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Cycloauration of pyridyl sulfonamides

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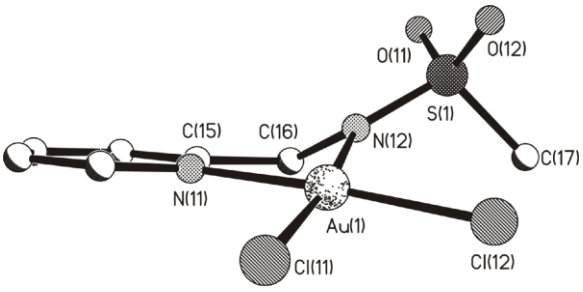
Synopsis

Reactions of $H[AuCl_4]$ with pyridyl-2-alkylsulfonamides $C_5H_4N(CH_2)_nNHSO_2R$ (n = 1,2; R = Me, Ph or *p*-C_6H_4Me) or 8-(*p*-tosylamino)quinoline in water gives high yields of cycloaurated complexes coordinated through the pyridyl (or quinolyl) nitrogen atom and the deprotonated nitrogen of the sulfonamide group.



(use Figure 3a for graphic)

Abstract

The pyridyl-2-alkylsulfonamides $C_5H_4N(CH_2)_nNHSO_2R$ (n = 1,2; R = Me, Ph or *p*-C_6H_4Me) and 8-(*p*-tosylamino)quinoline undergo facile cycloauration reactions with $H[AuCl_4]$ in water, giving metallacyclic complexes coordinated through the pyridyl (or quinolyl) nitrogen atom and the deprotonated nitrogen of the sulfonamide group. The complexes have been fully characterised by NMR spectroscopy, ESI mass spectrometry and elemental analysis. The X-ray crystal structures of two derivatives reveal the presence of non-planar sulfonamide nitrogen atoms. The complexes show low activity against P388 murine leukaemia cells, possibly as a result of their ease of reduction with mild reducing agents.

Keywords: Gold; Metallacycle; Sulfonamide; Cycloauration; Pyridine ligands

Introduction

Compared with the extensive chemistry of cyclometallated gold(III) complexes containing *C*,*N* donor ligands,[1] little research has been conducted on analogous cycloaurated complexes stabilised by *N*,*N*' donor ligands. Complexes derived from the primary amide picolinamide[2,3] **1** and substituted analogues **2**[4] and **3**[5], the dinuclear complex **4**[6] and the substituted 2-(pyrrol-2-yl)pyridine ligand **5**[7] are examples of the systems prepared. In addition, the ionic species **6-8** formed by the tridentate coordination of quinoline-derived ligands have also been investigated[8] and related gold(III) complexes containing anionic chelating *N*,*N*' ligands such as tri- and tetrakis-pyrazolylborates are

also known.[9] A recent report has described the cycloauration of bis(2-pyridylmethyl)amine, giving complex **9**.[10]

Because *C*,*N* stabilised complexes exhibit interesting chemistry and biological activity,[1] we wished to synthesise related *N*,*N*'-stabilised species and assess their chemical and biological properties. Pyridylsulfonamide compounds [of the type $C_5H_4N(CH_2)_nNHSO_2R$ (n = 1,2; R = Me, Ph or *p*-C_6H_4Me)] were attractive ligands for this study due to the ease of synthesis, the opportunity of introducing variable R groups and the possibility of variable ring sizes in the subsequent cyclometallated complexes. In addition, cyclometallated complexes of this type containing a variety of metals are also known in the literature and show interesting applications.[11] In this paper we describe the synthesis of six new auracyclic compounds and investigations into the reactivity and biological activity of these complexes.

Results and discussion

Syntheses

When the ligands HL^1 to HL^6 (Scheme 1) are refluxed in aqueous $H[AuCl_4]$ in a 1:1 mole ratio, the auracyclic compounds L^1AuCl_2 to L^6AuCl_2 (Scheme 2) are easily isolated in excellent yields by filtration of the yellow to brown solid that is present throughout the reaction, the exception being L^3AuCl_2 which required cooling to induce crystallisation. This synthetic procedure is analogous to the preparation of **1**[2,3] however, similar reactions of the secondary amines **10** and **11** only afforded the salts **12** and **13**.[7] The difference in the reactivity can be attributed to the decreased acidity of the NH protons in the ligands **10** and **11** relative to the sulfonamide counterparts. NMR and IR

spectroscopy, along with ESI mass spectrometry indicate the nitrogen donor ligands are coordinated to gold through the neutral pyridyl donor and the anionic amido group. The formulation was confirmed by X-ray crystal structures of the complexes L^3AuCl_2 and L^6AuCl_2.

Attempted preparation of the analogous four-membered auracyclic system L^7AuCl_2 from HL^7 proved unsuccessful. When HL^7 was refluxed with $H[AuCl_4]$ in either an aqueous or an acetonitrile/water (1:1) solution, or alternatively mixed with HL^7 in an aqueous acetonitrile solution of $H[AuCl_4]$ at room temperature, the only product was the salt $[H_2L^7][AuCl_4]$. This was identified by ^1H and ^{13}C NMR spectroscopy and the presence of both the $[H_2L^7]^+$ and $[AuCl_4]^-$ ions in positive- and negative-ion ESI mass spectra respectively.

X-ray crystal structures of L^3AuCl_2 and L^6AuCl_2

Single crystal X-ray structure analyses of L^3AuCl_2 and L^6AuCl_2 were carried out in order to confirm the bonding of the ligand to the gold. In both cases, the ligands are deprotonated at the sulfonamide nitrogen and bonded to the gold through the two nitrogen atoms, with the remaining sites on the metal occupied by two chloride ligands. L^3AuCl_2 crystallises with two independent molecules per unit cell. Diagrams of the molecular structures of L^3AuCl_2 and L^6AuCl_2, along with the atom numbering schemes, are shown in Figures 1 and 2 respectively. Important bond lengths and angles are presented in Tables 1 and 2.

For both L^3AuCl_2 and L^6AuCl_2, the geometry around the d^8 gold centre is essentially square planar, with the bite angle of the sulfonamide ligand less than 90° in

both cases (Table 2). In L^3AuCl_2, the atom with the greatest deviation from the metal coordination plane [defined by Au(1), N(1), N(2), Cl(1) and Cl(2)] is N(1) [0.0817(15) Å] and Au(1) [0.0280(10) Å] for molecules 1 and 2 respectively. For L^6AuCl_2, the gold atom shows the greatest deviation from the coordination plane [defined by Au(1), N(1), N(2), Cl(1) and Cl(2)], sitting 0.0514(8) Å above the plane.

In all cases, the coordination around the deprotonated sulfonamide nitrogen N(2) is not planar, and is slightly distorted towards tetrahedral geometry, with the angles around the nitrogen adding to 358.6° (molecule 1) and 344.2° (molecule 2) for L^3AuCl_2, and 353.7° for L^6AuCl_2. Such distortion has previously been observed and discussed by Otter *et al* for copper(II), cobalt(II) and palladium(II) compounds of the type ML_2 (L = *N*-(2-pyridin-2-yl-phenyl)-*p*-toluenesulfonamide).[12] In addition, similar cyclometallated gold(III)[13] and platinum(II)[14] compounds also show this type of behaviour.

In both molecules of L^3AuCl_2, the cycloaurated ring [defined by Au(1), C(1), C(5), N(1) and N(2)] is in a envelope conformation with N(2) sitting above the ring (by 0.286(2) Å and 0.206(2) Å for molecules 1 and 2 respectively). Due to the increased rigidity imposed by the aromatic ring system, in L^6AuCl_2 it is Au(1) that shows the greatest deviation from the plane [defined by C(1)-C(9), N(1) and N(2)], sitting 0.339(3) Å above the plane of the quinoline ring system (Figure 3).

For L^3AuCl_2 the gold-sulfonamide nitrogen bond length is shorter than the gold-pyridyl nitrogen bond length, but the opposite is observed in the structure of L^6AuCl_2. The rigidity imposed on the system by the quinoline moiety in L^6AuCl_2, in comparison to the flexibility of L^3AuCl_2 system, is the probable cause of this discrepancy.

NMR and IR spectroscopic characterisation

Compounds of the type $LAuCl_2$ were most suited to analysis by NMR spectroscopy. The effect of coordination of the gold to the ligand through the deprotonated sulfonamide nitrogen and pyridyl nitrogen could clearly be seen. The methylene protons of the ligands HL^1 - HL^3 appear as a doublet due to coupling to the NH proton of the sulfonamide group, whereas for HL^4 and HL^5 a triplet and an apparent quartet arise from the two methylene groups. Upon coordination to the gold, the methylene signals become either a singlet (for the five-membered ring systems) or two triplets (for the six-membered ring systems) providing unambiguous evidence for loss of the sulfonamide proton.

Coordination to the gold can clearly be seen in compounds L^1AuCl_2 (Figure 4) and L^2AuCl_2. A downfield shift of approximately 0.7 ppm is seen for H-1 (the proton adjacent to the coordinated pyridyl nitrogen) upon coordination to the gold, due to the proximity of the gold atom and the increased deshielding produced by the electron-withdrawing metal centre.

For the complexes L^4AuCl_2 and L^5AuCl_2 there appears to be fluxionality in the six-membered auracyclic rings at 30 °C, though contribution from inversion of an amide nitrogen which is distorted from planarity, although unlikely, cannot be discounted. The two methylene signals are seen as broad triplets; presumably if the system was not fluxional the multiplets would be much more complex due to the different stereochemical environment each proton inhabits.

The main points of interest in the IR spectra of the complexes are the loss of NH stretching frequencies (~3100 cm^{-1}) of the free ligands and a shift to lower wavenumbers for the SO_2 stretching modes, consistent with lengthening of the S=O bonds through movement of electrons onto the sulfonyl oxygen atoms. For example, the SO_2 stretches shift from 1164 cm^{-1} and 1327 cm^{-1} (for the asymmetric and symmetric stretches respectively) in HL^1 to 1146 cm^{-1} and 1306 cm^{-1} in the cycloaurated complex L^1AuCl_2.

ESI mass spectrometry

Analysis of the compounds L^1AuCl_2 – L^6AuCl_2 by ESI-MS was not overly effective for two reasons. Firstly, the compounds are neutral so must either pick up an ion (e.g. H^+ or Na^+) to be easily observed in the spectra or alternatively, coordination of a neutral species (e.g. pyridine) produces an easily detectable cation through displacement of Cl^-.[15] Secondly, because of the low ionisation ability of the neutral species, cationic impurity ions, namely the bis(cycloaurated) species such as $[(L^2)_2Au]^+$, dominate the spectra as a result of their high ionisation efficiency, a phenomenon observed previously in cyclometallated gold(III) dichoride species.[16] For example, when L^2AuCl_2 is analysed without ionisation aids (Figure 5a), the spectrum is dominated by the ion at *m/z* 691 due to $[(L^2)_2Au]^+$, although there is no evidence for the presence of this species in either the ^1H NMR spectrum or microanalytical results. Addition of NaCl to the sample before analysis produces ions at *m/z* 537 (21%) and 1051 (10%) corresponding to $[L^2AuCl_2 + Na]^+$ and $[2(L^2AuCl_2) + Na]^+$ respectively, however $[(L^2)_2Au]^+$ is still the dominant peak. Addition of strongly coordinating pyridine (py) to a solution of the compound in methanol forms species identified as $[L^2AuCl(py)]^+$ and $[L^2Au(OMe)(py)]^+$ at *m/z* 558

and 554 respectively, however the ion at *m/z* 691 (40%) is still present. Identification and confirmation of these ions is aided by the presence of chlorine(s) and thus unique isotope patterns. A similar pattern of behaviour was seen for all members of this family of compounds.

Biological activity

Previously, *C*,*N* cycloaurated complexes, in particular the compound (damp)$AuCl_2$, (damp = 2-[(dimethylamino)methyl]phenyl) and its derivatives have shown promising antitumour activity.[17] Little data exist on *N*,*N*'-stabilised cycloaurated complexes and for this reason complexes L^1AuCl_2 – L^5AuCl_2 were screened for antitumour activity against the P388 Murine Leukemia cell line. Results indicate an IC_{50} value of greater than 12500 ng mL^{-1} for all compounds, indicating little activity against this particular cell line.

Reactivity

When *C*,*N* cycloaurated dichloride species are reacted with tertiary phosphines, the chloride ligands may be displaced by coordination of the neutral phosphines to the gold or conversely, cleavage of the Au – N bond may occur with both Au – Cl bonds remaining intact; in each case gold(III) products are formed. Such reactions can give an indication of the strength of the gold-nitrogen bond and are dependent on the cycloaurated ligand present.[1]

Reaction of L^1AuCl_2 with PPh_3 in a 1:1 molar ratio in dichloromethane resulted in lightening of the solution from yellow to pale yellow. ESI-MS of the solution showed

ions corresponding to the gold(I) species $[Au(PPh_3)_2]^+$ (*m/z* 721), PPh_3 and $Ph_3P{=}O$. $^{31}P\text{-}\{^1H\}$ NMR spectroscopy of the solution gave peaks at δ 30 (br s) and 34 (s) ppm, the first of which arises from $Ph_3P{=}O$, and the second from an average of rapidly exchanging $[Au(PPh_3)_2]^+$ with free PPh_3.[18] Likewise, when L^1AuCl_2 was reacted with PPh_3 in a 1:2 ratio, ESI-MS gave ions due to $[Au(PPh_3)_2]^+$, PPh_3 and $Ph_3P{=}O$; the $^{31}P\text{-}\{^1H\}$ NMR spectrum again showed peaks at δ 30 (s) and 34 (s) ppm. Reaction of L^1AuCl_2 with thiosalicylic acid using previously established methods[19] resulted in immediate reduction and decomposition of the gold species to elemental gold. These results indicate that the *N*,*N*' cycloaurated ligands are not as effective at stabilising the Au(III) centre as are *C*,*N* cycloaurated ligands, so reactions can result in reduction of the gold(III), suggesting that these complexes may have limited utility.

Conclusions

Six new cycloaurated gold(III) complexes containing *N*,*N*' cyclometallated ligands have been synthesised and fully characterised, including the X-ray crystal structures of two of these complexes. Coordination to the gold is through pyridyl and deprotonated amide nitrogen atoms. Unlike the more common analogous *C*,*N* cyclometallated compounds, these complexes show lower stability, as reactions with reducing agents leads to reduction of Au(III) to Au(I) or elemental gold. The biological activity of these complexes against murine leukaemia cell lines is also low – possibly due to this lack of stability towards reduction.

Experimental

General

All reactions were carried out with no efforts at excluding air. 2-Picolylamine, 2-(2-aminoethyl)pyridine and 8-(*p*-tosylamino)quinoline (Aldrich) were used as supplied, as were *p*-toluenesulfonyl chloride (BDH), benzenesulfonyl chloride (BDH) and methanesulfonyl chloride (Riedel-de Haën). $H[AuCl_4].4H_2O$ was synthesised from gold metal by the literature procedure,[20] and yields of the dichloride complexes L^1AuCl_2 – L^6AuCl_2 are calculated assuming the above formulation. The sulfonamide ligands (all previously reported compounds[21,22,23]) were synthesised by the condensation of the appropriate sulfonyl chloride and amine, following the procedure reported for $HL^1$and HL^4.[24]

ESI mass spectra were obtained on a VG Platform II instrument operating at a cone voltage of 20 V, using methanol as the solvent after the compound was dissolved in a small amount of dichloromethane. IR spectra were recorded as KBr disks on a Digilab Scimitar FT-IR, and NMR spectra on a Bruker DRX 400 FT-NMR spectrometer, operating at 30 °C, with a series of ^1H, ^{13}C, DEPT-135, ^1H-^1H COSY, HMBC, HSQC and 1D-SELNOESY experiments utilised in the assignment of the NMR spectra.

Antitumour activities against the P388 murine leukemia cell line were determined at the University of Canterbury. Methods have been described previously,[25] and samples were analysed as 1:1 dichloromethane/methanol solutions.

Synthesis of L^1AuCl_2

HL^1 (0.560 g, 2.13 mmol) and $H[AuCl_4].4H_2O$ (0.877 g, 2.13 mmol) were added to water (75 mL) to give an orange suspension. This was refluxed with stirring for 3 h and cooled to room temperature. The orange precipitate that was present throughout the reaction was filtered, washed with water (2 × 10 mL) and isopropanol (2 × 10 mL) and air dried to give L^1AuCl_2 (0.918 g, 82%) as an orange solid. Found: C 29.6, H 2.5, N 5.3; $C_{13}H_{13}N_2SO_2AuCl_2$ requires C 29.6, H 2.5, N 5.3 %. NMR ($CDCl_3$): ^{1}H δ 2.40 (s, 3H, H-11), 4.88 (s, 2H, H-6), 7.26 (d, $^3J_{9,8}$ = 8.5 Hz, 2H, H-9), 7.62 (ddd, $^3J_{2,1}$ = 6.1 Hz, $^3J_{2,3}$ = 7.7 Hz, $^4J_{2,4}$ = 1.6 Hz, 1H, H-2), 7.73 (dd, $^3J_{4,3}$ = 7.8 Hz, $^4J_{4,2}$ = 1.6 Hz, 1H, H-4), 7.87 (d, $^3J_{8,9}$ = 8.5 Hz, 2H, H-8), 8.13 (td, $^3J_{3,2}$ = 7.7 Hz, $^3J_{3,4}$ = 7.8 Hz, $^4J_{3,1}$ = 1.5 Hz, 1H, H-3), 9.22 (dd, $^3J_{1,2}$ = 6.1 Hz, $^4J_{1,3}$ = 1.5 Hz, 1H, H-1); ^{13}C-{^{1}H} δ 21.7 (C-11), 61.6 (C-6), 121.7 (C-4), 125.5 (C-2), 127.8 (C-8), 129.7 (C-9), 138.0 (C-7), 143.2 (C-3), 143.6 (C-10), 147.5 (C-1), 166.9 (C-5) (See Scheme 3 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 551 (32%, $[L^1AuCl_2+Na]^+$), 719 (100%, $[(L^1)_2Au]^+$), 1079 (10%, $[2(L^1AuCl_2)+Na]^+$); (pyridine added) *m/z* 568 (28%, $[L^1Au(OMe)(py)]^+$), 572 (100%, $[L^1AuCl(py)]^+$), 719 (25%, $[(L^1)_2Au]^+$). IR: $\upsilon(SO_2)_{sym}$ 1306 (s), $\upsilon(SO_2)_{asym}$ 1146 (vs) cm^{-1}.

Synthesis of L^2AuCl_2

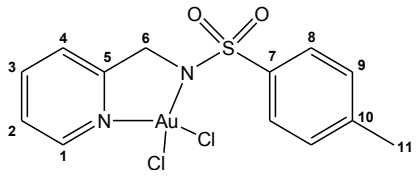
As for the synthesis of L^1AuCl_2, HL^2 (0.566 g, 2.28 mmol) was suspended in an aqueous (50 mL) solution of $H[AuCl_4].4H_2O$ (0.939 g, 2.28 mmol) and refluxed with stirring for 3 h. The precipitate that was present throughout was filtered and washed with water (2 × 10 mL) and isopropanol (2 × 10 mL). The yellow/brown solid was air dried to give L^2AuCl_2

(0.964 g, 82%). Found: C 27.9, H 2.1, N 5.4; $C_{12}H_{11}N_2SO_2AuCl_2$ requires C 28.0, H 2.2, N 5.5 %. NMR ($CDCl_3$): ^1H δ 4.91 (s, 2H, H-6), 7.47 (t, $^3J_{9,10}$ = 8.0 Hz, $^3J_{9,8}$ = 7.2 Hz, 2H, H-9), 7.53 (t, $^3J_{10,9}$ = 8.0 Hz, 1H, H-10), 7.63 (ddd, $^3J_{2,1}$ = 6.1 Hz, $^3J_{2,3}$ = 7.6 Hz, $^4J_{2,4}$ = 1.6 Hz, 1H, H-2), 7.74 (dd, $^3J_{4,3}$ = 7.8 Hz, $^4J_{4,2}$ = 1.6 Hz, 1H, H-4), 7.99 (d, $^3J_{8,9}$ = 7.2 Hz, 2H, H-8), 8.13 (td, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 7.8 Hz, $^4J_{3,1}$ = 1.5 Hz, 1H, H-3), 9.22 (dd, $^3J_{1,2}$ = 6.1 Hz, $^4J_{1,3}$ = 1.5 Hz, 1H, H-1); ^{13}C-{^1H} δ 61.6 (C-6), 121.7 (C-4), 125.5 (C-2), 127.7 (C-8), 129.0 (C-9), 141.2 (C-7), 143.2 (C-3), 132.7 (C-10), 147.5 (C-1), 166.7 (C-5) (See Scheme 3 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 537 (21%, $[L^2AuCl_2+Na]^+$), 691 (100 %, $[(L^2)_2Au]^+$), 1051 (10% $[2(L^2AuCl_2)+Na]^+$; (pyridine added) *m/z* 554 (40%, $[L^2Au(OMe)(py)]^+$), 558 (100% $[L^2AuCl(py)]^+$), 691 (40%, $[(L^2)_2Au]^+$). IR: $\upsilon(SO_2)_{sym}$ 1313 (s), $\upsilon(SO_2)_{asym}$ 1155 (vs) cm^{-1}.

Synthesis of L^3AuCl_2

HL^3 (0.200 g, 1.07 mmol) was dissolved in a solution of $H[AuCl_4].4H_2O$ (0.441 g, 1.07 mmol) in water (30 mL). Upon reaching reflux temperature, the yellow solution turned deep orange and remained this colour for the duration of the reflux (2 h). The clear solution was cooled in an ice bath which resulted in the deposition of orange/red microcrystals. These were filtered and washed with water (2 × 10 mL) and isopropanol (2 × 10 mL) and air dried to give L^3AuCl_2 (0.266 g, 55%). Found: C 18.1, H 1.9, N 6.0; $C_7H_9N_2SO_2AuCl_2$ requires C 18.6, H 2.0, N 6.2 %. NMR (d_6-DMSO): ^1H δ 3.10 (s, 3H, H-7), 4.96 (s, 2H, H-6), 7.80 (ddd, $^3J_{2,1}$ = 6.2 Hz, $^3J_{2,3}$ = 7.6 Hz, $^4J_{2,4}$ = 1.2 Hz, 1H, H-2), 8.05 (dd, $^3J_{4,3}$ = 7.7 Hz, $^4J_{4,2}$ = 1.2 Hz, 1H, H-4), 8.33 (td, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 7.7 Hz, $^4J_{3,1}$ = 1.4 Hz, 1H, H-3), 9.04 (dd, $^3J_{1,2}$ = 6.2 Hz, $^4J_{1,3}$ = 1.4 Hz, 1H, H-1); ^{13}C-{^1H} δ 41.9 (C-7), 61.1 (C-6), 122.1 (C-4), 125.6 (C-2), 143.8 (C-3), 146.5 (C-1), 166.2 (C-5)

(See Scheme 3 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 475 (100%, $[L^3AuCl_2+Na]^+$), 567 (84%, $[(L^3)_2Au]^+$), 927 (56%, $[2(L^3AuCl_2)+Na]^+$); (pyridine added) *m/z* 492 (45%, $[L^3Au(OMe)(py)]^+$), 496 (100%, $[L^3AuCl(py)]^+$). IR: $\upsilon(SO_2)_{sym}$ 1306 (s), $\upsilon(SO_2)_{asym}$ 1132 (vs) cm^{-1}.



Scheme 3: NMR numbering scheme for L^1AuCl_2 – L^3AuCl_2. For complex L^3AuCl_2, the methyl carbon is labelled C-7. Hydrogens are labelled according to the carbon they are directly bonded to.

Synthesis of L^4AuCl_2

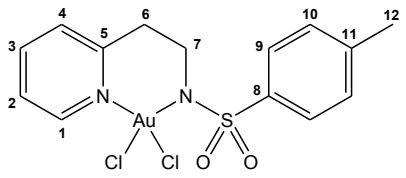
To an aqueous (30 mL) solution of $H[AuCl_4].4H_2O$ (0.531 g, 1.29 mmol), HL^4 (0.357 g, 1.29 mmol) was added and the yellow solution refluxed with stirring for 3.5 h. During this time a brown solid formed, which after cooling was filtered, dried and washed with water (2 × 10 mL) and ether (10 mL) to give L^4AuCl_4 (0.542 g, 78%). Found: C 31.1, H 2.9, N 5.3; $C_{14}H_{15}N_2SO_2AuCl_2$ requires C 31.0, H 2.8, N 5.2 %. NMR (d_6-DMSO): ^1H δ 2.31 (s, 3H, H-12), 3.23 (br t, 2H, H-7), 3.47 (t, $^3J_{6,7}$ = 6.3 Hz, 2H, H-6), 7.19 (d, $^3J_{10,9}$ = 8.2 Hz, 2H, H-10), 7.57 (d, $^3J_{9,10}$ = 8.2 Hz, 2H, H-9), 7.74 (ddd, $^3J_{2,1}$ = 6.0 Hz, $^3J_{2,3}$ = 7.7 Hz, $^4J_{2,4}$ = 1.5 Hz, 1H, H-2), 7.77 (dd, $^3J_{4,3}$ = 7.8 Hz, $^4J_{4,2}$ = 1.5 Hz, 1H, H-4), 8.26 (td, 1H, $^3J_{3,2}$ = 7.7 Hz, $^3J_{3,4}$ = 7.8 Hz, $^4J_{3,1}$ = 1.4 Hz, 1H, H-3), 8.91 (dd, $^3J_{1,2}$ = 6.0 Hz, $^4J_{1,3}$ = 1.4 Hz, 1H, H-1); ^{13}C-{^1H} δ 20.8 (C-12), 37.6 (C-6), 42.4 (C-7), 126.0 (C-2), 126.8 (C-

9), 127.7 (C-4), 129.4 (C-10), 137.8 (C-8), 142.2 (C-11), 143.8 (C-3), 149.7 (C-1), 155.5 (C-5) (See Scheme 4 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 565 (100%, $[L^4AuCl_2+Na]^+$), 747 (91%, $[(L^4)_2Au]^+$), 1107 (19%, $[2(L^4AuCl_2)+Na]^+$); (pyridine added) *m/z* 582 (50%, $[L^4Au(OMe)(py)]^+$), 586 (100%, $[L^4AuCl(py)]^+$). IR: $\upsilon(SO_2)_{sym}$ 1311 (s), $\upsilon(SO_2)_{asym}$ 1148 (vs) cm^{-1}.

Synthesis of L^5AuCl_2

HL^5 (0.329 g, 1.25 mmol) and aqueous (30 mL) $H[AuCl_4].4H_2O$ (0.515 g, 1.25 mmol) were refluxed with stirring for 3 h, resulting in the formation of a red/orange precipitate. This was filtered, washed with water (2 × 10 mL) and isopropanol (10 mL). The crude product was recrystallised by dissolving in minimum dichloromethane, filtering off the insoluble yellow precipitate, and adding diethyl ether to the filtrate until the solution went cloudy. The resulting dark red crystals were filtered and washed with diethyl ether (2 × 10 mL) and dried to give L^5AuCl_2 (0.436 g, 66%). Found: C 29.7, H 2.6, N 5.4; $C_{13}H_{13}N_2SO_2AuCl_2$ requires C 29.5, H 2.5, N 5.3 %. NMR (d_6-DMSO): ^1H δ 3.25 (br t, 2H, H-7), 3.48 (t, $^3J_{6,7}$ = 6.4 Hz, 2H, H-6), 7.41 (t, $^3J_{10,11}$ = 7.5 Hz, $^3J_{10,9}$ = 7.0 Hz, 2H, H-10), 7.48 (t, $^3J_{11,10}$ = 7.5 Hz, 1H, H-11), 7.70 (d, $^3J_{9,10}$ = 7.0 Hz, 2H, H-9), 7.75 (ddd, $^3J_{2,1}$ = 6.0 Hz, $^3J_{2,3}$ = 7.8 Hz, $^4J_{2,4}$ = 1.7 Hz, 1H, H-2), 7.77 (dd, $^3J_{4,3}$ = 7.7 Hz, $^4J_{4,2}$ = 1.7 Hz, 1H, H-4), 8.25 (td, $^3J_{3,2}$ = 7.8 Hz, $^3J_{3,4}$ = 7.7 Hz, $^4J_{3,1}$ = 1.4 Hz, 1H, H-3), 8.95 (dd, $^3J_{1,2}$ = 6.0 Hz, $^4J_{1,3}$ = 1.4 Hz, 1H, H-1); ^{13}C-{^1H} δ 37.6 (C-6), 42.4 (C-7), 126.0 (C-2), 126.7 (C-9), 127.7 (C-4), 128.9 (C-10), 131.9 (C-11), 140.6 (C-8), 143.9 (C-3), 149.7 (C-1), 155.5 (C-5) (See Scheme 4 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 547 (55%, $[L^5Au(OMe)Cl+Na]^+$), 551 (100%, $[L^5AuCl_2+Na]^+$), 1079 (25%,

[2(L^5AuCl_2)+Na]$^+$); (pyridine added) *m/z* 568 (100%, [L^5Au(OMe)(py)]$^+$), 572 (78%, [L^5AuCl(py)]$^+$). IR: $\upsilon(SO_2)_{sym}$ 1320 (s), $\upsilon(SO_2)_{asym}$ 1149 (vs) cm^{-1}.

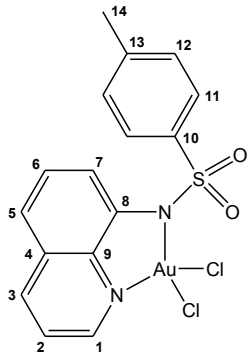


Scheme 4: NMR numbering scheme for L^4AuCl_2 and L^5AuCl_2. Hydrogens are labelled according to the carbon they are directly bonded to.

Synthesis of L^6AuCl_2

8-(*p*-Tosylamino)quinoline (0.176 g, 0.590 mmol) was suspended in aqueous (30 mL) H[$AuCl_4$].4H_2O (0.243 g, 0.590 mmol) and refluxed with stirring for 8 h. When the mixture reached reflux temperature, a brown solid formed that remained present throughout the duration of the reaction. The mixture was allowed to cool before being filtered, washed with H_2O (2 × 10 mL) and isopropanol (2 × 10 mL) and dried under vacuum, to give L^6AuCl_2 as a brown solid (0.241 g, 72 %). Found: C 33.9, H 2.3, N 5.0; $C_{16}H_{13}N_2SO_2AuCl_2$ requires C 34.0, H 2.3, N 5.0 %. NMR (d_6-DMSO): ^{1}H δ 2.30 (s, 3H, H-14), 7.26 (d, $^3J_{11,10}$ = 8.3 Hz, 2H, H-12), 7.67 (d, $^3J_{10,11}$ = 8.3 Hz 2H, H-11), 7.76 (t, $^3J_{6,7/5}$ = 7.7 Hz, 1H, H-6), 7.81 (dd, $^3J_{7,6}$ = 7.7 Hz, $^4J_{7,5}$ = 1.6 Hz, 1H, H-7), 7.86 (dd, $^3J_{5,6}$ = 7.7 Hz, $^4J_{5,7}$ = 1.6 Hz, 1H, H-5), 7.93 (dd, $^3J_{2,1}$ = 5.6 Hz, $^3J_{2,3}$ = 8.3 Hz, 1H, H-2), 8.92 (dd, $^3J_{3,2}$ = 8.3 Hz, $^4J_{3,1}$ = 1.1 Hz, 1H, H-3), 9.21 (dd, $^3J_{1,2}$ = 5.6 Hz, $^4J_{1,3}$ = 1.1 Hz, 1H, H-1); ^{13}C-{^{1}H} δ 21.1 (C-14), 123.5 (C-2), 124.3 (C-5), 125.9 (C-7), 126.8 (C-11), 129.7

(C-12), 130.0 (C-6), 130.7 (C-4), 138.8 (C-10), 143.3 (C-13), 143.7 (C-9), 144.0 (C-3), 146.0 (C-8), 148.1 (C-1) (see Scheme 5 for NMR numbering scheme). ESI-MS: (NaCl added) *m/z* 587 (100%, $[L^6AuCl_2+Na]^+$); (pyridine added) *m/z* 608 (100%, $[L^6AuCl(py)]^+$), 604 (35%, $[L^5Au(OMe)(py)]^+$). IR: $\upsilon(SO_2)_{sym}$ 1326 (s), $\upsilon(SO_2)_{asym}$ 1158 (vs) cm^{-1}.



Scheme 5: NMR numbering scheme for L^6AuCl_2. Hydrogens are labelled according to the carbon they are directly bonded to.

Attempted preparation of L^7AuCl_2

(i) Reflux with $H[AuCl_4]$ in water

HL^7 (0.310 g, 1.25 mmol) was refluxed with stirring in aqueous (30 mL) $H[AuCl_4].4H_2O$ (0.515 g, 1.25 mmol) for 1 h, after which a brown solid had formed. When cool, the solution was filtered and the solid washed with water (2 × 10 mL) and isopropanol (10 mL) to give 0.188 g (26%) of a brown solid, which was identified as the salt $[H_2L^7][AuCl_4]$. NMR ($CDCl_3$): ^1H δ (ppm) 2.38 (s, 3H, H-10), 6.80 (ddd, $^3J_{2,1}$ = 5.9 Hz, $^3J_{2,3}$ = 7.1 Hz, $^4J_{2,4}$ = 1.1Hz, 1H, H-2), 7.24 (d, $^3J_{8,7}$ = 8.1 Hz, 2H, H-8), 7.40 (dd, $^3J_{4,3}$ = 8.9 Hz, $^4J_{4,2}$ = 1.1 Hz, 1H, H-4), 7.64 (ddd, $^3J_{3,2}$ = 7.1 Hz, $^3J_{3,4}$ = 8.9

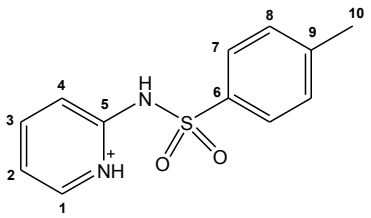
Hz, $^{4}J_{3,1}$ = 1.9 Hz, 1H, H-3), 7.79 (d, $^{3}J_{7,8}$ = 8.1 Hz, 2H, H-7), 8.34 (dd, $^{3}J_{1,2}$ = 5.9 Hz, $^{4}J_{1,3}$ = 1.9 Hz, 1H, H-1), NH not observed; ^{13}C-{^{1}H} δ 21.6 (C-10), 114.7 (C-2), 115.1 (C-4), 127.0 (C-7), 129.7 (C-8), 138.8 (C-6), 141.5 (C-1), 141.9 (C-3), 143.1 (C-9), 155.0 (C-5) (see Scheme 6 for NMR numbering scheme). ESI-MS: (positive ion, cone voltage 20V): *m/z* 249 (100%, $[H_2L^7]^+$); (negative ion, cone voltage 20V): *m/z* 339 (100%, $[AuCl_4]^-$).

(ii) Standing with H[AuCl$_4$] in MeCN/H$_2$O solution

HL^7 (0.108 g, 0.43 mmol) was dissolved in MeCN (5 mL) and added dropwise to aqueous (20 mL) $H[AuCl_4].4H_2O$ (0.177 g, 0.43 mmol). The solution was left to stand and after 2 weeks a light brown solid had formed. This was filtered and washed with water (2 × 10 mL) and ether (1 × 10 mL), to give 0.078 g (31%) of $[H_2L^7][AuCl_4]$, which was identified by ESI-MS and ^{1}H NMR spectroscopy.

(iii) Refluxing in 1:1 MeCN/H$_2$O

HL^7 (0.050 g, 0.20 mmol) and $H[AuCl_4].4H_2O$ (0.082 g, 0.20 mmol) were refluxed in aqueous (20 mL) MeCN (1:1) with stirring for 3 h. The solution was left to stand overnight and brown crystals were formed. These were subsequently identified as $[H_2L^7][AuCl_4]$ (0.037g, 31%).



Scheme 6: NMR numbering scheme for $[H_2L^7][AuCl_4]$. Hydrogens are labelled according to the carbon they are directly bonded to.

X-ray crystal structure determinations of L^3AuCl_2 and L^6AuCl_2

Single crystals of L^3AuCl_2 and L^6AuCl_2 suitable for X-ray structure analysis were obtained by slow diffusion of diethyl ether into a dichloromethane solution of the compounds, at room temperature and -20 °C respectively. L^3AuCl_2 crystallised as orange prisms with two independent molecules per unit cell, and L^6AuCl_2 as brown cubes as a CH_2Cl_2 solvate.

Intensity data and unit cell dimensions were obtained at the University of Auckland on a Bruker Smart CCD Diffractometer (L^3AuCl_2) and at the University of Canterbury on a Bruker Apex II Diffractometer (L^6AuCl_2). The data were corrected for absorption using SADABS.[26]

The structures of L^3AuCl_2 and L^6AuCl_2 were solved using the Patterson and Direct methods options of SHELXS-97[27] respectively. The gold atom was initially located, followed by the location of all other non-hydrogen atoms by a series of difference maps. Full-matrix least-squares refinement (SHELXL-97)[28] was based upon F_o^2 with all non-hydrogen atoms anisotropic, and hydrogen atoms in calculated positions.

Crystal and refinement data for the complexes are presented in Table 3. CCDC reference numbers 676314 and 676315 for L^3AuCl_2 and L^6AuCl_2 respectively.

Acknowledgements

We thank the University of Waikato for financial support of this work and the Tertiary Education Commission for a Top Achievers Doctoral Scholarship (KJK). We also thank Dr. Tania Groutso (University of Auckland) and Dr. Jan Wikaira (University of Canterbury) for collection of X-ray intensity data and Gill Ellis (University of Canterbury) for biological assay data. Mr. Bevan Jarman is also thanked for helpful discussions.

Table 1: A comparison of selected bond lengths (Å) for the crystal structures of L^3AuCl_2 (two independent molecules) and L^6AuCl_2

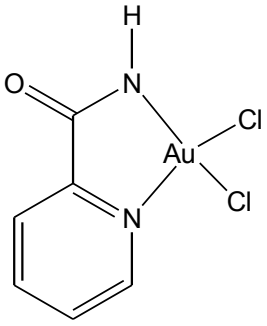
	L^3AuCl_2		**L^6AuCl_2**
	Molecule 1	Molecule 2	
Au(1) – Cl(1)	2.2872(10)	2.2807(10)	2.2789(8)
Au – Cl(2)	2.2720(10)	2.2800(10)	2.2637(9)
Au – N (ex py)	2.046(3)	2.037(3)	2.026(3)
Au – N (ex NH)	2.006(3)	2.021(3)	2.038(3)

Table 2: A comparison of selected bond angles (°) for the crystal structures of L^3AuCl_2 (including the two independent molecules) and L^6AuCl_2

	L^3AuCl_2		**L^6AuCl_2**
	Molecule 1	Molecule 2	
Cl(1) – Au(1)– Cl(2)	89.09(4)	90.17(4)	88.13(3)
Cl(1) – Au(1) – N(ex. py)	94.08(10)	93.89(10)	94.36(8)
N(ex py) – Au(1) – N(ex NH)	78.98(13)	82.09(13)	81.48(11)
N(ex NH) – Au(1) – Cl(2)	98.02(10)	93.79(10)	95.88(8)

Table 3: Crystal and refinement data for the complexes L^3AuCl_2 and L^6AuCl_2

Complex	$\mathbf{L^3AuCl_2}$	$\mathbf{L^6AuCl_2}$
Formula	$C_7H_9AuCl_2N_2O_2S$	$C_{16}H_{13}AuCl_2N_2O_2S \cdot CH_2Cl_2$
M_r	453.09	650.14
T/K	89	93
Crystal system	Triclinic	Monoclinic
Space group	P(-1)	$P2_1/n$
a (Å)	7.3424(1)	14.1782(6)
b (Å)	9.2813(1)	10.6792(5)
c (Å)	17.2700(2)	14.4771(6)
α (°)	99.383(1)	90
β (°)	95.785(1)	115.147(2)
γ (°)	102.127(1)	90
V ($Å^3$)	1124.06(2)	1984.2(2)
Z	4	4
D_{calc} (g cm^{-3})	2.677	2.176
$T_{max,min}$	0.1699, 0.1138	0.2950, 0.0597
Number of unique reflections	4562	6252
Number of observed reflections [I>2σ(I)]	4360	5476
R [I>2σ(I)]	0.0203	0.0293
wR_2 (all data)	0.0512	0.0868
Goodness of Fit	1.117	1.046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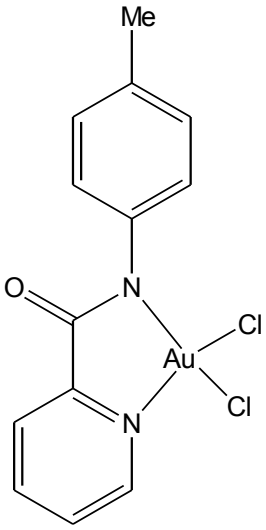
O
N
Au
Cl
Cl
N

1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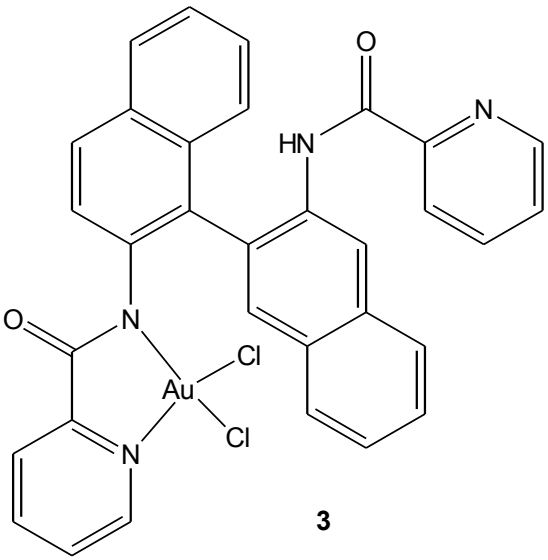
N
Au
Cl
Cl
N

2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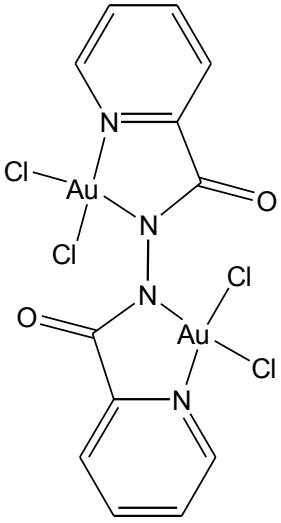
HN
O
N
Au
Cl
Cl
N

3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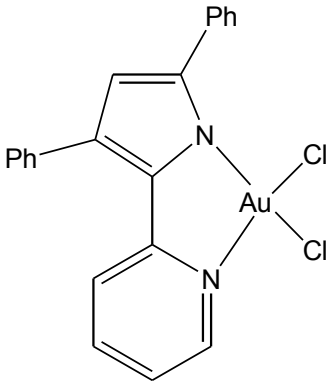
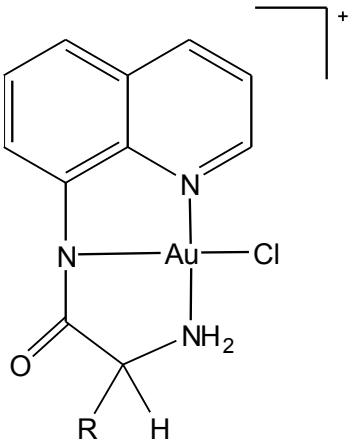
Cl
Au
O
Cl
N
N
Cl
O
Au
Cl
N

4


Ph
N
Ph
Cl
Au
Cl
N

5



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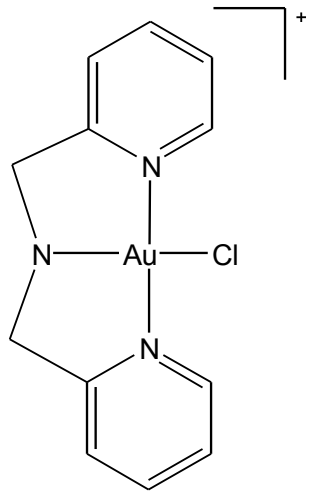

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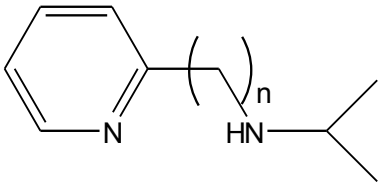

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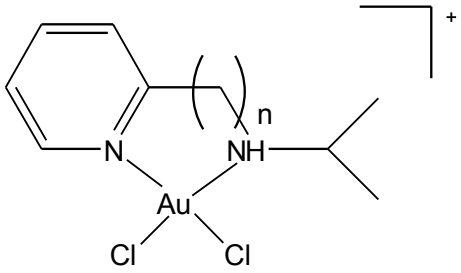
11 n = 2



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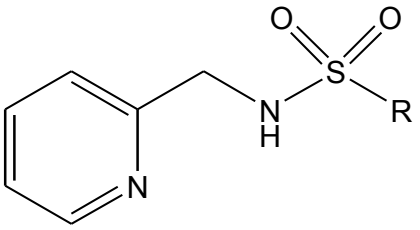
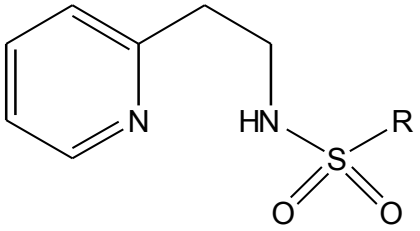
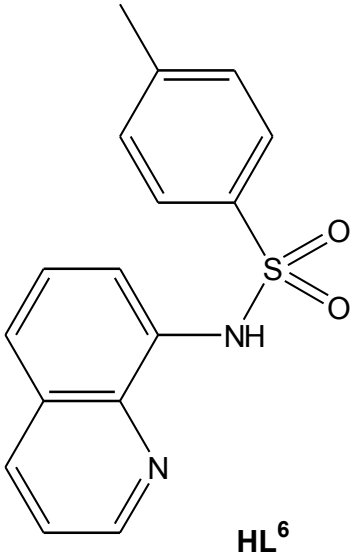
13 n = 2



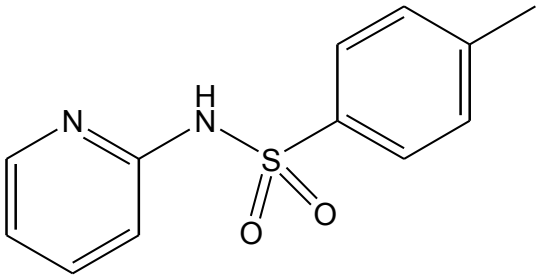
HL[1] R = *p*-$C_6H_4CH_3$
HL[2] R = C_6H_5
HL[3] R = CH_3



HL[4] R = *p*-$C_6H_4CH_3$
HL[5] R = C_6H_5

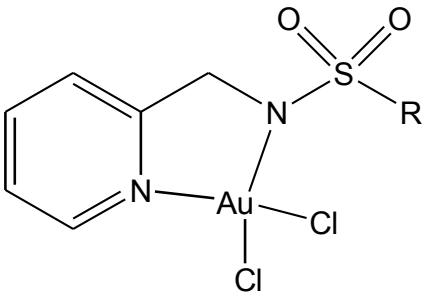


HL[6]

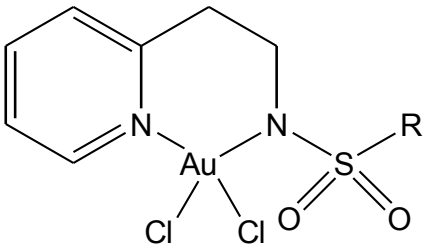


HL[7]

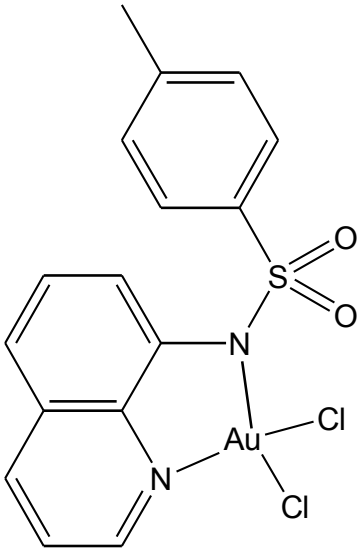
Scheme 1



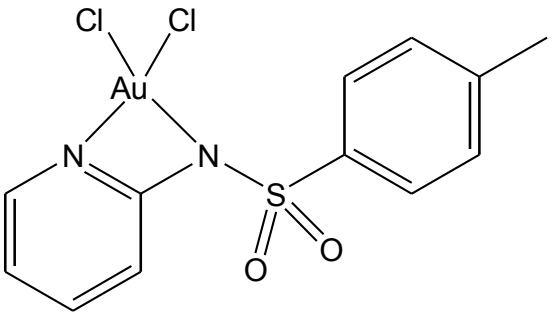
L[1]AuCl$_2$ R = *p*-$C_6H_4CH_3$
L[2]AuCl$_2$ R = C_6H_5
L[3]AuCl$_2$ R = CH_3



L[4]AuCl$_2$ R = *p*-$C_6H_4CH_3$
L[5]AuCl$_2$ R = C_6H_5



L[6]AuCl$_2$



L[7]AuCl$_2$

Scheme 2

Figure 1: Molecular structure of L^3AuCl_2, showing one of the independent molecules present in the unit cell, and the atom numbering scheme.

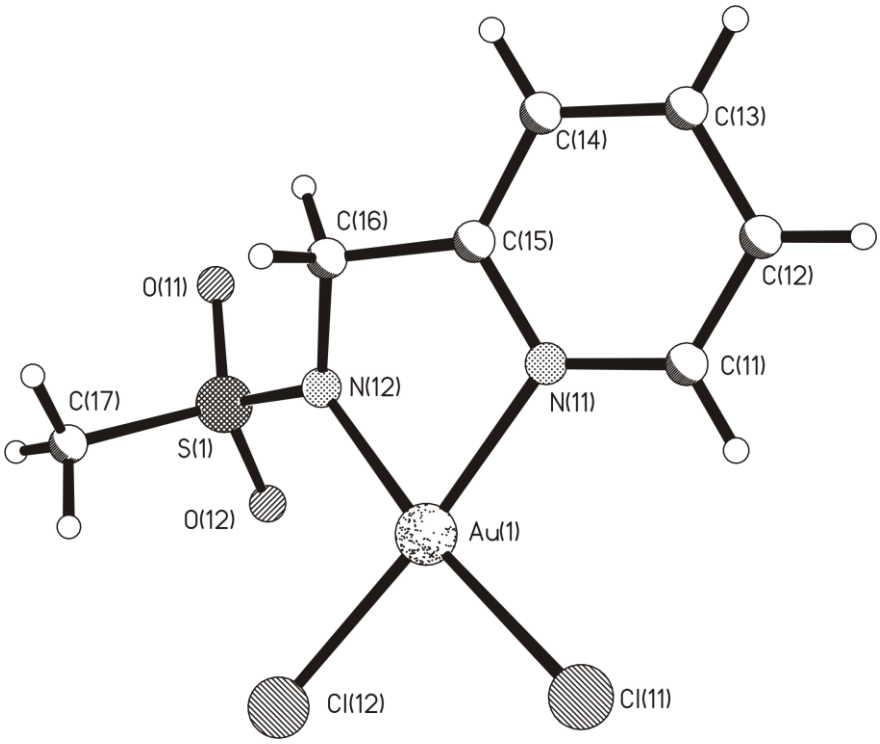


Figure 2: Molecular structure of L^6AuCl_2, showing the atom numbering scheme, with the dichloromethane solvent omitted for clarity.

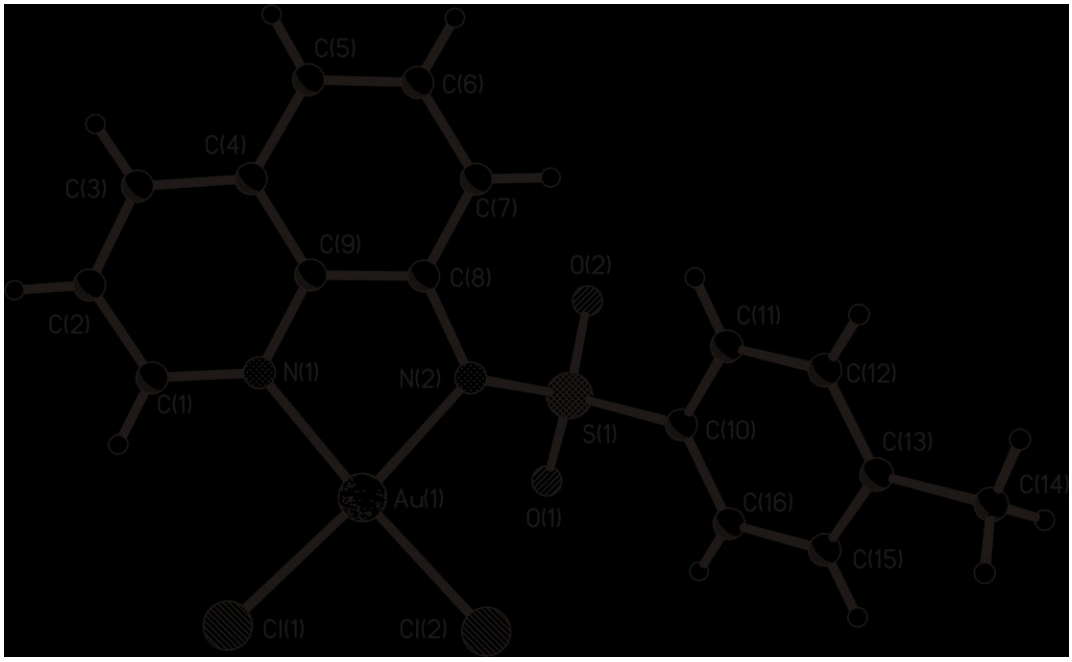
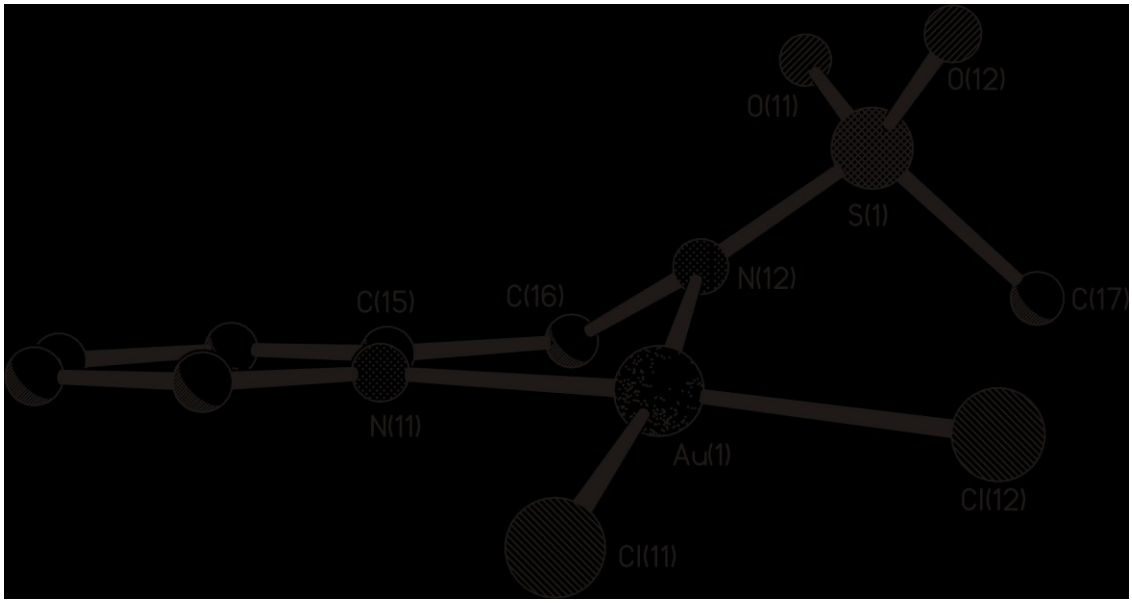


Figure 3: a) Structure of L^3AuCl_2 (molecule 1) showing the envelope conformation of the cycloaurated ring with N(2) sitting above the plane of the ring; b) crystal structure of L^6AuCl_2 showing the planarity of the quinoline group, with Au(1) sitting below the plane. For clarity, only the *ipso* carbon of the *p*-tolyl group of L^6AuCl_2 is shown and hydrogen atoms are omitted.



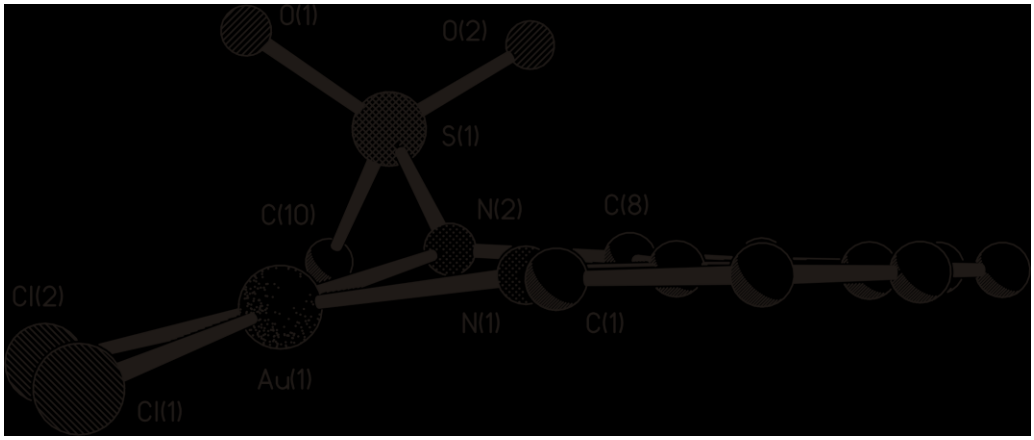


Figure 4: ^{1}H NMR spectra ($CDCl_3$, 300 MHz) of a) HL^1 and b) L^1AuCl_2, showing changes in spectra upon coordination of the ligand to gold.

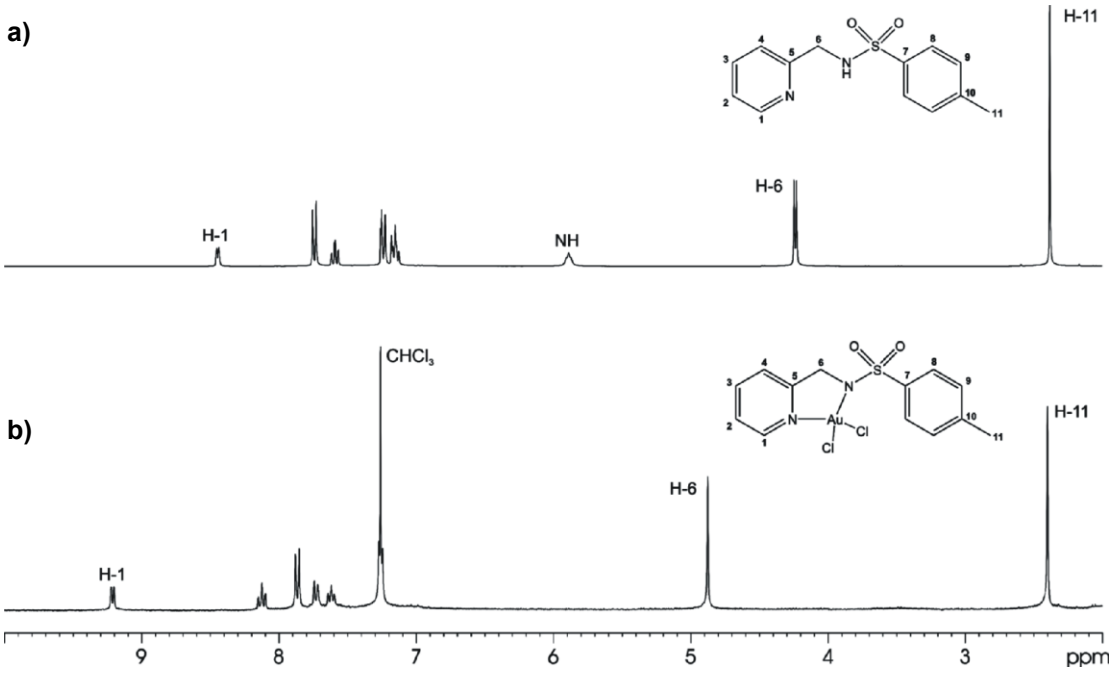
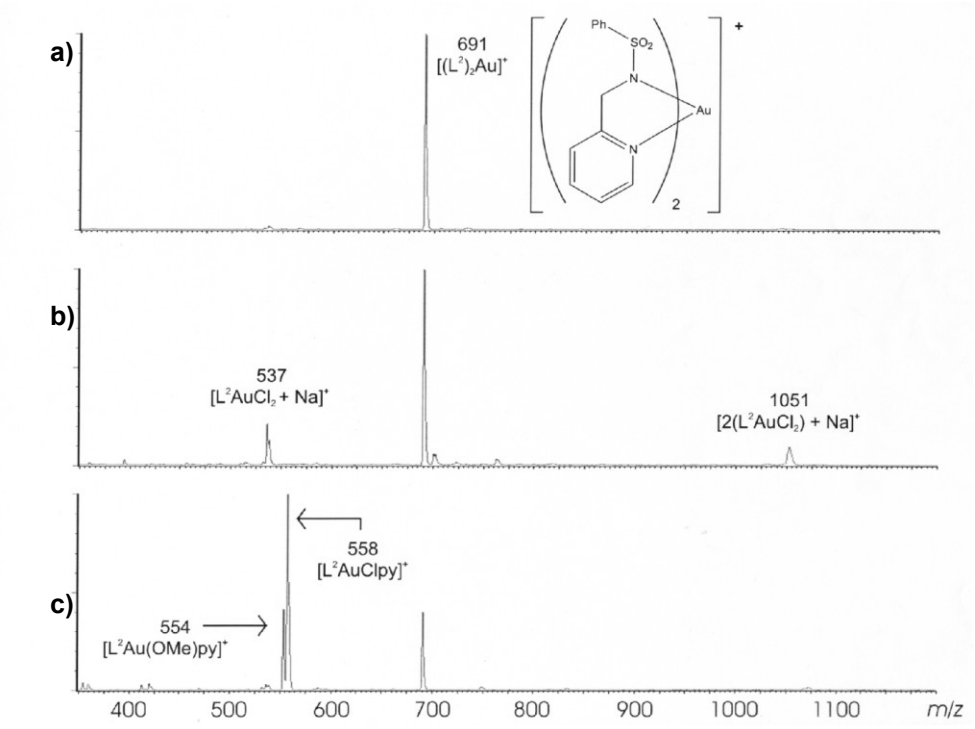


Figure 5: Positive ion ESI mass spectra (cone voltage 20 V, MeOH solvent) of L^2AuCl_2 showing the observed ions under different ionisation conditions: a) neat solution; b) with addition of NaCl; c) with addition of pyridine (py).



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