl bonds as in [(1,2-DACH)$AuCl_2$]$^+$ complexes (Al-Jaroudi et al. 2013). The [{(1,2-DACH)}Au(pn)]Cl_3 complexes **1–3** show N–H stretching frequencies generally lower in comparison with [{(1,2-DACH)}$AuCl_2$]Cl complexes (Table 2), most probably due to stronger hydrogen bonding interactions with the chloride anions in the [(1,2-DACH)Au(pn)]Cl_3 complexes. Furthermore the Au–N stretching frequencies are consistent with weaker Au–N bond strength in complexes **(1–3)** compared to [(1,2-DACH)$AuCl_2$]Cl complexes.

Solution NMR characterization

The ^{1}H and ^{13}C NMR chemical shifts of compounds **(1–3)** along with their corresponding free ligands are listed in Tables 4 and 5, respectively. All ^{1}H NMR spectra supported the structures of the synthesized complexes as indicated by the integration of the signals of C–H protons connected to the amino groups of the DACH and pn ligands. For instance, the ratio of the C-H protons attached to the amino groups in both DACH and pn for complex **3** is 1:2 as depicted in Figure S7. The ^{13}C NMR spectrum is also consistent with the complex's structure as shown in Figure S8. In the ^{1}H and ^{13}C NMR spectra of complexes (**1**, **2** and **3**), one-half of the total expected signals were noticed because of the C_2 symmetry axis. 1,2-diaminocyclohexane ring is considered as a rigid conformer that allowed, to distinguish the equatorial H3 and H6 from the axial H3 and H6 protons at room temperature. The signals of C–H protons connected to the amino groups for (DACH) occur in the spectra at 3.07 to 3.65 ppm, shifting downfield compared with the corresponding signals (2.23–2.25 ppm) in the free DACH ligand. On the other hand, the signals of C-H protons connected to the amino groups for pn appear in the spectra at 2.91 to 2.94 ppm, shifting slightly upfield compared with the corresponding signals (2.98 ppm) in the free ligand. The significant downfield shift was observed at 3.62 ppm for complex **1** with respect to the free DACH ligand at 2.23 ppm.

In ^{13}C NMR downfield shift was observed only for the carbon next to the bonding nitrogen and the others carbons in the complex for (DACH) showed an upfield shift. For instance, the chemical shifts of C3 and C4 for complex **1** are observed at 26.92 and 20.73 ppm, respectively, whereas, for free diamine ligand they occur at 35.26 and 26.36 ppm respectively. It is also worth to mention that complexes **1–3,** even though they have the same skeleton of DACH and pn, their NMR chemical shifts specifically for DACH ligands are not same due to a difference in stereochemistry upon complexation.

Solid-state NMR

At the spinning rate of 4 kHz, the isotropic signals for all complexes were not observed for the carbons, indicating the absence of the anisotropy that could take place due to the sp^3 hybridization of these atoms. Solid state NMR spectra of complexes **1** and **2** showed equivalency in the chemical shifts of carbon atoms (C1,C2), (C3,C6), (C4,C6) and (C1′,C2′) two sets of peaks, whereas, similar observation was not attained for carbon atoms of DACH in complex **3** as listed in Table 6. This indicates that complex **3** in the solid state lacks C_2 symmetry. In contrast, all synthesized complexes **1, 2** and **3** showed C_2 symmetry in the solution state as indicated earlier by solution ^{1}H and ^{13}C NMR.

Significant de-shielding in the solid state is observed with similarity in the chemical shift among all synthesized complexes (Table 6) which is a clear indication of formation of the prepared complexes in solid state.

Computational Study and Crystal structure of compound **1**

The molecular crystal structure of complex [(*cis*-DACH)Au(pn)]Cl_3 (**1**) is shown in Fig. 1. The selected bond distances and angles are given in Table S2. The complex is mononuclear and ionic consisting of a complex cation, $[(cis\text{-DACH})Au(pn)]^{3+}$ and three chloride ions in the outer sphere of the complex. The central Gold(III) atom is coordinated with four NH_2 donor groups of the *cis*-1,2-diaminocyclohexane and 1,3-diaminopropane ligands and adopts a somewhat distorted square planar geometry as indicated by the bond angles around gold (Table S2). The *cis* angles around gold are 87° and 93.2°, while the *trans* angles are 177.8°. The complex cation contains one five-membered chelate ring, AuN2C2 and one six-membered chelate cycle, AuN2C3. The cyclohexyl ring of 1,2-DACH attains a boat conformation. The Au1–N1 and Au1–N2 bond distances of 2.03(3) and 2.01(3) Å respectively, are similar to the reported values of the related structures (Al-Jaroudi et al. 2013; 2014). The similarity of bond angles around gold(III) ion in complex **1** provides an evidence for the presence of a centro-symmetric geometry in complex **1**. The complex cation and chloride ions are associated to each other through electrostatic and H-bonding interactions.

Deeper insight into the structural features was obtained by theoretical calculations. There is a good agreement between the experimental and calculated structural parameters for almost all bond distances and angles, which provides more support to the crystallographic findings (Table S2). The optimized structures of the $[(DACH)Au(pn)]^{3+}$ complexes obtained from the B3LYP/LANL2DZ level of calculations are shown in Figure S9. From the computed energetics of the four structures of the complex **1**–**3** (Table S3), the *trans* conformations were found more preferable compared to the *cis* conformations with a more than 3.59 kcal/mol energy difference. A possible explanation of this energy variation is the ring configuration of the DACH ligand, where in the *cis* form the CH_2 units experience more steric repulsion compared to that in the *trans* form.

Stability study of mixed diamine ligand gold(III) compounds

In order to check the stabilty of compounds, the ^1H and ^{13}C NMR spectra of the complexes were obtained upon immediate dissolution (to serve as reference spectra) and later at 24 h and after 7 days at 37 °C in D_2O and at room temperature in mixed DMSO-d_6/D_2O (2:1). Figures S10 and S11 illustrate the ^1H and ^{13}C NMR profiles of the compound **1**, just after mixing and after 7 days respectively. These compounds in the mixed DMSO-d_6/D_2O solvent system were found less stable at the experimental conditions, in which, dissociation of 1,3-diaminopropane (pn) out of the gold complexes was observed in 24 h. On the other hand, no dissociation was observed for 1,2-DACH. Among all synthesized complexes, the maximum dissociation for 1,3-diaminopropane (pn) after 7 days was experienced for compound **3** (approximately 50 %). The ^1H and ^{13}C NMR profiles of compound **3** in DMSO-d_6/D_2O at just after mixing and after 7 days are shown in Figures S12 and S13 respectively. The spectra after 7 days in DMSO-d_6/D_2O showed extra peak at 2.86 and 1.86 ppm and 37.26 and 25.77 ppm as shown in Figures S10 (b)-S11 (b), respectively, corresponding to the free pn ligand. It can be concluded that the bond between gold(III) and (1,2-DACH) is stronger than the bond between gold(III) and pn in the complexes **1**–**3**, suggesting that 1,3-diaminopropane (pn) is a better leaving group in these mixed ligands complexes.

Protein interaction studies of complexes **1**–**3**

The electrochemical behavior and interaction with model proteins of compounds **1**, **2** and **3** were investigated in a physiological environment through cyclic voltammetry (CV). The cyclic voltammetric curves of the complex **3** in absence and presence of different concentrations of hen egg white lysozyme and bovine serum albumin (BSA) are shown in Fig. 5a, b respectively. Table S4 summarizes the cyclic voltammetric data of the study. The btained cyclic voltammetric data indicated that gold(III) complexes show a well-defined reduction peak around −0.205 V, due to the occurrence of Au(III)/Au(0)

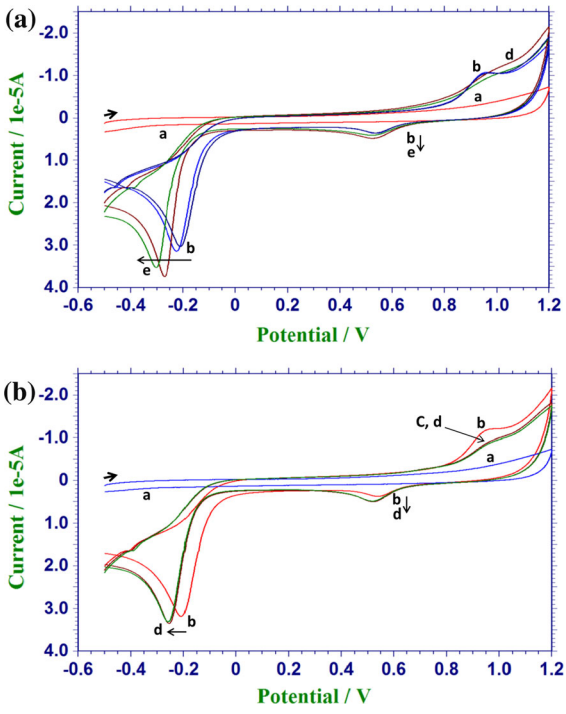


Fig. 5 Cyclic voltammograms in phosphate buffer aqueous solution (0.1 M, pH 7.0) at a GCE in absence (*a*) and presence (*b*) of 1.0 mM [{(1S,2S)-(+)-1,2-(DACH)}Au(pn)]Cl_3, and subsequent additions of **a** Lysozyme concentrations: (*c*) 0.7, (*d*) 7.0 and (*e*) 35 μM, and **b** BSA concentrations: (*c*) 7.5 and (*d*) 15 μM. Electrochemistry working conditions of scan rate, 100 mV/s and sample interval, 1 mV

reduction. In general, cyclic voltammetric results suggest that these compounds are relatively stable under the physiological conditions. The interactions of the present effective anticancer and antimetastatic gold(III) complexes with protein targets, deserve great attention, as they are believed to be at the basis of the mechanism of action of these innovative molecules. The interaction of complexes **3** with two well-known model proteins, namely, hen egg white lysozyme and bovine serum albumin (BSA) was also checked in the reference phosphate buffer medium. Figure 5a shows the interaction of 1 mM of compound **3** with 0.7, 7.0 and 35 μM lysozyme, that caused potential shifts of 20, 70 and 100 mV, respectively. Less potential shifts (50 and 56 mV) were obtained after the additions of 7.5 and 15 μM BSA protein to the same concentration of compound **3** (Table S4). Thus, compound **3** exhibits a stronger interaction with lysozyme from BSA protein. In view of the intrinsic complexity of this matter, it is evident that much work is needed in order to predict interactions of metallodrugs with proteins actually occurring inside cells.

Antiproliferative effects of gold(III) complexes **1**–**3** on prostate (PC3) and gastric (SCG7901) cancer cells

Gold(III) complexes with various ligands including Au–N, Au–S or Au–C bonds have been extensively developed and investigated for their bioactivities as antiproliferative agents (Burchenal et al. 1977; Bruck et al. 1984). In this work, a new series of gold(III) complexes (**1**–**3**) containing mixed 1,3-diaminopropane (pn) and 1,2-DACH ligands are being evaluated for antiproliferation against PC3 and SGC7901 cancer cell lines. Figures S2, S3 and 2 illustrated time dependent antiproliferative effects of complexes **1**, **2** and **3** respectively. In the time dependent experiments, the growth inhibition on PC3 and SGC7901cancer cells was studied using fixed concentration i.e. 10 μM. It is clearly evident from Figures S2, S3 and 2 that time dependent antiproliferative effects of *trans*-DACH complexes **2** and **3** on PC3 cancer cells are much better than those on SGC7901 cancer cells. However, it is vice versa for time-dependent antiproliferative effects for *cis*-DACH complex **1.** Complex **3** showed better cell inhibition against both PC3 and SGC7901 cell lines than complexes **1** and **2** as shown in Figures S2, S3 and 2. Gold(III) complexes **2** and **3** demonstrated a comparable cell inhibition; against tested cell lines as shown in Figure S3 and 2, whether the complexes exposure time was 24 or 72 h. All the gold(III) complexes showed lower cell inhibition against both cancer cell lines for 72 h exposure time compared to 24 h as shown in Figs. S2, S3 and 2.

As we know, the cell growth inhibition also depends on the concentration of the drug. So, we made concentration dependent cell growth inhibition study of gold(III) complexes **1**–**3** against human prostate PC3 and gastric SGC7901 cancer cell**s** by using 10 and 20 μM concentrations. The results were according to the expectation that the cell inhibition was augmented with the increase in concentration of the complexes **1**, **2** and **3** as shown in Figs. S4, S5 and 3 respectively. It is generally observed from Figures S4, S5 and 3 that concentration dependent antiproliferative effects of complexes **1**, **2** and **3** on Cancer PC3 cells are superior to those on SGC7901 cancer cells. In the concentration-dependent cell growth inhibition

study at two concentrations (10 and 20 μM), complex **1** showed much better cell inhibition against PC3 cancer cell line than complexes **3** and **2** as shown in Figures S4, S5 and 3. The complexes **2** and **3** demonstrated a comparable cell inhibition; against both PC3 and SGC7901 cell lines as shown in Figs. S5 and 3 respectively.

Figure 4 illustrated the comparison of time-dependent antiproliferative effects of 10 μM complexes **1**, **2** and **3** on both PC3 and SGC7901 cancer cells for 24 and 72 h. It has been observed that the order of time-dependent antiproliferative effect is complex **3** > complex **2** > complex **1** for both PC3 and SGC7901 cancer cells. Such comparative study leads to the conclusion that complex **3** is the most effective antiproliferative agent among the mixed ligand gold(III) complexes **1–3**.

Even though the exact mechanisms on antiproliferation of $[(DACH)Au(pn)]Cl_3$ type complexes on PC3 and SGC 7901 cancer cell lines remains vague. The significantly diminished renal toxicity of $[(DACH)Au(pn)]Cl_3$ complexes could be attributed to their different antiproliferative mechanism of action and selective sparing of the proximal tubular epithelial cells (Ahmed et al. 2012).

Most gold(III) compounds display reduced affinity for DNA and it seems reasonable that DNA is neither the primary nor the exclusive target for most gold(III) complexes. Although it was originally thought that gold(III) complexes might have the same molecular target as cisplatin, several lines of data indicated that proteins, rather than DNA, are targeted by gold complexes. It has been suggested that the tumor proteasome is an important target for gold(III) complexes and it has been shown that proteasome inhibition by gold(III) complexes is associated with apoptosis induction in breast cancer cells in vitro and in vivo (Milacic and Duo 2009). Some studies also suggest mitochondria as potential targets involved in the cytotoxic activities of gold(II) complexes since they markedly inhibit the activity of mitochondrial enzyme, thioredoxin reductase (Saggioro et al. 2007; Cattaruzza et al. 2011).The mechanism of the complexes is although not precisely delineated, the mechanisms associated with the inhibitory effects of complexes **1–3** on the proliferation of rapidly dividing cancer cells may be comprised of a cumulative impact on the induction of cell cycle blockage (Taatjes et al. 2008), interruption of the cell mitotic cycle (Takemura et al. 2013), apoptosis (programmed cell death) (Hayashi et al. 2014; Vivek et al. 2009; Niemeyer 2001; Pellegrino et al. 2005) and necrosis (premature cell death) (Allen et al. 1987).

In vitro cytotoxicity of gold(III) complexes **1–3** on prostate (PC3) and gastric (SCG7901) cancer cells

The in vitro cytotoxic effect of mixed ligand gold(III) diamine complexes against androgen-resistant prostate PC3 and human gastric SGC7901 cancer cells were studied using MTT assay. The in vitro cytotoxic activity depends on the exposure time and the concentration of complexes. For that reason, we used different concentrations and a 3-day exposure protocol to determine the IC_{50} values for all three complexes. The in vitro cytotoxicity in terms of IC_{50} values of cisplatin for PC3 and SGC7901 cells was included for a comparison.

The IC_{50} data for the Au(III) complexes **1, 2** and **3** showed in vitro cytotoxicity in a wide range of 1.1–10.2 μM concentrations of complexes for PC3 cells, as given in Table 8. For PC3 cancer cells, the order of in vitro cytotoxicity in terms of IC_{50} values is cisplatin (1.1 μM) > complex **3** (9.1 μM) > complex **1** (9.5 μM) > complex **2** (10.2 μM). It is known that lower the IC_{50} value, higher is the in vitro cytotoxicity. All three complexes showed similar cytotoxic activities, and they have lower potency *vis-a-vis* cisplatin. Complex **3** is comparitively better cytotoxic agent than **1** and **2** for PC3 cancer cells.

The IC_{50} data for the Au(III) complexes **1, 2** and **3** showed in vitro cytotoxicity in the range of 10.1–10.9 μM for SGC7901 cells, as given in Table 8. It is apparent from IC_{50} data for SGC7901 cancer cells that complexes **1, 2** and **3** showed in vitro cytotoxicity comparable to cisplatin. Complex **3** seems better cytotoxic agent than **1** and **2** for SGC7901 cancer cells. The order of in vitro cytotoxicity in terms of IC_{50} values is cisplatin (7.3 μM) > complex **3** (10.1 μM) > complex **1** (10.8 μM) > complex **2** (10.9 μM). It is worth mentioning that the in vitro cytotoxicity of the complexes **1–3** are fairly similar to cisplatin. There is no doubt that the present study would be helpful for further exploiting and defining the potential role of gold(III) complexes in combating against prostate and gastric cancers.

Conclusion

Three gold(III) complexes (**1**–**3**) containing 1,3-diaminopropane (pn) and 1,2-diaminocyclohexane (1,2-DACH) were prepared and characterized using a number of analytical techniques that support the formation of the mixed (pn and 1,2-DACH) ligands gold(III) complexes (**1**–**3**) with general formula [(1,2-DACH)Au(pn)]Cl_3 (1,2-DACH represent three isomeric ligands) The spectroscopic methods and NMR measurements confirm the formation of gold(III) complexes containing bidentate pn and 1,2-DACH ligands and coordinated via N-donor atoms. The X-ray structure of compound **1** demonstrates that gold atom in this compound adopts a distorted square-planar geometry. The computational studies demonstrate that [*trans*-(1,2-DACH)Au(pn)]$^{3+}$ isomer is slightly more stable than the [*cis*-(1,2-DACH)Au(pn)]$^{3+}$ isomer. According to antiproliferative effects of gold(III) complexes **1**–**3** on prostate (PC3) and gastric (SCG7901) cancer cells, the order of time-dependent antiproliferative effect is complex **3** with (1*S*,2*S*)*(+)*- configuration > complex **1** with *cis*- configuration > complex **2** with *trans*-configuration for both PC3 and SGC7901 cancer cells. Such comparative study leads to conclusion that complex **3** with (1*S*,2*S*)*(+)*- configuration of 1,2-DACH is the most promising antiproliferative agent among mixed ligand-based gold(III) complexes **1**–**3**. There is no doubt that the present study would be helpful for further exploiting and defining the potential role of gold(III) complexes in the treatment of human prostate and gastric cancers. In short, [{(1*S*,2*S*)-(+)-1,2-(DACH)}Au(pn)]Cl_3 might be a potential chemopreventative and chemotherapeutic agent against human gastric SGC7901 cancer cells. As complex **3** exhibits interaction with lysozyme and BSA proteins, we would like to recommend an in vivo anticancer evaluation of complex **3** for further exploration of its anticancer activity. Much work is also needed in order to predict interactions of these compounds with proteins actually occurring inside cells.

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Compliance with ethical standard

Conflict of interest The authors declared there is no conflict of interest.

Ethical statement The authors would like to confirm that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, as well as by the responsible authorities—tacitly or explicitly—at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Research involving human participants and/or animals and informed consent There was no experiment carried out using human or animals.

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