Synthesis and characterization of complexes of trialkyl- and triarylphosphine gold(I) with thiolated purines and pyrimidines: a class of bifunctional compounds with potential antitumor activity

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Abstract

New complexes of the type R_3PAuL or $(R_3PAu)_2(\mu\text{-L})$ where R = ethyl or phenyl and L = 6-thioguanine, 2,6-dithioxanthine, 2,4-dithiouracil and/or dithioerythritol have been prepared. These complexes have been identified by using elemental analysis, ^1H, ^{13}C and ^{31}P NMR spectroscopy. The structures have been proposed based on these spectroscopic studies. Sulfur appears to be the binding site in disubstituted complexes of 2,4-dithiouracil and 1,4-dithioerythritol, while the phosphine gold(I) moieties appear to be S and N bonded in 2,6-dithioxanthine and 6-thioguanine. The potential use of these complexes as antitumor drugs is discussed.

Introduction**

The reported evidence of antitumor activity of complexes of several metal ions, in addition to the well known activity of platinum complexes [1], underscores the potential efficacy of transition metal complexes as therapeutic agents in the clinical treatment of neoplastic diseases.

In the last decade, investigations of the antitumor activity of gold complexes received much attention. The gold(I) derivative, Auranofin, (2,3,4,6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-S) triethylphosphine gold(I), besides being a potent antiarthritic drug, has proved to be an effective cytotoxic agent against both B16 melanoma cells and P388 leukemia cells and to possess a significant *in vivo* antitumor activity in mice inoculated with the lymphocytic leukemia P388 [2, 3]. *In vitro* studies of He La cell cultures [4] indicate that Auranofin irreversibly inhibits DNA synthesis in a manner similar to that of cisplatin [5], while RNA and protein synthesis is less affected. Et_3PAuCl and Et_3PAuBr interact with the guanine and cytosine groups of calf thymus DNA in a non-denaturing fashion [6].

In an attempt to define a structure–activity relationship, a number of complexes of general formula LAuX has been examined for cytotoxicity *in vitro* and antitumor activity *in vivo* [7]. In general, it appears that trialkylphosphine and thiosugar ligands maximize the potency of the drug.

We have previously synthesized two binuclear complexes of gold with bridging dithiolate ligands [8], which were tested for antitumor activity against Ehrlich Ascites tumor cells in mice. In this work we present the synthesis and characterization of a number of complexes where gold(I) is coordinated to trialkyl- or triarylphosphine and to a thiolated nucleobase (e.g. 6-thioguanine, 2,6-dithioxanthine, 2,4-dithiouracil). The latter ligands possess antitumor activity on their own, 6-thioguanine in particular besides being a bacterial growth inhibitor is an established clinical agent for the therapy of human leukemia [9].

These thiolated molecules have seen only limited use in therapy as single agents. The possibility that they may act in a synergistic fashion with the R_3PAu^+ moiety as bifunctional antitumor agents provides a stimulus for synthesizing and characterizing these gold adducts.

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**Abbreviations: H_2DTE = dithioerythritol, its dianionic form abbreviated as DTE; s^6Gua = 6-thioguanine; s^2s^6Xan = 2,6-dithioxanthine; s^2s^4Ura = 2,4-dithiouracil.

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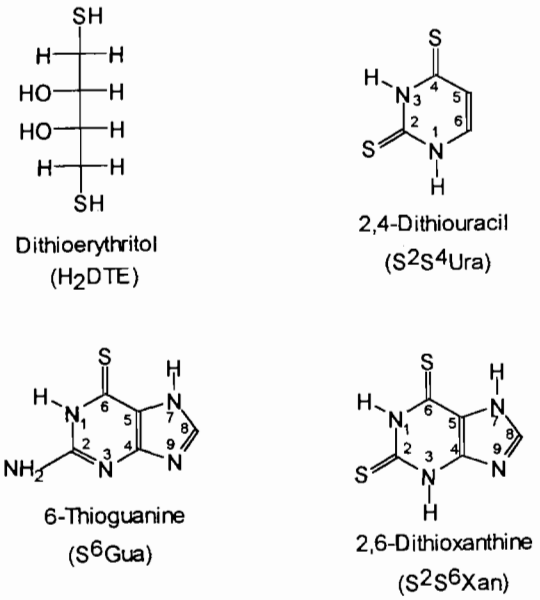

Fig. 1. Structures of the ligands.

The closely related 6-mercaptopurine and its Cu^{2+} complex are also reported to possess antiinflammatory activity [10] a property which is common with the gold(I)–thiolate drugs. The $(Et_3PAu)_2(\mu\text{-DTE})$ complex is the analogue of the triphenylphosphine gold(I) derivative previously reported [8], the ligand being a model for the widely investigated thioglucose complexes. The structures of the ligands are reported in Fig. 1.

Experimental

Reagents

Dithioerythritol and all thiolated bases were purchased from Sigma Biochemical Co. (St. Louis, MO, USA). Et_3PAuCl was generously provided by Smith Kline and French Laboratories; Ph_3PAuCl was prepared according to published procedures [11].

Spectroscopic measurements

IR spectra of the complexes were obtained as split mulls on Nicolet 5DXB FT IR and Perkin-Elmer 983G spectrometers in the 4000–180 cm^{-1} region.

^1H NMR spectra for DMSO-d_6 solutions were recorded on a Brucker WP 80 instrument operating at 80.13 MHz; chemical shifts are relative to internal TMS. $^{13}C\{^1H\}$ NMR spectra were obtained on a Brucker WM 250 multinuclear FT NMR spectrometer operating at 62.9 MHz. Chemical shifts δ were measured for solution in DMSO-d_6 and are reported relative to the sodium salt of 3-(trimethylsilyl)propionionic-2,2,3,3-d_4 acid (TSP) as an external reference.

Typical parameters were 45° pulse, 1.0 s repetition time and 16K data points. Most of the complexes were sparingly soluble in most solvents including DMSO. Therefore, although ^{13}C NMR spectra were run more than 24 h, resonances still could not be observed in some cases.

$^{31}P\{^1H\}$ NMR spectra were obtained for DMSO-d_6 or $CDCl_3$ solutions of the complexes on a Brucker WM 250 (multinuclear) NMR spectrometer operating at 101.3 MHz. Chemical Shifts are reported by using trimethyl phosphate (TMP, $\delta p = +2.74$ ppm relative to external reference 85% H_3PO_4) as an internal standard. Typical acquisition parameters were 45° pulse, 0.54 s repetition time and 16K data points. The spectral windows were -30 to $+110$ ppm. Approximately 5000–10 000 scans were accumulated for each NMR measurement.

Synthesis

All complexes are neutral and have been prepared by a simple metathetical reaction, driven by the nucleophilic attack of the anionic form of the ligands on the R_3PAuCl moiety, followed by displacement of the chloride ion.

C, H and N analyses were performed by UWM Chemistry Department, microanalytical service and by Laboratorio di Microanalisi, Dipartimento di Chimica Organica e Industriale dell'Universita, Milan (Italy). Analytical data and melting points are reported in Table 1.

$(Et_3PAu)_2(\mu\text{-DTE})$

H_2DTE (1.02 mmol, 157.3 mg) was dissolved in 20 ml of a mixture of ethanol and water (50% vol./vol.) and solid Et_3PAuCl (2 mmol, 701 mg) was added under vigorous stirring. A white precipitate appeared and the solution turned strongly acidic, indicating that reaction had occurred. The pH was adjusted to 6 with aqueous NaOH (0.10 M). Additional precipitate was formed. Stirring was continued for 1 h in the dark and at ice temperature. The solid was filtered then extracted with three aliquots of chloroform (5 ml each). The solutions were pooled together and evaporated to dryness (amber oil). The oil was kept over P_4O_{10} for 2 days, then attached to a vacuum line to yield a white crystalline solid. The compound is soluble in chlorinated solvents.

An attempted synthesis of the complex using absolute ethanol as a solvent, with no aqueous NaOH added, resulted in a mixture of solid products from which the Et_3P group was absent, as evidenced by ^{31}P NMR. Under these conditions apparently the thiolated ligand is causing the displacement of Et_3P from the gold moiety.

TABLE 1. Analytical data of the gold(I) compounds[a]

Compound	C (%)	H (%)	N (%)	Colour	m.p. (°C)
$(Et_3PAu)_2(\mu\text{-DTE})$	24.55 (24.65)	4.85 (4.87)		white	105
$(Et_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$	25.10 (24.71)	4.30 (4.23)	8.60 (8.68)	light yellow	123 dec.
$(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$	25.13 (25.56)	3.93 (3.57)	6.90 (7.04)	off white	205 dec.
$(Ph_3PAu)(s^6GuaH_{-1})H_2O$	42.93 (42.87)	3.29 (3.15)	10.89 (11.10)	white	234 dec.
$(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})H_2O$	44.70 (44.27)	3.20 (3.02)	6.36 (6.24)	yellow	
$(Ph_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})H_2O$	44.00 (43.97)	3.06 (2.82)	5.01 (4.98)	yellow	188 dec.
$(Ph_3PAu)_2(\mu\text{-}s^2s^4UraH_{-2})H_2O$	44.54 (44.69)	2.97 (2.99)	2.59 (2.54)	yellow	133

[a]The corresponding calculated values are given in parentheses.

$(Et_3PAu)_2(\mu\text{-}s^6GuaH_{-2})H_2O$

6-Thioguanine (1.15 mmol, 192 mg) was dissolved in water by the addition of nearly two equivalents of NaOH (final volume 15 ml). Solid Et_3PAuCl (1.98 mmol, 695 mg) was added under vigorous stirring. An orange product immediately precipitated. Stirring was continued for 1 h, the precipitate filtered, washed with water, ethanol and chloroform and dried in vacuum over P_4O_{10}; yield 84%.

$(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$

$(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$ was prepared under similar conditions as mentioned above by mixing the reactants in 2:1 ratio, under gentle heating and vigorous stirring.

(Ph_3PAu) and $(Ph_3PAu)_2(\mu\text{-}s^6$ or $\text{-}s^2s^6$-nucleobase) complexes

The synthesis of hydrated complexes $Ph_3PAu(s^6GuaH_{-1})$, $(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$, $(Ph_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$ follows the same procedure outlined above for the triethylphosphine gold(I) derivatives.

(Ph_3PAu)-thionucleobase complexes

To obtain the 1:1 or 2:1 triphenylphosphinegold(I) complexes with s^6Gua, first 1 equiv. (or slightly more until the solid ligand dissolved) or 2 equiv. of NaOH were added followed by addition of the stoichiometric amount of Ph_3PAuCl. The yellow precipitates were washed thoroughly with water, ethanol and chloroform and dried *in vacuo*.

The same procedure was used in order to obtain $(Ph_3PAu)_2(\mu\text{-}s^2s^4UraH_{-2})$ except that in this case the same complex was obtained irrespective of the stoichiometric ratios (2:1 or 1:1) employed.

The limited solubility of these complexes with the notable exception of $(Et_3PAu)_2(\mu\text{-DTE})$ appears to be the major drawback of the complexes as potential drugs.

Results and discussion

The thiolated purines and pyrimidines are all ambidentate ligands since they offer a multiplicity of potential binding sites such as nitrogen and sulfur. It is worth noting that while in the case of s^6Gua complexes the electrophilic attack on the thiolated base could be accomplished in two steps, yielding both $(Ph_3PAu)(s^6GuaH_{-1})H_2O$ and $(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})H_2O$ derivatives, for the dithiolated base s^2s^6Ura, the base is acting as a dianionic species regardless of the stoichiometry of the reactants employed. It should be noted here that all ligands reacted with Et_3PAuCl at a 2:1 ratio yielded only $(Et_3PAu)_2L$ type complexes.

In the solid state, 6-thioguanine exists in the thione form, as the tautomer with the hydrogen atom bonded to N(7) rather than to N(9) as found in the crystal structure of guanine [12].

However in solution, and as a function of pH, different tautomers can be present [13] and pK_a values of 8.2 and 11.6, respectively, are reported [14].

The crystal structure of 2,4-dithiouracil supports the notion that bond lengths and bond order of carbon–sulfur bonds in pyrimidines are position dependent since the C–S distance at the 4 position is 0.04 Å longer than at the 2 position, also reflecting a greater degree of polarization in the C(4)=S bond [15]. Under the

experimental conditions used in this work, the 'soft' nature of both sulfur donor atom and gold(I) metal ion is predominant over any degree of electronic density imbalance on the S donors.

In solution, the structure of 2,6-dithioxanthine may resemble that of 2,6-dithiocaffeine [16]. For the latter, in comparison with caffeine, dipole moment measurements indicate a strong modification of the moment caused by the replacement of the O atom linked to C(2) by a S atom and the practical absence of any change on a similar replacement of the O atom linked to C(6). This may be associated with unequal CS bonds in the dithiolated purine.

^{1}H NMR studies

Proton NMR spectra for selected ligands and complexes are reported in Table 2.

^{1}H NMR spectra were assigned according to Twanmoh *et al.* [17] and offer a clue as to which sites of the ambidentate ligands are involved with bonding to the R_3PAu^+ moieties.

The spectrum of s^6Gua in DMSO-d_6 shows a signal at 6.55 ppm corresponding to the protons of the exocyclic NH_2 group, a signal at 7.99 ppm associated with the C(8) proton and two signals at 11.98 and 12.70 ppm due to the protons attached to the heterocyclic nitrogens, the former being distinctly sharper than the latter.

6-Thioguanine in the solid state, exists in the thione form, with N(1) nitrogen bearing one hydrogen atom, while the second hydrogen, contrary to guanine, is bonded to N(7). In DMSO-d_6 solution, however, the presence of a 1H,7H tautomer in equilibrium with the 1H,9H tautomeric form, is suggested by the appearance of the broad signal at 12.70 ppm. In the monosubstituted complex $Ph_3PAu(s^6GuaH_{-1})$, the signal at 11.98 ppm is lost, suggesting binding of the R_3PAu^+ moiety to the sulfur atom of the base in its monoanionic form, s^6GuaH_{-1}.

Binding to sulfur is expected on the basis of the stronger affinity of R_3PAu^+, a class b (soft) species, for sulfur compared to nitrogen. The fact that also the N(7)/N(9) proton resonance is not observed is consistent with increased exchange broadening of the proton in the complex. A similar pattern was observed in the case of the $PhHg(s^6GuaH_{-1})$ complex [18] where the N(7)/N(9) proton appeared as a very broad signal (*c.* 12.7 ppm) following metallation at sulfur.

In the spectra of $(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$ and $(Et_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$ no signal is detected in the NH region since both hydrogens are lost, but additional evidence of binding to N(7) (or N(9)) comes through the C(8)H proton which appears as a broad signal at 7.76 and 7.59 ppm, respectively.

For complexes of thiolated nucleosides analogues (6-mercaptopurine) with divalent metal ions where a S(6)–N(7) five-membered chelate ring is formed, protons attached to the carbon atoms which are closest to the binding sites of the metal ions are known to shift more downfield than others [19], and labilization of the C(8) proton occurs as a result of the coordination binding of the metal ion to N(7) nitrogen of the purine base.

A similar downfield shift is observed when excess CH_3HgCl is added to a solution of 6-thioguanosine [20] where bonding to the thiolato group and coordination to N(7) is expected.

What we observe in the present case when the thiolated purine bases (s^6Gua and s^2s^6Xan) are acting as dianionic bases, is an upfield shift of the C(8)H signal. In contrast with the case of the thiolated nucleoside 6-thioguanosine, two hydrogens can be lost in 6-thioguanine, and since an extensive electron redistribution is to be expected on complete deprotonation (followed by metallation) of the base, the difference in electron density that occurs in relation with the S(6)–(thiolato)–N(7) chelate may ultimately be responsible for the opposite shift of the C(8)H signal.

Whether the binding to negatively charged nitrogen occurs at the N(7) or N(9) position cannot unequivocally be established.

The upfield shift of the exocyclic amino group in the s^6Gua complexes is also remarkable, but the integrated intensity of the signal (two protons) rules out the

TABLE 2. ^{1}H spectra of R_3PAuL complexes (L = s^6Gua and s^2s^6Xan)[a]

Ligand	H–C(8)	NH_2	H–N(1)	H–N(7)/N(9)	$Phenyl_{phos}$	CH_{3phos}	CH_{2phos}
s^6Gua	7.99(1)	6.55(2)	11.98(1)	12.70(1)(bd)			
$(Ph_3PAu)(s^6GuaH_{-1})$	7.71(1)	5.91(2)	n.o.		7.58		
$(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$	7.76(1)	5.62(2)			7.58 7.59		
$(Et_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$	7.59(1)	5.42(2)				1.13[b]	1.92[c]
s^2s^6Xan	8.16(1)		13.17(1)	13.64(2)(bd)			
$(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$	8.11(1)		13.0(bd)			1.10[d]	1.96[e]

[a]In DMSO-d_6; chemical shifts δ (ppm) from internal TMS; integrated intensities in parentheses; abbreviations; n.o. = not observed, bd = broad signal. [b]Doublet of triplets; $^3J(^{31}P\text{–}^1H) = 18.65$ Hz; $^3J(^1H\text{–}^1H) = 7.3$ Hz. [c]Doublet of quartets; $^2J(^{31}P\text{–}^1H) = 10.10$ Hz; $^3J(^1H\text{–}^1H) = 7.3$ Hz. [d]Envelope of 2 doublets of triplets. [e]Envelope of 2 doublets of quartets.

TABLE 3. $^{13}C\{H^1\}$NMR spectra of DTE and s^2s^4Ura complexes[a]

Compound	C(4)	C(2)	C(6)	C(5)	$C_{o,m}$	C_{para}	C_{ipso}			J_{cp}
s^2s^4Ura[c]	187.99	173.20	135.30	117.17						
$(Ph_3PAu)_2(\mu\text{-}s^2s^4Ura)$	178.05	152.85	[b]	118.23	134.48	131.51	129.26			
DTE						CHOH	CH_2S	CH_{3phos}	CH_{2phos}	
						75.19	28.26			
$(Et_3PAu)_2(\mu\text{-DTE})$						75.54	32.88	9.03	18.33	44.15
									17.85	49.31

[a]Given to low solubility of most complexes, a mixed solvent DMSO-d_6/$CHCl_3$ 1:2 vol./vol. was used, with TSP as an internal standard; chemical shifts (δ) in ppm; coupling costants (J) in Hz. [b]The C(6) signal is obscured under the triphenylphosphine resonances. [c]The δ values are in agreement with those reported in ref. 21.

possibility that a deprotonated amino group is involved in bonding to the gold moiety.

The ^1H NMR spectrum of 2,6-dithioxanthine shows the N(1)H signal at 13.17 ppm, while N(3)H and N(7)H coalesce in a broad signal at 13.64 ppm. This is at variance with what is reported in ref. 17, where all three hydrogens appear as a broad peak at 13.3 ppm. In the $(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$ only a broad peak at 13.0 ppm, whose integrated intensity corresponds to a single proton, is observed.

While these data give evidence of complexation of the base, no evidence is offered as to which sites are involved in bonding.

The observed shift of the C(8)H signal (0.05 ppm) is distinctly smaller than those previously recorded.

^{13}C NMR studies

The complexes of s^6Gua and s^2s^6Xan were insoluble in most organic solvents and this, in spite of the acquisition of more than 60 000 scans, prevented the possibility of obtaining suitable spectra.

The ^{13}C spectra obtained for the DTE and s^2s^4Uracil complexes are reported in Table 3 and are helpful for assigning the binding sites of R_3PAu^+ to the ligands: the shifts of greater magnitude are those relative to C(2) and C(4) in the s^2s^4Ura complexes, while it is only the carbon atom attached to the thiol group which is significantly shifted in the case of $(Et_3PAu)_2(\mu\text{-DTE})$, which leads to the conclusion that the triethylphosphinegold(I) moieties are bound to sulfur only [8].

^{31}P NMR studies

The ^{31}P NMR chemical shifts of some of these complexes are reported in Table 4. The ^{31}P NMR of $(Ph_3PAu)(\mu\text{-}s^6GuaH_{-1})$ and $(Ph_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$ are not reported because they are very insoluble in DMSO as well as in $CDCl_3$ solvents. It is interesting to note that $(Et_3PAu)_2(\mu\text{-}s^2s^6GuaH_{-2})$, $(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})$ and $(Ph_3PAu)_2(\mu\text{-}s^2s^6Gua_{-2})$ complexes, give two resonances. The S–Au–^{31}P resonance appeared at about 35 ppm and the N–Au–^{31}P resonance appeared at about 30 ppm.

TABLE 4. ^{31}P NMR chemical shifts of various $(R_3PAu)_2L$ type complexes in DMSO-d_6 or in $CDCl_3$ solvents

Complexes	δ^a	δ^b
$(Et_3PAu)_2(\mu\text{-DTE})$	36.36(s)[c]	34.97(s)
$(Et_3PAu)_2(\mu\text{-}s^6GuaH_{-2})$	35.65(br)[d]	34.80(br)
	29.90(br)	29.97(br)
$(Et_3PAu)_2(\mu\text{-}s^2s^6XanH_{-2})H_2O$	36.23(br)	34.65(br)
	26.16(br)	27.14(br)
$(Ph_3PAu)_2(\mu\text{-}s^2s^4UraH_{-2})H_2O$	34.92(s)	35.61(s)
$(Ph_3PAu)_2(\mu\text{-}s^6GuaH_{-2})H_2O$	36.84(br)	35.70(br)
	30.45(br)	29.10(br)

[a]In DMSO-d_6. [b]In $CDCl_3$. [c](s) sharp peak. [d](br) broad peak.

The ^{31}P NMR chemical shifts of thiolate or thione bonding of the various ligands to the R_3PAu^+ moiety have been reported in the literature in the 34–37 ppm range [22–25]. The ^{31}P NMR chemical shifts of N bonding to the R_3PAu^+ moiety are reported in the 28–31 ppm range [26–30]. Recently, Colacio *et al.* [28] studied the interaction of various 8-mercaptotheophyllinato and derivatives with triphenylphosphine and triethylphosphinegold(I) complexes under basic conditions. They reported S8 bonding for monodentate ligands and N7,S8 bonding for bridging complexes. These complexes were characterized by ^1H, ^{13}C, ^{31}P NMR and IR spectroscopy and also the X-ray structure was determined for the (8-mercaptotheophyllinato)-(triphenylphosphine)gold(I) complex. For the various complexes reported, the ^{31}P NMR chemical shifts were reported in the 36.29–38.66 ppm range for S-bonding to gold(I) complexes. The N-bonded gold(I) complexes gave resonances in the 29.72–29.83 ppm range. The

chemical shifts are reported for the above example using H_3PO_4 as an external standard and we used TMP as an internal standard. The difference between the two standards is about 2.74 ppm.

Hadjiliadis and co-workers [31, 32] have reported isolation of gold(I) and gold(III) complexes of guanosine and inosine for which they proposed binding at the N7 site.

The ν(Au–S) band in the IR spectra for all complexes was observed between 350 and 360 cm^{-1}. For most of the mono and dinuclear complexes, e.g. R_3P–Au–S or $\{[R_3P–Au]_2\mu$-S$\}$ complexes, a similar frequency range was reported [30]. There was no ν(Au–Cl) band observed at about 325 cm^{-1} which is the case for most of the R_3P–Au–Cl or RS–Au–Cl complexes [28, 30, 33].

Based on the structurally similar gold(I)–thiosugar complexes reported in the literature [1–6] which have shown anticancer activity, the complexes reported here may have antitumor activity. However, the low solubility of these complexes may be a hindrance to potential antitumor activity.

Conclusions

Based on the previous studies of gold(I)–thiosugar complexes reported earlier [1–9] and ^1H, ^{13}C and ^{31}P NMR spectroscopy data presented here, the structures proposed for the various gold(I) complexes are those shown in Fig. 2.

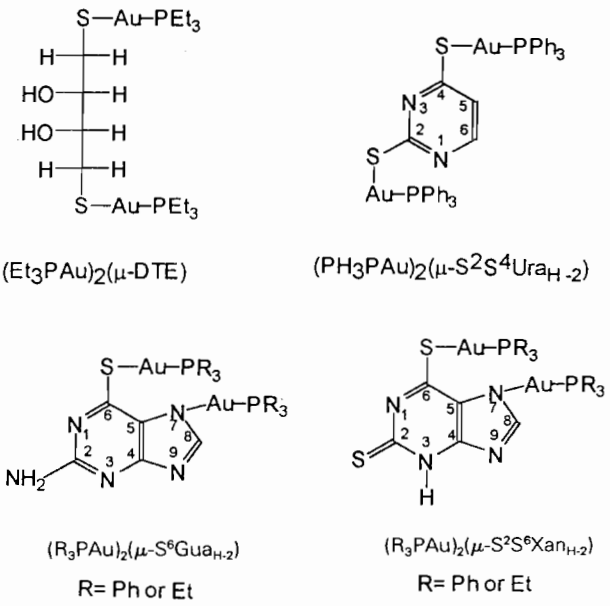

Fig. 2. Structures of the gold complexes.

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