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Synthesis, characterization, and biological activities of 2-phenylpyridine gold(III) complexes with thiolate ligands †

Daming Fan, Chang-Tong Yang,* John D. Ranford,* Jagadese J. Vittal* and Peng Foo Lee
Department of Chemistry, National University of Singapore, Singapore, 117543.
E-mail: chmyct@nus.edu.sg; kubalranford@yahoo.co.uk; chmjjv@nus.edu.sg

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A series of new 2-phenylpyridine Au(III) complexes [Au(ppy)X] with various thiolate ligands has been synthesized and characterized (X = (SCN)(NCS) (**1**), tlc (thiolactate) (**2**), tsc (thiosalicylate) (**3**), dmp (2,3-dimercapto-1-propanol) (**4**), dms (2,3-dimercaptosuccinic acid) (**5**), cys (cysteine) (**6**)). The crystal structure of [Au(ppy)(SCN)-(NCS)] (**1**) shows the two soft carbanion and sulfur donors mutually *cis* to each other in the thermodynamically most stable isomer. It is noteworthy that the two thiocyanate ions bind to gold through nitrogen (*trans* to C) and sulfur (*trans* to N) atom, respectively, with the Au–NCS group linear whereas the Au–SCN is bent. Crystal structures of [Au(ppy)(tsc)]·1.5H_2O (**3**) and [Au(ppy)(cys)]·0.5(Cl^- + ClO_4^- + H_2O) (**6**) show the expected square-planar coordination around the gold atom and the stronger *trans* influence groups S and C adopting the *cis*-orientated configuration. Complexes **1**–**5** have been tested *in vitro* against MOLT-4 human leukemia and C2Cl2 mouse tumour cell lines, where they are more cytotoxic than the clinically used cisplatin.

Introduction

Au(I) thiolate complexes have been used as antiarthritic and cancerostatic drugs since the late 1920s.[1–7] A series of Au(I) thiolate compounds with a coordinated phosphine have been shown to possess potent cytotoxic activity *in vitro* and anti-tumor activity *in vivo* against P388 leukemia cells.[8] In contrast to the extensive studies on Au(I) thiolate complexes,[9] studies on the biological chemistry of Au(III) thiolate complexes are substantially fewer. Laguna and co-workers reported the synthesis of Au(I) and Au(III) complexes with the 1-methyl-2-sulfanyl-1,2-dicarba-*closo*-dodecaborate ligand incorporating an *o*-carborane moiety.[10] Complexes with thiolate ligands incorporating an *o*-carborane backbone have potential as tumour-seeking drugs for boron neutron capture therapy.[11–13] A few novel Au(III) thiolate complexes have been reported with interest focusing on syntheses and structures.[14–20] Henderson recently reported that certain Au(III) complexes containing the chelated thiosalicylate (tsc) dianionic ligand showed high to very high antitumour activity against P388 leukemia cells.[21] It is noteworthy there are some Au(II) complexes containing xanthate ligands have been reported by Laguna and co-workers.[22] Certain Pt(II) thiosalicylate complexes have also shown high antimicrobial and antitumour activity as Au(III) is isoelectronic with Pt(II).[23] This suggests that this class of complexes offers potential for the development of novel anti-tumour active compounds.

As part of our studies into the chemical and biological properties of 2-phenylpyridine Au(III) complexes, we recently reported the synthesis, characterization, and cytotoxicity of several Au(III) complexes of various carboxylato ligands, which showed high cytotoxic against the MOLT-4 tumour cell lines.[24] In the present study, the series of 2-phenylpyridine Au(III) compounds was extended to search for antitumour active complexes with various thiolato ligands. Here we have used both monodentate (SCN^-) and bidentate (thiolactic acid, thiosalicylic acid, 2,3-dimercapto-1-propanol, *meso*-2,3-dimercaptosuccinic acid, L-cysteine) thiolate ligands to synthesize a new series of Au(III) thiolate complexes. We have also carried out *in vitro* cytotoxic tests to evaluate complexes for biological activity.

† Electronic supplementary information (ESI) available: ESMS data. See http://www.rsc.org/suppdata/dt/b3/b307610e/

Experimental

$Na[AuCl_4]$ and 2-phenylpyridine were obtained from Aldrich Chemical Co. Milwaukee, Wisconsin, USA. All other reagents were purchased from Fluka Chemie AG, Buchs, Switzerland.

NMR spectra were recorded on a Bruker ACF 300 (^1H, ^{13}C) spectrometer at 25 °C. Spectra were referenced to the solvent in each case. ESMS were obtained in positive-ion mode using a VG Platform II mass spectrometer and a 1: 1 v/v acetonitrile–water phase. Cone voltages were varied from 20 to 200 V in order to investigate the effect of higher voltages on fragmentation of parent ions. Confirmation of all species in this ESMS study was aided by comparison of the observed and predicted isotope distribution patterns. Theoretical isotope distribution patterns were calculated using the Isotope computer program.[25] The ESMS tests were carried out in the Department of Chemistry, University of Waikato, New Zealand. The elemental analyses were performed in the Microanalytical Laboratory, Department of Chemistry, National University of Singapore.

[Au(ppy)(SCN)(NCS)], 1. [Au(ppy)Cl_2] (0.14 g, 0.33 mmol) was dissolved in dichloromethane (40 ml) in a 100 ml round bottom flask. Sodium thiocyanate (0.062 g, 0.76 mmol) in water (10 ml) was added to the solution and the resulting mixture was stirred in the dark for 4 h. After filtering, the layers were separated and the yellow organic solution was dried over anhydrous magnesium sulfate. The solution was filtered, reduced to *ca.* 10 ml under reduced pressure, and treated with diethyl ether to induce crystallization. Crystallization was completed by cooling in a freezer. The yellow product was collected by filtration, washed with diethyl ether and dried *in vacuo*. Yield: 0.065 g (42%). Anal. for $C_{13}H_8AuN_3S_2$ (calcd in parentheses) C, 33.4 (33.4); H, 1.9 (1.7); N, 8.8 (9.0); S, 13.4 (13.7); Au, 42.4 (42.2)%.

[Au(ppy)(tlc)], 2. [Au(ppy)Cl_2] (0.13 g, 0.30 mmol) was dissolved in acetone (40 ml) in a 100 ml round bottom flask. To this solution was added solid silver nitrate (0.11 g, 0.60 mmol), and the reaction mixture was stirred at room temperature in the dark for 2 h. After the silver chloride filtered off, the filtrate was degassed for a few minutes and treated with sodium hydroxide (0.032 g, 0.60 mmol) and thiolactic acid (0.03 ml, 0.32 mmol) in a degassed mixture of water (5 ml) and acetone (5 ml). The colour immediately changed from white to yellow and become opaque. The mixture was allowed to stir at room temperature

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Table 1 Crystallographic data and structure refinement details for **1**, **3** and **6**

Complex	**1**	**3**	**6**
Formula	$C_{13}H_8AuN_3S_2$	$C_{18}H_{15}AuNO_{3.5}S$	$C_{14}H_{15}AuClN_2O_{4.5}S$
Formula weight	467.31	530.34	547.76
T/K	293(2)	293(2)	293(2)
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	*C*2	*Pbcn*	$P2_1$
a/Å	26.7450(1)	13.013(4)	13.4444(1)
b/Å	5.7751(3)	20.133(4)	10.1827(1)
c/Å	9.2660(5)	13.3317(2)	13.5174(1)
α/°	90	90	90
β/°	107.948(1)	90	116.695(1)
γ/°	90	90	90
V/Å^3	1361.5(1)	3492.7(13)	1653.288(17)
Z	4	8	4
μ/mm^{-1}	11.098	8.562	9.210
Reflns. collected	6286	20261	10751
Independent reflns.	3302	4431	6919
R_{int}	0.0521	0.0467	0.0271
R_1, wR_2 $[I > 2\sigma]$[a]	0.0394, 0.789	0.0489, 0.1072	0.0316, 0.0657

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

under N_2 for 2 h. The bright yellow solution was filtered and the filtrate was concentrated to dryness, washed with hexane and dried *in vacuo*. The solid was extracted with dichloromethane (3 × 10 ml) and the extract was reduced in volume. Diethyl ether was added to give a yellow powder of the complex. Yield: 0.048 g (35%). Anal. for $C_{14}H_{12}AuNO_2$ (calcd) C, 36.6 (36.9); H, 2.6 (2.6); N, 3.0 (3.1); S, 7.0 (7.1); Au, 43.5 (43.3)%.

[Au(ppy)(tsc)]·1.5H$_2$O, 3. [Au(ppy)Cl$_2$] (0.43 g, 1.0 mmol) was dissolved in acetone (50 ml) in a 100 ml round bottom flask and silver nitrate (0.34 g, 2.0 mmol) was added. The reaction mixture was stirred in the dark at room temperature for 2 h, and the silver chloride filtered off. The colourless filtrate was treated with thiosalicylic acid (0.16 g, 2.0 mmol) and sodium hydroxide (0.16 g, 4.0 mmol) in degassed water (3 ml). The resulting yellow solution was allowed to stir for 1 h. The solution was then filtered and the yellow filtrate was reduced in volume under reduced pressure until crystallization was just observed. Bright yellow crystals were obtained from vapour diffusion of diethyl ether into the acetone solution. Yield: 0.151 g (28%). Anal. for $C_{18}H_{15}AuNO_{3.5}S$ (calcd) C, 40.6 (40.8); H, 2.6 (2.8); N, 2.7 (2.6); S, 5.8 (6.0); Au, 37.4 (37.1)%.

[Au(ppy)(dmp)], 4. In a 100 ml Schlenk flask with a magnetic stirrer bar, [Au(ppy)Cl$_2$] (0.086 g, 0.20 mmol) was dissolved in dichloromethane (30 ml) and degassed with N_2. To this solution was added 2,3-dimercapto-1-propanol (0.021 ml, 0.20 mmol) in degassed methanol (20 ml). The reaction mixture was allowed to stir at room temperature under N_2 for 8 h. The bright yellow solution was filtered and the filtrate was concentrated to dryness, washed with hexane and dried *in vacuo*. The orange powder was recrystallized from dichloromethane–diethyl ether (1 : 1) at 0 °C. Yield: 0.035 g (36%). Anal. for $C_{14}H_{14}AuNOS_2$ (calcd) C, 35.2 (35.5); H, 2.9 (3.0); N, 3.1(3.0); S, 13.7 (13.5); Au, 41.9 (41.6)%.

[Au(ppy)(dms)], 5. A solution of [Au(ppy)Cl$_2$] (0.064 g, 0.15 mmol) in dichloromethane (25 ml) was prepared in a 100 ml Schlenk flask. *Meso*-2,3-dimercaptosuccinic acid (0.028 g, 0.15 mmol) in degassed acetonitrile (15 ml) was added. The reaction mixture was allowed to stir at room temperature under N_2 for 6 h. The yellow solution was filtered and the filtrate was concentrated to dryness, washed with hexane and dried *in vacuo*. The orange powder was recrystallized from dichloromethane–diethyl ether (1 : 1) at 0 °C. Yield: 0.032 g (40%). Anal. for $C_{15}H_{17}AuNO_4S_2$ (calcd) C, 33.6 (33.9); H, 2.2 (2.3); N, 2.5 (2.6); S, 11.7 (12.0) Au, 37.4 (37.1)%.

[Au(ppy)(cys)]·0.5(Cl$^-$+ClO$_4^-$+H$_2$O), 6. This complex was produced from an attempt to investigate the reaction of [Au(ppy)(ace)$_2$]·H$_2$O[23] with various biomolecules. Complex **6** was obtained through the reaction of [Au(ppy)(ace)$_2$]·H$_2$O (0.098 g 0.20 mmol) with L-cysteine (0.024 g, 0.20 mmol) in acetone–water. Sodium perchlorate was added to neutralize the charge of the compound. The above mixture was filtered and the yellow filtrate was concentrated and crystals produced by vapor diffusion of diethyl ether at 0 °C. Yellow crystals were obtained after 3 days. Yield: 0.029 g (26%). Anal. for $C_{14}H_{15}AuN_2O_{4.5}S$ (calcd) C, 32.9 (32.8); H, 2.8 (2.9); N, 5.7 (5.5); S, 6.3 (6.3); Au, 38.4 (38.5)%.

X-Ray crystallography

The diffraction experiments were carried out on a Bruker AXS SMART CCD diffractometer. The program SMART[26] was used for collecting the intensity data, for reflections indexing and for the determination of lattice parameters, SAINT[26] was used for integration of the intensity of reflections and scaling, SADABS[27] was used for absorption correction and SHELXTL[28] for space group and structure determination, least-squares refinements on F^2. Of the seven disordered positions of water molecules found in the lattice of **3**, five have the occupancy of 0.25 and two has the occupancy of 0.125, and no hydrogen atom was added to these disordered oxygen atoms. There are two independent molecules present in the asymmetric unit in **6**. The perchlorate anion and water molecules are not disordered. However, the chloride anion was disordered and two sets of orientation with occupancies of 0.5 and 0.5 were found. All non-H atoms were refined with anisotropic thermal parameters. Selected crystallographic data and refinement details are displayed in Table 1.

CCDC reference numbers 214284–214286.

See http://www.rsc.org/suppdata/dt/b3/b307610e/ for crystallographic data in CIF or other electronic format.

Cytotoxicity testing

Comparative cytotoxicity against the MOLT-4 human leukemia and C2C12 mouse tumour cell lines was assessed. A typical assay was set up by dispensing 30000 MOLT-4 cells in 70 μl RPMI 1640 medium supplemented with 10% foetal calf serum in to each well of a 96-well plate. The C2C12 cells were cultured in Dulbecco's modified Eagle's medium with 4 mM L-glutamine adjusted to contain 1.5 g L^{-1} sodium bicarbonate, 4.5 g L^{-1} glucose and 1.0 mM sodium pyruvate, 90%; fetal bovine serum, 10%. The test fractions were dissolved in DMSO

Table 2 ^{1}H NMR data for complexes **1**–**5** (δ, DMSO-d^{6} solutions)[a]

Complex	H^{11}	H^{9}	H^{8}	H^{5}	H^{2}	H^{10}	H^{4}	H^{3}	R
1	8.94	8.41	8.36	8.03	7.37	7.79	7.49	7.42	
2	8.76	8.41	8.33	8.03	7.34	7.68	7.53	7.46	4.42, 1.43
3	9.01	8.45	8.40	8.05	7.37	7.68	7.51	7.40	8.01, 7.62, 7.35, 7.29
4	8.92	8.41	8.32	8.07	7.37	7.66	7.62	7.40	4.98, 4.10, 3.64, 3.04; 4.88, 3.92, 3.48, 2.98
5	8.72	8.42	8.33	8.08	7.36	7.68	7.62	7.41	4.62, 4.14

[a] See Fig. 3 for ^{1}H numbering scheme.

Table 3 ^{13}C NMR data for complexes (δ, DMSO-d^{6} solutions)

Complex	2-phenylpyridine	R
1	122.1, 125.5, 127.2, 127.9, 129.4, 132.2, 143.4, 143.8, 147.7, 151.8, 162.9	104.2, 117.3
2	121.6, 125.7, 126.8, 127.7, 130.5, 131.7, 142.4, 143.7, 147.8, 157.3, 163.6	25.0, 78.6, 176.8
3	121.3, 125.2, 126.6, 127.5, 129.3, 131.4, 140.7, 143.5, 143.8, 148.1, 161.1	123.5, 127.4, 129.6, 130.6, 134.5, 145.1, 176.2
4	121.8, 125.6, 126.3, 127.3, 131.4, 131.9, 142.4, 143.8, 148.9, 161.4, 164.0	33.4, 46.3, 64.4; 33.0, 44.5, 63.7
5	121.8, 125.7, 126.4, 127.6, 130.9, 131.8, 142.6, 143.8, 147.9, 159.2, 163.8	45.3, 58.2, 170.6, 172.2

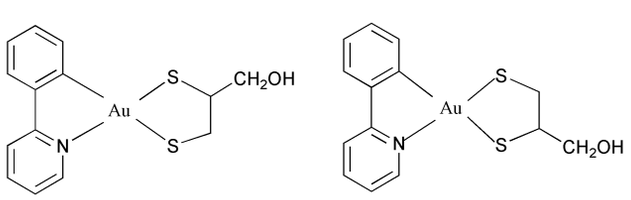
and added in 10 µl portions such that the final concentration of DMSO was 1.25% (v/v) in all wells. Controls received DMSO only. Following incubation of cells with test fractions for 14–16 h at 37 °C and 5% CO_2, 20 µl of a 5 mg ml^{-1} solution of 3[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazoliumbromide (MTT) was added into each well (MTT final concentration 1 mg ml^{-1}). Three hours later, 100 µl of lysing solution (20% sodium dodecyl sulfate dissolved in 50% DMF, pH adjusted to 4.7 with acetic acid) was added to each well. Cell lysis was facilitated by mechanical disruption and mixing, after which absorbance was read at 570 nm against the standard mixture of RPMI 1640 medium, MTT, and lysing solution as blank.

Results and discussion

Synthesis

Complexes **2** and **3** were synthesized by the same procedure as for [Au(ppy)(ac)$_2$] described in previous work.[24] [Au(ppy)Cl$_2$] reacted with silver nitrate stoichiometrically to produce the intermediate [Au(ppy)(NO$_3$)$_2$], and it was then reacted with appropriate thiolate salts to give yellow products.

Complexes **1**, **4**, and **5**, were prepared through direct substitution of chloride by the relevant thiolate ligands as sulfur has a stronger preference for gold than chloride. **4** was synthesized in a reaction of [Au(ppy)Cl$_2$] with 2,3-mercapto-1-propanol in degassed dichloromethane–methanol at room temperature to give a mixture of two isomers (Scheme 1). The isomers are distinguished by the position of the coordinated phenyl-C atom relative to the CH_2OH in the dmp ligand (*cisoid* or *transoid*). The two isomers were not separated but can be differentiated in NMR spectra. Complex **5** was prepared by same method in dichloromethane but it lacks geometric isomers due to the two-fold symmetry of the dms ligand.



cisoid, **Isomer 1** *transoid*, **Isomer 2**

Scheme 1

In an attempt to study the binding mode of Au(III) with biomolecules, the solution of [Au(ppy)(ac)$_2$]·H$_2$O[24] in acetone–water was treated with equimolar amounts of L-cysteine in this work, and sodium perchlorate was added to neutralize the charge of the yellow product **6**. Although L-cysteine is soluble in water, the solubility of **6** is poor in aqueous solution.

For purification, the complexes were redissolved in dichloromethane and filtered through a pasteur pipette containing a plug of glass wool, which removed insoluble impurities. Vapour diffusion of diethyl ether into the dichloromethane solution gave yellow needles of **1**. The bright yellow crystals of **3** and **6** were obtained by vapour diffusion of diethyl ether into concentrated acetone solutions.

Spectroscopic studies

The ^{1}H and ^{13}C chemical shift data are summarized in Tables 2 and 3, respectively (atom numbering scheme refer to Fig. 3). The ^{1}H NMR spectra of these thiolato complexes show that H^{11} and H^{2} resonances shift significantly upfield relative to the precursor complex [Au(ppy)Cl$_2$].[23] As for **4**, only one set of proton and carbon signals for the ppy ligand was observed. However, there are two sets of resonances when the dmp ligand is employed in **4** (see Tables 1 and 2) as a consequence of the two isomers present. The two set of signals are slightly different in chemical shift in a ratio of 1 : 1 corresponding to the presence of the two isomers. In the ^{1}H and ^{13}C NMR spectra of **2**, there is one set of signals for the tlc ligand. This is possibly due to only one configuration of this complex as the two softest ligands, sulfur and carbon, would be *cis* to each other. For the ^{13}C NMR spectrum in DMSO-d$_6$ of **6**, only one set of cysteine and ppy resonances is observed, suggesting that cysteine is bound to gold as a bidentate ligand. To establish the mode of binding, the coordination chemical shifts [$\Delta\delta = \delta$(complex) − δ(ligand)] of the signals for the three carbon atoms of cysteine were determined (Table 4). All were positive and the CH_2 group has the largest $\Delta\delta$ value. The carboxyl carbon showed a much smaller value than the other two carbon atoms. It is therefore likely that cysteine is bound to gold through sulfur and nitrogen, as would be expected for coordination to a soft metal. This assumption was confirmed by the crystal structure of [Au(ppy)(cys)]·0.5(Cl^- + ClO_4^- + H_2O), in which sulfur and nitrogen were coordinated to gold and the softest donors, carbon and sulfur, are mutually *cis* to each other. The ^{13}C NMR spectra of all complexes have a common feature in that C^{1} shows a strong downfield shift relative to other carbons in the ppy ligand as a result of direct binding to gold.

ESMS studies have been carried out on **2** and **3**, Table 5. Positive-ion ESMS has been shown to be a powerful technique in the characterizaion of thiolate complexes.[29] For both complexes, an intense parent ion was observed using cone voltages ranging from 20 to 50 V. The lack of fragmentation at such a high cone voltage indicates appreciable stability, and is in accord with the similar stability of other Au(III) complexes

Table 4 Chemical shifts for complex **6** in DMSO-d_6[a]

Compound	$SCH_2CH(NH_2)CO_2$	$SCH_2CH(NH_2)CO_2$	$SCH_2CH(NH_2)CO_2$
[Au(ppy)(cys)]	36.4	64.1	176.6
L-cysteine	27.2	58.2	174.8
$\Delta\delta$	+9.2	+5.9	+1.8

[a] $[\Delta\delta = \delta(\text{complex}) - \delta(\text{ligand})]$.

Table 5 ESMS data for complexes **2** (20 V) and **3** (50 V)

Complex **2**	Peaks/amu	Complex **3**	Peaks/amu
$(M + H)^+$	456 (68)[a]	$(M + H)^+$	504(100)[a]
$(M + NH_4)^+$	473 (10)	$(M + Na)^+$	526 (4)
$(2M + H)^+$	911 (100)	$(2M + H)^+$	1007 (36)
$(3M + NH_4)^+$	1383 (43)	$(2M + Na)^+$	1029 (10)
$(4M + NH_4)^+$	1838 (8)	$(3M + H)^+$	1510 (2)
		$(3M + Na)^+$	1532 (5)

[a] Relative intensities given in parentheses.

Table 6 Selected bond lengths (Å) and angles (°) for **1**

Au(1)–C(1)	2.012(8)	Au(1)–N(1)	2.064(6)
Au(1)–S(1)	2.304(3)	Au(1)–N(3)	2.048(9)
S(1)–C(12)	1.634(1)	S(2)–C(13)	1.612(1)
N(2)–C(12)	1.146(1)	N(3)–C(13)	1.142(1)
C(1)–C(2)	1.374(1)	C(1)–C(6)	1.391(1)
N(1)–C(11)	1.350(2)	N(1)–C(7)	1.336(2)
C(1)–Au(1)–S(1)	90.6(3)	S(1)–Au(1)–N(3)	94.4(3)
C(1)–Au(1)–N(1)	81.4(5)	N(1)–Au(1)–N(3)	93.5(5)
C(1)–Au(1)–N(3)	174.9(4)	N(1)–Au(1)–S(1)	171.6(4)
S(1)–C(12)–N(2)	173.1(1)	S(2)–C(13)–N(3)	175.9(1)
C(12)–S(1)–Au(1)	104.8(5)	C(13)–N(3)–Au(1)	173.7(9)
C(2)–C(1)–Au(1)	128.4(8)	C(6)–C(1)–Au(1)	111.8(6)
C(11)–N(1)–Au(1)	123.7(1)	C(7)–N(1)–Au(1)	114.1(8)
C(1)–C(6)–C(7)	118.0(8)	N(1)–C(7)–C(6)	114.5(8)

containing two chelated ligands.[21] These observations contrast markedly with facile decarboxylation of thiosalicylate ligands of Au(I)-containing ion $[Au(Htsc)_2]^-$, generated by addition of H_2tsc and triethylamine to [Au(tht)Cl] (tht = tetrahydrothiophene).[30] Thus, for complexes containing a chelated dianionic thiolato ligand, these show pronounced stability towards cone voltage-induced fragmentation.

Crystal structures

An ORTEP diagram of **1** with numbering scheme is presented in Fig. 1. Selected bond lengths and angles are listed in Table 6. The structure of **1** is essentially the same as other 2-phenylpyridine Au(III) complexes.[24] The Au(III)CSN_2 coordination sphere forms a planar unit (all deviations from the plane less than 0.02 Å). As expected, the soft carbanion and sulfur donors are mutually *cis* to each other in the thermodynamically most stable isomer. The mutually *cis* Au–C(1) and Au–S(1) bond lengths (2.012 (8) and 2.304 (3) Å respectively) are similar to those in the complex $[Au(damp)(H_2NC_6H_4S)]ClO_4$ (2.014(5) and 2.267(1) Å).[15] However, the *cis*-orientated Au–N(1) and Au–N(3) bond lengths (2.054(6) and 2.048(9) Å, respectively) are slightly different from the same unit complex $[Au(damp)(H_2NC_6H_4S)]ClO_4$ (2.118(4) and 2.138(4) Å).[15] The Au–N(3) (2.048(9) Å) bond distance is shorter than that in $[Au(damp)(H_2NC_6H_4S)]ClO_4$ even though it is *trans* to the carbanion. This may be due to the negatively charged nitrogen and consequently greater electron donation. It is noteworthy that two thiocyanate ions bind to gold in the structure are *via* nitrogen and the other through the sulfur, respectively. Thiocyanate, NCS^- is a linear ambidentate ligand which can bind to metals either through its nitrogen or its sulfur atom. With N bound, the M-NCS group is generally linear, and when S binds, the M–S–C angle is bent (*ca.* 110°). In **1**, the two angles Au(1)–N(3)–C(13) and Au(1)–S(1)–C(12) are 173.7(9) and 104.8(5)°, respectively, showing the exacted geometries. The two bond lengths N(3)–C(13) 1.142(1) Å, N(2)–C(12) 1.146(1) Å) are similar to each other, as is the case for another pair of bond lengths (S(1)–C(12) 1.634(1) Å, S(2)–C(13) 1.612(1) Å). In the IR spectrum, the two bands at 2115 and 2074 cm^{-1} in **1** could be assigned to thiocyanato (SCN^-) and isothiocynato (NCS^-) ligand, respectively.[31]

The binding mode of the thiocyanate ions in **1** leads to an interaction between gold and the terminal sulfur of thiocyanate from another molecule (Au ··· S, 3.412 Å) shown in Fig. 2. As discussed above, the soft nature of gold dictates the choice of sulfur as one donor; another thiocyanate anion binds to gold through nitrogen. Therefore, the remaining terminal sulfur is still a good coordination centre and can interact with gold in neighbouring molecules, forming a polymer structure. The intermolecular interaction is unusual and leads to the formation of an interesting polymer structure for **1**. This polymer structure may be attributed to the ability of thiocyanate to function as an ambidentate ligand.

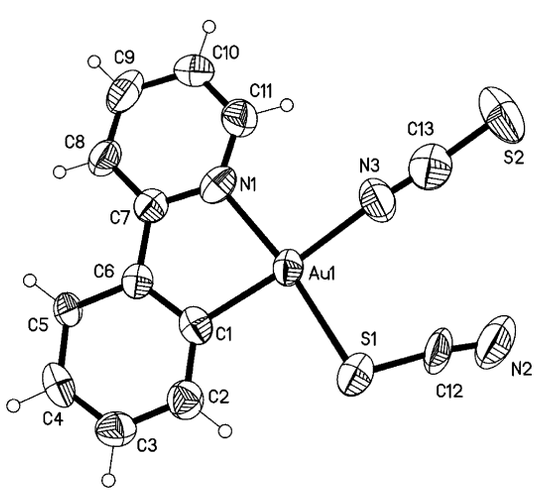


Fig. 1 A perspective view of **1** showing the numbering scheme.

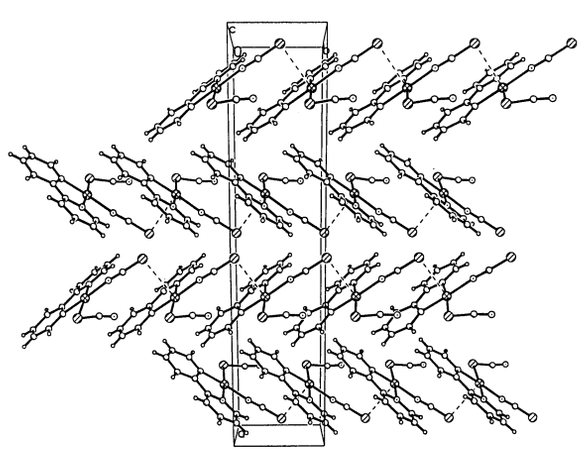


Fig. 2 The intermolecular interaction of Au–S in **1**.

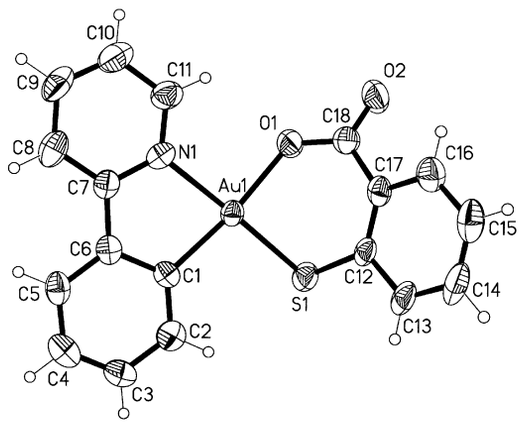


Fig. 3 An ORTEP diagram of **3** with the numbering scheme.

Table 7 Selected bond lengths (Å) and angles (°) for **3**

Au(1)–C(1)	1.998(7)	Au(1)–N(1)	2.074(6)
Au(1)–S(1)	2.276(2)	Au(1)–O(1)	2.057(6)
C(11)–N(1)	1.327(1)	C(7)–N(1)	1.351(1)
C(1)–C(2)	1.387(1)	C(1)–C(6)	1.416(1)
S(1)–C(12)	1.780(9)	C(12)–C(17)	1.391(1)
C(17)–C(18)	1.496(1)	C(17)–C(16)	1.377(1)
C(18)–O(1)	1.305(1)	C(18)–O(2)	1.234(1)
C(1)–Au(1)–S(1)	96.4(2)	O(1)–Au(1)–N(1)	91.9(3)
C(1)–Au(1)–N(1)	81.6(3)	O(1)–Au(1)–S(1)	90.1(2)
C(1)–Au(1)–O(1)	173.1(3)	N(1)–Au(1)–S(1)	177.9(2)
C(2)–C(1)–C(6)	118.7(7)	C(2)–C(1)–Au(1)	128.4(6)
C(11)–N(1)–C(7)	122.7(7)	C(11)–N(1)–Au(1)	123.6(6)
C(12)–S(1)–Au(1)	99.4(3)	C(12)–C(17)–C(18)	124.9(7)
C(18)–O(1)–Au(1)	127.6(5)	C(18)–C(17)–C(16)	115.7(8)
C(17)–C(18)–O(2)	118.8(8)	C(17)–C(18)–O(1)	121.0(7)
C(17)–C(12)–S(1)	125.0(6)	C(17)–C(12)–C(13)	119.3(8)

An ORTEP diagram of **3** with the atom numbering scheme is shown in Fig. 3. Selected bond lengths and angles are given in Table 7. The structure of **3** shows that the gold is square-planar, coordinated to the 2-phenylpyridine (ppy) forming a five-membered CN chelate ring and the thiosalcylate (tsc) forming a six-membered chelate ring. The ppy is co-planar with the gold coordination sphere whereas the phenyl ring of tsc is puckered about O(1) and S(1), forming an angle of 28.7(6)° to the plane of the gold coordination sphere. It is generally expected that two donors (carbon and sulfur) have the highest *trans* influence and are typically found *cis* to each other. The soft nature of Au(III) dictates the choice of the thiolate group as one donor; it is, as expected on *trans* influence grounds, *trans* to N. In the similar complexes [Au(tm)(damp)] (tm = mercaptosuccinate, damp = *C*,*N*-2-((dimethylamino)methyl)phenyl), [Au(damp)-(tsc)] (tsc = thiosalicylate), and [Au(tpy)(tsc)] (tpy = 2-(p-tolyl)-pyridine), the thiol group is also *trans* to nitrogen.[17,21,24] The carboxylate group of tsc coordinates to gold giving a six-membered chelate ring. The Au–S bond distance (2.276(2) Å) in **3** is very close to that of similar thiosalicylate complex [Au(tpy)(tsc)] (2.2776(8) Å)[24] but slightly longer than that in [Au(tm)(damp)] (2.23(2) Å).[21] Overall, the Au–S distance of **3** is in the range of values found for other Au(III) thiolate complexes, 2.26–2.40 Å.[16,17–20,32] The Au–C distance (1.998(7) Å) in **3** is shorter than that (2.035(7) Å) in [Au(ppy)(tdt)] (tdt = toluene 3,4-dithiolate);[15] whereas the Au–N distance is 2.074(6) in **3** and 2.079(5) Å in [Au(ppy)(tdt)], respectively, presumably due to the greater *trans* influence of S for the dithiolate compared with O of thiosalicylate. **3** appears to be an interesting example of a structure in which a gold atom is bound to four different donor atoms.

An ORTEP diagram of **6** is shown in Fig. 4. Selected bond lengths and angles are given in Table 8. The crystal structure of **6** shows that there are two independent molecules present in the asymmetric unit. The gold atom is in a square-planar co-ordination environment, bound to the terminal amino group, the deprotonated thiol group and σ-C^-, N of the ppy ligand. As expected, the cysteine is bound to gold as a bidentate ligand through the sulfur and nitrogen, giving a five-membered chelate ring. The adoption of this configuration is due to the fact that the soft nature of gold favours coordination of sulfur and nitrogen rather than oxygen. In the similar structure of **3**, sulfur and oxygen were bound to gold, forming a six-membered chelate ring. In both structures, the stronger *trans* influence groups S and C adopt the *cis*-orientated configurations. One other example of a Au(III) complex with the same CSN_2Au(III) donor set is [Au(damp)($H_2NC_6H_4S$)]ClO_4, in which the two softer C and S donors are also *cis* to each other.[15] The Au–S, Au–C, and Au–N(2) bond lengths in these two complexes are similar to each other. The Au–S bond distances (2.265(2) and 2.261(2) Å) in **6** are statistically the same as those found in **3** (2.276(2) Å) and [Au(ppy)(tdt)] (tdt = 3,4-toluenedithiolate) Au–S(2) = 2.258(2) Å, [Au(dmamp)($H_2NC_6H_4S$)]ClO_4 2.267(1) Å,[15] and [Au($N_2C_{10}H_7$($CMe_2C_6H_4$)-6)(SPh)](PF_6) 2.292(1) Å.[33]

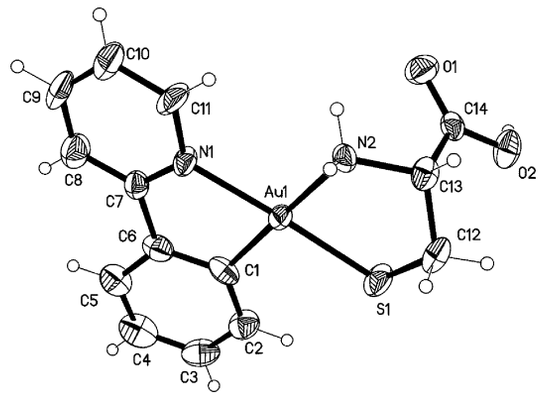


Fig. 4 An ORTEP diagram showing a perspective view of **6**.

Table 8 Selected bond lengths (Å) and angles (°) for **6**

Au(1)–C(1)	2.008(9)	Au(1)–N(1)	2.087(6)
Au(1)–S(1)	2.265(2)	Au(1)–N(2)	2.139(6)
S(1)–C(12)	1.810(9)	N(2)–C(13)	1.475(1)
C(12)–C(13)	1.513(1)	C(13)–C(14)	1.271(9)
C(1)–C(6)	1.395(1)	C(1)–C(2)	1.396(1)
N(1)–C(7)	1.333(1)	N(1)–C(11)	1.348(1)
Au(2)–C(15)	2.020(8)	Au(2)–N(3)	2.094(7)
Au(2)–S(2)	2.261(2)	Au(2)–N(4)	2.128(7)
S(2)–C(26)	1.833(9)	N(4)–C(27)	1.538(1)
C(1)–Au(1)–S(1)	94.3(3)	N(1)–Au(1)–N(2)	99.5(3)
C(1)–Au(1)–N(1)	80.4(4)	S(1)–Au(1)–N(2)	85.9(2)
C(1)–Au(1)–N(2)	176.5(3)	N(1)–Au(1)–S(1)	174.2(2)
C(12)–S(1)–Au(1)	98.7(3)	C(13)–N(2)–Au(1)	112.9(5)
S(1)–C(12)–C(13)	110.4(5)	N(2)–C(13)–C(12)	110.3(6)
O(1)–C(14)–O(2)	126.5(7)	N(2)–C(13)–C(14)	109.1(6)
O(1)–C(14)–C(13)	117.9(6)	O(2)–C(14)–C(13)	115.4(7)
C(7)–N(1)–Au(1)	115.9(5)	C(6)–C(1)–Au(1)	114.2(7)
C(11)–N(1)–Au(1)	124.6(6)	C(2)–C(1)–Au(1)	127.7(8)
C(15)–Au(2)–S(2)	93.7(2)	N(3)–Au(2)–N(4)	97.4(3)
C(15)–Au(2)–N(3)	81.2(3)	S(2)–Au(2)–N(4)	87.7(2)
C(15)–C(12)–N(4)	177.8(3)	S(2)–Au(2)–N(3)	174.9(2)

Cytotoxicity studies

Cytotoxicity data are given as IC_{50} values, the concentration of complex required to inhibit the growth of cells by 50% compared with that of a control (Table 9). Cisplatin data has also been included for comparison. *In vitro* cytotoxic activity of complexes **1**–**5** was determined against the human leukemia cell line MOLT-4 and the mouse tumour cell line C2C12. The results show that the cytotoxicity profile of these five complexes is similar to one another and comparable to the protocols in the previous paper, with IC_{50} values for MOLT-4 in the low-

Table 9 IC_{50} values (μM) against MOLT-4 and C2C12 cell lines

Complex	**1**	**2**	**3**	**4**	**5**	Cisplatin
MOLT-4	2.6	3.3	3.1	4.0	3.8	6.8
C2C12	11.0	15.5	6.0	9.0	18.0	14.7

micromolar range. The low values of IC_{50} could be interpreted that these complexes might have potential as antitumour agents. These gold complexes shown comparable toxicity to cisplatin (same range of IC_{50} values) on both cell lines. If compounds with IC_{50} values > 20 μM are considered as inactive,[34,35] all these novel gold thiolate complexes showed high biological activity on the two tumour cell lines tested in this work. In our previous work about gold carboxylate complexes, the results surprisingly shown that these complexes are inactive on C2C12 with the exception of the complex with cyclobutanedicarboxylate ligand.[24] Such differential cytotoxicity has been used as an indicator of antitumour activity.[36–38]

Conclusion

A new series of 2-phenylpyridine Au(III) complexes with a thiolate ligand has been synthesized and characterized spectroscopically. These thiolate Au(III) complexes are more stable than carboxylate complexes and are soluble in some organic solvents. They also exhibit cytotoxic properties. This finding leads us to believe that Au(III) complexes have potential antitumour properties for some human tumours. Full evaluation and exploitation are now needed to investigate the possibility of clinical use for these Au(III) complexes.

Acknowledgements

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