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Gold complexes with thiosemicarbazones: reactions of bi- and tridentate thiosemicarbazones with dichloro[2-(dimethylaminomethyl)phenyl-C^1,N]gold(III), [Au(damp-C^1,N)Cl_2]

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Dichloro[2-(*N*,*N*-dimethylaminomethyl)phenyl-C^1,N]gold(III), [Au(damp-C^1,N)Cl_2] (**1**), reacts with salicylaldehyde thiosemicarbazone (H_2saltsc), vanilline thiosemicarbazone (Hvantsc), *N*-methylpyrrole aldehyde thiosemicarbazone (Hmepyrtsc), pyridoxal methylthiosemicarbazone (H_2pydoxmetsc), 2-diphenylphosphinobenzaldehyde thiosemicarbazone (HPtsc) or variously substituted acetylpyridine thiosemicarbazones (HapRtsc; R = H, Me, Ph) with cleavage of the Au–N bond and protonation of the dimethylamino group. Compounds of general formulae $[Au(Hdamp\text{-}C^1)Cl(L)]^+$ (L = Hsaltsc$^-$, vantsc$^-$, mepyrtsc$^-$), $[Au(Hdamp\text{-}C^1)Cl(L)]^{2+}$ (L = H_2pydoxmetsc) or $[Au(Hdamp\text{-}C^1)(L)]^{2+}$ (L = Ptsc$^-$, apRtsc$^-$, R = H, Me, Ph) have been isolated and characterized. The presence of the σ-bonded 2-(dimethylaminomethyl)phenyl ligand is mandatory to prevent reduction of the gold(III) centre. The crystal structures of $[Au(Hdamp\text{-}C^1)Cl(Hsaltsc)](PF_6)$ (**3a**), $[Au(Hdamp\text{-}C^1)Cl(mepyrtsc)]Cl$ (**3c**), $[Au(Hdamp\text{-}C^1)Cl(H_2pydoxmetsc)]Cl_2\cdot MeOH$ (**4**), $[Au(Hdamp\text{-}C^1)(apPhtsc)]Cl_2\cdot 2$ MeOH (**5c**) and $[Au(Hdamp\text{-}C^1)(Ptsc)]Cl_2\cdot$ 1.5MeOH (**6**) have been elucidated, showing the gold atoms in distorted square-planar co-ordination environments. The potentially O,N,S-tridentate ligands H_2saltsc and H_2pydoxmetsc co-ordinate in a bidentate fashion and do not incorporate the OH groups in the chelating framework, whereas HapRtsc or HPtsc co-ordinate in a tridentate manner. Generally, one or more hydrogen atoms of the heterocyclic ligands and/or the NMe_2H^+ group form hydrogen bridges in the solid state structures. The preliminary results of antiproliferation tests on tumor cells demonstrate the considerable cytotoxicity of these new gold complexes.

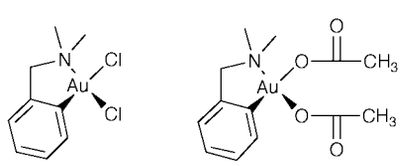
Introduction

Thiosemicarbazones (tautomeric forms, see **Ia** and **Ib**) and their

Ia **Ib**

metal complexes are of considerable interest because of their chemical and promising biological properties.[1,2] They can easily be modified by variation of the parent aldehyde or ketone used for the synthesis, particularly with compounds having additional potential co-ordinating sites (position R) or by substitutions on the terminal N position. Antibacterial,[3] antineoplastic,[4] antimalarial[5] and antiviral[6] behaviour has been found. Relationships are evident between chelate formation in the complexes and the *in vivo* activity.[7–10] This makes structural studies on thiosemicarbazone complexes interesting. Although a number of studies dealing with the complex-formation properties of this class of compounds exist,[11,12] comparatively few structural reports are published. They deal with iron(II), cobalt(III), nickel(II), copper(II), palladium(II), zinc(II), tin(II), tin(IV), bismuth(III), indium(III), cadmium(II) and mercury(II).[13–20] Recently, we reported preliminary details of the first gold complexes with this type of ligand.[21] Here, we describe the synthesis and structural characterization of thiosemicarbazone complexes of gold(III) additionally containing the 2-(dimethylaminomethyl)phenyl (damp$^-$) ligand.

Square-planar gold(III) complexes with the (damp-C^1,N)$^-$ ligand have been known since 1984.[22] Key compounds are the dichloro and diacetato complexes [Au(damp-C^1,N)Cl_2] (**1**) and



(1) **(2)**

$[Au(damp\text{-}C^1,N)(CH_3CO_2)_2]$[1] (**2**) which have recently been structurally characterized[23] and show distorted square-planar co-ordination spheres for the gold atoms. During ligand exchange reactions, the chloro or acetato ligands are preferentially replaced.[23–30] Only a few examples where the Au–N bond is cleaved have been reported.[30] Protonation of the liberated $N(CH_3)_2$ group, however, to the best of our knowledge has only been observed for gold compounds with heterocyclic thiols[31] and diphenylthiocarbazone (dithizone),[32] both ligand types which are related to the thiosemicarbazones under study here.

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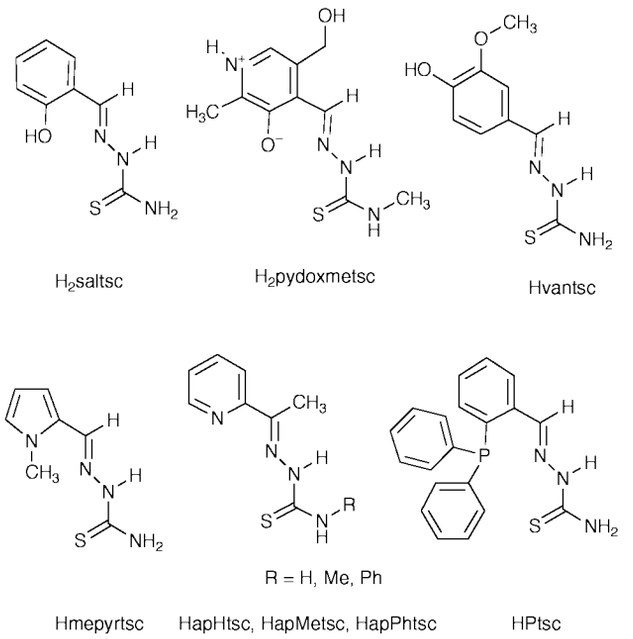


Fig. 1 Thiosemicarbazone ligands used throughout the experiments. All ligands are given in their thione form.

In a recent paper, some tumor cell toxicity studies of [Au(damp-C^1,N)Cl_2], which has structural and electronic analogies to *cis*-diamminedichloroplatinum(II), *cis*-platin, have been reported.[30] This makes further studies dealing with the ligand exchange behaviour of this complex and the biological activity of the resulting products interesting.

Here, we present syntheses and structural characterization of complexes which are obtained from the reaction of [Au(damp-C^1,N)Cl_2] with the thiosemicarbazones shown in Fig. 1. All ligands are given in their thione form, despite the fact that in solution thiosemicarbazones probably consist of an equilibrium mixture of thione (**Ia**) and thiol (**Ib**) tautomers.

Results and discussion

Starting from [Au(damp-C^1,N)Cl_2] and thiosemicarbazones, a variety of new gold complexes have been synthesized and structurally characterized. Scheme 1 summarizes the reactions performed and the products obtained. All ligands summarized in Fig. 1 react with (**1**) *via* exchange of the chloro ligands, cleavage of the Au–N bonds and protonation of the $N(CH_3)_2$ groups. This behaviour has also been observed for reactions with heterocyclic thiols or dithizone,[31,32] but is unusual with respect to the numerous Au(damp) complexes with various mono- or bidentate ligands which have the general formulae [Au(damp-C^1,N)(X)L^1]$^{0,2+}$ (X = L^1 or Cl) or [Au(damp-C^1,N)L^2]$^{0,2+}$, depending on the net charge of the ligands used.[23–30]

The reactions were performed in methanol–acetone solutions in which the sparingly soluble thiosemicarbazones readily dissolve after mixing with a solution of (**1**). Yellow to orange–red, air-stable products were obtained after reducing the solvent volume and/or diffusion of diethyl ether into solutions of the complexes. The yields are moderate due to serious problems during the isolation of crystalline compounds (see Experimental). Reduction of the gold(III) centre and formation of gold(I) compounds or elemental gold, however, has not been observed.

The thiosemicarbazones bind as N,S-chelates with monodeprotonation of the co-ordinating back-bone. The only exception, the co-ordination of H_2pydoxmetsc as a formally neutral chelating ligand, is explained by the zwitterionic character of this ligand and will be discussed later. The potential third co-ordination sites of H_2saltsc and H_2pydoxmetsc do not bind to gold, whereas $Ptsc^-$ and the acetylpyridine thiosemicarbazones exhibit tridentate co-ordination.

Table 1 Selected bond lengths (Å) and angles (°) in the complexes (**3a**), (**3b**) and (**3c**)

	(**3a**)	(**3b**)[a]	(**3c**)
Au–C(1)	2.039(7)	2.024(6)	2.029(8)
Au–S(11)	2.247(2)	2.249(2)	2.248(3)
Au–N(15)	2.115(6)	2.116(5)	2.106(7)
Au–Cl(1)	2.322(2)	2.320(2)	2.320(2)
C(12)–N(13)	1.364(11)	1.336(10)	1.356(11)
C(12)–N(14)	1.290(10)	1.295(8)	1.281(11)
N(14)–N(15)	1.385(9)	1.392(7)	1.383(9)
N(15)–C(16)	1.290(10)	1.276(8)	1.295(11)
S(11)–C(12)	1.758(8)	1.759(7)	1.763(9)
C(1)–Au–S(11)	87.4(2)	90.7(2)	88.7(2)
C(1)–Au–N(15)	171.8(3)	172.2(2)	172.6(3)
C(1)–Au–Cl(1)	92.2(2)	89.8(2)	91.5(2)
S(11)–Au–N(15)	84.5(2)	84.3(2)	84.1(2)
S(11)–Au–Cl(1)	178.70(8)	179.44(6)	178.8(1)
N(15)–Au–Cl(1)	95.9(2)	95.3(2)	95.7(2)

	D–H	H···A	D···A	D–H···A
Hydrogen bonds in (**3a**)				
N(8)–H(8)···Cl(1)	0.75(7)	2.47(8)	3.216(8)	168(7)
O(19)–H(19)···F(36)	0.86(9)	1.92(9)	2.769(9)	167(10)
Hydrogen bonds in (**3c**)				
N(8)–H(8)···Cl(2′)	0.87	2.43	3.224(8)	151
N(13)–H(13A)···Cl(2″)	1.01	2.03	2.987(8)	157
N(13)–H(13B)···Cl(2)	0.87	2.48	3.213(9)	142

Symmetry operations: (′) $1-x, -y, 1-z$; (″) $1-x, -y, 2-z$. [a] More details are contained in ref. 21. The atom labelling corresponds to that given in Fig. 2 for (**3a**).

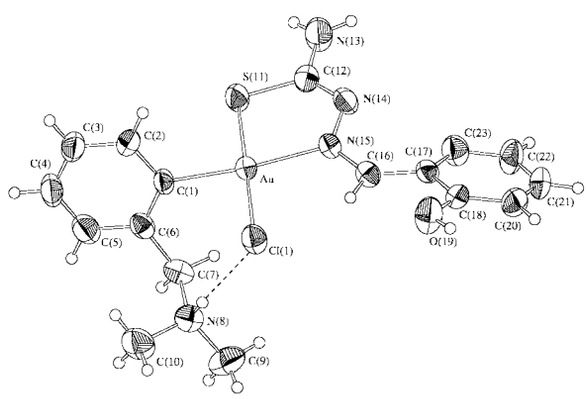
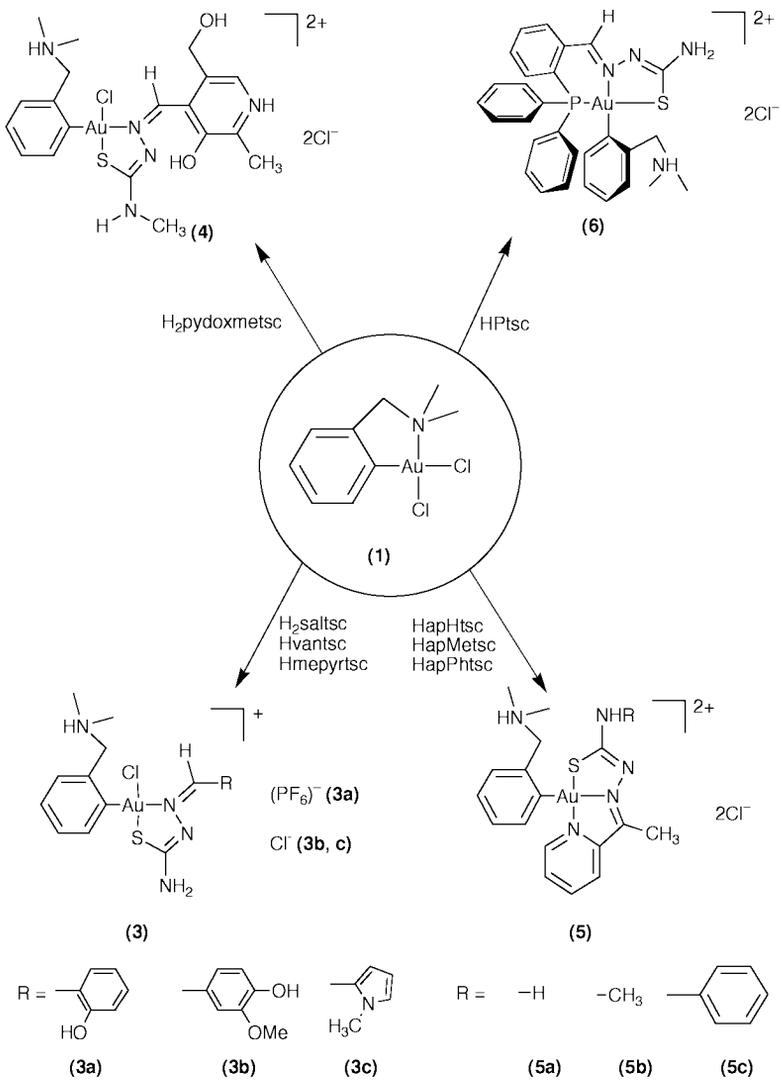


Fig. 2 ZORTEP representation[33] of the complex cation of (**3a**). Thermal ellipsoids represent 50% probability.

Pale yellow crystals of [Au(Hdamp-C^1)Cl(Hsaltsc)](PF_6) (**3a**) suitable for X-ray analysis were obtained by treating (**1**) with one equivalent of H_2saltsc and KPF_6. The formation of the cationic complex is supported by the occurrence of an intense peak in the FAB^+ mass spectrum of the compound at m/z = 561. The IR spectrum shows an O–H valency vibration at 3410 cm^{-1} and suggests that the OH group of the salicylaldehyde thiosemicarbazone does not contribute to the co-ordination. A band at 2677 cm^{-1} is in accordance with values found previously for monodentate (Hdamp-C^1) ligands with protonated $(CH_3)_2N$ groups[21,31,32] forming hydrogen bonds.

Fig. 2 shows an ellipsoidal representation[33] of the structure of the complex cation. Selected bond lengths and angles are summarized in Table 1. The thiosemicarbazone is only singly deprotonated and binds to gold *via* S and N. The almost ideally square-planar co-ordination sphere of the metal is completed by Cl^- and a monodentate Hdamp ligand. The position of the



Scheme 1

gold atom deviates from a least-squares plane formed by the donor atoms by only 0.003 Å. The Au–N bond is cleaved and the liberated dimethylamino group is protonated forming an intramolecular hydrogen bond to Cl(1). This has been verified by the localization of all hydrogen atoms attached to O or N atoms in the Fourier maps and refinement of their positions. Thus, the bonding situation is comparable with that in Au(damp) complexes with heterocyclic thiols/thiones which also contain protonated $(CH_3)_2N$ groups with the N(8)H proton included in hydrogen-bonded networks[31] and differs from that in $[Pt(C_{10}H_6NMe_2\text{-}C^2,N)(C_{10}H_6NHMe_2\text{-}C^2)Br]$ where the hydrogen atom is directed strictly towards the metal and an interaction with platinum is suggested.[34]

The bidentate co-ordination of the potentially tridentate salicylaldehyde thiosemicarbazone ligand is unusual and to our knowledge only one crystal structure with this bonding mode has been reported, $[Ru(Hsaltsc)_2(PPh_3)_2]$.[35] In the present case, the low affinity of gold to oxygen donor ligands may explain this bonding situation. The $Hsaltsc^-$ ligand has *Z* configuration with respect to the C(12)–C(14) bond which is required for the formation of the chelate ring, whereas the *E* configuration is found for the N(15)–N(16) bond which minimizes steric repulsions between the aromatic ring and Cl(1). Despite the expected delocalization of electron density in the thiosemicarbazone skeleton, alternating bond lengths are observed. This seems to be typical for co-ordinated thiosemicarbazones, independent of their bonding mode. Table 2 compares the values obtained for $[Au(Hdamp\text{-}C^1)Cl(Hsaltsc)]^+$ with the bonding situations in

Table 2 Comparison of bond lengths (Å) in selected salicylaldehyde thiosemicarbazone complexes. The labelling scheme refers to the IUPAC numbering as shown for **I**

Bond	$[Au(Hdamp\text{-}C^1)Cl(Hsaltsc)]^+$ [a]	$[Sn(Ph)_2(saltsc)]$[36]	$[Ni(H_2saltsc)]^{2+}$ [37]	Formal bond length [b]
$^1C{=}^2N$	1.29	1.30	1.28	1.22
$^2N{-}^3N$	1.39	1.40	1.36	1.48
$^3N{=}^4C$	1.29	1.30	1.35	1.22
$^4C{-}S$	1.76	1.73	1.70	1.81

[a] This work. [b] Sum of covalency radii.

five-co-ordinate $[Sn(Ph)_2(saltsc)]$,[36] which has a doubly-deprotonated, tridentate $saltsc^{2-}$ ligand, and $[Ni(H_2saltsc)_2]^{2+}$, where the octahedral co-ordination sphere of the metal is formed by two neutral $H_2saltsc$ ligands.[37] Only minor differences can be found between the gold and the tin compounds, in which the thiol form of the ligand (**Ib**) predominates, whereas the C–S bond is shorter in the neutral thiosemicarbazone ligands of the nickel complex. This suggests a higher proportion of the tautomeric thione form (**Ia**) in this compound.

The same type of product has been obtained for vanilline thiosemicarbazone (Hvantsc) and methylpyrrole thiosemicarbazone (Hmepyrtsc). We have previously reported the synthesis and structure of $[Au(Hdamp\text{-}C^1)Cl(vantsc)]Cl$ (**3b**) in a preliminary communication.[21] Therefore, only some basic

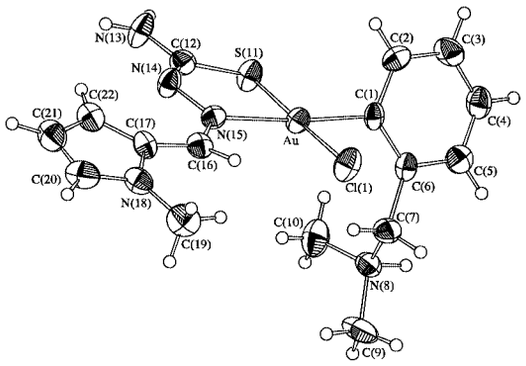


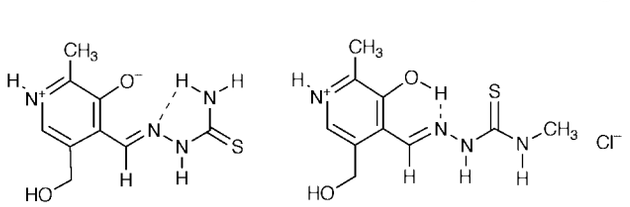
Fig. 3 ZORTEP representation[33] of the complex cation of (**3c**). Thermal ellipsoids represent 50% probability.

structural features of this complex are compared with its Hsaltsc$^-$ and mepyrtsc$^-$ analogues in Table 1. No changes in the co-ordination sphere of the metal or the thiosemicarbazone skeleton are evident as a result of changes in the periphery of the ligands. The largest structural *trans* influence is expected for the σ-bonded phenyl ring of (Hdamp) and, thus, the azomethine function of the thiosemicarbazone is situated *trans* to this position in all compounds. The phenyl rings of the Hdamp ligands are twisted against the coordination plane by 73° for (**3a**), 66° for (**3b**) and 64° for (**3c**).

Orange–red crystals of [Au(Hdamp-C^1)Cl(mepyrtsc)]Cl (**3c**) were obtained in very low yields due to the rapid decomposition of the compound and the formation of a black solid upon standing. Therefore, the spectroscopic studies were performed on a product obtained from a reaction mixture from which the solvent had been removed under vacuum immediately after a stirring period of 1 h. The identity of this product was checked by IR spectroscopy on the crystals. Mass and NMR spectra suggest a composition of [Au(Hdamp-C^1)Cl(thiosemicarbazonate)]Cl. An infrared band at 2693 cm^{-1} gives evidence for the protonation of the dimethylamino group and the formation of hydrogen bonds. Au–Cl vibrations can be detected at 315 cm^{-1}.

A ZORTEP plot of the cation of (**3c**) is given in Fig. 3. Important bond lengths and angles are contained in Table 1. The thiosemicarbazone is singly deprotonated and co-ordinates in a bidentate fashion *via* N and S, as described for (**3a** and **b**). The co-ordination sphere is planar with a maximum deviation of 0.029 Å from a least-squares plane formed by the atoms S(11), N(15), Cl(1), C(1) and Au. A hydrogen-bonded network including N(13), N(8) and symmetry-related positions of Cl(2), stabilizes the solid-state structure of the complex.

The condensation of 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carbaldehyde (pyridoxal) with thiosemicarbazide yields a hydrophilic thiosemicarbazone which is a versatile proligand. Metal complexes have been isolated with this tridentate ligand as a neutral thione,[38,39] monoanionic thiolate[40–42] or thionate,[38,43] or as a dianionic thiolate.[41] The proligand crystallizes in the zwitterionic form **IIa** with the pyridine nitrogen



IIa **IIb**

protonated and a non-protonated aromatic phenolic group.[44] The solid state structure is stabilized by a hydrogen bond between the NH_2 group and the azomethine nitrogen. This situation changes when the 4-*N*-methylthiosemicarbazone derivative of pyridoxal (H_2pydoxmetsc) **IIb** is examined. This compound crystallizes as a hydrochloride when it is prepared under the same conditions as described for **IIa**. The introduction of a methyl substituent at the terminal amino group changes the situation inside the molecule and another conformation is favoured. This is supported by the protonation of the hydroxyl group and the formation of a hydrogen bond between O(23) and N(15). A crystal structure analysis of pyridoxal methylthiosemicarbazone hydrochloride, which allowed the detection of the positions of all the acidic hydrogen atoms (Fig. 4), clearly shows the *Z* conformation about C(12)–N(14). Table 3 summarizes selected bond lengths and angles which indicate almost localised double bonds between S(11) and C(12) [1.669(5) Å] and N(15) and C(16) [1.287(6) Å]. The conformation of the proligand pre-forms a tridentate O,N,S chelating ligand.

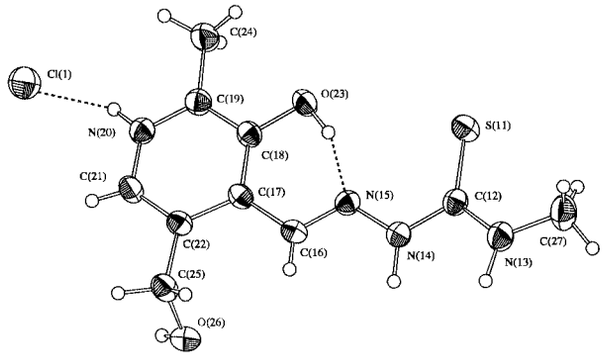


Fig. 4 ZORTEP representation[33] of H_2pydoxmetsc·HCl. Thermal ellipsoids represent 50% probability.

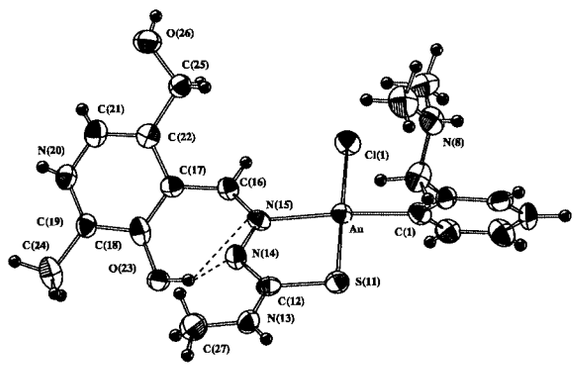


Fig. 5 ZORTEP representation[33] of the complex cation of (**4**). Thermal ellipsoids represent 50% probability. The labelling scheme of the damp ligand corresponds to that given in Fig. 2.

The reaction of H_2pydoxmetsc·HCl with [Au(damp-C^1,N)-Cl_2], however, results in a rotation about the N(15)–C(16) bond and the formation of a bidentate N,S-chelate. Pale yellow needles were isolated which contain [Au(Hdamp-C^1)Cl(H_2-pydoxmetsc)]Cl_2 (**4**) and one molecule of methanol per formula unit. Fig. 5 contains an ellipsoidal representation of the structure of the complex cation. Table 3 compares the bond lengths and angles with those obtained for H_2pydoxmetsc·HCl. The phenolic hydroxyl group and the pyridine nitrogen remain protonated, resulting in a zwitterionic ligand after deprotonation of N(14). This co-ordination behaviour is without precedent for a pyridoxal thiosemicarbazone, but may be understood with regard to the low tendency of gold to form bonds with oxygen donors. The S(11)–C(12) bond length of 1.764(13) Å favours the thiolate co-ordination mode. The rotation about the N(15)–C(16) bond minimizes steric interactions between the phenyl ring and the chloro ligands and allows hydrogen bonds between O(23) and N(14). An additional weak interaction between H(23) and N(15) leads to a three-centred hydrogen bond. The complex cations, the Cl^- anion and the incorporated methanol are involved in an extensive hydrogen-bonding network, as is illustrated in Fig. 6 and Table 3.

Table 3 Selected bond lengths (Å) and angles (°) in H_2pydoxmetsc·HCl and (**4**)

	H_2pydoxmetsc·HCl	(**4**)
Au–C(1)		2.015(12)
Au–S(11)		2.266(3)
Au–N(15)		2.130(10)
Au–Cl(1)		2.320(3)
S(11)–C(12)	1.669(5)	1.764(13)
C(12)–N(13)	1.339(6)	1.334(16)
C(12)–N(14)	1.379(6)	1.329(15)
N(14)–N(15)	1.357(5)	1.368(14)
N(15)–C(16)	1.287(6)	1.305(15)
C(16)–C(17)	1.457(6)	1.441(17)
C(1)–Au–S(11)		90.1(3)
C(1)–Au–N(15)		174.2(4)
C(1)–Au–Cl(1)		89.0(3)
S(11)–Au–N(15)		84.1(4)
S(11)–Au–Cl(1)		179.1(1)
N(15)–Au–Cl(1)		96.8(3)
Au–S(11)–C(12)		96.4(4)
S(11)–C(12)–N(13)	124.6(3)	116.2(8)
S(11)–C(12)–N(14)	122.9(3)	125.9(9)
C(12)–N(14)–N(15)	118.1(4)	115.0(10)
N(14)–N(15)–Au		118.5(7)
N(14)–N(15)–C(16)	119.0(4)	116.6(10)
N(15)–C(16)–C(17)	117.3(4)	130.1(10)

	D–H	H···A	D···A	D–H···A
Hydrogen bonds in H_2pydoxmetsc·HCl				
N(20)–H(20)···Cl(1)	0.86(7)	2.22(7)	3.050(4)	162(6)
O(23)–H(23)···N(15)	0.90(7)	1.69(7)	2.553(5)	159(6)
O(23)–H(23)···S(11)	0.90(7)	2.99(6)	3.622(3)	129(5)
O(26)–H(26)···Cl(1)^{I}	0.89(7)	2.24(7)	3.064(4)	153(6)
N(13)–H(13)···Cl(1)^{II}	1.04(6)	2.30(7)	3.280(4)	157(5)
N(14)–H(14)···O(26)^{III}	1.00(10)	1.86(10)	2.852(5)	169(8)
Hydrogen bonds in (**4**)				
O(30)–H(30)···Cl(3)^{IV}	0.84(15)	2.31(15)	3.050(15)	147(18)
N(8)–H(8)···Cl(2)	0.71(15)	2.34(15)	3.049(11)	170(15)
N(13)–H(13)···Cl(2)^{V}	0.71(14)	2.54(12)	3.170(11)	149(14)
O(23)–H(23)···N(14)	0.84(15)	1.72(16)	2.530(13)	157(17)
O(23)–H(23)···N(15)	0.86(15)	2.39(17)	3.074(14)	137(14)
O(26)–H(26)···Cl(2)^{VI}	0.81(17)	2.35(15)	3.095(10)	153(17)
N(20)–H(20)···Cl(3)^{IV}	0.7(2)	2.4(2)	3.012(13)	152(23)

Symmetry operations: (I) $1-x$, $3-y$, $-1-z$; (II) $1-x$, y, $1+z$; (III) $-x$, $3-y$, $-z$; (IV) $-x$, $2-y$, $-z$; (V) $1-x$, $1-y$, $1-z$; (VI) $1-x$, $1-y$, $-z$.

Thiosemicarbazones of heterocyclic aldehydes or ketones and their metal complexes have been studied extensively because some of the compounds are cancerostatic. The biological activities of the proligands are increased on co-ordination to iron or copper centres.[46] An S,N,N-chelating system has been found in all hitherto known cancerostatic thiosemicarbazone complexes.[47] We prepared gold complexes of HapHtsc, HapMetsc and HapPhtsc by reaction of the potentially tridentate proligands with (**1**). Additionally we used 2-(diphenylphosphino)benzaldehyde thiosemicarbazone for comparison.

The reaction of (**1**) with HapRtsc gave yellow solids which are readily soluble in organic solvents. Their IR spectra suggest triply co-ordinated tsc^- ligands or chelate-bonded $damp^-$ ligands due to the lack of Au–Cl vibrations which can clearly be observed for the complexes with bidentate thiosemicarbazones in the range between 300 and 330 cm^{-1}. IR bands between 2600 and 2700 cm^{-1}, however, give evidence for hydrogen bonds in the solid-state structures of the complexes. FAB^+ mass spectrometric studies of all three gold apRtsc complexes resulted in the detection of very intense $[Au(damp)(apRtsc)]^+$ peaks which do not allow unambiguous assignment of the structure of the

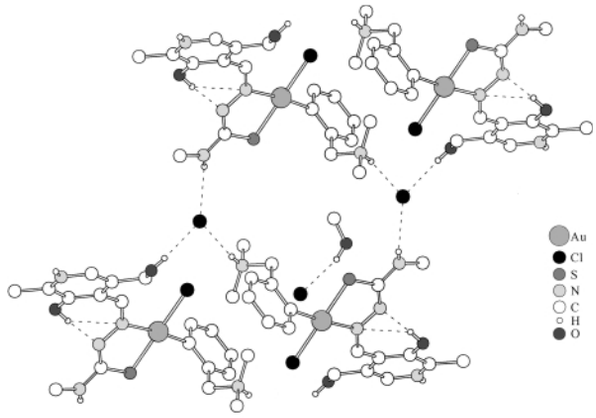


Fig. 6 Hydrogen-bonding network in (**4**). Only acidic H atoms are shown for clarity.[45]

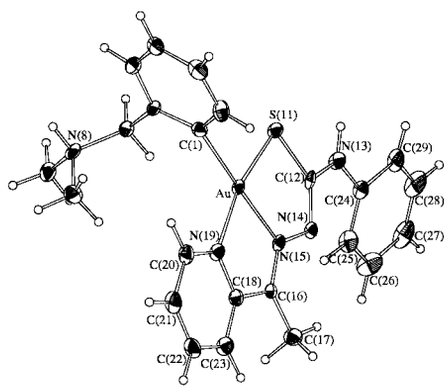


Fig. 7 ZORTEP representation[33] of the complex cation of (**5c**). Thermal ellipsoids represent 50% probability. The labelling scheme of the damp ligand corresponds to that given in Fig. 2.

complexes ($[Au(damp\text{-}C^1,N)(apRtsc\text{-}S,N)]^+$ or $[Au(damp\text{-}C^1)(apRtsc\text{-}S,N,N)]^+$). Therefore, we performed crystal structure analyses of the $apHtsc^-$ and $apPhtsc^-$ derivatives, which prove the solid-state structures of the complexes to be $[Au(Hdamp\text{-}C^1)(apRtsc\text{-}S,N,N)]^{2+}$. The N–H bond in the $NH(CH_3)_2^+$ group of the damp ligand is, obviously, easily cleaved in nitrobenzyl alcohol solution under the conditions applied in the mass spectrometer. $[Au(Hdamp\text{-}C^1)(apHtsc)]Cl_2\cdot 0.5H_2O$ (**5a**) crystallizes from methanol–diethyl ether solutions which contain small amounts of water. The presence of water favours the crystallization and the co-crystallized H_2O contributes to an extended hydrogen-bonding network, as do the chloride anions. The gold atom deviates from the least-squares plane formed by the donor atoms only by 0.046 Å. More details on the crystal structure of (**5a**) are contained in a preliminary communication which has been published recently.[21] In Table 4 selected bond lengths and angles are compared with the values found in $[Au(Hdamp\text{-}C^1)(apPhtsc)]Cl_2$ (**5c**). The labelling scheme of $[Au(Hdamp\text{-}C^1)(apHtsc)]^+$ follows that applied for the phenyl-substituted compound.

An ellipsoidal representation of the cation of (**5c**) is given in Fig. 7. The thiosemicarbazone ligand is not completely planar. The NH phenyl ring is bent out of the co-ordination plane by 15°. The S(11)–C(12) bond is surprisingly short at 1.677(8) Å, whereas C–S bond lengths between 1.76 and 1.79 Å have been found for all the other complexes discussed. This suggests the co-ordination of $apPhtsc^-$ as a monoanionic thione, as opposed to the thiolate mode which is preferred in the other complexes. A widespread delocalization of electron density over the whole ligand skeleton is also supported by the surprisingly short length of the C(12)–N(13) bond. The tridentate co-ordination mode of the $apRtsc^-$ ligands with two five-membered chelate rings leads to visible distortions in the

Table 4 Selected bond lengths (Å) and angles (°) in (**5a**) and (**5c**)

	(**5a**)[a]	(**5c**)
Au–C(1)	2.043(4)	1.915(8)
Au–S(11)	2.251(1)	2.194(2)
Au–N(15)	2.036(4)	1.904(6)
Au–N(19)	2.081(4)	2.035(7)
S(11)–C(12)	1.791(5)	1.677(8)
C(12)–N(13)	1.328(6)	1.267(9)
C(12)–N(14)	1.314(6)	1.318(11)
N(14)–N(15)	1.375(5)	1.295(8)
N(15)–C(16)	1.285(5)	1.282(10)
C(16)–C(18)	1.473(6)	1.366(10)
C(16)–C(17)	1.480(6)	1.397(11)
N(8)–H(8)	0.92(5)	0.81(9)
C(1)–Au–S(11)	96.5(1)	89.1(2)
C(1)–Au–N(15)	178.6(2)	178.6(3)
C(1)–Au–N(19)	99.1(2)	90.1(2)
S(11)–Au–N(15)	84.9(1)	84.1(4)
S(11)–Au–N(19)	163.6(1)	165.9(2)
N(15)–Au–N(19)	79.5(2)	75.9(3)
Au–S(11)–C(12)	94.7(2)	90.0(3)
S(11)–C(12)–N(13)	113.5(3)	108.1(6)
S(11)–C(12)–N(14)	126.2(4)	127.8(6)
C(12)–N(14)–N(15)	112.3(4)	115.4(6)
N(14)–N(15)–Au	121.7(3)	116.6(5)
C(16)–N(15)–Au	117.4(3)	119.5(5)
N(15)–C(16)–C(18)	114.7(4)	116.3(7)
C(16)–C(18)–N(19)	117.1(4)	111.9(7)
C(18)–N(19)–Au	111.3(3)	115.9(5)
C(20)–N(19)–Au	128.9(3)	128.1(6)
C(18)–N(19)–C(20)	119.7(4)	115.9(8)
N(14)–N(15)–C(16)	120.9(4)	123.7(6)

[a] Values are taken from a preliminary communication reported in ref. 21. The labelling of the atoms has been partially changed to match the labelling scheme given in Fig. 7 for (**5c**).

square-planar co-ordination environment of Au(III) resulting in N(19)–Au–S(11) angles of 163.6(1)° in (**5a**) and 165.9(2)° in (**5c**). The σ-bonded phenyl rings of the damp ligands are bent out of the co-ordination plane of the metal by 66.2° in [Au(Hdamp-C^1)(apHtsc)]$^{2+}$ and 76.4° in [Au(Hdamp-C^1)-(apPhtsc)]$^{2+}$ to minimize steric interactions.

A more bulky tridentate thiosemicarbazone, HPtsc, can be derived from 2-(diphenylphosphino)benzaldehyde.[47] HPtsc reacts with (**1**) forming a complex having the same basic structure as the apRtsc$^-$ complexes. [Au(Hdamp-C^1)(Ptsc)]Cl_2 (**6**) is a yellow solid which can be crystallized from methanol–diethyl ether as a solvate containing 1.5 equiv. MeOH per complex in the crystal lattice. The compound is stable in air and readily soluble in methanol. FAB$^+$ mass spectrometry shows $[M - H]^+$ and $[Au(Ptsc)]^+$ peaks, as has been observed previously for the acetylpyridine thiosemicarbazone complexes, and gives evidence for facile deprotonation of the Au(Hdamp-C^1) unit under mass spectrometric conditions. The ^{31}P resonance of the thiosemicarbazone is shifted from −13.2 ppm in the proligand to +29.2 ppm upon co-ordination to Au(III).

An ellipsoidal representation of the complex cation of (**6**) is shown in Fig. 8. Selected bond lengths and angles are summarized in Table 5. The distorted square-planar co-ordination sphere of gold is formed by four different donor atoms. The metal is situated 0.13 Å outside the least-squares plane formed by the donor atoms. 2-(Diphenylphosphino)benzaldehyde thiosemicarbazone is bonded as a monoanionic tridentate ligand forming 5- and 6-membered chelate rings. Thus, the phenyl ring which carries the thiosemicarbazone moiety is co-planar with the co-ordination plane. The damp phenyl ring, however, is almost perpendicular to this plane (angle between the planes: 79.9°). With this, it is almost parallel to one of the phenyl rings of the phosphine, as is evident from Fig. 8. The distances between related carbon atoms of these rings range between 3.4 and 5.3 Å. A similar situation has been observed in a comparable nickel(II) complex, [Ni(Ptsc)(py)]$^+$, where the pyridine ring is also arranged parallel to one of the phosphine phenyl groups (inter-ring distances between 3.1 and 4.2 Å).[48] Thus, weak interactions between the ring systems in both compounds cannot completely be ruled out, at least for their solid state structures.

Table 5 Selected interatomic distances (Å) and angles (°) for (**6**)

Au–C(1)	2.055(6)	C(12)–N(14)	1.301(7)
Au–S(11)	2.308(2)	N(14)–N(15)	1.372(6)
Au–N(15)	2.092(5)	N(15)–C(16)	1.287(7)
Au–P	2.308(2)	C(16)–C(21)	1.459(8)
S(11)–C(12)	1.772(6)	C(20)–C(21)	1.411(8)
C(12)–N(13)	1.323(7)	C(20)–P	1.803(6)
N(8)–H(8)	0.76(8)		
C(1)–Au–S(11)	91.0(2)	C(12)–N(14)–N(15)	116.8(5)
C(1)–Au–N(15)	171.9(2)	N(14)–N(15)–Au	118.4(3)
C(1)–Au–P	90.7(2)	N(14)–N(15)–C(16)	113.6(5)
S(11)–Au–N(15)	84.0(1)	C(16)–N(15)–Au	127.9(4)
S(11)–Au–P	172.89(5)	N(15)–C(16)–C(21)	131.5(5)
N(15)–Au–P	92.6(1)	C(16)–C(21)–C(20)	128.4(5)
Au–S(11)–C(12)	95.2(2)	C(21)–C(20)–P	122.0(4)
S(11)–C(12)–N(13)	115.8(4)	C(20)–P–Au	111.0(2)
S(11)–C(12)–N(14)	125.1(5)		

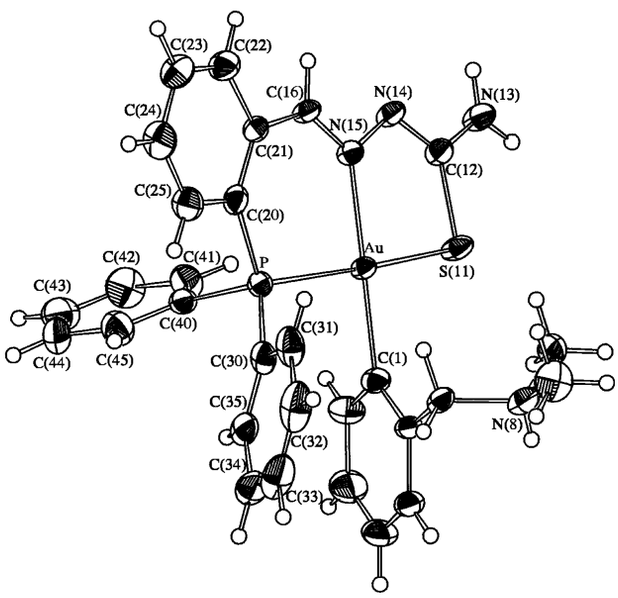


Fig. 8 ZORTEP representation[33] of the complex cation of (**6**). Thermal ellipsoids represent 50% probability. The labelling scheme of the damp ligand corresponds to that given in Fig. 2.

Preliminary tests of the antitumor activity carried out on human MCF-7 breast cancer cells indicate a high antiproliferative potency for the new compounds. At a concentration of 5 μM gold complexes with the thiosemicarbazone ligands HapHtsc, HapMetsc, HapPhtsc, HPtsc and H_2saltsc display exceedingly cytotoxic activity leading to cell death. After an incubation period of 216 h, τ ranges from −63.61 to −65.47%, thus being more effective than cisplatin ($\tau = -2.47\%$). This work is presently in progress in our laboratories and the results will be published elsewhere.[49]

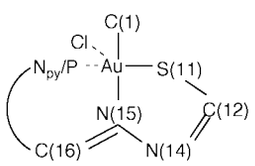
Conclusions

Cationic complexes are formed during the reaction of dichloro-[2-(dimethylaminomethyl)phenyl-C^1,N]gold(III) with thiosemicarbazones. A main structural feature of the resulting gold(III) compounds is the formation of ammonium functions from the liberated $N(CH_3)_2$ groups.

All complex molecules are involved in extended hydrogen-bonding networks with the counter ions and solvent molecules

Table 6 Comparison of selected bond lengths (Å) and angles (°) in the gold thiosemicarbazone complexes studied. For labelling scheme, see (**4**)

	(**3a**–**c**), (**4**)	(**5a**)	(**5c**)	(**6**)
Au–C(1)	2.02–2.04	2.04	1.92	2.06
Au–S(11)	2.25–2.27	2.25	2.19	2.31
Au–N(15)	2.11–2.13	2.04	1.90	2.09
Au–Cl/N_{py}/P	2.32	2.08	2.04	2.38
S(11)–C(12)	1.76	1.79	1.68	1.77
C(12)–N(14)	1.28–1.33	1.31	1.32	1.30
N(14)–N(15)	1.37–1.39	1.38	1.30	1.37
N(15)–C(16)	1.28–1.31	1.29	1.28	1.29
C(1)–Au–S(11)	87.4–90.7	96.5	89.1	91.04
S(11)–Au–N(15)	84.1–84.5	84.9	90.1	84.0
N(15)–Au–Cl/N_{py}/P	95.3–96.8	79.5	75.9	93.6
Cl/N_{py}/P–Au–C(1)	89.0–92.2	99.1	104.9	90.7
C(1)–Au–N(15)	171.8–174.2	178.6	178.6	171.9
S(11)–Au–Cl/N_{py}/P	178.7–179.4	163.6	165.9	172.9



III

which are frequently incorporated into the solid state structures of the compounds. A comparison of the main structural features of the complex cations is given in Table 6. The corresponding labelling scheme is briefly depicted in **III**. Since the bonding situation is very similar in all compounds, containing bidentate co-ordinated thiosemicarbazones, it has been summarized and compared with the complexes containing tridentate ligands. Whereas the observed C–S bond lengths prove the predominant contribution of the tautomeric thiolate form **Ib** to the bonding situation in almost all thiosemicarbazonato complexes discussed, the short C–S bond in (**5c**) is remarkable. This can, however, not be exclusively explained by the occurence of the thione form **Ia** in this compound, since the neighbouring C(12)–N(14) bond is not significantly lengthened and a short C(12)–N(13) bond is observed. Thus, the substitution of a phenyl ring on N(13) most probably leads to an extended π-system and increases the electron density in the co-ordination sphere of the metal. The observed bond angles around gold and the deviations from an ideal square co-ordination environment are due to the formation of the restricting bite angles of the 5-membered chelate rings.

First results from the antiproliferation tests on tumor cells prove the cytotoxicity of the new gold complexes. These promising results suggest that an intensification of such studies would be worthwhile.

Experimental

The thiosemicarbazone ligands used were prepared by refluxing equivalent amounts of thiosemicarbazide, 4-*N*-methylthiosemicarbazide or 4-*N*-phenylthiosemicarbazide (Aldrich) and the corresponding aldehydes or ketones (Aldrich, Fluka) in ethanol. They were characterized by their infrared and mass spectra. Tetrachloroauric acid was a gift from Degussa AG. [Au(damp-C^1,*N*)Cl_2] was synthesized by two transmetallations *via* [Hg(damp)Cl] following a procedure outlined in ref. 23.

Infrared spectra were recorded for KBr pellets on a Spectrum 1000 (Perkin-Elmer) FT IR spectrometer in the range between 4000 and 200 cm^{-1}. Routine EI^+ and FAB^+ spectra were measured with a TSQ spectrometer (Finnigan) with nitrobenzyl alcohol as matrix. ^1H and ^{13}C NMR spectra were recorded in dmso-d_6 with a DRX-250 spectrometer (Bruker) with TMS as standard. An Oxford NMR 300 Gemini 2000 (Varian) instrument with H_3PO_4 as internal standard was used to obtain ^{31}P NMR spectra.

Syntheses

[Au(Hdamp-C^1)Cl(Hsaltsc)]Cl. Salicylaldehyde thiosemicarbazone (100 mg, 0.5 mmol) was suspended in about 3 ml acetone and added to a solution of [Au(damp-C^1,*N*)Cl_2] (200 mg, 0.5 mmol) in 3 ml of a methanol–acetone (1 : 1 v/v) mixture. A clear yellow solution formed immediately which was stirred at room temperature for 2 h. The solvent was removed and the remaining yellow solid dissolved in methanol. Upon slow evaporation of the solvent a few tiny crystals were formed which were not suitable for an X-ray structure analysis. The majority of the product deposits as a yellow microcrystalline solid which is readily soluble in methanol, but almost insoluble in acetone or dichloromethane. Yield: 180 mg (60%). Elemental analysis, Found: C, 34.4; H, 3.4; N, 9.4; S, 5.4; Cl, 12.1; Calcd. for $C_{17}H_{21}N_4AuCl_2OS$: C, 34.2; H, 3.5; N, 9.4; S, 5.4; Cl, 11.9%. IR (ν_{max}/cm^{-1}): 3410 (O–H), 2677 (m, N–H^+, Hdamp-C^1), 1601–1456 (C=C, N=N), 324 (s, Au–Cl). ^1H-NMR (dmso-d_6, ppm): 10.85 (1H, s, br, NH^+), 9.0 (1H, s, OH), 8.17–7.0 (10H, m, phenyl, NH_2), 4.67 (2H, s, CH_2), 2.95 (6H, m, $2CH_3$). ^{13}C-NMR (dmso-d_6, ppm): 171.3 (CS), 164.7–116.9 (arom. C), 55.0 (CH_2), 42.8, 42.5 (CH_3, damp). FAB^+-MS: *m*/*z* = 561 {100%, M^+, [Au(Hdamp)(Hsaltsc)Cl]$^+$}, 525 {25%, [Au(Hdamp)(Hsaltsc)]$^+$}.

Crystals of the complex suitable for an X-ray structure determination were obtained for its PF_6^- salt (**3a**) formed *via* addition of KPF_6 to a solution of [Au(Hdamp-C^1)Cl(Hsaltsc)]Cl in methanol and slow evaporation of the solvent.

[Au(Hdamp-C^1)Cl(vantsc)]Cl (3b). [Au(damp-C^1,*N*)Cl_2] (314 mg, 0.79 mmol) and vanilline thiosemicarbazone (177 mg, 0.79 mmol) were suspended in 20 ml methanol and heated under reflux for 2 h to yield a clear yellow solution. The solvent was evaporated to dryness, the residue washed with cold acetone and the orange–red, microcystalline solid dried *in vacuo*. Yield: 450 mg (90%). Yellow crystals suitable for X-ray diffraction were obtained by slow evaporation of a methanol solution. Elemental analysis, Found: C, 35.0; H, 4.3; N, 9.2; S, 5.1; Cl, 11.5; Calcd. for $C_{18}H_{23}N_4AuCl_2O_2S$: C, 34.5; H, 3.9; N, 8.9; S, 5.1; Cl, 11.3%. IR (ν_{max}/cm^{-1}): 3439, 3334 (O–H, N–H), 2686 (N–H^+, Hdamp-C^1), 1600–1512 (C=C, N=N), 452 (Au–C), 316 (s, Au–Cl). ^1H-NMR (dmso-d_6, ppm): 10.51 (1H, s, br, NH^+), 10.18 (1H, s, OH), 7.96–6.78 (8H, m, phenyl), 7.72 (2H, s, NH_2), 4.31 (2H, s, CH_2), 3.67 (3H, d, OCH_3), 2.58 (6H, m, $2CH_3$). ^{13}C-NMR (dmso-d_6, ppm): 171.8 (CS), 153.2–117.5 (arom. C), 63.4 (CH_2), 57.8 (OCH_3), 44.1, 43.8 ($2CH_3$, damp). FAB^+-MS: *m*/*z* = 591 {100%, M^+, [Au(Hdamp)Cl(vantsc)]$^+$}, 555 {32%, [Au(Hdamp)(vantsc)]$^+$}.

[Au(Hdamp-C^1)Cl(mepyrtsc)]Cl (3c). [Au(damp-C^1,*N*)Cl_2] (200 mg, 0.5 mmol) was dissolved in 2 ml of a methanol–acetone mixture (1 : 1, v/v) and solid methylpyrrole thiosemicarbazone (91 mg, 0.5 mmol) added. The thiosemicarbazone rapidly dissolved and a clear red solution was formed which lightened after stirring for 1 h. The volume was slowly reduced by evaporation of the solvents and a few orange–red crystals deposited over a period of 24 h. More product was obtained by reducing the volume of the mother liquor under vacuum. However, the solid obtained rapidly decomposed to give a black powder. Satifactory IR, NMR and mass spectra were obtained immediately after separation of the solid. Yield: 73 mg, 25%. IR (ν_{max}/cm^{-1}): 3386, 3251 (N–H), 2693 (N–H^+, Hdamp-C^1), 1599–1559 (C=C, N=N), 451 (Au–C), 315 (s, Au–Cl). ^1H-NMR (dmso-d_6, ppm): 10.85 (1H, s, br, NH^+), 8.2 (2H, s, NH_2), 7.87–7.0 (8H, m, phenyl), 4.5 (2H, s, CH_2),

Table 7 X-Ray structure data collection and refinement parameters

	(**3a**)	(**3c**)	H_2pydoxmetsc·HCl	(**4**)·MeOH	(**5c**)·2MeOH	(**6**)·1.5MeOH
Formula	$C_{17}H_{21}AuClF_6N_4OPS$	$C_{16}H_{22}AuCl_2N_5S$	$C_{10}H_{15}ClN_4O_2S$	$C_{20}H_{31}AuCl_3N_5O_3S$	$C_{25}H_{34}AuCl_2N_5O_2S$	$C_{31}H_{37}N_4Cl_2O_{1.5}PS$
M/g mol^{-1}	706.8	584.31	290.77	724.9	736.50	820.54
Crystal dimension/mm	0.25 × 0.2 × 0.15	0.3 × 0.1 × 0.5	0.4 × 0.2 × 0.03	0.15 × 0.1 × 0.1	0.25 × 0.25 × 0.15	0.4 × 0.1 × 0.1
Crystal system	Monoclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/n$
Unit cell	a = 12.799(2) Å	a = 12.858(1) Å	a = 7.700(1)	a = 9.736(2) Å	a = 13.943(3) Å	a = 16.596(3) Å
	b = 10.504(1) Å	b = 12.559(3) Å	b = 8.050(1)	b = 11.180(1) Å	b = 13.410(4) Å	b = 11.257(1) Å
	c = 16.973(4) Å	c = 12.904(2) Å	c = 12.461(1)	c = 13.085(2) Å	c = 15.292(3) Å	c = 18.363(3) Å
			α = 74.08(1)°	α = 77.35(1)°		
	β = 93.38(1)°	β = 97.21(2)°	β = 75.85(1)	β = 84.75(1)°	β = 100.05(2)	β = 94.80(1)°
			γ = 64.49(1)	γ = 83.00(1)		
V/Å^3	2277.9(8)	2067.3(6)	663.2(1)	1376.3(8)	2815(1)	3418.6(7)
Z	4	4	2	2	4	4
Measurement temperature/°C	20	−65	−65	−120	−65	−65
Linear absorption coefficient/mm^{-1}	6.804	7.485	4.046	5.742	5.521	4.599
Measured reflections	5608	5083	3164	3345	6845	8241
Independent reflections/R_{int}	4938/0.036	4487/0.047	2253/0.063	3345	6099/0.0264	7455/0.0301
$R1$ (F)/$wR2$ (F^2)	0.0389/0.0811	0.0494/0.0772	0.0539/0.1927	0.0613/0.1234	0.0423/0.0969	0.0357/0.0804

3.18 (3H, NCH_3), 2.75 (6H, m, $2CH_3$). FAB$^+$-MS: m/z = 548 {27%, M^+, [Au(Hdamp)Cl(mepyrtsc)]$^+$}, 512 {15%, [Au(Hdamp)(mepyrtsc)]$^+$}.

[Au(Hdamp-*C*^{1})Cl(H_2pydoxmetsc)]Cl_2 (4). [Au(damp-C^1,N)Cl_2] (200 mg, 0.5 mmol) was dissolved in 5 ml of a methanol–acetone mixture (1 : 1, v/v) and pyridoxal thiosemicarbazone (127 mg, 0.5 mmol) suspended in a small amount of methanol was added. After stirring for 1 h the orange–red solution was decanted from a pale brown solid and reduced in volume by slow evaporation. Pale yellow crystals of [Au(Hdamp-C^1)Cl(H_2pydoxmetsc)]Cl_2·MeOH deposited which rapidly decomposed when removed from the solvent. Considerable amounts of an insoluble, finely powdered side-product was formed, which most probably consists of polymeric, reduced gold compounds. This prevented the isolation of larger amounts of (**4**) in sufficient purity to yield satisfactory elemental analyses. Samples of the crystalline gold(III) complex for spectroscopic studies were separated manually. Yield: *ca.* 10%. IR (ν_{max}/cm^{-1}): 3185 (O–H, N–H), 2820–2580 (m, N–H$^+$), 2100–2012 (N=C=S), 1560–1470 (C=C, N=N), 1001 (s, C=S), 751 (s, bisubstituted phenyl, damp), 452 (Au–C), 326 (s, Au–Cl). FAB$^+$-MS: m/z = 620 (35%, M^+, [Au(Hdamp)Cl(H_2pydoxmetsc)]$^+$), 584 (20%, [Au(Hdamp)-(H_2pydoxmetsc]$^+$).

[Au(Hdamp-*C*^{1})(apHtsc)]Cl_2 (5a). [Au(damp-C^1,N)Cl_2] (200 mg, 0.5 mmol) was dissolved in 5 ml of a methanol–acetone mixture (1 : 1, v/v) and HapHtsc (97 mg, 0.5 mmol) added in 3 ml acetone. The bright yellow solution was stirred at room temperature for 1 h and overlayered with diethyl ether. Yellow crystals of [Au(Hdamp-C^1)(apHtsc)]Cl_2·0.5H_2O grew within a few days. They were separated, washed with cold acetone and dried. Yield: 225 mg, 75%. Elemental analysis, Found: C, 34.1; H, 4.0; N, 11.8; S, 5.3; Cl, 11.9; Calcd. for $C_{17}H_{22}N_5AuSCl_2$: C, 34.3; H, 3.7; N, 11.8; S, 5.4; Cl, 11.8%. IR (ν_{max}/cm^{-1}): 3410, 3277, 3154 (N–H), 2629 (NH^+), 1625, 1604 (C=C, C=N), 488 (Au–C). ^{1}H-NMR (dmso-d_6, ppm): 11.2 (1H, s, br, NH^+), 8.95 (2H, s, br, NH_2), 8.4–7.4 (8H, m, phenyl), 4.5 (2H, m, CH_2), 2.6 (6H, s, $2CH_3$), 2.5 (3H, s, CH_3). ^{13}C-NMR (dmso-d_6, ppm): 177 (CS), 159.8–129.3 (12C, arom. C), 62.2 (CH_2), 42.7 (CH_3, damp), 42.2 (CH_3, damp), 14.7 (CH_3). FAB$^+$-MS: m/z = 524 {100%, [M − H^+], [Au(Hdamp)(apHtsc)]$^+$}, 390 {40%, [Au(apHtsc)]$^+$}.

[Au(Hdamp-*C*^{1})(apMetsc)]Cl_2 (5b). The compound was prepared as described for (**5c**) and was isolated in the form of yellow needles. Yield: 40 mg, 13%. IR (ν_{max}/cm^{-1}): 3405 (br, MeOH), 3287, 3147 (N–H), 2684 (NH^+), 1597 (C=N), 1570, 1548, 1513 (C=C), 425 (Au–C). FAB$^+$-MS: m/z = 538 {100%, [M − H]$^+$}, 507 {5%, [M − H − (NHMe)]$^+$}, 404 {42%, [Au(apMetsc)]$^+$}.

[Au(Hdamp-*C*^{1})(apPhtsc)]Cl_2 (5c). [Au(damp-C^1,N)Cl_2] (200 mg, 0.5 mmol) was dissolved in 5 ml of a methanol–acetone mixture (1 : 1, v/v) and HapPhtsc (135 mg, 0.5 mmol) was added as a solid in small portions. The thiosemicarbazone dissolved within a few minutes. After filtration, the orange–red reaction mixture was overlayered with diethyl ether and kept for crystallization. Yellow crystals deposited on the glass walls which were filtered off and dried under vacuum. Yield: 95 mg, 28%. Elemental analysis, Found: C, 41.0; H, 3.5; N, 9.8; S, 4.9; Cl, 10.5; Calcd. for $C_{23}H_{26}N_5AuSCl_2$: C, 41.2; H, 3.9; N, 10.5; S, 4.8; Cl, 10.6%. IR (ν_{max}/cm^{-1}): 3425 (br, Me–OH), 3216, 3179, 3119 (N–H), 2701 (NH^+), 1602 (C=N), 1555, 1510 (C=C), 455 (Au–C). ^{1}H-NMR (dmso-d_6, ppm): 11.25 (1H, s, NH), 11.12 (1H, s, br, NH^+), 8.51–7.2 (13H, m, arom.), 4.54 (2H, m, CH_2), 2.78 (3H, s, CH_3), 2.69 [6H, s, $N(CH_3)_2$]. ^{13}C-NMR (dmso-d_6, ppm): 161.3 (CS), 158.5–120.7 (arom. C), 61.4 (CH_2), 42.0 (CH_3), 41.3 (CH_3), 14.5 (CH_3). FAB$^+$-MS: m/z = 600 {65%, [M − H]$^+$], 507 {7%, [M − H − (NHPh)]$^+$}, 466 {50%, [Au(apPhtsc)]$^+$}.

[Au(Hdamp-*C*^{1})(Ptsc)]Cl_2 (6). [Au(damp-C^1,N)Cl_2] (200 mg, 0.5 mmol) and HPtsc (182 mg, 0.5 mmol) were stirred in 10 ml of a methanol–acetone mixture (1 : 1, v/v). After 2 h the bright yellow solution was filtered and overlayered with the same volume of diethyl ether. Yellow crystals of [Au(Hdamp-C^1)(Ptsc)]Cl_2·1.5MeOH deposited upon standing for a week. More product was obtained by evaporation of the solvent. The complex was washed with cold acetone and dried under vacuum. Yield: 115 mg, 30%. Elemental analysis, Found: C, 45.4; H, 3.6; N, 7.4; S, 4.5; Calcd. for $C_{29}H_{30}N_4AuPSCl_2$: C, 45.6; H, 3.9; N, 7.3; S, 4.2%. IR (ν_{max}/cm^{-1}): 2773 (NH^+), 1623 (s, C=N),

1501 (s, C=C), 750 (disubstituted damp-phenyl), 692 (monosubstituted phenyl), 434 (Au–C), 340 (Au–P). ^{1}H-NMR (dmso-d_6, ppm): 8.59 (1H, s, arom.), 8.15 (1H, m, arom.), 7.22–7.82 (17H, m, arom.), 4.48 (2H, s, CH_2), 2.75 (6H, s, $2CH_3$). ^{13}C-NMR (dmso-d_6, ppm): 172 (CS), 150.9, 135.8–127.7 (arom. C), 62.2 (CH_2), 42.9 (CH_3, damp). ^{31}P-NMR (dmso-d_6, ppm): +29.2 (proligand: −13.2). FAB$^+$-MS: m/z = 694 {28%, [M − H$^+$]}, 559 {9%, [Au(Ptsc)]$^+$}.

X-Ray structure determinations

The intensities for the X-ray determinations of (**3a**), (**3c**), (**5c**), (**6**) and H_2pydoxmetsc·HCl were collected on an automated single crystal diffractometer of the CAD4 type (Enraf-Nonius, Delft) with Mo-Kα radiation (Au complexes) or Cu-Kα radiation (H_2pydoxmetsc·HCl). The data set for (**4**) was obtained on a DIP 2000 Image Plate instrument (Enraf-Nonius) using standard procedures.

The programs HELENA[50] and DENZO[51] were applied for data reduction. The structures were solved by Patterson syntheses using SHELXS97.[52] Subsequent Fourier-difference map analyses yielded the positions of the non-hydrogen atoms. Refinement was performed using SHELXL97.[53] The positions of all hydrogen atoms bonded to N or O and possibly contributing to hydrogen bonds were derived from the final Fourier map and fully refined. All other H atoms were calculated for idealized positions and treated with the 'riding model' option of SHELXL97. Crystal data and more details of the data collections and refinements are contained in Table 7.

CCDC reference number 186/1796.

See http://www.rsc.org/suppdata/dt/a9/a908712e/ for crystallographic files in .cif format.

In vitro chemosensitivity assay

The antiproliferative activity of the gold complexes was tested on exponentially dividing human MCF-7 breast cancer cells according to a standardized microtitre assay.[54] The cells were seeded onto 96-well microtitre plates as a suspension with 17×10^5 cells ml^{-1}. After a 72 h preincubation period, this medium was exchanged for a new one containing the test compound at a concentration of 5 μM. Cell growth was stopped with glutardialdehyde after different incubation periods (max. incubation time: 216 h). The cells were then stored at 4 °C under PBS (phosphate buffered saline). Cell biomass was determined by a crystal violet staining technique as described in ref. 55 combined with UV detection. Cytocidal effect can be expressed as $\tau(\%) = [(T^* - C_0)/C_0] \times 100$. C_0 represents the mean optical density of the cell extract immediately before treatment and T^* the mean optical density of the cell extract after different incubation periods.

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