Synthesis, characterisation and biological activity of gold(III) catecholate and related complexes

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Abstract

The reactions of the cyclometallated gold(III) complexes [LAuCl$_2$] [L = 2-(dimethylaminomethyl)phenyl, 2-benzylpyridyl or 2-anilinopyridyl] with catechol, tetrachlorocatechol, or the cyclic α,β-diketone SCH(CO2Et)C(O)C(O)CH(CO2Et) give stable complexes containing five-membered Au-O-C-C-O rings. These represent the first examples of well-characterised gold(III) catecholate complexes. Similarly, reactions with 2-acetamidophenol [HOC$_6$H$_4$NHC(O)CH$_3$] give complexes with the related Au–N–C–C–O ring. The complexes were characterised by NMR spectroscopy, electrospray ionisation mass spectrometry, elemental microanalysis, and in the case of the complex [(2-benzylpyridyl)Au{OC$_6$H$_4$NC(O)CH$_3$}] by an X-ray crystal structure determination. Several complexes show high activity towards P388 murine leukemia cells.
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Keywords: Gold; Cyclometallated complexes; Catecholate complexes; Biological activity

1. Introduction

Since the serendipitous discovery that the simple platinum(II) coordination complex cisplatin, *cis*-[PtCl$_2$(NH$_3$)$_2$] showed potent anti-tumour activity, a very wide range of platinum(II) complexes have been screened. Today, a range of platinum(II) [and platinum(IV)] complexes are available in the clinic for cancer chemotherapy [1,2]. The similarity between platinum(II) and the isoelectronic (d^8) gold(III) suggests that certain complexes of the latter metal centre might also have promising cytotoxicity [3], though the cytotoxicity of gold(III) complexes has been less studied than gold(I) thus far [4]. Although many simple gold(III) complexes such as [AuCl$_4$]$^-$ are too strongly oxidising to show

useful anti-tumour properties [1,5,6], derivatives containing cyclo-aurated aryl-amine or aryl-pyridine ligands show much greater stability, and are not reduced by sulfur-based ligands such as thiols and related ligands [7–9]. This is significant, since sulfur-based reductants occur widely in the cysteinyl and methionine residues in biological materials. Initial studies in this area showed that the gold(III) complexes **1** show good anti-tumour activity, and both the chemistry and biological activity have been evaluated quite extensively [9–11].

We have found that the thiosalicylate analogue **2** also shows good activity against P388 leukaemia cells [7], though other derivatives containing alternative cyclo-aurated ligands did not show such good activity [12]. As part of the continuation of our studies in this area, in this paper we report the synthesis and evaluation of complexes containing bidentate, oxygen-donor catecholate ligands. While oxygen-donor ligands are widely used in platinum anticancer agents (e.g. cyclobutane-

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1,1-dicarboxylate in carboplatin), the increased lability of the gold(III) centre compared to platinum(II) [5,13] suggests that the use of less labile ligands might be required to maintain activity in the gold system. It was reasoned that the use of catecholate ligands might achieve this aim.

Little appears to have been previously reported on alkoxo complexes of gold(III) in general [14], or specifically in the area of catecholate complexes. A combination of catechol and aniline has been reported to extract gold(III) from HCl solution by formation of a gold(III) catecholate complex [15], but no gold(III) catecholate complexes have yet been characterised.
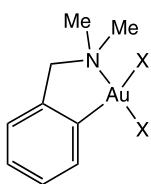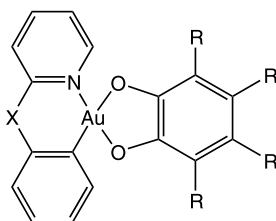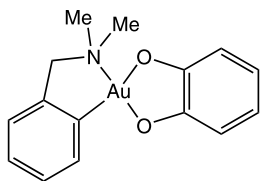

1a, X = Cl
1b, X = OC(O)CH$_3$
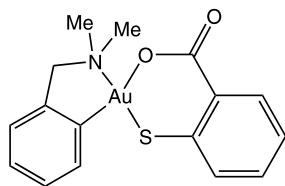
2
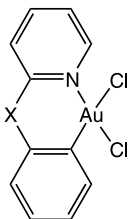
3a, X = NH
3b, X = CH$_2$

4a, X = NH, R = H
4b, X = CH$_2$, R = H
4c, X = NH, R = Cl
4d, X = CH$_2$, R = Cl

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2. Results and discussion

2.1. Synthesis of gold(III) catecholate complexes

Reactions of the readily prepared cyclo-aurated gold(III) dichloride complexes **3a** and **3b** with an excess

of catechol (1,2-dihydroxybenzene, pyrocatechol) or tetrachlorocatechol, together with an excess of trimethylamine base in hot methanol gave the catecholate complexes **4a**–**4d** which were isolated in an analytically pure state. In the same manner, complex **5** was prepared from **1a** and catechol. The preferred reaction method involves the addition of the base to a suspension of the appropriate catechol and gold(III) complex in hot methanol, whereupon the gold(III) complex rapidly reacts and dissolves, followed by rapid precipitation of the product in most cases. The tetrachlorocatecholate derivatives **4c** and **4d**, and compounds containing the 2-anilinopyridyl ligand (viz. **4a**), have relatively poor solubility in alcohols and chlorinated solvents, and were isolated by direct filtration from the reaction mixture. However, the benzylpyridyl catecholate complex **4b** was more soluble, and was precipitated from the reaction solution with water. Complex **5** did not immediately precipitate from the reaction solution upon addition of water, but reddish-brown microcrystals were deposited on slow evaporation of the solution at room temperature over several days. The compounds were isolated as orange to brown solids, which are moisture-stable, and appear to be reasonably light-stable. Satisfactory elemental microanalytical data were obtained for all complexes. The tetrachlorocatecholate complexes **4c** and **4d** were too insoluble in all common deuterated solvents for NMR spectroscopic characterisation to be carried out. Complexes **4a** and **4b** gave $[M+X]^+$ and $[2M+X]^+$ (X = H, Na) ions in their positive ion electrospray (ES) mass spectra.

In order to prepare derivatives with improved solubility, to facilitate both characterisation and biological testing, we turned our attention to complexes of commercially available 3,5-di-*tert*-butylcatechol. The reaction of **3a** with an excess of this catechol in the presence of excess trimethylamine gave a brown microcrystalline solid which gave excellent microanalytical data for the desired product. The positive-ion ES mass spectrum of the product yielded the expected $[M+H]^+$, $[M+Na]^+$ and $[2M+Na]^+$ ions. However, the ^{1}H-NMR spectrum of the crude product indicated that two isomers were produced (in an approximate ratio 3:2), which presumably have the 3-*tert*-butyl substituent *syn* or *anti* to the pyridine nitrogen, viz. structures **6a** and **6b**. However, assignment of resonances to individual isomers was not made.

The ligand 2-acetamidophenol is an analogue of a catechol, except that one OH group is replaced by an NHC(O)CH$_3$ group, which can act as a nitrogen donor ligand upon deprotonation. Using the same methodology as above, reaction of **3a** and **3b** with 2-acetamidophenol and excess trimethylamine gave the derivatives **7a** and **7b**, respectively. These complexes were isolated as air- and light-stable yellow solids in moderate yields, which give satisfactory microanalytical data and the

expected ions in the positive-ion ES mass spectra. ^{1}H-NMR spectra indicate that a single product is formed in each case. On the basis of a single-crystal X-ray diffraction study (described in Section 2.2), coupled with NMR spectroscopic characterisation on **7b**, the complexes are assigned the geometry which places the two lowest *trans*-influence donor ligand groups, namely the phenolate oxygen and the pyridine nitrogen, mutually *cis*. Other gold(III) complexes containing mixed donor ligand sets are well known to show such antisymbiosis [7,16]. The phenolate oxygen is assigned a lower *trans* influence than the NC(O)CH$_3$ group on the basis of [1]J(PtP) coupling constants in related platinum(II)–phosphine complexes of catecholate [17] and amidate [18] ligands.

A complete assignment of the ^{1}H- and ^{13}C-NMR assignments of **7b** was derived from detailed analyses of one- and two-dimensional NMR data, including DEPT135, COSY, TOCSY, SELTOCSY, NOEDIFF, NOESY, SELNOESY, gHSQC and HMBC spectral data. The atom numbering scheme is given in Fig. 1, with protons bearing the same number to the carbon to which they are attached. The full NMR assignment is given in Table 1. COSY, TOCSY and 1D-SELTOCSY data traced out three independent proton spin systems attributable to H-2, H-3, H-4 and H-5 (δ 7.59, 7.08, 7.16 and 7.18 ppm, respectively), H-9, H-10, H-11 and H-12 (δ 7.71, 8.02, 7.56 and 9.27 ppm, respectively) and H-14, H-15, H-16 and H-17 (δ 6.83, 6.94, 6.63 and 7.64 ppm, respectively). The marked downfield shift experienced by H-12 (δ 9.27 ppm) can be attributed to the proximity of this proton to the N1 atom.
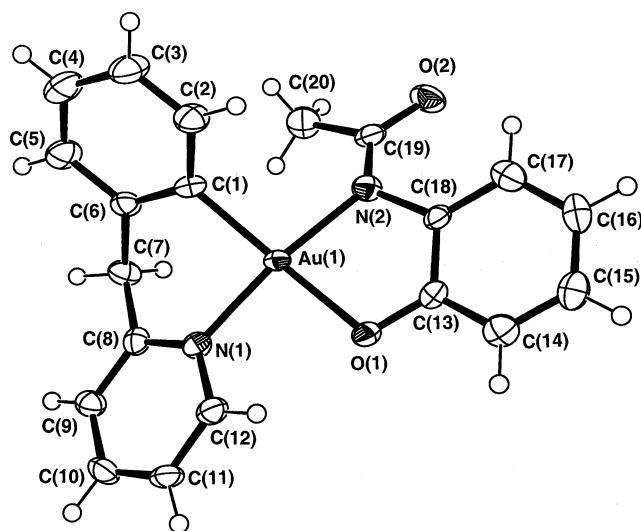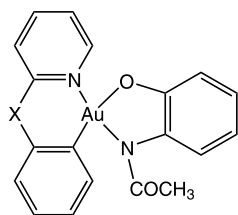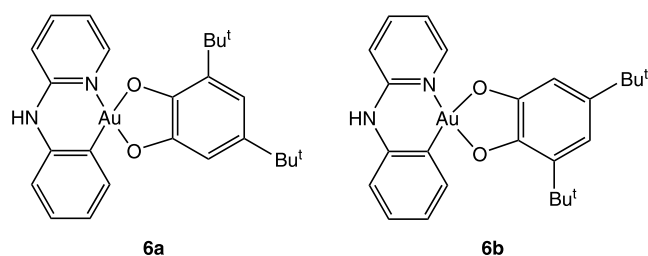

Fig. 1. Molecular structure of molecule 1 of [(2-benzylpyridyl)-Au{N(COCH$_3$)C$_6$H$_4$O}] (**7b**) showing the atom numbering scheme. Thermal displacement ellipsoids are depicted at the 50% probability level.

Table 1
^{1}H- and ^{13}C-NMR assignments (δ ppm in CDCl$_3$) determined for [(2-benzylpyridyl)Au{N(COCH$_3$)C$_6$H$_4$O}] (**7b**)
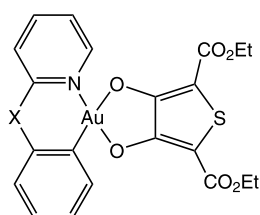
Atom	Type	[13]C	[1]H	
1	C	135.9		
2	CH	133.6	7.59	br d, $J = 7.7$ Hz
3	CH	127.6	7.08	ddd, $J = 7.7, 6.5, 2.5$ Hz
4	CH	127.9	7.16	~td, $J = 7.4, 1.2$ Hz
5	CH	127.6	7.18	m (overlapped by H-4)
6	C	131.0		
7	CH$_2$	47.4	4.29	s (2H)
8	C	156.2		
9	CH	126.1	7.71	br d, $J = 7.7$ Hz
10	CH	141.9	8.02	~td $J = 7.7, 1.5$ Hz
11	CH	124.3	7.56	ddd, $J = 5.9, 7.4, 1.5$ Hz
12	CH	149.5	9.27	dd, $J = 5.9, 1.5$ Hz
13	C	160.6		
14	CH	116.1	6.83	ddd, $J = 8.0, 1.4$ Hz
15	CH	125.3	6.94	ddd, $J = 8.0, 7.2, 1.5$ Hz
16	CH	116.1	6.63	ddd, $J = 7.9, 7.2, 1.4$ Hz
17	CH	124.1	7.64	dd, $J = 7.9, 1.5$ Hz
18	C	143.1		
19	C=O	173.8		
20	CH$_3$	27.6	2.02	s (3H)

The H-7 methylene protons (δ 4.29 ppm) exhibited NOESY and 1D-SELNOESY correlations to H-5 (δ 7.18 ppm) and H-9 (δ 7.71 ppm) and a weak correlation to the protons of H-20 methyl group (δ 2.02 ppm). The methyl group protons exhibited NOEDIFF, NOESY and 1D-SELNOESY correlations to H-2 (δ 7.59 ppm) and H-17 (δ 7.64 ppm). The foregoing considerations lead to a unique assignment of the six doublet-like and six triplet-like [3]J coupled aryl proton signals ($J = 5.9$–8.0 Hz), each of which also exhibited a resolvable [4]J coupling ($J = 1.2$–2.5 Hz). Thereafter consideration of correlations observed in the gHSQC spectrum for protonated carbons, and in the gHMBC spectrum for protonated and quaternary carbons led to an unequivocal assignment of the ^{13}C-NMR resonances of **7b**. The resonances of the C-8 (δ 156.1 ppm), C-13 (δ 160.6 ppm) and C-18 (δ 143.1 ppm) atoms were consistent with the location of these atoms adjacent to the N1, O1 and N2 atoms, respectively.

Complexes **8a** and **8b** derived from the α,β-diketone SCH(CO$_2$Et)C(O)C(O)CH(CO$_2$Et) ligand were also synthesised using the same methodology, and were fully characterised. This diketone has been found to coordinate to both platinum(II) [17] and rhodium(III) [19] as a dioxolene dianion, giving a five-membered M–O–C–C–O ring system related to the catecholate ligand. An attractive feature of this type of complex is the potential to vary the solubility characteristics by simple variation of the ester substituent, however, in this study, only the ethyl ester derivative was used. The symmetrical nature

6a **6b**

7a, X = NH **8a**, X = NH
7b, X = CH$_2$ **8b**, X = CH$_2$

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Table 2
Selected bond lengths (Å) and bond angles (°) for [(2-benzylpyridyl)Au{N(COCH$_3$)C$_6$H$_4$O}] (**7b**) (data for both independent molecules are listed for comparison)

Molecule 1		Molecule 2	
Bond lengths			
Au(1)−C(1)	2.005(7)	Au(2)−C(31)	2.018(7)
Au(1)−N(1)	2.053(6)	Au(2)−N(3)	2.042(6)
Au(1)−O(1)	2.055(5)	Au(2)−O(3)	2.053(5)
Au(1)−N(2)	2.008(6)	Au(2)−N(4)	2.014(7)
O(1)−C(13)	1.352(9)	O(3)−C(43)	1.363(10)
N(2)−C(18)	1.447(9)	N(4)−C(48)	1.439(10)
Bond angles			
N(1)−Au(1)−O(1)	90.8(2)	N(3)−Au(2)−O(3)	89.9(2)
O(1)−Au(1)−N(2)	83.3(2)	O(3)−Au(2)−N(4)	83.4(3)
N(2)−Au(1)−C(1)	97.8(3)	N(4)−Au(2)−C(31)	99.5(3)
C(1)−Au(1)−N(1)	89.7(3)	C(31)−Au(2)−N(3)	87.7(3)
Au(1)−O(1)−C(13)	109.0(4)	Au(2)−O(3)−C(43)	108.4(4)
Au(1)−N(2)−C(18)	109.3(5)	Au(2)−N(4)−C(48)	108.3(5)
N(2)−C(18)−C(13)	115.0(6)	N(4)−C(48)−C(43)	116.1(7)
O(1)−C(13)−C(18)	119.5(6)	O(3)−C(43)−C(48)	118.9(7)
C(6)−C(7)−C(8)	113.2(6)	C(36)−C(37)−C(38)	112.1(6)

of the ligand is also attractive in preventing the formation of mixtures of isomers.

The aliphatic region in the ^{1}H-NMR spectrum of complex **8b** showed two distinct multiplets at δ 4.3 and 1.3 ppm. The former consists of two quartets (due to the inequivalent ethyl ester CH$_2$ groups) and one overlapping singlet due to the CH$_2$ group of the benzylpyridyl ligand. Likewise, the multiplet at δ 1.3 ppm consists of two overlapping triplets, due to the inequivalent ethyl CH$_3$ groups. Two CH$_2$ (δ 60.1 and 60.4 ppm) and two CH$_3$ (δ 14.4 and 14.5 ppm) resonances were also observed in the ^{13}C-{^{1}H}-NMR spectrum of **8b**. The slight inequivalence of these ethyl groups occurs due to the asymmetric nitrogen−carbon coordination at the gold centre.

2.2. X-ray structure of complex [(2-benzylpyridyl)Au{N(COCH$_3$)C$_6$H$_4$O}] (7b)

An X-ray crystal structure determination was carried out on this complex, in order to confirm the mode of

binding of the N, O donor to the gold(III) centre. Suitable crystals (orange plates) were obtained by diffusion of diethyl ether into a dichloromethane solution of the complex. The complex crystallises with two independent molecules in the unit cell. The structure determination confirms the formulation of the complex as a gold(III) complex of the doubly deprotonated CH$_3$CONHC$_6$H$_4$OH ligand. Fig. 1 shows the atom labelling scheme for molecule 1, and selected bond lengths and angles for both molecules are given in Table 2. The two molecules are fairly similar, the main difference being the conformation of the six-membered ring involving the gold and the benzylpyridyl ligand. In molecule 1 (illustrated), the CH$_2$ group is pointing down, but in molecule 2 (in the same orientation) it is pointing up. This puckered ring system is typical for the benzylpyridyl ligand, as observed previously in the dichloride **3b** [20].

The gold centres have a slightly distorted square-planar geometry, as expected, with the sum of bond angles around the gold atoms in molecules 1 and 2 being 361.6 and 360.5°, respectively. In both molecules, the two longest Au−X bonds are to the pyridine nitrogen [Au(1)−N(1), 2.053(6) Å] and the phenolate oxygen [Au(1)−O(1), 2.055(5) Å]. These are respectively *trans* to higher *trans* influence amidate and aryl ligands. The Au−NC(O)CH$_3$ bond distances [Au(1)−N(2), 2.008(6) Å and Au(2)−N(4), 2.014(7) Å] are very comparable with the Au−NC(O)CH$_3$ bond distance *trans* to the NMe$_2$ group in the gold(III) ureylene derivative **9** [2.014(5) Å] [21].

2.3. Biological activity of gold(III) catecholate and related complexes

Antitumour activity against murine P388 leukemia cells, together with antibacterial activity against three selected bacteria (*Eschericia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*) and three fungi (*Candida albicans*, *Trichophyton mentagrophytes* and *Cladosporium resinae*) were determined for the benzylpyridyl complexes **4b**, **7b** and **8b** (which had greatest solubility) together with the di-*tert*-butyl catecholate derivative **6**, and the benzylamine catecholate derivative **5**. Data are summarised in Table 3.

High antitumour activity was shown by the catecholate complexes **4b** and **5**, and the di-*tert*-butylcatecholate mixture **6**. The other derivatives tested, with acetamidophenolate and dioxolene ligands, showed only moderate activity. In the antimicrobial assays, both the catecholate **4b** and acetamidophenolate **7b** complexes showed high activity against a number of organisms, but there appeared to be some selectivity, with both compounds showing highest activity against *B. subtilis* and *P. aeruginosa*, and much lower activity against *T. mentagrophytes* and *C. resinae*. Complex **5** also showed considerable activity against *T. mentagrophytes*, *B. subtilis* and *C. albicans*. The mixture **6a/6b** showed little antimicrobial activity. Overall, these results are highly promising and suggest that a more detailed study of the biological activity of this general class of complex could identify complexes with improved biological activities. A study of related metallacyclic derivatives of gold(III) could also prove fruitful.

3. Experimental

3.1. General

All ^{1}H-NMR spectra were recorded at 300.13 MHz on a Bruker AC300 spectrometer in CDCl$_3$ unless otherwise stated, with the exception of **7b** and **8b**. One- and two-dimensional NMR spectra for **7b** and **8b** were determined at 27 °C using a Bruker DRX400 spectrometer fitted with Z-axis pulse-field-gradient hardware and an inverse 5 mm probe-head. Bruker-supplied pulse programs were used to acquire ^{1}H, ^{13}C, DEPT135, COSY, TOCSY, SELTOCSY, NOEDIFF, NOESY, SELNOESY, gHSQC and gHMBC spectral data. Chemical shifts are reported relative to TMS where $\delta_{CHCl_3} = 7.26$ ppm (^{1}H) or $\delta_{CDCl_3} = 77.1$ ppm (^{13}C).

Electrospray mass spectra were recorded on a VG Platform II instrument in positive-ion mode, using methanol as the mobile phase. A cone voltage of 50 V was found to give optimal spectral intensity and clarity. Infrared spectra were recorded as KBr disks on a BioRad FTS40 spectrometer. Melting points were determined on a Reichert-Jung hotstage apparatus and are uncorrected. Elemental analyses were obtained by the University of Otago Campbell Microanalytical Laboratory. All reactions were carried out in laboratory reagent grade methanol without further purification. Dichloromethane and diethyl ether were purified by distillation from calcium hydride and sodium-benzophenone ketyl, respectively. Complex **1a** was prepared by the literature procedure [22]. Complexes **3a** and **3b** were prepared by minor modifications of the literature procedures [23,24] excepting that longer reaction times were employed (24 and 16 h, respectively). The cyclic diketone SCH(CO$_2$Et)C(O)C(O)CH(CO$_2$Et) was prepared by the literature procedure [17]. Catechol (BDH), tetrachlorocatechol monohydrate (Aldrich), 3,5-di-*tert*-butylcatechol (Aldrich), 2-acetamidophenol (Aldrich) and aqueous trimethylamine (BDH, 25–30%, w/v) were used as supplied.

3.2. Synthesis of complex **4a**

Aqueous trimethylamine (2 ml, excess) was added to a mixture of **3a** (200 mg, 0.458 mmol) and catechol (100 mg, 0.909 mmol) in hot methanol (30 ml), and the mixture was refluxed for 20 min giving an orange solution which deposited orange-brown microcrystals. After cooling to room temperature, the product was

Table 3
Antitumour (P388 leukemia) [a] and antibacterial and antifungal [b] activities for selected gold(III) catecholate and related derivatives

Complex	Antitumour IC$_{50}$ (μM)	Antimicrobial activity					
		E. coli	*B. subtilis*	*P. aeruginosa*	*C. albicans*	*T. mentagrophytes*	*C. resinae*
4b	0.66	6	12	10	6	3 [c]	5
5	0.46	8	10	6	11	10	6
6a/6b	1.1	0	5	0	0	3 [c]	0
7b	2.5	8	15	13	10	6 [c]	3
8b	3.7	2	6	3	3	6	1

[a] The concentration of sample (in μM) required to reduce the cell growth of the P388 leukemia cell line (ATCC CCL 46) by 50%.
[b] Inhibition zone as excess radius (mm) from a 6-mm diameter disc containing 2 mg of sample. Zero indicates no growth inhibition.
[c] In these cases, there was only some growth retardation.

filtered off, washed with cold methanol (15 ml) and dried under vacuum for 2 h to give 187 mg (86%) of **4a**. M.p. > 230 °C (decomp.). Found: C, 42.7; H, 3.6; N, 5.8. $C_{17}H_{13}N_2AuO_2$ requires C, 43.1; H, 2.8; N, 5.9%. ESMS: (cone voltage = 50 V) m/z 475 (30%, $[M+H]^+$), 497 (100%, $[M+Na]^+$), 949 (10%, $[2M+H]^+$), 971 (55%, $[2M+Na]^+$). ^{1}H-NMR: δ 9.1 (1H, d, $^3J = 6.54$ Hz), 8.0 (1H, d, $^3J = 8.1$ Hz), 7.9 (1H, d, $^3J = 7.8$ Hz), 7.3 (1H, d, $^3J = 8.6$ Hz), 7.3 (1H, t, $^3J = 7.4$ Hz), 7.1 (1H, d, $^3J = 7.9$ Hz), 7.0 (2H, overlapping t+t), 6.5 (1H, d, $^3J = 7.5$ Hz), 6.5 (1H, d, $^3J = 7.6$ Hz), 6.4 (1H, t, $^3J = 7.4$ Hz), 6.3 (1H, t, $^3J = 6.3$ Hz) ppm.

3.3. Synthesis of complex 4b

Aqueous trimethylamine (2 ml, excess) was added to a hot mixture of **3b** (200 mg, 0.149 mmol) and catechol (100 mg, 0.909 mmol) in hot methanol (30 ml), and the mixture was refluxed for 20 min giving a brown solution. Water (40 ml) was added and after cooling to room temperature, the resulting orange-brown micro-crystals were filtered off, washed with water (5 ml) and diethyl ether (10 ml) and dried under vacuum for 2 h to give 147 mg (68%) of **4b**. The product was recrystallised by vapour diffusion of diethyl ether into a dichloromethane solution of the complex. M.p. 158–160 °C. Found: C, 45.6; H, 2.8; N, 2.9. $C_{18}H_{14}NAuO_2$ requires C, 45.6; H, 3.0; N, 3.0%. ESMS: (cone voltage = 50 V) m/z 474 (55%, $[M+H]^+$), 496 (25%, $[M+Na]^+$), 947 (30%, $[2M+H]^+$), 969 (65%, $[2M+Na]^+$). ^{1}H-NMR: δ 9.3 (1H, d, $^3J = 5.2$ Hz), 8.1 (1H, t, $^3J = 7.7$ Hz), 7.8 (1H, d, $^3J = 6.4$ Hz), 7.7 (1H, d, $^3J = 7.6$ Hz), 7.5 (1H, t, $^3J = 6.7$ Hz), 7.2 (3H, m, overlapping d+t+t), 6.8 (1H, d, $^3J = 7.6$ Hz), 6.7 (1H, d, $^3J = 7.7$ Hz), 6.6 (1H, t, $^3J = 7.4$ Hz), 6.5 (1H, t, $^3J = 7.4$ Hz) ppm.

3.4. Synthesis of complex 4c

Following the method for **4a**, an orange-brown powder (259 mg, 91%) was obtained starting from **3a** (200 mg, 0.458 mmol), tetrachlorocatechol monohydrate (200 mg, 0.752 mmol) and aqueous trimethylamine (2 ml, excess). M.p. > 230 °C (decomp.). Found: C, 33.4; H, 1.9; N, 4.5. $C_{17}H_{13}N_2AuCl_4O_2$ requires C, 33.1; H, 2.1; N, 4.6%.

3.5. Synthesis of complex 4d

Following the method for **4a**, a brown powder (215 mg, 76%) was obtained starting from **3b** (200 mg, 0.459 mmol), tetrachlorocatechol monohydrate (200 mg, 0.752 mmol) and aqueous trimethylamine (2 ml, excess). M.p. > 230 °C (decomp.). Found: C, 34.2; H, 1.5; N, 2.3. $C_{18}H_{14}NAuCl_4O_2$ requires C, 35.2; H, 2.3; N, 2.3%.

3.6. Synthesis of complex 5

A suspension of **1a** (200 mg, 0.498 mmol) with catechol (200 mg, 1.82 mmol) in methanol (30 ml) with trimethylamine (2 ml) was refluxed for 20 min giving a dark orange-brown solution. Water (50 ml) was added, and the solution cooled and allowed to slowly evaporate at room temperature. After several days, dark reddish-brown microcrystals had formed, which were filtered off, washed with water, and dried under vacuum. Yield 60 mg (27%). M.p. 126–128 °C. Found: C, 40.4; H, 3.9; N, 2.9. $C_{15}H_{16}NAuO_2$ requires C, 41.0; H, 3.7; N, 3.2%. ESMS: (cone voltage = 50 V) m/z 440 (100%, $[M+H]^+$), 879 (20%, $[2M+H]^+$), 901 (30%, $[2M+Na]^+$). ^{1}H-NMR: δ 7.61–6.52 (m, Ph), 4.28 (s, 2H, CH_2), 3.36 (s, 6H, CH_3) ppm.

3.7. Synthesis of complex 6a/6b

Following the method for **4a**, brown microcrystals (234 mg, 87%) were obtained starting from **3a** (200 mg, 0.458 mmol), 3,5-di-*tert*-butylcatechol (150 mg, 0.676 mmol) and aqueous trimethylamine (2 ml, excess). The product was recrystallised by vapour diffusion of diethyl ether into a dichloromethane solution of the complex. M.p. 159–160 °C. Found: C, 51.3; H, 4.7; N, 4.8. $C_{25}H_{29}N_2AuO_2$ requires C, 51.2; H, 5.0; N, 4.8%. ESMS: (cone voltage = 50 V) m/z 586 (45%, $[M+H]^+$), 609 (100%, $[M+Na]^+$), 1173 (10%, $[2M+H]^+$), 1195 (30%, $[2M+Na]^+$).

3.8. Synthesis of complex 7a

Following the method for **4a**, yellow microcrystals (192 mg, 81%) were obtained starting from **3a** (200 mg, 0.458 mmol), 2-acetamidophenol (100 mg, 0.662 mmol) and aqueous trimethylamine (2 ml, excess). M.p. > 230 °C (decomp.). Found: C, 44.1; H, 3.0; N, 8.1. $C_{19}H_{16}N_3AuO_2$ requires C, 44.3; H, 3.1; N, 8.2%. ESMS: (cone voltage = 50 V) m/z 516 (55%, $[M+H]^+$), 538 (100%, $[M+Na]^+$), 1053 (10%, $[2M+Na]^+$) ppm.

3.9. Synthesis of complex 7b

A mixture of **3b** (200 mg, 0.149 mmol), 2-acetamidophenol (100 mg, 0.662 mmol) and aqueous trimethylamine (2 ml, excess) in methanol (30 ml) was refluxed for 20 min giving a brown solution. Water (40 ml) was added and the orange solution left to crystallise for 2 days. The resulting yellow microcrystals were filtered, washed with water (15 ml) and dried under vacuum for 2 h to give 199 mg (84%) of **7b**. The product was recrystallised by vapour diffusion of diethyl ether into a dichloromethane solution of the complex. M.p. 159–162 °C. Found: C, 46.7; H, 3.1; N, 5.3. $C_{20}H_{17}N_2AuO_2$

requires C, 46.7; H, 3.3; N, 5.5%. ESMS: (cone voltage = 50 V) m/z 515 (65%, [M+H]$^+$), 537 (100%, [M+Na]$^+$), 1029 (20%, [2M+H]$^+$), 1051 (50%, [2M+Na]$^+$) ppm.

3.10. Synthesis of complex 8a

Following the method for **4a**, an orange-brown powder (229 mg, 80%) was obtained starting from **3a** (200 mg, 0.458 mmol) $SCH(CO2Et)C(O)C(O)CH(CO_2Et)$ (120 mg, 0.465 mmol) and aqueous trimethylamine (2 ml, excess). M.p. > 230 °C (decomp.). Found: C, 40.5; H, 2.9; N, 4.4. $C_{21}H_{19}N_2AuO_6S$ requires C, 40.4; H, 3.1; N, 4.5%. IR: ν(CO region) 1658 cm^{-1} (vs).

3.11. Synthesis of complex 8b

Following the method for **4a**, a yellow-brown powder (232 mg, 81%) was obtained starting from **3b** (200 mg, 0.459 mmol) $SCH(CO2Et)C(O)C(O)CH(CO_2Et)$ (120 mg, 0.465 mmol) and aqueous trimethylamine (2 ml, excess). M.p. 172–174 °C. Found: C, 41.5; H, 3.0; N, 2.1. $C_{22}H_{20}NAuO_6S$ requires C, 42.4; H, 3.2; N, 2.3%. IR: ν(CO region) 1680 cm^{-1} (vs). ESMS: (cone voltage = 50 V) m/z 624 (10%, [M+H]$^+$), 646 (100%, [M+Na]$^+$), 1269 (60%, [2M+Na]$^+$). ^{1}H-NMR: δ 9.2 (d, $^3J = 5.8$ Hz), 8.1 (t, $^3J = 7.7$ Hz), 7.8 (d, $^3J = 7.3$ Hz), 7.7 (d, $^3J = 7.4$ Hz), 7.6 (t, $^3J = 6.4$ Hz), 7.2 (t, $^3J = 7.0$ Hz), 7.1 (m, overlapping t+t), 4.3 (CH$_2$, q, $^3J = 7.1$ Hz), 4.3 (CH$_2$, m, overlapping q+s), 1.4 (CH$_3$, t, $^3J = 7.1$ Hz), 1.3 (CH$_3$, t, $^3J = 7.1$ Hz) ppm.

3.12. X-ray structure determination on complex 7b

Crystals were obtained by vapour diffusion of diethyl ether into a dichloromethane solution of the complex at room temperature.

Unit cell parameters and intensity data were collected using a Siemens SMART CCD diffractometer, using standard collection procedures, with monochromatic Mo–K$_\alpha$ X-rays (0.71073 Å). Corrections for absorption and other effects were carried out with SADABS [25]. All other calculations used the SHELX-97 programs [26]. The structure was solved by direct methods, and developed with refinement based on F^2. The complex crystallises with two independent molecules in the unit cell. Selected bond lengths and angles are given in Table 1. Crystal, data collection and refinement details for the structure determination are given in Table 4.

The similarity in the scattering factors of nitrogen and carbon potentially hampers discrimination between the elements in the C(1) and N(1) positions [likewise for C(31) and N(3)] and analysis of bond parameters in the structure provided no clear distinction of the two elements. The assignment provided is based on analysis

Table 4
Crystal, collection and refinement data for the structure determination of [(2-benzylpyridyl)Au{N(COCH$_3$)C$_6$H$_4$O}] (**7b**)

Empirical formula	$C_{20}H_{17}AuN_2O_2$
Formula weight	514.32
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
$\quad a$ (Å)	18.546(5)
$\quad b$ (Å)	10.159(3)
$\quad c$ (Å)	17.768(4)
$\quad b$ (°)	96.151(3)
V (Å^3)	3328.4(14)
Z	8
D_c (g cm^{-3})	2.053
Diffractometer	Siemens SMART CCD
Radiation, wavelength (Å)	Mo–K$_\alpha$, $\lambda = 0.71073$
Temperature (K)	203(2)
θ range for data collection (°)	2.21–26.46
Reflections collected	42 095
Independent reflections	6802 [$R_{int} = 0.0582$]
Absorption coefficient (mm^{-1})	8.856
$F(0 0 0)$	1968
Solution by	direct methods
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6802/0/453
Goodness-of-fit on F^2	1.111
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0479$, $wR_2 = 0.1301$
R indices (all data)	$R_1 = 0.0514$, $wR_2 = 0.1344$
Largest difference peak (e Å^{-3})	3.137
Largest difference hole (e Å^{-3})	−4.869
Programs used	SHELXS-97 and SHELXL-97 [26]

of the U_{iso} values of the atoms, 0.023, 0.024, 0.026 and 0.023 for N(1), C(1), N(3), and C(31), respectively. The alternative arrangement in which the N(1) and C(1) atoms are interchanged provides U_{iso} values of 0.014, 0.033, 0.017 and 0.033 for C(1), N(1), C(31) and N(3), respectively.

3.13. Biological assays

Assays were carried out by the commercial service offered by the Marine Chemistry Group, Department of Chemistry, Canterbury University, New Zealand. Samples were dissolved in 3:1 methanol–dichloromethane prior to testing. Antitumour assays were carried out by determining, by means of a twofold dilution series, the concentration of sample in ng ml^{-1} required to reduce the cell growth of the P388 leukemia cell line (ATCC CCL 46) by 50%. The sample of interest was incubated for 72 h with the P388 murine leukemia cells. IC$_{50}$ values were determined by measurement of the absorbance values when the yellow dye MTT tetrazolium is reduced by healthy cells to the purple dye MTT formazan. Mitomycin C was included in the assays as a positive control.

The antimicrobial assays were carried out by measuring the inhibition zone as an excess radius (mm) from a

6-mm diameter filter paper disk containing 2 mg of sample, which was placed on a seeded agar plate containing the organism tested.

4. Supplementary material

Crystallographic data (excluding structure factors) for the structure described in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 215337. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail deposit@ ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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