# Synthesis and Characterisation of Cycloaurated Gold(III) Complexes with Bidentate (O,O), (N,S) and (S,S) Chelating Ligands


THE UNIVERSITY OF
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*Te Whare Wānanga o Waikato*

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of

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at
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by

**Tiffany Sharee Smith**

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# Abstract

The reaction of C,N-coordinated gold(III) dihalides; $BpAuCl_2$ (Bp = 2-benzylpyridyl), $AnpAuCl_2$ (Anp = 2-anilinopyridyl) and $TypAuCl_2$ (Typ = 2-tolylpyridyl) with catecholate ligands in hot methanol and trimethylamine produced metallacycles with structural isomers of the general formula (C,N)Au{O,O}. Similarly, $BpAuCl_2$ and $AnpAuCl_2$ were reacted with thiourea ligands to form complexes giving high yield and good purity with the general formula $(C,N)Au\{PhNCSNR_2\}^+$, by means of the addition of $BPh_4^-$ for precipitation. X-ray crystal structures of the compounds $[AnpAu\{PhNCSNMe_2\}]BPh_4$ and $[AnpAu\{PhNCSNCy_2\}]BPh_4$ confirmed the coordination of the thiourea to the gold centre through the N and S atoms. In both cases the geometry around the gold atom is square-planar with complex $[AnpAu\{PhNCSNCy_2\}]BPh_4$ showing a slightly more puckered conformation than $[AnpAu\{PhNCSNMe_2\}]BPh_4$ due to the sterically bulky cyclohexyl groups attached. Some thiourea derivatives were tested against P388 murine leukaemia cells with complex $[AnpAu\{PhNCSNHPh\}]BPh_4$ showing promising anti-tumour activity.

When thiourea ligands were replaced by dithiophosphinate and dithiophosphate ligands the reaction proceeded at room temperature without the need for the presence of a base. Relatively low yields of impure metallacycles with the general formula $(C,N)Au\{S_2PR_2\}^+$ were obtained on the addition of $BPh_4^-$ or $BF_4^-$. Attempts to improve purity by varying batches of starting materials, anion and solvents used were unsuccessful. X-ray crystal data from a single crystal of $[(C,N)Au\{S_2PPh_2\}]BPh_4$ shows the reduction of gold(III) to gold(I) forming a known polymeric gold(I) dithiophosphinate complex. In order to extend this study the synthesis of complexes with the general formula $R_2PS_2AuCl_2$ was attempted, but no new compounds were characterised.

Where possible, all new compounds reported in this thesis were characterised by ES-MS, IR, NMR, melting point and micro-elemental analysis.

# Acknowledgements

Firstly, I would like to thank my supervisor Bill Henderson for his extensive help and guidance throughout my research project. Without his enthusiasm and dedication none of this would have been possible.

I would like to say a huge thank you to Pat Gread and Wendy Jackson for endless supplies of chemicals, glassware, advice, laughs and also their help with ES-MS. Very special thank you to Professor Alistair Wilkins for all the hours teaching me all I know about NMR with such enthusiasm, care and advice, eventually converting me to the NMR enthusiast I am today. To Brian Nicholson a huge thank you for acting like a second supervisor, for the variety of un-answered questions he has helped me with and for the solving of my X-ray crystal data. I would also like to thank Dr. Tania Groutso at the University of Auckland for the collection of X-ray crystal structure data.

To my close friend Aaron Andersen a special thank you for not only running bioassays of my samples but also for the many laughs, good times and friendship throughout our years at university. To my fellow lab mates, friends and staff here at the University of Waikato, a huge thanks for all the help, advise, laughs and distractions throughout my time here, it made every day that much more enjoyable and at sometimes more frustrating, but without the friendships and bonds made my time here would not have been the same.

And finally, my family, for all the support and love they have given me throughout my time at university, for always believing in my abilities and pushing me every step of the way, while wearing all the stress that came along with that. A special dedication to my father and nana, whom have shown me that no matter what life throws at you, through strength and dedication if you truly work hard anything is possible. For these reasons I dedicate my work and this thesis to them.

I would like to thank the University of Waikato for a Masters Scholarship award.

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# List of Abbreviations

| | | |
|---|---|---|
| RA | - | rheumatoid arthritis |
| NMR | - | nuclear magnetic resonance spectroscopy |
| IR | - | infrared spectroscopy |
| ES-MS | - | electrospray mass spectrometry |
| DEPT | - | distortion less enhancement by polarisation transfer |
| COSY | - | correlation spectroscopy |
| HSQC | - | heteronuclear single quantum correlation |
| HMBC | - | heteronuclear multiple bond correlation |
| NOESY | - | nuclear Overhauser effect spectroscopy |
| NOE | - | nuclear Overhauser effect |
| ROESY | - | rotating-frame Overhauser effect spectroscopy |
| TOSCY | - | total correlation spectroscopy |
| DMSO-$d_6$ | - | deuterated dimethyl sulfoxide |
| DCM | - | dichloromethane |
| damp | - | 2-(dimethylaminomethyl)phenyl |
| Bp | - | 2-benzylpyridyl |
| Anp | - | 2-anilinopyridyl |
| Typ | - | 2-(*p*-tolyl)pyridyl |
| $H_2$az | - | alizarin |
| sym | - | symmetric (IR) |
| asym | - | asymmetric (IR) |
| δ | - | chemical shift ppm (NMR) |
| *m/z* | - | mass to charge ratio (ES-MS) |
| s | - | singlet (NMR), strong (IR) |
| d | - | doublet (NMR) |
| t | - | triplet (NMR) |
| m | - | multiplet (NMR) |
| br | - | broad (NMR, IR) |
| *J* | - | coupling constant in Hz (NMR) |

# Chapter One

# *A Brief Review on the Medicinal Uses of Gold*

## 1.1 History of Gold

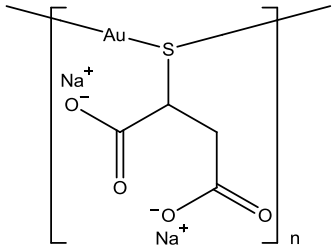
The earliest application of gold as a therapeutic agent was use by the Chinese, and can be related back to as early as 2500BC where ancient Arabic, Indian and Chinese physicians used gold preparations for the treatment of a wide variety of ailments. In medieval Europe, *aurum potabile*, used by alchemists, was an elixir which had numerous recipes, many of which contained a small amount of gold. By the 17$^{th}$ century gold cordial could be found in the new pharmacopoeias which were advocated for the treatment of ailments such as melancholy, fainting, fevers, and falling sickness[1].

Later in the 19th century a mixture of gold chloride and sodium chloride, 'muriate of gold and soda', $Na[AuCl_4]$ was used in the treatment of syphilis. Gold has since featured widely throughout history in medicinal agents. In 1890 Robert Koch, a German physician, demonstrated that $[Au(CN)_2]^-$ was bacteriostatic agent against tubercle bacillus, an effective treatment for syphilis. By the 1920's gold compounds were being used for the treatment of tuberculosis but were later shown to be ineffective[1].

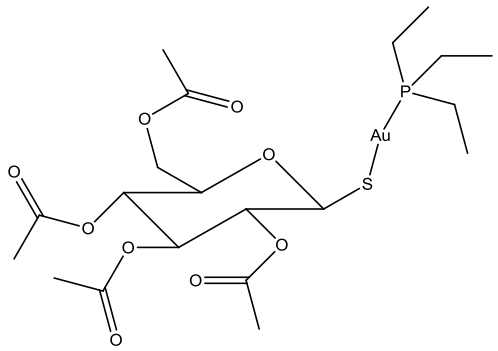
The suggestion that tubercle bacillus was a causative agent for rheumatoid arthritis (RA) led to the proposal that gold could be implemented as a treatment option. This was supported by the observation that during the time these gold compounds were used in the treatment of syphilis, patients taking the gold drug had dramatic improvements in arthritic conditions. Trials were undertaken to investigate gold compounds in the treatment of RA. After 30 years of debate concerning the

efficacy of gold as a treatment for RA a clinical study was carried out that confirmed the effectiveness of gold compounds against RA[1].

Today gold(I) thiolates, namely sodium aurothiomalate (Myocrysin®) **1**, Auranofin **2**, are used for the treatment of RA. In addition, gold complexes continue to be screened for activity as anti-HIV, anti-microbial and anti-malarial agents with the bulk of the research being in the pursuit of novel chemotherapeutic agents[2].




**1**




**2**

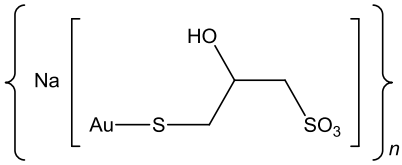
The following discussion briefly reviews the important history of gold medical research and information allowing further understanding of why gold based drugs are now an accepted part of modern medicine. It is by no means a full comprehensive review, rather giving insight into why this topic of research was chosen. Detailed reviews have been published on the topic by Fricker[1], Tiekink[3] and Shaw[4].

## 1.1.1 Gold in Rheumatoid Arthritis (RA)

The first application of gold compounds in medicine, known as chrysotherapy, was reported in 1935. Chrysotherapy was primarily used to reduce inflammation and to slow disease progression in patients with RA[1]. The most effective compounds were gold(I) thiolates which involve AuSR units, R being a suitable organic group, with the two most widely used Class I compounds in chrysotherapy being sodium aurothiomalate **1** and aurothioglucose **4**[1].

Five main Au(I) complexes are currently used throughout the world to treat RA[5]. These are; sodium aurothiomalate (Myocrysin®) **1**, Auranofin **2** (both mentioned

above), sodium aurothiopropanol sulfonate (Allocrysin Limière®) **3** aurothioglucose (Solganol®) **4** and sodium aurothiosulfate (Sanocrysin®) **5**.

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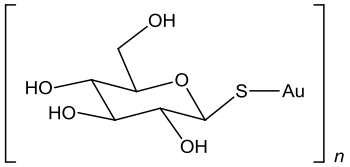


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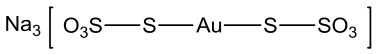



**5**

Two classes of gold compounds are used in the treatment of RA, grouped according to their related chemistry which dictates their mode of administration and therefore, the pharmacodynamics of distribution. The first class of compounds are generally polymeric, charged and water soluble. By contrast, the second class of compounds are monomeric, neutral and lipophilic. The Au(I) thiolates **1**, **3**, **4** and **5** are members of Class I, these are water soluble and therefore are able to be administered intravenously on a weekly basis. A crystal structure determination is available for aurothiosulfate **5**. This structure demonstrates that gold has the tendency to exist in linear coordination geometries showing a polymeric backbone consisting of S-Au-S bonds[6], with all other Class 1 gold compounds having the similar gold to sulfur ratio of 1:1 in order to achieve analogous S-Au-S entities.

This conclusion is supported by the crystal structure determination of aurothiomalate **1** which shows a polymeric structure with the backbone existing as two spirals. The structures of aurothiopropanol sulfonate **3** and aurothioglucose **4** have not to date been determined, but were proposed to be polymeric with bridging thiolate ligands[7]. Studies involving X-ray techniques such as EXAFS (extended X-ray absorption fine structure) by Sadler *et al*[8] and Elder *et al*[9] confirmed the first direct evidence of a polymeric configuration

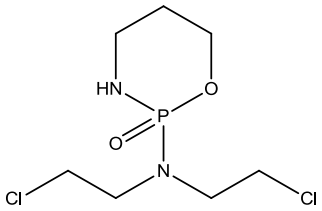
Auranofin **2**, a member of Class II, was introduced as a RA drug in 1985[1]. This compound contains a triethylphosphine and thiolate bound to the gold atom, allowing for lipid solubility. Auranofin can therefore be administrated orally,

typically in capsules containing 3-6 mg 'gold' on a daily basis. The X-ray crystal structure of Auranofin, solved by Hill and Sutton[10], demonstrates that in contrast to the polymeric Au(I) thiolates, auranofin is monomeric with the triethylphosphine ligand *trans* to a tetraacetylthioglucose ligand.

Classes I and II drugs rapidly undergo substitution reactions of one sort or another on administration and therefore are regarded as prodrugs[5]. Although the exact mechanism is unknown it is proposed that the gold-based drugs undergo substitution reactions in the body with sulfur-containing proteins such as albumin, and the tripeptide glutathione. A more detailed review on the possible mechanism of action has been published by Shaw *et al*[4].

## 1.1.2 Gold(I) Compounds and their Anti-Cancer Activity

Investigation into gold compounds as possible anti-tumour agents was suggested when biological activity exhibited by known anti-tumour agents such as cyclophosphamide **6**, 6-mercaptopurine **7** and methotrexate **8** displayed immunosuppressive and anti-inflammatory characteristics. In support of these findings were the results of a long-term study of patients undergoing chrysotherapy, revealing little or no risk of malignant diseases, suggesting a connection between the use of RA drugs and cancer chemotherapy treatments[4].

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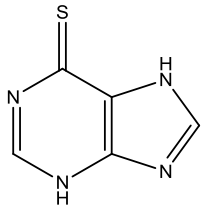


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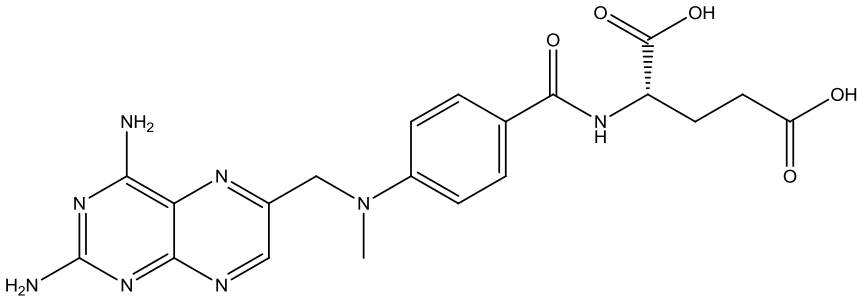
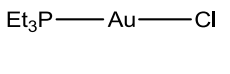



**8**

The first comprehensive study into the anti-tumour potential of gold compounds began in the mid-to-late 1980's[11]. The key outcome of this study concluded that gold was essential for elevated potency. The results also demonstrated that the most promising class of compounds, containing gold(I), were the P-Au-S analogues much like the structure of Auranofin **2**. Auranofin was found to be active against the P388 Leukaemia and HeLa cell lines *in vitro*. Later, Tiekink *et al*[3] showed that gold(I) bis-thiolates, S-Au-S, were generally inactive as were non-phosphine and non-thiolate compounds, indicating that the most promising activity was that of gold(I) compounds containing a P-Au-S backbone.

Triethylphosphine gold(I) chloride, $Et_3PAuCl$ **9**, a compound similar to the well known Auranofin complex has shown potent cytotoxicity *in vitro* but less *in vivo* than Auranofin. It is thought the replacement of the thiosugar moiety of Auranofin with a chloride reduces selectivity of the metal complex *in vivo* systems in a way which is not seen *in vitro*[12].

Widespread interest in the potential activity of these compounds led to the evaluation of anti-tumour activity in a range of bridged digold complexes. The most active complex was found to be [ClAu(μ-dppe)AuCl] **10** (dppe=1,2-bis(diphenylphosphino)ethane), which showed greater activity against P388 leukaemia cells than Auranofin. The dppe ligand was found to be responsible for the anti-tumour activity with the dppe oxide, a biologically inactive form of the ligand, produced as a by-product of metabolism. It was later shown that the gold dppe complex has higher anti-tumour activity then that of the ligand alone, therefore suggesting the role of the gold centre may be to prevent oxidation of the dppe ligand[13].

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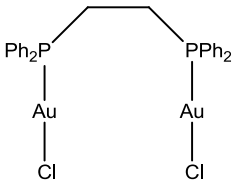


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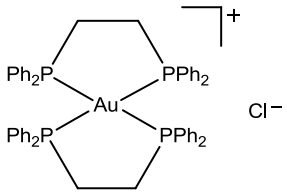


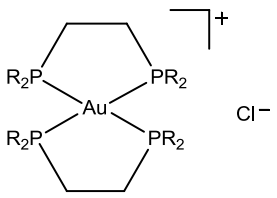

**11**

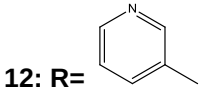
In the 1980's Berners-Price *et al*[14] investigated a number of active diphosphine-bridged-digold complexes which, in presence of excess diphosphine ligand, were

readily converted into the bis-chelated species. This investigation found that thiol-containing human plasma and bovine serum was able to induce the conversion of the bridged compounds to the bis-chelated ion $[Au(dppe)_2]^+$**11**.

Research into the thermodynamics and kinetics of $[Au(dppe)_2]^+$ **11** demonstrated an unusually high thermodynamic stability in contrast to that seen in linear complexes. This characteristic allows the compound to be more stable to ligand exchange reactions, an important feature as this results in the complex being less reactive to thiols[15]. These properties were believed to be associated to the presence of the five membered chelate rings and the bulky phenyl groups attached to the phosphorus atoms, blocking attack of the gold ion. It is suggested that this cation **11** may be a metabolite of the bridged species, demonstrated by the rapid conversion of [STgAu(dppe)AuSTg] (STg = *β*-D-thioglucose) to complex **11** in a biological environment[16].

$[Au(dppe)_2]Cl$ is active in its own right as well as in combination with cisplatin, (*cis*-$PtCl_2(NH_3)_2$), against P388 leukaemia and various sarcomas in mice. Results of the activity of $[Au(dppe)_2]Cl$ against cisplatin resistant P388 leukaemia cells were found to be as efficacious as the results in cisplatin-sensitive lines. While no specific target molecules or mode of action for $[Au(dppe)_2]^+$ have yet been identified, it is believed that the site of action for the compound is mitochondria in the cell[14,16]. Although the development of bis(diphospho)gold(I) complexes resulted in compounds with promising cytotoxicity and anti-tumour properties, they never reached clinical trials due to high cardio-toxicity in rabbits[17].

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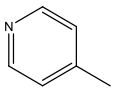


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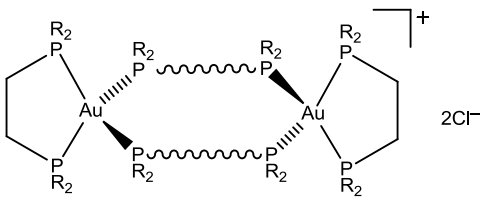
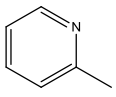
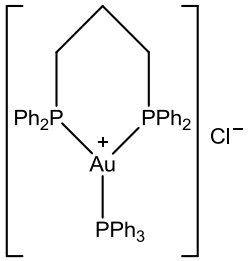



**14: R=**

The next generation of compounds, adapted from this class of complex, was bis[1,2-bis(di-n-pyridylphosphino)ethane] gold(I) (n=2-,3- or 4-) **12-14** chloride complexes. The aim was to vary the phenyl substituents in $[Au(dppe)_2]Cl$ to determine the effect of aqueous solubility, where replacement of the phenyl with pyridyl groups resulted in a decrease in the lipophilicity of the diphosphine ligand[18]. The 2-pyridyl complex **14** observed similar activity to the parent $[Au(dppe)_2]Cl$ complex against P388 leukaemia and B16 melanoma in mice, while the 4-pyridyl derivative **13** was completely inactive in all tumour models but toxic to mice[14,18].

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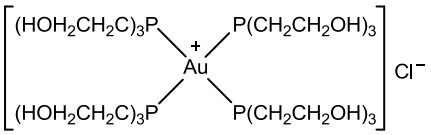
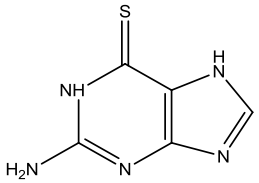



**16**

Bis(diphospho)gold(I) analogue **15** a three coordinate complex incorporating both a mono and bidentate phosphine ligand demonstrates high *in vitro* cytotoxicity against a range of cancer cell lines, with notable potent activity against the breast tumour cell line MDF-7[19]. Alternatively complex **16** contains all monodentate phosphine ligands in a tetrahedral coordination. This hydrophilic compound shows promising activity against prostrate, colon and gastric carcinomas[20].

It was concluded that the presence of the phosphine gold(I) moiety increases the potency of the biologically active thiols. Thus greater overall cytotoxicity is observed for the phosphine gold(I) thiolates in comparison with the free thiols. This was further confirmed when Au(I) phosphine complexes of the well known anti-cancer drugs 6-mercaptopurine **7** and 6-thioguanine **17** were synthesised, resulting in analogues with greater activities then the un-coordinated drugs alone[5]. In contrast the Au(I) derivative of the active thiosemicarbazone **18** is less cytotoxic than the ligand itself[4].



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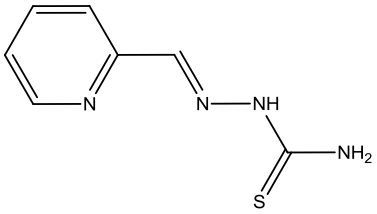
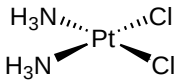


**18**

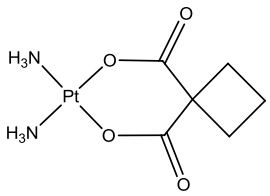
## 1.1.3 Gold(III) Complexes and their Anti-Cancer Activity

In 1965, while investigating the effects of electric fields on *Escherichia coli (E. coli)* bacteria, Barnett Rosenberg discovered that electrolysis using platinum electrodes generated a soluble platinum complex which inhibited binary fission in this bacterium. It was noticed that although bacterial cell growth was not inhibited, cell division was retarded, forming long filaments up to 300 times their normal length[21]. After various experiments it was found that the active compound was the square planar Pt(II) salt, *cis*-$PtCl_2(NH_3)_2$, produced from reaction of the electrode and the nutrient medium solution, known as cisplatin **19**[22]. This discovery led to investigations finding that cisplatin was highly effective against sarcomas in rats, prompting further extension of research on other tumour cell lines. In 1978 cisplatin was approved for use in testicular and ovarian cancers, becoming one of the most widely used anti-cancer drugs in the Western world.



**19**

Despite the fact that cisplatin treatment is effective against several types of solid tumours, its efficacy is limited by toxic side effects and tumour resistance in some cell lines. The regular occurrence of secondary malignancies prompted research aimed at finding new drugs with higher cytotoxicity and fewer undesirable outcomes. A very wide range of platinum(II) [and platinum(IV)] complexes have been screened *via* clinical trials for anti-cancer activity, including Carboplatin **20**[23], Oxaliplatin **21**[24] (both Pt(II)) and Iproplatin **22**[23] (Pt(IV)). Only Carboplatin and Oxaliplatin have since entered clinical use.

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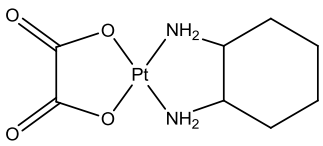
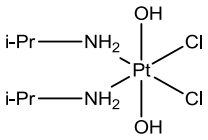



**21**

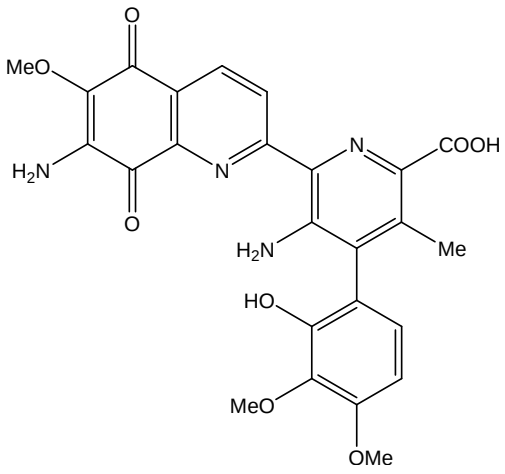



**22**

Due to the chemical similarities between gold(III) and platinum(II) (both form square planar $d^8$ complexes), it has been reasoned that gold(III) complexes might also exhibit anti-tumour properties. Although a substantial amount of work has previously been done on gold(I), historically little has been done on gold(III), mainly due to the ease of reduction to either gold(I) or gold(0). However, the few examples of gold(III) complexes have shown strong tumour cell growth inhibiting effects and increased cytotoxicity therefore gaining increasing interest.

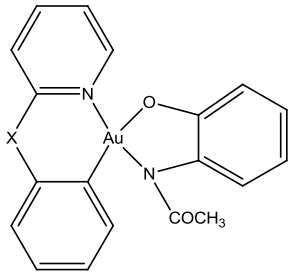
The gold(I) complexes used to treat RA are thought to be pro-drugs that undergo substitution through the course of metabolism. Therefore it can be postulated that gold(III) complexes may act as carriers to transport known anti-cancer compounds to the site of cancer. This coordination of an anti-cancer drug to a metal centre is believed act as a slow release mechanism while also protecting the drug against metabolic degradation before it reaches the target cells[5].

Streptonigrin **23**, produced by *Streptomyces flocculus,* is a metal dependent quinone-containing antibiotic which has been shown to exhibit anti-tumour activity, although highly toxic. Highly stable Au(III) complexes with streptonigrin have been created which show activity against P388 leukaemia cells *in vitro*, exhibiting similar effectiveness to streptonigrin itself. While the definite structure of this complex is unknown, it is thought to contain a 1:1 ratio of Au(III) to streptonigrin. It has been proposed that the reduction of Au(III) to Au(I), within the cell, allows the release of the streptonigrin molecule which then exerts a cytotoxic effect[25].

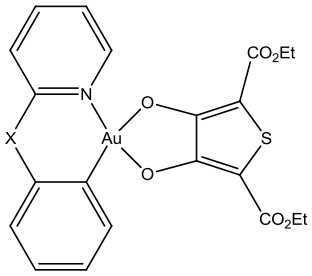



**23**

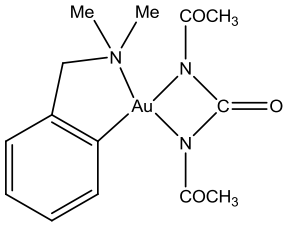
Although many simple gold(III) complexes such as $[AuCl_4]^-$ are too strongly oxidising to show useful anti-tumour properties, derivatives containing cycloaurated aryl-amine or aryl-pyridine ligands **24-28** show much greater stability, and are not reduced by sulfur-based ligands such as thiols and related ligands. This is significant since sulfur based reductants occur widely in the cysteinyl and methionine residues in biological materials[26].




**24: X=NH**
**25: X=$CH_2$**




**26: X=NH**
**27: X=$CH_2$**



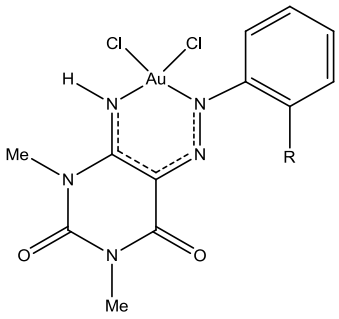

**28**

Three main types of gold(III) complexes have shown activity; **(a)** coordination compounds (with N-polydentate), macrocyclic ligands or dithiocarbamato ligands with a S-donor atom, **(b)** organometallic complexes with an N-C (e.g. DAMP = *o*-$C_6H_4CH_2NMe_2$) or CNC-pincer backbone, or **(c)** gold(III) complexes containing "bioligands" (e.g. naturally occurring amino acids)[27].

Gold complexes are now quite well known for showing biological and catalytic activity. Complexes containing cycloaurated ligands, typically a bidentate nitrogen-carbon donor, are of high interest due to the stabilisation of the gold(III)

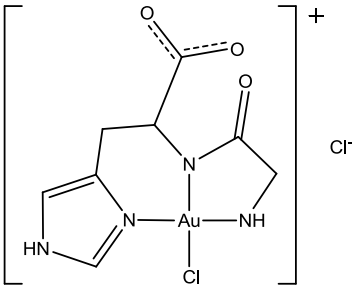
state against reduction. However, the number of ligands that form with cycloaurated gold(III) are relatively few compared with that of platinum group metals[28].

In 1989 Kivekäs *et al*[29] characterised and isolated the complexes **29-31**. *In vivo*, compounds **29** and **30** show an $IC_{50}$ comparable to that of cisplatin against HeLa cells. However, with complex **31** a ten-fold higher concentration was required to produce similar growth inhibition with no obvious reason for this result. The proposed structure of these compounds were determined through infrared spectroscopy (IR) and were found to contain a square-planar gold atom coordinated to the ligand through the azo and amino groups with remaining coordination sites occupied by chloride ligands.




**29: R=H**
**30: R=Cl**
**31: R=COOH**

Carotti[30] and co-workers established the importance of using biological ligands, such as peptides, to increase the chance a compound would exhibit biochemical activity. To investigate cytotoxicity and DNA binding properties the previously characterised complex $GlyHisAuCl_2$[31] was synthesised by reacting gold(III) with glycine histidine dipeptide (GH). This complex **32** showed $IC_{50}$ values comparable to cisplatin when assayed against cisplatin sensitive (A2780) and resistant (A2780/S) cell lines. Studies on analogous complexes of GH with Zn(II), Co(II), Pt(II) and Pd(II) were shown to be only weakly cytotoxic. The GH ligand itself exhibited no cytotoxic activity. From these observations Carotti[30] and co-workers were able to demonstrate the importance of the Au(III) centre for cytotoxicity.

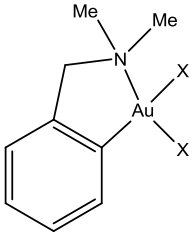



**32**

## 1.2 Cyclometallated Gold(III) Systems

The metallacyclic chemistry of gold(III) is scarcely developed, although interest in the synthesis of gold(III) complexes in the recent years has resulted in increased research in this area[32]. Owing to the ease of reduction of gold(III) in mildly reducing biological media, it was reasoned that softer ligands such as nitrogen and carbon donors would achieve stabilisation of the gold centre. Gold(III) compounds involving a σ-bonded phenyl, naphthyl or similar group are known to observe much higher stability in biological media than those containing N, O donors[33].

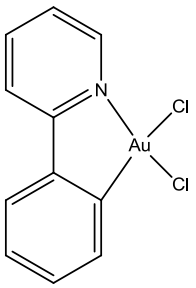
Most work on cycloaurated gold(III) complexes have been carried out on the damp complex **33** (damp = 2-(dimethylaminomethyl)phenyl). This is due to its good solubility characteristics and promising cytotoxicity and toxicity profile compared with cisplatin[34]. These damp type complexes have a carbon-metal bond that strongly donates electrons to the metal ion making it much more resistant to reduction. Investigation into the activity of damp complexes demonstrated cytotoxicity against bladder and ovarian cancer cell lines, with the acetate **35** and malonato **37** damp complexes exhibiting activity comparable to cisplatin against human HT1376 bladder cancer in animals[35].



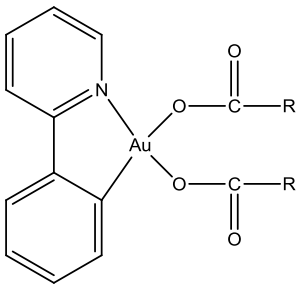

**33: X=Cl**
**34: X=SCN**
**35: X=acetato**
**36: X=oxalato**
**37: X=malonato**

Diacetato complex **35**, a derivative of the damp complex, shows more than a 1000 fold increase in aqueous solubility while retaining comparable broad spectrum antibacterial activity and cytotoxicity relative to the parent compound **33**. Hydrolysis of this complex in aqueous solution is similar to that of cisplatin, with the first acetate group replaced much faster than the second. However, in contrast to cisplatin which interacts with DNA primarily through the $N_7$ atoms of guanine groups[36], reactions of **35** with guanine were shown to display a preference for $N_1$, $N_3$ or $NH_2$, suggesting a different mechanism of action to cisplatin[37]. Further studies into the activity of compounds **34-37** showed that **35** along with **37** displayed anti-tumour activity similar to cisplatin against human xenograph models, whereas **36** was found to be inactive. **34** exhibited a lower solubility in aqueous solution than **33** so it was not evaluated *in vivo*[38].

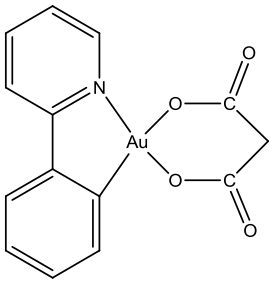
*In vitro* studies of the previously known [Au(ppy)$Cl_2$] (ppy = phenylpyridyl) complex **38**[39] and novel derivatives **39-42** were also investigated[40]. These compounds were all found to be active against the MOLT-4 human leukaemia cell line, showing slightly higher cytotoxicity than cisplatin. All five gold(III) complexes were inactive against C2Cl2 mouse tumour cell lines with the exception of complex **41**, showing that it may be the ligand attached that demonstrates the biological activity. O-donor ligand derivatives **39-42** of the [Au(ppy)$Cl_2$] complex show higher aqueous solubility while structurally resembling cisplatin.



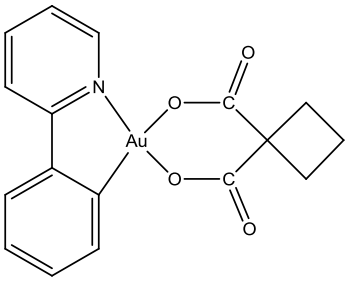

**38**




**39: R=Me**
**40: R=Ph**

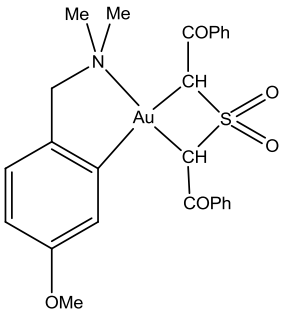



**41**

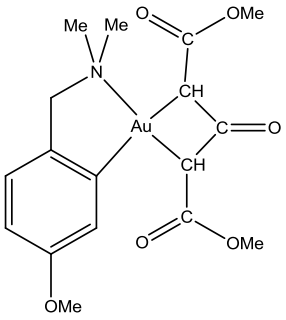



**42**

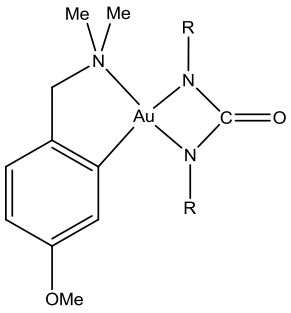
Previous work at the University of Waikato has been focused on the formation of metallacycles containing two ring systems, with Henderson *et al*[32,41-43], synthesising some of the first examples of gold complexes containing two rings **43-53**. This was achieved by the use of silver(I) oxide, a much stronger reagent then the commonly used trimethylamine, with the ability to act as both a halide abstracting agent (as it is a source of $Ag^{+}$) and a strong base.



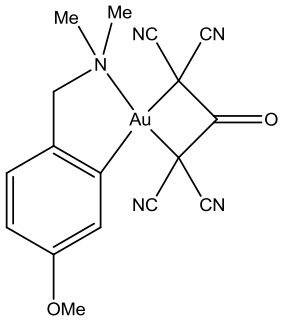

**43**



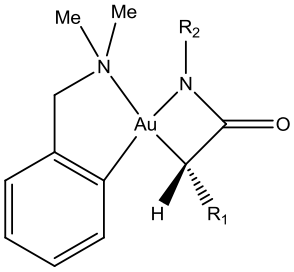

**44**



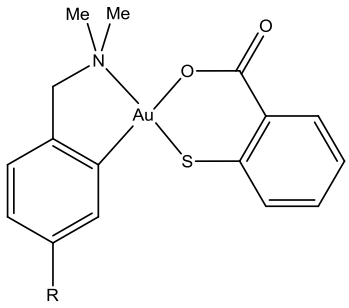

**45: R=Ph**
**46: R=COMe**



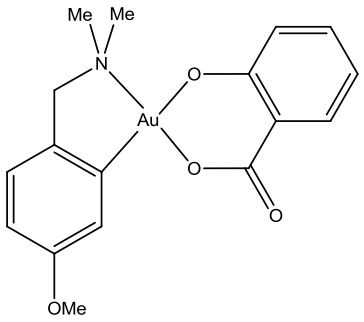

**47**




**48: R=OMe, $R_1$=CN, $R_2$=$CO_2$Et**
**49: R=OMe, $R_1$=COPh, $R_2$=Ph**
**50: R=OMe, $R_1$=COMe, $R_2$=Ph**
**51: R=H, $R_1$=COMe, $R_2$=Ph**



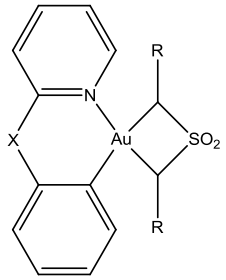

**52: R=OMe**
**53: R=H**



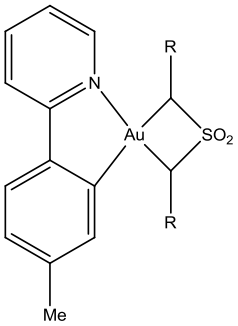

**54**

The preferential route to form metallacycles, predominantly used in this research, utilises a tertiary amine as a base, such as $Me_3N$ or $Et_3N$. These reactions can be carried out *via* refluxing methanol resulting in simple isolation, high yields and good purity by the simple addition of water. Henderson *et al*[44] reported the synthesis of previously known complex **43** by means of a more convenient synthetic route using trimethylamine as a base in replacement of the silver(I) oxide. With this method new complexes **44-54** were prepared, demonstrating that compounds synthesised using a tertiary amine base gave products showing lower light sensitivity, less coloured and observed few traces of gold-containing impurities or silver salts[44].

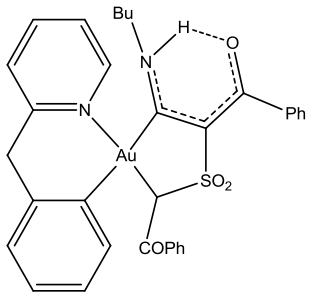
Synthesis of complex **60** was facilitated by an insertion reaction into the Au-C bond of complex **55**. Insertion of isonitrile into the Au-C bond is followed by a proton transfer giving rise to a hydrogen-bonded, planar, six-membered ring. Thiosalicylate[41] **61-64** and catecholate systems[42] **65-73** were synthesised using the more conventional tertiary amine method. Compound **61** however required synthesis using $AgNO_3$ to remove the chloride ligands, followed by treatment with NaOH and thiosalicylic acid.



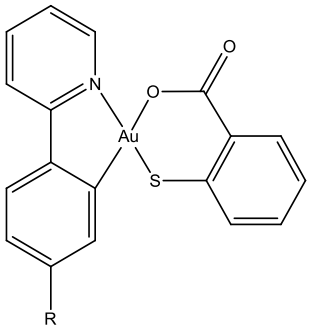

**55: X=$CH_2$, R=COPh**
**56: X=NH, R=COPh**
**57: X=$CH_2$, R=CN**



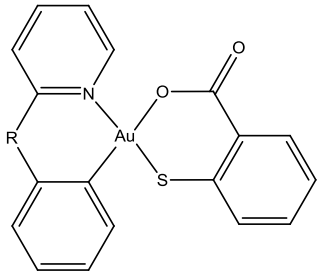

**58: R=COPh**
**59: R=CN**



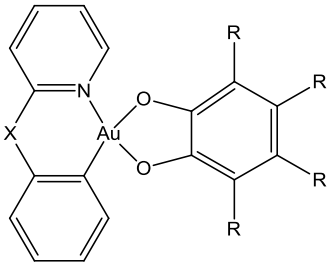

**60**



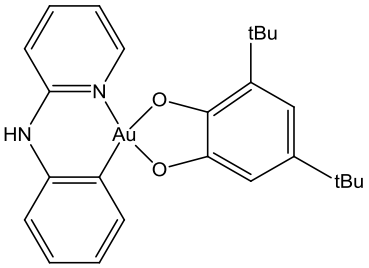

**61: R=H**
**62: R=Me**




**63: R=$CH_2$**
**64: R=NH**




**65: X=NH, R=H**
**66: X=$CH_2$, R=H**
**67: X=NH, R=Cl**
**68: X=$CH_2$, R=Cl**

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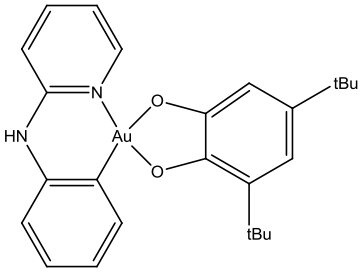


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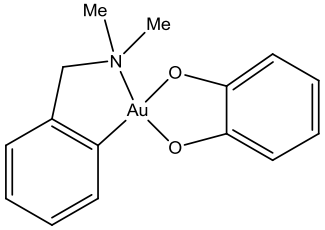


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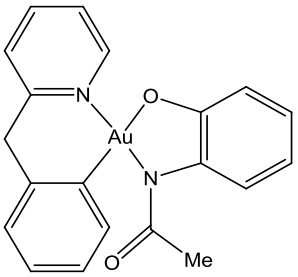


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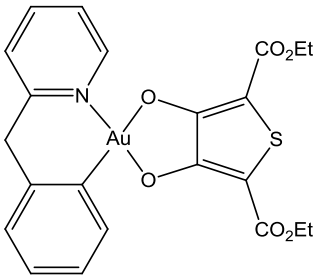


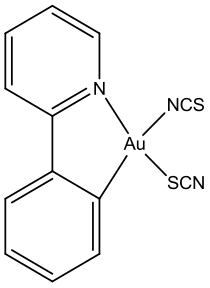

**73**

Selections of these complexes were tested for anti-tumour activity against P388 leukaemia cell lines, with most displaying moderate activity. $IC_{50}$ values were shown to range from 0.7 to >120.6(μM), with the tolypyridine complex **62** and catecholate derivatives **66**, **69**, **70** and **71** all showing the highest anti-tumour activity. Complexes **61**, **63** and **64** demonstrated only moderate to poor activity.

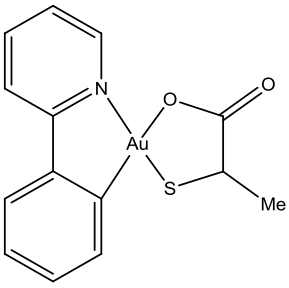
The relative activity observed in these compounds was believed to be associated to their solubility characteristics. This is demonstrated by the bioactive damp complex **71** being more soluble than its inactive analogues **65** and **66**. Consequently results for these less soluble complexes represent a minimum activity, with the true activity likely to be somewhat higher. Complexes **43** and **60** were shown to be freely soluble in biological media, consequently demonstrating higher activity then that of less soluble complexes. Ortner and Abram further reported the reaction of the damp complex **33** with heterocyclic thiols[45], thiosemicarbazones'[45,46] and diphenylthiocarbazone[47], demonstrating the formation of novel Au(III) thiosemicarbazone complexes through cleavage of the Au-N bond and protonation of the resulting amine group. This observation has been the suggested reason behind the good solubility characteristics of the damp complex, verified again by the more soluble methoxy-damp thiosalicylate derivate **52** showing more activity in bioassay than the less soluble damp derivative **53**.
Later, Fan *et al*[48] synthesised a range of new 2-phenylpyridine Au(III) complexes with thiolate ligands **74-78**. These complexes were evaluated for cytotoxic activity against the human leukaemia cell line MOLT-4 and the mouse tumour cell line C2C12, with results shown in Table 1.1. The results of these five compounds showed a cytotoxicity profile similar to each other and higher toxicity than cisplatin in the same assay.

***Table 1.1:*** *$IC_{50}$ values (μM) against MOLT-4 and C2C12 cell line*

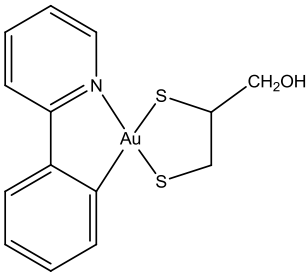
| Complex | 74 | 75 | 76 | 77 | 78 | cisplatin |
|---|---|---|---|---|---|---|
| MOLT-4 | 2.6 | 3.3 | 3.1 | 4.0 | 3.8 | 6.8 |
| C2Cl2 | 11 | 15.5 | 6.0 | 9.0 | 18.0 | 14.7 |




**74**




**75**

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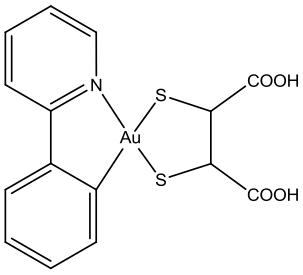


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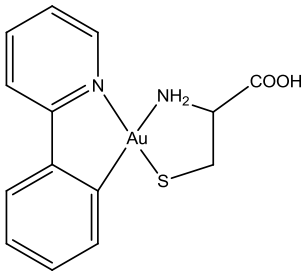
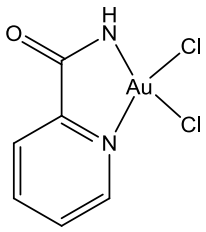


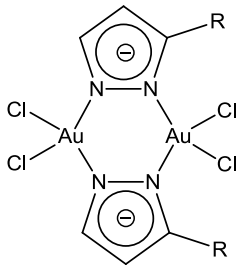

**78**

## 1.2.1 N,N Systems

Three of the first Au(III) compounds containing uninegative bidentate N-N ligands to be evaluated for anti-cancer activity were compounds **79**-**81**. These three Au(III) complexes structurally resemble cisplatin, where the geometry around the gold atom is square planar with two *cis*-coordinated chlorides and nitrogens. However, it is unknown if compound **80** exists as a *cisoid* or *transoid* isomer. Cytotoxicity studies on these compounds in vitro against the human tumour cell line MALT-4 and the mouse tumour line C2Cl2 showed that compounds **80** and **81** had $IC_{50}$ values in the low micro-molar range, displaying higher toxicity (lower $IC_{50}$ values) than cisplatin. In contrast **79** displayed no activity [49].



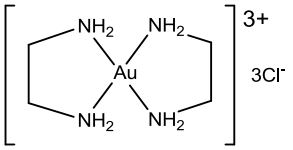

**79**



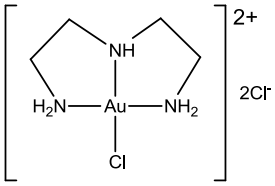

**80: R=H**
**81: R=Me**

Due to the growing interest in Au(III) auracycles, Messori *et al*[50] synthesised compounds **82-86** demonstrating good solubility and stability in physiological environments. The antiproliferative properties of these compounds were measured *in vitro* against the human ovarian carcinoma cell line A2780 showing cytotoxicity in the order of **86**>>**85**>**82**,**83**>>**84**. Compounds **83-85** showed only moderate cytotoxic properties while compound **86** displayed activity 5-15 times greater, exceeding that of cisplatin under particular assay conditions[50]. Cytotoxic activities of the free ligands were also tested. Results showed that the terpyridine and o-phenanthroline moiety alone exhibited important cytotoxic activity while the other three ligands ethylenediamine, diethylenetriamine, and cyclam were devoid of any activity. These findings, alongside that of low cytotoxicity shown by isostructural $[Pt(en)_2]^{2+}$ and $[Pt\text{-}(dien)Cl]^{+}$ compounds, supports the hypothesis that the activity seen in **82** and **83** can be attributed to the presence of the gold(III) centre. However the anti-tumour activity observed for compounds **84** and **85** may be attributed to the release of the active ligand when the compound is reduced.

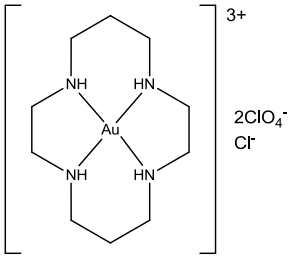
Results obtained for this group of complexes demonstrate that the presence of good leaving groups on the gold(III) centre (i.e. hydrolysable chloride groups) does not seem to be an essential requirement for biological activity as in the case for cisplatin. This is shown by complex **82**, with no gold-bound chlorides, having similar cytotoxicity as **83** which contains a gold-coordinated chloride. Complex **84** was poorly cytotoxic, possibly due to over-stabilisation by the cyclam ligand, allowing poor reactivity[51].



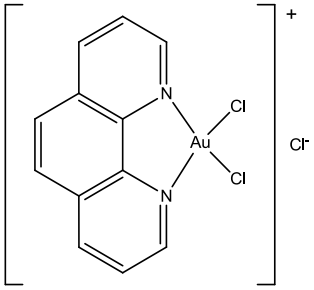

**82**



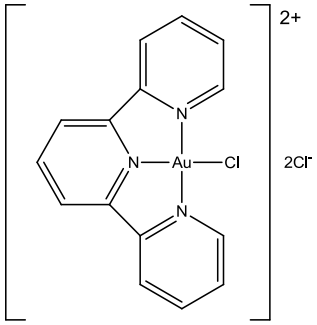

**83**




**84**

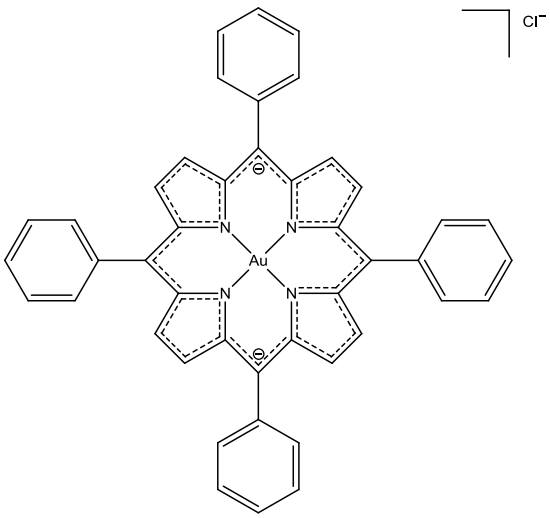



**85**




**86**

To further increase the stability of Au(III), Che and co-workers synthesised the square planar complex [Au(TTP)]Cl **87**, showing the well known tetraphenylporphyrin ligand bound to Au(III)[52-54]. Due to the macrocyclic effect this complex is very stable towards reduction in biological environments. *In vitro* screening of **87**, against cisplatin and multi-drug resistant cells, showed that this compound had high anticancer activity with $IC_{50}$ values in the submicromolar range. The highest activity this complex displayed was against nasopharyngeal carcinoma demonstrating activity 100 times higher than that of cisplatin.




**87**

## 1.2.2 Dithiocarbamate Systems

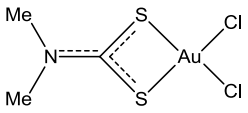
Investigation into dithiocarbamate complexes as a choice of ligand toward cyclometallated gold(III) compounds developed increasing interest due to their efficacy as inhibitors of cisplatin-induced nephrotoxicity, without decreasing the cisplatin anti-tumour activity. Platinum(II) and palladium(II) complexes containing these dithiocarbamate ligands have been recently reported to show greater cytotoxic activity than that of cisplatin **19**, and in addition show no cross-resistance with cisplatin and low nephrotoxicity levels *in vitro* and *in vivo*[55].

Success with the damp complexes mentioned in Section 1.2 led to investigations into the synthesis of other Au(III) complexes that could also be stabilised by electron-donating ligands. Fregona *et al*[55,56] synthesised a group of square planar Au(III) complexes containing the dithiocarbamate ligand, one of which was complex [Au(dmdt)$X_2$] (dmdt = N,N-dimethyldithiocarbamate and X = $Cl^-$, $Br^-$) **88**. Dithiocarbamate, a negatively charged ligand, donates two sulfur atoms to form a four membered chelate ring with a metal ion. The structure of this ligand is such that it strongly donates electron density to the metal ion, resulting in stabilisation of the gold(III) centre[35], analogous to the damp ligand.

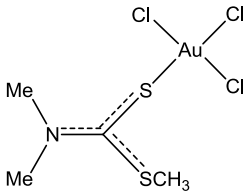
Gold(III) complexes of this type have been selected very carefully to closely reproduce the structural features of cisplatin with almost square planar geometry and at least two *cis*-gold(III) halogen bonds that undergo hydrolysis easily. The remaining coordination positions are occupied by dithiocarbamate ligands. These compounds were shown to be more cytotoxic than cisplatin as well as displaying activity against cisplatin-resistant lines, therefore suggesting a different mechanism of action to platinum drugs[55].

The gold(III) analogues **88-90** of cisplatin have been evaluated for their cytotoxic activity *in vitro* towards a panel of human tumour cell lines including cisplatin resistant and sensitive cell lines. Two particular gold(III) derivatives of *N*,*N*-dimethyldithiocarbamate **88** and ethylsarcosinedithiocarbamate **90** were shown to be 1-4 fold the toxicity of cisplatin, and were also able to overcome some intrinsic and acquired resistance to cisplatin itself. Furthermore, the

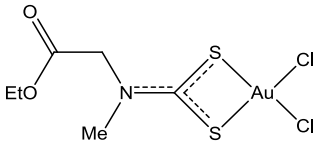
dimethyldithiocarbamate ligand itself is not shown to be toxic, therefore suggesting that it is in fact the gold(III) centre that is responsible for the biological activity observed.




**88**



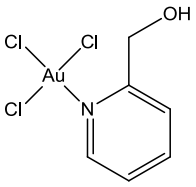

**89**



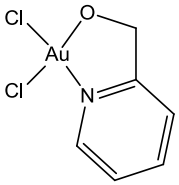

**90**

## 1.2.3 N,O Systems

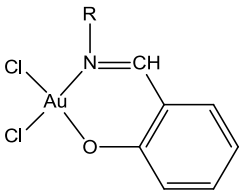
Calamai *et al*[57-59] synthesised and investigated N,O complexes **91-93**, with the selection of compounds dictated by their structural similarities to cisplatin. X-ray crystal structures of these complexes shows that the gold atom is square planar with two or more chloride ions coordinated to the metal in a *cis* arrangement.




**91**




**92**




**93**

In aqueous solution the gold(III) complexes **91-93** undergo rapid hydrolysis of the coordinated chloride ligands. The rate of hydrolysis of these compounds depends simultaneously on proton and chloride concentrations, exhibiting behaviour much like that of cisplatin with rapid loss of the first chloride ion followed by a slower loss of the second. The rate of hydrolysis is greatly accelerated under physiological conditions[58,59].

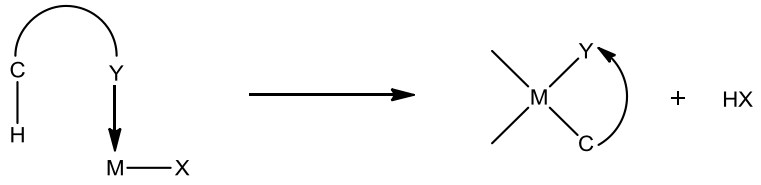
To test the theory that gold(III) undergoes reduction in the presence of protein residues with exposed sulfur groups, Calamai[57] and co-workers reacted complexes **91** and **92** with albumin and transferrin. Reaction with albumin resulted in rapid reduction of gold(III) to gold(I). In contrast when reacted with transferrin a modification of the complex occurred without reduction giving gold(I). The difference in reactivity between these two proteins can be tentatively attributed to

the presence of free cysteine (Cys) residue in the serum albumin. However within transferrin all Cys are unavailable due to disulfide bridges therefore reduction does not occur.

Anti tumour activities of compounds **91** and **92** were tested against human tumour cell lines, both sensitive and resistant to cisplatin. While results displayed only moderate cytotoxicity of the gold(III) compounds, comparable to $AuC1_4^-$, they were also shown to display low potency. When tested against cisplatin-sensitive tumour cell lines, the cytotoxicity of the gold(III) complexes was lower than cisplatin, but when tested against cisplatin-resistant tumour cell lines the gold(III) complexes demonstrated activity 2-3 times that of cisplatin[57].

## 1.3 Cyclometallation Chemistry of Gold(III)

Metallacycles, Scheme 1.1, play an important role in inorganic and organometallic compounds and are usually defined as a 'ring containing at least one metal centre'. Traditionally metallacycles refer to compounds containing two metal-carbon bonds within a ring system, but now can be referred to as those which contain a transition metal (M) with a covalent bond to a carbon atom and a coordinate bond to a heteroatom such as traditional Group 15 and 16 donors O, S, Se, N, P, As (Y). This diverse class of compounds results in a vast number of possible complexes containing metallacycles which can refer to rings of any size with multiple atoms of any element[60].




***Scheme 1.1:*** *Common cyclometallation reaction resulting in a general cyclometallated compound. Y is any atom or bond capable of forming a coordinate bond; M is a transition metal and X is an appropriate leaving group.*

In 1963, Kleiman and Dubeck[61] reported the first cyclometallated transition metal compound, synthesised by the reaction of dicyclopentadienylnickel and

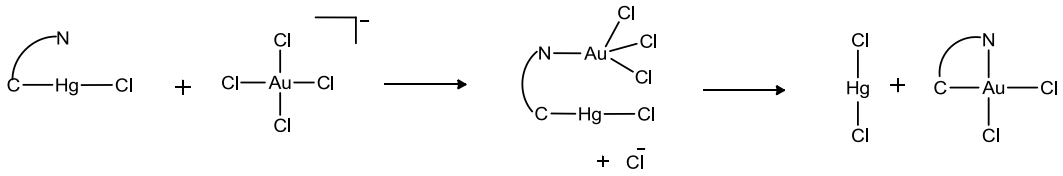
azobenzene both in the absence and presence of a solvent. Since then, vast numbers of cyclometallated compounds have been reported in the literature with applications as catalysis[62] and in organic synthesis[63], biology[64] and materials science[65].

The following discussion focuses on the history of gold(III) cyclometallated compounds with emphasis on those used in this research. There are two main routes to cyclometallated gold(III) compounds, namely transmetallation from a corresponding organomercury derivative or direct reaction with a gold(III) source. A large number of reviews have been published in the area of general cyclometallation[66,67] and in particular gold compounds[68,69].

### 1.3.1 Cyclometallation from Organomercury Reagents

The formation of organogold compounds is often difficult to achieve by direct cycloauration, instead the more conventional method adopted is a transmetallation reaction using an appropriate mercury(II) precursor. This process is generally required when synthesising monoorganogold(III) derivatives with five-membered chelate rings, and is most commonly done with potential chelate ligands such as azobenzene or damp.

Transmetallation reactions using normal solvents such as acetone or acetonitrile have been shown to be fairly efficient but at times require finely balanced equilibria. The addition of $Me_4NCl$, or increasing the polarity of the solvent, is also shown to help induce the precipitation of $(Me_4N)_2[Hg_2Cl_6]$ and drive the reaction towards the cyclometallated gold compound. Though the exact mechanism of this transmetallation is unknown, it has been postulated that these reactions proceed *via* a bridged intermediate as shown in Scheme 1.2[68].




***Scheme 1.2:*** *General transmetallation scheme for the formation of Au(III) cyclometallated compounds*[68].

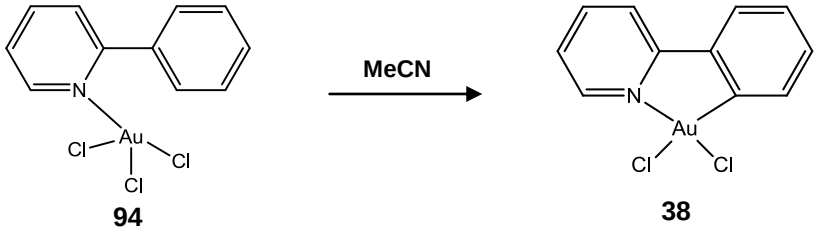
In 1984 Vicente *et al*[70] established a new method for preparing the dampAuCl$_2$ complex **33**. Here the reaction of the damp mercury derivative, dampHgCl, with [AuCl$_3$(tht)] (tht = tetrahydrothiophene) and Me$_4$NCl in acetone gives a solution of the desired product, dampAuCl$_2$. This complex was also shown to be prepared by the reaction of [Me$_4$N][AuCl$_4$] with [Hg(2-C$_6$H$_4$CH$_2$NMe$_2$)C1] or [Hg(2-C$_6$H$_4$CH$_2$NMe$_2$)$_2$] in either a 1:1 or 1:2 mole ratio. Shortly after, Bonnardel *et al*[71] became interested in the route of synthesis of aryl-gold(III) compounds using the latter transmetallation method to synthesise a wide range of new gold(III) C,N chelates.

Parish *et al*[72] later demonstrated that even when metallacyclic complexes of gold(III) could be synthesised through direct reaction, transmetallation reactions were still observed to be much quicker and resulted yields 2-4 times that of direct cycloauration.

## 1.3.2 Direct Cyclometallation

Cycloauration is believed to proceed through nitrogen assisted activation of a C-H bond using gold(III) sources such as NaAuCl$_4$, HAuCl$_4$ and AuCl$_3$.2H$_2$O. However this is difficult to achieve.

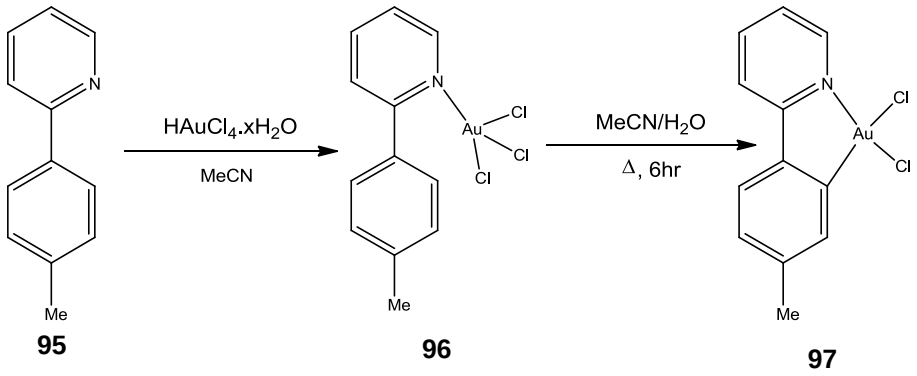
In 1931 Kharasch and Isbell[73] synthesised complexes phenylAuCl$_2$, tolylAuCl$_2$, diphenylAuCl$_2$ and methylsalicylateAuCl$_2$. These were the first reported examples of arylgold(III) derivatives, formed by direct reaction of gold chloride with benzene, toluene and methyl salicylate in petroleum ether. In contrast when benzenes with potentially coordinating substituents were reacted with auric chloride species such as **94** were produced. It was later found by Constable and Leese[39] that warming **94** in acetonitrile resulted in ortho-metallation to give **38**. The complex obtained through Scheme 1.3 results in an identical compound to that obtained by transmetallation reactions. Due to the successful synthesis of these complexes through direct metallation, many five and six membered cycloaurated gold(III) complexes have since been reported.




***Scheme 1.3:*** *Reaction scheme for the ortho-metallation of Au(III) trichloride adducts, as shown by Constable and Leese[39].*

## 1.3.3 Five Membered Ring Systems

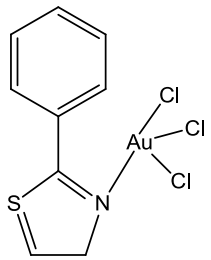
Cyclometallation commonly, but not exclusively, results in the formation of five membered rings. Smaller rings are shown to result in strain and are consequently less stable[74], therefore five membered auracycles are most generally formed *via* transmetallation using the appropriate mercury precursor, though examples of direct synthesis are also known. Henderson *et al*[75] reported the synthesis of the 2-(*p*-tolyl)pyridine derivative **97** as shown in Scheme 1.4. This compound shows advantages over the classic phenylpyridine metallacycle **38** as the methyl group allows for quick identification through NMR analysis and easy distinction between the phenyl and pyridyl rings in X-ray crystallographic studies.



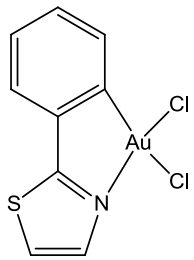

***Scheme 1.4:*** *Reaction scheme of the formation of 2-tolylpyridineAuCl$_3$ (73% yield) and 2-tolylpyridineAuCl$_2$ (38% yield) as shown by Henderson et al[75].*

Later Fuchita *et al*[76] succeeded in the cycloauration of 1-ethyl-2-phenylimidazole (Hphtz), a ligand other than the well known pyridine derivatives. Here, when

Hphtz is reacted with $H[AuCl_4]\cdot 4H_2O$ in ethanol the reaction results in the $[H(Hphtz)][AuCl_4]$ salt only, whereas when reacted with $Na[AuCl_4]\cdot 2H_2O$ or $AuCl_3\cdot 4H_2O$ in aqueous acetonitrile the reaction affords the $[AuCl_3(Hphtz–N)]$ adduct **98**. Upon heating **98** in 1,2-dichloroethane in the presence $AgBF_4$ the cycloaurated complex **99** is obtained.




**98**

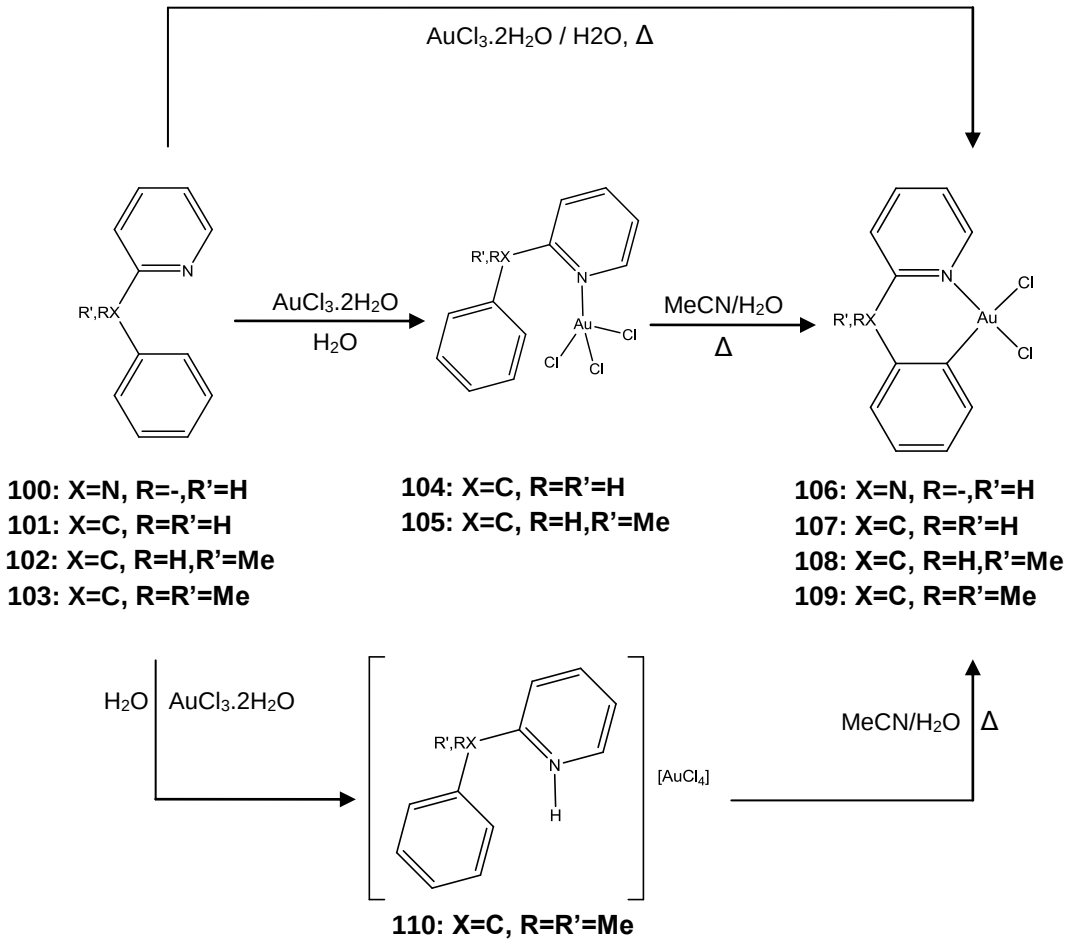



**99**

## 1.3.4 Six Membered Ring Systems

Although entropy is less favourable, the direct synthesis of six-membered metallacycles has been shown to proceed more readily than that of five-membered systems. Nitrogen-containing ligand precursors such as 2-benzylpyridines HL [$NC_5H_4$-($CH_2Ph$)-2, -(CHMePh)-2 and ($CMe_2Ph$)-2] often lead to the formation of a coordination products of the type $AuCl_3(L)$ as shown further detail by Scheme 1.5. When C-H bond activation is not spontaneous, refluxing the analogous coordination complex $AuCl_3(L)$ in a polar solvent can induce cycloauration[77,78].

When complexes **101**-**103** were directly reacted with $AuCl_3.2H_2O$ in refluxing water products **107**-**109** were isolated in high yields. However when the same complexes were reacted at room temperature adducts **104** and **105** or salt **110** were formed. Nevertheless by warming these complexes in aqueous acetonitrile the metallacycles **106**-**109** can be formed, as depicted in Scheme 1.5.

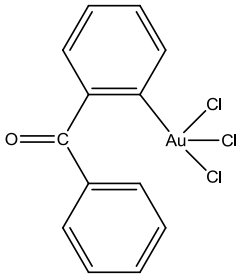



***Scheme 1.5:*** *Reactions of 2-substituted pyridine derivatives.*

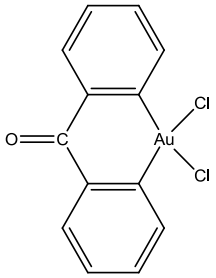
On the other hand complex **106** is formed *via* the direct reaction of 2-Anilinopyridine (HAnp) **100** with $Na[AuCl_4]$, in replacement of $AuCl_3.2H_2O$, in refluxing water as shown by Scheme 1.5. Here the reaction proceeds through direct activation of an *ortho* C-H bond of the phenyl moiety leaving a deprotonated anionic ligand, which then coordinates to the gold(III) centre through the pyridine-N and phenyl *ortho*-C atoms to form a 6-membered chelate ring[79]. A year later Fuchita *et al*[80] synthesised the same complex **106** by the reaction of 2-anilinopyridine with $H[AuCl_4]\cdot 4H_2O$ or $Na[AuCl_4]\cdot 2H_2O$ stirred in ethanol at room temperature, resulting in a slightly higher yield.

When $[AuCl_3(Hpcp)]$ (Hpcp = 2-benzoylpyridine) **111** is refluxed in aqueous acetonitrile no reaction takes place. However when the same complex **111** is

reacted with $AgO_2CCF_3$ in propionitrile complex **112** is formed, albeit in low yields. The analogous synthesis of similar six-membered auracycles 2-phenoxy- and 2-(phenylsulfanyl)-pyridine has also been observed to occur *via* the conversion of the trichloride intermediate[76].




**111**




**112**

## 1.4 Conclusion

Synthetic methods above show that a vast range of Au(III) dichloride materials are able to be synthesised with relative ease. As these complexes contain labile chloride ligands, closely resembling that of cisplatin, they are suitable precursors for development and further study. The aim of this thesis has been directed towards replacing the chloride ligands with soluble bidentate chelating ligands to produce interesting new cycloaurated gold(III) complexes that may demonstrate increased solubility and exciting biological activity.

# Chapter Two

## *Synthesis and Characterisation of Gold(III) Complexes with O,O Chelating Ligands*

## 2.1 Introduction

Gold, one of the most noble of all metals, shows a low affinity for binding to oxygen. Despite this fact, a number of Au-O compounds have been synthesised with gold in oxidation states ranging from -I to +III[81]. The mismatch of the hard, basic oxygen ligand with the soft gold centre results in compounds with relatively weak Au-O linkages[82] which are consequentially rather thermally unstable. This characteristic of weak bonds also results in high reactivity, hence suggesting Au-O bonds may display interesting reaction chemistry. Gold(I) complexes with the general formula L-Au-X, where L is a soft ligand and X is a hard anionic ligand derived from an oxo- or a carboxylic acid, play roles as catalytically active species[83], catalytic precursors[84], 'auration' reactions and can be used for gold deposition processes[85].

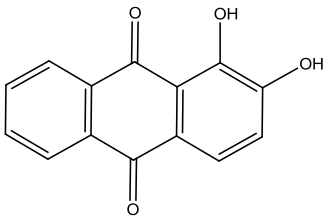
The purpose of this chapter was to investigate Au(III) O-donor complexes using ligands such as maltol, alizarin and 3,4-dihydroxybenzaldehyde as candidate O,O chelate ligands of auracycles.

Alizarin, 1,2-dihydroxyanthraquinone **113**, a dye molecule extracted from 'madder' *Rubia tinctorum* was used in Moroccan traditional pharmacology for its healing effects on weakness. This complex belongs to the dihydroxyanthraquinone family comprising of compounds known to exhibit biological and pharmaceutical

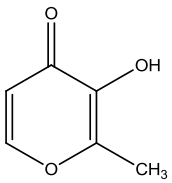
properties. Quinizarin, an analogue of alizarin, is a component of several anthracycline (derived from Streptomyces bacterium) anti-tumour antibiotics[86]. Nowadays, alizarin can be easily synthesised from anthraquinone[87] an aromatic organic compound.

Alizarin can act as a mordant dye for cotton, wool and silk. This occurs through fixation of the molecule to the metal ions in the textile fabric. This ability of alizarin to complex with metal ions has many applications. These include the analysis of soils, plants, natural and waste water, synthesis of ion-exchange resin matrix[87-90], catalytic properties[91], analysis of human blood serum by spectrometric determination of calcium and magnesium, chemical modification of electrodes for voltametric determination of metal cations[92] and the ability to act as a metal indicator due to the sharp colour change during alizarin-metal complexation[93].

In 1567, the aptitude of alizarin as a biological stain was first noted. This was discovered when alizarin was added to animal feed resulting in the red staining of their teeth and bones. Today this chemical is commonly used in medical studies involving calcium as alizarin complexes with free (ionic) calcium resulting in precipitation, allowing tissue containing calcium to stain red immediately on immersion in alizarin. Therefore alizarin is found to be useful in studies involving bone growth, osteoporosis, bone marrow, calcium deposits, cellular signalling, gene expression and many more medical investigations that involve calcium functions[86].




**113**

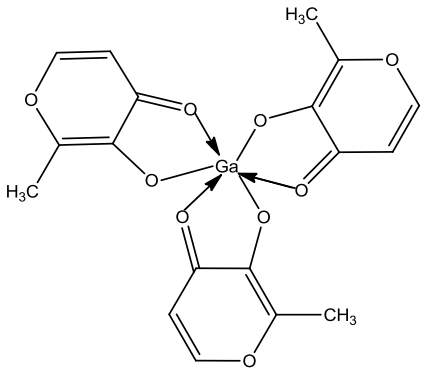



**114**

Maltol **114** is a naturally occurring organic compound found in the bark and pine needles of the larch tree. This flavonoid is primarily used as a flavour enhancer in food such as coffee, chicory, soybeans, baked cereals, bread crusts and other products[94]. Maltol is perceived as a desirable ligand as it is naturally occurring and

soluble in hot water, chloroform and other polar solvents. Like related hydroxyl-4-pyrones maltol binds to hard metal centres such as $Fe^{3+}$, $Ga^{3+}$, $Al^{3+}$, and $VO^{2+}$. In 2000, Bernstein *et al*[95] and Reffit *et al*[96] reported the ability of maltol to enhance the oral bioavailability of gallium and iron, with Kaneko *et al*[97] a few years later, demonstrating increased aluminium uptake due to maltol.

Galliummaltolate, (tris(3-hydroxy-2-methyl-4H-pyran-4-onato))gallium(III) **115**, is a coordination complex consisting of a trivalent gallium cation coordinated to three maltolate ligands. The design of this compound was based on a ferric maltol complex, a known compound with the ability to provide iron in a biologically available form. This gallium maltolate complex has undergone clinical and preclinical testing as a potential therapeutic agent for cancer, infectious disease, inflammatory disease and appears to have low toxicity when administered orally[98]. The attractive features and proven applicability of maltol with similar metal centres indicate that this complex could act as a chelate ligand of cycloaurated gold(III) compounds.




**115**

A wide range of platinum(II) [and platinum(IV)] complexes (shown in Figure 2.1) with oxygen donor ligands such as oxalate and malonate have been synthesised and screened for activity since the serendipitous discovery of cisplatin **19**. Most of these complexes demonstrated moderate to poor anticancer activity with exception of [Pt(en)ox] (**c**, Figure 2.1) which displays high toxicity, appearing to act on the neuromuscular system and resulting in death within a few hours. Complexes **20** carboplatin[23] and **21** oxaliplatin[24], as discussed in Section 1.1.3, show good anti-tumour activity and have since entered clinical use[99].

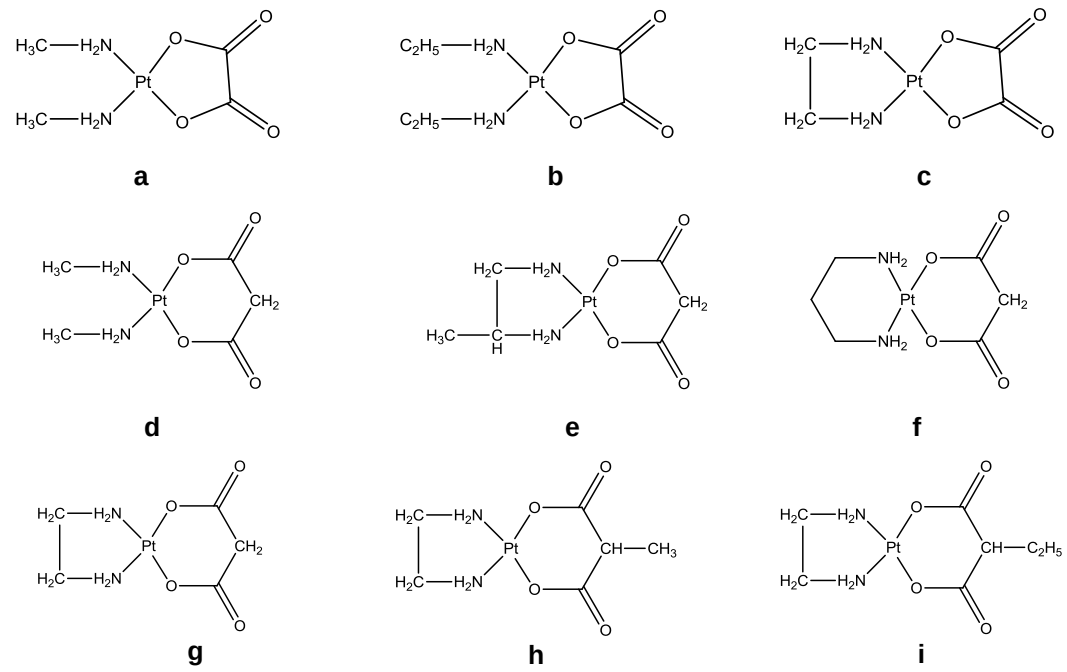
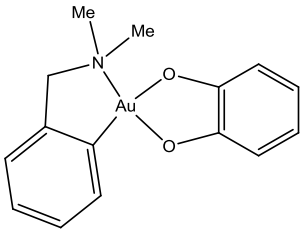
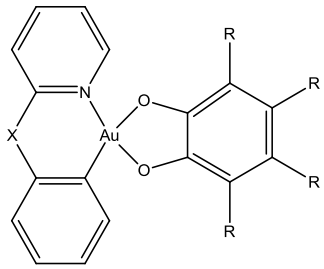



***Figure 2.1:*** *Various amine complexes (**a**-**i**) containing oxalate and malonate ligands [PtA,X] or [PtAX].*

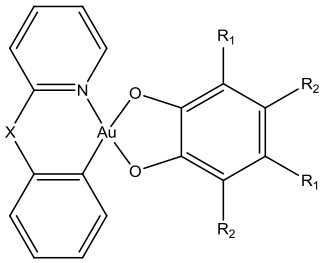
Oxygen donor ligands are widely employed in platinum anticancer agents. It was suggested, that because the gold(III) centre is labile in comparison to the platinum(II), the use of the less labile oxygen ligands may maintain the activity of the gold system. Until Goss *et al*[26] created complexes **116-124**, little had been reported on aryloxo gold(III) compounds, especially in the area of catecholate complexes. The compounds **116-124** are therefore the first examples of well characterised gold(III) catecholate complexes. They are formed by cyclometallated gold(III) complexes reacted with catechol, tetrachlorocatechol and cyclic α,β-diketone resulting in stable complexes with Au-O-C-C-O five-membered rings.




**116**




**117: X=NH, R=H**
**118: X=$CH_2$, R=H**
**119: X=NH, R=Cl**
**120: X=$CH_2$, R=Cl**

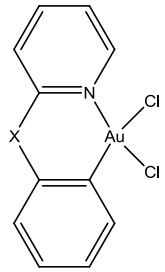



**121: X=NH, $R_1$=tBu, $R_2$=H**
**122: X=$CH_2$, $R_1$=tBu, $R_2$=H**
**123: X=NH, $R_1$=H, $R_2$=tBu**
**124: X=$CH_2$, $R_1$=H, $R_2$=tBu**

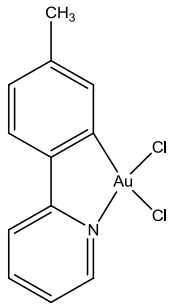
Anti-tumour activity of these compounds was tested against murine P388 leukaemia cells. High anti-tumour activity was observed by the catecholate complexes **116**, **118** and the di-*tert*-butylcatecholate mixture **121-124**. The other derivatives tested showed only moderate activity. These highly promising results imply that a more in-depth study into this general class of complexes and their biological activity could identify other complexes with further improved biological activities[26].

## 2.2 Results and Discussion

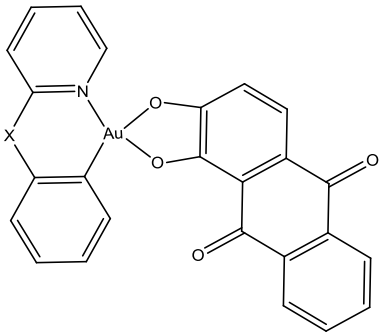
The reactions of complexes AnilinopyridylAu$Cl_2$[80] (Anp Au$Cl_2$) **125**, BenzylpyridylAu$Cl_2$[77] (Bp Au$Cl_2$) **126** and TolypyridylAu$Cl_2$[75] (Typ Au$Cl_2$) **127** with catechol, alizarin and 3,4-dihydroxybenzaldehyde in refluxing methanol, in the presence of excess trimethylamine base gave products **117**, **118** and **128-132** in reasonable yield as deep maroon red to orange solids. All new complexes synthesised in this chapter comprise of more than one isomer, as also observed in catecholate complexes synthesised by Goss *et al*[26]. Compounds **117**[26] and **118**[26] are known compounds. All products, with the exception of **132**, were characterised by ES-MS, NMR, IR, melting point and elemental analysis**.** Compounds **128-130** were sparingly soluble in DMSO, and no other NMR solvent, allowing for only proton NMR analysis. To obtain $^{13}C$ spectra solid state NMR spectroscopy was required. Complexes **128-131** were all obtained as neutral complexes while **132**, a cationic species, was isolated as its chloride salt.



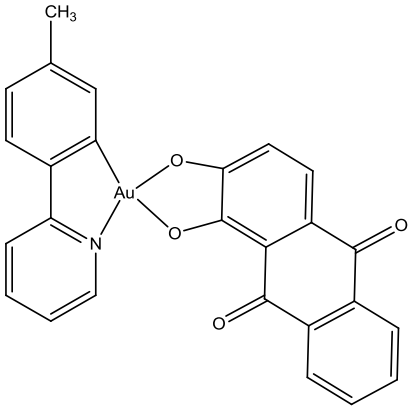

**125: X=NH**
**126: X=$CH_2$**



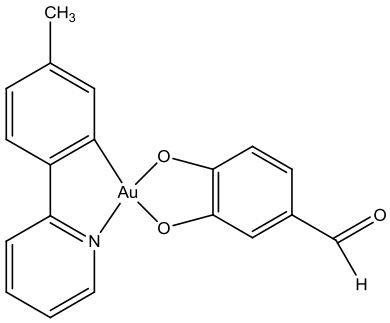

**127**



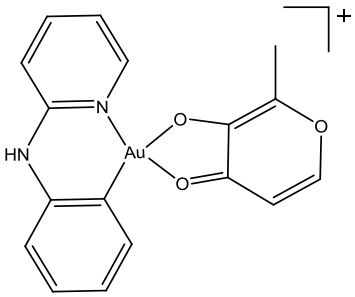

**128: X=NH**
**129: X=$CH_2$**




**130**




**131**




**132**

Compound **128** produced satisfactory micro-elemental results within 1% of theoretical values. All complexes were dried under vacuum prior to analysis; however **129-131** produced microanalytical data with carbon compositions lower than expected. The differences in composition appear to be due to organic solvents, with $^{1}H$ NMR spectra showing a signal corresponding to methanol. Addition of methanol to theoretical calculations of these complexes results in compositions that agree with the experimental data within accepted error limits.

NMR analysis of complex **132** showed low purity therefore elemental analysis data was not collected. Satisfactory crystals of these complexes were not able to be obtained.

***Characterisation of [TypAuO$_2$(C$_6$H$_3$)CHO], 131***

Two structural isomers of **131** were considered, corresponding to the aldehyde functional group bonded at either the C15 (Isomer A, Scheme 2.3) or C16 (Isomer B, Scheme 2.3) position of the catechol ring, respectively. As there is free rotation about the C-C bond of the aldehyde group, two conformers for each structural isomer were also considered (A1, A2, B1, B2) where the aldehyde group is co-planar to the catechol ring. Through NMR characterisation and density functional theory calculations it was determined that the major isomer of complex **131** was Isomer A, and minor Isomer B, as shown in Scheme 2.3. Further characterisation description can be found in Section 2.2.2.

## 2.2.1 Spectroscopic and Mass Spectrometric Characterisation

### 2.2.1.1 NMR Spectroscopy

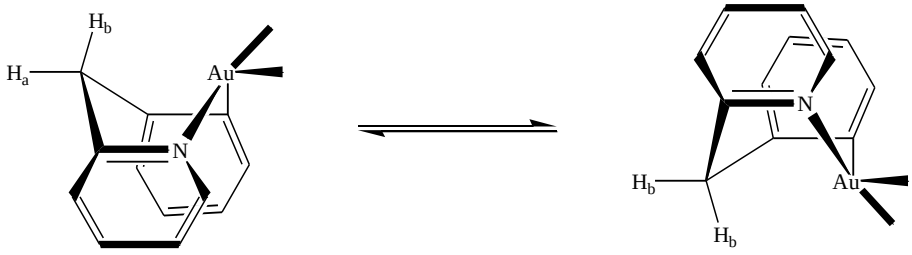
$^1$H, $^{13}$C, DEPT135, COSY and HSQC spectra were acquired in DMSO-$d_6$ solvent for compound **131**, only $^1$H and COSY spectra were acquired for compounds **128-130** which were too insoluble in common deuterated solvents ($CDCl_3$, $D_2O$ and DMSO-$d_6$) over the timescale needed to acquire satisfactory $^{13}$C spectra. Solid state NMR was therefore used to acquire $^{13}$C NMR spectra, further NMR details can be found in Appendix II.

Due to the presence of structural isomers, NMR analysis of compounds **128-131** afforded complex sets of overlapping signals in the aromatic regions of the $^1$H spectra. Some distinct signals were observed (e.g. signals in the 8-9 ppm region assignable to the aryl proton adjacent to the pyridyl N atom) but full NMR characterisation of all compounds present in the samples and distinction of isomers were not made. Integration of the aromatic region was used to ascertain that the expected numbers of signals were present and to estimate the relative contribution of solvent present. Due to the complexity of the spectra, NMR was

primarily used as an indication of sample purity, in which aside from an observed methanol solvent peak, showed a good degree of purity.

The $^{1}$H NMR spectrum of compound **128**, which included the anilinopyridyl moiety, exhibited a singlet signal at 10.93 ppm corresponding to the N-H proton. Compounds **130** and **131**, each of which possessed a tolylpyridyl moiety showed singlet signals at 2.68 ppm and 2.44 ppm respectively, corresponding to the tolyl methyl group signal of this ligand.

Benzylpyridyl gold(III) chloride, used here as a starting material, usually displays the characteristic AB doublet of doublets pattern[100], as depicted in Figure 2.2; **A**, this is due to the two bridging methylene protons being in different chemical environments. The signal observed indicates that there is no inversion (at 300K, on the NMR timescale) between the two boat conformations and therefore the protons remain in either the axial or the equatorial positions, allowing splitting of the signal and observation of $^{2}$J (HaHb) geminal coupling. Fuchita *et al*[101] have previously discussed this inversion process as depicted in Scheme 2.1.




***Scheme 2.1:*** *Inversion of the six-membered boat ring in the 2-benzylpyridine ligand.*

However, the benzylpyridyl derivative **129** shows that the doublet of doublet signals observed from $BpAuCl_2$[77], as described above, converge and produce two broad singlets which are easily visible in the $^{1}$H NMR spectrum, Figure 2.2; **B**. Here the two overlapping broad singlets are observed due to the two structural isomers of the ligand. In each isomer no resolvable coupling is observed between the methylene protons creating a line broadening effect which results in a broad

singlet. This is most likely due to a strong polarising π bond effect from the carbonyl groups in the attached ligand.

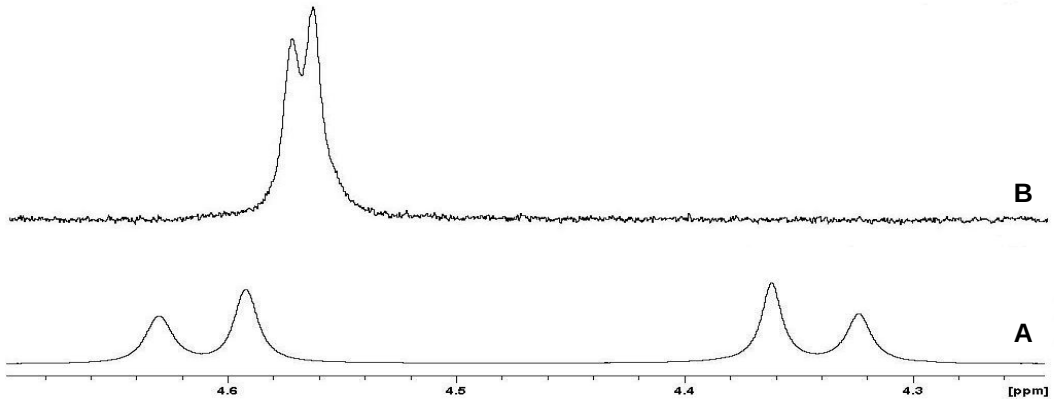



***Figure 2.2:*** *$^{1}$H NMR (400 MHz) spectra showing effect of ligand coordination to starting material $BpAuCl_2$* ***126****. Spectrum* ***A*** *demonstrates a doublet of doublet pattern observed in starting material $BpAuCl_2$* ***126****, spectrum* ***B*** *represents analogous signal observed in complex* ***129****.*

Proton NMR data for complex **126**, a starting material for the synthesis of other species, was determined in $CDCl_3$ and in DMSO-$d_6$. Comparison of this data identified significant solvent effects. In DMSO-$d_6$ the proton NMR spectrum showed four doublet and four triplet signals in the aromatic region, representing all protons on the two aromatic rings. The characteristic AB doublet of doublets pattern from the methylene group, as described above, was also observed. This NMR data corresponds to the observations reported by Cinellu *et al*[77] for complex **126**.

The aryl region of the $^{1}$H NMR spectrum of **126** in $CDCl_3$ displayed three doublets, three triplets and a multiplet that arose from the overlap of a doublet and triplet signal. The proton attached to the carbon adjacent to the nitrogen of the benzylpyridyl moiety displayed a doublet, which occurred at 9.17 ppm in the DMSO spectrum was shifted further up field to 9.36 pm in $CDCl_3$ while the triplet signal at 8.25 ppm in DMSO was further downfield in $CDCl_3$ at 8.05 ppm.

The characteristic inter ring $CH_2$ signals appeared at essentially the same position (ca 4.61, 4.06 ppm (J = 15.2 Hz) **A** and 4.61, 4.34 (J = 15.1 Hz) **B**) in both

solvents but show a larger splitting in $CDCl_3$. There is no evidence that this has been previously discussed in the literature. It is thought that these observations may arise from dipole interactions between $CDCl_3$ or $(CD_3)_2SO$ and $BpAuCl_2$. Due to the superior dispersion of signals observed in Figure 2.2, and increased solubility of complexes in DMSO–$d_6$ this was the solvent of choice. Accordingly DMSO–$d_6$ was used to determine the NMR spectra of all other compounds reported in this thesis.

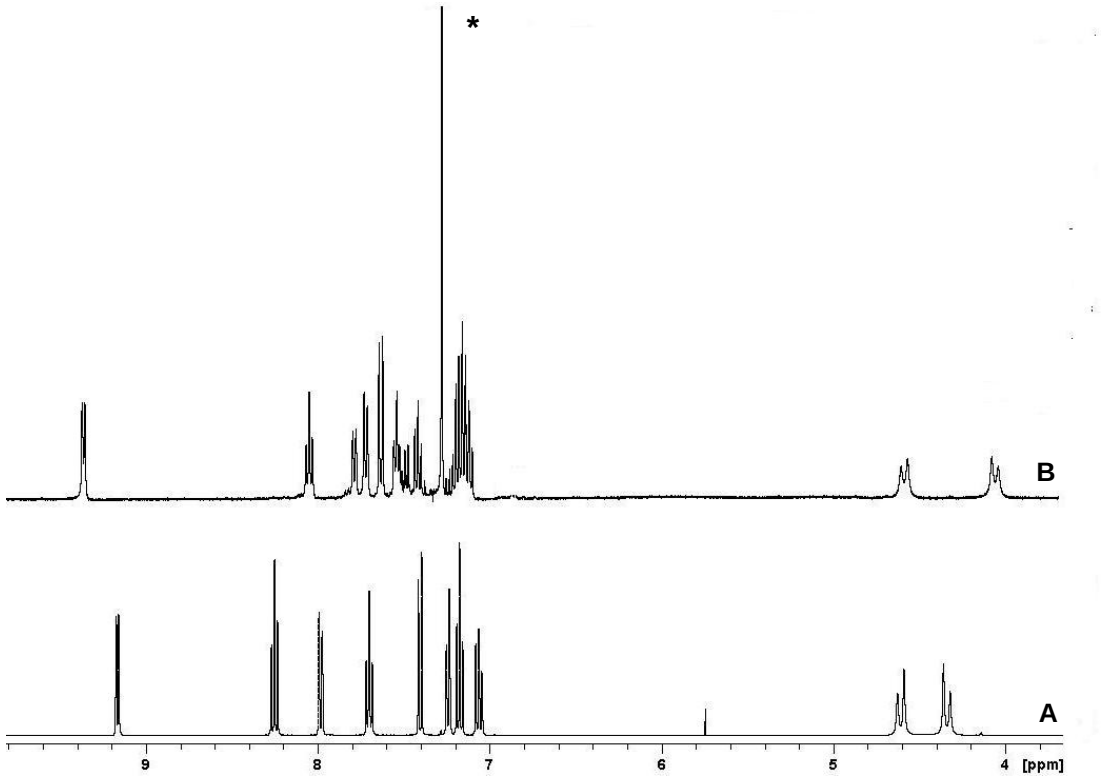



***Figure 2.3:*** *$^1$H NMR (400 MHz) spectra showing effect of different solvents used when analysing starting material $BpAuCl_2$* ***126****. Spectrum* ***A*** *demonstrates the pattern observed in DMSO, spectrum* ***B*** *in $CDCl_3$.*represents $CHCl_3$ solvent line.*

Unexpectedly the proton NMR of **128-131** also included a large singlet signal at 3.4 ppm. This signal can be assigned to the methyl group of MeOH. This suggests that even though all compounds were dried under vacuum on a Schlenk line that some solvent remained.

***NMR analysis of [AnpAu(maltolate)]Cl, 132:***

Proton NMR analysis of complex **132** displayed proton signals that would support the desired product **132**. Inspection of the $^{1}H$ NMR spectrum showed an absence of a signal corresponding with the methyl environment found on the maltol ligand. Further investigation of $^{1}H$-$^{1}H$ COSY spectrum demonstrated that the required $CH_3$ correlation was not observed suggesting that the proton signals obtained did not arise from complex **132**. Analysis of this compound on ESI-MS indicated a main cationic species at 535 m/z, later assigned as a bis-$Anp_2Au^+$ complex, as shown by Scheme 2.2, in Section 2.2.1.3. It was concluded that the observed proton signals, similar to that of what would be expected from the desired [AnpAu(maltolate)]Cl complex, were signals correlating to the reaction by-product bis-$Anp_2Au^+$. This was further confirmed on integration of proton peaks. After many trials to synthesise this complex, all of which were unsuccessful, it was decided to no longer pursue this idea.

### 2.2.1.2 IR Spectroscopy

The alizarin derivatives **128-130** show stretches in the C=O region 1642–1652 $cm^{-1}$, while the dihydroxybenzaldehyde derivative **131** showed a C=O stretch at 1660 $cm^{-1}$. These stretches are at a slightly shifted wavenumber compared to the ν(C=O) stretch in the free ligands, alizarin (1633 and 1664 $cm^{-1}$) and dihydroxybenzaldehyde (1647-1655 $cm^{-1}$), presumably due to the electron-withdrawing gold atom. The IR spectrum of the un-coordinated ligands show two clear ν(C=O) signals, with their analogous gold(III) derivatives exhibiting only one broadened signal.

Upon co-ordination of alizarin and dihydroxybenzaldehyde to the gold(III) centre, O-H stretching bands (3400-3300 $cm^{-1}$ and 3369 $cm^{-1}$ for alizarin and dihydroxybenzaldehyde ligands respectively) were partially lost indicating that the oxygen atoms were deprotonated and subsequently coordinated to the gold centre. C-O stretches observed in complexes **128-131** were predominantly unaffected by coordination to the gold centre.

### 2.2.1.3 Electrospray Mass Spectrometry (ES-MS)

All new compounds synthesised in this chapter were good candidates for ES-MS due to the presence of carbonyl groups which have the ability to attract protons or positively charged sodium ions. All samples were first dissolved with a few drops of dichloromethane and further diluted in methanol.

Alizarin derivatives **128**-**130** displayed intense peaks at *m/z* values of 627, 626 and 626 respectively. Molecular weights of these compounds are approximately 604, 603 and 603 g $mol^{-1}$ therefore these main signals were able to be assigned as their $[M+Na]^+$ ions. Complexes **129** and **130** observed no peak correlating to a $[M+H]^+$ in any of the spectra, however complex **128** and dihydroxybenzaldehyde derivative **131** displayed both a $[M+H]^+$ and $[M+Na]^+$ ion.

[AnpAu(maltolate)]Cl, **132**, displayed a peak at *m/z* 493 corresponding to the parent ion $[M]^+$ while also showing a peak at *m/z* 535, Figure 2.4. This ion is attributed to a by-product commonly observed when using compounds $AnpAuCl_2$ and $BpAuCl_2$, giving a peak at m/z 535 and 533 respectively as discussed by Dinger *et al*[42]. Scheme 2.2 illustrates the formation of the bis-cycloaurated bis-$Anp_2Au^+$ species as a reaction by-product.

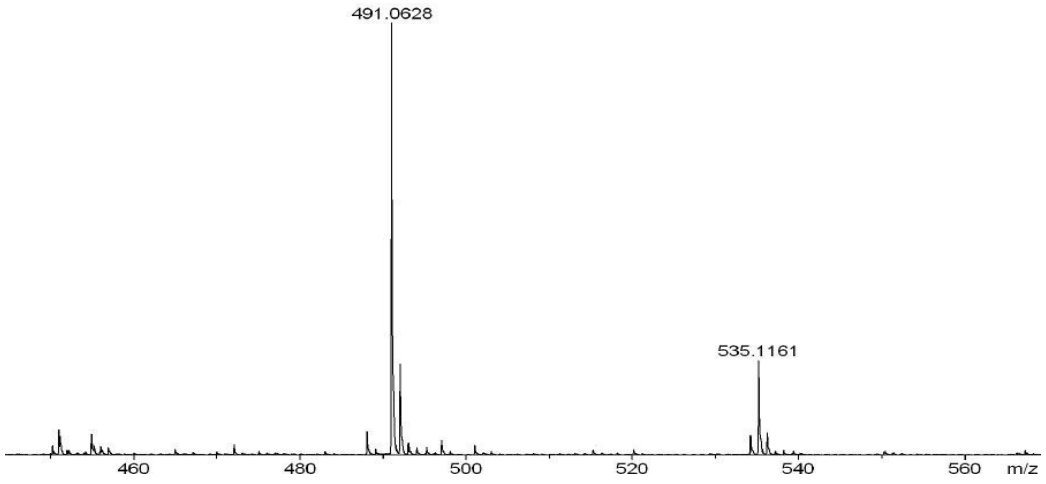
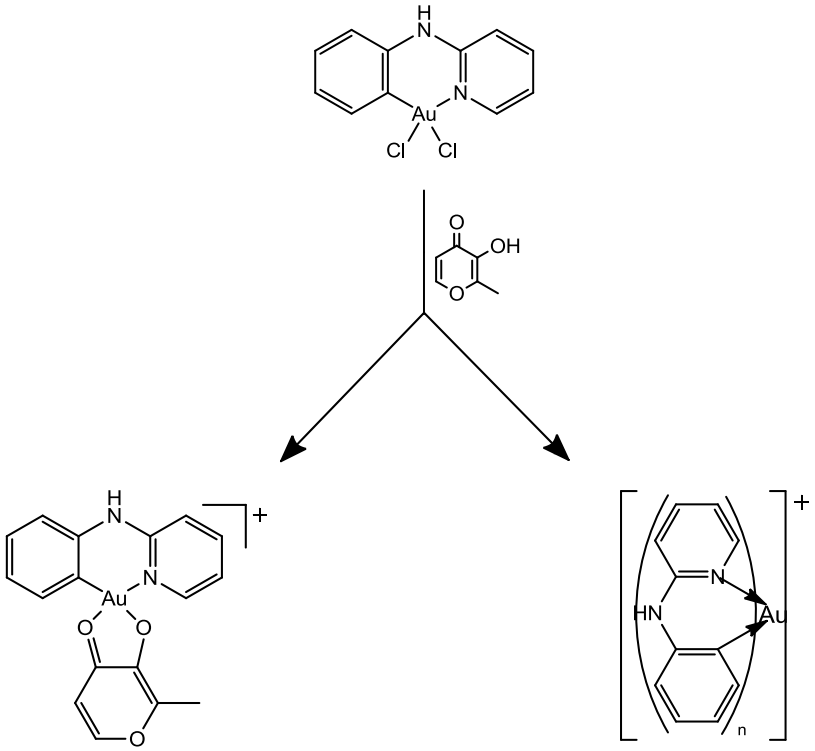



***Figure 2.4:*** *ES-MS Spectrum of $[AnpAu(maltolate)]^+$* ***132*** *in MeOH, recorded at capillary exit 80 V, showing desired $[M]^+$ signal of* ***132*** *at m/z 491 and bis-cycloaurated by-product* ***133*** *at m/z 535.*




**132** **133**

***Scheme 2.2:*** *Diagram displaying the route of synthesis to the desired complexes **132**, and bis-cycloaurated species **133**.*

## 2.2.2 Further Characterisation of complex $AnpAuO_2(C_6H_3)CHO$, (131)

### 2.2.2.1 Spectroscopic Characterisation

The proton NMR spectrum of compound **131** was consistent with the presence of two isomers of this compound in the sample solution. For example, two readily identifiable aldehydic protons, observed in a 1:3.1 ratio at 9.71 and 9.67 ppm (Figure 2.5) can be attributed to the H-19 resonances of isomer forms of compound **131**. The existence of isomeric forms of compound **131** can be rationalised by the attachment of the dihydroxybenzaldehyde ligand in two ways, as demonstrated in Scheme 2.3.

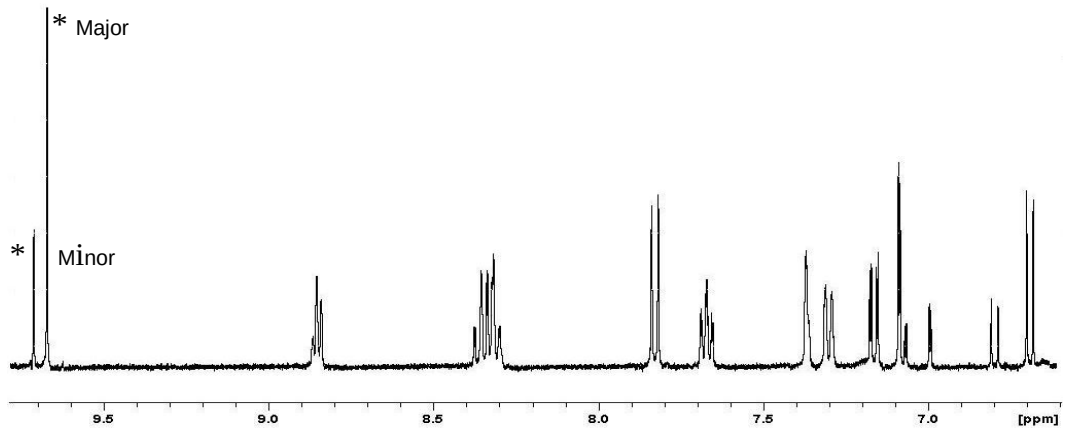
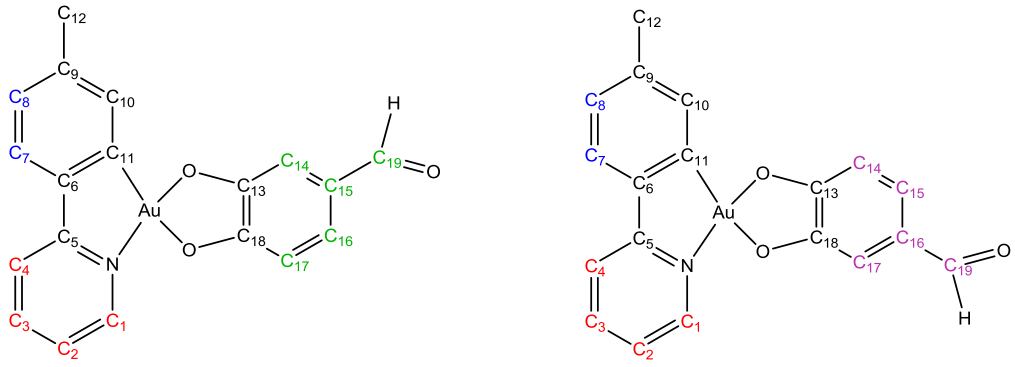



***Figure 2.5:*** *$^{1}$H NMR (400 MHz) spectrum of complex **131** aryl and aldehydic protons, including major and minor aldehydic proton signals at 9.67 and 9.71 ppm respectively.*




***Scheme 2.3:*** *Shows numbering scheme for each isomer. Isomer **A** (left), Isomer **B** (right), colour relates to Figures 2.6 and 2.7.*

The 2D-COSY and HSQC spectra were consistent with the presence of two isomers of **131** since major and minor peaks in a ca 3.1:1 ratio were observed for the majority of the COSY and HSQC correlation peaks. This observation facilitated the derivation of complete sets of signal assignments of this compound without providing insight into which isomer was predominant.

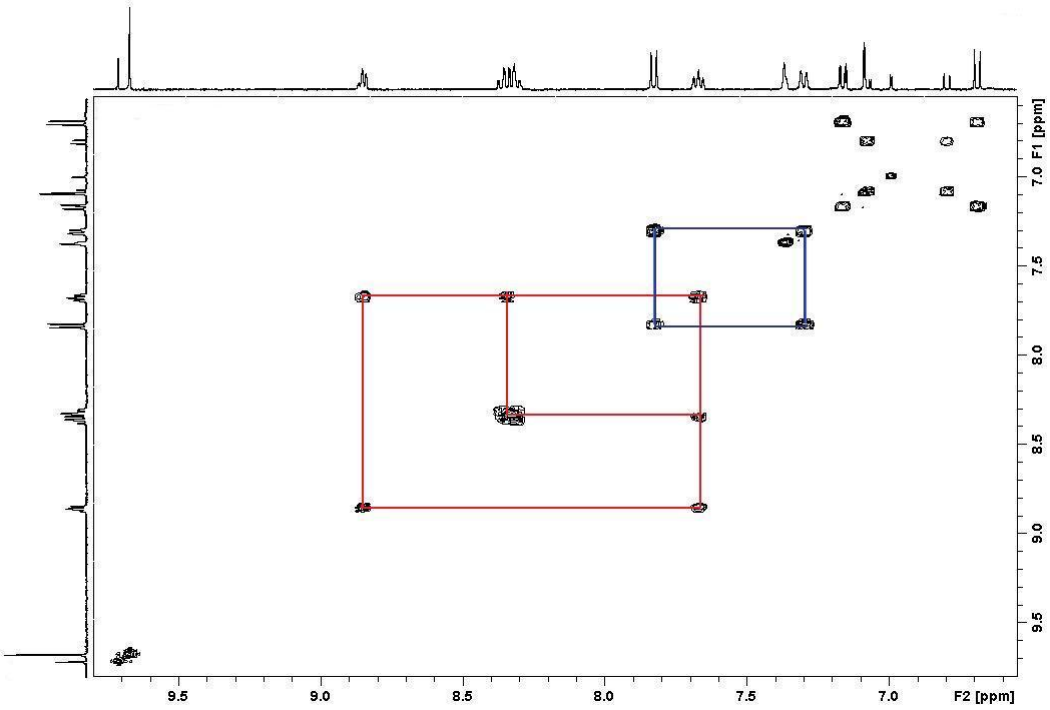



***Figure 2.6:*** *$^{1}$H COSY NMR (400 MHz) spectrum of **131** showing $^{1}$H-$^{1}$H correlations between proton environments in the aromatic region.*

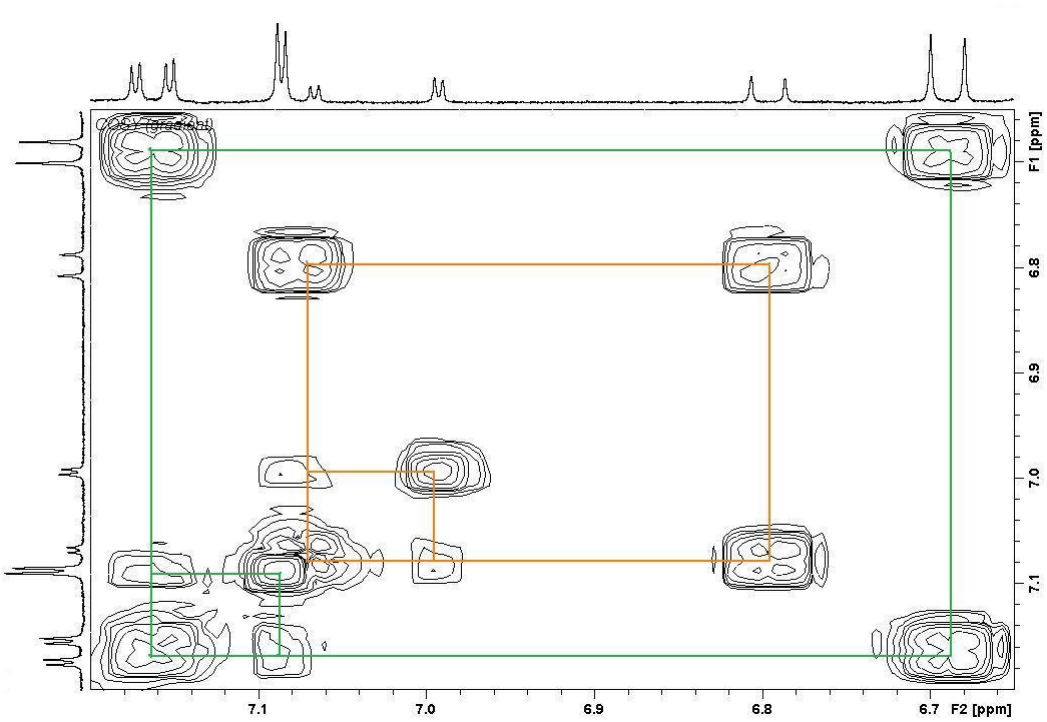



***Figure 2.7:*** *$^{1}$H COSY NMR (400 MHz) spectrum of **131** showing close up $^{1}$H-$^{1}$H correlations of the isomer pattern in the dihydroxybenzaldehyde region. Green correlations represent the dominant isomer, while orange correlations refer to the minor isomer, as referenced to Scheme 2.3.*

Upon analysis of the HSQC spectrum, correlations between proton and carbon signals from both the major and minor isomers were observed, allowing the full assignment of the protonated carbons. All quaternary carbons were identified by the comparison of DEPT135 and $^{13}C$ NMR spectra. Tables of full assignments of both isomers can be found in the experimental Section 2.4 (see Tables 2.1 and 2.2).

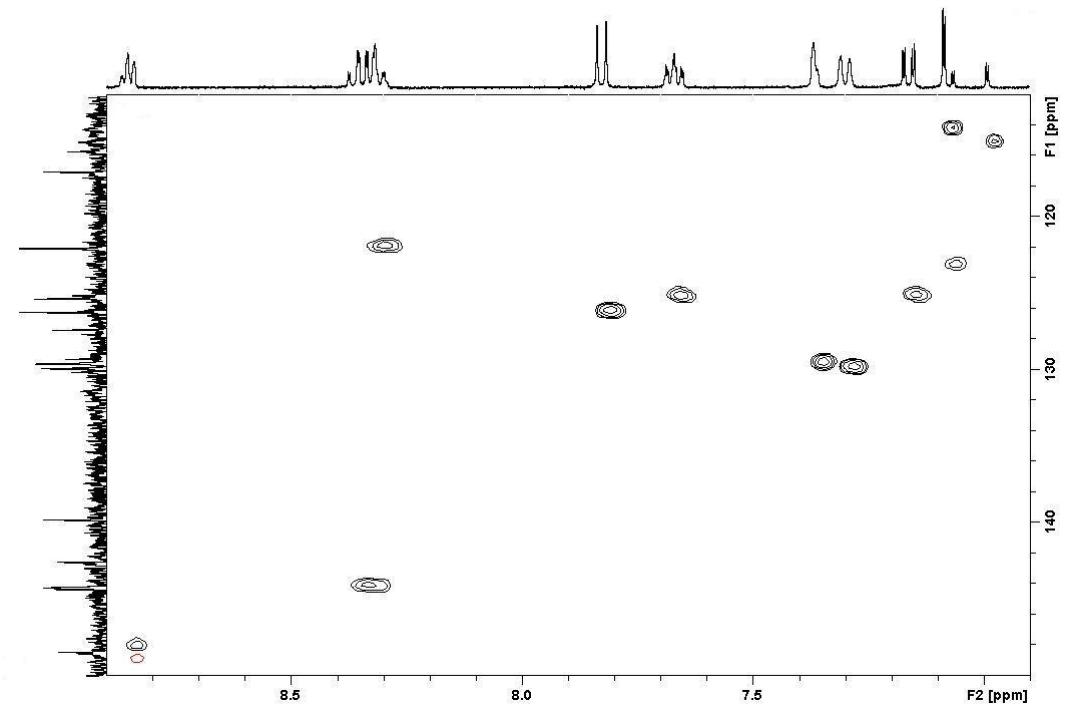



***Figure 2.8:*** *$^{1}H$-$^{13}C$ HSQC NMR (400 MHz) spectra of **131** showing $^{1}H$-$^{13}C$ correlations.*

It was hypothesised that NOESY correlations might serve to distinguish the major and minor isomers. Some weak correlations were seen in the NOESY spectrum but were insufficient to allow identification of the dominant isomer. To adequately identity the two isomers theoretical calculations were carried out to predict NMR chemical shifts.

### 2.2.2.2 Theoretical Characterisation Discussion

$^{1}H$ NMR shifts were calculated for complex **131** to distinguish between Isomers **A** and **B** (Scheme 2.3) using density functional theory (DFT). It was predicted that the aldehyde proton signal of isomer **A** occurs at 9.91 ppm and is slightly upfield of the equivalent signal of **B** at 9.95 ppm. The calculated difference between these

two signals is 0.06 ppm showing good agreement with the difference observed experimentally of 0.04 ppm. On the basis of the calculated $^{1}$H NMR spectrum, **A** is assigned as the major product and **B** as the minor product.

### 2.2.3 Discussion

The results of elemental analysis of **128-131** did not give percentages that matched the proposed complexes. This discrepancy in results is thought to be due to solvent co-crystallising with the sample. On inspection of the proton NMR a peak was observed at 3.4 ppm corresponding with the methylene shift of methanol. Further investigation found that addition of methanol to the elemental percentage calculations resulted in the experimental values showing a much closer correlation to expected values.

It was established *via* NMR analysis that all new complexes synthesised in this chapter have structural isomers. Complexes **128-130** displayed a 1:1 isomeric ratio while **131** was observed in a 3.1:1. With the exception of complex **131** and its individual isomers identified through density functional theory calculations, full characterisation of all structural isomers was beyond the scope of this thesis project.

Although alizarin is a water soluble dye, once complexed to a metal centre it appears to lose its aqueous solubility. Therefore recommendations for future work would be directed at using O,O bidentate ligands which include more soluble substituents that are not involved in the chelation to the metal centre. This would suggest that once complexed, these ligands would retain their solubility characteristics and result in new cyclometallated gold(III) complexes showing higher aqueous solubility. Investigation into biological activity of the complexes synthesised in this chapter is also recommended.

## 2.3 Conclusion

Four new gold(III) catecholate complexes (catecholate = $RC_6H_n(OH)_2$) have successfully been synthesised and characterised. These appear to be the first gold

compounds of this type to be reported. Structural characterisation using NMR suggests all compounds form structural isomers, however no crystals were obtained and therefore complete characterisation of geometry and bonding was not able to be made. Biological activities of these complexes are unknown as testing facilities were unavailable during the timeline of this project.

## 2.4 Experimental

### 2.4.1 General

All reactions were carried out with no effort made to exclude either air or light. The solvents used were drum grade. $AnpAuCl_2$ **125**[80], $BpAuCl_2$ **126**[77], $TypAuCl_2$ **127**[75] and known catecholate complexes **117** and **118** were prepared from literature methods using 2-benzylpridine, 2-anilinopyridine, 2-tolylpyridine (Aldrich), catechol and trimethylamine (BDH), synthesis details can be found in Appendix I. Likewise alizarin ($H_2az$) and dihydroxybenzaldehyde derivatives used alizarin (BDH) and 3,4-dihydroxybenzaldehyde (Aldrich) respectively without purification. I.R. spectra were recorded with a Perkin Elmer Spectrum 100, FT-IR Spectrometer. Melting points were measured (Buchi, M-560) and molecular weights were determined by ES-MS (Bruker MicroTOF) and were acquired in dichloromethane (DCM)/methanol. NMR data of soluble complexes were acquired on Bruker AVIII-400 spectrometer using DSMO as a solvent, whereas solid state was acquired on AVII-300. Further NMR details can be found in Appendix II. Elemental analysis was performed by the Chemistry Department of the University of Otago.

***Synthesis of $HAuCl_4.xH_2O$***

In the fume hood, gold nuggets were very gently stirred (magnetic stir bar) with excess aqua regia in a conical flask, covered with a watch glass, and heated to a very gentle boil until the gold was dissolved. The solution was boiled down to 10-15 mL, and fresh concentrated hydrochloric acid (HCl, 50 mL) was then added. This was boiled down to 10-15 mL again, with the addition of HCl (50 mL) and boiling down repeated another two times. After the final addition of HCl the solution was then boiled down gently to approximately 10 mL and cooled. The

golden yellow crystalline product was stored in a tightly stoppered glass vial sealed with parafilm.

***Synthesis of AnpAu(az), 128:***

The procedure was similar to that for complex **117**. $AnpAuCl_2$ (24.6 mg; 0.056 mmol) and alizarin (24.3 mg; 0.101 mmol, excess) were stirred in refluxing methanol (30 mL) giving an orange solution. Trimethylamine (2 mL, excess) was added and the resulting deep purple/maroon solution was further refluxed for 20 min. This was left until cool, filtered, and the product washed with cold MeOH (2 × 10 mL) and dried under vacuum to give 31.2 mg (92%) of purple/maroon solid.

| | |
|---|---|
| Melting Point: | 210-212 ºC (decomposed) |
| IR: | υ(C-O, br) = 1370 $cm^{-1}$, υ(C=O) = 1642 $cm^{-1}$; υ(N-H) = 3300 $cm^{-1}$ |
| Microanalysis: | Found: C= 48.6%, H =2.5%, N= 4.4%<br>$C_{25}H_{15}AuN_2O_4$.MeOH requires: C= 49.1%, H= 3.0%, N= 4.4% |
| ES-MS: | Capillary exit 100 V: *m/z* 627 (100%, $[M+Na]^+$), 353 (100%, unidentified) |
| NMR: | $^1$H: δ, 6.76 (d, 0.6H, *J=7.9 Hz*), 6.86 (d, 0.4H, *J=7.9 Hz*), 7.04 (m, 1H), 7.14 (m, 2H), 7.35 (m, 2H), 7.46 (d, 0.4H, *J=8.2 Hz*), 7.57 (d, 0.6H, *J=8.2 Hz*), 7.80 (m, 2H), 7.96 (m, 1.4H), 8.14 (m, 2H), 8.55 (d, 0.6H, *J= 7.5 Hz*), 9.03 (d, 0.6H, *J=6.8 Hz*), 9.43 (d, 0.4H, *J=6.3 Hz*), 10.93 (br s, NH)<br>$^{13}$C: δ, 182.1, 178.2 (s, C=O)<br>* $^1$H and $^{13}$C NMR shifts represent both isomers in mixture |

***Synthesis of BpAu(az), 129:***

The procedure was similar to that for complex **118**. $BpAuCl_2$ (19.2 mg; 0.044 mmol) and alizarin (26.5 mg; 0.110 mmol, excess) were stirred in refluxing methanol (30 mL) giving an orange solution. Trimethylamine (2 mL, excess) was added and the resulting deep maroon solution was further refluxed for 20 min. Distilled water (40 mL) was added, and the mixture was left until cool, filtered,

and product was washed with cold MeOH (2 × 10 mL) and dried under vacuum to give 21.7 mg (82%) of bright dark red/maroon solid.

| | |
|---|---|
| Melting Point: | 194-195 ºC (decomposed) |
| IR: | $\upsilon$(C-O) = 1016 $cm^{-1}$; $\upsilon$(C=O) = 1649 $cm^{-1}$ |
| Microanalysis: | Found: C= 49.8%, H= 2.9%, N= 2.1% |
| | $C_{26}H_{16}AuNO_4$.2MeOH requires: C= 50.4%, H= 3.6%, N= 2.1% |
| ES-MS: | Capillary exit 100 V: *m/z* 626 (100%, $[M+Na]^+$), 353 (100%, unidentified) |
| NMR: | $^1$H: δ, 4.57 (br s, 0.5H), 4.58 (br s, 0.5H), 6.85 (d, 0.5H, *J=8.3 Hz*), 6.94 (d, 0.5H, *J=8.3 Hz*), 7.16 (t, 0.5H, *J=15.3 Hz*), 7.31 (m, 2.5H), 7.53 (t, 1H, *J=15.7 Hz*), 7.64 (d, 0.5H, *J=8.8 Hz*), 7.81 (m, 3H), 7.91 (t, 0.5H, *J=14.0 Hz*), 8.11 (m, 3H), 8.37 (m, 1H), 9.16 (d, 0.5H, *J=6.1 Hz*), 9.28 (d, 0.5H, *J=6.1 Hz*) |
| | $^{13}$C: δ, 179.4 (br s, C=O), 45.6 (s, $\underline{C}H_2$) |
| | * $^1$H and $^{13}$C NMR shifts represent both isomers in mixture |

***Synthesis of TypAu(az)$_2$ 130:***

The procedure was similar to that for complex **117**. $TypAuCl_2$ (25.0mg; 0.057mmol) and alizarin (23.0 mg; 0.096mmol, excess) were stirred in refluxing methanol (30 mL) giving an orange solution. Trimethylamine (2 mL, excess) was added and the resulting deep maroon solution was further refluxed for 20 min. This was left until cool, filtered, and the product washed with cold MeOH (2 × 10 mL) and dried under vacuum to give 24.4 mg (86%) of bright red solid.

| | |
|---|---|
| Melting Point: | 217-219 ºC (decomposed) |
| IR: | $\upsilon$(C-O) = 1014 $cm^{-1}$, $\upsilon$(C=O) = 1652 $cm^{-1}$, $\upsilon(CH_3)$ = 1370 $cm^{-1}$ |
| Microanalysis: | Found: C= 50.8%, H= 2.7%, N= 2.2% |
| | $C_{26}H_{16}AuNO_4$.MeOH requires: C= 51.0%, H= 3.2%, N= 2.2% |

ES-MS: Capillary exit 100 V: *m/z* 627 (100%, $[M+Na]^+$), 353 (100%, unidentified)

NMR: $^1H$: δ, 2.68 (br s, 3H), 5.75 (s, 1H), 6.88 (d, 0.5H, *J=8.2 Hz*), 6.98 (d, 0.5H, *J=8.2 Hz*), 7.32 (m, 1.5H), 7.52 (d, 0.5H, *J=8.2 Hz*), 7.64 (d, 0.5H, *J=8.2 Hz*), 7.70 (m, 1H), 7.84 (m, 3.5H), 8.16 (m, 2H), 8.39 (m, 2H), 8.85 (d, 0.5H, *J=5.8 Hz*), 9.00 (d, 0.5H, *J=5.8 Hz*)

$^{13}C$: δ, 179.9 (br s, 2 C=O), 21.7 (s, $CH_3$)

* $^1H$ and $^{13}C$ NMR shifts represent both isomers in mixture

***Synthesis of TypAuO$_2$(C$_6$H$_3$)CHO, 131:***

The procedure was similar to that for complex **117**. $TypAuCl_2$ (20.5 mg; 0.047 mmol) and dihydroxybenzaldehyde (10.9 mg; 0.045 mmol) were stirred in refluxing methanol (30 mL) giving a white cloudy solution. Trimethylamine (2 mL, excess) was added and the resulting golden solution was further refluxed for 20 min. This was left to sit for 7 days, after which a red/orange solid formed. This was filtered and air dried to give 9.9 mg (35%) of bright orange to red solid.

Melting Point: 198-199 ºC (decomposed)

IR: υ(C=O) = 1660 $cm^{-1}$, υ($CH_3$, bend) = 1376 $cm^{-1}$, υ(C-O) = 1040 $cm^{-1}$

Microanalysis: Found: C= 44.3%, H= 2.9%, N= 2.7% (no repeat analysis)
$C_{19}H_{14}AuNO_3$.MeOH requires: C= 45.0%, H= 3.4%, N= 2.6%

ES-MS: Capillary exit 100 V: *m/z* 502 (100%, $[M+H]^+$), 353 (100%, unidentified), 524 (100%, $[M+Na]^+$)

NMR:

***Table 2.1:*** *$^1H$ and $^{13}C$ Chemical shifts of **131** Isomer **A**, recorded at 400 MHz, at 300 K in DMSO. Chemical shifts referenced to DMSO.*

| Atom | Type | $^{13}C$ | $^1H$ | |
|---|---|---|---|---|
| 1 | CH | 148.5 | 8.83 | *~d,d, J = 6.61, 1.6* |
| 2 | CH | 125.3 | 7.67 | *~t,d, J = 6.61, 1.6* |
| 3 | CH | 144.2 | 8.35 | *m*, overlapping with H4 |
| 4 | CH | 121.9 | 8.35 | *m*, overlapping with H3 |

| Atom | Type | $^{13}C$ | $^{1}H$ | |
|---|---|---|---|---|
| 5 | C | 166.9 | | |
| 6 | C | 159.7 | | |
| 7 | CH | 126.3 | 7.82 | *d*, *J* = 7.9Hz |
| 8 | CH | 129.8 | 7.29 | *d, J=Hz* |
| 9 | C | 144.3 | | |
| 10 | CH | 129.5 | 7.37 | *br s* |
| 11 | C | 139.7 | | |
| 12 | $CH_3$ | 21.9 | 2.44 | *s* |
| 13 | C | 163.7 | | |
| 14 | CH | 114.2 | 7.08 | *d*, *J = 8.1 Hz* |
| 15 | C | 142.5 | | |
| 16 | CH | 125.2 | 7.16 | *d, J = 8.0Hz* |
| 17 | CH | 117.1 | 6.98 | |
| 18 | C | 162.6 | | |
| 19 | CHO | 190.5 | 9.67 | s |

***Table 2.2:*** *$^{1}H$ and $^{13}C$ Chemical shifts of **131** Isomer **B**, recorded at 400 MHz, at 300 K in DMSO. Chemical shifts referenced to DMSO.*

| Atom | Type | $^{13}C$ | $^{1}H$ | |
|---|---|---|---|---|
| 1 | CH | 148.5 | 8.83 | *~d,d, J = 6.61, 1.6* |
| 2 | CH | 125.3 | 7.67 | *~t,d, J = 6.61, 1.6* |
| 3 | CH | 144.2 | 8.35 | *m*, overlapping with H4 |
| 4 | CH | 121.9 | 8.35 | *m*, overlapping with H3 |
| 5 | C | 166.9 | | |
| 6 | C | 159.7 | | |
| 7 | CH | 126.3 | 7.82 | *d*, *J* = 7.9 Hz |
| 8 | CH | 129.8 | 7.29 | *d, J=Hz* |
| 9 | C | 144.3 | | |
| 10 | CH | 129.5 | 7.37 | *br s* |
| 11 | C | 139.7 | | |
| 12 | CH3 | 21.9 | 2.44 | *s* |
| 13 | C | 163.7 | | |
| 14 | CH | 115.7 | 6.79 | *d*, *J = 8.0 Hz* |
| 15 | CH | 123.1 | 7.06 | *d, J = 1.9 Hz* |
| 16 | C | 129.8 | | |
| 17 | CH | 115.0 | 6.92 | *d, J = 1.9 Hz* |
| 18 | C | 162.6 | | |
| 19 | CHO | 191.2 | 9.71 | *s* |

***Synthesis of [AnpAu(maltolate)Cl, 132:***

The procedure was similar to that for complex **117**. $AnpAuCl_2$ (50.1 mg; 0.115 mmol) and maltol (15.6 mg; 0.124 mmol) were stirred in refluxing methanol (30 mL) giving a white cloudy solution. Trimethylamine (2 mL, excess) was added and the resulting yellow solution was further refluxed for 20 min. This was left until cool, filtered, the product washed with cold MeOH (2 × 10 mL) and then

dried under vacuum to give 23.7 mg (43%) of creamy yellow solid. Attempts at purification were unsuccessful even when reflux times from 2-30 min were trialled

Alternative Synthesis:

An alternative method adapted from the method of aurathietane-3,3-dioxide using $Ag_2O$[41] was trialled. $AnpAuCl_2$ (50.0 mg; 0.115 mmol), maltol (14.5 mg; 0.115 mmol) and $Ag_2O$ (39.9 mg, 0.285 mmol) were mixed in dichloromethane (30 mL) and refluxed for 2 h. No positive results were obtained using this synthetic method.

***Complex $TypAuO_2C_6H_3CHO$, 131:***

All density functional theory calculations were completed using Gaussian 09, Revision A.01[102]. Geometry optimisations were completed using the B3LYP density functional method with the 6-31G(d) basis set for H, C, N, and O atoms and the LANL2DZ basis set and effective core potential for Au.

All geometry optimizations and subsequent NMR calculations were carried out in dimethylsulfoxide solvent using the integral equation formalism polarised continuum model (IEFPCM). A single point NMR calculation was run with the Gauge-Independent Atomic Orbital (GIAO) method using the B3LYP functional and 6-311++G(2d,2p) basis set for the H, C, N and O atoms and the LANL2DZ basis set and effective core potential for Au. Relative chemical shifts were obtained by comparison to TMS calculated with the same theoretical approach. The chemical shifts for A1/2 and for B1/2 have each been averaged to account for free rotation of the C-C bond over the time scale of the NMR experiments.

# Chapter Three

## *Synthesis, Characterisation and Biological Activity of Gold(III) Thiourea Compounds*

## 3.1 Introduction

Thioureas are versatile ligands able to coordinate to a metal centre either as neutral ligands, monoanions or as dianions. The most attractive feature of thiourea chemistry is the ease of synthesis of substituted thioureas $R^1R^2N\text{-}C(S)NHR^3$, as they are readily obtained from the amine $R^1R^2NH$ and isothiocyanate $R^3NCS$. This allows the synthesis of a diverse range of derivatives by modification of the substituents on nitrogen, hence changing their physical and chemical properties. In addition to this the hard nitrogen and soft sulfur provide a multitude of bonding possibilities[103,104].

Thioureas and thiourea complexes have wide variety of use, ranging from modification of textile and dyeing treatments[105], production and modification of synthetic resins, production of pharmaceuticals, electroplating, mercury extraction in waste water, gold and silver leaching from minerals[106] as well as demonstrating antioxidant activity in biochemistry[107].

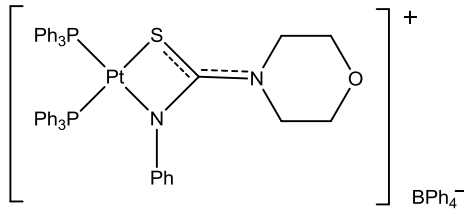
The use of thiourea $NH_2C(S)NH_2$ as an extracting agent for precious metals has received considerable interest over the years, specifically as an alternative lixiviant for gold. Laboratory testing has shown that thioureation of gold shows lower environmental impact, easier handling and greater sensitivity with faster kinetics than gold dissolution. In the late 1990's Ubaldin[106] and co-workers demonstrated, in laboratory testing, that thiourea leaching permitted 84% Au recovery after a 6 hour reaction period.

In 1979, Filipski *et al*[108] investigated the ability of thiourea complexes to reverse the cross-links that form between cisplatin and DNA, without causing any apparent breakdown of the DNA. The ability of thiourea complexes to recover intact DNA from Pt-DNA (platinum bound DNA), by acting as competing ligands, shows useful application in studies aimed at the biological effects of Pt compounds. During this study Filipski *et al* found that in isolated DNA thiourea complexes were able to reverse Pt(II)-induced DNA cross-links and lethal lesions. Thiourea analogues have since been reported to display potent HIV inhibitory[109], anti arthritic and anticancer activity[110].

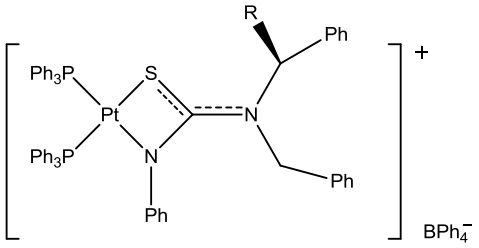
The purpose of this chapter was to investigate thiourea complexes as potential ligands toward Au(III). The expectations in undertaking these reactions was to create more stable Au(III) complexes with higher solubility in biological media, with the general aim of creating new complexes showing anticancer activity.

The literature contains a vast number of Pt complexes containing thiourea ligands, many of which have shown promising activity. Investigation into the coordination chemistry of MeNHC(S)NH(CN) with Pt(II) complexes demonstrated that the thiourea ligand was able to bond as a dianion through the S and NMe groups, as a monoanion bonding through the S, or acting as a chelating ligand through the S and N[103]. These findings increased the interest in the reactions of these thioureas with other metal halide complexes.

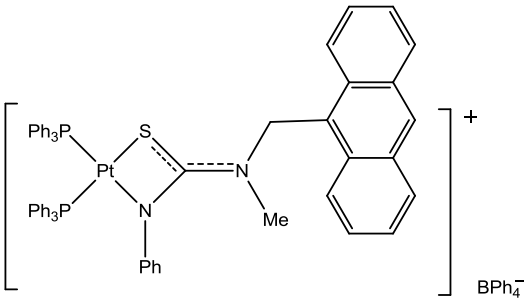
Henderson *et al*[111] reported the synthesis of Pt(II) thiourea complexes bonding through either N,S-chelating mode or in an S-bonded monodentate mode. Complexes **134-146** contain four membered Pt-N-C-S rings in contrast to trisubstituted thioureas containing benzoyl substituents which bond through S and O to give six-membered rings. These complexes were synthesised by the reaction of *cis*-$[PtCl_2(PPh_3)_2]$ with its corresponding thiourea in refluxing methanol, in the presence of trimethylamine base. The resulting solutions contained cationic platinum-thiourea monoanion **134-142**, **145**, **146** and dianion **143**, **144** complexes, isolated as $BPh_4^-$ salts.



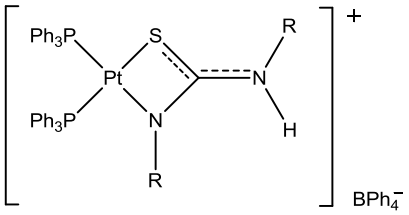
**134**



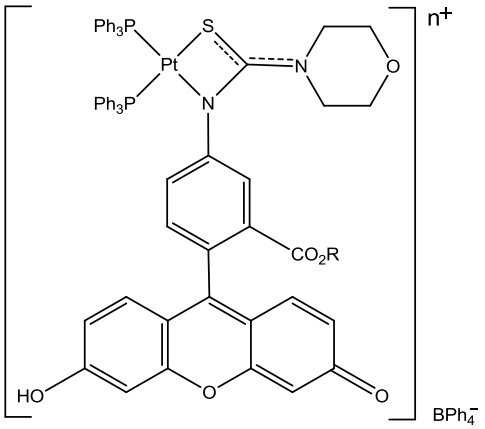
**135: R=H**
**136: R=Me**



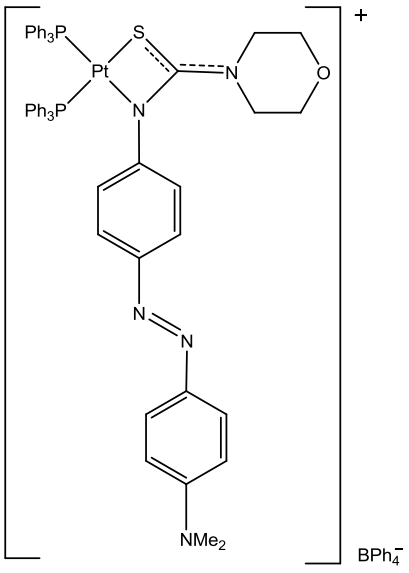
**137**



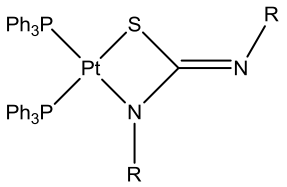
**138: R=Ph**
**139: R=Et**



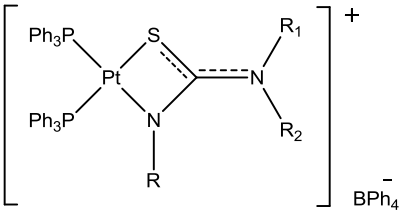
**140: R=H; n=1**
**141: R=-; n=0**



**142**




**143: R=Ph**
**144: R=Et**

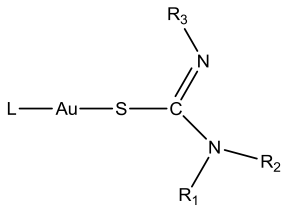



**145: $R_1$=CN; $R_2$=H**
**146: $R_1$=H; $R_2$=CN**

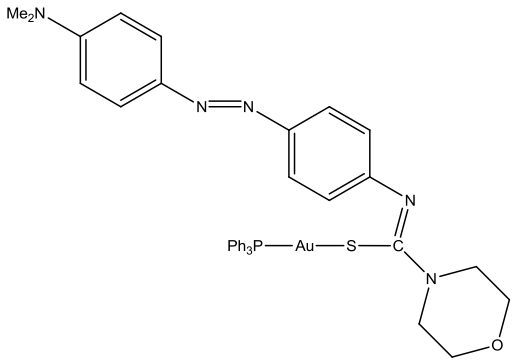
Subsequently, due to the success of the Pt(II) thiourea complexes, research into reactions of thioureas with other transition metals were investigated. Again Henderson *et al*[103] demonstrated that the air and moisture stability of these ligands allowed for successful synthesis of monoanion and dianion thiourea complexes of rhodium(III) and ruthenium(II). In 2004, Yang and co-workers demonstrated the ability of the sterically bulky N,N′-disubstituted cyclic thiourea−Pd(0) complex to act as highly active catalysts for Heck reactions of aryl iodides and bromides with olefins[112].

***Gold(I) and thioureas***

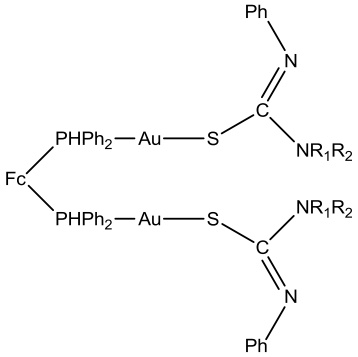
As mentioned above, as early as 1976 the potential of acidic thioureas as reagents for leaching gold was known. Owing to the recent success with thiourea ligands, Henderson *et al*[104] synthesised a series of phosphine gold(I) complexes containing monoanionic thiourea ligands. Thiourea ligands, with at least one hydrogen can exist in a tautomeric thiolate form, acting much like thiolate-type ligands. Complexes **147-160** were formed on reaction of the precursor chloro complexes $Ph_3PAuCl$, $Cy_3PAuCl$, $dppf(AuCl)_2$ or $dppe(AuCl)_2$ with thiourea ligand in methanol, in the presence of trimethylamine base.



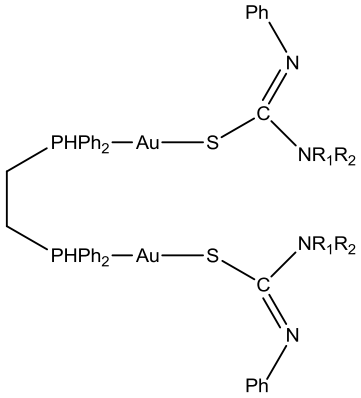

**147: L=$PPh_3$, $R_1R_2$=$(CH_2CH_2)_2O$, $R_3$=Ph**
**148: L=$PPh_3$, $R_1R_2$=$(CH_2CH_2)_2S$, $R_3$=Ph**
**149: L=$PPh_3$, $R_1R_2$=$(CH_2Ph)_2$, $R_3$=Ph**
**150: L=$PPh_3$, $R_1R_2$=$Me_2$, $R_3$=Ph**
**151: L=$PPh_3$, $R_1R_2$=$Me_2$, $R_3$=p-$C_6H_4NO_2$**
**152: L=$PPh_3$, $R_1R_2$=$(CH_2)_4$, $R_3$=Ph**
**153: L=$PPh_3$, $R_1R_2$=$(CH_2)_5$, $R_3$=Ph**
**154: L=$PPh_3$, $R_1R_2$=HMe, $R_3$=CN**
**155: L=$PCy_3$, $R_1R_2$=$Me_2$, $R_3$=Ph**
**156: L=$PCy_3$, $R_1R_2$=$(CH_2CH_2)_2O$, $R_3$=Ph**




**157**




**158: Fc=$Fe(\eta^5\text{-}C_5H_4)_2$, $R_1R_2$=$(CH_2CH_2)_2O$**




**159: $R_1R_2$=$(CH_2CH_2)_2O$, $R_3$=Ph**
**160: $R_1R_2$=HMe, $R_3$=CN**

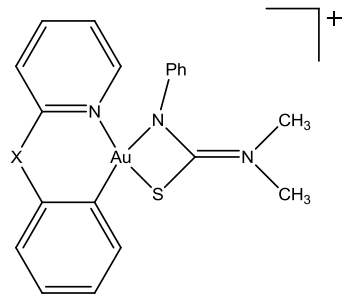
Selections of these complexes shown above were screened for activity against P388 murine leukaemia cells. Results showed moderate to low cytotoxicity of most compounds, with complexes **148**, **152** and **153** showing the greatest activity. This activity may be linked to the substituents in the $R_1$ and $R_2$ positions, with greater activity shown by complexes with small, hydrophobic alkyl groups.

While many gold(I) thiourea complexes are known, few gold(III) thiourea compounds have been investigated. This chapter details the synthesis of auracycles containing thiourea moieties. All novel compounds were subsequently

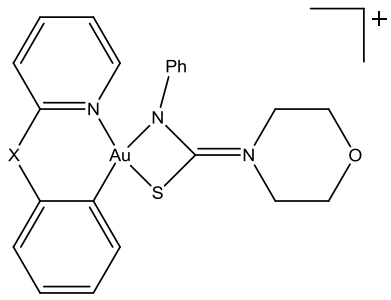
characterised and a small number of these were bio-assayed for activity against murine P388 leukaemia tumour cell lines.

## 3.2 Results and Discussion

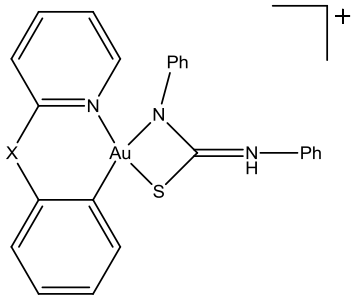
The complexes $BpAuCl_2$ and $AnpAuCl_2$ were reacted with PhNHCSNHPh, $PhNHCSNMe_2$, $PhNHCSN(C_2H_4)_2O$ and $PhNHCSNCy_2$ in hot methanol using $Me_3N$ to remove $Cl^-$ ligands with the addition of $BPh_4^-$ to give products **161-168** in reasonable yields as bright to pale yellow solids. All products were characterised by ES-MS, NMR, IR and melting point. Elemental analysis was carried out for compounds **161**, **163**, **165** and **167**. All complexes were partially soluble in common organic solvents such as DCM, acetone and DMSO.



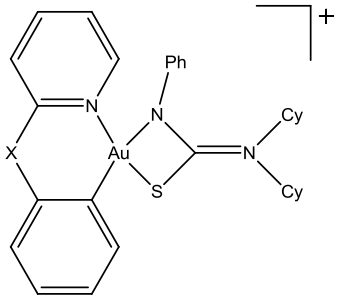

**161: X=NH**
**162: X=$CH_2$**




**163: X=NH**
**164: X=$CH_2$**




**165: X=NH**
**166: X=$CH_2$**




**167: X=NH**
**168: X=$CH_2$**

Compound **167** produced satisfactory micro-elemental results within 1% of theoretical values. All complexes were dried under vacuum prior to analysis; however **161**, **163** and **165** produced microanalytical data with carbon compositions higher than expected. The differences in composition do not appear

to be due to organic solvents, with $^{1}H$ NMR spectra void of any signal corresponding to solvents. NMR analysis of benzylpyridine derivatives showed low purity therefore elemental analysis data was not collected.

### 3.2.1 X-ray Crystal Structures of [AnpAuPhNCSNMe$_2$]BPh$_4$ (161) and [AnpAuPhNCSNCy$_2$]BPh$_4$ (167)

The X-ray crystal structure determinations of **161** and **167** were carried out in order to obtain the geometry, orientation and bonding of the thiourea ligand around the gold(III) centre. Crystal structures were solved by direct methods and routinely developed and refined. H atoms were placed in calculated positions except for the N-H which was located and refined. Views of the structures are shown in Figures 3.1-3.3 along with the atom numbering scheme. Selected bond lengths and angles are presented in Tables 3.1 and 3.2. Tables of complete final position and thermal parameters, bond lengths and angles are included in Appendix IV.

The crystal structure of **161** demonstrates a square planar gold(III) complex. Here bidentate coordination of the thiourea ligand to the gold centre forms through N-Au-S bonds giving a 4-membered Au-S-C-N ring system. The geometry around the gold atom is square-planar with the sum of the angles adding to 360.02º (within standard deviations of 360º), showing this complex to be perfectly planar. No atom deviates from the gold coordinated least square plane (defined by S1, N2, N1, Au and C1) by more than 0.04 Å. The four membered metallocyclic ring is slightly puckered, with an angle between planes Au, S1, N3 and C1, S1, N3 of 4.9º.

The anilinopyridyl moiety of **161** has a puckered conformation with a fold angle of 25.8º between planes N3, Au, S1 and N3, C1, S1. All bond distances and its conformation is comparable to the X-ray crystal structure of anilinopyridyl gold(III) chloride[79].

The thiourea ligand of **161** coordinates so that the two highest *trans* influence ligands are mutually *cis*, in this case $N_{thiourea}$ is attached in the *cis* position to the corresponding $N_{anilinopyridyl}$, with the sulfur atom having a lower *trans* influence than C21. Angles around N3 of the thiourea ligand add to 354.2º, showing high planarity. N4 lies within the plane of C1, S1, N3 with the methyl groups C41 and C51 respectively showing a slight twist of 7º in respect to the C1, S1, N3 plane.

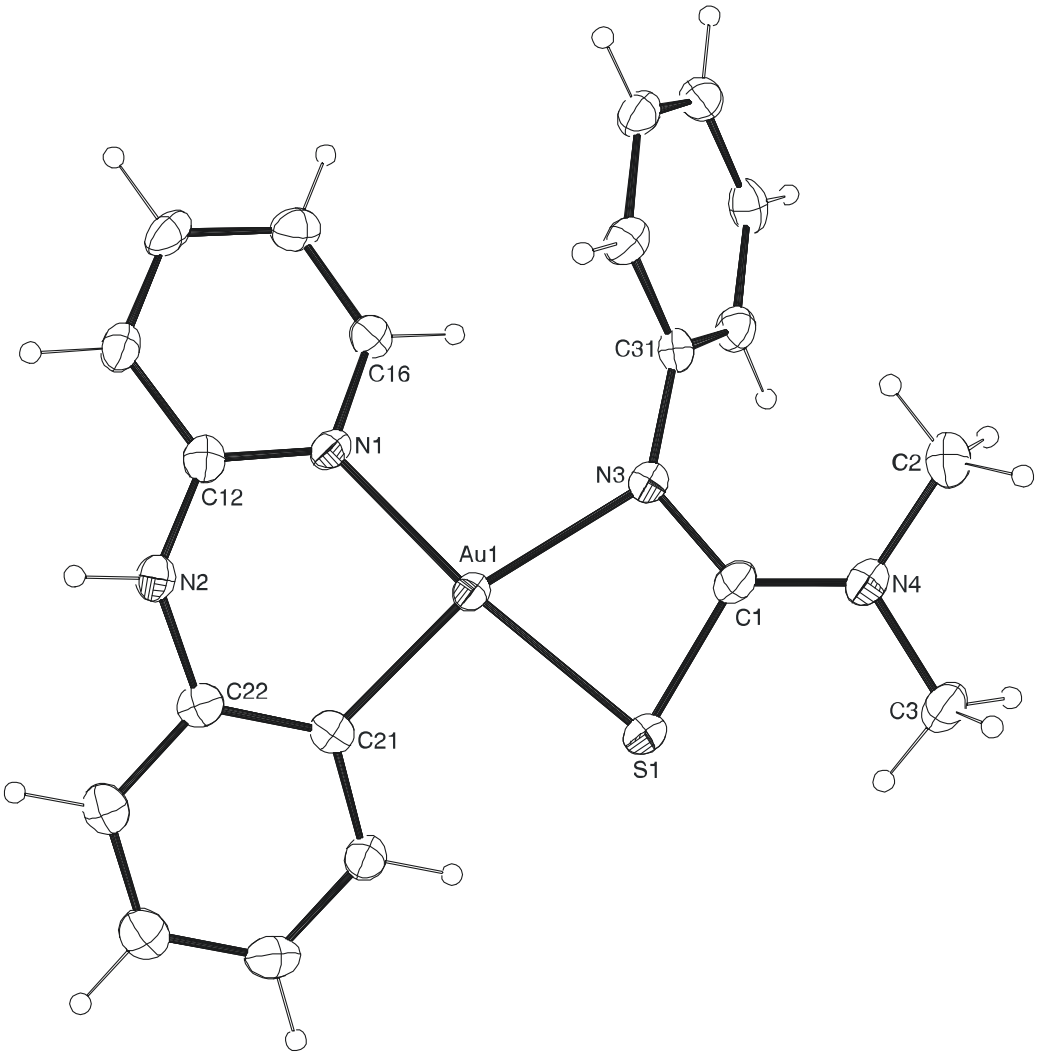



***Figure 3.1:*** *Perspective view of the X-ray crystal structure of the cation of complex [AnpAuPhNCSNMe$_2$]BPh$_4$* ***161****, showing the atom labelling scheme. Thermal ellipsoids are shown at the 50 % probability level. The tetraphenylborate anion has been omitted for clarity.*

***Table 3.1:*** *Selected bond lengths (Å) (estimated standard deviations in parentheses) for [AnpAuPhNCSNMe$_2$]BPh$_4$* ***161*** *and [AnpAuPhNCSNCy$_2$]BPh$_4$* ***167****.*

| Bond | 161 | 167 |
|---|---|---|
| Au – N1 | 2.068(3) | 2.071(2) |
| Au – C21 | 2.020(3) | 2.019(3) |
| Au – N3 | 2.137(3) | 2.128(2) |
| Au – S1 | 2.277(8) | 2.283(7) |
| S1 – C1 | 1.771(3) | 1.776(3) |
| C1 – N3 | 1.343(4) | 1.324(3) |
| N1 – C12 | 1.339(4) | 1.349(4) |
| C21 – C22 | 1.385(5) | 1.401(4) |
| N1 – C16 | 1.369(5) | 1.368(3) |
| C21 – C26 | 1.397(5) | 1.394(4) |

***Table 3.2:*** *Selected bond angles (°) (estimated standard deviations in parentheses) between [AnpAuPhNCSNMe$_2$]BPh$_4$* ***161*** *and [AnpAuPhNCSNCy$_2$]BPh$_4$* ***167****.*

| Angle | 161 | 167 |
|---|---|---|
| N1 – Au – C21 | 89.53(10) | 90.83(13) |
| S1 – Au – N3 | 69.82(7) | 69.86(7) |
| C21 – Au – S1 | 96.26(9) | 95.56(10) |
| N1 – Au – N3 | 104.41(9) | 103.74(11) |
| Au – N3 – C31 | 127.52(18) | 124.10(2) |
| Au – N3 – C1 | 99.67(18) | 98.90(2) |
| C1 – N3 –C31 | 127.04(2) | 122.50(3) |

In comparison complex **167**, a very similar derivative of **161**, shows a difference in geometry due to the bulky cyclohexyl groups attached. Complex **167** shows an angle between planes Au, C1, N3 and C1, S1, N3 of 11º, showing a higher deviation from planarity. N4 lies within the C1, S1, N3 plane however the cyclohexyl groups attached twist by 20º so that one cyclohexyl ring is found to be above the plane and the other below. These bulky cyclohexyl groups crowd the phenyl ring attached to the N4 so pushing it away to give a structure that is quite puckered. N4 shows pyramidal characteristics, with angles around the nitrogen adding to only 345.5º, less than the 360º expected and approximately observed by the planar complex **161**. Cyclohexyl groups show puckered chair conformations as expected.

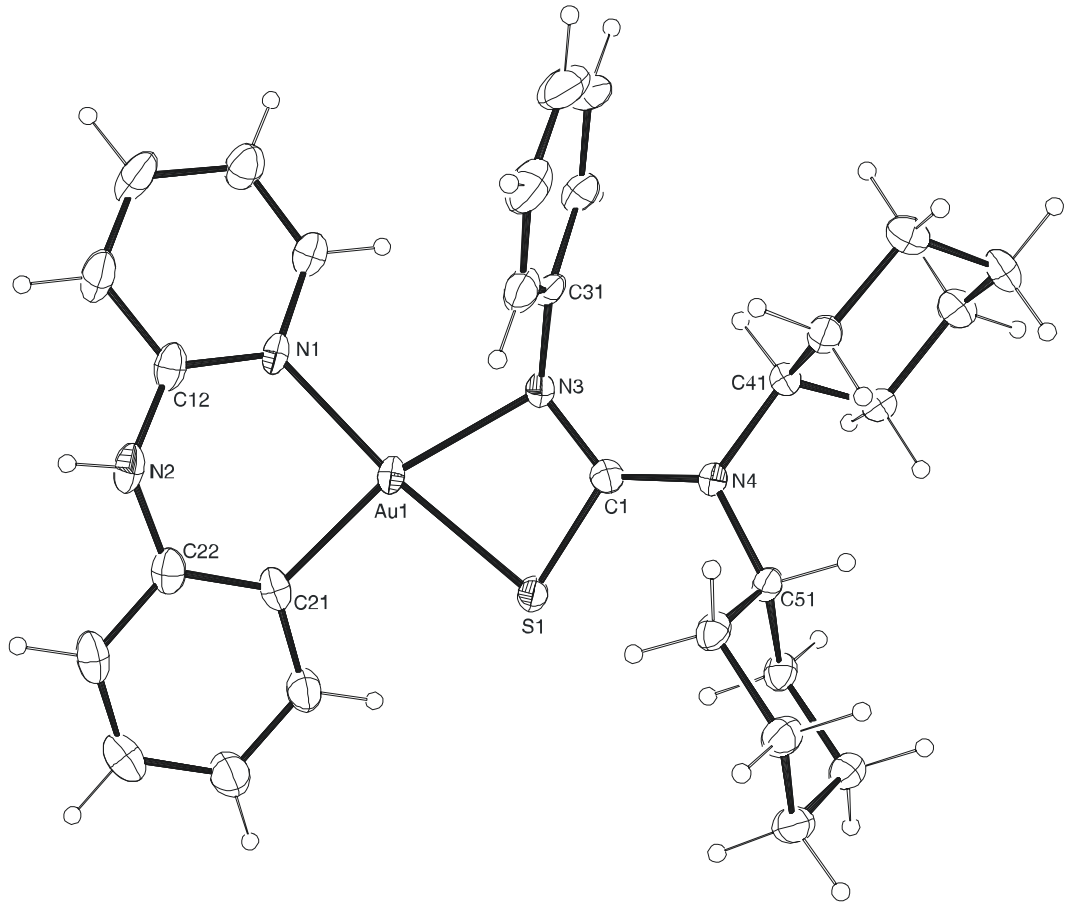



***Figure 3.2*** *Perspective view of the structure of the cation of complex [AnpAuPhNCSNCy$_2$]BPh$_4$* ***167****, showing the atom labelling scheme. Thermal ellipsoids are shown at the 50 % probability level. The tetraphenylborate anion has been omitted for clarity.*

The Au-S1 and Au-N3 bond lengths of the chelating thiourea complex **161** [2.283(7) and 2.128(2) Å] observe a longer Au-S, but shorter Au-N bond distance than that of **167** [2.277(8) and 2.137(3) Å]. This suggests that the steric crowding observed in complex **167** also results in the lengthening of the Au-N bond.

Upon superimposing both structures it is easily confirmed that complex **167** shows a more puckered conformation than that of **161**, with the phenyl group orientated approximately perpendicular to the four membered S-Au-C-N ring system in each case. This is shown in Figure 3.3 giving side views of each structure.

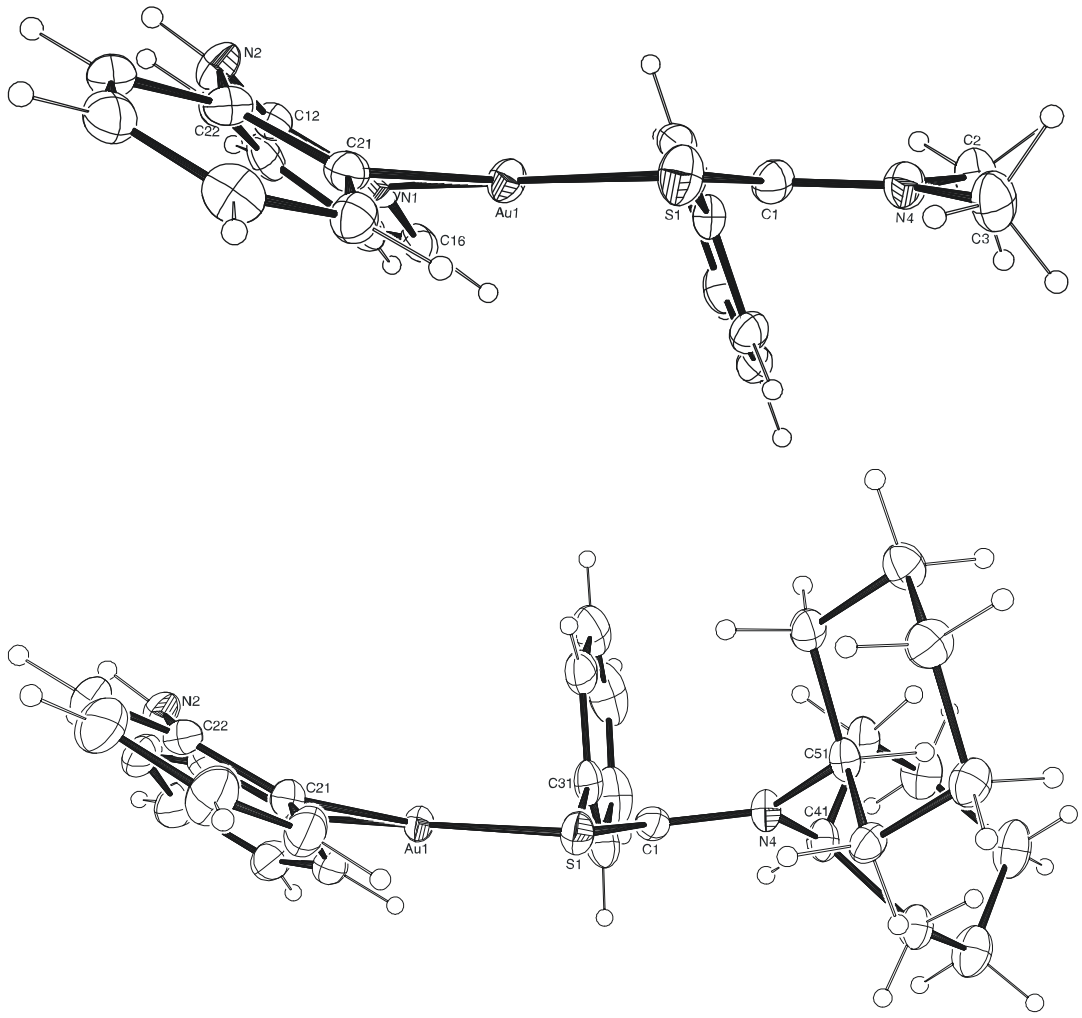
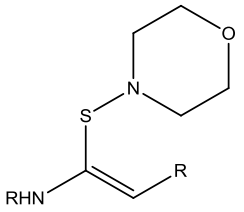


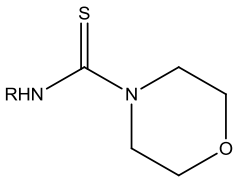

***Figure 3.3:*** *Side view of the X-ray crystal structures of the cation of complexes [AnpAuPhNCSNMe$_2$]BPh$_4$* ***161*** *and [AnpAuPhNCSNCy$_2$]BPh$_4$* ***167****, with* ***167*** *showing non-planarity relative to the Au(III) atom. Thermal ellipsoids are shown at the 50 % probability level. The tetraphenylborate anion has been omitted for clarity.*

Inspection of the thiourea moiety core, defined by N3-C-N4-S, shows S-C and N-C bond lengths of both crystals which suggest electronic delocalisation in the thiourea ligand. The S-C bond distances in **161** and **167** [1.776(3) and 1.771(3) Å, respectively] demonstrate an intermediate bond length when compared to organic compounds **169**[113] and **170**[114], containing single and double C-S bonds of 1.801(3) and 1.691(3) Å respectively, with the average bond length in most thioureas around 1.681 Å[115]. Examination of thiourea C-N bonds in complexes **161** and **167** [ca. 1.343(4) and 1.324(3) Å] in comparison to **169** and **170** with the double and single C-N bonds 1.267 and 1.355 Å respectively, also shows bond distances

between that of a double and single bond in both crystal structures, suggesting there is partial double bond character in both the C-S and C-N bonds.




**169**




**170**

All bond distances in these crystal structures are comparable to known and characterised complexes of Pt(II) thiourea systems **134-146**[104,111], with slight deviations to Au-S bond distances, presumably due to the higher electronegativity of gold and the substituents attached to the thiourea chelating ligand. The Au-S distances in **161** (2.283(7) Å) and **167** (2.277(8) Å) are towards the short end of the range of values displayed by corresponding Pt(II)-S complexes.

In the crystal structure of **167** the final difference map contained a residual peak of 2.4 e $Å^{-3}$ which was in a position that could have potentially arisen from oxidation of the S atom. It was hypothesised this would generate an oxidised form of **167** incorporating an S=O group, which may have co-crystallised with **167**, shown by Figure 3.4. To test this hypothesis two oxidation experiments were investigated using oxidising agents $H_2O_2$ and $HAuCl_4$ in an attempt to generate an S=O species, further described in experimental Section 2.5.2, without success. In addition no evidence for any species with *m/z* 697 could be seen in ES-MS of the crystals used for the X-ray experiments therefore suggesting that the X-ray result was an artifact and therefore omitted from the refinement.

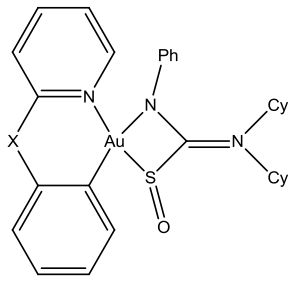



***Figure 3.4:*** *Diagram showing the potential oxidised form of* ***167*** *incorporating an S=O group.*

## 3.2.2 Spectroscopic and Mass Spectrometric Characterisation

### 3.2.2.1 NMR Spectroscopy

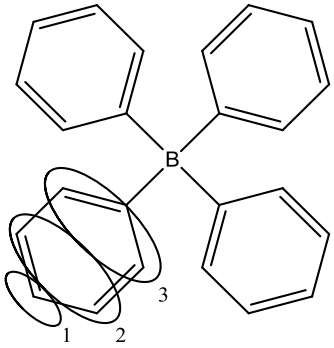
$^{1}$H, COSY, $^{13}$C, DEPT135 and HSQC spectra were acquired for all compounds. Additional NMR data was recorded for complexes containing the 2-benzylpyridyl moiety. Due to the complex overlapping of signals in the aromatic regions of the $^{1}$H spectra, full NMR assignments of all compounds could not made, however integration of the aromatic region was used to ascertain that the expected number of signals were present.

Due to the complexity of the spectra NMR data was primarily used as an indicator of sample purity, where it was apparent that all gold(III) anilinopyridyl derivatives showed good purity. Elemental data determined for compounds **161**, **163** and **165** did not completely match the experimental results suggesting that solvent molecules may have been retained in the analyses specimens. However proton NMR revealed the absence of solvent molecules and other potential impurity signals (eg: phthlates, tap grease, silicones, etc).

Compounds containing the anilinopyridyl moiety all exhibited a singlet peak in the region 10.5-10.8 ppm in their $^{1}$H spectra, postulated to be the NH proton. This was confirmed by COSY and HSQC spectra which were devoid of a correlation between this proton and other protons or a carbon atom respectively. All quaternary carbons were identified by the comparison of DEPT135 and $^{13}$C NMR data.

All new gold(III) thiourea compounds prepared in this chapter are cationic, containing a $BPh_4^-$ anion for precipitation. $^{1}$H NMR spectra of complexes **161-168** show two large triplets and one multiplet signal that corresponds to the $BPh_4^-$ anion. The two triplet peaks can be associated to the environments **1** (*para*) and **2** (*meta*) in Scheme 3.1. In an isolated phenyl ring the remaining environment **3** (*ortho*) it would be expected to show a doublet, however it was observed as a multiplet. This observation is due to the presence of an NMR active boron atom ($^{10}$B or $^{11}$B which have nuclear spin of 3/2 and 3 respectively) in the anion. When the proton NMR signal of the *ortho* protons was expanded it was apparent that the

multiplet signal was comprised of overlapping doublets of quadruplets (80% contribution) and doublets of heptuplets (20% contribution) depending on the isotope of boron in the anion. Integration of the $^{1}H$ spectrum showed that the mixture of cation to anionic species was not in the expected 1:1 ratio, with the exception of complex **167**.




***Scheme 3.1:*** *Diagram showing proton environments of $BPh_4^-$ observed in $^{1}H$ NMR spectra (shown below). Circled areas represent all proton environments observed in each phenyl group. Due to the tetrahedral pseudo symmetry of the anion, only these three environments are seen.*

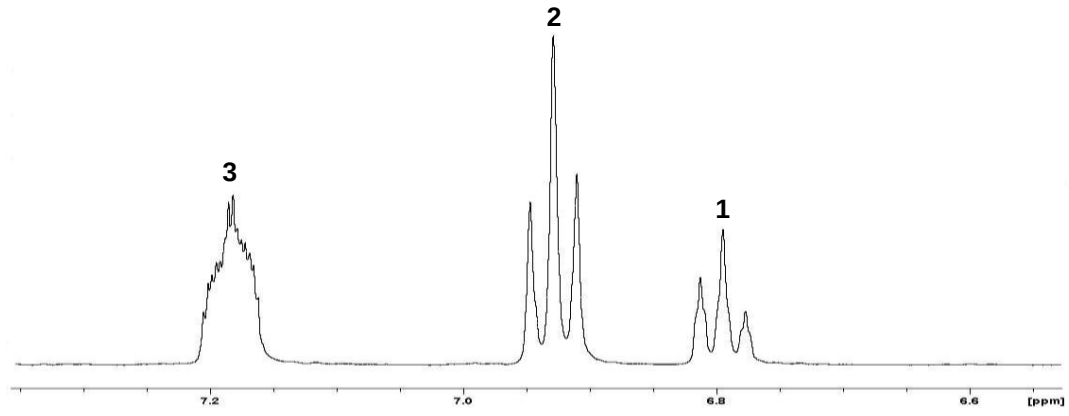



***Figure 3.5:*** *$^{1}H$ NMR spectrum showing proton signals from the different environments of anion $BPh_4^-$. Environments1, 2 and 3 refer to Scheme 3.1.*

Possible reasoning for this observation is the co-crystallisation of $Me_3NH^+BPh_4^-$ with coordination complexes **161**-**166** and **168**. This has previously been reported by Henderson *et al*[116] with the X-ray crystal structure determination of $[(Ph_3P)_2Pt$-

$(SC_6H_4CO_2)^{\cdots}HNEt_3]^+[BPh_4]^-$, showing that hydrogen-bonding between the NH proton and the carbonyl group of the thiosalicylate ligand can occur. NMR data showed that all complexes containing the 2-benzylpyridyl moiety had proton spectra that were overwhelmed by $BPh_4^-$ anion signals, as depicted in Figure 3.5. Integration of the observed anion signals, relative to a singlet signal in the $^1H$ spectrum at 2.8 ppm assignable to the methylene protons in $Me_3NH$, gave a 4:9 ratio of the triplet signal **1** (Figure 3.5) to that of the methyl groups. This supported the proposal of the co-crystallisation of $Me_3N^+BPh_4^-$. However as no crystals of the benzylpyridine derivatives were able to be obtained this rationale could not be confirmed.

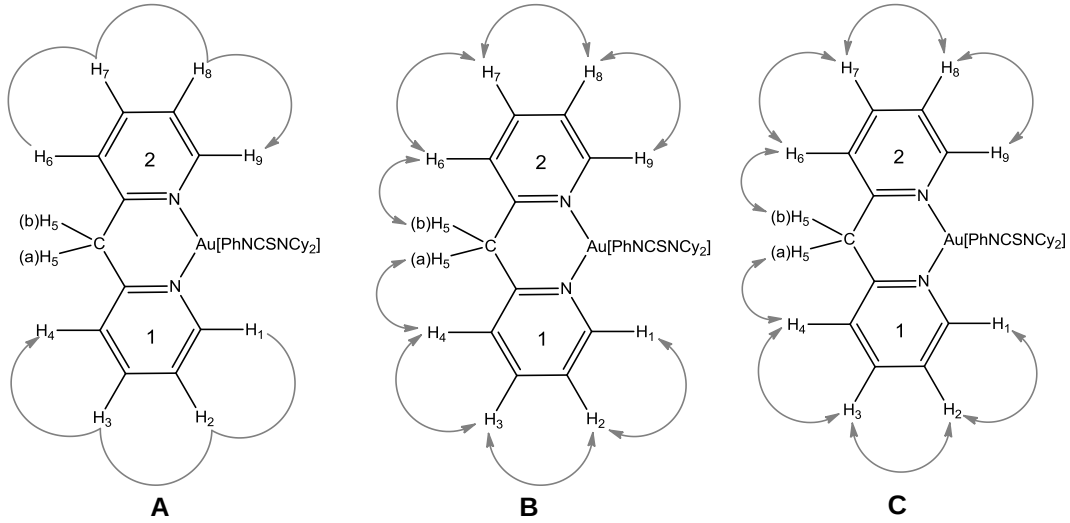
For this reason proton signals of complexes **162**, **164** and **166** were carefully examined in expanded $^1H$ and COSY NMR spectra, however integration of proton signals was not considered to be informative due to the complexity and overlapping of signals in the proton spectra. Very few carbon signals were also observed from the real complexes due to the overwhelming amount of anion present in these 2-benzylpyridyl derivatives.

#### 3.2.2.2 NMR Analyses of Complexes Containing the 2-benzylpyridyl Moiety

Due to the complexity of the spectra acquired from the presence of anion $BPh_4^-$, an alternative synthesis using simpler $BF_4^-$ anion was trialled with complex **168**. However the resulting NMR spectra showed that this complex still contained unknown impurities. Nonetheless careful analyses of TOCSY, NOESY, COSY, HSQC and selective 1D-SELROESY data allowed for the characterisation of all protons in complex **168**. NMR details and observations for this analysis are described below, with full NMR assignments found in experimental Section 3.5.2 and further NMR details in Appendix II.

Due to the sample containing a mixture of several products and/or impurities, the NMR approach was to identify a unique starting signal and utilise correlations exhibited by such a proton in $^1H$, NOESY, COSY, TOCSY and SELROESY spectra to derive a complete set of proton assignments. Correlated protonated

carbon signals were subsequently identified at 2D (rather than 1D) resolution (± 0.5 ppm). NMR assignment strategy and ring numbering scheme are shown in Scheme 3.2 below.




***Scheme 3.2:*** *Diagrammatic depictions of the NMR assignment strategy; A) $^{3}J$ COSY correlations signals through bonds, B) TOCSY correlations identifying complete spin system, C) NOESY signals showing correlations through space.*

The proton H-1, adjacent to the nitrogen in the benzylpyridyl moiety (ring 1; see Scheme 3.2) was easily identifiable due to its upfield shift (8.44 ppm). The $^{1}$H-$^{1}$H COSY spectrum subsequently showed other mutually coupled nearest neighbours (eg: H-2, H-3 and H-4). Signals arising from a second mutually coupled 4-proton spin system (ring 2 protons: see Scheme 3.2) were also was observed in the COSY spectrum. Identification of these signals was difficult due to the overlap of some of the ring 2 proton signals.

This difficulty was addressed in a TOCSY experiment performed with a 'long range' spin lock mixing time of 160 msec. In this spectrum each of the aryl protons exhibited correlations to all other protons within the same spin system. Provided at least one distinct proton in each ring system was accessible the chemical shifts of the remaining 3 protons were able to be uniquely identified.

Long range correlations between the $CH_2$ group and some of the 2-benzylpyridyl protons were was also observed in the TOCSY spectrum.

1D-SELROESY or NOESY experiments identified which protons exhibited through space ROESY or NOESY (NOE) correlations to the $CH_2$ group on the middle ring system. By selectively exciting the $CH_2$ signal in a SELROESY experiment, it was possible to see which ring 1 and ring 2 aryl protons were adjacent to the $CH_2$ group in the respective aromatic rings. In the case of complex **168** ROESY correlations were observed between the methylene protons and the aryl protons at 7.36 and 7.03 ppm. Knowing that the signal at 7.03 ppm arose from a ring 1 proton which exhibited TOCSY correlation to the distinctive H-1 proton it could then be deduced that the signal at 7.36 ppm was from the H-6 on ring 2. Subsequently COSY correlations identified the H-7, H-8 and H-9 resonances.

Identification of the correlated $^{13}C$ signals was made by overlaying 1D-slices extracted from the TOCSY spectrum on the HSQC spectrum. This allowed the assignment of the protonated aryl carbons and the methylene carbon (Experimental Section 3.4, Table 3.3).

The cyclohexyl rings were far removed from any aromatic area of the $^{1}H$ NMR spectrum, therefore identification of the proton and carbon signals through inspection of $^{1}H$, COSY, $^{13}C$ and DEPT135 spectra were easily made.

Therefore, it has been shown that through selective experiments and careful examination identification of signals correlating to complex **168** could be made, showing that this complex is infact within the sample, in an unknown amount.

### 3.2.2.3 IR Spectroscopy

The IR spectrum of thiourea ligands $PhNHC(S)NHMe_2$, $PhNHC(S)N(C_2H_4)_2O$, PhNHC(S)NHPh and $PhNHC(S)NHCy_2$ all exhibited strong C=S stretches in the region 1112–1173 $cm^{-1}$ and N-H stretches in the region ~3300-3500 $cm^{-1}$. Upon coordination of the analogous thiourea to the gold(III) centre these stretches were reduced. The IR spectra of the resulting gold(III) thiourea derivatives **161-168** all

showed stretches in the C=N region 1542-1651 $cm^{-1}$. These observations indicate that the sulfur and nitrogen atoms coordinate to the gold centre, therefore resulting in a loss of double bond C=S character and gain in C=N character, while deprotonating the nitrogen.

This effect was not as pronounced in the PhNHC(S)NHPh derivatives as the regions of interest contained a large number of strong overlapping bands making assignment difficult.

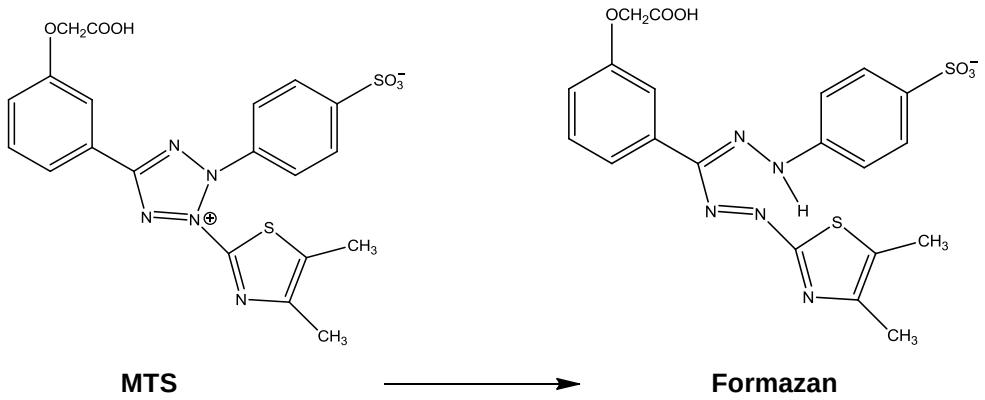
### 3.2.2.4 Electrospray Mass Spectrometry (ES-MS)

All new compounds synthesised in this chapter were good candidates for ES-MS due to their cationic nature, allowing ease of analysis. All complexes were dissolved using a few drops of DCM and further diluted in MeOH prior to analysis. ES-MS of compounds **161-168** all showed intense $[M]^+$ ions. The analogous bis-$Anp_2Au^+$ and bis-$Bp_2Au^+$ cation with *m/z* values of 535 and 533 respectively were also observed to a lesser extent.

### 3.2.2.5 Biological Activity

Biological testing facilities were unavailable during the timeline of this project, therefore the anti-tumour activity of compounds **161**, **163**, **165-167** were run by fellow peer Aaron Andersen, at AgResearch, Hamilton. Details of the assay procedures can be found in experimental Section 3.4.3 and results are reported in Figure 3.6.

The CellTiter 96 Aqueous One Cell Proliferation Assay (Promega) is a colorimetric method for determining the number of viable cells in proliferation to assess the cytotoxicity of a compound (e.g. the less viable cells remaining after administration of the complex, the greater the toxicity). The reagent used in this method contains a tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(-4-sulfophenyl)-2H-tetrazolium, inner salt, MTS] also known as Owen's reagent. MTS is reduced by cells to give a coloured formazan product that is soluble in tissue culture media (Scheme 3.3)




***Scheme 3.3:*** *Structure of MTS tetrazolium and the reduction product formazan.*

This assay was used to determine the concentration of the test sample required to reduce the P388 murine leukaemia cell line growth by 50%, the $IC_{50}$ value. The quantity of the formazan product is measured at 490 nm with a spectrophotometer. To compensate for turbidity a measurement is also taken at 360 nm, and subtracted from the measurement at 490 nm. The percentage inhibition of P388 cell growth by a sample can be determined by comparing the absorbance of a test well to that of the control, Triton X-100. A plot of absorbance against the logarithm of the sample concentration allows the $IC_{50}$ value to be obtained (ng $mL^{-1}$) from the antilog of the 50% value.

With the exception of [AnpAuPhNCSNHPh]$BPh_4$, **165**, all compounds displayed low anti-tumour activity towards the P388 murine leukaemia cell line. Complex **165** demonstrated a 51.1% growth inhibition at concentration 3125 ng $mL^{-1}$with $IC_{50}$ value of 3.46 µM. This $IC_{50}$ value is comparable to those of some catecholate[26] and thiolate[42] Au(III) metallacycles against the same cell line.

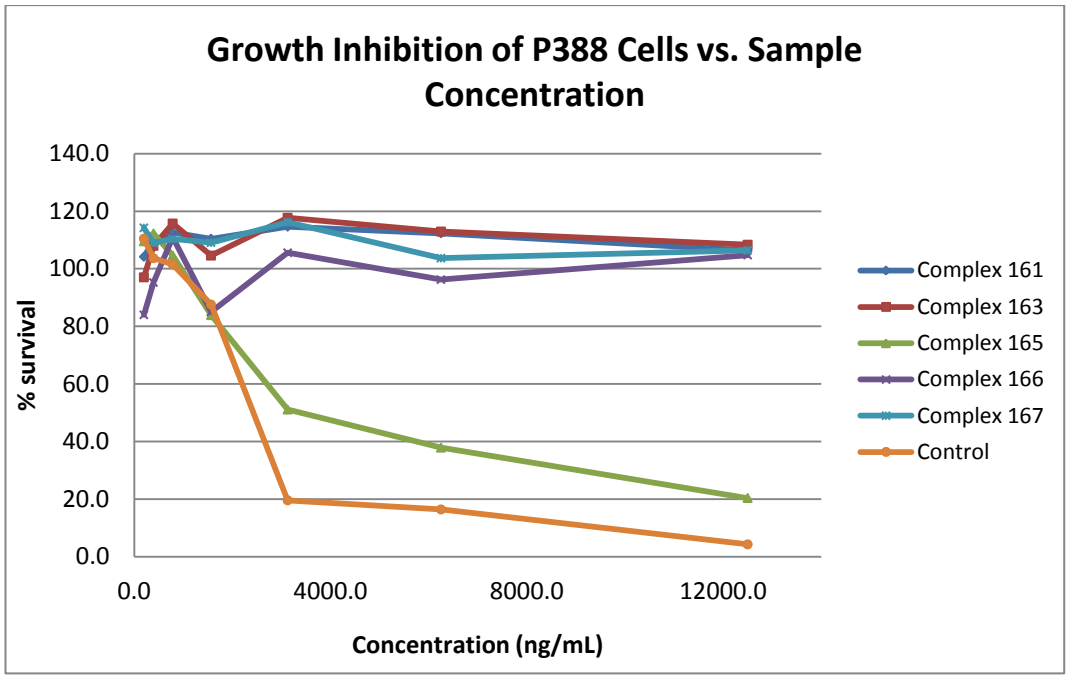



***Figure 3.6:*** *Growth inhibition of samples [AnpAuPhNCSNMe$_2$]BPh$_4$* ***161****, [AnpAuPhNCSN(C$_2$H$_4$)$_2$]BPh$_4$* ***163****, [AnpAuPhNCSNHPh]BPh$_4$* ***165****, [BpAuPhNCSNHPh]BPh$_4$* ***166*** *and [AnpAuPhNCSNCy$_2$]BPh$_4$* ***167*** *against P388 Murine leukaemia cells in vitro. Control = Triton.*

## 3.2.3 Discussion

After repeated attempts to purify, recrystallise and synthesise complexes **162**, **164**, **166** and **168** using a variety of independently synthesised batches of BpAuCl$_2$ compounds to overcome any impurities in individual samples, it was concluded that a pure sample of these complexes using the methods in this thesis could not be obtained. ES-MS analysis confirmed the formation of the desired products; with further evidence of synthesis provided for complex **168** through a range of NMR experiments. This demonstrated that although the sample was not pure, the desired complex was confirmed to be synthesised within the sample.

Due to the impurity of some of the complexes in this chapter future research could be directed at synthesising new cyclometallated gold(III) complexes using alternative C,N-coordinated gold(III) dihalides as precursors. The successful synthesis of the complexes containing the anilinopyridyl moiety, in addition to biological activity observed by complex [AnpAuPhNCSNHPh]BPh$_4$ **165**, suggests

that the thiourea ligands used in this chapter have potential applicability as chelating ligands towards other auracycles. Precipitation of these cationic complexes using alternative anions is also recommended to avoid the formation of reaction by-products involving $BPh_4^-$ and to obtain better quality NMR data. Further changes to reaction conditions and solvents may also help to improve purity and yields. Additional investigation into the biological activity of these complexes is also suggested.

## 3.3 Conclusion

Four new gold(III) thiourea complexes (thiourea = $NRCSNR_2$) have successfully been synthesised and characterised, with a further four new complexes obtained in low purities and yields. To the best of our knowledge, these are the first gold compounds of this type to be reported. The X-ray crystal structures of $[AnpAuPhNCSNHMe_2]BPh_4$, **161**, and $[AnpAuPhNCSNHCy_2]BPh_4$**167**, have been solved and indicate that the thiourea ligands are co-ordinated to the gold centre through S-Au-N bonds. In both cases, the geometry around the gold(III) centre is square planar, with the anilinopyridyl moiety showing slight puckering. The packing diagram showed no unusual intermolecular contacts for either crystal structure.

Five of the new compounds **161**, **163**, **165-167** were bio-assayed against P388 leukaemia cells in order to assess their anti-tumour activity. Complex **165** was found to show good activity, while the other complexes were either inactive or too insoluble in biological media.

## 3.4 Experimental

### 3.4.1 General

The reactions were carried out with no efforts at excluding either air or light. The solvents used were drum grade. $AnpAuCl_2$ **126**[80] and $BpAuCl_2$ **125**[77] were prepared from literature procedures. All thiourea ligands had previously been synthesised in this laboratory following literature procedures[111] by the reaction of

PhNCS with the appropriate secondary amine in diethyl ether, giving white crystalline products. PhNHC(S)NHPh was from Aldrich. Compounds were stored in the freezer to slow down decomposition. ES-MS were acquired in methanol solvent with addition of a small amount of DCM. All NMR spectra were acquired in DMSO. Further information on instruments used for characterisation of complexes is provided in Chapter one, Section 2.4. Additional NMR specifications can be found in Appendix II.

***Synthesis of [AnpAuPhNCSNHMe$_2$]BPh$_4$, 161:***

The complex AnpAuCl$_2$ (21.4 mg; 0.049 mmol) and PhNHCSNHMe$_2$ (12.7 mg, 0.056 mmol) were stirred in methanol (25 mL) giving a yellow solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added. After stirring the warmed mixture for 5 min, solid NaBPh$_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 32.6 mg (69%) of yellow solid.

| | |
|---|---|
| Melting Point: | 112-113 ºC (decomposed on further heating) |
| IR: | υ(C-S) = 706 cm$^{-1}$, υ(C=N) = 1604 cm$^{-}$1, υ(N-H) = 3319 cm$^{-1}$ |
| Microanalysis: | Found: C= 64.2%, H= 5.2%, N= 6.1%<br>$C_{48}H_{40}AuBN_4S$ requires: C= 61.1%, H= 4.7, N= 6.5% |
| ES-MS: | Capillary exit 120 V: *m/z*: 545 (100%, [M]$^+$) |
| NMR: | $^1$H: δ, 2.74 (s, 3H), 2.88 (br s, 3H), 6.39 (t, 1H, *J=13.6 Hz*), 6.79 (t, 4H, *J=14.3 Hz*), 6.93 (t, 10H, *J=14.9 Hz*), 7.03 (t, 1H, *J=14.6 Hz*), 7.19 (m, 12H), 7.22 (d, 1H, *J=5.0 Hz*) 7.28 (t, 1H *J=14.9 Hz*), 7.35 (d, 1H, *J=8.0 Hz*), 7.39 (t, 1H, *J=14.8 Hz*) 7.48 (d, 1H, *J=6.3 Hz*), 7.81 (t, 1H, *J=15.7 Hz*), 10.78 (s, N<u>H</u>)<br>$^{13}$C: δ, 170.2, 164.7-163.1, 147.4, 140.1, 113.2 (aryl <u>C</u>), 39.42 (s, <u>C</u>H$_3$) |

***Synthesis of [BpAuPhNCSNHMe$_2$]BPh$_4$, 162:***

The complex $BpAuCl_2$ (20.5 mg; 0.047 mmol) and $PhNHCSNMe_2$ (10.5 mg; 0.058 mmol) were stirred in methanol (25 mL), giving a white cloudy solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a pale yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 40.1 mg (94%) of pale yellow solid.

| | |
|---|---|
| IR: | υ(C-S) = 710 cm$^{-1}$, υ(C=N) = 1600 cm$^{-1}$ |
| ES-MS: | Capillary exit 120 V: *m/z*: 544 (100%, [M]$^+$) |
| NMR: | $^1$H: δ, 2.79 (s), 4.06-4.24 (d of d), 6.79 (t, anion*, *J=14.6 Hz*), 6.93 (t, anion*, *J=14.9 Hz*), 7.03 (t), 7.17 (m, anion*) 7.38 (m), 7.56 (d), 8.04 (m) |
| | *refer to NMR Spectroscopy Section 3.2.2.1, anion signals here overlap with the remaining signals from this complex. |

***Synthesis of [AnpAuPhNCSN(C$_2$H$_4$)$_2$O]BPh$_4$, 163:***

The complex $AnpAuCl_2$ (20.5 mg, 0.047 mmol) and $PhNHCSN(C_2H_4)_2O$ (33.8 mg; 0.152 mmol, excess) were stirred in methanol (25 mL), giving a yellow solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a bright yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 40.1 mg (94%) of light yellow solid.

| | |
|---|---|
| Melting Point: | 112-113 ºC (decomposed on further heating) |
| IR: | υ(C-S) = 707 cm$^{-1}$, υ(C=N) 1581 cm$^{-1}$, υ(br, N-H) = 3436 cm$^{-1}$ |
| Microanalysis: | Found: C= 64.9%, H= 5.6%, N= 5.5% |

$C_{46}H_{42}AuBN_4OS$ requires: C= 60.9%, H= 4.7%, N= 6.2%

ES-MS: Capillary exit 120 V: *m/z*: 587 (100%, $[M]^+$)

NMR: $^1$H: δ, 3.34 (br s, 4H), 3.57 (br s, 4H), 6.39 (t, 1H, *J=13.4 Hz*), 6.79 (t, 4H, *J=14.3 Hz*), 6.93 (t, 16H, *J=14.7 Hz*), 7.04 (t, 1H, *J=14.7 Hz*), 7.19 (m, 12H), 7.31 (t, 1H, *J=1473 Hz*), 7.34 (m, 2H), 7.42 (m, 3H), 7.83 (t, 1H, *J=15.7 Hz*), 10.79 (s, NH)s

$^{13}$C: δ, 169.1, 164.1-163.1, 147.4, 141.1, 113.1 (aryl C), 65.6 (s, $CH_2$), 47.8 (s, $CH_2$)

***Synthesis of [BpAuPhNCSN(C$_2$H$_4$)$_2$O]BPh$_4$, 164:***

The complex $BpAuCl_2$ (20.0 mg, 0.046 mmol) and $PhNHCSN(C_2H_2)_2O$ (12.6 mg; 0.057 mmol, excess) were stirred in methanol (25 mL), giving a clear solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a pale yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a pale yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 36.4 mg (87%) of dull pale yellow solid.

IR: υ(C-S) = 710 cm$^{-1}$, υ(C=N) = 1581 cm$^{-1}$

ES-MS: Capillary exit 120 V: *m/z*: 586 (100%, $[M]^+$)

NMR: $^1$H: δ, 2.71 (s), 4.06-4.24 (d of d), 6.79 (t, anion*, *J=14.4 Hz*), 6.93 (t, anion*, *J=14.8 Hz*), 7.03 (t), 7.18 (m, anion*) 7.37 (m), 7.56 (d), 8.03 (m)

*refer to NMR Spectroscopy Section 3.2.2.1, anion signals here overlap with the remaining signals from this complex.

***Synthesis of [AnpAuPhNCSNHPh]BPh$_4$, 165:***

The complex $AnpAuCl_2$ (20.5 mg; 0.047 mmol) and PhNHCSNHPh (11.7 mg, 0.051 mmol, excess) were stirred in methanol (25 mL), giving a yellow solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving no colour change. After stirring the warmed mixture for 5 min, solid

$NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 32.6 mg (69%) of bright yellow solid.

| | |
|---|---|
| Melting Point: | 111-112 ºC (decomposed) |
| IR: | $\upsilon$(C-S) = 710 $cm^{-1}$, $\upsilon$(C=N) = 1542 $cm^{-1}$, $\upsilon$(N-H)= 3347$cm^{-1}$ |
| Microanalysis: | Found: C= 67.4%, H= 5.8%, N= 6.2% |
| | $C_{48}H_{40}AuBN_4S$ requires: C= 63.1%, H= 4.4%, N= 6.1% |
| ES-MS: | Capillary exit 120 V: *m/z*: 593 (100%, $[M]^+$) |
| NMR: | $^1$H: δ, 6.50 (t, 1H, *J=13.5 Hz*), 6.79 (t, 8H, *J=14.3 Hz*), 6.91 (t, 21H, *J=14.7 Hz*), 6.99 (m, 2H), 7.08 (d, 1H, *J=7.8 Hz*) 7.16-7.25 (m, 26H), 7.41 (d, 1H, *J=9.1 Hz*), 7.65 (d, 1H, *J=6.5 Hz*), 7.86 (t, 1H, *J=15.6 Hz*) 10.57 (s, NH) |
| | $^{13}$C: δ, 169.1, 164.6-163.1, 147.5, 141.1, 113.2 (aryl C) |

***Synthesis of [BpAuPhNCSNHPh]$BPh_4$, 166:***

The complex $BpAuCl_2$ (20.1 mg; 0.046 mmol) and PhNHCSNHPh (10.6 mg; 0.046 mmol, excess) were stirred in methanol (25 mL), giving a clear solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a bright yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a pale yellow precipitate. The was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 9.2 mg (22%) of pale yellow solid.

| | |
|---|---|
| IR: | $\upsilon$(C-S) = 710 $cm^{-1}$, $\upsilon$(C=N) = 1651 $cm^{-1}$ |
| ES-MS: | Capillary exit 120 V: *m/z*: 592 (100%, $[M]^+$) *m/z*: 353 (92%, $[BpAuBp]^+$) |
| NMR: | $^1$H: δ, 6.79 (t, anion*, *J=14.5 Hz*), 6.92 (t, anion*, *J=14.8 Hz*), 7.17 (m, anion*) 7.33 (t, 1H, *J=15.1 Hz*), 7.48 (d, 1H, |

*J=8.6 Hz*), 7.58 (t, 1H, *J=13.9 Hz*), 7.70 (d, 1H, *J=8.0 Hz*), 7.99 (t, 1H, *J=14.7 Hz*), 8.96 (d, 1H, *J=4.9 Hz*)

*refer to NMR Spectroscopy Section 3.2.2.1, anion signals here overlap with the remaining signals from this complex.

***Synthesis of [AnpAuPhNCSNCy$_2$]BPh$_4$, 167:***

The complex $AnpAuCl_2$ (21.0 mg; 0.048 mmol) and $PhNHCSNCy_2$ (17.6 mg; 0.056 mmol, excess) were stirred in methanol (25 mL), giving a yellow solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a pale yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 39.9 mg (83%) of bright yellow solid.

| | |
|---|---|
| Melting Point: | 141-143 ºC (decomposed) |
| IR: | υ(C-S) = 703 $cm^{-1}$, υ(C=N) = 1629 $cm^{-1}$, υ(N-H) = 3347 $cm^{-1}$ |
| Microanalysis: | Found: C= 64.6%, H= 5.8%, N= 5.6% |
| | $C_{54}H_{56}AuBN_4S$ requires: C= 64.8%, H= 5.6%, N= 5.6% |
| ES-MS: | Capillary exit 40 V: *m/z*: 681 (100%, $[M]^+$), *m/z*: 353 (12%, bis-$[Anp_2Au]^+$) |
| NMR: | $^1$H: δ, 0.98 (m, 6H), 1.46-1.66 (t of d, 10H), 1.94 (br s, 4H), 6.40 (t, 1H, *J=13.6 Hz*), 6.78 (t, 4H, *J=14.2 Hz*), 6.92 (t, 8H, *J=14.8 Hz*), 7.02 (t, 1H, *J=14.8 Hz*), 7.18 (m, H), 7.23 (d, 1H, *J=7.8 Hz*), 7.36-7.26 (m, H), 7.40 (t, 1H, *J=15.5 Hz*), 7.56 (d, 1H, *J=6.7 Hz*), 7.78 (t, 1H, *J=15.5 Hz*), 10.71 (s, N<u>H</u>) |
| | $^{13}$C: δ, 171.7, 164.6-163.1, 147.6, 143.2, 113.8 (aryl <u>C</u>), 31.2, 26.0, 24.8, 25.2 (<u>C</u>$H_2$) |

***Synthesis of [BpAuPhNCSNCy$_2$]BPh$_4$, 168:***

The complex $BpAuCl_2$ (20.6 mg; 0.047 mmol) and $PhNHCSNCy_2$ (23.6 mg; 0.074 mmol, excess) were stirred in methanol (25 mL), giving a clear solution. This was gently warmed to 50 ˚C and aq. trimethylamine (2 mL, excess) added giving a yellow solution. After stirring the warmed mixture for 5 min, solid $NaBPh_4$ (0.180 g, 53 mmol) was added, along with water (20 mL), resulting in the immediate formation of a pale yellow precipitate. This was stirred for a further 5 min and the solid isolated by filtration, washed with water (2 x 20 mL) and petroleum spirits (10 mL), then dried under vacuum to give 27.7 mg (58%) of dull pale yellow solid.

IR: $\upsilon$(C-S) = 710 cm$^{-1}$, $\upsilon$(C=N) = 2343 cm$^{-1}$

ES-MS: Capillary exit 160 V: *m/z*: 353 (100%, bis-[Bp$_2$Au]$^+$), *m/z*: 680 (70%, [M]$^+$)

Alternative Synthesis: The same procedure and methods were used as above, with $BF_4^-$ used in place of the $BPh_4^-$ anion. $BpAuCl_2$ (12.1 mg; 0.028 mmol) and $PhNHCSNCy_2$ (30.3 mg; 0.095 mmol, excess) were stirred in heated MeOH (20 mL) in the presence of aq. trimethylamine (2 mL, excess). Addition of $NaBF_4$ (18.0 mg, 207 mmol) resulted in 16.3 mg (59%) of light yellow solid.

NMR:

.

***Table 3.3**: $^1$H and $^{13}$C Chemical shifts of **168**, recorded at 400 MHz, 300 K in DMSO Chemical shifts referenced to DMSO.*

| Atom | Type | $^{13}$C | $^1$H |
|---|---|---|---|
| 1 | CH | 149.5 | 8.44 |
| 2 | CH | 121.8 | 7.16 |
| 3 | CH | 137.0 | 7.63 |
| 4 | CH | 123.4 | 7.03 |
| 5 | $CH_2$ | 42.1 | 4.18 |
| 6 | CH | 120.0 | 7.36 |
| 7 | CH | 128.5 | 7.17 |
| 8 | CH | 121.7 | 6.89* |
| 9 | CH | 122.2 | 6.89* |

*Signals were overlapped

## 3.4.2 X-ray Crystal Structure of [AnpAuPhNCSNMe$_2$]BPh$_4$ (161) and [AnpAuPhNCSNCy$_2$]BPh$_4$ (167)

Crystals were obtained of **167** by vapour diffusion of ether into dichloromethane, conversely crystals of **161** were obtained by liquid/liquid diffusion of dichloromethane and petroleum spirits.

***Data Collection:***

Intensity data and unit cell dimensions were obtained on a Bruker SMART CCD diffractometer at the University of Auckland.

***Solution and Refinement:***

The crystal structures of **161** and **167** were solved by direct methods and routinely developed and refined. X-ray structures confirmed that the thiourea ligand was co-ordinated to the Au(III) centre *via* the nitrogen and sulfur atoms. H atoms were placed in calculated positions except for the N-H one which was located and refined. The final difference map of complex **167** contained a residual peak of 2.4 e Å$^{-3}$ which was in a position that potentially could have arisen from oxidation of the S atom, bridging to an Au atom in a symmetry related molecule, therefore this was tested as follows.

***Oxidation of [AnpAu(PhNCSNCy$_2$)]BPh$_4$***

1. [AnpAuPhNHCSNCy$_2$]BPh$_4$ **167** (5.0 mg; 0.005 mmol) was dissolved in methanol (10 mL) following addition of one mole equivalent of $H_2O_2$ 30% (2 mg), and stirred at room temperature. Sample analyses were run using ES-MS immediately on mixing, one h and 24 h after initial addition. After 24 h fresh $H_2O_2$ 30% (2 mg, excess) was added and sample analyses run again on ES-MS.

2. Experimental procedure follows similar principle to procedure **1**, using starting material $HAuCl_4$ as the oxidising agent. [AnpAuPhNHCSNCy$_2$]BPh$_4$ **167** (3.1 mg; 0.004 mmol) was dissolved in methanol (10 mL) following addition of $HAuCl_4.3H_2O$ (25 mg), and were

stirred at room temperature. Sample analyses were run using ES-MS immediately on mixing, one h and 24 h after initial addition.

In all consecutive samples taken over a 24 h experimental period while using $H_2O_2$ no obvious peak around the expected *m/z* 697 was observed. After 24 h fresh $H_2O_2$ (2 mg, excess) was added to hasten oxidation, as previously added $H_2O_2$ may have decomposed before sufficient time was allowed for its role an oxidant. After analysis on ES-MS there was still no obvious sign of the peak *m/z* 697.

To be certain oxidation was not occurring $H_2O_2$ was exchanged for starting material $HAuCl_4$. This was carried out because if excess starting material was available it could induce oxidation. ES-MS of all consecutive samples taken over a 24 h period exhibited a very small peak at the desired *m/z* 697, but due to the small size of this peak it was therefore concluded that there was insufficient evidence to prove oxidation was occurring. After 24 h the compound had been completely decomposed and no evidence of the parent ion was present.

### 3.4.3 Bioassay experimental procedure

Compounds **161**, **163**, **165**, **166** and **167** were previously made up to a 0.1 mol/L concentration in methanol, an aliquot of this was dried under nitrogen, leaving 0.1mg of sample. A description of the Media used can be found in Appendix III.

To each sample (0.1 mg) cell media (500 µL) was added to give an initial dilution (1 mg/mL). This was mixed by pipetting up and down. From each solution sample was removed (200 µL) and mixed with cell media (1400 µL) resulting in solutions (25000 ng/mL) for microtitre plate addition. A subsample from each solution (100 µL) was removed and added to appropriate wells (A1-A10) on a 96 well microtitre plate. Cell media (50 µL) was added to wells B1-H10. Sample was removed (50 µL) from A1 and added to B1, giving a 2-fold dilution. Six 2-fold dilutions were repeated from B1-H1. This was subsequently repeated for samples A2-A10. To each well P388 leukaemia cells (10,000 cells in 50 µL of cell media) were added.

Each plate was run with Triton positive control (10-fold dilutions from 0.1%, A11-H11), blank without cells (100 µL cell media, A12) and blank with cells (10,000 cells in 100 µL cell media, C12-F12). Microtitre plate was incubated (35º, 72 h). Indicator (MTS, 20 µL) was then added to each well and further incubated (35º, 4 h). Plates were scanned using a plate reader (490 and 360 nm).

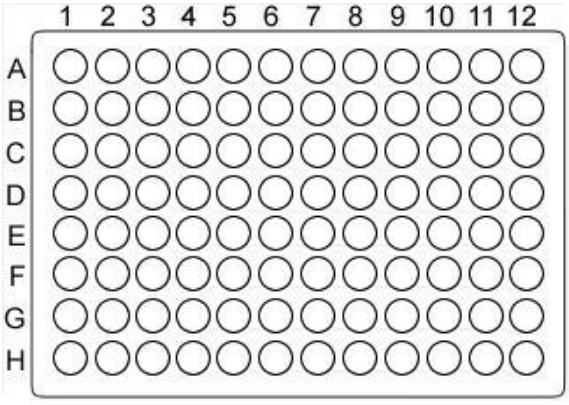



***Figure 3.7:*** *96 well Microtitre plate diagram.*

# Chapter Four

## *Synthesis and Characterisation of Gold(III) Dithiophosphinate and Dithiophosphate Compounds*

## 4.1 Introduction

Thiophosphorus ligands are an important class of sulfur donor ligands, with members of this group including dithiophosphates ($R_2O_2PS_2$), dithiophosphinates ($R_2PS_2$) and dithiophosphonates ($R(OR)PS_2$). Dithiophosphinate complexes on their own have been found to possess important biological properties and also inhibit hydrocarbon oxidation[117].

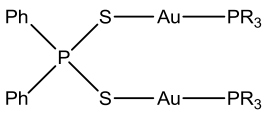
Dithiophosphinates are well known and extensively studied compounds, presumably due to their ease of synthesis and tendency to complex to virtually all metals. Soft donor dithiophosphinate ligands $R_2PS_2^-$ are capable of forming complexes with main group and transition metal ions, particularly metal ions with soft Lewis acid character[118]. The anion $^{i}Bu_2PS_2^-$ (di-isobutyldithiophosphinate) is readily available as its sodium salt and is used industrially for the flotation of sulfide ores in the mineral processing industry[119]. This ligand has come under increased interest due to its ability to impart lipophilic character when attached to metal complexes. Dithiophosphinate complexes also have increased air and moisture stability, allowing for isolation and characterisation of those which contain heavy metals[120].

***Gold(I) and dithiophosphinates***

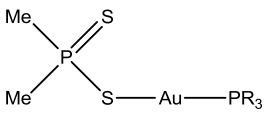
The chemistry of gold-sulfur compounds facilitates a variety of applications, ranging from surface science[121] to medicine[122,123]. Gold(I) dithiophosphinate compounds have recently been utilised as sensitisers in photographic films[124] and it has also been suggested that the luminescent properties of gold have possible use as photosensors[125]. The organophosphor-1,1-dithiolato class of compounds which includes dithiophosphinates, have demonstrated extensive usefulness as anti-oxidant additives in the oil and petroleum industry[126], in insecticide derivatives[126,127] and in metal ore extraction agents. While dithiophosphinic acids $R_2P(S)SH$ have been known for a long time, gold(I) complexes of these ligands have not been extensively studied.

The first reported examples of gold(I) dithiophosphinate complexes was in 1968 discovered by Kuchen *et al*[128] and obtained by the reduction of gold(III), requiring the separation of several by-products. However, little research into metal dithiophosphinate complexes was carried out between this discovery and the 1990's. In 1995, Saisios and Tiekink reported the first diaryldithiophosphinate of gold with the structure of $[AuS_2PPh_2]_2$ **178**[129]. This complex was established as a decomposition product with a non-reproducible synthesis and was later found to have the wrong space group structure determination, *I*4.

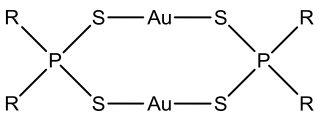
Following this work, a study on gold(I) dithiophosphinate complexes was reported by Schmidbaur[130] and co-workers. Their main focus was to use dithiophosphinate anions $[R_2PS_2]^-$ as potential bidentate ligands in the hopes of forming clustering centres for gold(I) cations, illustrated by compounds $Me_2P(S)SAuPR_3$ **171** and $[Ph_2P\{SAu(PR_3)\}_2]^+$ **178**[131]. The symmetrical complex **178** was shown by X-ray crystal diffraction to have Au---Au interactions.




**171: R=Me**
**172: R=Ph**
**173: R=o-Tol**




**174: R=Me**
**175: R=Ph**
**176: R=o-Tol**



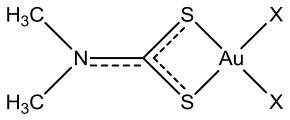

**177: R=Me**
**178: R=Ph**
**179: R=OEt**
**180: R=o-Tol**

Compound **179** is readily prepared from its sodium salt of the ligand $Na[S_2P(OEt)_2]$ whereas the analogue **178** can be obtained by direct synthesis of $[Ph_2PS_2]_2$ with the appropriate precursor. While many gold(I) dithiophosphinate complexes are known, few gold(III) dithiophosphinate compounds have been investigated. This chapter details the synthesis of auracycles containing dithiophosphinate moieties.

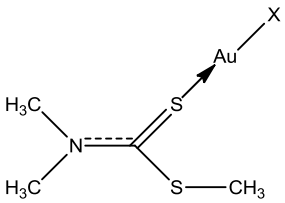
***Dithiophosphinates as potential ligands***

In 2004, Ronconi *et al*[55] reported the synthesis of gold(I) and gold(III) dithiocarbamate derivatives, designed to mimic the main features of cisplatin. These complexes therefore exhibit square planar geometry and include at least two *cis*-gold(III)-halogen bonds for ease of hydrolysis, with the remaining coordination sites occupied by an anionic bidentate or neutral monodentate dithiocarbamate ligand.

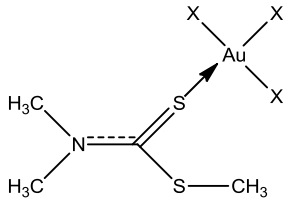
Complexes **181-189** were obtained by the direct reaction in water of the desired dithiocarbamate ligand (as its sodium salt) with $KAuX_4$ in a 1:1 or 2:1 molar ratio to give stoichiometric adducts.



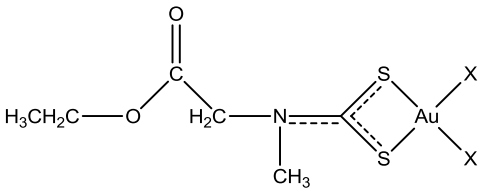

**181: X=Cl**
**182: X=Br**



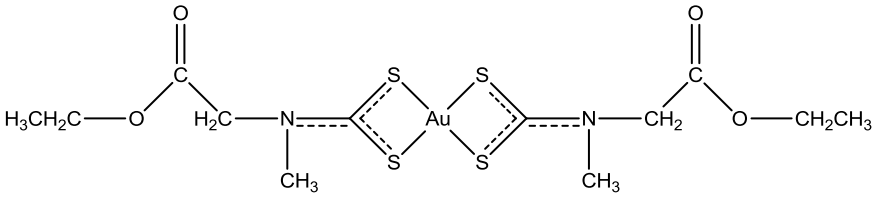

**183: X=Cl**
**184: X=Br**




**185: X=Cl**
**186: X=Br**




**187: X=Cl**
**188: X=Br**



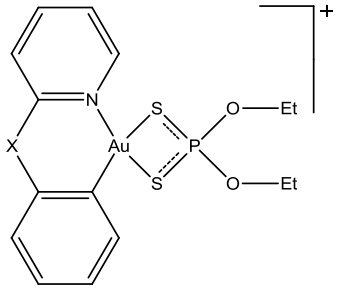
**189**

All gold dithiocarbamate complexes synthesised were subsequently tested for their *in vitro* activity towards a panel of human tumour cell lines. Gold(III) derivatives of N,N-dimethyldithiocarbamate and ethylsarcosinedithiocarbamate in particular, demonstrated a 1 to 4 fold higher activity than cisplatin as well as significantly overcoming both intrinsic and acquired resistance to cisplatin itself. All other complexes also showed good activity.

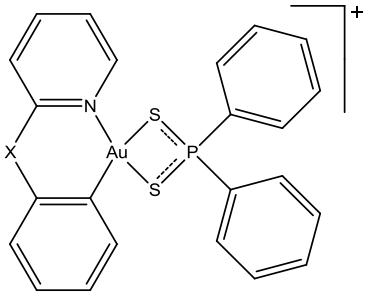
Due to the success of these complexes it was proposed to extend this theory to the direct reaction of $HAuCl_4$ with dithiophosphinate ligands, as an alternative to dithiocarbamate ligands, while also investigating reactivity towards $(C,N)AuCl_2$ cycloaurated complexes. This chapter therefore details the synthesis of novel auracycles containing dithiophosphinate moieties, all new compounds were subsequently characterised as entirely as achievable.

## 4.2 Results and Discussion

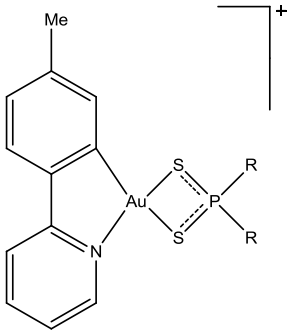
The complexes $AnpAuCl_2$ **125**, $BpAuCl_2$ **126** and $TypAuCl_2$ **127** were reacted with $Ph_2P(S)SH$, $NH_3S_2P(OEt)_2$ and $NaS_2P^iBu_2$ in methanol and stirred at room temperature. Addition of anion $BPh_4^-$ or $BF_4^-$ resulted in products **190-197** as yellow to pale yellow solids. Suitable products were characterised by ES-MS, NMR, and IR with elemental analysis carried out on complexes **190-193**. All compounds were soluble in the common solvents (acetone, dichloromethane and DMSO). Crystals were obtained by both vapour diffusion of ether into dichloromethane and liquid/liquid diffusion of dichloromethane and petroleum spirits.



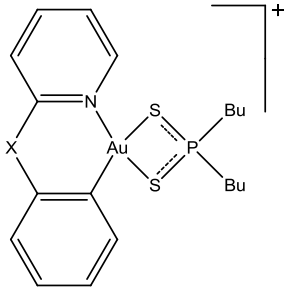
**190: X=NH**
**191: X=$CH_2$**



**192: X=NH**
**193: X=$CH_2$**



**194: R=Ph**
**195: R=OEt**



**196: X=NH**
**197: X=$CH_2$**

Complexes **190** and **191** produced microanalytical data with carbon compositions lower than expected, whereas complexes **192** and **193** produced lower carbon compositions. The differences in composition do not appear to be due to organic solvents, with $^1$H NMR spectra void of any signal corresponding to solvents. NMR analysis of complexes **194-197** showed low purity therefore elemental analysis data was not collected.

## 4.2.1 Spectroscopic and Mass Spectrometric Characterisation

### 4.2.1.1 Electrospray Mass Spectrometry

All new compounds synthesised in this chapter were good candidates for ES-MS due to their cationic nature. Complexes were dissolved using a few drops of DCM and further diluted in MeOH. ES-MS of compounds **190-197** all showed primary $[M]^+$ ion peaks.

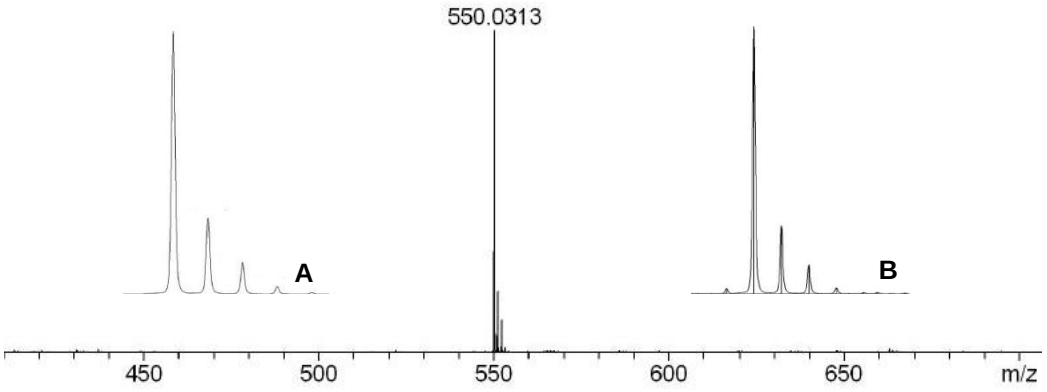



***Figure 4.1:*** *ES-MS Spectrum of [BpAuS$_2$P(OEt)$_2$]BPh$_4$* ***191*** *in dichloromethane (DCM) and MeOH, recorded at capillary exit 160 V, showing [M]$^+$ ion of desired product. Insert* ***A*** *shows generated isotope pattern while insert* ***B*** *shows the experimental isotope pattern of* ***191****.*

### 4.2.1.2 NMR Spectroscopy

$^1$H, COSY, $^{13}$C, DEPT 135, HSQC, NOESY, TOSCY, selective ROESY and $^{31}$P spectra were acquired for compounds **192** and **193** while only $^1$H, COSY and $^{13}$C were acquired for complexes **190**-**191**, **194**-**197**. Due to the presence of other reaction products and/or starting material NMR spectra determined for the latter group of compounds were complex with overlapping and unknown signals which could not be uniquely assigned. Therefore detailed NMR characterisation of complexes **190**, **191**, **194**-**197** was not attempted.

All new gold(III) dithiophosphinate compounds made in this chapter are cationic, therefore require an anion of precipitation. Upon using anion $BPh_4^-$, as described in more detail in Chapter three (Section 3.2.2.1), three signals are observed with the boron atom creating splitting in the neighbouring proton signals of the anion. Due to the complexity of these signals, and overlap with other aromatic areas complete assignment could not be made. To overcome this problem the alternative synthesis using $BF_4^-$ as the anion was trialled with all complexes. However NMR spectra of the resulting products still contained unknown impurities and/or reaction by-products. Therefore following the NMR strategy used in Chapter Three (Section 3.2.2.2) careful analyses of TOCSY, NOESY, COSY, HSQC and 1D-SELROESY data allowed for the characterisation of all protons and protonated carbons in complex **192**, the purest of all six compounds. For mixed

samples individual proton signals were not fully resolved, therefore only some coupling constants were able to be assigned.

#### 4.2.1.3 IR Spectroscopy

The dithiophosphinate and dithiophosphate derivatives **190-197** show asymmetric P-S stretches in the region 647–654 $cm^{-1}$, and symmetric P-S stretches in the region 519–564 $cm^{-1}$. Complexes containing the $S_2P(OEt)_2$ moiety also observed strong stretching frequencies in the ~1400 $cm^{-1}$ region correlating to the $CH_2$ and $CH_3$ groups. Ramirez *et al*[132] reported IR stretches from $Sn(S_2PPh_2)$ at 620 $cm^{-1}$ $\upsilon_{asym}(P\text{-}S_2)$ and 550 $cm^{-1}$ $\upsilon_{sym}(P\text{-}S_2)$, comparable to that reported here.

The IR spectrum of $NH_3S_2P(OEt)_2$ shows strong absorptions in the P-S region of 676 and 576 $cm^{-1}$. Coordination to the gold(III) complex results in a decrease in the stretching frequency of the P-S region to 648 and 531 $cm^{-1}$ for the anilinopyridyl derivative **190** and 654 and 564 $cm^{-1}$ for the benzylpyridyl derivative **191**. Both $NH_3S_2P(OEt)_2$ analogues show much weaker signals than observed in the free ligand indicating that the sulfur atoms are coordinated to the gold centre.

On the other hand, IR spectra of $Ph_2P(S)SH$ shows four absorptions at 542, 639, 689 and 708 $cm^{-1}$ in the P-S stretching region. This is thought to be due to the presence of decomposition product $Ph_2P(S)\text{-}S\text{-}S\text{-}(S)PPh_2$ in the sample of $Ph_2P(S)SH$ used. Therefore the true P-S stretches of diphenyldithiophosphinic acid were not able to be indubitably distinguished from the $Ph_2P(S)\text{-}S\text{-}S\text{-}(S)PPh_2$ impurity. Artem'ev *et al*[133] reported similar stretches when synthesising analogous dithiophosphinates through the reaction of secondary phosphines with elemental sulfur and hydrazine. The characteristic S-H absorption at ~2400 $cm^{-1}$ in the acid was not observed in compounds **192-194**, indicating this bond was lost.

### 4.2.2 X-Ray Crystal Structure of a Single Crystal Obtained from [(Anp)Au($S_2PPh_2$)]$BPh_4$ (192) and [(Bp)Au($S_2PPh_2$)]$BPh_4$ (193)

The X-ray crystal structure determinations of **192** and **193** were carried out in order to obtain the geometry, orientation and bonding of the dithiophosphinate ligand around the gold(III) centre. Views of the structure obtained are shown in Figure 4.2. Structures were solved by direct methods and routinely developed and refined. X-ray crystal data collected from a single crystal was not that of the desired complexes, **192** and **193**, instead showing the structure of a known Au(I) polymeric complex with alternating attached dithiophosphinate ligands.

This complex **178** was first reported by Siasios and Tiekink[134] and structurally investigated in 2001 by Van Zyl *et al*[131], where supplementary crystal data information can be found. Van Zyl *et al* demonstrated this complex to be in the space group I4/m with the presence of short Au-Au interactions (2.9610(3) Å) as confirmed by X-ray crystallography. Literature shows the synthesis of this complex **178**[131] occurs *via* the direct reaction of $Ph_2P(S)$-S-S-$(S)PPh_2$ and [Au(THT)Cl] (THT = tetrahydrothiophene).

Here, X-ray crystal structure analyses were run at a slightly lower temperature than in the literature, therefore show slightly smaller dimensions in this characterisation. Crystals were yellow in colour and long needle like in shape. Further discussion on the believed synthesis and results of this complex can be found in the following Section 4.2.2.1.

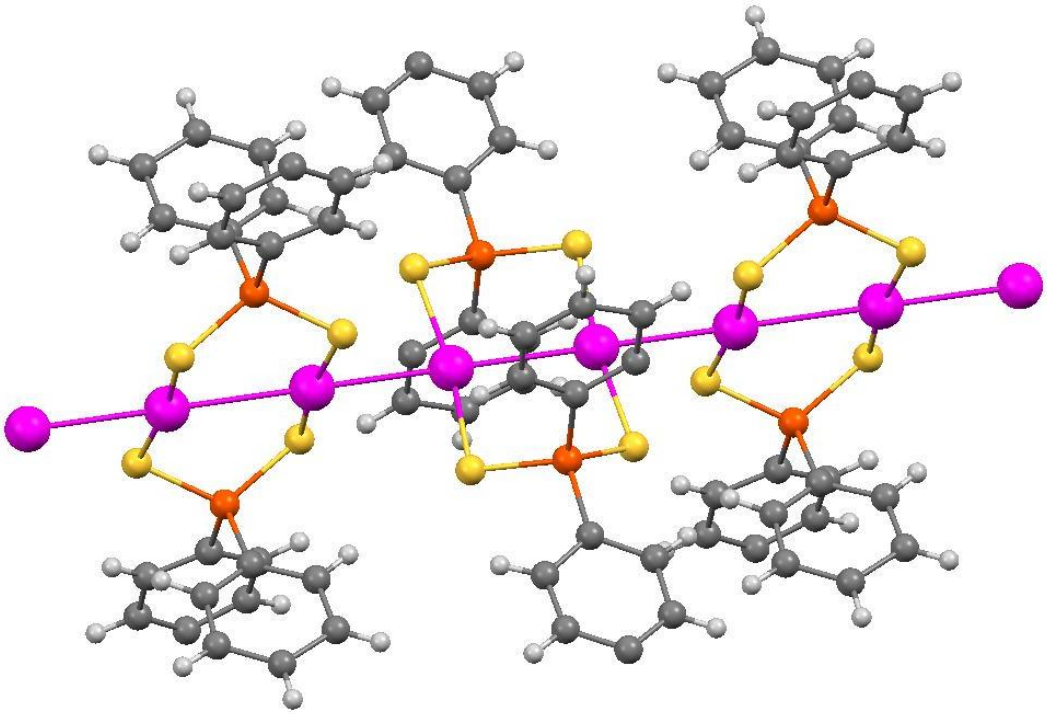


***Figure 4.2:*** *X-ray crystal structure observed from a single crystal obtained from complexes [(Anp)Au($S_2PPh_2$)]$BPh_4$* ***192*** *and [(Anp)Au($S_2PPh_2$)]$BPh_4$* ***193****. Diagram displays a Au(I) polymeric structure with Au(I)-Au(I) interactions.*

### 4.2.2.1 Discussion of Complexes [(Anp)Au($S_2PPh_2$)]$BPh_4$ (192) and [(Bp)Au($S_2PPh_2$)]$BPh_4$ (193)

ES-MS of complexes **192** and **193** displayed the expected $[M]^+$ parent ions at *m/z* 615 and *m/z* 614 respectively, as shown in Figure 4.3. It is clear by this observation that these complexes have been synthesised, showing strong positive results when analysed by ES-MS due to their cationic nature. Complex **178** is not observed in the ES-MS spectrum, this is due to the complex being a neutral polymeric species with no easily ionised sites i.e. sulfur atoms are not easily protonated.

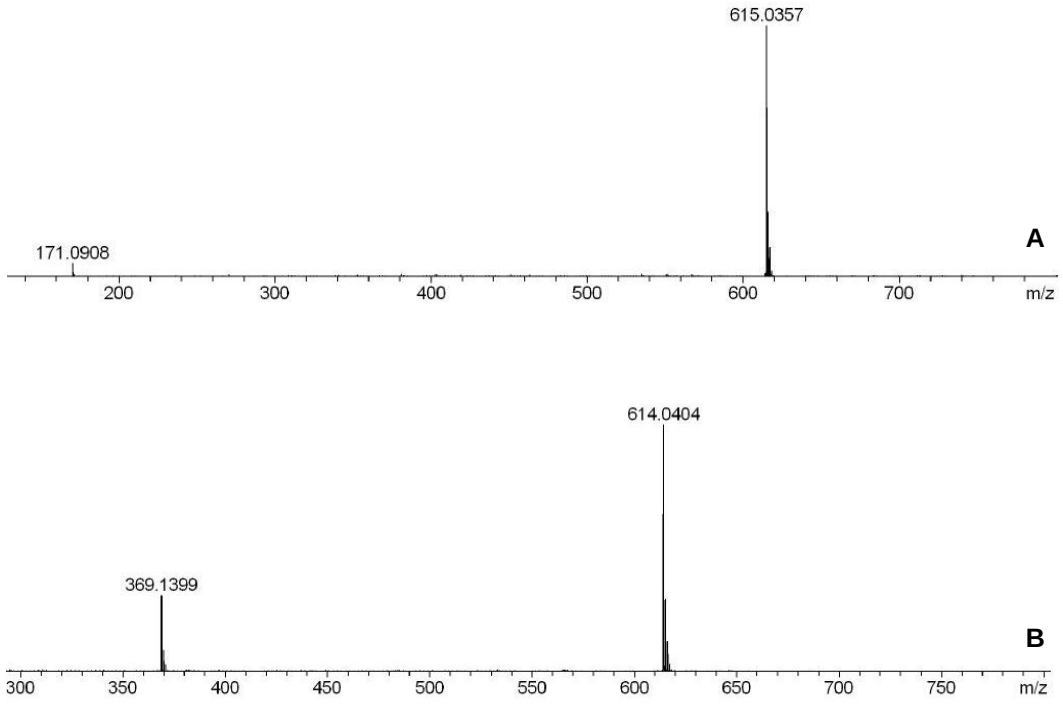
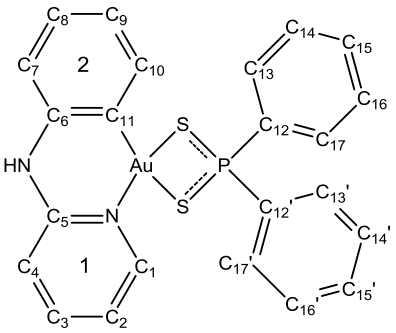



***Figure 4.3:*** *ES-MS Spectra showing desired $[M]^+$ signals of A) $[AnpAuS_2PPh_2]BPh_4$* ***192*** *and B) $[BpAuS_2PPh_2]BPh_4$* ***193*** *in DCM and MeOH, recorded at cone voltage 160 V.*

To further characterise these complexes a series of NMR data were acquired following the NMR strategy used in Chapter Three (Section 3.2.2.2). Careful analyses of TOCSY, NOESY, COSY, HSQC and 1D-SELROESY data allowed for the characterisation of all protons and protonated carbons in complex **193**. On the other hand, NMR of complex **192** shows a mixture of at least three compounds. The $^1$H NMR spectrum of **192** included three doublet like signals in the region 7.9-8.1 ppm attributable to the H-1 protons of the anilinopyridyl moieties, shown in Figure 4.4. Each of these protons exhibited signals to four neighbouring protons which occurred in the vicinity of 7.7 (H3), 6.9 (H2) and 6.8 (H4) ppm (ring 1, Scheme 4.1), together with evidence of three four-spin proton signals (ring 2, Scheme 4.1) observed in the region 7.0-7.6 ppm (see Figure 4.4). The complexity of spectra was such that individual assignments of the 8 protons in each of the three anilinopyridyl moieties could not be unequivocally established. It was also noted that over time the $^1$H spectrum of the mixture became more

complex, indicating decomposition of compounds in the mixture may be occurring.




***Scheme 4.1:*** *Atom numbering scheme for NMR assignment of complex* ***192****.*

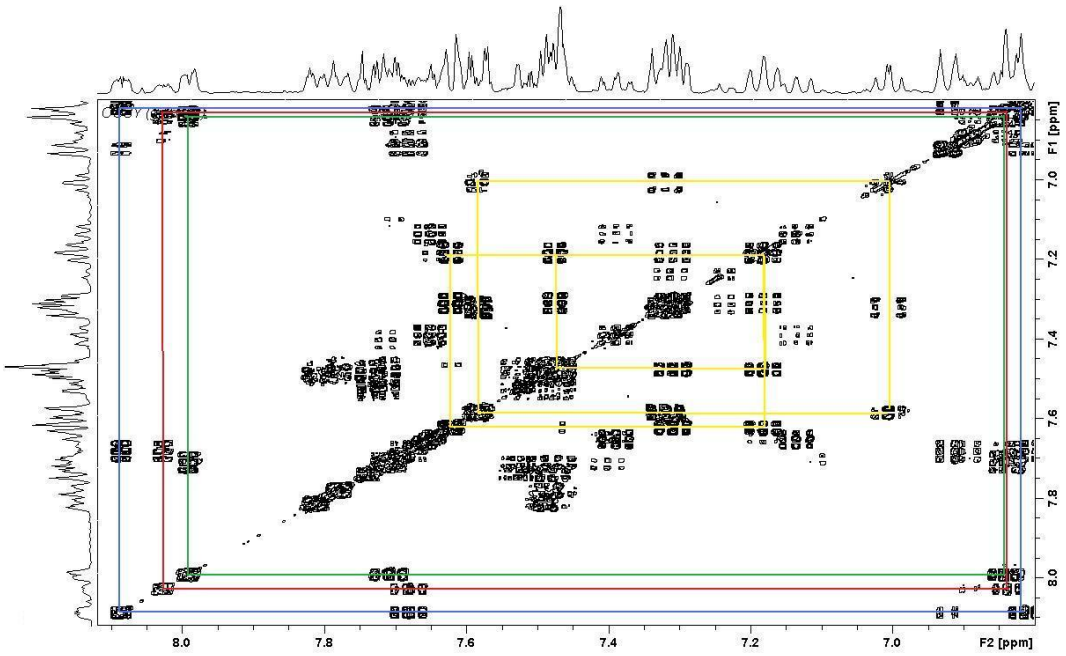



***Figure 4.4:*** *$^{1}$H COSY NMR (400 MHz) spectrum of mixture from* ***192*** *showing $^{1}$H-$^{1}$H correlations between proton environments in the aromatic region. The 3 x H-1 signal correlation patterns were observed at 7.8-8.1 ppm (blue, red and green correlation lines), arising from the 4 protons in ring 1. 3 x correlations patterns (yellow, orange and black correlation lines) were also tentatively identified as arising from the 4 protons in ring 2.*

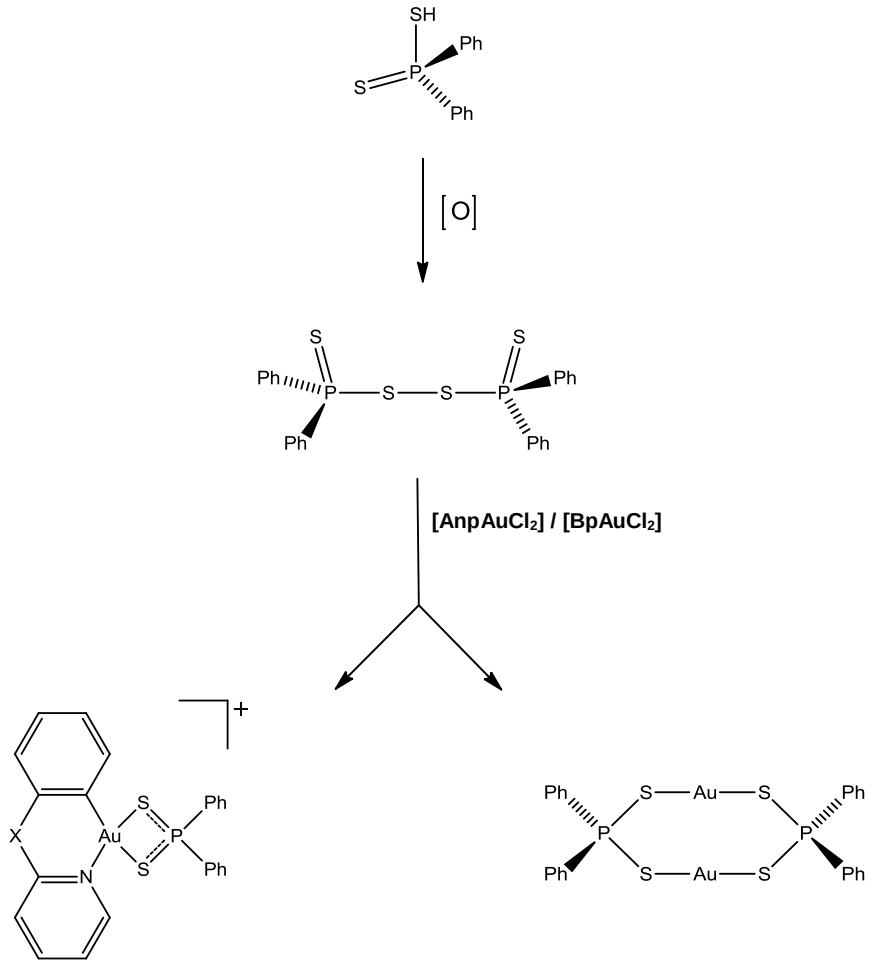
In order to clarify results the purity of starting materials $Ph_2P(S)SH$ and $NH_3S_2PO_2Et_2$ were checked using $^{31}P$ NMR. $^{31}P$ NMR of $NH_3S_2PO_2Et_2$ showed a single resonance at 114.0 ppm in DMSO, while $Ph_2P(S)SH$ gave an array of signals, believed to be due to the DMSO oxidising the sulfur (SH group). Therefore, these samples were re-run in $CDCl_3$, as indicated in literature[132]. Surprisingly the $^{31}P$ NMR spectra of $NH_3S_2PO_2Et_2$ in $CDCl_3$ was found to exhibit multiple resonances, believed to be due to reaction with the solvent, therefore was concluded to be pure by analysis in DMSO. On the other hand $^{31}P$ NMR spectra of $Ph_2P(S)SH$ in $CDCl_3$ observed two signals at 69.52 and 55.85 ppm assignable to $Ph_2P(S)SH$ and $Ph_2P(S)$-S-S-$(S)PPh_2$ respectively. Similar signals were observed by Ramirez *et al*[132] when using diphenyldithiophosphinic acid in studies with inorganic tin complexes. Ramirez *et al*[132] found that decomposition of the $Ph_2P(S)SH$ ligand occurred over time resulting in the subsequential formation of $Ph_2P(S)$-S-S-$(S)PPh_2$.

$^{31}P$ NMR spectra of complexes **192** and **193** were run in $CDCl_3$ showing the presence of a singlet at 70.2 and 67.0 ppm respectively, which can be attributed to the species $Ph_2P(S)$-S-S-$(S)PPh_2$. $^{31}P$ signals arising from the desired complexes $AnpAuS_2PPh_2$ **192** and $BpAuS_2PPh_2$ **193** were observed at 67.0 and 64.1 ppm respectively, showing comparable $^{31}P$ shifts to four member Al-S-P-S ring systems observed by Davies *et al*[135]. Here signals are slightly shifted to a lower field presumably due to the presence of the gold(III) centre.

During experimental procedures described in Section 4.5, the reaction of $Ph_2P(S)SH$ with $BpAuCl_2$ or $AnpAuCl_2$ in MeOH also results in the synthesis of known complex **178**. It is believed that during the reaction oxidation of $Ph_2P(S)SH$ forms $Ph_2P$-(S)-S-S-(S)-$PPh_2$, the starting material used by Van Zyl *et al*[131] in the synthesis of complex **178**. This observation of decomposition was also seen by Ramirez *et al*[136], here it was concluded that the resulting complex $Cl_2Sn(Ph_2PS_2)_2$ was formed by the oxidative addition between $SnCl_2$ and $Ph_2P(S)$-S-S-$(S)PPh_2$, as reported for analogous complex $Cl_2Sn(Et_2PS_2)_2$.

Due to these previously known observations it is thought that complex **178** is formed through the oxidation of the dithiodiphenylphosphinic acid, resulting in

the reduction of gold(III), in starting materials $AnpAuCl_2$ and $BpAuCl2_2$ , to gold(I). Gold(I) shows a high affinity for $S_2PPh_2^-$ therefore resulting in complex $[Au(Ph_2PS_2)_2]$ as shown by Scheme 4.2, while also aiding in oxidation of excess dithiodiphenylphosphinic acid.




***Scheme 4.2:*** *Postulated route of synthesis of desired gold(III) compounds **192** and **193** (left), and reduced gold(I) species **178** (right) .*

It can also be proposed that the oxidation of $NH_4S_2P(OEt)_2$ may occur during reaction with gold(III) complexes giving an analogous species $(OEt)_2P(S)$-S-S-$(S)P(OEt)_2$, consequently contributing to the complexity of the $^1H$ NMR spectrum. This hypothesis was further supported by the presence of two signals present in the $^{31}P$ NMR spectrum of $[TypAuS_2P(OEt)_2]BF_4$.

Over time additional resonances were observed in both $^{31}P$ and $^{1}H$ NMR spectra other than the assigned $Ph_2P(S)SH$, $NH_4S_2P(OEt)_2$ and $Ph_2P(S)\text{-}S\text{-}S\text{-}(S)PPh_2$, $(OEt)_2P(S)\text{-}S\text{-}S\text{-}(S)P(OEt)_2$ signals respectively, demonstrating that further decomposition had occurred.

### 4.3.3 Discussion

Preliminary studies of complexes **190-197** show ES-MS evidence that these compounds were synthesised using the experimental procedures described in Section 4.5. Synthesis using $NaBPh_4$ as an anion for precipitation gave inconclusive NMR and elemental results. The alternative synthesis using $NaBF_4$ was trialled, again yielding complexes with impurities as shown by NMR analysis. After repeated attempts to purify, recrystallise and synthesise these complexes using a variety of independently synthesised batches of starting materials, it was concluded that pure samples of these complexes using methods in this thesis could not be obtained.

On further investigation of the purity of $Ph_2P(S)SH$ using $^{31}P$ NMR analysis it was established that the decomposition product $Ph_2P(S)\text{-}S\text{-}S\text{-}(S)PPh_2$ was observed. Upon addition of this by-product to elemental analysis calculations a much closer theoretical to experimental correlation was established. This further suggests that this by-product is an impurity within the sample.

It can be suggested that the reduction of gold(III) to gold(I) is due to the diphenyldithiophosphinic acid acting as a reducing agent as well as the co-ordinating ligand, therefore alternative dithiophosphinate ligands could be used in future synthetic attempts. Investigation into the variation of the substituents attached to the dithiophoshine group may result in new cyclometallated gold(III) complexes with increased solubility. Future research could be directed at alternative synthetic routes using purer starting materials.

## 4.4 Conclusion

Five new gold(III) dithiophosphinate and three gold(III) dithiophosphate complexes (dithiophosphinate = $R_2PS_2$, dithiophosphate = $R_2O_2PS_2$) have been synthesised, albeit with low purity and yield. Structural characterisation using NMR gave complex spectra due to the presence of impurities and/or reaction by-products resulting in full characterisation of only one of the complexes. Crystals of complexes **192** and **193** were obtained but displayed a known polymeric Au(I) structure, acquired through the reduction of gold(III) to gold(I), therefore no characterisation of geometry and bonding was obtained. Biological activities of these complexes are unknown as testing facilities were unavailable during the timeline of this project.

## 4.5 Experimental

### 4.5.1 General

The reactions were carried out with no efforts at excluding either air or light. The solvents used were drum grade. $AnpAuCl_2$ **125**[80], $BpAuCl_2$ **126**[77] and $TypAuCl_2$ **127**[75] were prepared from literature procedures. Dithiophosphinate ligands, ammonium-O,O-diethyldithiophosphate, diphenyldithiophosphinic acid (Alfa Aesar) and $Na^+Bu_2PS_2^-$ (Cytec Industries) were used without purification. Compounds were stored in the freezer to slow down decomposition. ES-MS were acquired in methanol solvent with addition of small amount of dichloromethane. All $^1H$ and $^{13}C$ NMR spectra were acquired in DMSO, while $^{31}P$ NMR spectra were run in $CDCl_3$. Further information on tools used in characterisation of complexes is provided in Chapter One (Section 2.4) and further NMR details can be found in Appendix II.

***Synthesis of $[AnpAuS_2P(OEt)_2]BPh_4$, 190:***

$AnpAuCl_2$ (11.3 mg; 0.026 mmol) and ammoniumO,O-diethyldithiophosphate (10.1 mg; 0.50 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow solution. After 5 min of stirring $NaBPh_4$ (180 mg, 53 mmol) and distilled water (60 mL) was added and the resulting pale yellow cloudy solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and

stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 3.2 mg (14%) of pale yellow solid.

IR: $\upsilon_{asym}(P\text{-}S_2) = 648\ cm^{-1}$, $\upsilon_{sym}(P\text{-}S_2) = 531\ cm^{-1}$

Microanalysis: Found: C= 45.1%, H= 3.7%, N= 4.1%
$[AnpAuS_2P(OEt)_2]BPh_4$ requires: C= 53.8%, H= 4.5%, N= 3.2%

ES-MS: *m/z*: 551 (100%, $[M]^+$), *m/z* 171 (39%, $[C_{11}H_{11}N_2]^+$)

Alternative Synthesis: The same procedure and methods were used, with $BF_4^-$ used in place of the $BPh_4^-$ anion. $AnpAuCl_2$ (55.7 mg; 0.012 mmol) and ammonium-O,O-diethyldithiophosphate (206 mg; 0.101 mmol, excess) were stirred in MeOH (20 mL) at room temperature. Addition of $NaBF_4$ (180 mg, 0.207 mmol), NaCl (180 mg; 310 mmol) and water (60 mL) resulted in 19.4 mg (24%) of pale yellow solid.

***Synthesis of $[BpAuS_2P(OEt)_2]BPh_4$, 191 :***

$BpAuCl_2$ (19.6 mg; 0.045 mmol) and ammoniumO,O-diethyldithiophosphate (15.0 mg; 0.74 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a slightly yellow solution. After 5 min of stirring $NaBPh_4$ (180 mg, 53 mmol) and distilled water (60 mL) was added and the resulting pale yellow solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 28.4 mg (73%) of light yellow solid.

IR: $\upsilon_{asym}(P\text{-}S_2) = 654\ cm^{-1}$, $\upsilon_{sym}(P\text{-}S_2) = 564\ cm^{-1}$

Microanalysis: Found: C= 49.8%, H= 4.2%, N= 1.8%
$[BpAuS_2P(OEt)_2]BPh_4$ requires: C= 55.2%, H= 4.6%, N= 1.6%

ES-MS: *m/z*: 550 (100%, $[M]^+$), *m/z* 369 (14%, unidentified)

Alternative Synthesis: The same procedure and methods were used, with $BF_4^-$ used in place of the $BPh_4^-$ anion. $BpAuCl_2$ (7.5 mg; 0.017 mmol) and ammonium-O,O-diethyldithiophosphate (12.0 mg; 0.027 mmol, excess) were stirred in MeOH

(20 mL) at room temperature. Addition of $NaBF_4$ (18.0 mg, 207 mmol), NaCl (18.0 mg; 310 mmol).and water (60 mL) resulted in 7.0 mg (64%) of light yellow solid.

***Synthesis of [AnpAuS$_2$PPh$_2$]BPh$_4$, 192:***

$AnpAuCl_2$ (11.0 mg; 0.025 mmol) and diphenyldithiophosphinic acid (16.3 mg; 0.64 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow to orange solution. After 5 min of stirring $NaBPh_4$ (18.0 mg, 53 mmol) and distilled water (60 mL) was added and the resulting cloudy yellow solution was stirred for a further 5 min. NaCl (18.0 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 18.4 mg (73%) of pale yellow solid.

| | |
|---|---|
| IR: | $\upsilon_{asym}(P\text{-}S_2) = 648\ cm^{-1}$, $\upsilon_{sym}(P\text{-}S_2) = 564\ cm^{-1}$ |
| Microanalysis: | Found: C= 58.9%, H= 4.5%, N= 2.4% |
| | $[AnpAuS_2PPh_2]BPh_4.[(S_2PPh_2)_2]$ requires: C= 59.5%, |
| | H= 4.2%, N= 2.0% |
| ES-MS: | *m/z*: 615 (100%, $[M]^+$), *m/z* 169 (26%, $[C_{11}H_9N_2]^+$) |

Alternative Synthesis: The same procedure and methods were used, with $BF_4^-$ used in place of the $BPh_4^-$ anion. $AnpAuCl_2$ (25.3 mg; 0.058 mmol) and diphenyldithiophosphinic acid (30.2 mg; 0.121 mmol, excess) were stirred in MeOH (20 mL) at room temperature. Addition of $NaBF_4$ (18.0 mg, 207 mmol), NaCl (18.0 mg; 310 mmol) and water (60 mL) resulted in 39.6 mg (97%) of pale yellow solid.

***Synthesis of [BpAuS$_2$PPh$_2$]BPh$_4$, 193:***

$BpAuCl_2$ (21.6 mg; 0.086 mmol) and diphenyldithiophosphinic acid (15.0 mg; 0.74 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a slightly yellow solution. After 5 min of stirring $NaBPh_4$ (180 mg, 53 mmol) and distilled water (60 mL) was added and the resulting white suspension was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 30.9 mg (67%) of white to light yellow solid.

Microanalysis: Found: C= 59.0%, H= 4.1%, N= 1.5%
$[BpAuS_2PPh_2]BPh_4.[(S_2PPh_2)_2]$ requires: C= 59.8%, H= 4.2%, N= 1.9%

Alternative Synthesis: The same procedure and methods were used, with $BF_4^-$ used in place of the $BPh_4^-$ anion. $BpAuCl_2$ (10.4 mg; 0.024 mmol) and diphenyldithiophosphinic acid (14.5 mg; 0.057 mmol, excess) were stirred in MeOH (20 mL) at room temperature. Addition of $NaBF_4$ (180 mg, 207 mmol), NaCl (18.0 mg; 310 mmol) and water (60 mL) resulted in 11.0 mg (65%) of light yellow solid.

IR: $\upsilon_{asym}(P\text{-}S_2) = 647\ cm^{-1}$, $\upsilon_{sym}(P\text{-}S_2) = 564\ cm^{-1}$

ES-MS: Capillary exit 80 V: *m/z*: 614 (100%, $[M]^+$), *m/z* 168 (31%, unidentified), *m/z* 168 (10%, $[C_{12}H_{10}N]^+$)

NMR:

***Table 4.1:*** *$^1H$ and $^{13}C$ Chemical shifts of $[BpAuS_2PPh_2]BF_4$* ***193****, recorded at 400 MHz, 300 K in DMSO. Chemical shifts referenced to DMSO.*

| Atom | Type | $^1H$ | $^{13}C$ | |
|---|---|---|---|---|
| 1 | CH | 8.50 | 148.5 | *d*, *J* = 7.6 Hz |
| 2 | CH | 7.27 | 128.1 | |
| 3 | CH | 7.38 | 128.3 | |
| 4 | CH | 7.03 | 132.3 | *d*, *J* = 7.7 Hz |
| 5 | C | - | - | |
| 6 | $CH_2$ | 4.23 | 41.5 | |
| 7 | C | - | - | |
| 8 | CH | 7.14 | 123.9 | *d*, *J* = 7.7 Hz |
| 9 | CH | 7.28 | 128.1 | *t*, *J* = 7.4 Hz |
| 10 | CH | 7.49 | 128.7 | |
| 11 | CH | 7.76 | 138.1 | |
| 12 | C | - | - | |
| 13 | C | - | - | |
| 14, 16, 14', 16' | CH | 7.38 | 128.3 | |
| 15, 16, 17 | CH | 8.00 | 130.7 | |
| 15', 16', 17' | CH | 7.92 | 130.8 | |

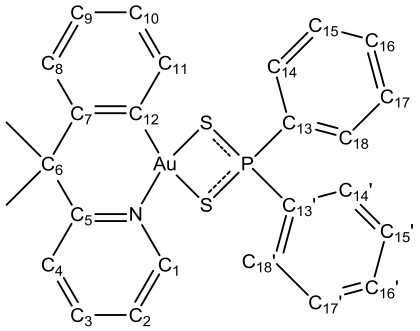



***Figure 4.5:**: Atom numbering scheme for NMR assignment of complex **193**.*

***Synthesis of [TypAuS$_2$PPh$_2$]BF$_4$, 194:***

TypAuCl$_2$ (10.5 mg; 0.024 mmol) and diphenyldithiophosphinic acid (21.3 mg; 0.085 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow solution. After 5 min of stirring $NaBF_4$ (180 mg, 53 mmol) and distilled water (60 mL) was added and the resulting cloudy yellow solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 3.6 mg (21%) of light yellow solid.

IR: $\upsilon_{asym}$(P-S$_2$) = 647 cm$^{-1}$, $\upsilon_{sym}$(P-S$_2$) = 541 cm$^{-1}$

ES-MS: Capillary exit 80 V: *m/z* 614 (100%, $[M]^+$), *m/z* 533 (28%, $[TypAuTyp]^+$), 353 (26%, unidentified)

***Synthesis of [Typ(Au)S$_2$P(OEt)$_2$]BF$_4$, 195:***

TypAuCl$_2$ (8.5 mg; 0.019 mmol) and ammoniumO,O-diethyldithiophosphate (34.3 mg; 0.169 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow solution. After 5 min of stirring $NaBF_4$ (180 mg, 53 mmol) and distilled water (60 mL) was added and the resulting cloudy yellow solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 3.4 mg (27%) of yellow solid.

ES-MS: Capillary exit 200 V: *m/z*: 550 (100%, $[M]^+$), 353 (13%, unidentified)

***Synthesis of [AnpAuS$_2$PBu$_2$]BPh$_4$, 196:***

AnpAuCl$_2$ (24.2 mg; 0.056 mmol) and NaS$_2$P$^i$Bu$_2$ 50% aqueous (300 mg; 0.110 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow solution. After 5 min of stirring NaBF$_4$ (180 mg, 53.0 mmol) and distilled water (30 mL) was added and the resulting slightly cloudy yellow solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 7.4 mg (14%) of yellow solid.

IR: $\upsilon_{asym}$(P-S$_2$) = 593 cm$^{-1}$, $\upsilon_{sym}$(P-S$_2$) = 519 cm$^{-1}$

ES-MS: Capillary exit 80 V: *m/z*: 575 ([M]$^+$)

***Synthesis of [BpAuS$_2$PBu$_2$]BPh$_4$, 197:***

BpAuCl$_2$ (21.8 mg; 0.050 mmol) and NaS$_2$P$^i$Bu$_2$ (50% aq., 300 mg; 0.110 mmol, excess) were stirred in methanol (20 mL) at room temperature giving a yellow solution. After 5 min of stirring NaBF$_4$ (180 mg, 53 mmol) and distilled water (30 mL) was added and the resulting slightly cloudy yellow solution was stirred for a further 5 min. NaCl (180 mg; 310 mmol) was added and stirred for another 5 min. The product was filtered, washed with water (5 × 10 mL) and dried under vacuum to give 3.4 mg (7%) of creamy white solid.

ES-MS: Capillary exit 80 V: *m/z*: 574 ([M]$^+$)

***Attempted synthesis of hypothesised AuCl$_2$.S$_2$PR$_2$ complex:***

This method was modified from the of synthesis of complex **181** established by Ronconi *et al*[55]. A solution of NaS$_2$P$^i$Bu$_2$ 50% aqueous, in water (2 mL) was added drop wise under continuous stirring to an aqueous solution (2 mL) of HAuCl$_2$.3H$_2$O (100 mg; 0.30 mmol). As drops of 50% aqueous NaS$_2$P$^i$Bu$_2$ were added, a red/brown precipitate was observed. After addition of all NaS$_2$PBu$_2$ the precipitate turned a darker red/brown. The solid was isolated by filtration and washed with water (20 mL) leaving a black precipitate. The resulting product was insoluble in DCM and gave unsuccessful ES-MS results; hence these systems were not further investigated.

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# Appendix I

***Literature synthesis of $AnpAuCl_2$***[80]

An ethanol solution of 2-anilinopyridine (128 mg, 0.752 mmol) was added to a solution of $H[AuCl_4].4H_2O$ (104 mg, 0.251 mmol) in the same solvent (50 mL) and the resulting solution is stirred at room temperature. After 15 h the resulting yellow precipitate is filtered off and washed with diethyl ether to give complex $AnpAuCl_2$.

***Literature synthesis of $BpAuCl_2$***[77]

An aqueous solution (20 mL) of $HAuCl_4.3H_2O$ (1 mmol) was added to pure $NC_5H_4(CH_2Ph)$-2 (169 mg, 1 mmol): the resulting yellow suspension was refluxed until the precipitate became white (ca. 8 h). The solid product was filtered off and air dried to give 350 mg (80%) of $BpAuCl_2$.

***Literature synthesis of $TypAuCl_2$***[75]

A solution of 2-(p-tolyl)pyridine (192 mg, 1.13 mmol) in MeCN (3 mL) was added to an aqueous solution (30 mL) of $HAuCl_4.2H_2O$ (340 mg, 1.0 mmol) and the solution allowed to stand overnight. The yellow crystals were filtered, washed with water and dried in vacuo to give 343 mg (73%) of $TypAuCl_3$. The resulting product $TypAuCl_3$ (345 mg, 0.73 mmol) in aqueous MeCN (1:1, 40 mL) was heated to reflux for 6 h, during which time a pale yellow solid formed. The solid was filtered from the hot mixture, and air-dried to give 115 mg (38%) of $TypAuCl_2$ as a pale yellow fluffy solid.

***Literature synthesis of AnpAu(catecholate)***[26]

Aqueous trimethylamine (2 mL, excess) was added to a mixture of $AnpAuCl_2$ (200 mg) and catechol (100 mg) in hot methanol (30 mL) and mixture refluxed for 20 min giving an orange solution which deposited orange-brown microcrystals. After cooling to room temperature, product is filtered off washed with cold methanol (15 mL) and dried under vacuum for 2 h.

***Literature synthesis of BpAu(catecholate)***[26]

Aqueous trimethylamine (2 mL, excess) was added to a mixture of $BpAuCl_2$ (200 mg) and catechol (100 mg) in hot methanol (30 mL) and mixture refluxed for 20 min giving a brown solution. Water (40 mL) was added and after cooling to room temperature, the resulting orange-brown microcrystals were filtered off washed water (5 mL), diethyl ether (10 mL) and dried under vacuum for 2 h. The product was then recrystallised by vapour diffusion of diethyl ether into dichloromethane solution of the complex.

# Appendix II

## Bruker AVIII-400

### *$^{1}H$*

Typically spectra were acquired in DMSO-$d_6$ using 5 mm BBI or BBFO probes installed in a Bruker AVIII-400 spectrometer. $^{1}$H NMR spectra (400.13 MHz) were typically acquired across a 18 ppm window with 32K data points using a 90º pulse and a repetition rate (AQ+D1) of 5.5 sec. Unless otherwise stated the probe temperature was 300K.

### *$^{13}C$*

$^{13}$C and DEPT135 NMR spectra (100.62 MHz) were typically acquired across a 240 ppm window with 32K data points using a 45º pulse and a repetition rate (AQ+D1) of 2.2 sec. Unless otherwise stated the probe temperature was 300K

#### *1D-selective and 2D Spectra*

COSY, TOCSY, ROESY, NOESY, HMBC and HSQC spectra were acquired using standard Bruker supplied pulse programme with spectral windows adjusted to cover the range of signals observed in the samples analysed. Spinlock correlation (mixing) times (D9) for TOSCY and 1D-SELOESY spectra were varied from 20 and 160 msec depending on whether short or long correlations were desired. DEPT135 and HSQC spectra were optimised for a $^{1}J$ value (CNST2) of 145 Hz

1D-SELTOCSY spectra were acquired using a low power 180º refocusing shaped pulse (80,000 µsec, power level SP2dB = 75 dB) centred on the signal of interest. 1D-SELNOESY spectra were run with a NOESY evolution time (D6) of 0.5 sec, while 1D-SELROESY spectra were acquired with a spinlock time of 0.2 sec.

## Bruker AVII-300

### *$^{13}C$*

$^{13}C$ (75.47 MHz) solid state spectra were acquired using an AVRII-300 Spectrometer fixed with a 4 mm MAS BB/$^{1}H$ probe. Typically spectra were run across a 270 ppm window using 1K data points and repetition rate (AQ+D1) of 2.02 sec. The $^{13}C$ 90º pulse time was 6000 msec at 0.5 dB. Probe temperature was 300K. All spectra were proton decoupled.

# Appendix III

***Media for Bioassays***

Mixture of Dulbecco's Modified Eagle Media (90%, high D-glucose formula with L-glutamine) and fetal bovine serum (10%, sourced in New Zealand by Sigma Chemicals Co.) with penicillin-streptomycin (1 mL per 100 mL, penicillin G salt and Streptomycin Sulphate in 0.85% saline).

# Appendix IV

***Crystal and Refinement data for 161 and 167***

| **Empirical formula** | $C_{54}H_{56}AuBN_4S$ | $C_{44}H_{40}AuBN_4S$ |
|---|---|---|
| **Formula weight** | 1000.86 | 864.64 |
| **Temperature** | 98(2) K | 95(2) K |
| **Wavelength** | 0.71073 Å | 0.71073 Å |
| **Crystal system** | Monoclinic<br>Space group: P $2_1/n$ | Monoclinic<br>Space group: C 2/c |
| **Unit cell dimensions** | a = 10.9780(3) Å<br>b = 15.6043(4) Å<br>c = 26.1326(6) Å<br>β = 90.147(2)˚ | a = 32.4207(5) Å<br>b = 13.7033(2) Å<br>c = 19.9928(3) Å<br>β = 124.780(1)˚ |
| **Volume** | 4476.6(2) $Å^3$ | 7295.39(19) $Å^3$ |
| **Z, Calculated density** | 4, 1.485 $g/cm^3$ | 8, 1.574 $g/cm^3$ |
| **Absorption coefficient** | 3.375 $mm^{-1}$ | 4.128 $mm^{-1}$ |
| **F(000)** | 2032 | 3456 |
| **Crystal size** | 0.12 x 0.10 x 0.05 mm | 0.22 x 0.22 x 0.08 mm |
| **Reflections collected / unique** | 87559 / 10758 [R(int) = 0.0844] | 45995 / 9035 [R(int) = 0.0983] |
| **Completeness to theta** | 27.50 100.0 % | 28.35 99.0 % |
| **Absorption correction** | Semi-empirical from equivalents | Semi-empirical from equivalents |
| **Max. and min. transmission** | 0.8494 and 0.6875 | 0.7336 and 0.4636 |
| **Refinement method** | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| **Data / restraints / parameters** | 10758 / 0 / 553 | 9035 / 0 / 465 |
| **Goodness-of-fit on $F^{\wedge 2}$** | 1.018 | 0.957 |
| **Final R indices [I>2σ(I)]** | R1 = 0.0314, wR2 = 0.0585 | R1 = 0.0268, wR2 = 0.0505 |
| **R indices (all data)** | R1 = 0.0532, wR2 = 0.0648 | R1 = 0.0537, wR2 = 0.0545 |
| **Largest diff. peak and hole** | 2.388 and -0.629 $Å^3$ | 0.986 and -0.835 $Å^3$ |