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**Multinuclear PGM Complexes of Thiosemicarbazones:  
Synthesis, Characterisation and Biological Activity**

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University of Cape Town

November 2010

**Multinuclear PGM Complexes of Thiosemicarbazones:  
Synthesis, Characterisation and Biological Activity**

A dissertation submitted to the

University of Cape Town

In fulfilment of the requirements for the degree of

Master of Science

By

**Tameryn Stringer**



Department of Chemistry

University of Cape Town

Supervisor: Dr. G. S. Smith

November 2010

## Declaration

---

I declare that “**Multinuclear PGM Complexes of Thiosemicarbazones: Synthesis, Characterisation and Biological Activity**” is my own work and to the best of my knowledge has never been submitted for any degree or examination in any university. All sources of information used are cited, acknowledged and completely referenced.

Signed by candidate

.....

Ms Tameryn Stringer

.....25/11/2010.....

Date

University of Cape Town

## Acknowledgements

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## **Publications and conference contributions**

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### **Journal article**

*Published in Polyhedron, 2009, 28, 2839.*

Tameryn Stringer, Prinessa Chellan, Bruno Therrien, Nelusha Shunmoogam-Gounden, Denver T. Hendricks and Gregory S. Smith, *Synthesis and Structural Characterization of Binuclear Palladium(II) Complexes of Salicylaldimine Dithiosemicarbazones.*

### **Conference Contributions**

*Poster Presentation at the INORGANIC Conference 2009, Bloemfontein, South Africa.*

Tameryn Stringer and Gregory S. Smith, *Mono-, Di- and Trinuclear Palladium Complexes of Thiosemicarbazones: Synthesis, Characterization and Biological Activity.*

University of Cape Town

## Abstract

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A series of mono- and dithiosemicarbazone ligands were prepared by simple Schiff-base condensation reactions between thiosemicarbazides and various substituted salicylaldehydes. In addition, a new series of thiosemicarbazone compounds, which we have called “trithiosemicarbazones”, have been prepared using similar chemical procedures as the mono- and dithiosemicarbazone compounds. These compounds were characterised using elemental analysis, Fourier Transform-Infrared (FT-IR), and Nuclear Magnetic Resonance ( $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$ ) spectroscopy. New compounds were also characterised by Electrospray Ionisation mass spectrometry (ESI-MS).

A new series of neutral Pd(II) and Pt(II) PTA mono-, di- and trinuclear thiosemicarbazone complexes have also been synthesised using templated reactions between various substituted salicylaldimine thiosemicarbazone ligands and metal precursors of the general formula *cis*-[M(PTA)<sub>2</sub>Cl<sub>2</sub>], where M = Pd or Pt. Characterisation of these complexes was achieved by common analytical and spectroscopic techniques: elemental analysis, ESI-MS, FT-IR, and NMR ( $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$  and  $^{31}\text{P}\{^1\text{H}\}$ ) spectroscopy. Single crystal X-ray diffraction was used to confirm the molecular structure of a mononuclear Pd(II) derivative and reveals tridentate coordination of the thiosemicarbazone, with sulfur in the thiolate form, to the metal centre. *In vitro* biological evaluation of selected complexes and their free ligands was carried out to investigate their potential anticancer (against *WHCO1* oesophageal cancer cells) and antiparasitic activity (against the T1 strain of *T. vaginalis*). The mononuclear Pd(II) complexes were found to display activity in both evaluations. In some instances the complexes tested displayed better activity than their parent ligands. The dinuclear and some trinuclear complexes did not display sufficient solubility in the testing medium and therefore were not evaluated.

As an extension of the afore-mentioned study, a series of cationic arene-ruthenium(II) mono- and dinuclear thiosemicarbazone complexes were prepared from the reaction of  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})\text{Cl}]_2$  and  $[\text{Ru}(\eta^6\text{-C}_6\text{H}_5(\text{CH}_2)_3\text{COOH})(\mu\text{-Cl})\text{Cl}]_2$  with benzaldehyde thiosemicarbazones. The analytical and spectroscopic techniques support the structure and

## Abstract

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composition of these complexes. Single crystal structure determination was carried out on a mononuclear derivative and revealed coordination of the ( $\eta^6$ -*p*-cymene)ruthenium(II) complex in a pseudo-tetrahedral, piano-stool conformation. The anticancer activity of these compounds was investigated and two of the complexes displayed moderate cytotoxicity against the *WHCO1* cell-line.

University of Cape Town

## Abbreviations

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ACN	Acetonitrile
Ac	Acetylpyridine
ATSC	anthraldehyde thiosemicarbazone
Ax	Axial
br	broad
ca.	approximately
CI	Confidence Interval
COD	cyclooctadiene
COSY	Correlation spectroscopy
d	doublet
DCM	dichloromethane (methylene chloride)
dd	doublet of doublets
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphine)butane
DNA	Deoxyribonucleic Acid
EA	Elemental Analysis
en	ethylenediamine
EPR	Enhanced Permeability and Retention
ESI	Electrospray Ionisation
Et	ethyl
eq	equivalent(s)
Eq	equatorial
FT-IR	Fourier Transform-Infrared
GI <sub>50</sub>	50% growth inhibition
IC <sub>50</sub>	half maximal inhibitory concentration
H2Bz	2-benzoylpyridine
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
imi	imidazole
ind	indazole
LD <sub>50</sub>	median lethal dose
Lit	Literature
m	multiplet

## Abbreviations

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Me	methyl
MHz	Megahertz
m.p.	melting point
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MS	Mass Spectrometry
m/z	mass to charge ratio
n/d	not determined
NMR	Nuclear Magnetic Resonance
OMe	methoxy
PAT	Polyamine Transporter
PBMC	Peripheral Blood Mononuclear Cells
PGM	Platinum Group Metal
Ph	phenyl
PHA	phytohaemagglutinin
PPI	poly(propylene)imine
ppm	parts per million
PTA	1,3,5-triaza-7-phosphaadamantane
RNR	Ribonucleotide Reductase
s	singlet
t	triplet
<sup>t</sup> Bu	tertiary butyl
tert	tertiary
TSC	thiosemicarbazone
q	quartet
qn	quintet

# **CHAPTER 1**

## **Introduction and Brief Overview of Metal-Containing Thiosemicarbazone Compounds as Biological Agents**

University of Cape Town

### 1.1. Cancer: A brief overview

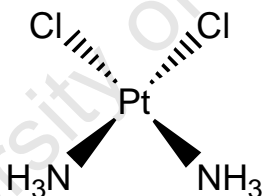
Cancer is described as a disease caused by uncontrolled growth and reproduction of abnormal cells.<sup>1</sup> The invasion of the adjoining parts of the body by the cancer is referred to as metastasis. If the spread of these cells is not prevented, death of the individual often occurs. Cancer is caused by many factors such as smoking of tobacco, chemical exposure to carcinogens or radiation (external factors), as well as inherited mutations, hormones and immune conditions (internal factors).<sup>1</sup> Most cancers require multiple steps in order to develop and the process may take several years to reveal itself. Ageing is another factor that contributes to the development of cancer. The occurrence of cancer increases dramatically with age and this may be due to a build-up of risks for specific cancers. The risk accumulation, combined with ineffective cellular repair mechanisms may result in cancer development.<sup>2</sup>

After heart disease, cancer is the second major cause of death globally. In 2004, 13% of the deaths that occurred worldwide were directly related to cancer.<sup>2</sup> The most common cancers that contribute towards millions of deaths each year include breast, liver, colorectal, stomach as well as lung cancer.<sup>2</sup> Certain cancers can be prevented by eliminating exposure to tobacco and other factors that accelerate the process. Some malignancies can be detected before cells become cancerous and can be treated by surgery, radiotherapy or chemotherapy.<sup>3</sup> Targeted therapy is another commonly used treatment. Surgery is implemented when the cancerous growth can be surgically removed from the body. This usually occurs in the early stages of the disease. Radiotherapy uses radiation to treat cancer. The radiotherapy is targeted at the cancerous part of the body<sup>4</sup> and it uses high energy particles such as radioactive sources to destroy or damage these cells.<sup>5</sup> Chemotherapy uses drugs to weaken and destroy cancer cells in the body, including cells at the original site of cancer and any cancer cells that may have spread to other parts of the body.<sup>6</sup> Targeted therapy is a term that refers to a medication or drug that targets a specific pathway in the development of a tumour by blocking these pathways.<sup>7</sup> Chemo- and targeted therapy are also non-invasive techniques whereby drugs are administered intravenously or orally. Some of these drugs include metal-containing compounds that are quite effective against certain cancer strains.



## 1.2. Metal-containing compounds as anticancer agents

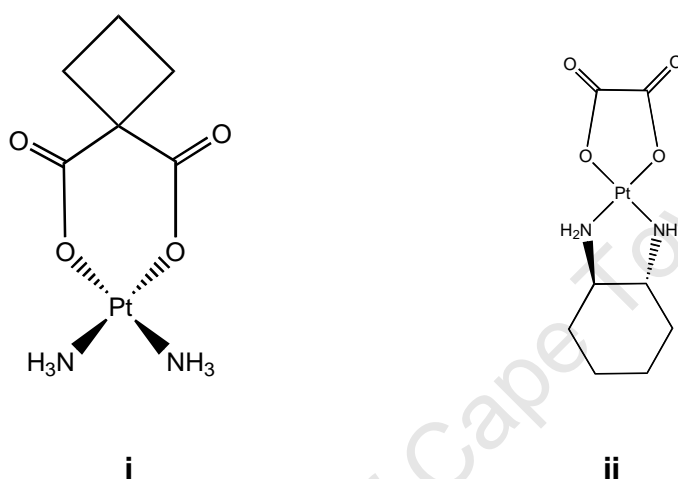
Metal-containing compounds have been used therapeutically for many years. One of the reasons for their frequent use as potential therapeutic agents is due to their high reactivity.<sup>8-10</sup> The most influential discovery of a metal-containing therapeutic agent was made in 1964 when Rosenberg and co-workers<sup>11</sup> discovered the anticancer activity of *cis*-diamminedichloroplatinum(II), commonly referred to as cisplatin (Figure 1.1). To date, cisplatin is regarded as the most effective as well as most frequently used anticancer drug.<sup>12</sup> It is understood that this compound interacts with DNA causing damaging effects which in turn leads to cell apoptosis (programmed cell death). Cisplatin is administered into the patient's bloodstream where it remains neutral, however, once it crosses the cell membrane the chlorido atoms are displaced by water, giving rise to a cationic metal species. The complex then interacts with nitrogen atoms of two adjacent DNA bases (particularly N7 of purine). As a result, the DNA becomes bent and is recognised by High-Mobility Group (HMG) proteins. These proteins then bind and therefore prevent the repair of the DNA.<sup>13</sup>



**Figure 1.1:** Cisplatin, a powerful anticancer drug frequently used today

Since the discovery of cisplatin, many structural analogues have been synthesised and their biological properties tested. An example of a second generation platinum drug is *cis*-diamine-1,1-cyclobutane dicarboxylate platinum (carboplatin), which is similar in structure to cisplatin as it consists of two *cis*-amines, but differs in that the chloride groups are replaced by a bidentate dicarboxylate (Figure 1.2.i). Its biological mechanism is analogous to that of cisplatin and is also commonly used as a clinical agent.<sup>12</sup>

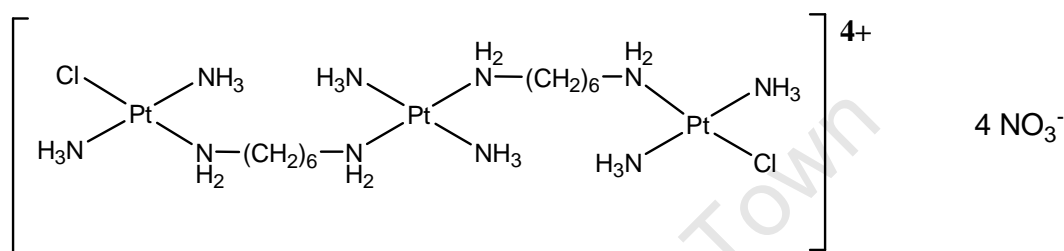
Although these agents are still in use today, there are some limitations. These arise due to the development of drug resistance in various cancer cells. In addition to this, they also exhibit some toxic properties.<sup>12</sup> Further research into the development of structural analogues is therefore crucial to subdue the effects of drug resistance. Oxaliplatin (Figure 1.2.ii), another analogue of cisplatin, was found to be an effective treatment for gastric cancer and displayed activity against cisplatin resistant cell-lines.<sup>14</sup>



**Figure 1.2:** Second generation Pt drugs i) carboplatin and ii) oxaliplatin

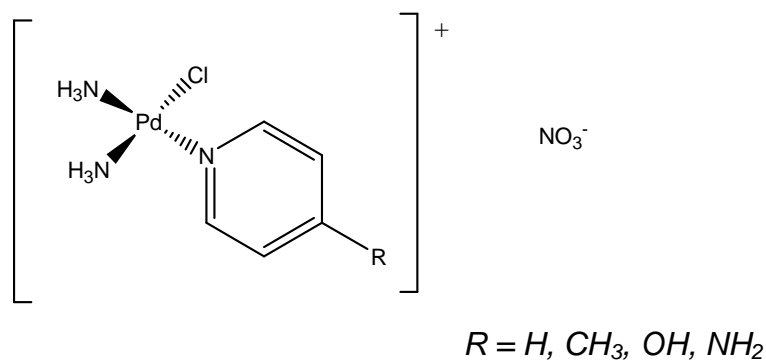
With the exception of carboplatin and oxaliplatin, many mononuclear derivatives fail to display improved pharmacological properties in comparison to cisplatin when undergoing clinical trials.<sup>15</sup> This is mainly attributed to the similarities of the cellular mechanisms of these mononuclear analogues. In order to overcome this, the idea of designing and synthesising multinuclear derivatives was investigated to perhaps give rise to compounds possessing innovative mechanisms. Dinuclear platinum complexes possessing two platinum centres linked by a variable amine length chain were designed with the intent to form different DNA adducts than the mononuclear compounds. Specifically, these dinuclear derivatives would form “long-distance” DNA cross-links (intra- or interstrand), which are unavailable to the mononuclear derivatives.<sup>16</sup> To improve on the binding ability of these compounds, trinuclear platinum complexes were investigated. BBR3464 (Figure 1.3) is an example of this kind of complex. This compound possesses two Pt(NH<sub>3</sub>)<sub>2</sub>Cl units linked by a platinum tetraamine unit. Tests against various cisplatin resistant human cell-lines revealed

considerable activity of this compound displaying  $IC_{50}$  (drug concentration that reduces the number of living cells by 50%) values at least 20-fold lower than cisplatin. Further investigation suggested that this compound possessed a distinct cellular mechanism of action, which possibly contributes to its potent activity.<sup>17</sup> Since this discovery, BBR3464 has undergone Phase II clinical trials but was found to be highly toxic and therefore further studies with this compound is not recommended.<sup>18</sup> There is therefore scope to develop other multinuclear containing compounds possessing similar activity but displaying lower toxicity.



**Figure 1.3:** BBR3464, a multinuclear platinum complex

In addition to platinum, palladium is another example of a platinum group metal (PGM) that displays promise in terms of its cytotoxic abilities. Palladium complexes are structurally analogous to platinum complexes and many compounds are known to exhibit greater lability when compared to their platinum analogues.<sup>19</sup> Palladium-containing compounds of the form  $[Pd(en)(L)Cl]NO_3$  (where en = ethylenediamine and L = pyridine, 4-methylpyridine, 4-hydroxypyridine or 4-aminopyridine), Figure 1.4, have exhibited cytotoxic behaviour comparable to cisplatin. These compounds have displayed activity against the human leukaemia cell-line, *HL-60*.<sup>20</sup>

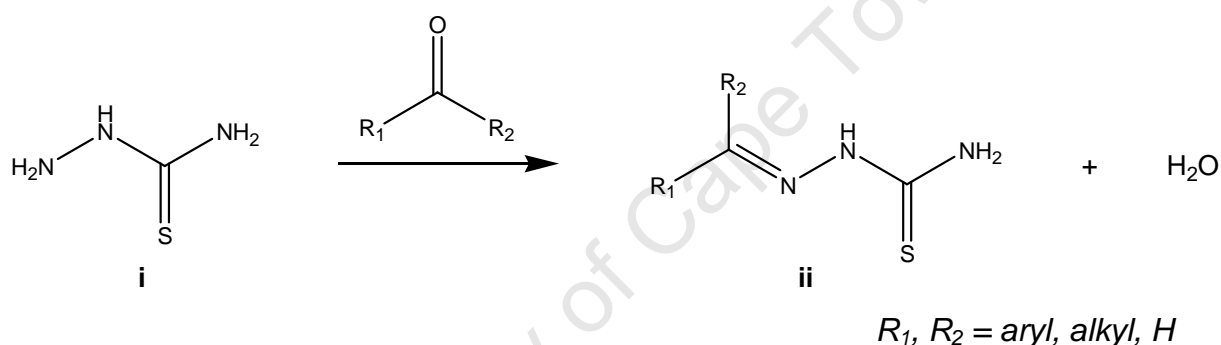


**Figure 1.4:** Palladium compounds displaying anticancer activity

Until now, very few PGM compounds have reached advanced clinical trial stages.<sup>21,22</sup> This limited success may be attributed to a lack of structural diversity in many of these complexes.

### 1.3. Thiosemicarbazones: synthesis and anticancer activity

Thiosemicarbazones are examples of compounds that exhibit great structural diversity as they possess various donor atoms, including nitrogen and sulfur, which can coordinate to electron-deficient metals (palladium and platinum) in a variety of ways. Thiosemicarbazones are prepared by means of Schiff-base condensation reactions between thiosemicarbazides (Figure 1.5.i) and substituted aldehydes/ketones to give rise to the desired thiosemicarbazones (Figure 1.5.ii).

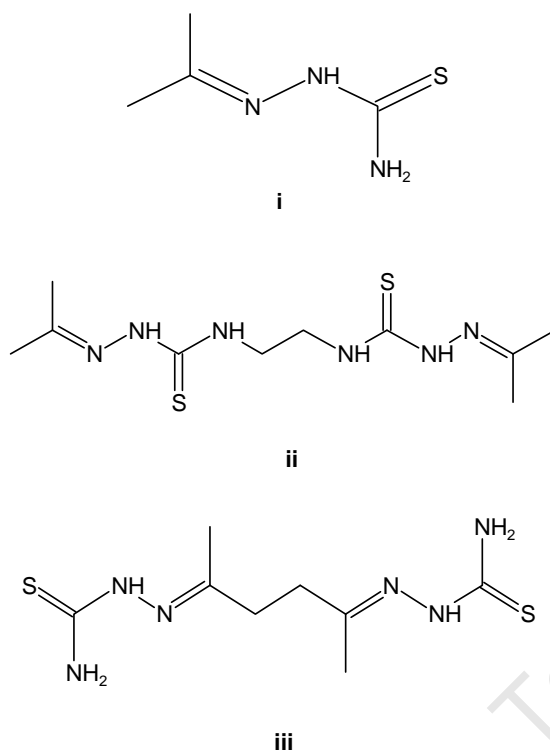


**Figure 1.5:** The general preparation of many thiosemicarbazones

Thiosemicarbazones can be classified into three main groups:

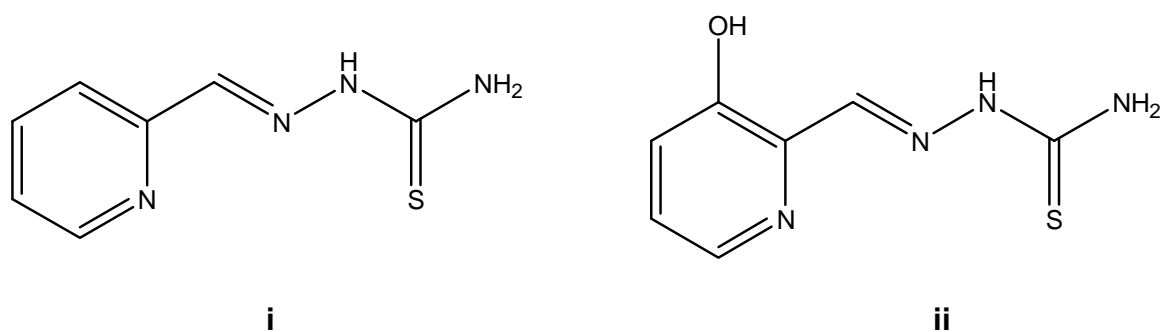
- monothiosemicarbazones (Figure 1.6.i)
- dithiosemicarbazones (Figure 1.6.ii)
- bis(thiosemicarbazones) (Figure 1.6.iii)

Monothiosemicarbazones, as their name suggests, consist of one thiosemicarbazone moiety, while bis(thiosemicarbazones) consist of two moieties linked via their imine nitrogens to an organic spacer. Dithiosemicarbazones also constitute two thiosemicarbazone moieties; however, these are linked to an organic spacer via their amine nitrogen atoms.<sup>23</sup>



**Figure 1.6:** Three classes of thiosemicarbazones i) monothiosemicarbazones ii) dithiosemicarbazones iii) bis(thiosemicarbazones)

Thiosemicarbazones have received considerable attention due to their potential pharmacological applications.<sup>24,25</sup> Monomeric N-heterocyclic 2-formylpyridine<sup>26</sup> (Figure 1.7.i) and 3-hydroxy-2-formylpyridine<sup>27,28</sup> (Figure 1.7.ii) thiosemicarbazones exhibit anticancer properties. Previous investigation of these anticancer abilities revealed that having the heterocyclic atom adjacent to the thiosemicarbazone side chain contributes favourably towards the activity of the compound. A conjugated N-N-S system also further enhances the activity.<sup>29</sup>

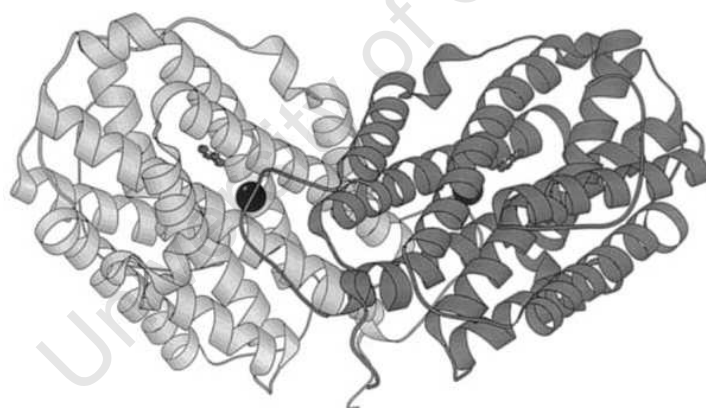


**Figure 1.7:** N-heterocyclic thiosemicarbazones that possess anticancer activity

The biological mechanism of action of most thiosemicarbazones involves the inhibition of DNA synthesis by three possible mechanisms:<sup>30</sup>

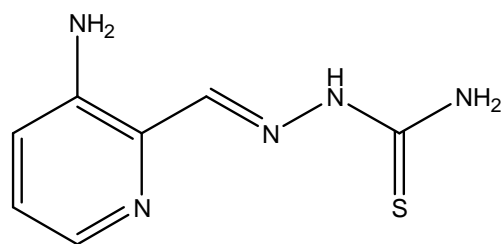
- blocking of the enzyme ribonucleotide reductase
- blocking or retarding base replication by binding to DNA
- or creating DNA ruptures

The mechanism involving ribonucleotide reductase (RNR) is the most widely accepted mechanism. RNR is an enzyme responsible for the conversion of the four standard nucleotides i.e., 5'-di (or tri) phosphoadenosine, -cytidine, -guanosine and -uridine, to their 2'-deoxyribonucleotide counterparts and therefore provides the necessary precursors for DNA synthesis and repair.<sup>31</sup> Mammalian RNR (Figure 1.8) is made up of two subunits, R1 and R2, which provide unique targets to inhibit the enzyme.<sup>32</sup> R1 is the binding site for nucleotides and is also the target for certain anticancer drugs.<sup>33</sup> The second subunit, R2, is a metal binding site that requires a tyrosine free radical and non-heme iron for its activity.<sup>34</sup>



**Figure 1.8:** Ribbon structure of a mouse R2 subunit within ribonucleotide reductase<sup>35</sup>

A well known thiosemicarbazone RNR inhibitory agent currently being evaluated in various clinical trials is 3-aminopyridine-2-carboxaldehyde thiosemicarbazone or triapine (Figure 1.9). It has been reported to inhibit the R2 subunit of RNR through alteration of the tyrosine free radical and it is also a strong iron chelator.<sup>36a</sup> Most thiosemicarbazone compounds are believed to inhibit the enzyme in a similar manner.<sup>36b</sup>

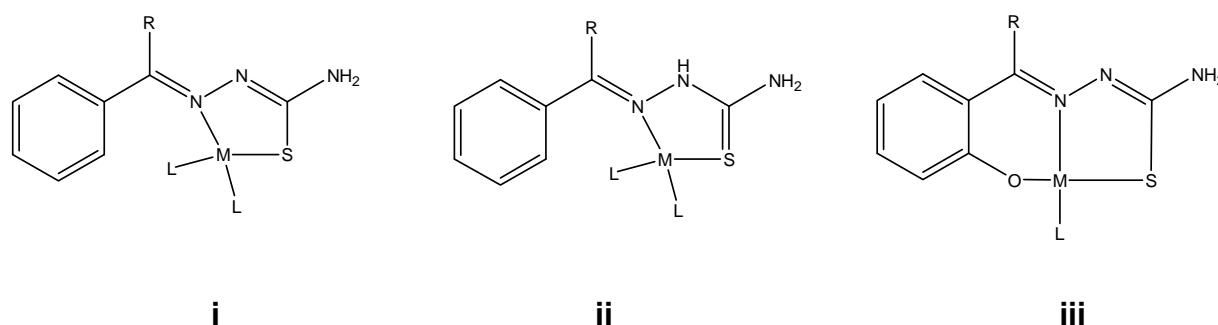


**Figure 1.9:** Structure of Triapine, an inhibitor of ribonucleotide reductase

There are a vast number of thiosemicarbazones that display antitumour activity in addition to the above mentioned compound. Metal complexes of thiosemicarbazones have been synthesised and have also exhibited antitumoural abilities. In some cases these complexes displayed enhanced activity in comparison to their ligand counterparts. Studies have shown that some thiosemicarbazone complexes of iron and copper have shown greater cell destruction than their corresponding ligands.<sup>29</sup>

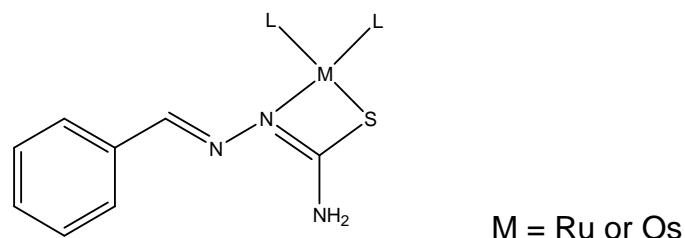
#### 1.4. Modes of coordination occurring within thiosemicarbazone complexes

There are various ways in which metal centres can coordinate to a free thiosemicarbazone ligand. Thiosemicarbazones containing two donor atoms such as nitrogen and sulfur, are more commonly considered to be bidentate ligands. Coordination usually involves dissociation of the hydrazinic proton, resulting in the formation of a five-membered chelate ring (Figure 1.10.i).<sup>37</sup> Complexation of the ligand can also occur in the thione form depending on the metal involved (Figure 1.10.ii). Tridentate coordination may also occur, provided a third donor site such as oxygen is incorporated into the thiosemicarbazone ligand (Figure 1.10.iii).<sup>37</sup>



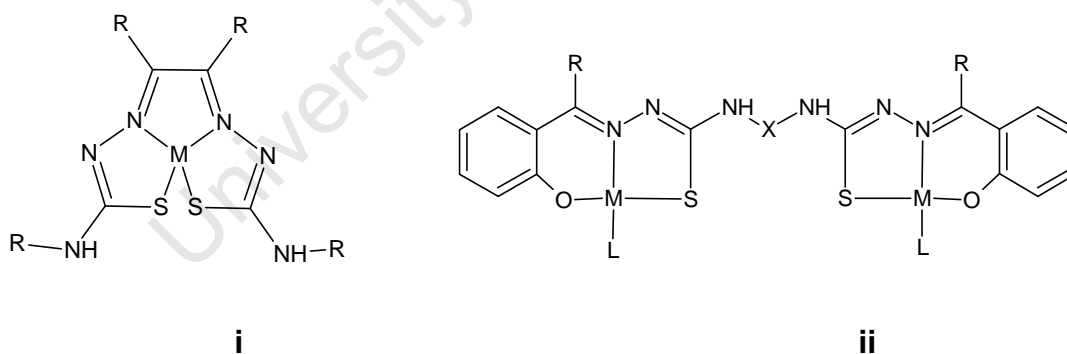
**Figure 1.10:** Possible modes of coordination of thiosemicarbazones i) bidentate (thiolate)  
ii) bidentate (thione) iii) tridentate

In addition to the afore-mentioned, there are various other ways in which coordination can occur. For example, complexes containing four-membered chelate rings with metals such as ruthenium and osmium with salicylaldehyde and benzaldehyde thiosemicarbazones have also been reported.<sup>38,39</sup> In these cases coordination occurs to the thiolate sulfur and the hydrazinic nitrogen as displayed in Figure 1.11.



**Figure 1.11:** Unusual mode of coordination observed for thiosemicarbazone complexes containing ruthenium and osmium

Bis(thiosemicarbazones) are usually tetradentate ligands as coordination of one metal centre may occur in an S-N-N-S manner (Figure 1.12.i). The spatial arrangement of the sulfur and nitrogen atoms of a dithiosemicarbazone allows for the coordination of more than one metal centre (Figure 1.12.ii).<sup>23</sup>



**Figure 1.12:** Possible modes of coordination via i) bis(thiosemicarbazones)  
ii) dithiosemicarbazones

### 1.5. Anticancer activities of some PGM mono- and bis(thiosemicarbazone) complexes

A number of thiosemicarbazone metal complexes have been synthesised and tested for their anticancer ability. Some of the transition metals incorporated into these

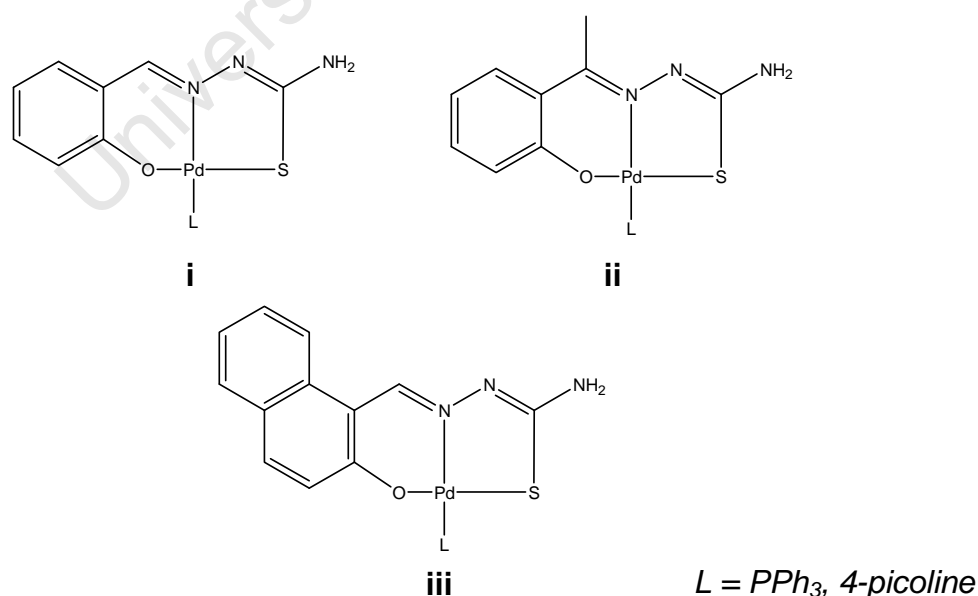


thiosemicarbazone complexes include Cu, Au, Ni, Sn, Pd, Pt and Ru.<sup>40</sup> More pertinent to our study we will look at some examples of platinum group metals including palladium, platinum and ruthenium complexes that have been evaluated for their anticancer properties.

### 1.5.1. Palladium thiosemicarbazone complexes

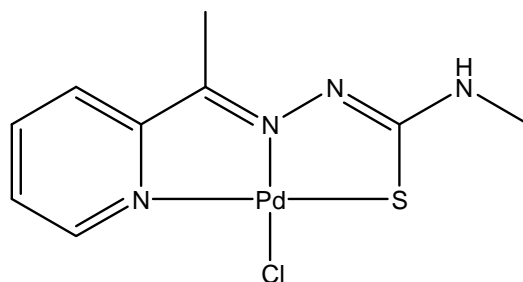
#### *Monothiosemicarbazone complexes*

Polymeric complexes of the type  $[Pd(TSC)]_n$ , where TSC = salicylaldehyde thiosemicarbazone (TSC1), 2-hydroxyacetophenone thiosemicarbazone (TSC2) or 2-hydroxynaphthaldehyde thiosemicarbazone (TSC3), were obtained and reaction with two monodentate ligands (L), where L =  $PPh_3$  or 4-picoline, affording the complexes  $[Pd(TSC1)(L)]$  (Figure 1.13.i),  $[Pd(TSC2)(L)]$  (Figure 1.13.ii) and  $[Pd(TSC3)(L)]$  (Figure 1.13.iii). These complexes were screened for their cytotoxicity along with cisplatin, BCNU, 5-fluorouracil (5-FU) and hydroxyurea, which are clinical drugs. These studies were carried out in two human tumour cell-lines, i.e. promyelocytic leukaemia (*HL-60*) and histiocytic lymphoma (*U-937*). Studies revealed that  $[Pd(TSC2)(PPh_3)]$  showed the lowest  $IC_{50}$  value and was more cytotoxic than the reference drugs in both cell-lines.<sup>37</sup>



**Figure 1.13:** Palladium complexes of the general form  $[Pd(TSC)(L)]$  that exhibit cytotoxicity





**Figure 1.15:** Pd(II) complex derived from 2-acetylpyridine thiosemicarbazone-N-Me displaying cytotoxic behaviour

### *Bis(thiosemicarbazone) complexes*

Cyclopalladated complexes derived from  $\alpha$ -diphenyl ethanedione bis(thiosemicarbazone) and  $\alpha$ -diphenyl ethanedione bis(4-ethylthiosemicarbazone) were evaluated for potential cytotoxic activity. The cytotoxic activities of the ligands and complexes were tested against human *A2780* and *A2780cisR* ovarian carcinoma cell-lines and the ligands were found to display higher activity compared to the complexes. The lack of activity displayed by the palladium complexes is probably attributed to the presence of four bulky phenyl groups which may sterically hinder metal–DNA interactions.<sup>43</sup>

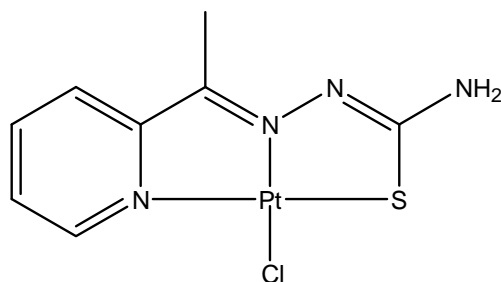
### 1.5.2. Platinum thiosemicarbazone complexes

#### *Monothiosemicarbazone complexes*

The effect of 2-acetylpyridine thiosemicarbazone (AcTSC) Pt(II) derivatives,  $[\text{Pt}(\text{AcTSC})_2] \cdot \text{H}_2\text{O}$ ,  $[\text{Pt}(\text{AcTSC})\text{Cl}]$  and  $[\text{Pt}(\text{HAcTSC})_2]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$  against leukaemia *P388* cells was investigated. It was found that  $[\text{Pt}(\text{AcTSC})_2] \cdot \text{H}_2\text{O}$  induced the greatest antitumour effects, while  $[\text{Pt}(\text{AcTsc})\text{Cl}]$  and  $[\text{Pt}(\text{HAcTsc})_2]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$  displayed marginal effects. The complexes also display decreased toxicity in comparison to the free ligands.<sup>44</sup>

Reaction of  $\text{Na}_2[\text{PtCl}_4]$  with 2-acetylpyridine thiosemicarbazone (HAcTSC) in various stoichiometric amounts afforded three platinum complexes  $[\text{Pt}(\text{AcTSC})\text{Cl}]$  (Figure 1.16),  $[\text{Pt}(\text{HAcTSC})_2]\text{Cl}_2$  and  $[\text{Pt}(\text{AcTSC})_2]$ . These complexes were screened against

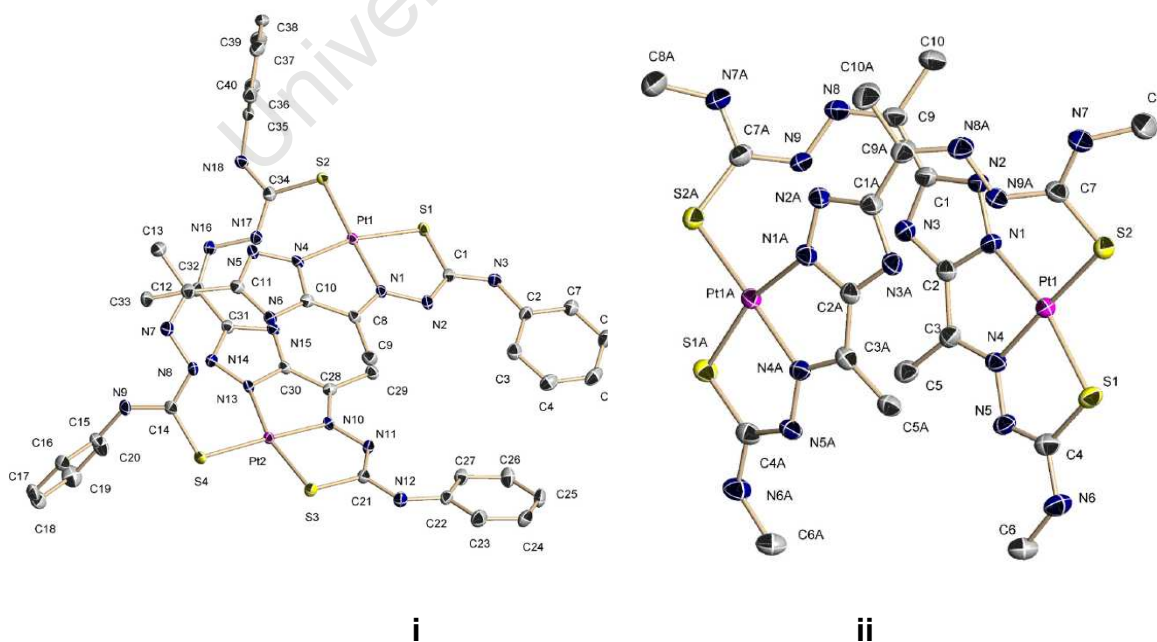
leukaemia P388.  $[\text{Pt}(\text{AcTSC})_2]$  was found to be the most effective in inducing antitumour effects. The rest of the compounds exhibited marginal effects.<sup>45</sup>



**Figure 1.16:**  $[\text{Pt}(\text{ACTSC})\text{Cl}]$  displays marginal effects against leukaemia P388

### Bis(thiosemicarbazone) complexes

Pt(II) complexes derived from 3,5-diacetyl-1,2,4-triazol bis(4-phenylthiosemicarbazone) ( $\text{H}_5\text{L}^1$ ), 3,5-diacetyl-1,2,4-triazol bis(thiosemicarbazone) ( $\text{H}_7\text{L}^2$ ), 3,5-diacetyl-1,2,4-triazol bis(4-methylthiosemicarbazone) ( $\text{H}_5\text{L}^3$ ) and 3,5-diacetyl-1,2,4-triazol bis(4-ethylthiosemicarbazone) ( $\text{H}_5\text{L}^4$ ) were evaluated *in vitro* for their potential anticancer activity. The complexes  $[\text{Pt}(\mu\text{-H}_3\text{L}^1)]_2$ ,  $[\text{Pt}(\mu\text{-H}_5\text{L}^2)]_2$ ,  $[\text{Pt}(\mu\text{-H}_3\text{L}^3)]_2$  and  $[\text{Pt}(\mu\text{-H}_3\text{L}^4)]_2$  were screened against human A2780 and A2780cisR epithelial ovarian carcinoma cell-lines for their cytotoxic activity. The  $\text{IC}_{50}$  values obtained were found to be comparable to that of cisplatin.<sup>46</sup> Figure 1.17 displays the molecular structures of  $[\text{Pt}(\mu\text{-H}_3\text{L}^1)]_2$  (Figure 1.17.i) and  $[\text{Pt}(\mu\text{-H}_3\text{L}^3)]_2$  (Figure 1.17.ii).

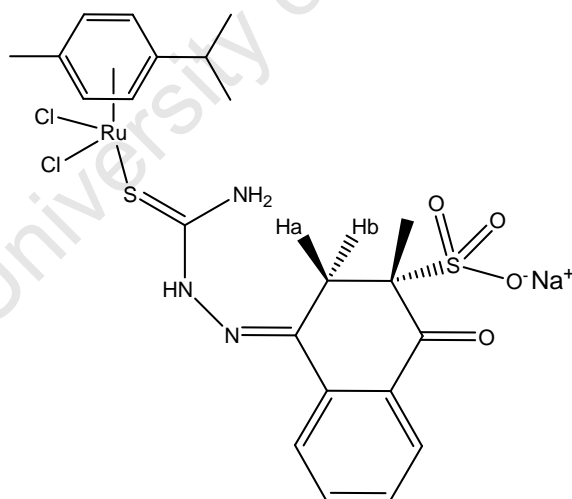


**Figure 1.17:** Molecular structures of dimeric complexes i)  $[\text{Pt}(\mu\text{-H}_3\text{L}^1)]_2$  and ii)  $[\text{Pt}(\mu\text{-H}_3\text{L}^3)]_2$ <sup>46</sup>

### 1.5.3. Ruthenium thiosemicarbazone complexes

#### *Monothiosemicarbazone complexes*

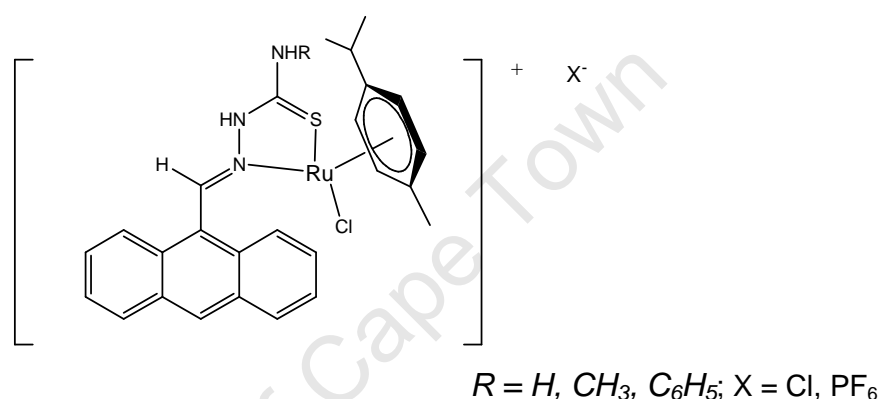
A neutral ruthenium vitamin K<sub>3</sub> derived thiosemicarbazone complex of the form [Ru( $\eta^6$ -*p*-cymene)(K<sub>3</sub>TSC)Cl<sub>2</sub>] (Figure 1.18) was evaluated for its *in vitro* cytotoxic activity against a panel of cancer cell-lines including human adenocarcinoma (*HeLa*), human myelogenous leukaemia (*K562*), human malignant melanoma (*Fem-X*), human breast carcinoma (*MDA-MB-361* and *MDA-MB-453*) and normal cells. The complex showed low to moderate activity with an IC<sub>50</sub> = 152.10  $\mu$ M for the *Fem-X* cells and an IC<sub>50</sub> = 101.84  $\mu$ M for the *MDA-MB-361* cells. Against *HeLa*, *K562* and *MDA-MB-453* cell-lines, the complex exerted moderate dose dependent antiproliferative activity, with IC<sub>50</sub> values of 62.50, 71.26 and 62.46  $\mu$ M, respectively. The complex was more active against the normal control cells, with an IC<sub>50</sub> = 61.10  $\mu$ M for non-stimulated resting peripheral blood mononuclear cells (PBMC) and IC<sub>50</sub> = 40.38  $\mu$ M for PBMC stimulated by phytohaemagglutinin (PHA), which stimulates cell division.<sup>47</sup>



**Figure 1.18:** A neutral ruthenium vitamin K<sub>3</sub> derived thiosemicarbazone complex of the form [Ru( $\eta^6$ -*p*-cymene)(K<sub>3</sub>tsc)Cl<sub>2</sub>]

A series of half-sandwich arene ruthenium complexes (Figure 1.19) containing bidentate thiosemicarbazone ligands have also been evaluated for potential biological activity against breast adenocarcinoma (*MCF-7* and *MDA-MB-231*) and

colorectal carcinoma cells (*HCT-116* and *HT-29*). The compounds have the general formula  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})(\text{R-ATSC})\text{Cl}]\text{X}$  (ATSC = 9-anthraldehyde thiosemicarbazone, R = H, CH<sub>3</sub> or C<sub>6</sub>H<sub>5</sub>; and X = Cl<sup>-</sup> or PF<sub>6</sub><sup>-</sup>). The complexes show good cytotoxic profiles against *MCF-7* and *MDA-MB-231* as well as *HCT-116* and *HT-29* cell-lines. All the complexes displayed moderate cytotoxic potencies against all cell-lines. The complex where R = CH<sub>3</sub> and X = Cl<sup>-</sup> was the most active against all cell-lines. It is also observed that as the R group increases in size, there is an overall decrease in potency of the compound. Another observation is that the compounds exhibit better activity towards the *MDA-MB-231* cells.<sup>48</sup>

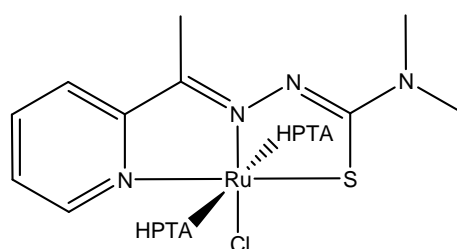


**Figure 1.19:** Complexes of the general formula  $[\text{Ru}(\text{R-ATSC})(\eta^6\text{-}p\text{-cymene})\text{Cl}]\text{X}$  investigated as potential anticancer agents

The reaction of  $[\text{Ru}(\text{dppb})(\text{H}_2\text{O})\text{Cl}_3]$  (dppb = 1,4 bis(diphenylphospine)butane) with 2-benzoylpyridine thiosemicarbazone (H2Bz) and its *N*(4)-methyl (H2Bz4Me) and *N*(4)-phenyl (H2Bz4Ph) derivatives gave three complexes i.e.  $[\text{Ru}(\text{dppb})(\text{H2Bz})\text{Cl}]\text{Cl}$ ,  $[\text{Ru}(\text{dppb})(\text{H2Bz4Me})\text{Cl}]\text{Cl}$  and  $[\text{Ru}(\text{dppb})(\text{H2Bz4Ph})\text{Cl}]\text{Cl}$ . Cytotoxic studies were carried out using these compounds on the *MCF-7*, *TK-10* and *UACC-62* human tumour cell-lines. The precursor  $[\text{Ru}(\text{dppb})(\text{H}_2\text{O})\text{Cl}_3]$  exhibits cytotoxic activity against the three cell-lines. H2BzDH, H2Bz4M, and  $[\text{Ru}(\text{dppb})(\text{H2Bz4M})\text{Cl}]\text{Cl}$  show a selective cytotoxic effect against the *UACC-62* cell-line.<sup>49</sup>

Two ruthenium(II) triphenylphosphine complexes of 2-acetylpyridine *N*<sup>4</sup>,*N*<sup>4</sup>-dimethylthiosemicarbazone (HL<sup>1</sup>) and phenanthrenequinone thiosemicarbazone (HL<sup>2</sup>), namely  $[\text{Ru}(\text{L}^1)(\text{PPh}_3)_2\text{Cl}]$  and  $[\text{Ru}(\text{L}^2)(\text{PPh}_3)_2\text{Cl}]$ , were obtained. Also treatment of  $[\text{Ru}(\text{DMSO})_4\text{Cl}_2]$  with HL<sup>1</sup> and 1,3,5-triaza-7-phosphaadamantane (PTA) gave a

highly water-soluble complex of the form  $[\text{Ru}(\text{L}^1)(\text{HPTA})_2\text{Cl}]\text{Cl}_2 \cdot \text{C}_2\text{H}_5\text{OH} \cdot \text{H}_2\text{O}$  (Figure 1.20). The complex shows strong antiproliferative activity in the low micromolar concentration range against the ovarian carcinoma cell-line, *41M* ( $\text{IC}_{50} = 0.87 \mu\text{M}$ ) and moderate activity in the breast cancer cell-line, *SK-BR-3* ( $\text{IC}_{50} = 39 \mu\text{M}$ ). The activity of the compound is 6.5- and 5.4-times higher at  $\text{pH} = 6.0$  than at  $\text{pH} = 7.4$  against the non-small cell lung cancer cell-line, *A549* and the colon carcinoma cell-line, *HT-29* ( $\text{GI}_{50} = 24$  and  $8.0 \mu\text{M}$  at  $\text{pH} = 6.0$  for *A549* and *HT-29*, respectively).<sup>50</sup>

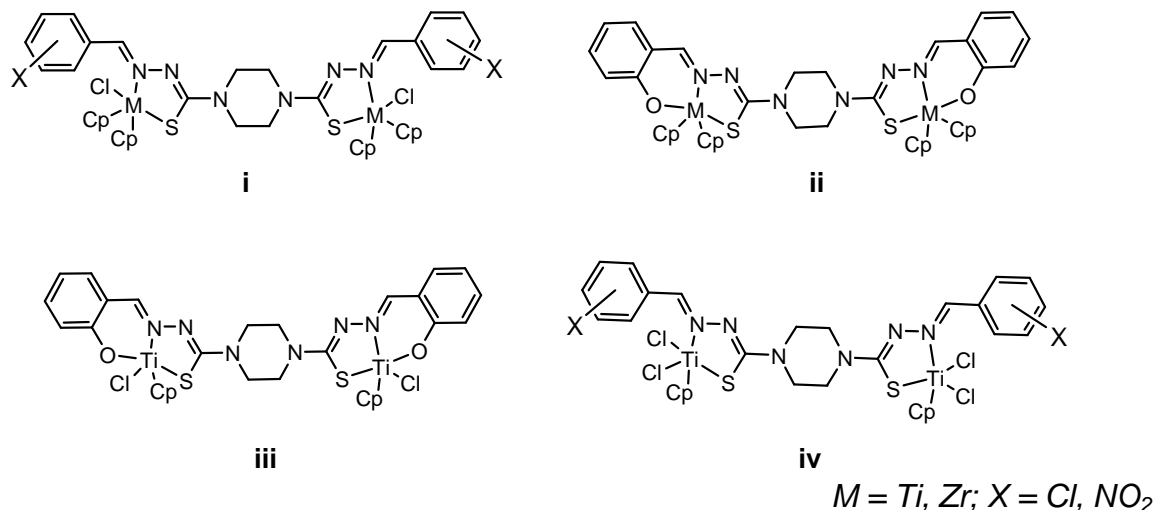


**Figure 1.20:** A water-soluble complex with pH-dependent antiproliferative activity

### 1.6. Synthesis and applications of some dithiosemicarbazone complexes

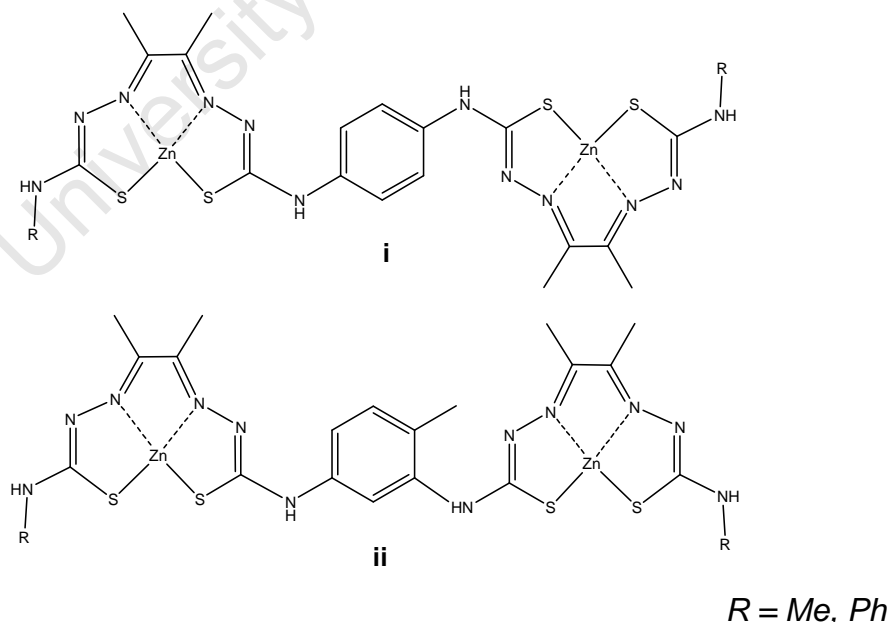
The synthesis and anticancer abilities of dithiosemicarbazone complexes containing palladium, platinum and ruthenium have not been fully explored in literature. Generally, platinum group metal complexes of these ligands are scarce. Here follows some examples of dithiosemicarbazone complexes containing various transition metals.

Ethylene-bridged dithiosemicarbazone copper complexes were synthesised by Gringas *et al.*<sup>51</sup> These complexes were tested as antifungal agents against the cellulosic microorganism *Chaetomium globosum* and were found to exhibit activity.<sup>51</sup> Antibacterial studies were carried out on various piperazine-bridged titanium and zirconium complexes (Figure 1.21). These complexes were found to display antifungal activity. In addition to this, the zirconium complexes exhibited better activity in comparison to the titanium complexes.<sup>52</sup>



**Figure 1.21:** Structures of binuclear titanium(IV) and zirconium(IV) complexes of piperazine dithiosemicarbazones

Various other dithiosemicarbazones containing zinc,<sup>53</sup> lanthanum(III),<sup>54</sup> praseodymium(III),<sup>54</sup> nickel,<sup>23</sup> cobalt<sup>23</sup> and copper<sup>23</sup> have been synthesised but investigation of their potential applications has not been fully exploited. Dilworth *et al.*<sup>53</sup> reported on the synthesis of various bimetallic zinc thiosemicarbazone complexes with rigid aromatic linkers (Figure 1.22) as well as non-rigid linkers.

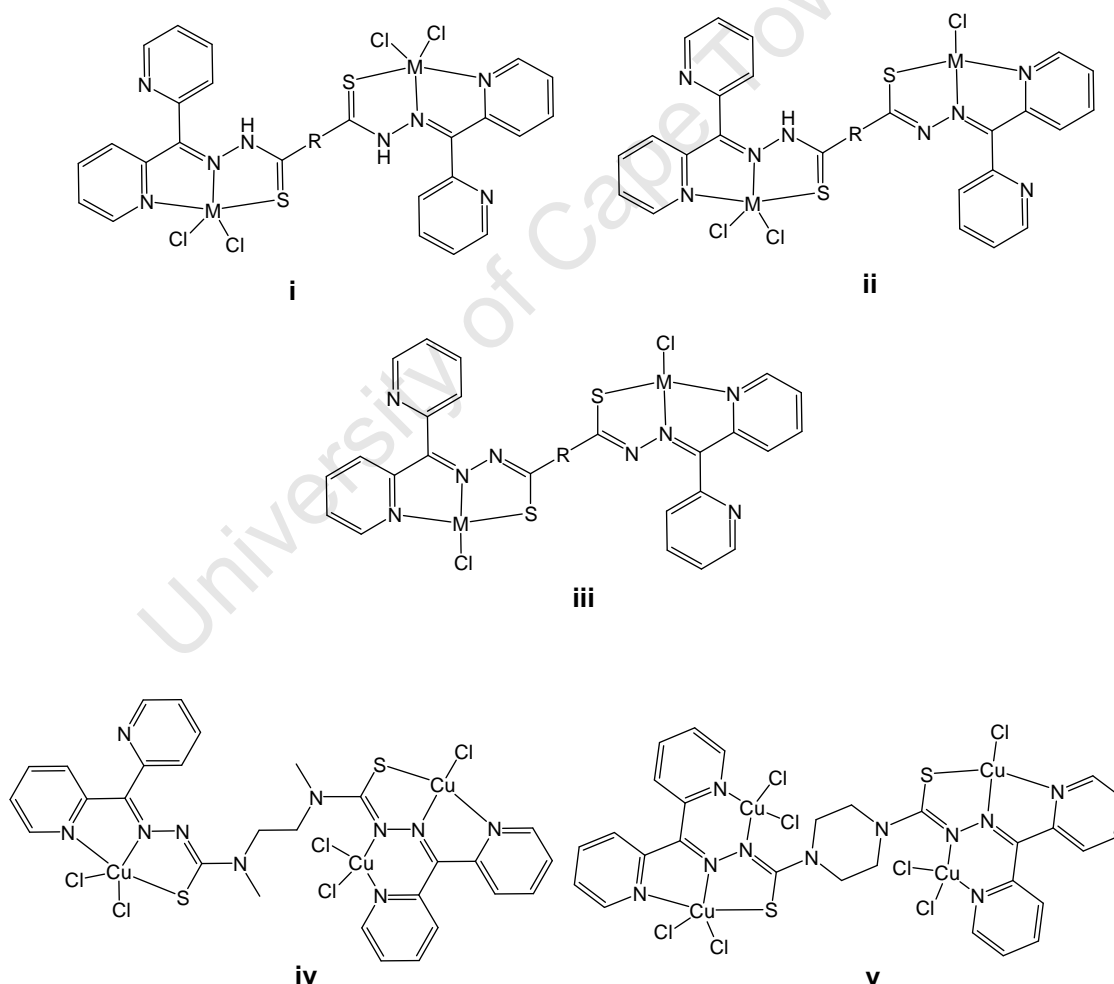


**Figure 1.22:** Examples of rigid bimetallic thiosemicarbazone complexes synthesised by Dilworth and co-workers<sup>53</sup>



The synthesis of La(III) and Pr(III) complexes of the type  $[(Ln(L)(H_2O)Cl)_2]$ , where  $Ln = La(III)$  or  $Pr(III)$  and  $L =$  piperazine dithiosemicarbazone ligands derived from benzaldehyde, 4-nitrobenzaldehyde and 2-methoxybenzaldehyde, was reported by Tripathi *et al.*<sup>54</sup> These complexes were prepared and characterised using common spectroscopic techniques.<sup>54</sup>

Bis(di-2-pyridyl ketone) dithiosemicarbazone complexes containing cobalt(II), nickel(II) and copper(II) have been prepared and reported by West *et al.*<sup>23</sup> The dithiosemicarbazones were prepared from piperazine and ethylene dithiosemicarbazides and subsequently complexed to afford bi- (Figure 1.23.i, ii and iii), tri- (Figure 1.23.iv) and tetranuclear complexes (Figure 1.23.v).



$M = Co(II), Ni(II)$ ;  $R =$  piperazine,  $N, N'$ -dimethyl ethylenediamine

**Figure 1.23:** Multinuclear complexes of dithiosemicarbazones

More recently, novel dithiosemicarbazone palladium(II) complexes derived from various salicylaldehydes (Figure 1.24) have been synthesised and characterised, however, the study of their biological properties have proved to be problematic due to their low solubility in DMSO and water. Only their respective ligands were thus evaluated for activity.<sup>55</sup> The ligands displayed moderate activity against various oesophageal cancer cell-lines (*WHCO1*, *WHCO5* and *WHCO6*) with  $IC_{50}$  values ranging between 1.24 and 30.97  $\mu$ M. The insolubility of these Pd(II) complexes may be attributed to the incorporation of  $PPh_3$  as part of these complexes.<sup>55</sup>

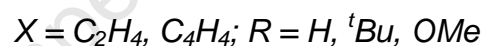
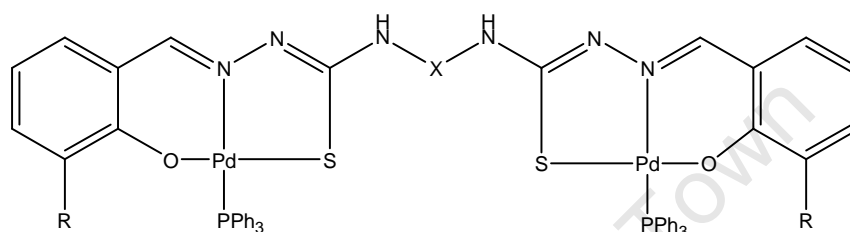


Figure 1.24: Novel Pd(II) salicylaldiminato dithiosemicarbazone complexes

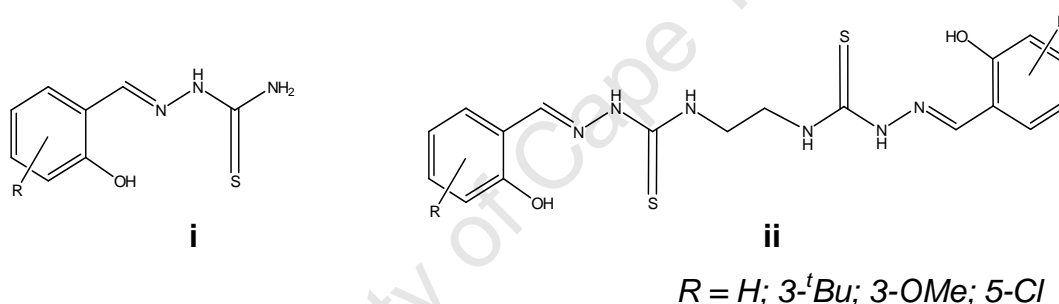
## 1.7. Aims and Objectives

### 1.7.1. Aims

Due to the vast biological properties that most thiosemicarbazone compounds possess, as discussed in this chapter, it would be interesting to investigate the structural and biological properties of various thiosemicarbazone platinum group metal (PGM) complexes. Studying the biological properties of some palladium compounds has previously been problematic due to their low water-solubility.<sup>55</sup> This study therefore aims to synthesise a range of mono-, di- and trinuclear thiosemicarbazone compounds by incorporating a water-soluble phosphine ligand, 1,3,5-triaza-7-phosphaadamantane (PTA), as part of these complexes to investigate their potential anticancer activity in mammalian oesophageal cancer cells as well as their antiparasitic activity against the *T. vaginalis* parasite.

## 1.7.2. Specific Objectives

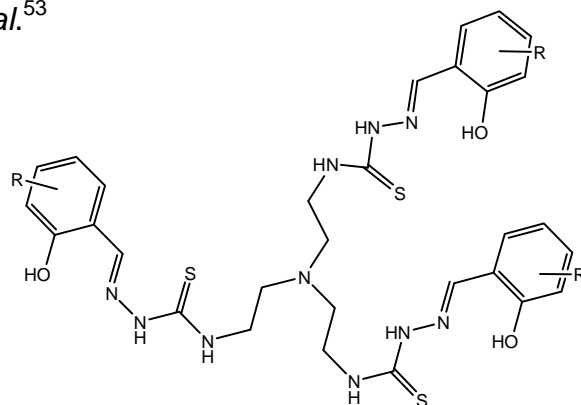
- To synthesise a series of monothiosemicarbazone salicylaldehyde ligands (Figure 1.25.i) containing various aryl substituents for complexation.
- To prepare similar dithiosemicarbazone salicylaldehyde ligands (Figure 1.25.ii) containing an ethylene spacer from ethane-1,2-dithiosemicarbazide and various salicylaldehydes. Based on our previous work, it was found that complexes containing alkyl bridging moieties displayed better solubility than those with bridging aryl moieties.<sup>55</sup> Dilworth *et al.*<sup>53</sup> have also attempted the synthesis of dithiosemicarbazones with longer chain lengths such as propane, however isolation of the product was problematic and therefore we have decided to explore the activity of compounds containing ethylene spacers only.



**Figure 1.25:** Thiosemicarbazone ligands to be synthesised in this study

- In addition to the above mentioned thiosemicarbazone ligands, the preparation of a new kind of thiosemicarbazone system is investigated using various salicylaldehydes. This system comprises three thiosemicarbazone moieties linked by their amino nitrogen atoms to a nitrogen core by ethyl linkers, thus affording trithiosemicarbazone ligands (Figure 1.26). Similar ligand systems have displayed promising antimalarial activity against a chloroquine-resistant *W2* strain of the parasite *P. falciparum*.<sup>56</sup> Preparation of these compounds will allow us to compare the effect of increasing size on biological activity. Reports have shown that larger molecules are able to penetrate and be retained inside tumour cells more efficiently than healthy cells.<sup>57</sup> This is mainly attributed to the Enhanced Permeability and Retention (EPR) effect which is experienced by tumour cells selectively.<sup>57</sup> The preparation of these trithiosemicarbazone

compounds is carried out by adapting methodologies previously used by Dilworth *et al.*<sup>53</sup>



$R = H; 3\text{-}^t\text{Bu}; 3\text{-OMe}; 5\text{-Cl}$

**Figure 1.26:** Novel trithiosemicarbazone ligands investigated in this study

These specific ligands have been chosen in order to investigate the effect of increasing size and the number of thiosemicarbazone moieties on biological activity.

- To complex these ligands with  $cis\text{-}[\text{Pd}(\text{PTA})_2\text{Cl}_2]^{58}$  and  $cis\text{-}[\text{Pt}(\text{PTA})_2\text{Cl}_2]^{59}$  to afford the corresponding mono- (Figure 1.27.i), di- (Figure 1.27.ii) and trinuclear (Figure 1.27.iii) complexes.

The rationale behind the synthesis of these specific complexes stems from the hypothesis that using water-soluble phosphine ligands such as 1,3,5-triaza-7-phosphaadamantane (PTA), would potentially increase the overall solubility of these compounds in a DMSO-water medium (medium in which the biological testing is usually done) and therefore biological studies could be carried out.



- Characterisation of the proposed compounds is carried out using Nuclear Magnetic Resonance spectroscopy (NMR), Infrared spectroscopy (IR), Elemental Analysis (EA) as well as Electrospray Ionisation Mass Spectrometry (ESI-MS). Isolation of some of the complexes as crystals suitable for single crystal X-ray diffraction to provide insight into their modes of coordination.
- Lastly, to investigate the *in vitro* biological properties of selected ligands and complexes against the mammalian oesophageal cancer cell-line, *WHCO1* and against the parasite *T. Vaginalis*.

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## **CHAPTER 2**

# **Synthesis and Characterisation of Salicylaldimine Thiosemicarbazones**

University of Cape Town

## 2.1. Introduction

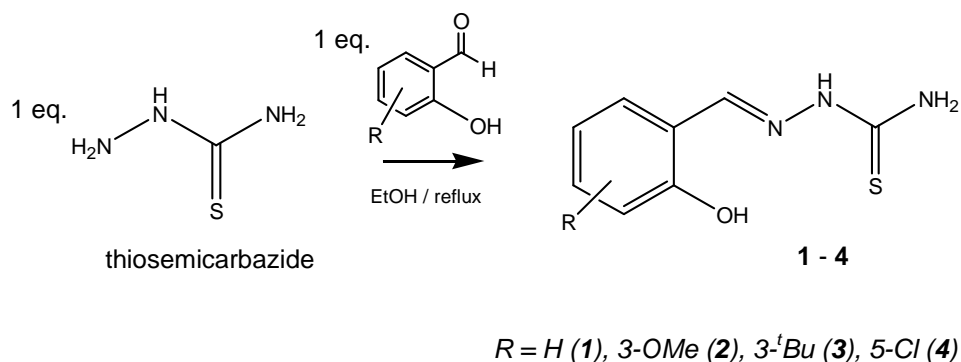
Thiosemicarbazones exhibit various biological properties including antimalarial, antibacterial and antitumoural.<sup>1-3</sup> Salicylaldimine thiosemicarbazones (TSCs) have exhibited antiproliferative activity on a range of tumour cell-lines and are therefore candidates as potential tumour agents.<sup>4</sup> Salicylaldimine thiosemicarbazones are Schiff-base compounds formed from condensation of various substituted salicylaldehydes and thiosemicarbazide precursors. The main objectives of this study were to synthesise a range of salicylaldimine TSC compounds for complexation to various platinum group metals (Chapter 3), in order to evaluate their biological activity against *WHCO1* oesophageal cancer cells and *T. vaginalis* (Chapter 5). Previous investigation of the biological activity of mono- and dithiosemicarbazones derived from salicylaldehydes displayed promising results.<sup>5,6</sup> The preparation of a new thiosemicarbazone system has been investigated in this study. This system comprises of three thiosemicarbazone moieties linked by their amino nitrogen atoms to a nitrogen core by ethyl linkers. We have therefore coined the term “trithiosemicarbazones” to describe these compounds. These compounds were prepared in order to compare the effect of increasing size on biological activity. This chapter describes the synthesis and characterisation of various mono-, di- and trithiosemicarbazone salicylaldimine ligands for complexation. The anticancer properties of these ligands have also been evaluated and are discussed in Chapter 5.

## 2.2. Preparation of monothiosemicarbazones (1 – 4)

### 2.2.1. Synthetic approach and physical properties

Four monothiosemicarbazone salicylaldimine compounds (1-4) were synthesised by simple Schiff-base condensation reactions between various functionalised salicylaldehydes (salicylaldehyde, 3-methoxy salicylaldehyde, 3-tert-butyl-salicylaldehyde and 5-chlorosalicylaldehyde) and thiosemicarbazide (Scheme 2.1). The reactants were refluxed in ethanol for approximately 6 hours, yielding white solids that precipitate from solution upon cooling of the reaction mixture. The products were washed with cold ethanol, dried *in vacuo* and isolated in moderate to good yields. The melting points of

these ligands were determined and found to be thermally stable, which compares favourably with literature.<sup>5,7-9</sup>



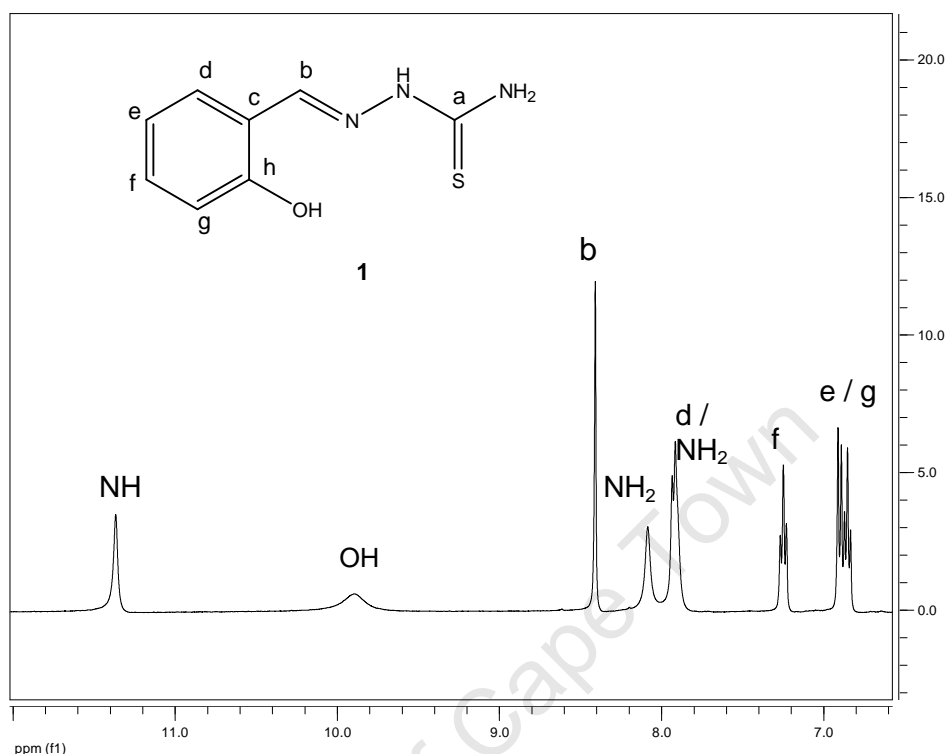
**Scheme 2.1:** Preparation of salicylaldehyde monothiosemicarbazones

## 2.2.2. Characterisation

### <sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy

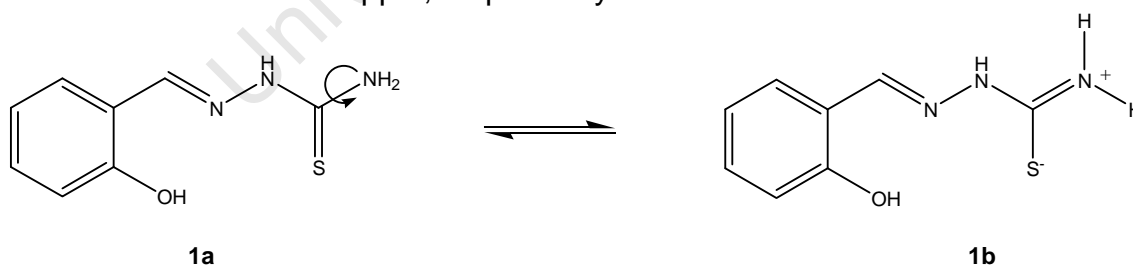
The NMR spectra of these ligands were recorded in DMSO-*d*<sub>6</sub>. Figure 2.1 displays an example of a typical <sup>1</sup>H NMR spectrum of one of these monothiosemicarbazones. Some <sup>1</sup>H NMR assignments here and elsewhere were made using 2D Correlation spectroscopy (COSY). Generally these ligands exhibit similar trends on comparison of their spectra. The most important signal to note is the imine signal. The imine proton signals occur as sharp singlets in the region of 8.26-8.42 ppm. This therefore confirms condensation of the respective salicylaldehydes with thiosemicarbazide. Also worth noting is the position of the signal for the hydrazinic proton. Signals for the hydrazinic protons occur as singlets relatively downfield in their respective spectra, between 11.25 and 11.36 ppm. Signals for the phenolic protons are generally broad singlets that occur between 9.16 and 10.03 ppm. Peaks for the terminal amino protons approximately occur at 7.90 ppm and are observed as one singlet in the spectra of compounds **3** and **4**. In the case of **1** and **2**, each terminal amino proton signal is observed as a separate singlet. This is due to restricted rotation of the amino group about the C-N bond axis caused by delocalization of the lone pair of electrons of the NH<sub>2</sub> nitrogen (Figure 2.2). This phenomenon has been observed in literature.<sup>10-12</sup> Tautomerism occurs in thiocarbonyl compounds in a similar manner to that of

ketone compounds. An equilibrium exists between thione and thiolate form. The thione form predominates as the bond energy of the C=N compared to C=S bond is greater thus verifying greater stability of the thiocarbonyl.



**Figure 2.1:**  $^1\text{H}$  NMR spectrum of salicylaldimine monothiosemicarbazone (**1**)

The aromatic protons are observed in the region of 6.78-7.92 ppm. The protons of the methyl substituents for compounds **2** (OMe) and **3** ( $^t\text{Bu}$ ) are found at 3.32 and 1.38 ppm, respectively.



**Figure 2.2:** Delocalization of terminal nitrogen lone pairs

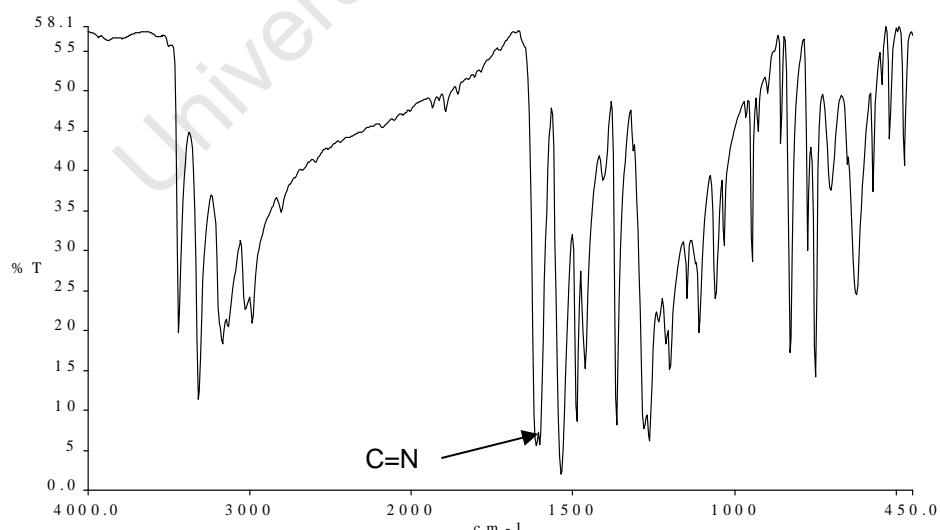
### $^{13}\text{C}\{^1\text{H}\}$ Nuclear Magnetic Resonance Spectroscopy

The  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of each compound displays the expected number of carbon signals, further supporting the structure and composition of these compounds.  $^{13}\text{C}\{^1\text{H}\}$  NMR assignments here and elsewhere were made with

the aid of 2D Heteronuclear Single Quantum Coherence (HSQC) spectroscopy. Signals for the thione carbon atoms occur between 177.76 and 177.99 ppm. The imine carbon signals appear in the region of 137.60-147.01 ppm. Signals for the phenolic carbon atoms are observed between 154.98-156.25 ppm in the case of **1**, **3** and **4**. The phenolic carbon signal of compound **2** is observed at 147.83 ppm, which is further upfield in comparison to the other three compounds. This is mainly attributed to the electronic effects of the electron-donating methoxy group.

### *Infrared Spectroscopy*

Further supporting evidence of the synthesis of these ligands is observed in the infrared (IR) spectra of these compounds. Particular attention is drawn to the appearance of absorption bands in the region of 1614-1657  $\text{cm}^{-1}$ . These bands represent the imine  $\nu(\text{C}=\text{N})$  stretching frequencies of the monothiosemicarbazones, confirming Schiff-base condensation of the respective precursors. The  $\nu(\text{O}-\text{H})$  and  $\nu(\text{N}-\text{H})$  bands for the phenolic oxygens and hydrazinic nitrogens, respectively, are observed in the region of 3100-3400  $\text{cm}^{-1}$ . These frequencies are in accordance with literature data for the same type of compounds.<sup>4</sup> The  $\nu(\text{C}=\text{S})$  absorption bands appear between 830 and 822  $\text{cm}^{-1}$ . Figure 2.3 displays the infrared spectrum of ligand **1**.



**Figure 2.3:** IR spectrum of salicylaldimine monothiosemicarbazone (**1**)

The spectroscopic data obtained thus supports the preparation of these ligands. Table 2.1 summarises selected spectroscopic data mentioned above.

Table 2.1

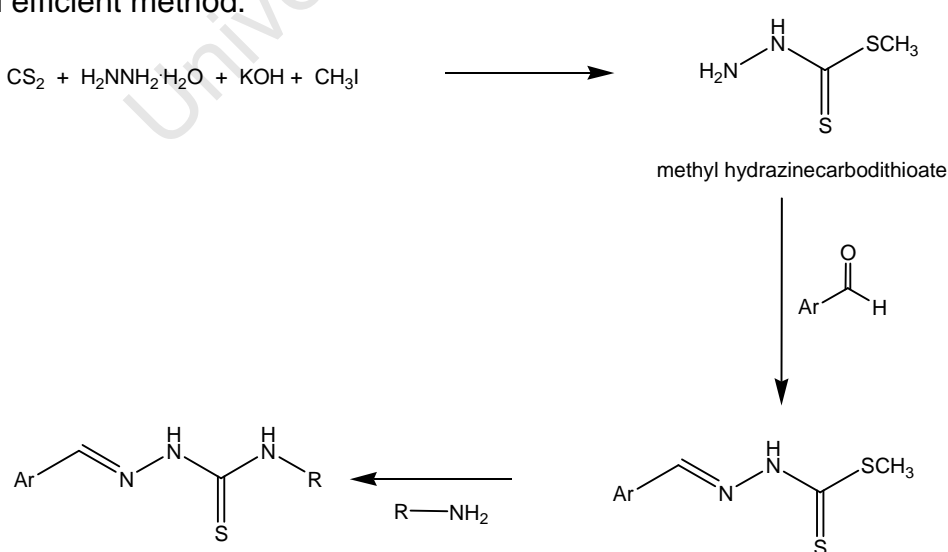
Selected spectroscopic data obtained for monothiosemicarbazones (1-4)

Compound	R	NMR (ppm)				IR (cm <sup>-1</sup> )
		<sup>1</sup> H		<sup>13</sup> C		-C=N-
		-HC=N-	-NH-	-C=N-	-C=S	
1	H	8.40	11.36	140.02	177.76	1615
2	3-OMe	8.42	11.29	139.76	177.78	1622
3	3- <sup>t</sup> Bu	8.26	11.25	147.01	177.94	1614
4	5-Cl	8.30	11.30	137.60	177.99	1657

### 2.3. Preparation of dithiosemicarbazones (6-9)

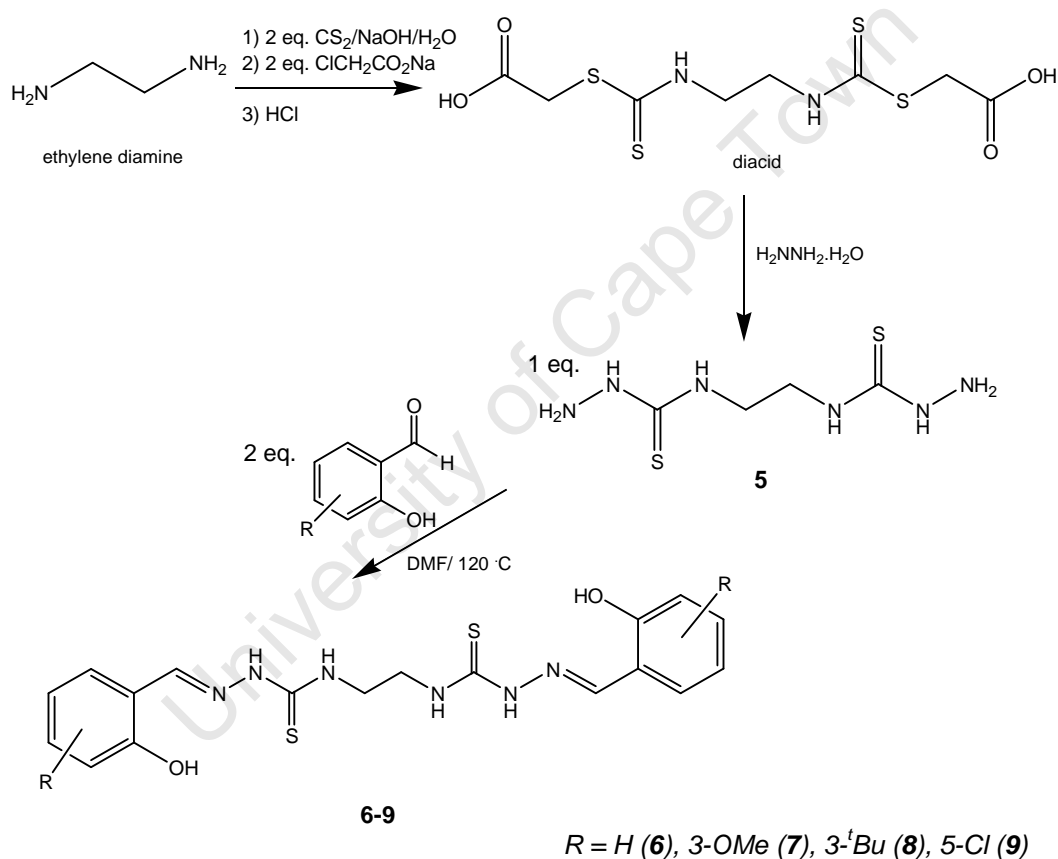
#### 2.3.1. Synthetic approach and physical properties

Salicylaldimine dithiosemicarbazone ligands may be prepared by two routes. One method involves a three step synthetic sequence in which methyl hydrazinecarbodithioate (Scheme 2.2) is prepared and condensed with aldehydes, after which the S-methyl group of the compound obtained is displaced by the desired amine by means of a nucleophilic addition reaction giving rise to the desired dithiosemicarbazone. Although this route has been successfully utilised by Klayman *et al.*,<sup>13</sup> it was decided to utilise a more viable and efficient method.



**Scheme 2.2:** One route towards the preparation of thiosemicarbazones

Four ethylene-bridged salicylaldehyde thiosemicarbazone derivatives were synthesised using methodology outlined in Scheme 2.3. The procedure involves the synthesis of ethane-1,2-dithiosemicarbazide (**5**) utilising the method outlined by Dilworth *et al.*<sup>14</sup> The method involves the preparation of the dithiosemicarbazide from ethylenediamine via a diacid precursor (Scheme 2.3). The diacid formed is then treated with excess hydrazine hydrate which displaces the carboxylic acid moiety by nucleophilic addition to the thiocarbonyl forming the desired thiosemicarbazide. The product is obtained as a white powder that precipitates from solution in good purity but in a low yield, 40%.



**Scheme 2.3:** Method employed to prepare the desired salicylaldehyde thiosemicarbazones

Due to the poor solubility of the dithiosemicarbazide in most organic solvents with the exception of DMSO and DMF, condensation of **5** with the aforementioned salicylaldehydes were carried out in DMF to give rise to the required ligands in good yields. The ligands obtained are soluble in DMF and



were therefore isolated by means of precipitation with water.<sup>6</sup> These Schiff-base reactions can be carried out in alcoholic solvents but require extended reaction time periods for completion due to the low solubility of **5** in these solvents. Melting points of compounds **6-8** agree with literature,<sup>6</sup> while the new 5-chloro dithiosemicarbazone derivative (**9**) displays similar thermal stability in comparison to the other members of the series.

### 2.3.2. Characterisation

#### *<sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy*

Evidence for the preparation of dithiosemicarbazones **6-9** is clearly depicted in the <sup>1</sup>H NMR spectra of these ligands. Figure 2.4 displays the <sup>1</sup>H NMR spectrum of ligand **6**. These dithiosemicarbazone ligands possess a 2-fold symmetry about the ethane bridge and we therefore see one set of signals for equivalent hydrogens. As seen with the spectra of the monothiosemicarbazones, the imine signals appear between 8.29 and 8.41 ppm. The signals attributed to the aliphatic protons of the ethylene bridge appear as a singlet in the region of approximately 3.80 ppm. Peaks for the amino protons adjacent to the ethylene spacer appear as a singlet between 8.56 and 8.74 ppm. Signals attributed to the hydrazinic protons (which are the NH protons adjacent to the imine moiety) appear downfield in a region similar to their monomeric counterparts (11.41-11.56 ppm). Signals for the methyl protons corresponding to the methoxy substituent of **7** is observed at 3.80 ppm, while signals for the <sup>t</sup>Bu protons of **8** are observed at 1.39 ppm.

#### *<sup>13</sup>C{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy*

The <sup>13</sup>C{<sup>1</sup>H} NMR spectra of these dithiosemicarbazone compounds display the appropriate number of signals in each case. The spectrum of **9** was of particular importance since it is a new ligand and has not been reported in literature. It displays all the expected signals, with the signal for the thione carbon appearing at 178.11 ppm and the imine carbon signal at 138.34 ppm. This is in close agreement with the shifts of the corresponding monothiosemicarbazone derivative (177.99 and 137.60 ppm). The remaining dithiosemicarbazone ligands (**6-8**) display signals in the region of 177.23-

177.88 ppm and 139.44-147.66 ppm for their thione and imine carbon atoms, respectively. Signals for the phenolic carbon atoms are found in the range of 155.85-156.22 ppm for compounds **6**, **8** and **9**, while the same signal is found at 147.78 ppm for **7**. This is consistent with data obtained for the monothiosemicarbazones.

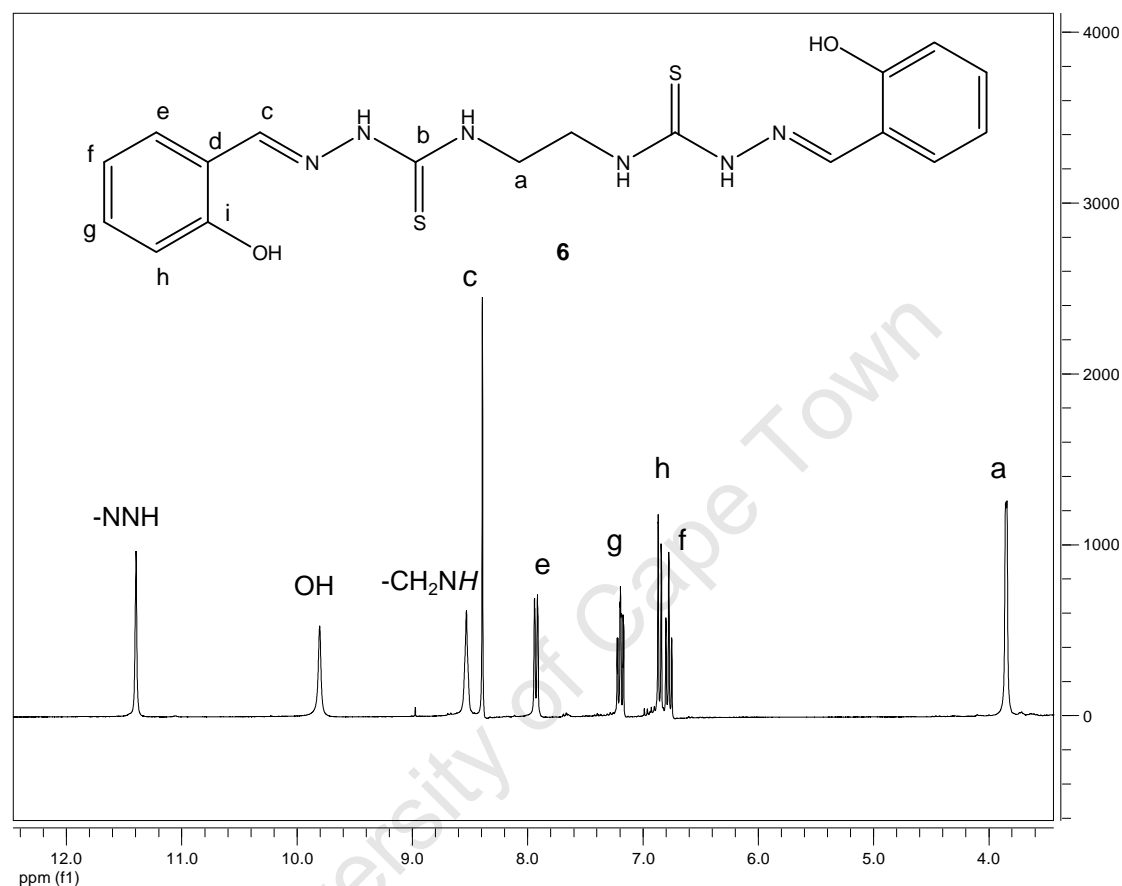


Figure 2.4:  $^1\text{H}$  NMR spectrum of salicylaldehyde dithiosemicarbazone (**6**)

### Infrared Spectroscopy

Absorption bands in the region of  $1598\text{-}1671\text{ cm}^{-1}$  are assigned to the  $\nu(\text{C}=\text{N})$  stretching frequencies of these compounds. Absorption bands for the  $\nu(\text{C}=\text{S})$  frequencies are observed at lower energies in comparison to the monothiosemicarbazones, with the exception of compound **8**, which occurs at a slightly higher frequency than its monomeric counterpart. Absorption bands in the region of  $3000\text{-}3300\text{ cm}^{-1}$  are attributed to the  $\nu(\text{O-H})$  and  $\nu(\text{N-H})$  stretching frequencies for the phenolic, hydrazinic and amino moieties. Table 2.2 summarises selected spectroscopic data for compounds **6-9**.

Table 2.2

Selected spectroscopic data obtained for dithiosemicarbazones (6-9)

Compound	R	NMR (ppm)				IR (cm <sup>-1</sup> )
		<sup>1</sup> H		<sup>13</sup> C		-C=N-
		-HC=N-	-NH-	-C=N-	-C=S	
6	H	8.39	11.47	139.64	177.23	1618
7	3-OMe	8.41	11.50	139.44	177.23	1671
8	3- <sup>t</sup> Bu	8.29	11.41	147.66	177.88	1598
9	5-Cl	8.36	11.56	138.34	178.11	1616

### Elemental Analysis and Mass Spectrometry

Microanalysis of these compounds was found to be consistent with the calculated values. Electrospray Ionisation (ESI) mass spectrometry was carried out on compound **9**. The spectrum displayed a base peak corresponding to the molecular ion at  $m/z$  485 ( $[M]^+$ ).

## 2.4. Preparation of trithiosemicarbazones (11-14)

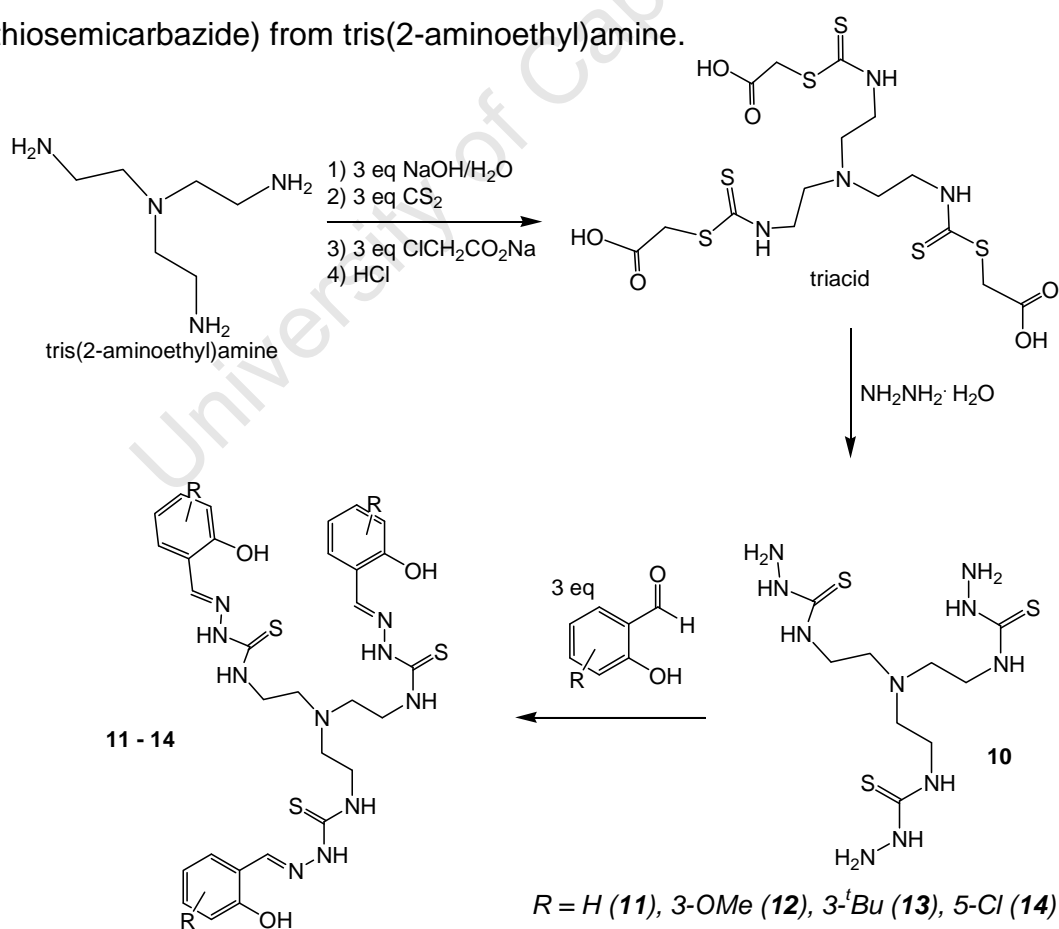
### 2.4.1. Synthetic approach and physical properties

Targeted therapy, where drugs selectively interact or harm abnormal cells, is an area of great importance. This kind of therapy also results in reduced side effects in comparison to other treatments. Incorporation of drugs onto polyamines may improve their selectivity towards tumour cells. Polyamines are naturally occurring agents that are found in large amounts in mammalian cells and are essential for cell growth.<sup>15</sup> Previous studies carried out on these systems reveal that these agents are able to transport cytotoxic drugs into tumour cells.<sup>16</sup> Tumour cells import polyamines by means of a polyamine transporter (PAT) in order to sustain their growth. The transporter is able to tolerate modified polyamines, therefore drug incorporated polyamines are able to penetrate the tumour cells via the PAT.<sup>17</sup>

Since thiosemicarbazones possess cytotoxic properties, they serve as good candidates for incorporation onto polyamines. As mentioned in the previous

chapter, another advantage in using larger systems is that these compounds are able to be retained more efficiently in tumour cells than in normal cells. This phenomenon is known as the “Enhanced Permeability and Retention” (EPR) effect.<sup>18</sup> Based on this, the preparation of a new class of thiosemicarbazone compound has been investigated in this study.

Salicylaldehyde TSC moieties have been incorporated onto tris(2-aminoethyl)amine yielding trimeric compounds. These compounds have been termed trithiosemicarbazones because they possess three thiosemicarbazone moieties linked to a central core (in this case a nitrogen atom) by their amino nitrogen atoms. The preparation of these compounds was carried out using chemistry similar to that of the previously mentioned dithiosemicarbazones, adapting the chemistry for the preparation of ethane-1,2-dithiosemicarbazide accordingly (Scheme 2.4). This particular method involved the preparation of tris(2-aminoethyl) thiosemicarbazide (**10**) (trithiosemicarbazide) from tris(2-aminoethyl)amine.



**Scheme 2.4:** Preparation of trithiosemicarbazones

A solution of the tris(2-aminoethyl)amine in water was treated with carbon disulfide, sodium chloroacetate and HCl, presumably affording a triacid precursor, which is further reacted with hydrazine hydrate to deliver the required product. The trithiosemicarbazide was obtained as an oily-like substance and was dried at roughly 110 °C. Upon cooling the product solidifies to give rise to a yellowish powder in a yield of 23%. It does however absorb moisture from the atmosphere upon prolonged exposure.

Further reaction of **10** with salicylaldehyde, 3-methoxysalicylaldehyde, 3-<sup>t</sup>Bu-salicylaldehyde and 5-chlorosalicylaldehyde in ethanol or methanol resulted in the desired trithiosemicarbazone ligands (**11-14**). Addition of water to the resulting solution gives rise to yellow powders, with the exception of **13**, which is obtained as a yellow oil.

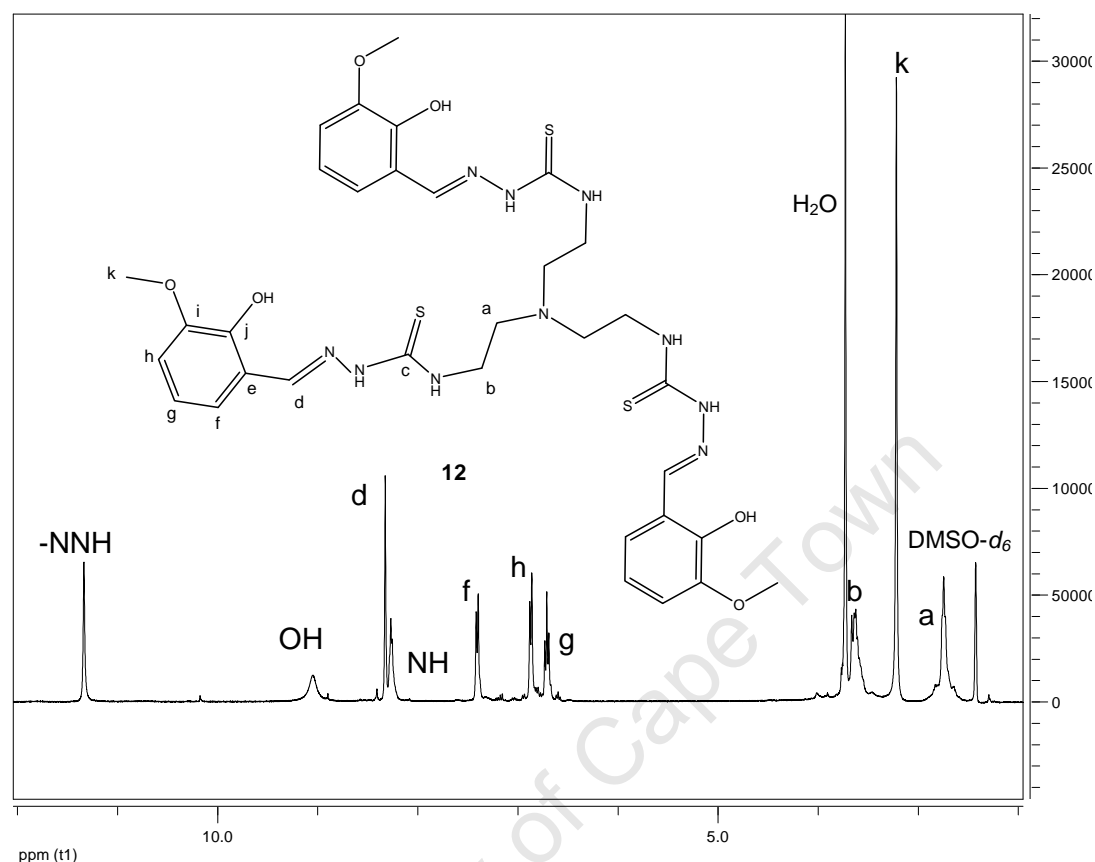
These trithiosemicarbazone ligands display enhanced solubility in most organic solvents (ethanol, methanol, methylene chloride) in comparison to their mono- and dithiosemicarbazone counterparts at ambient temperature. Ligand **13** was isolated in a different manner, due to its inability to precipitate from solution. In this particular case the solvent (MeOH) was completely removed giving rise to a yellow oil, which was re-dissolved in approximately 20 cm<sup>3</sup> of methylene chloride. The extract was washed several times with water to remove any unreacted aldehyde. The methylene chloride was evaporated and the resulting oil dried under vacuum.

#### 2.4.2. Characterisation

##### *<sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy*

The proton NMR spectra of the trithiosemicarbazone compounds bear great similarity to the spectra of their mono- and dithiosemicarbazone counterparts. The spectrum of compound **12** is depicted in Figure 2.5. Similar to the dithiosemicarbazones, the trithiosemicarbazones possess a 3-fold symmetry and thus one signal is seen for each equivalent proton. Signals for the imine protons are found between 8.35 and 8.57 ppm. The hydrazinic proton signals

appear in the range of 11.34-11.50 ppm. Signals for the phenolic protons are observed fairly downfield between 9.18 and 10.22 ppm.



**Figure 2.5:**  $^1\text{H}$  NMR spectrum of 3-methoxy trithiosemicarbazone (**12**)

The major difference between the spectra of these compounds and the mono- and di- derivatives is attributed to the presence of the methylene protons of the alkyl bridges. These signals are found at approximately 2.85 and 3.75 ppm, for  $\text{H}_a$  and  $\text{H}_b$  respectively.

### $^{13}\text{C}\{^1\text{H}\}$ Nuclear Magnetic Resonance Spectroscopy

The methylene carbon signals are found between 41.57-42.60 ppm ( $\text{C}_b$ ) and between 52.50-53.42 ppm ( $\text{C}_a$ ). Signals for the thione carbon atoms appear in the region of 176.88-177.64 ppm, while the imine carbon atom signals are found between 137.28 and 140.00 ppm. The phenolic carbon signals are observed between 154.98-157.15 ppm for **11**, **13** and **14**. The same signal for compound **12** is found at a lower shift (147.85 ppm) in comparison to the

other ligands of this particular series. This is in accordance with the mono- and dithiosemicarbazone derivatives.

### ***Infrared Spectroscopy***

Absorption bands for the imine stretching frequencies are observed in the region between 1605 and 1650  $\text{cm}^{-1}$ . These bands further support condensation of the respective salicylaldehydes with **10**. Absorption bands for the  $\nu(\text{C}=\text{S})$  frequencies are found at similar frequencies in comparison to the dithiosemicarbazones. Similar energies are also observed for the  $\nu(\text{O}-\text{H})$  and  $\nu(\text{N}-\text{H})$  stretching frequencies as the mono- and dithiosemicarbazones. Table 2.3 displays selected infrared as well as NMR data for these new ligands.

**Table 2.3**

Spectroscopic data obtained for trithiosemicarbazones (**11-14**)

<i>Compound</i>	<i>R</i>	<i>NMR (ppm)</i>				<i>IR (cm<sup>-1</sup>)</i>
		<sup>1</sup> H		<sup>13</sup> C		<i>-C=N-</i>
		<i>-HC=N-</i>	<i>-NH-</i>	<i>-C=N-</i>	<i>-C=S</i>	
<b>11</b>	H	8.38	11.34	140.00	177.64	1620
<b>12</b>	3-OMe	8.43	11.47	139.16	176.88	1605
<b>13</b>	3- <sup>t</sup> Bu	8.27	11.39	147.19	177.28	1651
<b>14</b>	5-Cl	8.35	11.50	137.28	177.02	1618

### ***Elemental Analysis and Mass Spectrometry***

The elemental analysis obtained for these ligands was in agreement with the expected values. The data obtained for **11** was consistent with the calculated values of this compound which attests to its purity. Mass spectrometry also supported the integrity of these compounds. Compound **10** displayed a base peak at  $m/z$  369 corresponding to the  $[\text{M}+\text{H}]^+$  ion. Compounds **11**, **12** and **14** all displayed base peaks in their respective spectra, corresponding to their molecular ions at  $m/z$  681, 771 and 785, respectively. The spectra of compound **13** displayed a peak with 5% intensity at  $m/z$  849 which agrees

with the molecular weight of the ligand. A base peak at  $m/z$  489 corresponds to the fragment  $[M+3ACN+2H]^{2+}$ .

## 2.5. Conclusion

Four new trithiosemicarbazone ligands (**11-14**) and one dithiosemicarbazone ligand (**9**) was prepared and characterised using common analytical and spectroscopic techniques. The synthesis of these compounds is clearly depicted in their spectroscopic data. In addition to this, microanalysis and mass spectrometry further support their integrity. Although the mono-, di- and trithiosemicarbazone compounds are somewhat different structurally, their spectroscopic similarities are vast. These compounds were found to be extremely stable in air and at elevated temperatures. The trithiosemicarbazone ligands display better solubility than their mono- and dimeric counterparts in solvents such as DCM, MeOH and DMSO at ambient temperature.

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## **CHAPTER 3**

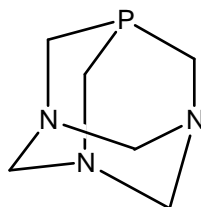
# **Synthesis and Characterisation of Pd(II) and Pt(II) Salicylaldiminato Thiosemicarbazone Complexes**

University of Cape Town

### 3.1. Introduction

The chemistry of transition metal complexes of thiosemicarbazones has received considerable attention due to their diverse activities.<sup>1,2</sup> The biological activity of many thiosemicarbazones often increase on coordination to a particular metal ion. Lipophilicity (which controls the rate of entry of a particular molecule into a cell) is sometimes also altered by metal coordination. Certain side effects can also be reduced upon complexation of the thiosemicarbazone ligand and in some cases the complexes display activities not exhibited by the free ligand.<sup>3</sup> Combining thiosemicarbazones with metals such as palladium(II) and platinum(II) results in synergistic inhibition of tumour growth and may lead to improvements in its effectiveness as chemotherapeutic agents.<sup>4-6</sup>

Although many thiosemicarbazones exhibit activity, most of them exhibit poor solubility in a number of solvents, including water. In order to evaluate the activity of these compounds, a sample is often solubilised in DMSO and diluted accordingly. If the compound possesses low water-solubility, precipitation often occurs from the culture medium during *in vitro* evaluation, which may result in unreliable and non-reproducible data. Incorporation of water-soluble groups may enhance the solubility in water or may assist in the prevention of precipitation of the compounds when being evaluated in water. A water-soluble ligand that has received attention in the field of catalysis as well as medicinal chemistry is 1,3,5-triaza-7-phosphaadamantane (PTA) (Figure 3.1).



**Figure 3.1:** PTA, a water-soluble phosphine ligand used in catalysis and biological studies

A wide range of metal complexes bearing this particular phosphine have been prepared and their biological properties investigated. Metals such as gold,

ruthenium, rhodium, platinum and palladium have been utilised for coordination.<sup>7</sup> *Trans*-[Pt(SC<sub>4</sub>H<sub>3</sub>N<sub>2</sub>)<sub>2</sub>(PTA)<sub>2</sub>], *trans*-[Pt(SC<sub>5</sub>H<sub>4</sub>N)<sub>2</sub>(PTA)<sub>2</sub>] and [Au(SC<sub>4</sub>H<sub>3</sub>N<sub>2</sub>)(PTA)] are examples of complexes that contain the PTA ligand.<sup>8</sup> These compounds were synthesised and their cytotoxicity tested against ovarian, colon, renal, breast, lung and melanoma cancer cell-lines and displayed considerable cytotoxic activities.<sup>8</sup> [Ru( $\eta^6$ -arene)(PTA)Cl<sub>2</sub>] complexes (RAPTA-type) inhibit secondary tumour growth (a tumour that has spread from its original (primary) site of growth to another site) in various cell-lines.<sup>9</sup> Pt(II) complexes bearing PTA and thiocarbamate esters such as *trans*-[Pt(SC(OMe)=NC<sub>6</sub>H<sub>4</sub>R)<sub>2</sub>(PTA)<sub>2</sub>] (R = H, Cl, OMe, NO<sub>2</sub>, Me) were tested *in vitro* in four human cancer cell-lines (*CH1*, *HT29*, *A549*, *SK-OV-3*) using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. IC<sub>50</sub> values obtained for some of these complexes were lower when compared to cisplatin.<sup>10</sup> Considering this and several other examples, the use of PTA as a co-ligand is therefore supported for the use in medicinal chemistry and therefore can be incorporated as part of thiosemicarbazone complexes.

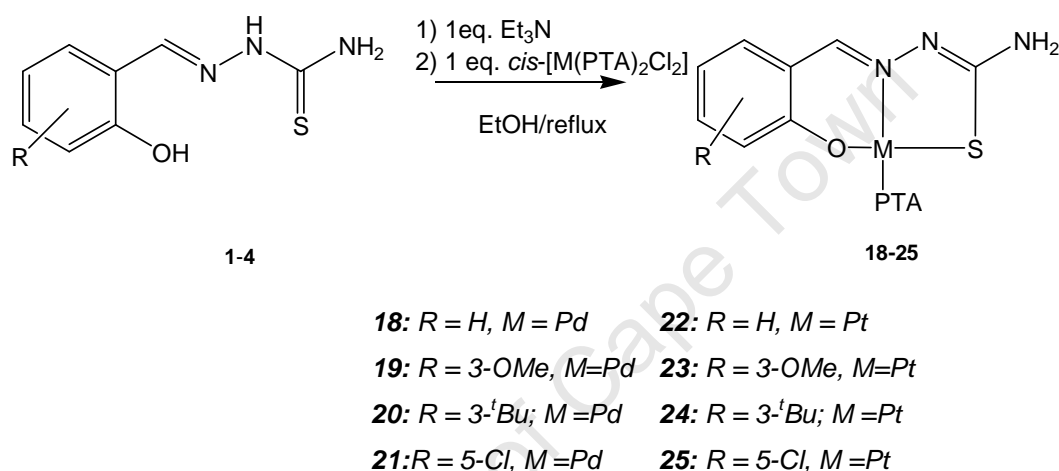
### 3.2. Pd and Pt salicylaldiminato PTA monothiosemicarbazones (18-25)

#### 3.2.1. Synthetic approach and physical properties

With the aim of synthesising Pd(II) and Pt(II) thiosemicarbazone complexes containing PTA, the monothiosemicarbazones mentioned in Section 2.2 were reacted with two metal precursors of the general formula *cis*-[M(PTA)<sub>2</sub>Cl<sub>2</sub>], where M = Pd or Pt. Treatment of 1 equivalent of *cis*-[Pd(COD)Cl<sub>2</sub>] (**15**)<sup>11</sup> with 2 equivalents of PTA in methylene chloride and stirring for 5 hours at room temperature, gave rise to *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (**16**).<sup>12</sup> The product was obtained as a yellow powder in 96% yield. *Cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (**17**) was prepared by a metathesis reaction between 1 equivalent of K<sub>2</sub>[PtCl<sub>4</sub>] and 2.1 equivalents of PTA in a mixture of ethanol and water at 60 °C for approximately 2 hours, giving rise to an off-white powder in a yield of 78%.<sup>13</sup>

Reaction of these metal precursors with the respective monothiosemicarbazones in the presence of triethylamine for 5-24 hours

(Scheme 3.1) afforded the required Pd(II) (**18-21**) and Pt(II) (**22-25**) salicylaldiminato monothiosemicarbazones in high yields. These complexes (**18-25**) were isolated as yellow amorphous solids. The use of triethylamine promotes coordination of the metal in an O-N-S tridentate manner following the abstraction of the phenolic proton in each ligand. This mode of coordination is well documented in literature for similar systems.<sup>14-17</sup> These complexes (**18-25**) are soluble in DMSO but display low solubility in other organic solvents such as alcohols.



**Scheme 3.1:** Synthesis of Pd and Pt salicylaldiminato monothiosemicarbazones

### 3.2.2. Characterisation

#### <sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy

Due to the similarities between the palladium and platinum complexes, the discussion of their spectroscopic properties will be combined. Table 3.1 highlights some <sup>1</sup>H NMR data. Analysis of the data revealed that complexation of free ligands occurs in a dianionic manner through the thiolate sulfur and phenolic oxygen. This is supported by the absence of signals accounting for the phenolic and hydrazinic protons in the spectrum of each complex. Coordination of the sulfur in the thiolate form as opposed to the thione form is thus observed. There are two types of methylene protons present in the PTA ligand. One type is assigned to the P-CH<sub>2</sub>-N protons, which occur as a singlet in the region of 4.40 ppm. Signals for the protons of

the N-CH<sub>2</sub>-N moiety possess an AB spin system (giving rise to an AB spin pattern) and appear as two doublets, due to geminal coupling, at 4.50 ppm. One doublet corresponds to the three N-CH<sub>ax</sub>-N protons, while the other is observed for the three N-CH<sub>eq</sub>-N protons. This is consistent with other PTA transition metal complexes.<sup>18-20</sup>

Table 3.1

NMR spectroscopic data obtained for monothiosemicarbazone complexes (18-25)

Compound	M	R	<sup>1</sup> H NMR (ppm)	
			HC=N-	<sup>4</sup> J <sub>P-H</sub> Value (Hz)
18	Pd	H	8.21	13.18
19	Pd	3-OMe	8.27	13.20
20	Pd	3- <sup>t</sup> Bu	8.28	13.48
21	Pd	5-Cl	8.30	13.00
22	Pt	H	8.57	11.21
23	Pt	3-OMe	8.51	11.24
24	Pt	3- <sup>t</sup> Bu	8.56	11.37
25	Pt	5-Cl	8.55	11.11

In both cases (Pd and Pt), the signal for the imine proton splits to form a doublet. This is expected if the metal centre coordinates to the azomethine nitrogen as well, supporting the notion of coordination in a tridentate manner. The splitting of imine signal into a doublet is attributed to coupling of the phosphorus nucleus (of the PTA ligand) to the nucleus of the imine proton situated four bonds away. This phenomenon is documented in literature for similar triphenylphosphine complexes.<sup>14-17</sup> The coupling constants obtained for the Pd complexes range between 13.00 and 13.48 Hz, while the Pt complexes display *J* values ranging between 11.11 and 11.37 Hz (Table 3.1). The variance in coupling constants can be attributed to the difference in electronegativity or size of the two metals. When comparing the shifts of the complexes compared to their free ligands there are some noteworthy differences. In the case of the Pd(II) complexes, a shift of the imine signal upfield (ca. 8.20 ppm) is observed in comparison to the free

monothiosemicarbazones. In contrast, the Pt(II) complexes display shifts of these signals downfield (ca. 8.50 ppm). A typical  $^1\text{H}$  NMR spectrum for these mononuclear compounds is shown in Figure 3.2.

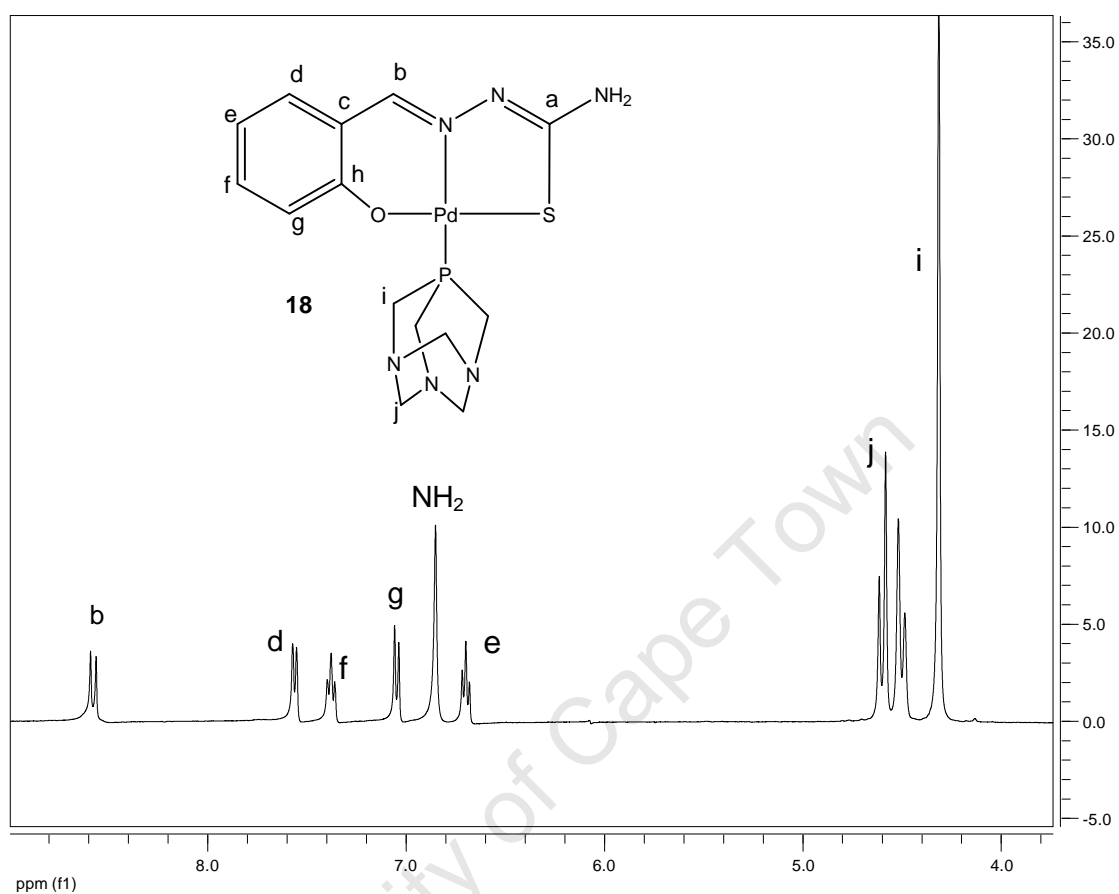


Figure 3.2:  $^1\text{H}$  NMR Spectrum of complex 18

### $^{13}\text{C}\{^1\text{H}\}$ Nuclear Magnetic Resonance Spectroscopy

$^{13}\text{C}\{^1\text{H}\}$  NMR spectroscopy also aided in confirming the mode of coordination of these complexes. Overall the signals accounting for the phenolic carbon atoms appear to shift downfield for both the Pd(II) and Pt(II) systems upon coordination (156.00 ppm in the ligands vs 160.00 ppm in the complexes). This same phenomenon is observed for the azomethine carbon signals (140.00 ppm in the ligands vs 146.00 ppm in the complexes). In contrast to this, the signals corresponding to the thiolate carbon are found more upfield (172.00 ppm) in comparison to the free ligands (178.00 ppm) which is consistent with increased electron-density at the thiolato sulfur atom due to back- $\pi$  donation.<sup>4</sup> Selected resonances are quoted in Table 3.2.

**$^{31}\text{P}\{^1\text{H}\}$  Nuclear Magnetic Resonance Spectroscopy**

$^{31}\text{P}\{^1\text{H}\}$  NMR spectroscopy was employed in order to monitor the shift of the  $^{31}\text{P}$  signal upon complexation of the metal precursors. The phosphorus signals of the free *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (**16**) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (**17**) species are observed at -23.60 and -49.19 ppm, respectively. The latter also displays platinum satellites ( $^1J_{\text{Pt-P}} = 3302.10$  Hz) due to coupling to the spin active  $^{195}\text{Pt}$  nucleus which has a natural abundance of 34%. Compounds **18-21** exhibit signals in the region of -40.00 ppm, while the corresponding Pt derivatives (**22-25**) display typical resonances at approximately -60.00 ppm. The Pt-P coupling constants observed for compounds **22-25** are consistent with the  $^1J_{\text{Pt-P}}$  constant observed for the free *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] precursor. Table 3.2 provides some relevant data obtained for these complexes.

**Table 3.2**NMR spectroscopic data for monothiosemicarbazone complexes (**18-25**)

Compound	M	R	$^{13}\text{C}\{^1\text{H}\}$		$^{31}\text{P}\{^1\text{H}\}$
			NMR (ppm)		NMR (ppm)
			-C-S	-C=N-	[ $^1J_{\text{Pt-P}}$ value (Hz)]
<b>18</b>	Pd	H	171.17	147.57	-40.70
<b>19</b>	Pd	3-OMe	172.01	148.16	-39.37
<b>20</b>	Pd	3- <sup>t</sup> Bu	170.95	149.51	-43.77
<b>21</b>	Pd	5-Cl	171.98	146.51	-40.06
<b>22</b>	Pt	H	172.56	145.90	-61.37 [3344.43]
<b>23</b>	Pt	3-OMe	172.58	145.66	-56.80 [3334.90]
<b>24</b>	Pt	3- <sup>t</sup> Bu	172.40	147.81	-60.71 [3341.70]
<b>25</b>	Pt	5-Cl	174.11	145.72	-58.07 [3338.67]

**Infrared Spectroscopy**

Infrared spectroscopy is another diagnostic tool used to confirm the mode of coordination occurring within molecules. Coordination of ligands **1-4** in the thiolate form implies that a second imine bond forms upon deprotonation of the hydrazinic nitrogen. Therefore two distinct absorption bands should be



observed in the infrared spectra of the complexes. The IR spectra do indeed reveal two absorption bands in the region between 1590 and 1655  $\text{cm}^{-1}$  attributed to the C=N stretching frequencies (Figure 3.3). Bands of higher frequency are observed between 1615 and 1653  $\text{cm}^{-1}$ , while bands of lower frequency are observed between 1592 and 1598  $\text{cm}^{-1}$ . Coordination of the azomethine nitrogen to the metal is supported by a shift of the existing imine band of the ligand towards lower energy.<sup>21,22</sup> The new band that forms in the region of 1600  $\text{cm}^{-1}$  is as a result of deprotonation of the hydrazinic nitrogens forming a second imine bond.

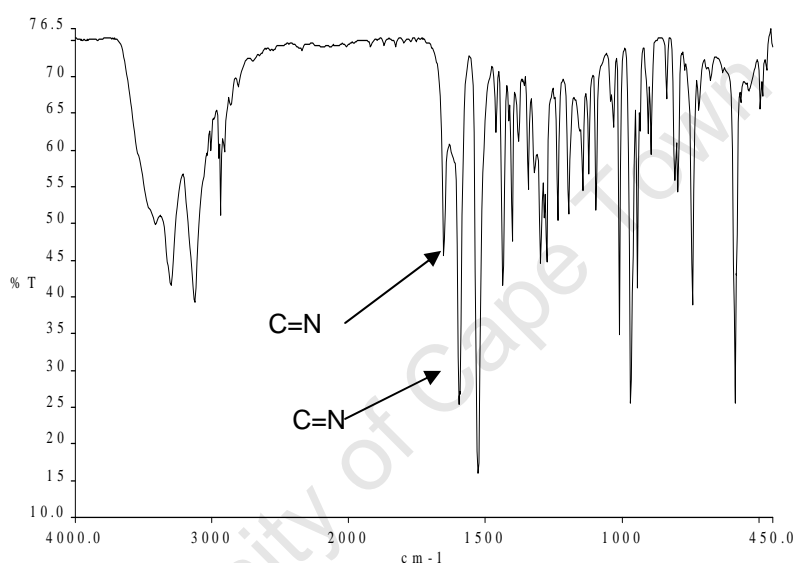


Figure 3.3: Infrared spectrum of complex 18

### ***Elemental Analysis and Mass Spectrometry***

Elemental analysis of these compounds was found to be consistent with the expected values. ESI mass spectrometry was also conducted on these complexes and the results support the structure and composition of these complexes. The mass spectrum of **22** displayed a peak of 50% intensity corresponding to the protonated form of the complex ( $m/z$  546,  $[\text{M}+\text{H}]^+$ ). Compounds **18-20** display base peaks in their spectra corresponding to their respective molecular ions at  $m/z$  457, 487 and 513. The spectra of **21** and **23-25** display base peaks corresponding to the protonated form of these complexes at  $m/z$  493 (**21**), 576 (**23**), 602 (**24**) and 581 (**25**).

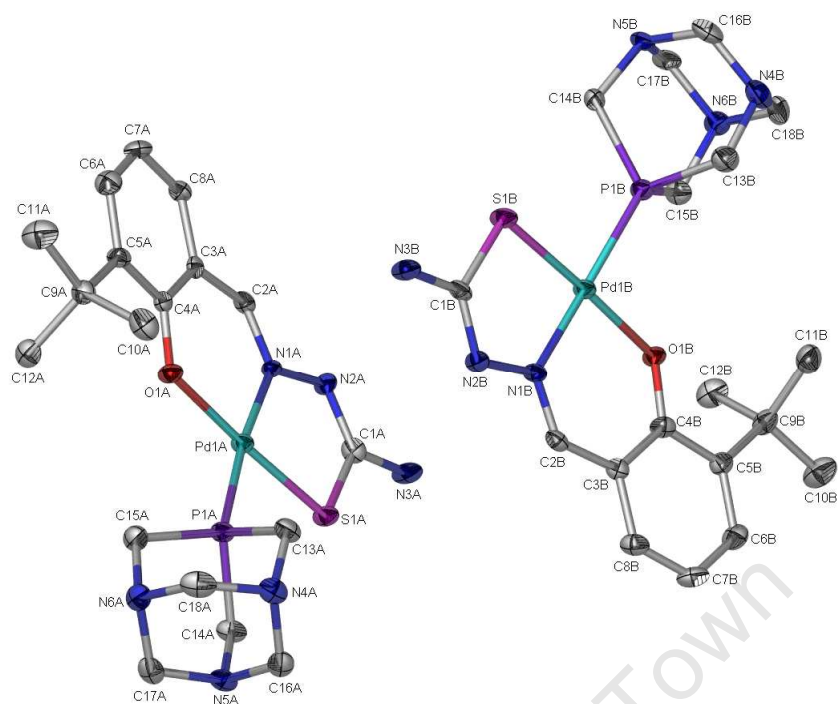
**Single Crystal X-Ray Diffraction Studies**

To further confirm the structure of these complexes, crystals suitable for X-ray structure determination were obtained for complex **20**. Crystals were grown from dimethylsulfoxide (DMSO) at room temperature. Table 3.3 lists selected bond parameters. The molecular structure depicts coordination of the 3-*tert*-butyl salicylaldimine monothiosemicarbazone ligand in a tridentate manner to the palladium centre via the phenolic oxygen, imine nitrogen and sulfur atom in a slightly distorted square-planar geometry. The structure confirms that the fourth coordination site is occupied by a PTA ligand *trans* to the imine nitrogen (Figure 3.4).

**Table 3.3**Selected bond lengths (Å) and angles (°) for complex **20**

Pd(1A)–O(1A)	2.028(2)	O(1A)–Pd(1A)–N(1A)	93.40(9)
Pd(1A)–N(1A)	2.012(3)	N(1A)–Pd(1A)–S(1A)	84.45(8)
Pd(1A)–S(1A)	2.2389(9)	O(1A)–Pd(1A)–P(1A)	91.85(7)
Pd(1A)–P(1A)	2.2461(10)	S(1A)–Pd(1A)–P(1A)	90.19(3)
N(1A)–C(2A)	1.293(4)	O(1A)–Pd(1A)–S(1A)	177.08(7)
N(2A)–C(1A)	1.313(4)	N(1A)–Pd(1A)–P(1A)	173.71(8)

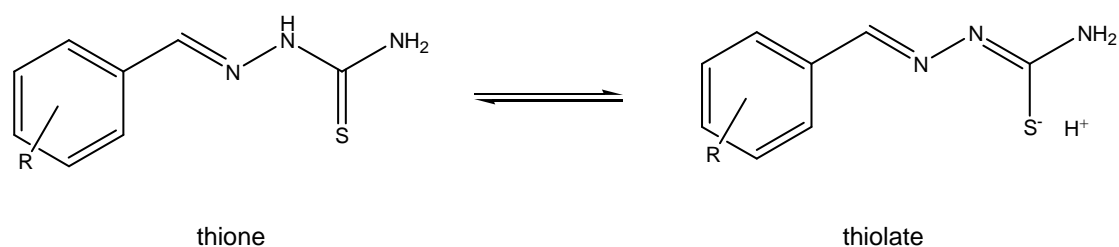
The structure shows the formation of a six- and a five-membered chelate ring upon coordination. The structure displays O(1A)–Pd(1A)–N(1A) and N(1A)–Pd(1A)–S(1A) bond angles of 93.40(9) and 84.45(8)°, respectively. O(1A)–Pd(1A)–P(1A) and S(1A)–Pd(1A)–P(1A) bite angles of 91.85(7) and 90.19(3)°, respectively, can also be seen. These angles indicate a square-planar geometry with slight distortion around the Pd centre, as these angles deviate slightly from ideal behaviour.



**Figure 3.4:** Molecular structure of complex **20** with the hydrogen atoms omitted for clarity

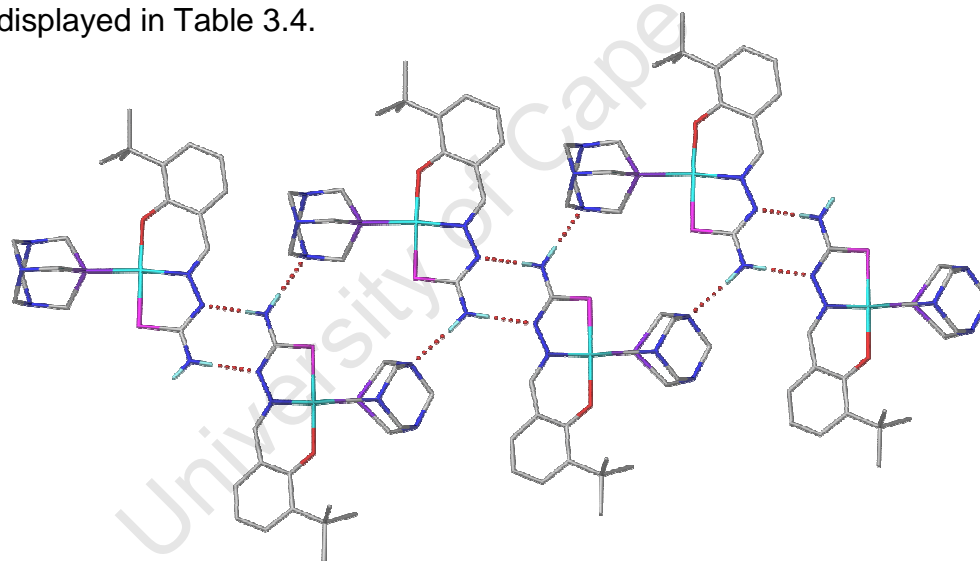
In comparison to similar monomeric and dimeric Pd triphenylphosphine thiosemicarbazone complexes, Pd–O, Pd–N, Pd–S and Pd–P bond distances appear quite similar.<sup>15–17</sup> Thiosemicarbazones can exist in two tautomeric forms i.e. the thione or the thiolate form as depicted in Figure 3.5. Coordination of this particular thiosemicarbazone occurs via the thiolate form, rather than the thione form due to the formation of a second imine bond between C(1A) and N(2A). A value of 1.313(4) Å is assigned to this bond, further supporting the notion that the C(1A)–N(2A) bond tends towards double-bond character upon coordination. Comparison of the C(1A)–N(2A) length to the C(1A)–N(3A) bond length, shows that the latter is slightly longer (1.349(4) Å) and therefore suggests single-bond character. The C–S bond length is also found to be consistent with coordination of sulfur in the thiolate form, with a value of 1.754(4) Å. A previous study by Halder *et al.*,<sup>15</sup> based on similar monomeric complexes reported C–S values of approximately 1.74 Å. In simple systems it would be expected that a single C–S bond length would be approximately 1.82 Å and a double bond would exhibit a length of 1.56 Å. The length obtained in this study, therefore appears

to be an intermediate length between the two and has been reported in literature.<sup>23</sup>



**Figure 3.5:** Possible tautomeric forms displayed by thiosemicarbazones

Examination of the crystal packing arrangement revealed an extensive arrangement of hydrogen bonding between each molecule (Figure 3.6). Closer inspection of this packing arrangement revealed hydrogen bonding of one molecule to two adjacent molecules via the N2 atoms, amino hydrogens and a nitrogen atom belonging to the PTA group. The details of this bonding are displayed in Table 3.4.



**Figure 3.6:** Two dimensional crystal packing arrangement of complex **20** depicting hydrogen bonding

**Table 3.4**

Hydrogen bond parameters for complex **20**

D-H...A	Bond distances / Å			Bond angle / °
	D-H	H...A	D...A	DHA
N(3A)-H(3A1)N...N(2B)	0.905(18)	2.162(19)	3.066(4)	178(3)

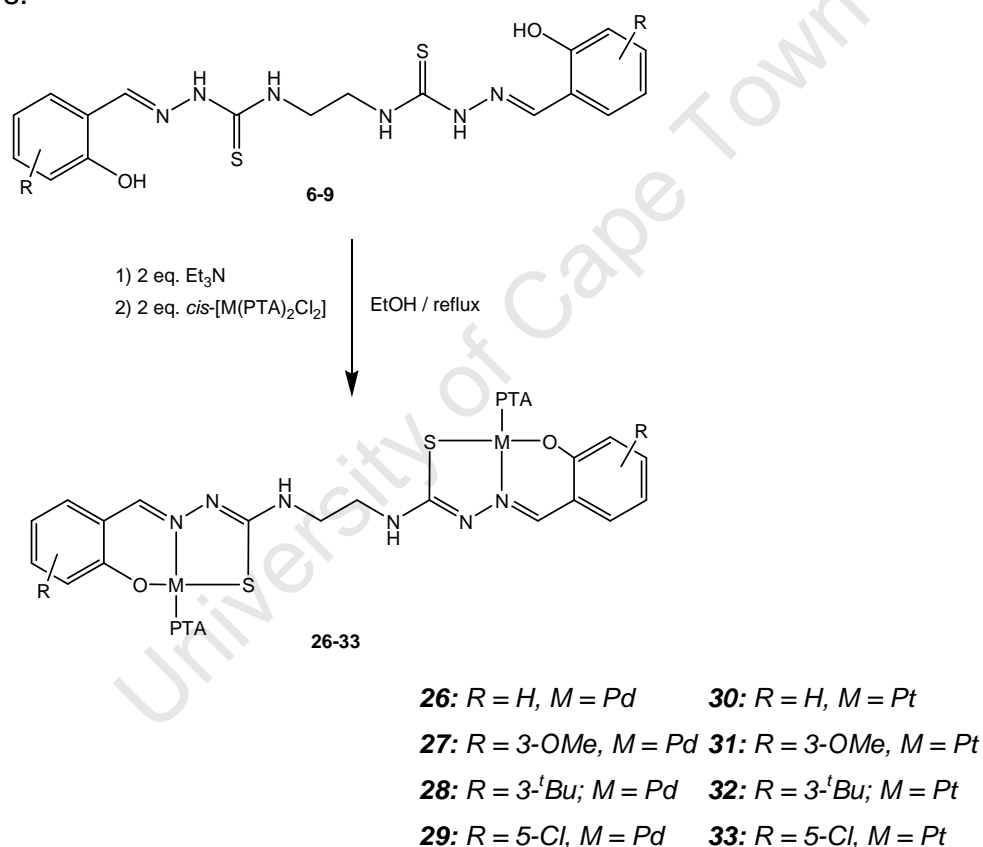
The information obtained herein, in addition to their spectral properties, supports the integrity of the rest of the complexes, thus allowing

rationalisation of the mode of coordination based on the various bond parameters obtained for complex **20**.

### 3.3. Pd and Pt salicylaldiminato PTA dithiosemicarbazones

#### 3.3.1. Synthetic approach and physical properties

The dinuclear salicylaldiminato complexes were synthesised using the same procedure as for the mononuclear derivatives, however, a 1:2, ligand:metal ratio was used in order to obtain the required dinuclear analogues (Scheme 3.2). The reactions were carried out under reflux conditions in ethanol for 5-48 hours.



**Scheme 3.2:** Synthesis of salicylaldiminato dithiosemicarbazone Pd and Pt complexes

In the case of compound **28**, complexation was carried out at room temperature for 72 hours. When comparing the reactivity of the two metal precursors, it is observed that complexation of the ligands with the Pt(II) precursor occurs more readily than with its Pd(II) counterpart. The Pd(II)

(26-29) and Pt(II) (30-33) thiosemicarbazone complexes were isolated as yellow solids in good yields.

### 3.3.2. Characterisation

#### <sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy

Similar trends are observed in the proton NMR spectra for the dinuclear complexes (Figure 3.7) in comparison to their mononuclear analogues. NMR spectral data could not be obtained for **32**, due to its insoluble nature in most deuterated solvents. Complexation of the dithiosemicarbazones is supported by the absence of the hydrazinic and phenolic proton signals in each spectrum. The appearance of signals for the protons of the PTA supported the coordination of PTA as a co-ligand in each complex.

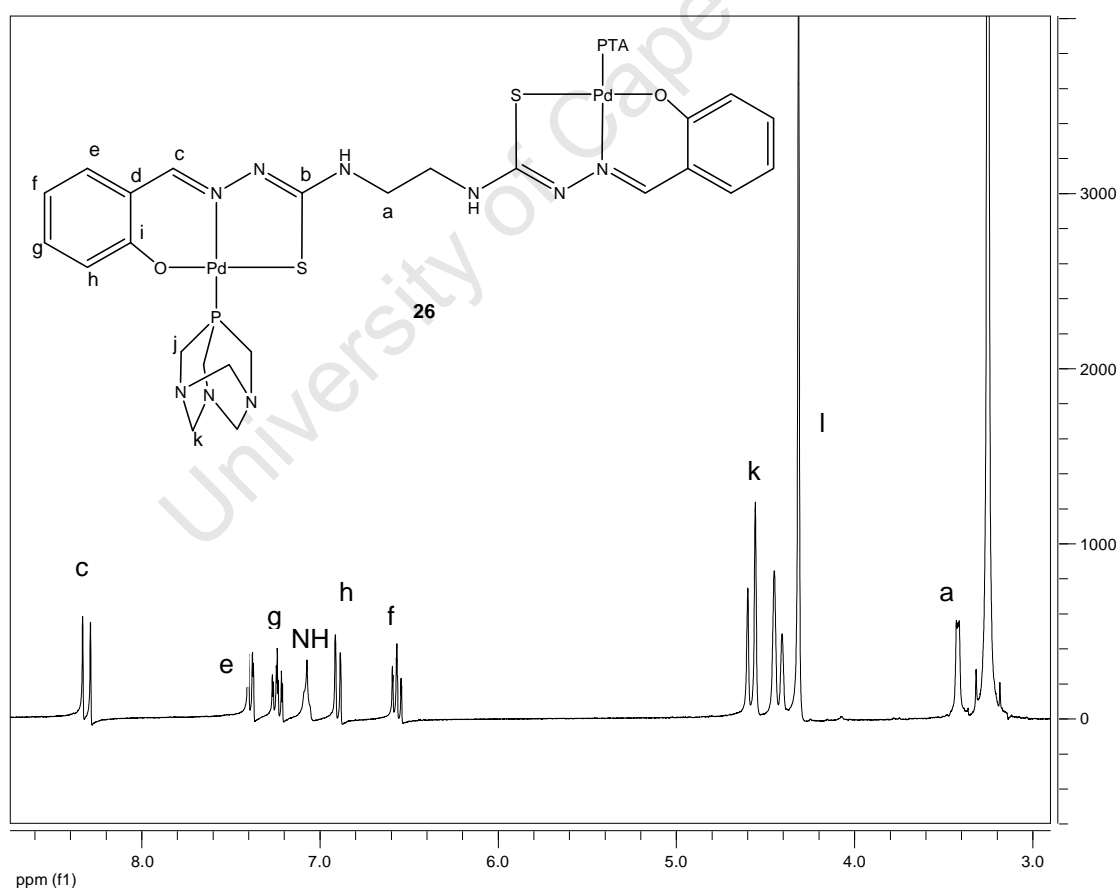


Figure 3.7: <sup>1</sup>H NMR spectrum of complex **26**

Splitting of the imine signal into a doublet is also observed due to coupling to the phosphorus nuclei of the PTA ligand. A shift of the imine proton signal is

observed in all cases when compared to the spectra of the free ligands. Table 3.5 depicts the imine proton resonances and their corresponding coupling constants. In addition to this, a singlet in the region of 3.50 ppm is observed for the CH<sub>2</sub> protons of the ethylene bridge in each case. From the data it can be concluded that the metal coordinates to each half of the free ligand in a tridentate manner.

**Table 3.5:**

Selected spectroscopic data obtained for dithiosemicarbazone complexes (**26-33**)

<i>Compound</i>	<i>M</i>	<i>R</i>	<sup>1</sup> H NMR (ppm) -HC=N-	<sup>4</sup> J <sub>P-H</sub> Value (Hz)
<b>26</b>	Pd	H	8.31	13.15
<b>27</b>	Pd	3-OMe	8.29	13.17
<b>28</b>	Pd	3- <sup>t</sup> Bu	8.33	13.47
<b>29</b>	Pd	5-Cl	8.31	12.95
<b>30</b>	Pt	H	8.67	11.19
<b>31</b>	Pt	3-OMe	8.65	11.18
<b>32<sup>a</sup></b>	Pt	3- <sup>t</sup> Bu	-	-
<b>33</b>	Pt	5-Cl	8.64	10.99

<sup>a</sup> Insoluble in common deuterated solvents

### <sup>13</sup>C{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy

All the complexes, with exception of **20**, **24** and **25** due to their poor solubility to record measurable spectra, were characterised using <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy. The data obtained for the remainder of the complexes was consistent with the data of the mononuclear compounds. Noticeable shifts of the thiolate carbon signals support complexation of the ligands (178.00 ppm in the free ligands vs 172.00 ppm in the complexes) as seen with complexes **18-25**.

### <sup>31</sup>P{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy

As seen with the mononuclear complexes, the dinuclear compounds also afford singlets in their <sup>31</sup>P spectra with chemical shifts similar to their

mononuclear counterparts (-40.00 ppm (Pd) and -60.00 ppm (Pt)). This attests to the purity of these compounds and supports coordination of the metal precursors to the dithiosemicarbazones in a similar manner to the monothiosemicarbazones. Similar Pt-P coupling constants (~3300.00 Hz) are also observed for the dinuclear Pt(II) complexes as compared to their mononuclear analogues. Table 3.6 displays selected  $^{13}\text{C}\{^1\text{H}\}$  and  $^{31}\text{P}\{^1\text{H}\}$  NMR shifts for these complexes.

Table 3.6

Selected spectroscopic data obtained for dithiosemicarbazone complexes (26-33)

Compound	M	R	$^{13}\text{C}\{^1\text{H}\}$ NMR (ppm)		$^{31}\text{P}\{^1\text{H}\}$ NMR (ppm)
			-C-S	-C=N-	[ $^1J_{\text{Pt-P}}$ value (Hz)]
26	Pd	H	170.83	149.08	-40.55
27	Pd	3-OMe	170.15	148.07	-39.22
28 <sup>a</sup>	Pd	3- <sup>t</sup> Bu	-	-	-40.28
29	Pd	5-Cl	170.88	147.12	-39.92
30	Pt	H	172.45	147.46	-61.47 [3329.69]
31	Pt	3-OMe	164.80	144.17	-60.18 [3321.44]
32 <sup>b</sup>	Pt	3- <sup>t</sup> Bu	-	-	-
33 <sup>a</sup>	Pt	5-Cl	-	-	-61.60 [3343.30]

<sup>a</sup> Insufficient solubility to record a measurable  $^{13}\text{C}$  NMR spectrum

<sup>b</sup> Insoluble in common deuterated solvents

### Infrared Spectroscopy

Since two absorption bands were observed in the infrared spectrum of each mononuclear compound, it was assumed that this would hold true for the dinuclear compounds. However, only compounds **30**, **31** and **33** displayed two bands for each imine stretching frequency in their respective spectra. This may be due to an overlap of the various absorption bands and therefore both imine absorption bands appear as one sharp band.



**Elemental Analysis and Mass Spectrometry**

Most of the microanalysis data obtained was consistent with the expected values. In some cases calculation of the expected values was carried out using solvent inclusion and agreed with the data obtained. Solvated water molecules were found to be present in samples **26**, **27**, **30** and **33**. Despite extensive drying, virtually no improvement was observed. These samples were also submitted for ESI mass spectrometry, with the exception of **32** due to its insoluble nature. The results (Table 3.7) obtained for ESI-MS further support their integrity.

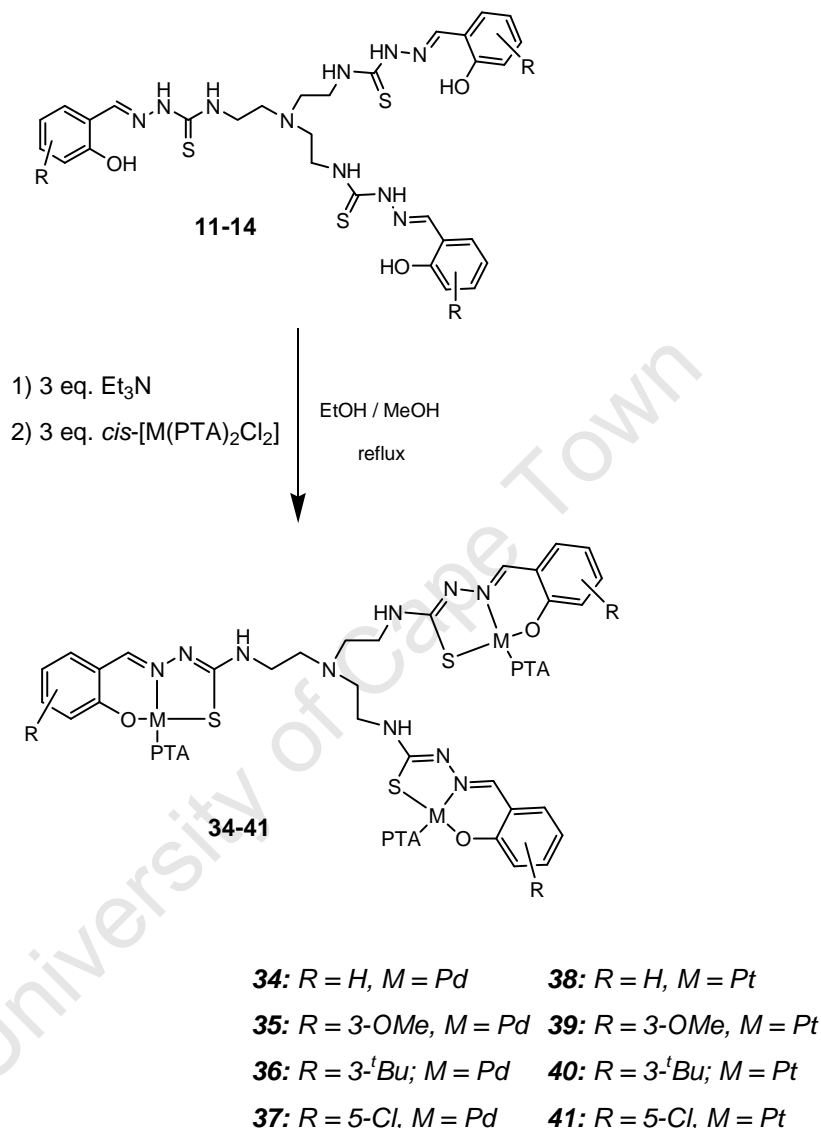
**Table 3.7**ESI mass spectrometry data for dithiosemicarbazone complexes (**26-31** and **33**)

<b>Compound</b>	<b>M</b>	<b>R</b>	<b>m/z (intensity, %)</b>	<b>Assignment</b>
<b>26</b>	Pd	H	247 (30)	$[M+2H+2Na]^{4+}$
			941 (50)	$[M+H]^+$
<b>27</b>	Pd	3-OMe	1001 (100)	$[M+H]^+$
<b>28</b>	Pd	3- <sup>t</sup> Bu	365 (100)	$[M+H+2Na]^{3+}$
			1052 (10)	$[M]^+$
<b>29</b>	Pd	5-Cl	1009 (5)	$[M+H]^+$
<b>30</b>	Pt	H	1117 (100)	$[M]^+$
<b>31</b>	Pt	3-OMe	1177 (100)	$[M]^+$
<b>33</b>	Pt	5-Cl	1117 (100)	$[M-Cl]^+$
			1187 (30)	$[M+H]^+$

**3.4. Pd and Pt salicylaldiminato PTA trithiosemicarbazones****3.4.1. Synthetic approach and physical properties**

The trithiosemicarbazones mentioned in Section 2.4, were reacted in a similar manner to the mono- and dinuclear derivatives with *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (**16**) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (**17**).<sup>12,13</sup> Complexation of these ligands with the metal

precursors in the presence of triethylamine for 6-48 hours (Scheme 3.3) afforded the proposed Pd(II) and Pt(II) salicylaldiminato trithiosemicarbazone complexes in various yields (14-87%). These complexes were isolated as yellow-orange solids.



**Scheme 3.3:** Synthesis of salicylaldiminato trithiosemicarbazone complexes

Most of these reactions proceeded readily when refluxing in ethanol and methanol giving rise to the desired products. In the case of complex **36**, NMR data indicated unreacted *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (**16**) despite different synthetic attempts and purification methods. Complexes **39** and **41** were prepared in a similar manner to the other compounds of this series, however 50% v/v EtOH/H<sub>2</sub>O and 50% v/v MeOH/H<sub>2</sub>O were used as the solvents, respectively.

Complexes **36** and **40** were synthesised by stirring the reactants at room temperature. Unlike the mono- and dinuclear derivatives some of these compounds display slightly enhanced solubility in organic solvents including DMSO.

### 3.4.2. Characterisation

#### *<sup>1</sup>H Nuclear Magnetic Resonance Spectroscopy*

Due to the similarities between the Pd(II) and Pt(II) complexes, their spectroscopic properties are discussed collectively (Table 3.8). Analyses suggest coordination of each thiosemicarbazone moiety in a dianionic manner to each metal centre. This is supported by the absence of signals accounting for the phenolic and hydrazinic protons in the spectrum of each of these complexes. This suggests coordination of the trithiosemicarbazone in the thiolate form as observed for the mono- and dinuclear derivatives. Figure 3.8 shows the <sup>1</sup>H NMR spectrum of one of these compounds.

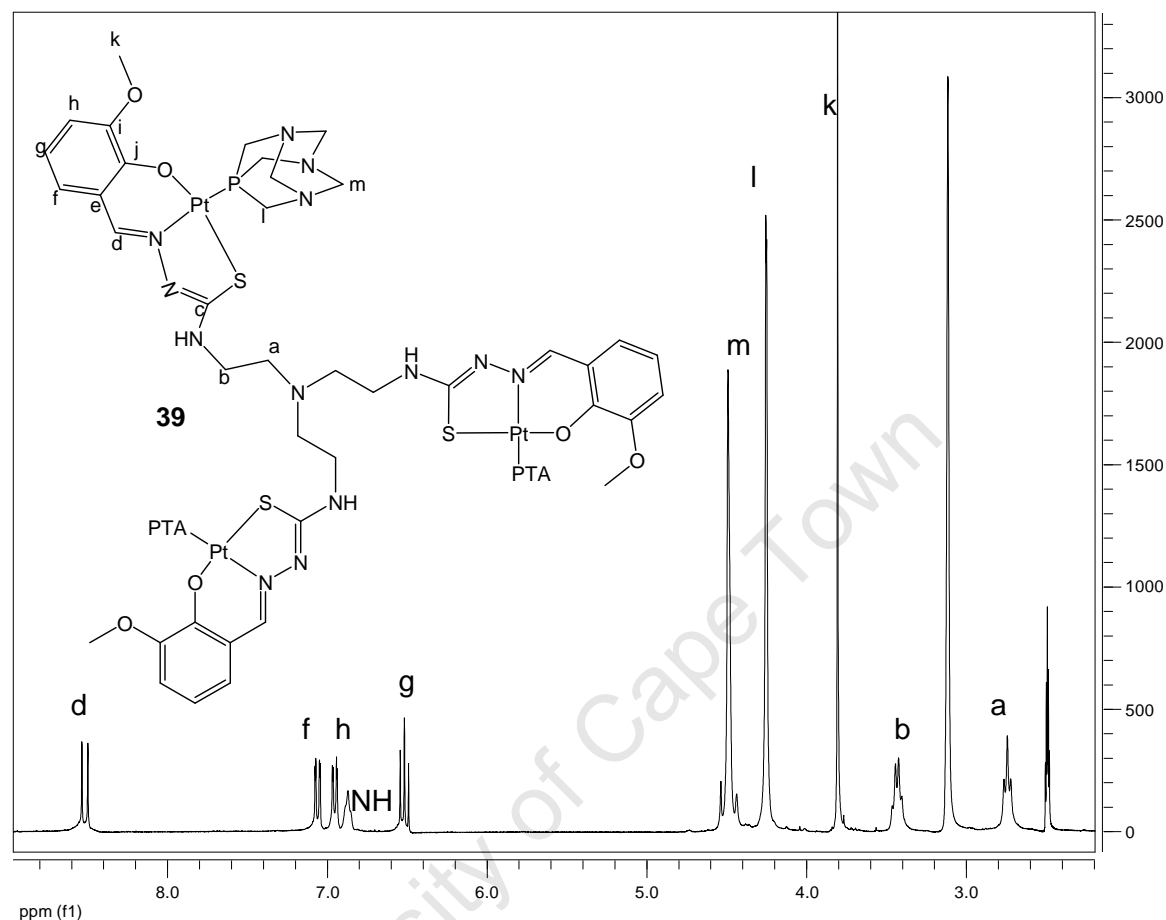
**Table 3.8**

Spectroscopic data obtained for trithiosemicarbazone complexes (**34-41**)

<i>Compound</i>	<i>M</i>	<i>R</i>	<sup>1</sup> H NMR (ppm) -HC=N-	<sup>4</sup> J <sub>P-H</sub> Value (Hz)
<b>34</b>	Pd	H	8.31	12.99
<b>35</b>	Pd	3-OMe	8.33	13.18
<b>36</b>	Pd	3- <sup>t</sup> Bu	8.26	13.44
<b>37</b>	Pd	5-Cl	8.19	12.92
<b>38</b>	Pt	H	8.57	11.20
<b>39</b>	Pt	3-OMe	8.51	11.22
<b>40</b>	Pt	3- <sup>t</sup> Bu	8.58	11.35
<b>41</b>	Pt	5-Cl	8.53	11.04

Similar to the mono- and dinuclear analogues, signals corresponding to the aliphatic protons of the PTA ligand appear in the region of 4.50 ppm. In most cases an AB spin system is observed for the N-CH<sub>2</sub>-N protons of the ligated

PTA with the exception of **39**, where the N-CH<sub>2</sub>-N protons are equivalent and therefore appear as a singlet accounting for 18 protons.



**Figure 3.8:** <sup>1</sup>H NMR spectrum of 3-methoxysalicylaldiminato trithiosemicarbazone Pt Complex (**39**)

In both the Pd(II) and Pt(II) complexes, the signal for the imine proton appears as a doublet due to coordination of the metal-phosphine moiety to the azomethine nitrogen resulting in <sup>4</sup>J<sub>P-H</sub> coupling of the spin-active <sup>31</sup>P nucleus and that of the azomethine proton. The coupling constants obtained for the Pd complexes range between 12.92 and 13.44 Hz, while the Pt complexes exhibit *J* values between 11.04 and 11.35 Hz. When comparing the shifts of the complexes and the free ligands there are some significant differences. In the case of the Pd(II) complexes a shift of the imine signal upfield (ca. 8.20 ppm) is observed in comparison to the free trithiosemicarbazones (ca. 8.40 ppm). In contrast the Pt(II) complexes display shifts downfield (ca. 8.60 ppm) in comparison to the free ligands.

### **<sup>13</sup>C{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy**

Overall the signals accounting for the phenolic carbon atoms appear to shift downfield for both the Pd and Pt systems upon coordination. The same phenomenon is also observed for the azomethine carbon signals. Shifts from approximately 140.00 ppm to 150.00 ppm are observed. In contrast, signals corresponding to the thiolate carbon of the complexes (170.00 ppm) are found more upfield in comparison to the free ligands (177.00 ppm). This is mainly attributed to an increased electron-density at the site of coordination due to  $\pi$  back-bonding at the thiolato sulfur.<sup>4</sup>

### **<sup>31</sup>P{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy**

<sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy was employed in order to further confirm complexation of the ligand to the respective metal precursors. As with the mono- and dinuclear derivatives, compounds (**34-37**) display singlets in the region of -40.00 ppm, while the corresponding Pt derivatives (**38-41**) display typical resonances at approximately -60.00 ppm. The coupling constants observed for the Pt compounds are consistent with <sup>1</sup>J<sub>Pt-P</sub> constants of the afore-mentioned complexes. Typical <sup>13</sup>C{<sup>1</sup>H} and <sup>31</sup>P{<sup>1</sup>H} NMR resonances and coupling constants are observed in Table 3.9.

### **Infrared Spectroscopy**

Coordination of ligands **11-14** in the thiolate form suggests that a second imine bond forms upon deprotonation of the hydrazinic nitrogen. Two absorption bands are found in the spectrum of most of the compounds, absorption bands of higher frequency are observed between 1621 and 1631 cm<sup>-1</sup>, while bands of lower frequency are observed between 1592 and 1599 cm<sup>-1</sup>. The former is attributed to the new imine bond upon complexation. The latter is attributed to the existing imine bond which shifts to lower frequency upon coordination to the metal. The  $\nu(\text{C}=\text{S})$  bands of the ligand appear less intense in the complexes and are observed at lower frequencies which corresponds to typical  $\nu(\text{C}-\text{S})$  frequencies. This suggests coordination of the

metal to sulfur in the thiolate form after deprotonation of the hydrazinic proton and appear consistent with similar tridentate TSC systems.<sup>21-23</sup>

**Table 3.9**

Selected spectroscopic data obtained for trithiosemicarbazone complexes (34-41)

Compound	M	R	<sup>13</sup> C{ <sup>1</sup> H} NMR (ppm)		<sup>31</sup> P{ <sup>1</sup> H} NMR (ppm)
			-C-S	-C=N-	[ <sup>1</sup> J <sub>Pt-P</sub> value (Hz)]
34	Pd	H	171.15	147.57	-40.55
35	Pd	3-OMe	170.82	148.16	-36.00
36	Pd	3- <sup>t</sup> Bu	169.41	149.51	-40.11
37	Pd	5-Cl	170.69	146.51	-36.32
38	Pt	H	172.32	145.90	-61.49 [3348.80]
39	Pt	3-OMe	171.51	145.66	-56.90 [3333.81]
40	Pt	3- <sup>t</sup> Bu	171.31	147.81	-60.76 [3340.49]
41	Pt	5-Cl	172.36	145.72	-58.19 [3341.09]

### Elemental Analysis and Mass Spectrometry

Although elemental analysis of these compounds was found to be consistent with the expected values, in some cases the microanalysis revealed the presence of water molecules as seen with the dinuclear compounds. Mass spectrometry data also supports the integrity of these complexes. In most cases the ESI spectra displayed peaks of the form  $[M+2H]^{2+}$  as the base peaks. Peaks of the form  $[M+H]^+$  and  $[M]^+$  are also observed, although with lower intensities. Table 3.10 displays some results obtained from the ESI mass spectrometry analysis.

Table 3.10

ESI mass spectrometry data for the trithiosemicarbazone complexes (34-41)

<i>Compound</i>	<i>M</i>	<i>R</i>	<i>m/z (intensity, %)</i>	<i>Assignment</i>
34	Pd	H	1466 (25)	[M+H] <sup>+</sup>
35	Pd	3-OMe	1556 (100)	[M] <sup>+</sup>
			778 (20)	[M+2H] <sup>2+</sup>
36	Pd	3- <sup>t</sup> Bu	1634 (30)	[M] <sup>+</sup>
			818 (70)	[M+2H] <sup>2+</sup>
37	Pd	5-Cl	1569 (10)	[M] <sup>+</sup>
			785 (90)	[M+2H] <sup>2+</sup>
38	Pt	H	1731 (50)	[M] <sup>+</sup>
39	Pt	3-OMe	1821 (44)	[M] <sup>+</sup>
			912 (10)	[M+2H] <sup>2+</sup>
40	Pt	3- <sup>t</sup> Bu	1900 (60)	[M] <sup>+</sup>
			951 (100)	[M+2H] <sup>2+</sup>
41	Pt	5-Cl	1835 (30)	[M] <sup>+</sup>
			918 (55)	[M+2H] <sup>2+</sup>

### 3.5. Conclusion

Overall, the mono-, di- and trinuclear Pd(II) and Pt(II) complexes exhibit similar physical and spectroscopic properties. All complexes were obtained using templated synthetic chemical procedures very effectively in moderate to good yields. The spectroscopic and analytical data undoubtedly support their composition and structure. Although these compounds display a slight improvement of solubility in some organic solvents including DMSO in comparison to similar triphenylphosphine complexes, little to no improvement was observed in water. The thiosemicarbazone complexes that were prepared are insoluble in water and this is mainly attributed to the

thiosemicarbazone moiety. The solubility of these compounds did not improve substantially despite the use of a water soluble co-ligand. There has also been a report of self-aggregation of these thiosemicarbazone systems which may contribute to their water-insoluble nature.<sup>24</sup>

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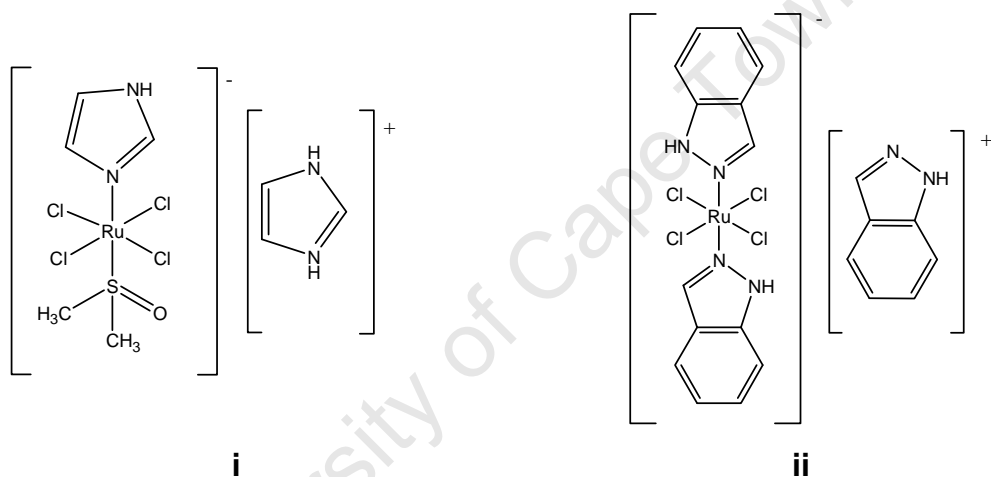
## **CHAPTER 4**

# **Synthesis and Characterisation of ( $\eta^6$ -Arene)Ruthenium(II) Thiosemicarbazone Complexes**

University of Cape Town

## 4.1. Introduction

Platinum-based drugs have been used clinically in recent years.<sup>1</sup> Many of these compounds, however, exhibit high toxicity as well as drug resistance which limits their clinical applications.<sup>2,3</sup> Ruthenium compounds have therefore been considered as a viable alternative to classical platinum-containing compounds. Many ruthenium compounds are less toxic than platinum based drugs and in some cases are found to be selective towards cancer cells.<sup>4,5</sup> Two ruthenium(III) complexes that have successfully completed phase I clinical trials,  $[\text{imiH}]\text{trans-}[\text{Ru}(\text{N-imi})(\text{S-dms})\text{Cl}_4]$  (NAMI-A) (Figure 4.1.i) and  $[\text{indH}]\text{trans-}[\text{Ru}(\text{N-ind})_2\text{Cl}_4]$  (KP1019) (Figure 4.1.ii), where imi = imidazole and ind = indazole, provided the initial breakthrough into this field of research.<sup>6-10</sup>



**Figure 4.1:** Ru(III) complexes in clinical trials towards the treatment of cancer

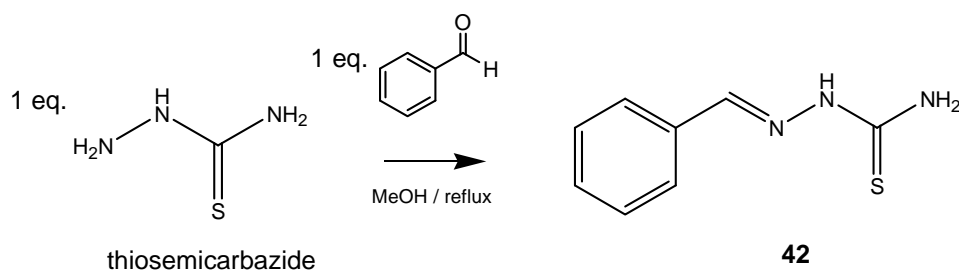
Half-sandwich organometallic arene ruthenium(II) complexes have attracted considerable interest as potential anticancer agents. Recently complexes of the type  $[\text{Ru}(\eta^6\text{-arene})(\text{en})\text{Cl}][\text{PF}_6]$  (en = ethylenediamine) have exhibited promising anticancer activity.<sup>11</sup> This part of the study therefore focused on the preparation of thiosemicarbazones using arene ruthenium(II) precursors for complexation to potentially obtain more soluble and potent complexes for biological testing. The focus of this section is therefore two-fold, i.e. (1) to produce more soluble complexes for testing and (2) to employ the use of ruthenium as a viable alternative to platinum and palladium.

## 4.2. Preparation of thiosemicarbazone ligands (42-46)

### 4.2.1. Synthetic approach and physical properties

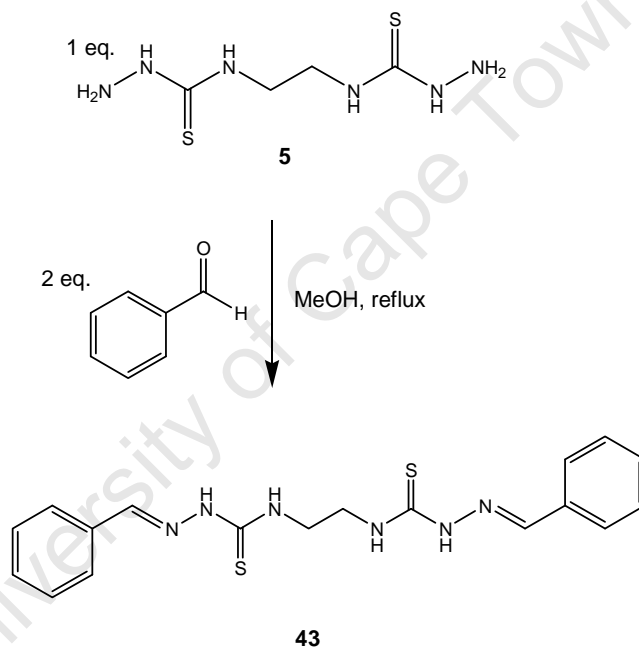
The chemistry and biological activity of arene ruthenium complexes has been investigated extensively in recent years.<sup>12</sup> These complexes are usually prepared using similar procedures and reactions proceed without major complications, provided an appropriate ligand system is introduced. In this study thiosemicarbazones derived from benzaldehyde were used. Reaction of benzaldehyde monothiosemicarbazone (**42**) with the arene ruthenium(II) precursor revealed that thiosemicarbazones not possessing any heteroatoms on the aryl ring provide the best systems for coordination to ruthenium in the desired manner, as this would limit the number of coordination sites for the metal (see Section 4.3). Recent literature also reports the use of anthraldehyde thiosemicarbazones as appropriate scaffolds for coordination of thiosemicarbazones to ruthenium arene precursors.<sup>13</sup> Arene ruthenium(II) *p*-chloroacetophenone phenylthiosemicarbazone complexes were also prepared for the use in the transfer hydrogenation of ketones.<sup>14</sup> Based on this it was decided to prepare mono-, di- and trithiosemicarbazones derived from a simple system such as benzaldehyde for subsequent reaction with arene ruthenium precursors.

Benzaldehyde monothiosemicarbazone (**42**) was prepared similarly to the salicylaldimine monothiosemicarbazones mentioned in Section 2.2. Thiosemicarbazide, suspended in methanol, was refluxed with benzaldehyde resulting in a clear solution. Excess water was added to the solution to precipitate a white solid which upon characterisation proved to be the desired product. Scheme 4.1 outlines the preparation of **42**.



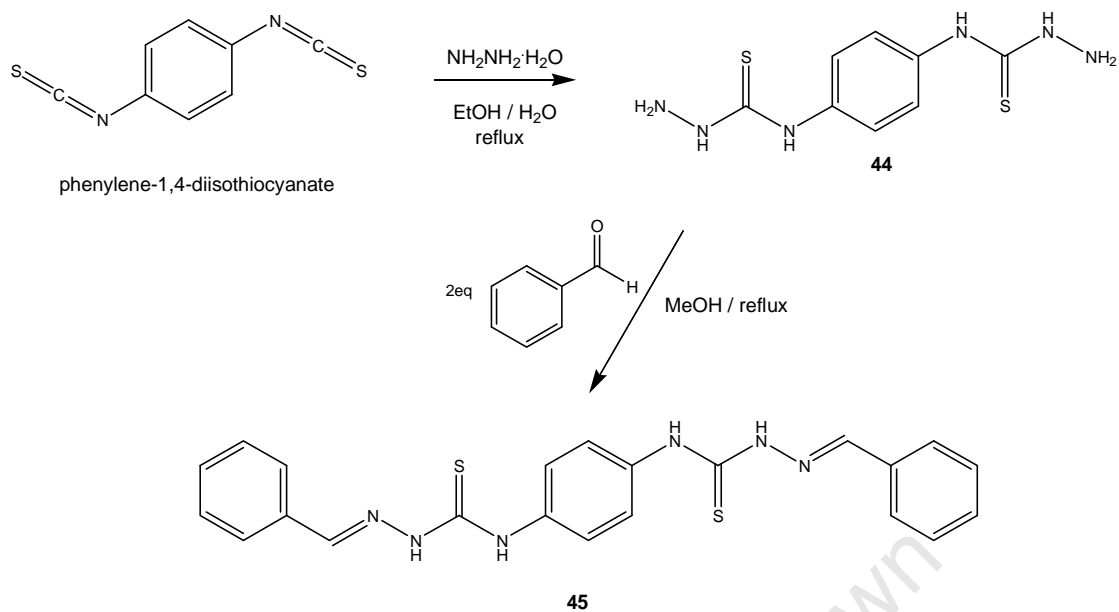
**Scheme 4.1:** Preparation of benzaldehyde monothiosemicarbazone (**42**)

Ethane-1,2-benzaldehyde dithiosemicarbazone (**43**) was prepared in a 68% yield by refluxing benzaldehyde and ethane-1,2-dithiosemicarbazide (**5**) in a 2:1 mole ratio in methanol (Scheme 4.2). Subsequent reaction of this ligand with the *p*-cymene ruthenium(II) precursor (see Section 4.3), did not give rise to the desired dinuclear complex. No proposed structure was discernible from the  $^1\text{H}$  NMR spectrum obtained. It was then decided to alter the ligand system slightly in order to investigate the reactivity of these dithiosemicarbazones with ruthenium. It was believed that the spacer may perhaps contribute towards the outcome of these reactions. It was thought that alteration of the more flexible ethane bridge to a rigid, electron-withdrawing benzene moiety may aid in the attainment of the proposed dinuclear complex.



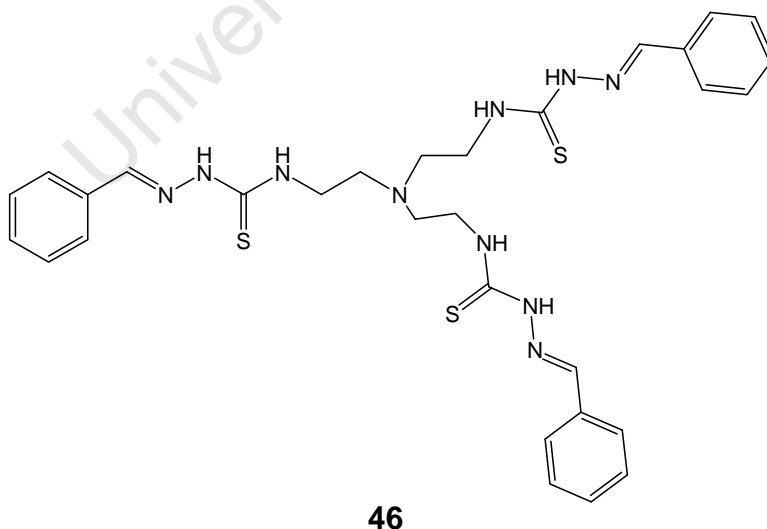
**Scheme 4.2:** Preparation of a non-rigid dithiosemicarbazone (**43**)

Benzene-1,4-dithiosemicarbazide (**44**) was prepared by a procedure previously reported by Dilworth *et al.*<sup>15</sup> Commercially available phenylene-1,4-diisothiocyanate is treated with hydrazine hydrate in a mixture of water and ethanol resulting in the rigid dithiosemicarbazide.<sup>15</sup> Benzene-1,4-benzaldehyde dithiosemicarbazone (**45**) was prepared by means of a Schiff-base condensation reaction between benzaldehyde and benzene-1,4-dithiosemicarbazide in MeOH under reflux conditions. The preparation of these compounds is outlined in Scheme 4.3.



**Scheme 4.3:** Preparation of a rigid dithiosemicarbazone (**45**)

A trithiosemicarbazone derivative was also prepared for complexation with ruthenium. The non-rigid trimeric derivative **46** (Figure 4.2), was prepared from tris(2-aminoethyl) thiosemicarbazide and benzaldehyde as per the trithiosemicarbazone salicylaldehyde ligands by refluxing the contents in ethanol giving rise to a cream powder in a 53% yield.



**Figure 4.2:** Benzaldehyde trithiosemicarbazone (**46**) prepared in this study

#### 4.2.2. Characterisation

##### *$^1\text{H}$ Nuclear Magnetic Resonance Spectroscopy*

The NMR spectra of ligands **42-46** were recorded in DMSO- $d_6$ . Signals accounting for the azomethine hydrogen atoms are observed between 8.04 and 8.06 ppm for compounds **42**, **43** and **46**. This particular signal appears more downfield in the case of **45** which is attributed to the presence of the electron-withdrawing phenyl spacer. The signal for the hydrazinic proton is also observed relatively downfield, at approximately 12.06 ppm, in comparison to the rest of the compounds where the signals appear between 11.31 and 11.45 ppm. The presence of signals for the hydrazinic protons suggests that the thiosemicarbazones exist as neutral ligands with the sulfur in the thione form. Signals for the aliphatic bridges are observed as a singlet at 3.87 ppm for ligand **43** and at 2.70 and 3.45 ppm, respectively, for compound **46**. A sharp singlet is observed at 7.92 ppm for the protons of the phenyl bridge of ligand **45**.

##### *$^{13}\text{C}\{^1\text{H}\}$ Nuclear Magnetic Resonance Spectroscopy*

The  $^{13}\text{C}\{^1\text{H}\}$  NMR data obtained for these compounds supports the  $^1\text{H}$  NMR spectral results. Signals for the imine carbon atoms are observed between 142.47 and 143.30 ppm. The thione carbon signals are seen in the region of 176.43 and 178.40 ppm. The spectra of these ligands exhibit the appropriate number of signals, thus supporting their structure. The detailed  $^1\text{H}$  NMR and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectral data are given in the experimental section. Table 4.1 gives selected spectral data obtained for these benzaldehyde thiosemicarbazone ligands.

Table 4.1

NMR spectroscopic data obtained for the benzaldehyde thiosemicarbazone ligands

Compound	NMR (ppm)			
	$^1\text{H}$		$^{13}\text{C}$	
	-HC=N-	-NH-	-C=N-	-C=S
<b>42</b>	8.05	11.31	142.73	178.40
<b>43</b>	8.06	11.45	142.86	178.01
<b>45</b>	8.52	12.06	143.30	176.43
<b>46</b>	8.04	11.38	142.47	177.58

### Infrared Spectroscopy

Due to the limited solubility of these ligands in many organic solvents, solid-state infrared studies were used to evaluate these compounds. These experiments were carried out using KBr pellets. Strong absorption bands observed in the region of 1591 and 1634  $\text{cm}^{-1}$  are attributed to the C=N stretching frequencies. The presence of these bands supports the structure of these compounds. The absorption bands confirm condensation of benzaldehyde with the respective thiosemicarbazides. The thione (C=S) stretching frequencies occur at approximately 870  $\text{cm}^{-1}$ , thus providing further evidence that these ligands exist as their thione tautomers.

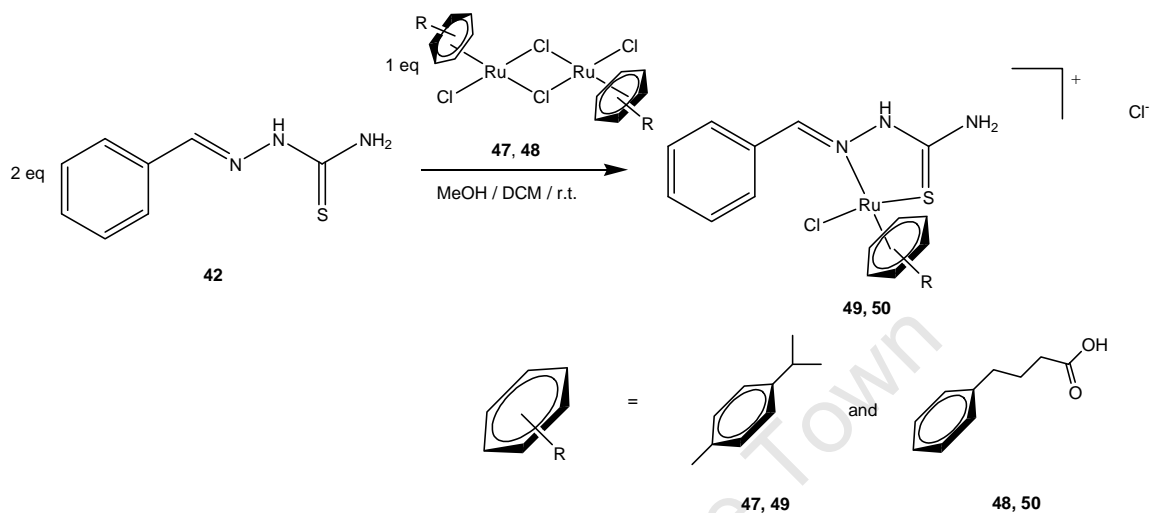
## 4.3. Preparation of ( $\eta^6$ -Arene)ruthenium(II) TSC complexes (47-52)

### 4.3.1. Synthetic approach and physical properties

Reaction of the afore-mentioned benzaldehyde thiosemicarbazone ligands with two ruthenium arene precursors, i.e.  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})\text{Cl}]_2$  (**47**)<sup>16</sup> and  $[\text{Ru}(\eta^6\text{-C}_6\text{H}_5(\text{CH}_2)_3\text{COOH})(\mu\text{-Cl})\text{Cl}]_2$  (**48**),<sup>17</sup> was investigated (Scheme 4.5). All reactions were carried out at ambient temperature in either dichloromethane or methanol. The reaction of **42** with  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})\text{Cl}]$  in MeOH at room temperature resulted in a red solution which upon concentration and addition of diethyl ether resulted in precipitation of the cationic complex **49** as a red powder in a yield of 62%. Ligand **42** was also complexed with  $[\text{Ru}(\eta^6\text{-C}_6\text{H}_5(\text{CH}_2)_3\text{COOH})(\mu\text{-Cl})\text{Cl}]_2$  in a similar manner to the

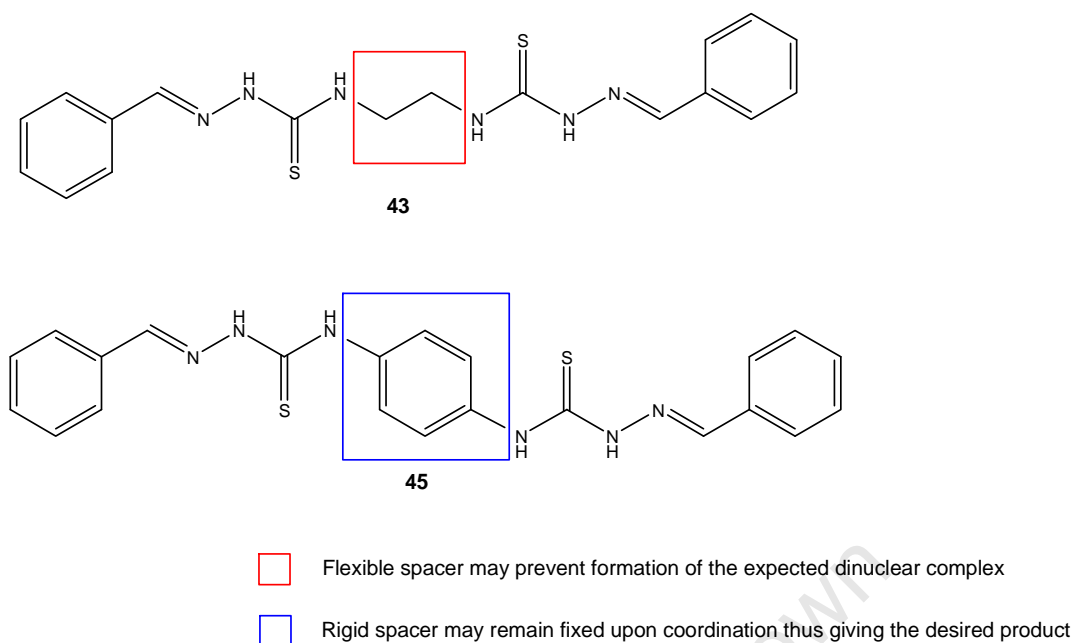


*p*-cymene derivative, giving rise to a red solid (**50**). The reaction mixture was filtered, washed with diethyl ether and dried *in vacuo* resulting in a red powder in 75% yield. These complexes were obtained as their chloride salts.



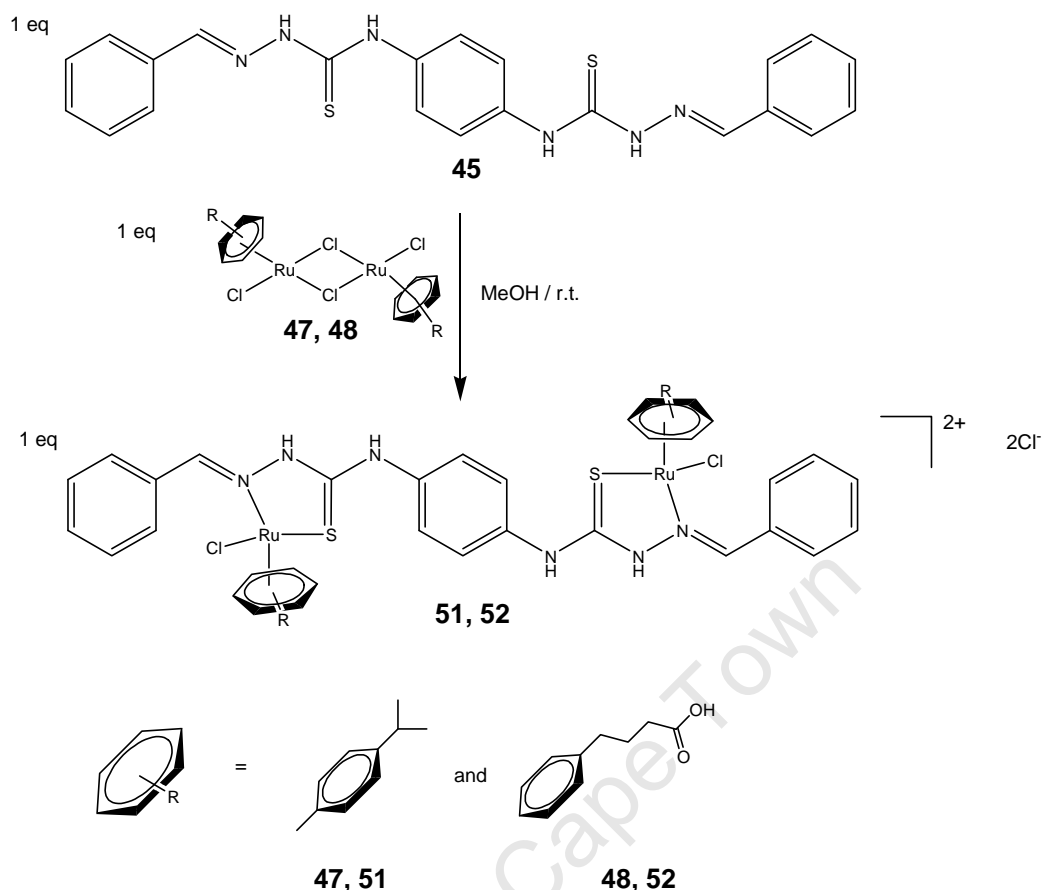
**Scheme 4.5:** Preparation of mononuclear arene-ruthenium(II) complexes (**49** and **50**)

The dinuclear complexes were obtained using similar chemical procedures as outlined above. The compounds obtained from the reactions involving the rigid dithiosemicarbazone (**45**) display a similar mode of coordination to the mononuclear compounds. The results obtained from the reaction involving ligand **43** were inconclusive. The product of this reaction displayed similar physical properties to the mononuclear derivative (reddish powder, similar solubility profile). The  $^1\text{H}$  NMR spectrum suggests the formation of a thiosemicarbazone ruthenium complex, however broadened and overlapping peaks made identifying the compound difficult. It is believed that perhaps the flexibility of the spacer may affect the outcome of the reaction. The flexible nature of the spacer may prevent coordination of the metal to each side of the ligand only and perhaps additional ruthenium thiosemicarbazone species are formed as the non-rigid ligand (**43**) (Figure 4.3) can orientate in various ways. The rigid derivative (**45**) is not able to orientate as much and thus ruthenium coordinates in the proposed manner.



**Figure 4.3:** Two dithiosemicarbazone systems (**43** and **45**) investigated in this study

Compound **45** was reacted in MeOH with  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})\text{Cl}]_2$  (**47**) at room temperature (Scheme 4.6). The red-orange solution obtained was evaporated, DCM added and diethyl ether utilised to precipitate the product. The orange powder (**51**) was isolated in 59% yield. Ligand **45** was also complexed with  $[\text{Ru}(\eta^6\text{-C}_6\text{H}_5(\text{CH}_2)_3\text{COOH})(\mu\text{-Cl})\text{Cl}]_2$  (**48**) giving rise to an orange powder in a yield of 89% (**52**).



**Scheme 4.6:** Preparation of dinuclear arene ruthenium complexes (**51** and **52**)

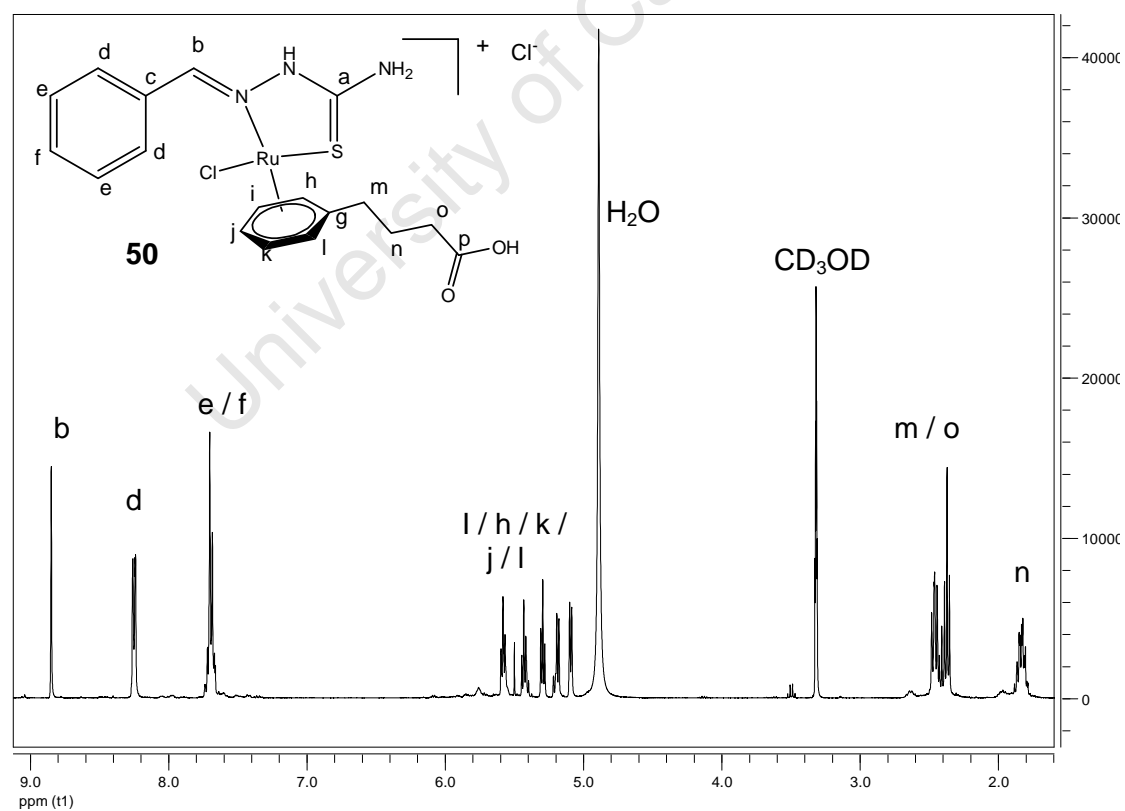
The reaction involving trithiosemicarbazone **46** with the *p*-cymene dimer gave a similar result to the reaction involving the non-rigid dithiosemicarbazone ligand (**43**). The reason why these particular reactions were not successful is not completely understood. This question will thus be left for a future investigation.

### 4.3.2. Characterisation

#### $^1\text{H}$ Nuclear Magnetic Resonance Spectroscopy

The NMR spectra of the ruthenium *p*-cymene complexes (**49** and **51**) were run in  $\text{CDCl}_3\text{-}d$ , while the spectra of the carboxylic acid derivatives (**50** and **52**) were obtained in  $\text{CD}_3\text{OD-}d_4$ . Figure 4.4 displays a representative  $^1\text{H}$  NMR spectrum for a carboxylic derived complex (i.e. complex **50**). Evaluation of the spectra revealed that upon complexation of the respective ligands to the respective metal precursors, there is a loss of two-fold symmetry of the

*p*-cymene and the carboxylic acid arene ligands. The loss of symmetry is evidenced by the appearance of four sets of doublets in the region of 4.60 and 5.40 ppm accounting for the protons of the *p*-cymene rings of complexes **49** and **51**. The methyl substituents of the isopropyl group are observed as two distinct doublets in the aliphatic region of the spectra which further confirms the loss of planarity as the two methyl groups are non-equivalent. These methyl protons are observed at 1.07 and 1.13 ppm for complex **49** and at 1.09 and 1.15 ppm for complex **51**. The presence of the hydrazinic protons suggest coordination of the ligands in the thione form to the metal. In the case of the carboxylic acid derivatives (**50** and **52**), three sets of triplets and two sets of doublets are observed for the arene ring and are found in the region of 5.00–5.50 ppm. This loss of symmetry may suggest that these complexes have similar modes of coordination. The loss of planarity is also consistent with the spectroscopic data obtained for similar arene-ruthenium(II) complexes observed in literature.<sup>13,18</sup>



**Figure 4.4:**  $^1\text{H}$  NMR spectrum of arene-ruthenium(II) complex **50**

Singlets for the imine protons are observed at 9.05 (**49**), 8.81 (**50**), 9.04 (**51**) and 8.90 ppm (**52**). A downfield shift is observed for these signals of the free ligands upon coordination to ruthenium. This suggests coordination of the metal to the imine nitrogen atom as the signal becomes more deshielded in each case. This is also observed for other arene-ruthenium thiosemicarbazone complexes.<sup>13</sup> From this data it is believed that the ligands coordinate in a neutral manner to the ruthenium metal via the imine nitrogen and thione sulfur atoms thus giving rise to stereogenic ruthenium centres.

### **<sup>13</sup>C{<sup>1</sup>H} Nuclear Magnetic Resonance Spectroscopy**

The <sup>13</sup>C{<sup>1</sup>H} NMR spectra of **49** and **51** are very similar. The carbon signals attributed to the methyl group of the *p*-cymene moiety is observed at ca. 18.00 ppm. The signals for the two carbon atoms of the methyl groups of the isopropyl moiety are found at approximately 21.00 and 23.00 ppm, respectively. Signals for the thione carbon atoms are found at 177.54 and 175.97 ppm for **49** and **51**, respectively. These signals are found at similar chemical shifts for the free ligands with values of 178.40 and 176.43 ppm for ligands **42** and **45**. The imine signals are found relatively downfield (~161.00 ppm) in comparison to the free ligands (~140.00 ppm), supporting coordination of the imine nitrogen to ruthenium.

Signals for the aliphatic carbon atoms of the arene moiety for complexes **50** and **52** appear between 25.00 and 33.00 ppm. The carbonyl carbon atom signals of the carboxylic acid moiety occur at 174.98 and 170.61 ppm, respectively. Signals for the thione carbon atoms appear at similar shifts to the *p*-cymene derivatives with signals observed at 177.82 and 174.77 ppm. The imine signals for these complexes are also observed at 162.35 and 164.86 ppm which is slightly more deshielded than the same signals of the *p*-cymene derivatives. The <sup>13</sup>C{<sup>1</sup>H} NMR spectra of these complexes undoubtedly attests to the preparation of these complexes. Chapter 7 gives a detailed account of the NMR spectroscopic data of these compounds. Table 4.2 gives selected NMR data for these complexes.

**Table 4.2**

NMR spectroscopic data obtained for arene-Ru(II) TSC complexes

<b>Complex</b>	<b>NMR (ppm)</b>			
	<b><math>^1\text{H}</math></b> <b>-HC=N-</b>	<b>-C=O</b>	<b><math>^{13}\text{C}</math></b> <b>-C=N-</b>	<b>-C=S</b>
<b>49</b>	9.05	-	161.65	177.54
<b>50</b>	8.81	174.98	162.35	177.82
<b>51</b>	9.04	-	161.45	175.97
<b>52</b>	8.90	170.61	164.86	174.77

**Infrared Spectroscopy**

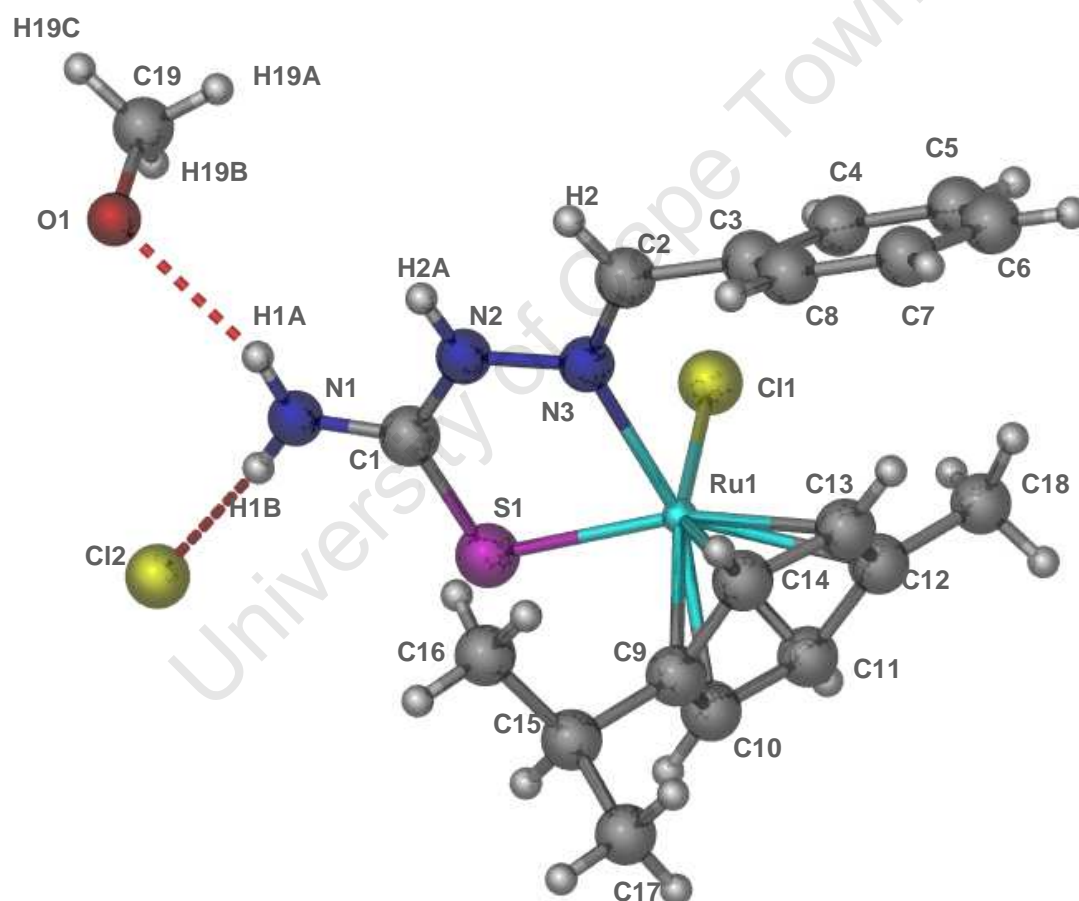
It is noteworthy that the absorption patterns for these complexes are similar. The imine (C=N) absorption bands for the two *p*-cymene derivatives appear at ca. 1616  $\text{cm}^{-1}$ , while these stretching frequencies appear at 1600  $\text{cm}^{-1}$  for compounds **50** and **52**. Absorption bands for the C=S stretching frequencies are found at similar frequencies to that of their corresponding free ligands, which suggests that the ligand remains in the thione form when coordinated to ruthenium. Bands at approximately 1700  $\text{cm}^{-1}$  are attributed to the C=O stretching frequencies of the arene ligands for compounds **50** and **52**.

**ESI Mass Spectrometry and Elemental Analysis**

The ESI mass spectra of these complexes do not display molecular ion peaks for these compounds, however, a base peak corresponding to the fragment of the form  $[\text{M}-\text{H}-2\text{Cl}]^+$  is observed for **49**, while a peak of 85% intensity corresponding to the fragment  $[\text{M}-5\text{H}-4\text{Cl}+2\text{Na}]^+$  is observed for **51**. A fragment corresponding to  $[\text{M}-\text{H}-2\text{HCl}]^+$  is observed for **50**, while a base peak accounting for  $[\text{M}-2\text{Cl}-\text{CO}_2]^{2+}$  is observed for complex **52**. Elemental analysis confirmed the composition of these compounds. The data obtained for **49**, **50** and **52** is consistent with the proposed structures.

### Single Crystal X-Ray Diffraction Studies

The mode of coordination of one of these compounds was determined using single crystal X-ray diffraction. The molecular structure of complex **49** is illustrated in Figure 4.5. Crystals suitable for structure determination were grown by slow diffusion of diethyl ether into a 5:1 v/v MeOH and DCM solution. The compound crystallises in the monoclinic space group  $C2/c$ . The compound crystallises as its chloride salt along with one molecule of methanol (Figure 4.5). This is one of a few examples of a half-sandwich thiosemicarbazone arene-ruthenium(II) complex that has been structurally characterised.



**Figure 4.5:** Molecular structure of  $(\eta^6\text{-}p\text{-cymene})\text{ruthenium(II)}$  benzaldehyde TSC complex **49**

The molecular structure confirms the coordination of the thiosemicarbazone ligand (**42**) in a neutral manner with the ruthenium metal centre through the N-S donor atoms in a bidentate fashion via the thione sulfur and imine

nitrogen atoms. The complex adopts the commonly observed piano-stool geometry of many half-sandwich arene-ruthenium(II) complexes.<sup>13,14,18-21</sup> In this case, the *p*-cymene ring forms the seat of the piano-stool, while the bidentate thiosemicarbazone (N, S) and the chlorido ligand form the three legs of the stool. Selected bond parameters are quoted in Table 4.3.

**Table 4.3**

Selected bond lengths (Å) and angles (°) for complex **49**

Ru(1)-Cl(1)	2.402(15)	N(3)-Ru(1)-S(1)	81.87(12)
Ru(1)-S(1)	2.357(15)	N(3)-Ru(1)-Cl(1)	83.41(11)
Ru(1)-C(9)	2.204(5)	S(1)-Ru(1)-Cl(1)	86.50(5)
Ru(1)-C(10)	2.165(5)		
Ru(1)-C(11)	2.242(5)		
Ru(1)-C(12)	2.263(6)		
Ru(1)-C(13)	2.190(6)		
Ru(1)-C(14)	2.175(5)		

Internuclear distances of 2.201 between Cl(2) and H1(B) as well as 2.295 Å between H(1A) and O(1) of the solvated MeOH molecule is indicative of hydrogen bonding. The ruthenium centre adopts a pseudo-tetrahedral geometry as the *p*-cymene ligand essentially occupies one coordination site. Bond angles of 81.87(12), 83.41(11) and 86.50(5)° are observed for N(3)-Ru(1)-S(1), N(3)-Ru(1)-Cl and S(1)-Ru(1)-Cl(1), respectively. On closer examination of the bond lengths, it appears as though the *p*-cymene ligand is asymmetrically coordinated to the metal centre as the Ru-C<sub>arene</sub> bond lengths are variable. This is also observed for a similar anthraldehyde TSC complex.<sup>13</sup> It is believed that the distortion may minimise steric interaction between the *p*-cymene ligand and the thiosemicarbazone. An average Ru-C<sub>arene</sub> bond length of 2.207 Å is observed and is in accordance with similar arene-ruthenium(II) half-sandwich compounds.<sup>13,19</sup>



#### 4.4. Conclusion

The preparation and characterisation of four new cationic organometallic arene-ruthenium(II) complexes has been discussed in this section. The characterisation of these complexes is in accordance with the proposed structures. Based on the molecular structure of **49**, it is believed that the thiosemicarbazone ligands coordinate in a bidentate manner to form cationic complexes. These complexes are readily soluble in most common organic solvents (DCM,  $\text{CHCl}_3$ , MeOH, EtOH, DMSO etc). These compounds therefore display improved solubility compared to the palladium and platinum salicylaldiminato complexes mentioned in Chapter 3 and are good candidates for biological evaluation.

#### 4.5. References

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## **CHAPTER 5**

# **Anticancer and Antiparasitic Activity of Thiosemicarbazones and their Complexes**

University of Cape Town

### 5.1. Introduction

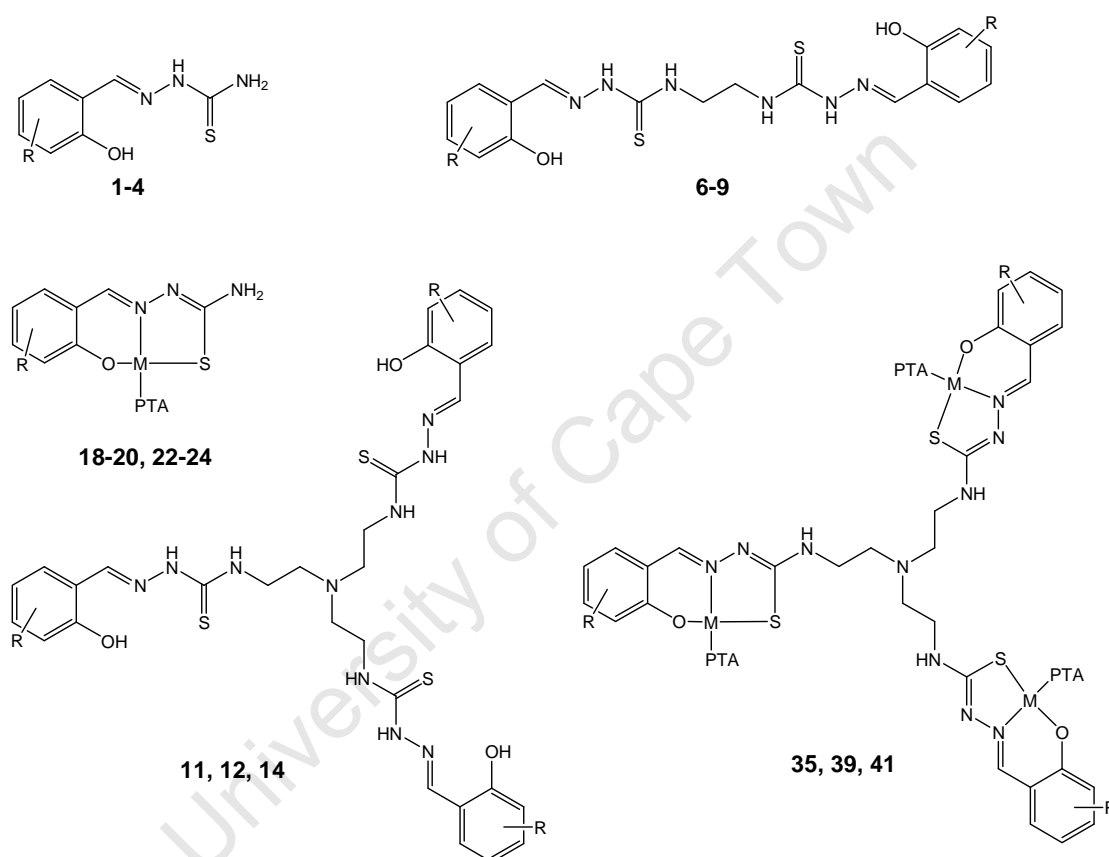
The use of mononuclear thiosemicarbazone platinum group metal complexes as potential anticancer agents has been investigated extensively as discussed in Chapter 1. Investigation into the biological activity of larger TSC molecules is limited in literature. This therefore prompted our investigation into the design and synthesis of larger thiosemicarbazone systems for biological evaluation. The design of trithiosemicarbazone compounds as potential anticancer agents stemmed from the phenomenon that macromolecules are able to accumulate more efficiently in tumour cells in comparison to healthy cells.<sup>1</sup> This phenomenon is referred to as the Enhanced Permeability and Retention (EPR) effect.

Tumourous cells display increased vascular permeability due to an increased porosity of surrounding blood vessels. This aids in the diffusion of macromolecules into the cancerous cells. Once inside the cells, the molecules are retained due to poor lymphatic drainage by the tumour cell.<sup>1</sup> This therefore promotes the use of larger compounds for selective targeting of abnormal cells. Although the systems investigated in this study are not considered to be macromolecules, it is worthwhile investigating the effect of varying size and nuclearity on biological activity. Recently, poly(propylene) imine (PPI) dendrimers possessing arene-ruthenium(II) moieties have been found to show cytotoxicity which is dependent on the size of the molecule.<sup>2</sup> It was observed that complexes of higher molecular weight (generation 2) show increased efficacy against tumour cell growth than their corresponding mononuclear analogues.<sup>2</sup> This chapter discusses the results obtained from the biological evaluation of selected thiosemicarbazone ligands and complexes. These compounds were screened for their anticancer and antiparasitic activity against the *WHCO1* oesophageal cancer cell-line and the T1 strain of *T. vaginalis*.

## 5.2. Anticancer studies

## 5.2.1. Anticancer evaluation of salicylaldimine TSC compounds

Anticancer data was obtained for selected salicylaldimine thiosemicarbazone compounds (Figure 5.1) discussed in Chapters 2 and 3. The results obtained for these tests are summarised in Table 5.1. The compounds were screened *in vitro* for their antiproliferative activity on the *WHCO1* oesophageal cancer cell-line.



**Figure 5.1:** General structures of thiosemicarbazone compounds screened against *WHCO1* cells (R and M defined in Table 5.1)

Oesophageal cancer is one of the most commonly occurring tumours that exist and therefore new chemotherapeutics are constantly required to overcome drug resistance.<sup>3</sup> Thiosemicarbazones are good candidates as potential anticancer agents due to their vast biological applications. In this study compounds showing insufficient solubility in aqueous DMSO were tested as suspensions or excluded from biological evaluation. The activity is

expressed in terms of an  $IC_{50}$  value, which is the minimum concentration of the compound required to inhibit 50% of cell proliferation. The lower the concentration, the more effective the compound is.

Table 5.1

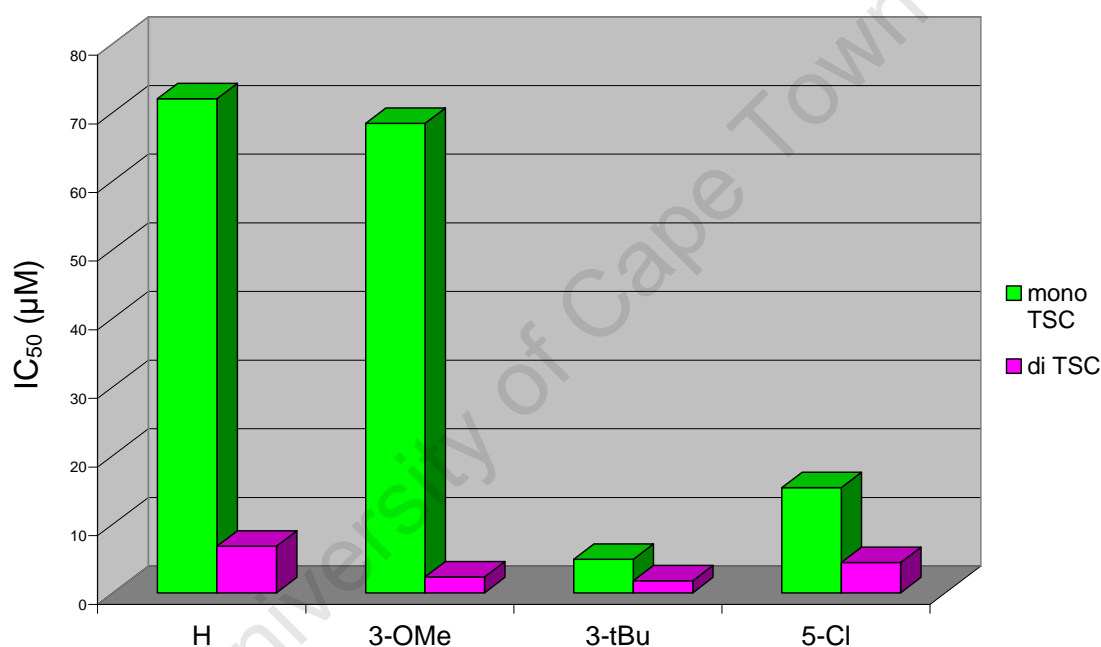
$IC_{50}$  values obtained for the *in vitro* anticancer studies on selected compounds TSC

Compound	R	Type	M	$IC_{50}$ ( $\mu M$ )	95%
					Confidence Interval (CI)
1	H	mono	-	72.00	50.49 - 102.70
2	3-OMe	mono	-	68.40	15.43 - 303.10
3	3- <sup>t</sup> Bu	mono	-	4.89	3.38 - 7.06
4	5-Cl	mono	-	15.34	12.42 - 18.96
6	H	di	-	6.81	5.87 - 7.88
7	3-OMe	di	-	2.34	1.51 - 3.62
8	3- <sup>t</sup> Bu	di	-	1.75	1.32 - 2.32
9	5-Cl	di	-	4.43	3.79 - 5.17
11	H	tri	-	> 200	-
12	3-OMe	tri	-	32.98	24.20 - 44.95
14	5-Cl	tri	-	4.42	3.65 - 5.34
18	H	mono	Pd	1.37	1.10 - 1.70
19	3-OMe	mono	Pd	1.04	0.97 - 1.10
20	3- <sup>t</sup> Bu	mono	Pd	1.05	0.82 - 1.35
22	H	mono	Pt	68.59	20.45 - 230.10
23	3-OMe	mono	Pt	17.43	3.796 - 80.06
24	3- <sup>t</sup> Bu	mono	Pt	11.79	n/d*
35	3-OMe	tri	Pd	> 200	-
39	3-OMe	tri	Pt	> 200	-
41	5-Cl	tri	Pt	3.14	1.26 - 7.84

\*Confidence interval could not be determined

From table 5.1, the results for both the monothiosemicarbazone ligands (1-4) and dithiosemicarbazones (6-9) reveal moderate to good cytotoxicity. Comparison of these two systems shows that the ligands possessing the

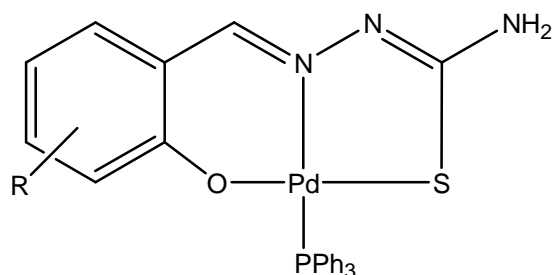
tertiary butyl moiety (**3** and **8**) display the best cytotoxicity in each series. In addition to this, the dithiosemicarbazone ligands display better activities with  $IC_{50}$  values ranging between 1.75 and 6.81  $\mu\text{M}$ . The trithiosemicarbazone ligands (**11** and **12**) display moderate to weak activity, while the 5-chloro derivative (**14**) displays the best activity with an  $IC_{50}$  value of 4.42  $\mu\text{M}$ . It seemed that varying the number of thiosemicarbazone moieties from two to three does not lead to an appreciable increase in the activity of the compound. On the other hand, extension of the monothiosemicarbazone systems to dithiosemicarbazone ligands leads to an increase in activity against the *WHCO1* cell-line (Figure 5.2).



**Figure 5.2:** Graphical representation depicting the activity between mono- and dithiosemicarbazone ligands

The results obtained for the mononuclear palladium complexes (**18-20**) are promising as all three compounds exhibit enhanced cytotoxicity with  $IC_{50}$  values lower than 2  $\mu\text{M}$ . It is noteworthy that these Pd(II) complexes show better activities compared to cisplatin which displayed moderate potency ( $IC_{50} = 13 \mu\text{M}$ ) against the *WHCO1* cell-line.<sup>4</sup> Cisplatin was not screened during this particular evaluation, but was carried out in a previous study on the same cell-line using the same protocol.<sup>4</sup> The biological evaluation of similar mononuclear salicylaldimine complexes, where the PTA co-ligand is replaced

by a triphenylphosphine group (Figure 5.3), were previously reported and tested against the same cell-line.<sup>5</sup>



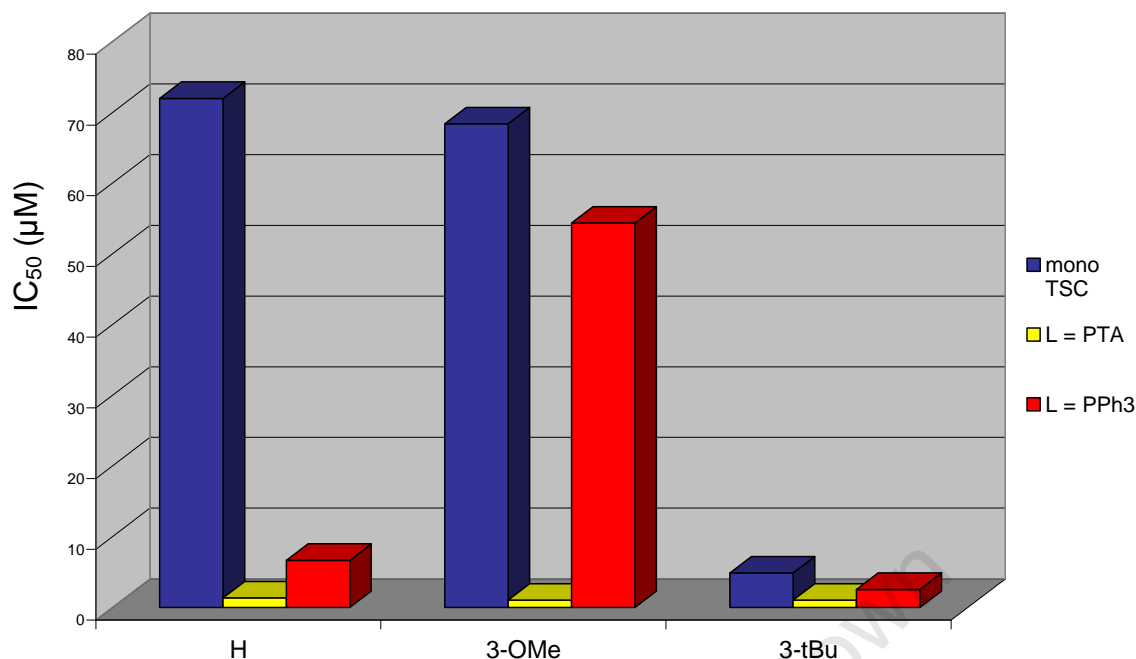
*R = H, 3-OMe, 3-<sup>t</sup>Bu, 5-Cl*

**Figure 5.3:** Similar triphenylphosphine complexes previously reported

Comparison of the results revealed that the PTA derivatives display enhanced activity in comparison to their PPh<sub>3</sub> counterparts.<sup>5</sup> This may be attributed to enhanced solubility of the PTA complexes in the cultivation medium. Although the PTA derivatives are not water-soluble, the presence of the PTA ligand may alter the lipophilic nature of these compounds, thus aiding permeability of the compound into the cell more effectively. IC<sub>50</sub> values of 6.68 (R = H), 54.38 (R = 3-<sup>t</sup>Bu) and 2.56 μM (R = 3-OMe) were observed for the triphenylphosphine analogues.<sup>5</sup>

Although the R group appears to play a substantial role on the activity of the triphenylphosphine derived complexes, this is not the case with the PTA analogues. The R group has a miniscule effect on the activity as the IC<sub>50</sub> values obtained for complexes **18-20** are quite similar and are found in the range of 1.00 μM. This implies that the phosphine ligand plays a significant role on cytotoxicity in comparison to the substituent on the aryl ring in this case. Comparison of the activity of the phosphine complexes to their monothiosemicarbazone ligands reveal that the complexes do display enhanced cytotoxicity and this has also been observed in literature.<sup>6,7</sup> Figure 5.4 depicts the results obtained for the monothiosemicarbazone ligands (mono TSC) and their corresponding Pd(II) complexes where the co-ligand (L) is either PTA or PPh<sub>3</sub>.





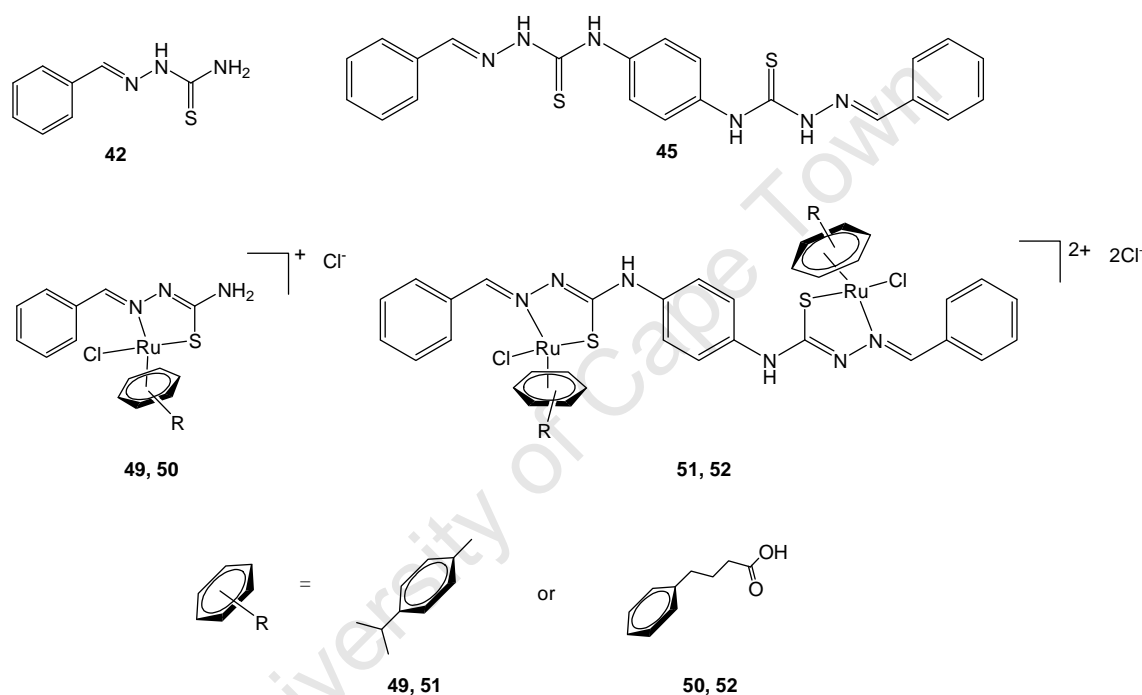
**Figure 5.4:** Graphical representation of the activity of monothiosemicarbazones and their Pd(II) complexes

Comparison of the activity between the Pd(II) and Pt(II) PTA complexes shows that the palladium derivatives display much better activity. Previous reports have suggested that Pd(II) complexes that possess sulfur-containing ligands display better cytotoxic behaviour than complexes containing other metals because the Pd(II) complexes are more labile and are able to be transported towards DNA more efficiently.<sup>8</sup> Another possible reason for low activity of the Pt(II) complexes could be due to poor solubility in the testing medium.

The dithiosemicarbazone ligands display the best activity in comparison to the other ligand systems. The activity of their metal complexes could not be evaluated, however, due to their low solubility in the testing medium. In addition to the afore-mentioned compounds, anticancer data was also obtained for the trithiosemicarbazone complexes (**35**, **39** and **41**), however only complex **41** (where R = 5-Cl and M = Pt) displayed activity. The IC<sub>50</sub> value obtained for this particular complex was 3.14 µM, which is comparable to the activity of its free ligand **14** (IC<sub>50</sub> value of 4.42 µM).

### 5.2.2. Anticancer evaluation of ( $\eta^6$ -arene)-ruthenium(II) complexes

The ( $\eta^6$ -arene)-ruthenium(II) complexes (**49-52**) as well as their corresponding benzaldehyde ligands (**42** and **45**) discussed in Chapter 4 were also evaluated for their anticancer activity against the *WHCO1* oesophageal cancer cell-line by means of a colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. This assay is used to monitor the inhibition of cell growth. The structures of these compounds are displayed in Figure 5.5.



**Figure 5.5:** ( $\eta^6$ -arene)-ruthenium(II) complexes evaluated against *WHCO1*

The results of this particular evaluation are summarised in Table 5.2. With the exception of ligand **45** and complex **52**, the compounds displayed low cytotoxicity in comparison to cisplatin ( $13 \mu\text{M}$ ) for this particular cell-line. The diacid arene complex **52** displayed moderate cytotoxicity against this particular cell-line, giving an  $\text{IC}_{50}$  value of approximately  $8.96 \mu\text{M}$ . The complex does not display any enhanced activity in comparison to its free ligand (**45**) which displayed good antitumour activity with an  $\text{IC}_{50}$  value of  $0.21 \mu\text{M}$ .

Table 5.2

IC<sub>50</sub> values obtained for the *in vitro* anticancer studies of arene-ruthenium(II) complexes and their corresponding TSC ligands

Compound	Type	Arene	IC <sub>50</sub> (μM)	95% Confidence Interval (CI)
42	mono	-	> 200	-
45	di	-	0.21	0.11 - 0.38
49	mono	<i>p</i> -cymene	81.13	69.87 - 94.21
50	mono	acid derivative	> 200	-
51	di	<i>p</i> -cymene	> 200	-
52	di	acid derivative	8.96	1.26 - 63.78

The cytotoxicity of these particular compounds are low and it may be that these compounds do not enter the cells effectively thus preventing accumulation of these compounds inside the cells. Low *in vitro* cytotoxic activity has often been observed for potential ruthenium anticancer agents, including NAMI-A (a ruthenium(III) drug that has successfully completed phase I clinical trials<sup>9</sup>). Many ruthenium compounds have been found to display enhanced cytotoxicity *in vivo* despite low *in vitro* activity. In these cases the compounds have increased activity against tumour metastases.<sup>10-13</sup>

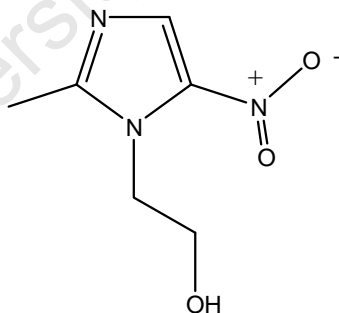
Although, the compounds discussed in Table 5.2 may not display remarkable *in vitro* activity, it is possible that they may exhibit considerable activity when evaluated *in vivo*. Further studies therefore should implemented in order to evaluate the potential of these compounds as antiproliferative agents.

### 5.3. Antiparasitic studies

In addition to their antitumoural properties, certain thiosemicarbazone compounds possess antibacterial, antifungal, antiviral as well as antiparasital activity.<sup>14-20</sup> A selection of thiosemicarbazones have been evaluated against

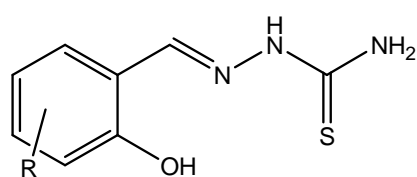
various parasitic strains including *Plasmodium falciparum*, (a malarial parasite) and *Trypanosoma brucei* (a parasite that causes sleeping sickness) and were found to be effective against these microorganisms.<sup>21</sup> Some of these thiosemicarbazone compounds have also been classified as cysteine protease inhibitors. The proteases are enzymes that degrade polypeptides and are able to induce apoptosis of cells. In the search towards more effective biological agents, a series of thiosemicarbazone inhibitors of *Trypanosoma cruzi* cysteine protease, cruzain, have been identified.<sup>15</sup> The *Trichomonas vaginalis* parasite secretes cysteine proteases that are able to induce apoptosis of human vaginal epithelial cells.<sup>22</sup> This particular parasite is the causative agent of trichomoniasis, a sexually transmitted disease which commonly causes infection of the urogenital tract in women.<sup>23</sup>

Metronidazole (Figure 5.6) is a common drug used to combat trichomoniasis in humans. However, 5% of people infected display resistance towards this particular drug.<sup>24</sup> Thiosemicarbazone compounds may be an effective alternative treatment against the *T. vaginalis* parasite.

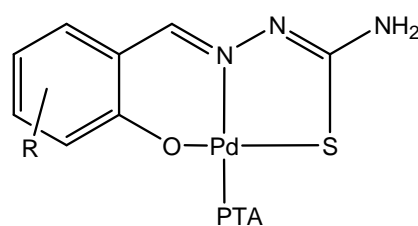


**Figure 5.6:** 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol (metronidazole), a drug used to treat trichomoniasis

Selected monomeric compounds (Figure 5.7) were thus screened against *Trichomonas vaginalis in vitro* in order to evaluate these compounds as potential cysteine protease inhibitors. Their average percentage growth inhibition against the parasite is displayed in Table 5.3.



1-4



18-21

$R = H$  (1, 18); 3-OMe (2, 19); 3-<sup>t</sup>Bu (3, 20); 5-Cl (4, 21)

**Figure 5.7:** Monomeric thiosemicarbazones evaluated against *T. vaginalis*

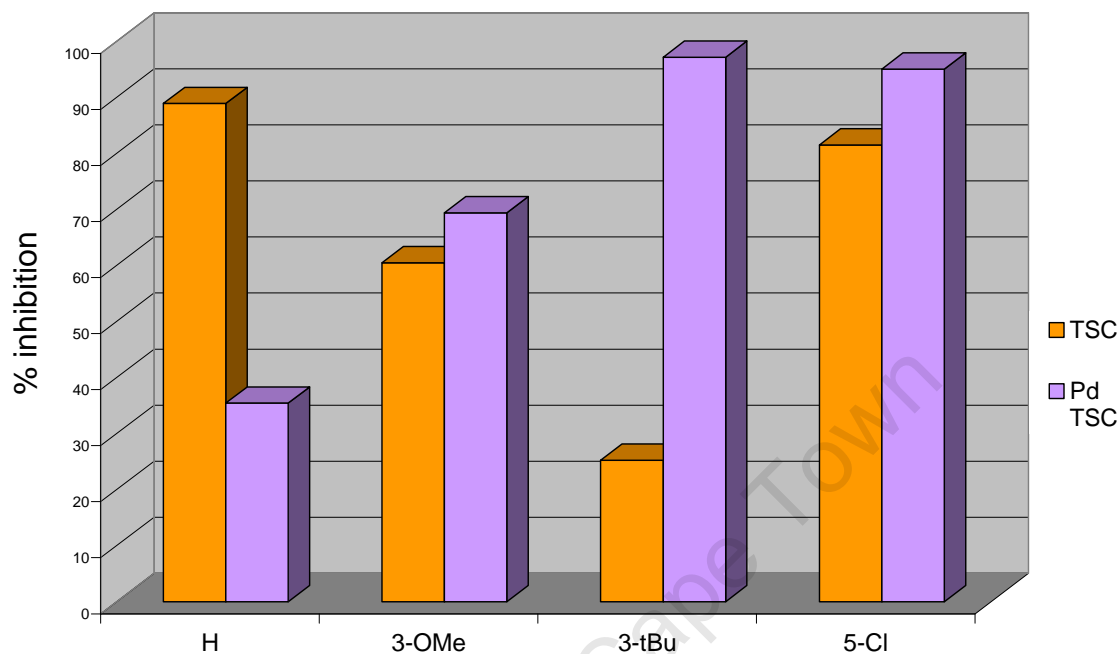
**Table 5.3**

Percentage inhibition of monothiosemicarbazones screened against *T. vaginalis* T1

<b>Compound</b>	<b>R</b>	<b>M</b>	<b>Average % inhibition</b>
1	H	-	88.89
2	3-OMe	-	60.47
3	3- <sup>t</sup> Bu	-	25.23
4	5-Cl	-	81.47
18	H	Pd	35.44
19	3-OMe	Pd	69.39
20	3- <sup>t</sup> Bu	Pd	97.16
21	5-Cl	Pd	95.02

Since the mononuclear palladium PTA thiosemicarbazones displayed the best activity against the *WHCO1* oesophageal cancer cell-line *in vitro* and did not present any major solubility issues during the evaluation, it was decided that these compounds as well as their corresponding ligands would be screened for potential antiparasital activity. Monothiosemicarbazone ligands (1-4) and their corresponding palladium PTA complexes (18-21) were screened against the T1 strain of *T. vaginalis*. Comparison of the data obtained for the ligands and the complexes, with the exception of complex 18, revealed that the

complexes display better inhibition against the T1 strain than their corresponding ligands. Figure 5.8 gives a graphical representation of the results obtained for this particular set of experiments.



**Figure 5.8:** Graphical representation comparing the effect of complexation on inhibition of *T. vaginalis* T1

As seen with many other TSC compounds, lipophilicity is modified by coordination of the metal and therefore an enhancement in activity may be observed.<sup>25</sup> In some cases the metal may act as a vehicle aiding in activation of the ligand once inside the cell. With respect to these compounds, complexes **20** (<sup>t</sup>Bu) and **21** (Cl) display the best inhibition against the growth of the parasite with more than 90% growth inhibition observed.

Comparison of the free tertiary butyl ligand (**3**) to its corresponding complex (**20**) reveals a 4-fold increase in inhibition attributed to coordination by palladium. In the case of the unsubstituted compounds (**1** and **18**), the free ligand (**1**) displays better inhibition than its complex (**18**). There is a minute difference in activity between the 5-chloro substituted ligand (**4**) and its complex (**21**) as these compounds inhibited 81.47 and 95.02% of the growth of the parasite, respectively. Based on this, it appears as though compounds

possessing a chloro substituent on the aryl ring display enhanced efficacy and further mechanistic studies should be carried out on these compounds. In the case of the complexes it appears that a substituent on the aryl ring improves the inhibitory abilities of these compounds as the unsubstituted derivative displays the lowest percentage inhibition of the parasite.

#### 5.4. Conclusion

With regards to the anticancer experiments, the results show that coordination of palladium to the monothiosemicarbazone ligands does enhance the antiproliferative activity of these compounds, possibly due to increased lipophilicity. The results also reveal that the Pd(II) complexes display better activity in comparison to the Pt(II) analogues which may be attributed to the lability of the metal or the solubility of the complex. Surprisingly, the trithiosemicarbazone compounds did not display any remarkable activity in comparison to the other molecules. Further investigation of these systems, should be carried out in order to develop more effective therapeutics using these kinds of systems. Overall, the mononuclear Pd(II) PTA complexes displayed the best results with  $IC_{50}$  values in the low micromolar range compared to the rest of the screened compounds and should be considered as agents with potential antitumour properties. Further *in vitro* studies including mechanistic studies or perhaps *in vivo* screenings should be pursued on these compounds in future.

The arene-ruthenium(II) complexes did not display any remarkable *in vitro* activity. Nevertheless, it may be possible that these compounds may exhibit considerable activity when evaluated *in vivo*. In addition to the anticancer activity of these compounds, the monothiosemicarbazones and their Pd(II) complexes exhibit moderate to good antiparasitic activity. It appears that compounds possessing a chloro substituent on the aryl ring display enhanced efficacy and in the case of the complexes, the presence of a substituent on the aryl ring improves the inhibitory abilities.

Thiosemicarbazones thus exhibit a wide range of biological applications based on literature precedence as well as the investigations carried out in this study. Based on the data presented in this study, the mono-, di- and trithiosemicarbazone compounds possess the potential to be used as biological agents, however, further investigation into improving the solubility of these compounds needs to be prioritised. While some compounds may not have displayed any significant anticancer or antiparasitic activity against the cell-line or strain tested, these compounds may be active against other strains and also may be used for other biological purposes. These compounds may possess antimalarial, antibacterial, antifungal or even antiviral activity. Further biological studies should thus be implemented on these compounds in future.

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**CHAPTER 6**

**Conclusions**  
**and**  
**Future Aspects**

University of Cape Town

### 6.1. General conclusions

Thiosemicarbazones possess a wide variety of biological applications and therefore the main focus of this study was to prepare a series of salicylaldimine thiosemicarbazones and their corresponding palladium and platinum complexes in order to evaluate their potential anticancer activity. The preparation of salicylaldimine thiosemicarbazones was achieved by simple Schiff-base condensation of various substituted salicylaldehydes and thiosemicarbazides. These salicylaldimine ligands were complexed using two metal precursors of the general formula *cis*-[M(PTA)<sub>2</sub>Cl<sub>2</sub>], where M = Pd and Pt. In addition to the salicylaldiminato complexes, a series of ( $\eta^6$ -arene)ruthenium(II) complexes were also prepared from benzaldehyde thiosemicarbazones for biological evaluation.

The ligands and complexes have been characterised by <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H} and <sup>31</sup>P{<sup>1</sup>H} (salicylaldiminato complexes) NMR spectroscopy, FT-IR spectroscopy, ESI-mass spectrometry and elemental analysis. Molecular structures of complexes **20** and **49** were obtained using X-ray diffraction analysis to further confirm their mode of coordination. The molecular structure of complex **20** revealed that the salicylaldimine ligand coordinates to the palladium centre in a tridentate manner through the phenolic oxygen, imine nitrogen and thiolate sulfur, resulting in a slightly distorted square-planar geometry around the palladium centre. The molecular structure of **49** showed that the benzaldehyde thiosemicarbazone coordinates in a bidentate manner to the ruthenium centre, giving rise to a cationic complex. The structure also shows coordination of the ( $\eta^6$ -*p*-cymene)ruthenium(II) complex in a pseudo-tetrahedral, piano-stool conformation.

Selected salicylaldiminato and ( $\eta^6$ -arene)ruthenium(II) complexes were screened for potential anticancer activity against *WHCO1* cancer cells. The mononuclear Pd(II) salicylaldimine complexes exhibit good activity in comparison to the rest of the complexes screened against this particular cell-line. The rest of the screened compounds, including the ( $\eta^6$ -arene)ruthenium(II) complexes, did not display good activity at the

concentration tested. The low activity of the palladium and platinum complexes can be attributed to low solubility of some of these compounds in the testing medium. Although the ruthenium complexes do not exhibit any remarkable *in vitro* activity, they may exhibit activity when evaluated *in vivo*.

In addition to the anticancer evaluation, the mononuclear Pd(II) complexes and their parent ligands, were screened *in vitro* for potential antiparasitic activity against the T1 strain of *T. vaginalis*. Some of the complexes and the monothiosemicarbazone ligands possessed moderate to good activity against this strain. In particular, the complexes that possessed the 3-<sup>t</sup>Bu and 5-Cl substituents displayed the best activity, with more than 90% inhibition observed.

## 6.2. Future aspects

Thiosemicarbazone compounds are prepared using efficient methods in good yields and many of these compounds (mono-, di- and trithiosemicarbazones) exhibit promising biological activity. Water-solubility plays a significant role in determination of the biological potential of these compounds. If compounds do not possess sufficient solubility in the cultivation medium, the compounds may not be evaluated for biological activity. Improving the water-solubility of these compounds therefore needs to be prioritised in order to test potential therapeutic agents.

Further mechanistic *in vitro* studies should be pursued on the compounds that presented good activity. These compounds should be evaluated in order to ascertain whether they do indeed act by inhibition of the enzyme ribonucleotide reductase (RNR). Particularly, it would be interesting to determine whether the di- and trimeric compounds undergo similar cellular mechanisms to that of the monomeric analogues. Cellular uptake studies should also be implemented in order to investigate the effectiveness of the active compounds. In the case of the compounds that do not display any remarkable *in vitro* activity, *in vivo* studies may be useful to study their potential activity.

# **CHAPTER 7**

## **Experimental Section**

University of Cape Town

## 7.1. Materials

Thiosemicarbazide, hydrazine hydrate, sodium chloroacetate, 1,5-cyclooctadiene, salicylaldehyde, 3-*tert*-butyl-salicylaldehyde, 5-chloro-salicylaldehyde, 3-methoxy-salicylaldehyde, 1,3,5-triaza-5-phosphaadamantane, ethylenediamine, 1,4-phenylene diisothiocyanate and tris(2-aminoethyl)amine were purchased from Sigma-Aldrich. Triethylamine was purchased from Fluka. Palladium dichloride, potassium tetrachloroplatinate and ruthenium trichloride trihydrate was received as a donation from Anglo Platinum. Solvents were purchased from Kimix and Merck. All reagents and solvents were used as received. Ethane-1,2-dithiosemicarbazide (**5**) and benzene-1,4-dithiosemicarbazide (**44**) were prepared according to literature methods.<sup>1</sup> *Cis*-[Pd(COD)Cl<sub>2</sub>] (**15**),<sup>2</sup> *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (**16**),<sup>3</sup> *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (**17**),<sup>4</sup> [Ru( $\eta^6$ -*p*-cymene)( $\mu$ -Cl)Cl]<sub>2</sub> (**47**),<sup>5</sup> and [Ru( $\eta^6$ -C<sub>6</sub>H<sub>5</sub>(CH<sub>2</sub>)<sub>3</sub>COOH)( $\mu$ -Cl)Cl]<sub>2</sub> (**48**)<sup>6</sup> were prepared using literature procedures.

## 7.2. Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded using a Varian Mercury 300 spectrometer (<sup>1</sup>H at 300.077 MHz, <sup>13</sup>C at 75.454 MHz, <sup>31</sup>P at 121.472 MHz), a Varian Unity 400 spectrometer (<sup>1</sup>H at 399.953 MHz, <sup>13</sup>C at 100.577 MHz, <sup>31</sup>P at 161.903 MHz) or a Bruker 400 FT spectrometer (<sup>1</sup>H at 400.200 MHz, <sup>13</sup>C at 100.600 MHz, <sup>31</sup>P at 162.000 MHz). Coupling constants are recorded in Hz. Si(CH<sub>3</sub>)<sub>4</sub> (0.00 ppm) was used to calibrate the <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} chemical shifts. The <sup>31</sup>P{<sup>1</sup>H} spectra were measured using H<sub>3</sub>PO<sub>4</sub> as the internal standard. The Samples were submitted in dimethylsulfoxide-*d*<sub>6</sub> unless otherwise stated. Some <sup>1</sup>H NMR assignments were made using 2D Correlation spectroscopy (COSY). <sup>13</sup>C{<sup>1</sup>H} NMR assignments were made with the aid of 2D Heteronuclear Single Quantum Coherence (HSQC) spectroscopy.

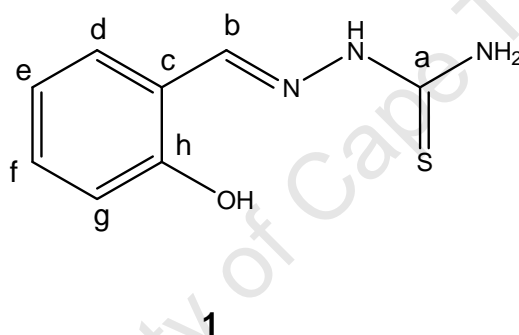
Infrared (IR) spectra were determined using a Perkin Elmer Spectrum One FT-IR spectrometer and was carried out in the solid state using KBr pellets unless stated otherwise. Elemental analyses of these compounds were

performed using a Thermo Flash 1112 Series CHNS-O Analyser. ESI-mass spectrometry was used to further characterise new compounds and determinations were carried out using a Waters API Quattro instrument in either the positive or negative mode. Melting points are corrected and were determined on a Reichert Thermoar hot stage microscope.

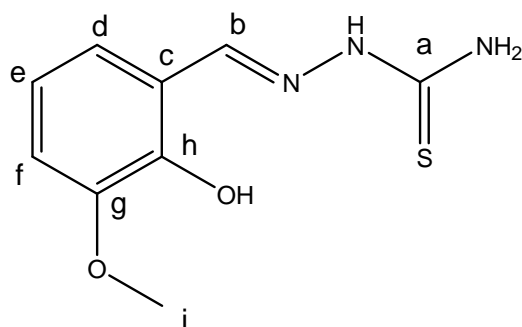
### 7.3. Synthesis of salicylaldimine TSC ligands

#### 7.3.1. Synthesis of monothiosemicarbazone salicylaldimine ligands

*Synthesis of salicylaldimine monothiosemicarbazone*<sup>7</sup>



Thiosemicarbazide (0.514 g, 5.64 mmol) and salicylaldehyde (0.6 cm<sup>3</sup>, 5.64 mmol) were refluxed in ethanol (30 cm<sup>3</sup>) for 6 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol. The product was isolated as a white powder (0.741 g, 68%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 6.86 (2H, m, H<sub>e</sub>, H<sub>g</sub>); 7.24 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.58, H<sub>f</sub>); 7.92 (2H, m, H<sub>d</sub>, NH<sub>2</sub>); 8.08 (1H, s, NH<sub>2</sub>); 8.40 (1H, s, H<sub>b</sub>); 9.84 (1H, s, OH); 11.36 (1H, s, NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 115.95 (C<sub>g</sub>); 119.10 (C<sub>e</sub>); 120.14 (C<sub>c</sub>); 126.78 (C<sub>d</sub>); 130.86 (C<sub>f</sub>); 140.02 (C<sub>b</sub>); 156.25 (C<sub>h</sub>); 177.76 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 830 (C=S); 1615 (C=N). **Elemental analysis** calculated for C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>SO: C, 49.21; H, 4.65; N, 21.53; S, 16.42%. Found: C, 49.74; H, 4.84; N, 21.01; S, 16.05%. **M.p.** 210-213 °C; Lit: 210 °C.

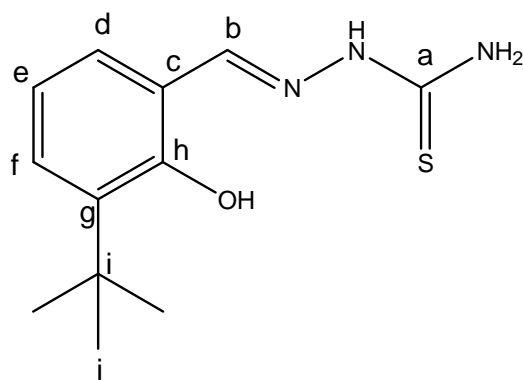
Synthesis of 3-methoxysalicylaldimine monothiosemicarbazone<sup>8</sup>

2

Thiosemicarbazide (0.194 g, 2.13 mmol) and 3-methoxy-salicylaldehyde (0.323 g, 2.12 mmol) were refluxed in ethanol (30 cm<sup>3</sup>) for approximately 6 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol. The product was isolated as a white powder (0.409 g, 86%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.32 (3H, s, H<sub>i</sub>); 6.78 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.91, H<sub>e</sub>); 6.97 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.45, <sup>3</sup>J<sub>H-H</sub> = 8.02, H<sub>f</sub>); 7.48 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.25, <sup>3</sup>J<sub>H-H</sub> = 7.96, H<sub>d</sub>); 7.88 (2H, s, NH<sub>2</sub>); 8.42 (1H, s, H<sub>b</sub>); 9.16 (1H, s, OH); 11.29 (1H, s, NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 55.83 (C<sub>i</sub>); 112.93 (C<sub>f</sub>); 118.23 (C<sub>d</sub>); 118.84 (C<sub>e</sub>); 120.61 (C<sub>c</sub>); 139.76 (C<sub>b</sub>); 145.92 (C<sub>g</sub>); 147.83 (C<sub>h</sub>); 177.78 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 822 (C=S); 1622 (C=N). **Elemental analysis** calculated for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>SO<sub>2</sub>: C, 47.98; H, 4.92; N, 18.66; S, 14.23%. Found: C, 47.74; H, 4.91; N, 18.44; S, 14.50%. **M.p.** 222-227 °C; Lit: 220-222 °C.



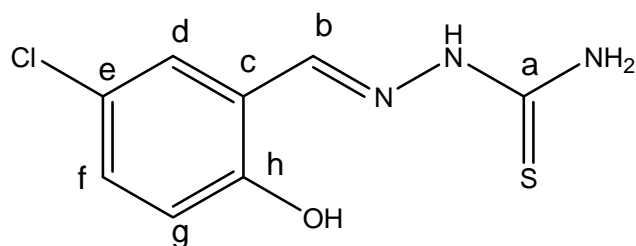
Synthesis of 3-*tert*-butylsalicylaldimine monothiosemicarbazone<sup>9</sup>



**3**

Thiosemicarbazide (0.335 g, 3.68 mmol) and 3-*tert*-butyl-salicylaldehyde (0.63 cm<sup>3</sup>, 3.68 mmol) were refluxed in ethanol (30 cm<sup>3</sup>) for 6 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol. The product was isolated as a white crystalline powder (0.671 g, 73%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.38 (9H, s, H<sub>i</sub>); 6.85 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.71, H<sub>e</sub>); 7.28 (2H, m, H<sub>d</sub>, H<sub>f</sub>); 7.94 (2H, s, NH<sub>2</sub>); 8.26 (1H, s, H<sub>b</sub>); 9.95 (1H, s, OH); 11.25 (1H, s, NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 29.19 (C<sub>i</sub>); 34.29 (C<sub>j</sub>); 118.41 (C<sub>c</sub>); 119.07 (C<sub>e</sub>); 128.25 (C<sub>d</sub>); 129.27 (C<sub>f</sub>); 136.59 (C<sub>g</sub>); 147.01 (C<sub>b</sub>); 155.32 (C<sub>h</sub>); 177.94 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 827 (C=S); 1614 (C=N). **Elemental analysis** calculated for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>SO: C, 57.34; H, 6.82; N, 16.72; S, 12.75%. Found: C, 57.31; H, 6.87; N, 16.68; S, 12.78%. **M.p.** 245-249 °C; Lit: 254-257 °C.

Synthesis of 5-chlorosalicylaldimine monothiosemicarbazone<sup>10</sup>

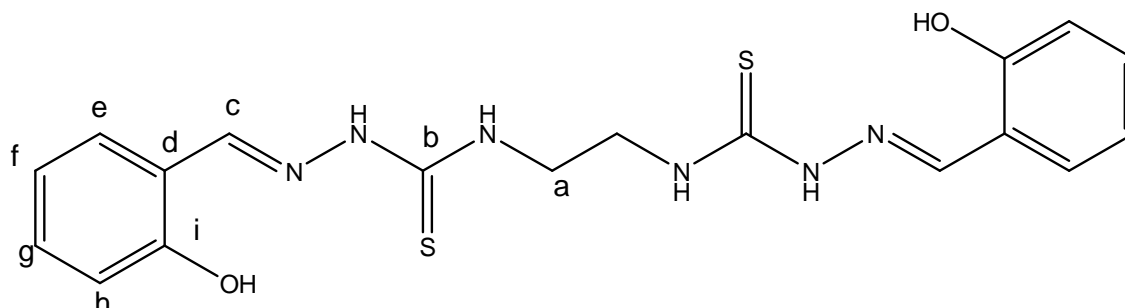


4

Thiosemicarbazide (0.848 g, 9.30 mmol) and 5-chloro-salicylaldehyde (1.459 g, 9.32 mmol) were refluxed in ethanol (30 cm<sup>3</sup>) for 6 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol. The product was isolated as an amorphous white solid (1.399 g, 66%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 6.85 (1H, d, <sup>3</sup>*J*<sub>H-H</sub> = 8.74, H<sub>g</sub>); 7.17 (1H, dd, <sup>4</sup>*J*<sub>H-H</sub> = 2.75, <sup>3</sup>*J*<sub>H-H</sub> = 8.71, H<sub>f</sub>); 8.01 (3H, m, H<sub>d</sub>, NH<sub>2</sub>); 8.30 (1H, s, H<sub>b</sub>); 10.03 (1H, s, OH); 11.30 (1H, s, NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 117.59 (C<sub>g</sub>); 122.20 (C<sub>c</sub>); 123.29 (C<sub>d</sub>); 125.38 (C<sub>e</sub>); 130.15 (C<sub>f</sub>); 137.60 (C<sub>b</sub>); 154.98 (C<sub>h</sub>); 177.99 (C<sub>a</sub>). **FT-IR** (KBr): (*v*<sub>max</sub>, cm<sup>-1</sup>) 829 (C=S); 1657 (C=N). **Elemental analysis** calculated for C<sub>8</sub>H<sub>8</sub>N<sub>3</sub>SOCl: C, 41.83; H, 3.51; N, 18.30; S, 13.96%. Found: C, 41.84; H, 3.48; N, 17.78; S, 14.20%. **M.p.** 292 °C; Lit: 290 °C.

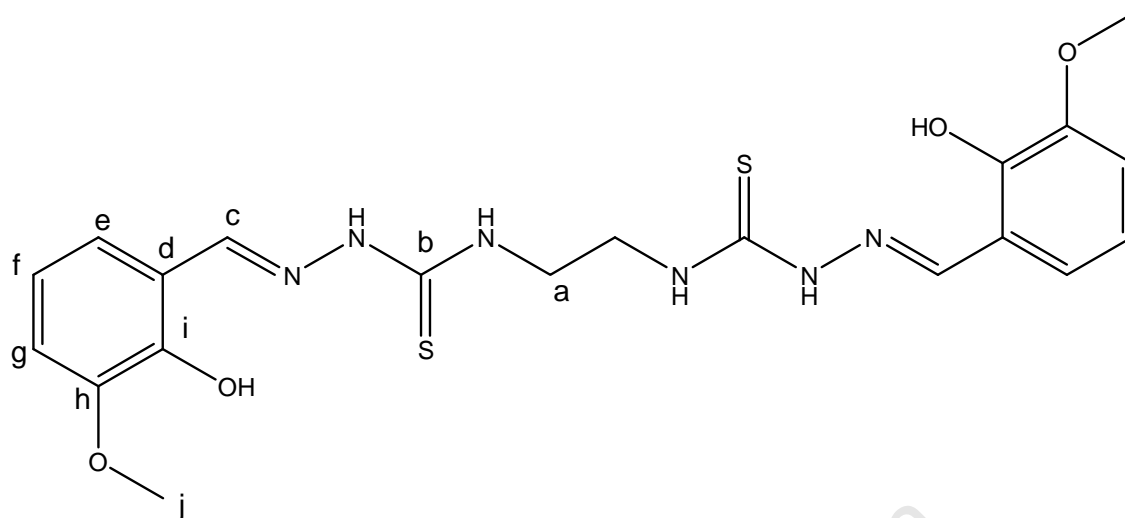
## 7.3.2. Synthesis of dithiosemicarbazone salicylaldehyde ligands

Synthesis of salicylaldehyde dithiosemicarbazone<sup>11</sup>



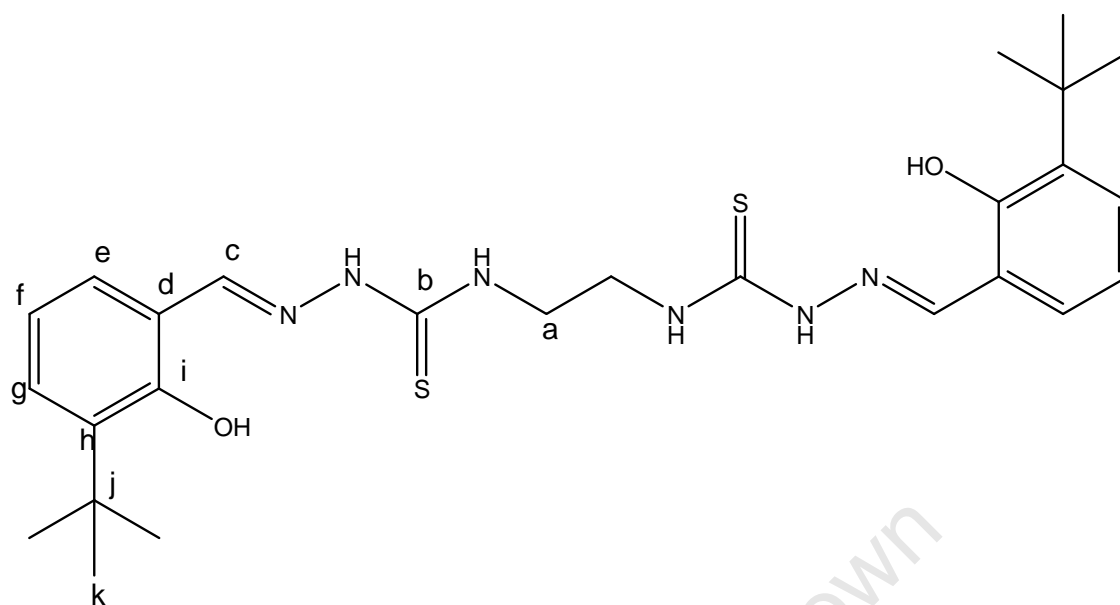
## 6

Ethane-1,2-dithiosemicarbazide (0.207 g, 0.99 mmol) and salicylaldehyde (0.21 cm<sup>3</sup>, 1.99 mmol) were reacted in DMF (20 cm<sup>3</sup>) at 120 °C for 5 hours. The product was obtained by precipitation with water. The precipitate was filtered on a Büchner funnel, washed with water and dried in the oven at 110 °C to remove water. The product was isolated as a light yellow powder (0.363 g, 88%). <sup>1</sup>H NMR (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.83 (4H, s, H<sub>a</sub>); 6.77 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.72, H<sub>f</sub>); 6.85 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 8.17, H<sub>h</sub>); 7.19 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.53, H<sub>g</sub>); 7.96 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.73, H<sub>e</sub>); 8.39 (2H, s, H<sub>c</sub>); 8.57 (2H, s, C<sub>a</sub>NH); 9.86 (2H, s, OH); 11.47 (2H, s, -C<sub>b</sub>NHN-). <sup>13</sup>C{<sup>1</sup>H} NMR (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 43.32 (C<sub>a</sub>); 115.85 (C<sub>h</sub>); 118.99 (C<sub>f</sub>); 120.22 (C<sub>d</sub>); 126.61 (C<sub>e</sub>); 130.78 (C<sub>g</sub>); 139.64 (C<sub>c</sub>); 156.22 (C<sub>i</sub>); 177.23 (C<sub>b</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 803 (C=S); 1618 (C=N). **Elemental analysis** calculated for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>S<sub>2</sub>O<sub>2</sub>: C, 51.90; H, 4.84; N, 20.17; S, 15.40%. Found: C, 51.18; H, 5.11; N, 20.30; S, 16.16%. **M.p.** 223-227 °C; Lit: 222-224 °C.

Synthesis of 3-methoxysalicylaldimine dithiosemicarbazone<sup>11</sup>

## 7

Ethane-1,2-dithiosemicarbazide (0.204 g, 0.97 mmol) and 3-methoxy-salicylaldehyde (0.308 g, 2.02 mmol) were reacted in DMF (20 cm<sup>3</sup>) at 120 °C for 5 hours. The product was obtained by precipitation with water. The precipitate was filtered on a Büchner funnel, washed with water and dried in the oven at 110 °C. The product was isolated as a pale yellow powder (0.452 g, 98%). <sup>1</sup>H NMR (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.80 (6H, s, H<sub>j</sub>); 3.83 (4H, s, H<sub>a</sub>); 6.73 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.98, H<sub>f</sub>); 6.94 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.03, H<sub>g</sub>); 7.58 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.86, H<sub>e</sub>); 8.41 (2H, s, H<sub>c</sub>); 8.56 (2H, s, C<sub>a</sub>NH); 9.12 (2H, s, OH); 11.50 (2H, s, -C<sub>b</sub>NHN-). <sup>13</sup>C{<sup>1</sup>H} NMR (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 43.32 (C<sub>a</sub>); 55.79 (C<sub>j</sub>); 112.84 (C<sub>g</sub>); 118.14 (C<sub>e</sub>); 118.74 (C<sub>f</sub>); 120.68 (C<sub>d</sub>); 139.44 (C<sub>c</sub>); 145.80 (C<sub>h</sub>); 147.78 (C<sub>i</sub>); 177.23 (C<sub>b</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 813 (C=S); 1671 (C=N). **Elemental analysis** calculated for C<sub>20</sub>H<sub>24</sub>N<sub>6</sub>S<sub>2</sub>O<sub>4</sub>: C, 50.40; H, 5.08; N, 17.63; S, 13.46%. Found: C, 49.79; H, 5.74; N, 17.36; S, 12.82%. **M.p.** 244-246 °C; Lit: 245-247 °C.

Synthesis of 3-*tert*-butylsalicylaldimine dithiosemicarbazone<sup>11</sup>

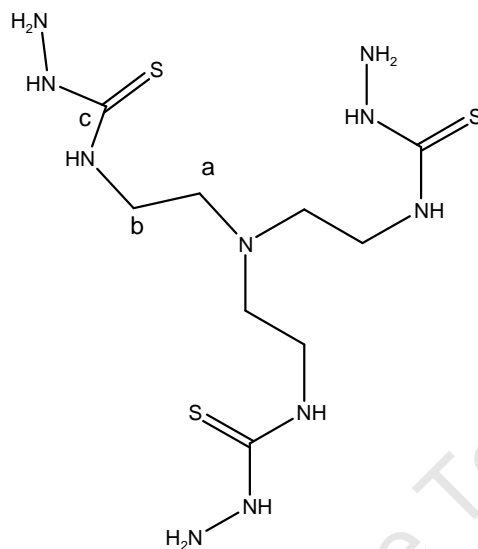
## 8

Ethane-1,2-dithiosemicarbazide (0.223 g, 1.07 mmol) and 3-*tert*-butylsalicylaldehyde (0.36 cm<sup>3</sup>, 2.15 mmol) were reacted in DMF (20 cm<sup>3</sup>) at 120 °C for 5 hours. The product was obtained by precipitation with water. The precipitate was filtered on a Büchner funnel, washed with water and dried in the oven at 110 °C. The product was isolated as a pale yellow powder (0.568 g, 82%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.39 (18H, s, H<sub>k</sub>); 3.84 (4H, s, H<sub>a</sub>); 6.84 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.67, H<sub>f</sub>); 7.24 (4H, m, H<sub>e</sub> & H<sub>g</sub>); 8.29 (2H, s, H<sub>c</sub>); 8.60 (2H, s, -C<sub>a</sub>NH-); 9.96 (2H, s, OH); 11.41 (2H, s, -C<sub>b</sub>NHN-). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 30.06 (C<sub>k</sub>); 35.15 (C<sub>j</sub>); 44.33 (C<sub>a</sub>); 119.52 (C<sub>f</sub>); 120.02 (C<sub>d</sub>); 129.14 (C<sub>e</sub>); 129.99 (C<sub>g</sub>); 137.49 (C<sub>h</sub>); 147.66 (C<sub>c</sub>); 156.00 (C<sub>i</sub>); 177.88 (C<sub>b</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 855 (C=S); 1598 (C=N). **Elemental analysis** calculated for C<sub>26</sub>H<sub>36</sub>N<sub>6</sub>S<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C, 57.11; H, 7.00; N, 15.37; S, 11.73%. Found: C, 57.55; H, 6.58; N, 16.44; S, 12.80%. **M.p.** 224 °C; Lit: 220-223 °C.



## 7.3.3. Synthesis of salicylaldimine trithiosemicarbazone ligands

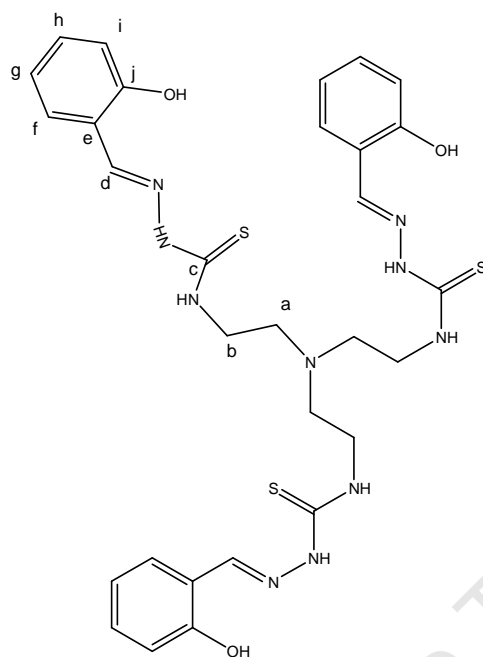
Synthesis of tris(2-aminoethyl) thiosemicarbazide (trithiosemicarbazide)



10

Tris(2-aminoethyl)amine (1.87 cm<sup>3</sup>) was added to a solution of NaOH (1.502 g, 0.037 mol) in water (25 cm<sup>3</sup>). To this solution, CS<sub>2</sub> (2.27 cm<sup>3</sup>) was added and the mixture stirred for 4 hours giving rise to an orange solution. Sodium chloroacetate (4.375 g, 0.037 mol) was added to the solution and stirred for 16 hours. The solution was then acidified with 2M HCl (12 cm<sup>3</sup>) to form a yellow precipitate. To this mixture, NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (10 cm<sup>3</sup>) was added and the solution stirred at 90°C for 2 hours. The solution was then removed from the heat and stirred overnight yielding an oily off-white substance. The product was dried in the oven at 115 °C and upon cooling a pale yellow solid is obtained (1.059 g, 23%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.68 (6H, m, H<sub>a</sub>); 3.56 (6H, m, H<sub>b</sub>); 4.43 (6H, s, NH<sub>2</sub>); 7.87 (3H, s, C<sub>b</sub>NH); 8.60 (3H, s, NH<sub>2</sub>NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 41.73 (C<sub>b</sub>); 53.57 (C<sub>a</sub>); 181.76 (C<sub>c</sub>). **Elemental analysis** calculated for C<sub>9</sub>H<sub>24</sub>N<sub>10</sub>S<sub>3</sub>: C, 29.34; H, 6.54; N, 38.01; S, 26.09%. Found: C, 30.65; H, 6.10; N, 33.33; S, 23.31%. **ESI-MS**: *m/z* 369 (100%, [M+H]<sup>+</sup>).

## Synthesis of salicylaldehyde trithiosemicarbazone

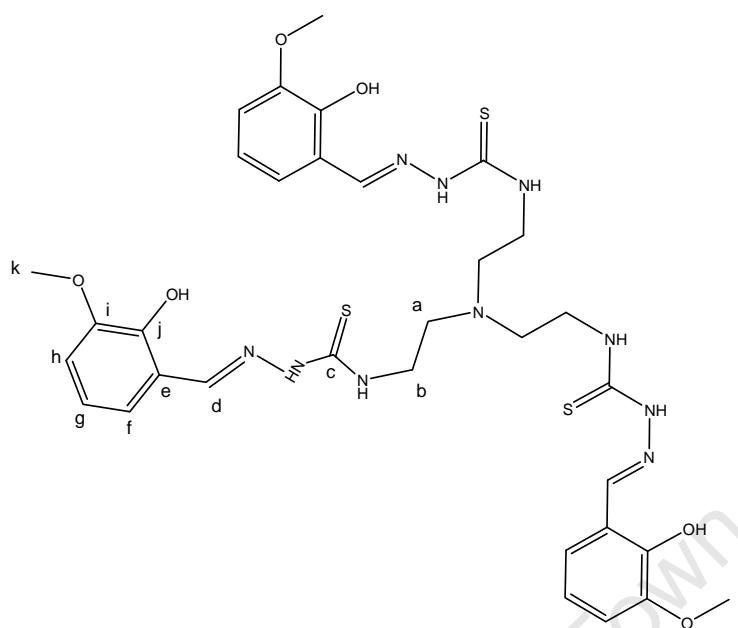


11

Trithiosemicarbazide (0.146 g, 0.40 mmol) was added to hot ethanol (30 cm<sup>3</sup>). To this mixture, salicylaldehyde (0.13 cm<sup>3</sup>) was added and the mixture refluxed for 8 hours and stirred for a further 16 hours at room temperature. The volume of the yellow solution was reduced and water added to precipitate the desired product. The product was then filtered on a Büchner funnel, washed with water and isolated as a yellow powder (0.207 g, 77%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.85 (6H, m, H<sub>a</sub>); 3.72 (6H, m, H<sub>b</sub>); 6.85 (6H, t, <sup>3</sup>J<sub>H-H</sub> = 8.82, H<sub>i</sub> & H<sub>g</sub>); 7.20 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 8.82, H<sub>h</sub>); 7.84 (3H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.62, <sup>3</sup>J<sub>H-H</sub> = 7.79, H<sub>f</sub>); 8.33 (3H, m, C<sub>b</sub>NH); 8.38 (3H, s, H<sub>d</sub>); 9.79 (3H, s, OH); 11.34 (3H, s, -C<sub>c</sub>NHN-). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 42.60 (C<sub>b</sub>); 53.42 (C<sub>a</sub>); 116.83 (C<sub>i</sub>); 120.07 (C<sub>g</sub>); 121.09 (C<sub>e</sub>); 127.27 (C<sub>f</sub>); 131.77 (C<sub>h</sub>); 140.00 (C<sub>d</sub>); 157.15 (C<sub>j</sub>); 177.64 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 803 (C=S); 1620 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>36</sub>N<sub>10</sub>S<sub>3</sub>O<sub>3</sub>: C, 52.92; H, 5.33; N, 20.57; S, 14.12%. Found: C, 52.86; H, 5.43; N, 19.72; S, 12.77%. **ESI-MS**: *m/z* 681 (100%, [M]<sup>+</sup>). **M.p.** 133-137 °C.



## Synthesis of 3-methoxysalicylaldimine trithiosemicarbazone

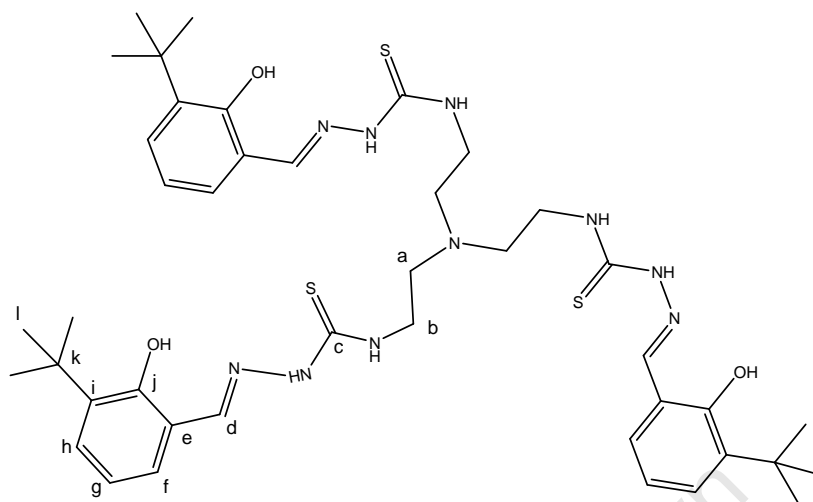


## 12

Trithiosemicarbazide (0.060g, 0.16 mmol) was added to hot ethanol (30 cm<sup>3</sup>). To this mixture, 3-methoxy-salicylaldehyde (0.076 g, 0.50 mmol) was added and the mixture refluxed for 10 hours and stirred for a further 16 hours at room temperature. The solution was concentrated and water added to precipitate the desired product. The product was then filtered on a Büchner funnel, washed with water and isolated as a yellow amorphous solid (0.078 g, 62%).

**<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.71 (6H, m, H<sub>a</sub>); 3.63 (6H, m, H<sub>b</sub>); 3.71 (9H, s, H<sub>k</sub>); 6.70 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 8.04, H<sub>g</sub>); 6.86 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 7.88, H<sub>h</sub>); 7.40 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 7.82, H<sub>f</sub>), 8.26 (3H, s, C<sub>b</sub>NH); 8.32 (3H, s, H<sub>d</sub>); 9.04 (3H, s, OH); 11.33 (3H, s, -C<sub>e</sub>NHN-). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 41.57 (C<sub>b</sub>); 52.50 (C<sub>a</sub>); 55.82 (C<sub>k</sub>); 112.85 (C<sub>h</sub>); 117.86 (C<sub>f</sub>); 118.89 (C<sub>g</sub>); 120.73 (C<sub>e</sub>); 139.16 (C<sub>d</sub>); 145.87 (C<sub>i</sub>); 147.85 (C<sub>j</sub>); 176.88 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 883 (C=S); 1605 (C=N). **Elemental analysis** calculated for C<sub>33</sub>H<sub>42</sub>N<sub>10</sub>S<sub>3</sub>O<sub>6</sub>: C, 51.41; H, 5.49; N, 18.17; S, 12.47%. Found: C, 50.33; H, 5.61; N, 20.93; S, 13.42%. **ESI-MS**: *m/z* 771 (100%, [M]<sup>+</sup>). **M.p.** 154-157 °C.

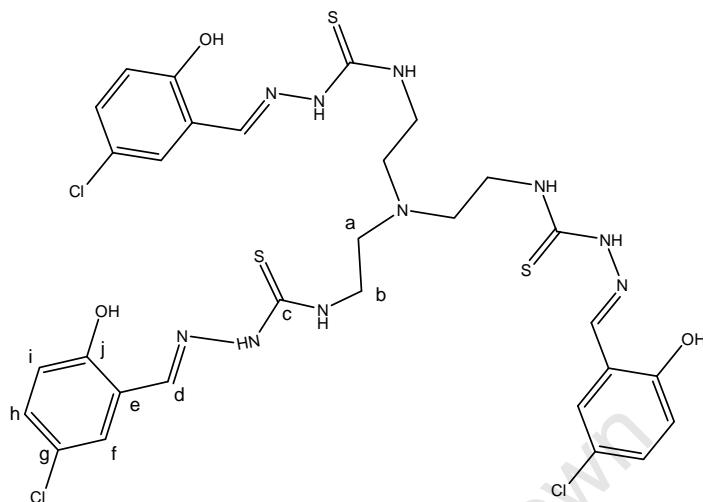
## Synthesis of 3-tert-butylsalicylaldimine trithiosemicarbazone



## 13

Trithiosemicarbazide (0.269g, 0.729 mmol) was added to hot ethanol (30 cm<sup>3</sup>). To this mixture, 3-tert-butylsalicylaldehyde (0.36 cm<sup>3</sup>) was added and the mixture refluxed for 8 hours and stirred overnight at room temperature. The solvent was removed completely giving rise to a yellow oil. The oil was dissolved in DCM and the product washed with water in a separating funnel to remove any unreacted aldehyde. The DCM was completely removed giving rise to a dark yellow oil (0.521 g, 84%). <sup>1</sup>H NMR (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.36 (27H, m, H<sub>l</sub>); 2.86 (6H, m, H<sub>a</sub>); 3.72 (6H, m, H<sub>b</sub>); 6.84 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.65, H<sub>g</sub>); 7.24 (6H, m, H<sub>h</sub> & H<sub>f</sub>); 8.25 (3H, s, -C<sub>b</sub>NH-); 8.27 (3H, s, H<sub>d</sub>), 10.14 (3H, s, OH); 11.39 (3H, s, -C<sub>c</sub>NHN-). <sup>13</sup>C{<sup>1</sup>H} NMR (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 25.46 (C<sub>k</sub>); 34.91 (C<sub>i</sub>); 42.52 (C<sub>b</sub>); 52.83 (C<sub>a</sub>); 119.16 (C<sub>g</sub>); 119.83 (C<sub>e</sub>); 128.90 (C<sub>f</sub>); 129.72 (C<sub>h</sub>); 137.24 (C<sub>i</sub>); 147.19 (C<sub>d</sub>); 155.86 (C<sub>j</sub>); 177.28 (C<sub>c</sub>) FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 854 (C=S); 1646 (C=N). **Elemental analysis** calculated for C<sub>42</sub>H<sub>60</sub>N<sub>10</sub>O<sub>3</sub>S<sub>3</sub>: C, 59.40; H, 7.12; N, 16.50; S, 11.32%. Found: C, 54.55; H, 7.28; N, 18.34; S, 12.36%. **ESI-MS**: *m/z* 849 (5%, [M]<sup>+</sup>); 489 (100%, [M+3ACN+2H]<sup>2+</sup>).

## Synthesis of 5-chlorosalicylaldimine trithiosemicarbazone



## 14

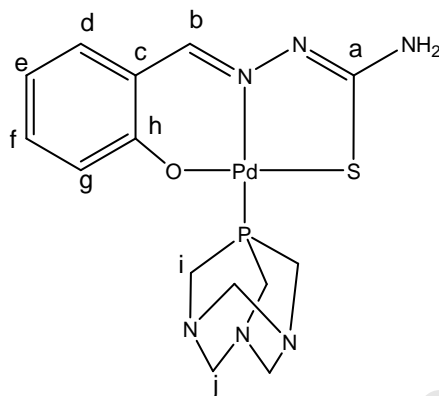
Trithiosemicarbazide (0.122 g, 0.33 mmol) was added to hot ethanol (30 cm<sup>3</sup>). To this mixture, 5-chloro-salicylaldehyde (0.155 g, 0.99 mmol) was added and the mixture refluxed for 8 hours and stirred overnight at room temperature. The solvent was concentrated and water was added to precipitate the desired product. The product was then filtered on a Büchner funnel, washed with water and isolated as a yellow powder (0.226 g, 87%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.87 (6H, m, H<sub>a</sub>); 3.75 (6H, m, H<sub>b</sub>); 6.91 (3H, d, <sup>3</sup>*J*<sub>H-H</sub> = 8.72, H<sub>i</sub>); 7.24 (3H, dd, <sup>4</sup>*J*<sub>H-H</sub> = 2.66, <sup>3</sup>*J*<sub>H-H</sub> = 8.73; H<sub>h</sub>); 7.98 (3H, d, <sup>4</sup>*J*<sub>H-H</sub> = 2.62, H<sub>f</sub>); 8.35 (3H, s, H<sub>d</sub>); 8.57 (3H, m, -C<sub>b</sub>NH-); 10.22 (3H, s, OH); 11.50 (3H, s, -C<sub>c</sub>NHN-). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 41.58 (C<sub>b</sub>); 52.56 (C<sub>a</sub>); 117.63 (C<sub>i</sub>); 122.20 (C<sub>e</sub>); 123.26 (C<sub>f</sub>); 124.98 (C<sub>g</sub>); 130.11 (C<sub>h</sub>); 137.28 (C<sub>d</sub>); 154.98 (C<sub>j</sub>); 177.02 (C<sub>c</sub>). **FT-IR** (KBr): (*v*<sub>max</sub>, cm<sup>-1</sup>) 821 (C=S); 1618 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>33</sub>N<sub>10</sub>S<sub>3</sub>O<sub>3</sub>Cl<sub>3</sub>: C, 45.95; H, 4.24; N, 17.86; S, 12.26%. Found: C, 45.28; H, 4.42; N, 17.29; S, 12.27%. **ESI-MS**: *m/z* 785 (100%, [M+H]<sup>+</sup>). **M.p.** 141-145 °C.

## 7.4. Synthesis of palladium and platinum salicylaldiminato complexes

## 7.4.1. Synthesis of monothiosemicarbazone complexes

## 7.4.1.1. Monothiosemicarbazone Pd(II) complexes

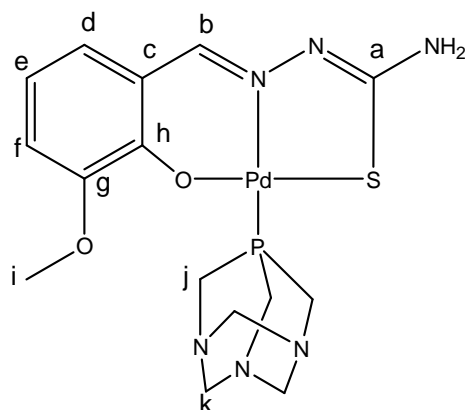
Synthesis of salicylaldiminato monothiosemicarbazone palladium(II) PTA complex



18

Salicylaldimine monothiosemicarbazone (0.055 g, 0.28 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.138 g, 0.28 mmol) were refluxed in ethanol for 10 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product obtained was a yellow powder (0.098 g, 77%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 4.31 (6H, s, H<sub>i</sub>); 4.42 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 13.07, H<sub>j(Eq)</sub>); 4.57 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.98, H<sub>j(Ax)</sub>); 6.56 (3H, m, NH<sub>2</sub>, H<sub>e</sub>); 6.89 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 8.34, H<sub>g</sub>); 7.23 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 8.58, H<sub>f</sub>); 7.37 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.77, <sup>3</sup>J<sub>H-H</sub> = 7.93, H<sub>d</sub>); 8.21 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 13.18, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.70 (1P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 49.94 (C<sub>i</sub>); 71.87 (C<sub>j</sub>); 114.17 (C<sub>g</sub>); 117.83 (C<sub>c</sub>), 120.59 (C<sub>e</sub>); 132.25 (C<sub>d</sub>); 134.00 (C<sub>f</sub>); 147.57 (C<sub>b</sub>); 161.70 (C<sub>h</sub>); 171.17 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1595 (C=N), 1615 (C=N). **Elemental analysis** calculated for C<sub>14</sub>H<sub>19</sub>N<sub>6</sub>SPOPd: C, 36.81; H, 4.19; N, 18.40; S, 7.02%. Found: C, 36.77; H, 4.24; N, 17.97; S, 6.87%. **ESI-MS**: *m/z* 457 (100%, [M]<sup>+</sup>). **M.p.** 262 °C.

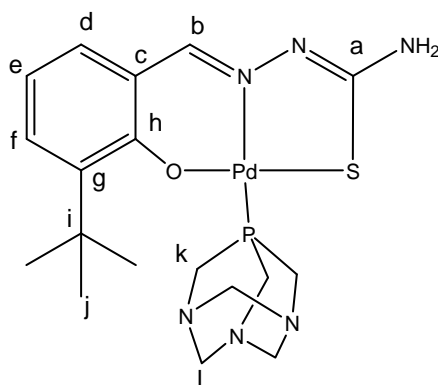
Synthesis of 3-methoxysalicylaldiminato monothiosemicarbazone palladium(II) PTA complex



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3-Methoxy salicylaldimine monothiosemicarbazone (0.053 g, 0.23 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.114 g, 0.233 mmol) were refluxed in ethanol for 8 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol followed by diethyl ether. The product obtained was a yellow powder (0.092 g, 81%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.84 (3H, s, H<sub>i</sub>); 4.41 (6H, s, H<sub>j</sub>); 4.51 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 13.17, H<sub>k(Eq)</sub>); 4.64 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.69, H<sub>k(Ax)</sub>); 6.56 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.79, H<sub>e</sub>); 6.64 (2H, s, NH<sub>2</sub>); 6.95 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.53, <sup>3</sup>J<sub>H-H</sub> = 7.59, H<sub>f</sub>); 7.07 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.50, <sup>3</sup>J<sub>H-H</sub> = 8.13, H<sub>d</sub>); 8.27 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 13.20, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -39.37 (1P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 50.83 (C<sub>j</sub>); 57.00 (C<sub>k</sub>); 72.68 (C<sub>j</sub>); 114.17 (C<sub>e</sub>); 114.89 (C<sub>f</sub>); 118.50 (C<sub>c</sub>); 126.79 (C<sub>d</sub>); 148.16 (C<sub>b</sub>); 151.72 (C<sub>g</sub>); 153.74 (C<sub>h</sub>); 172.01 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1596 (C=N), 1623 (C=N). **Elemental analysis** calculated for C<sub>15</sub>H<sub>21</sub>N<sub>6</sub>SPO<sub>2</sub>Pd: C, 37.00; H, 4.35; N, 17.27; S, 6.58%. Found: C, 37.18; H, 4.38; N, 16.14; S, 6.01%. **ESI-MS**: *m/z* 487 (100%, [M]<sup>+</sup>); 975 (20%, [2M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

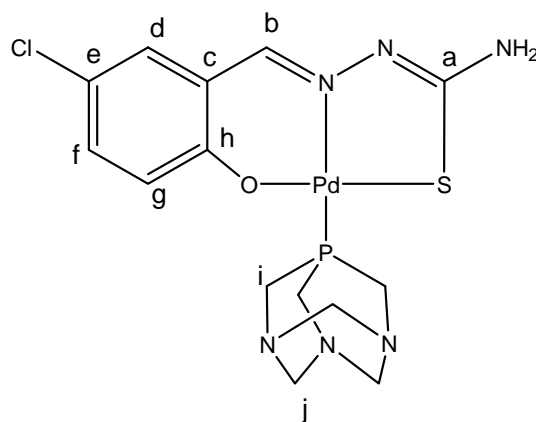
Synthesis of 3-*tert* butylsalicylaldiminato monothiosemicarbazone palladium(II) PTA complex



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3-*tert* Butyl salicylaldimine monothiosemicarbazone (0.050 g, 0.20 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.096 g, 0.19 mmol) were refluxed in ethanol for 8 hours. The precipitate was filtered and the product washed with ethanol and ether. The product obtained was a yellow amorphous solid (0.080 g, 80%). <sup>1</sup>H NMR (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.51 (9H, s, H<sub>j</sub>); 4.43 (6H, s, H<sub>k</sub>); 4.53 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 13.38, H<sub>l(Eq)</sub>); 4.62 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.68, H<sub>l(Ax)</sub>); 6.60 (3H, m, NH<sub>2</sub>, H<sub>e</sub>); 7.32 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.91, H<sub>d</sub>, H<sub>f</sub>); 8.28 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 13.48, H<sub>b</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -43.77 (1P, s, PTA). <sup>13</sup>C{<sup>1</sup>H} NMR (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 30.04 (C<sub>i</sub>); 35.88 (C<sub>j</sub>); 48.92 (C<sub>k</sub>); 72.66 (C<sub>l</sub>); 114.46 (C<sub>e</sub>); 118.84 (C<sub>c</sub>); 131.67 (C<sub>d</sub>); 133.89 (C<sub>f</sub>); 139.36 (C<sub>g</sub>); 149.51 (C<sub>b</sub>); 161.85 (C<sub>h</sub>); 170.95 (C<sub>a</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1593 (C=N), 1643 (C=N). **Elemental analysis** calculated for C<sub>18</sub>H<sub>27</sub>N<sub>6</sub>SPOPd: C, 42.15; H, 5.30; N, 16.39; S, 6.25%. Found: C, 42.24; H, 5.35; N, 17.45; S, 5.65%. **ESI-MS**: *m/z* 513 (100%, [M]<sup>+</sup>); 591(10%, [M+DMSO]<sup>+</sup>). **M.p.** no melting < 300 °C.

Synthesis of 5-chlorosalicylaldiminato monothiosemicarbazone palladium(II) PTA complex

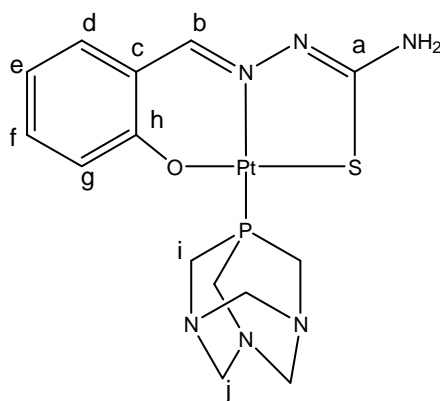


## 21

5-Chlorosalicylaldimine monothiosemicarbazone (0.050 g, 0.22 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.106 g, 0.22 mmol) were refluxed in ethanol for 24 hours. The precipitate obtained was filtered and the product washed with ethanol and diethyl ether. The product was obtained as a yellow powder (0.097 g, 92%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 4.31 (6H, s, H<sub>i</sub>); 4.42 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 13.12, H<sub>j(Eq)</sub>); 4.58 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.91, H<sub>j(Ax)</sub>); 6.75 (2H, s, NH<sub>2</sub>); 6.97 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 9.02, H<sub>g</sub>); 7.27 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 2.84, <sup>3</sup>J<sub>H-H</sub> = 9.00, H<sub>i</sub>); 7.55 (2H, d, <sup>4</sup>J<sub>H-H</sub> = 2.83, H<sub>d</sub>); 8.30 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 13.00, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.06 (1P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 49.94 (C<sub>i</sub>); 71.86 (C<sub>j</sub>); 117.03 (C<sub>g</sub>); 119.08 (C<sub>c</sub>); 122.39 (C<sub>e</sub>); 131.65 (C<sub>d</sub>); 132.03 (C<sub>f</sub>); 146.51 (C<sub>b</sub>); 160.36 (C<sub>h</sub>); 171.98 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1595 (C=N), 1630 (C=N). **Elemental analysis** calculated for C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>SOCIPdP: C, 34.23; H, 3.69; N, 17.11; S, 6.53%. Found: C, 34.37; H, 3.77; N, 17.96; S, 5.92%. **ESI-MS**: *m/z* 493 (100%, [M+H]<sup>+</sup>); 571 (10%, [M+DMSO+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

## 7.4.1.2. Monothiosemicarbazone Pt(II) complexes

Synthesis of salicylaldiminato monothiosemicarbazone platinum(II) PTA complex

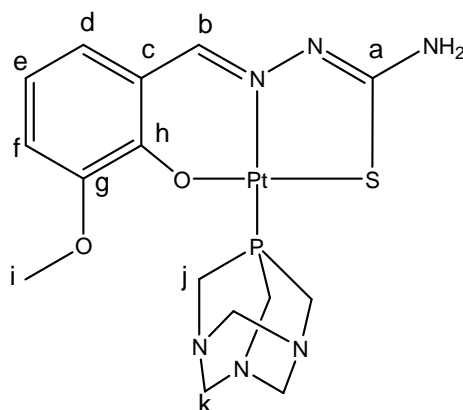


22

Salicylaldimine monothiosemicarbazone (0.047 g, 0.24 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.135 g, 0.23 mmol) were refluxed in ethanol for 5 hours and stirred for an additional 16 hours at room temperature. The precipitate was filtered using a Büchner funnel and the yellow product washed well with ethanol and diethyl ether (0.103 g, 81%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 4.31 (6H, s, H<sub>i</sub>); 4.49 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.97, H<sub>j(Eq)</sub>); 4.59 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.76, H<sub>j(Ax)</sub>); 6.69 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.28, H<sub>e</sub>); 6.85 (2H, s, NH<sub>2</sub>); 7.04 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 8.44, H<sub>g</sub>); 7.37 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.58, H<sub>f</sub>); 7.56 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 7.79, H<sub>d</sub>); 8.57 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 11.21, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -61.37 (1P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3344.43. **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 49.35 (C<sub>i</sub>); 71.96 (C<sub>j</sub>); 115.03 (C<sub>g</sub>); 118.05 (C<sub>c</sub>), 120.71 (C<sub>e</sub>); 132.07 (C<sub>d</sub>); 133.69 (C<sub>f</sub>); 145.90 (C<sub>b</sub>); 159.74 (C<sub>h</sub>); 172.56 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1598 (C=N), 1653 (C=N). **Elemental analysis** calculated for C<sub>14</sub>H<sub>19</sub>N<sub>6</sub>OSPtP: C, 30.83; H, 3.51; N, 15.41; S, 5.88%. Found: C, 30.36; H, 3.44; N, 14.85; S, 5.95%. **ESI-MS**: *m/z* 546 (50%, [M+H]<sup>+</sup>). **M.p.** 262 – 264 °C (with decomposition).



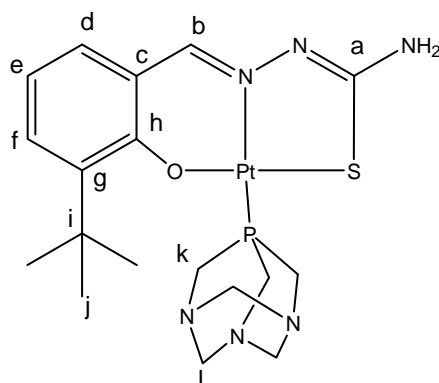
Synthesis of 3-methoxysalicylaldiminato monothiosemicarbazone platinum(II)  
PTA complex



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3-Methoxy salicylaldimine monothiosemicarbazone (0.048 g, 0.21 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.123 g, 0.21 mmol) were refluxed in ethanol for 5 hours and stirred for an additional 16 hours at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and ether. The product obtained was a yellow amorphous solid (0.110 g, 90%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.82 (3H, s, H<sub>i</sub>); 4.30 (6H, s, H<sub>j</sub>); 4.48 (3H, d, <sup>2</sup>*J*<sub>H-H</sub> = 13.49, H<sub>k(Eq)</sub>); 4.56 (3H, d, <sup>2</sup>*J*<sub>H-H</sub> = 12.76, H<sub>k(Ax)</sub>); 6.59 (1H, t, <sup>3</sup>*J*<sub>H-H</sub> = 7.80, H<sub>e</sub>); 6.70 (2H, s, NH<sub>2</sub>); 6.99 (1H, d, <sup>3</sup>*J*<sub>H-H</sub> = 6.44, H<sub>f</sub>); 7.13 (1H, d, <sup>3</sup>*J*<sub>H-H</sub> = 7.04, H<sub>d</sub>); 8.51 (1H, d, <sup>4</sup>*J*<sub>P-H</sub> = 11.24, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -56.80 (1P, s, PTA), <sup>1</sup>*J*<sub>Pt-P</sub> = 3334.90. **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 49.56 (C<sub>j</sub>); 56.27 (C<sub>i</sub>); 72.05 (C<sub>k</sub>); 113.74 (C<sub>e</sub>); 114.21 (C<sub>f</sub>); 118.00 (C<sub>c</sub>); 125.57 (C<sub>d</sub>); 145.66 (C<sub>b</sub>); 151.06 (C<sub>g</sub>); 172.58 (C<sub>a</sub>). **FT-IR** (KBr): (*v*<sub>max</sub>, cm<sup>-1</sup>) 1593 (C=N), 1623 (C=N). **Elemental analysis** calculated for C<sub>15</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub>SPtP: C, 31.30; H, 3.68; N, 14.61; S, 5.57%. Found: C, 31.53; H, 3.67; N, 14.50; S, 5.36%. **ESI-MS**: *m/z* 576 (100%, [M+H]<sup>+</sup>). **M.p.** 294 – 297 °C (with decomposition).

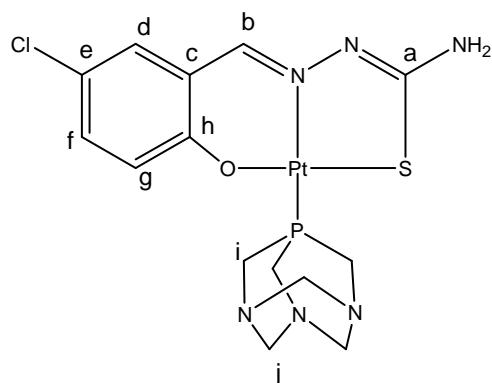
Synthesis of 3-*tert* butylsalicylaldiminato monothiosemicarbazone platinum(II)  
PTA complex



## 24

3-*tert* Butyl salicylaldimine monothiosemicarbazone (0.058 g, 0.23 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.127 g, 0.22 mmol) were refluxed in ethanol for 5 hours and stirred at room temperature for an additional 16 hours. The precipitate was washed with ethanol followed by diethyl ether and dried *in vacuo*. The product obtained was a yellow amorphous solid (0.112 g, 85%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.48 (9H, s, H<sub>j</sub>); 4.33 (6H, s, H<sub>k</sub>); 4.52 (3H, s, H<sub>i</sub>); 6.63 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 7.59, H<sub>e</sub>); 6.69 (2H, s, NH<sub>2</sub>); 7.37 (2H, m, H<sub>d</sub>, H<sub>f</sub>); 8.56 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 11.37, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -60.71 (1P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3341.70. **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 30.13 (C<sub>i</sub>); 36.04 (C<sub>j</sub>); 51.46 (C<sub>k</sub>); 72.87 (C<sub>l</sub>); 115.54 (C<sub>e</sub>); 119.24 (C<sub>c</sub>); 130.14 (C<sub>d</sub>); 133.79 (C<sub>f</sub>); 139.04 (C<sub>g</sub>); 147.81 (C<sub>b</sub>); 159.40 (C<sub>h</sub>); 172.40 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1594 (C=N), 1642 (C=N). **Elemental analysis** calculated for C<sub>18</sub>H<sub>27</sub>N<sub>6</sub>OSPtP: C, 35.94; H, 4.52; N, 13.97; S, 5.33%. Found: C, 36.09; H, 4.50; N, 13.53; S, 5.01%. **ESI-MS**: *m/z* 602 (100%, [M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

Synthesis of 5-chlorosalicylaldiminato monothiosemicarbazone platinum(II)  
PTA complex



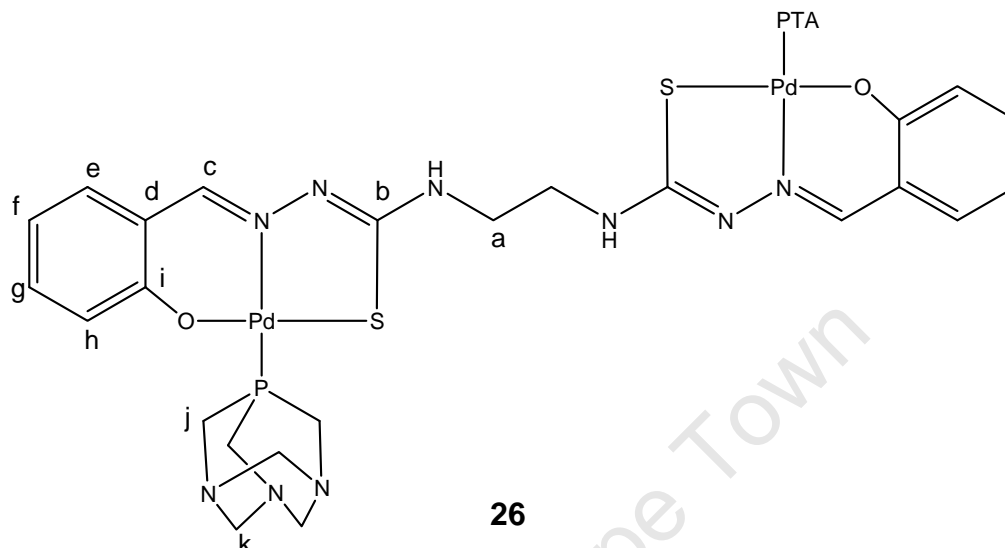
## 25

5-Chlorosalicylaldimine monothiosemicarbazone (0.058 g, 0.25 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.148 g, 0.25 mmol) were refluxed in ethanol for 5 hours and stirred overnight at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product was dried *in vacuo* and obtained as a bright yellow powder (0.139 g, 94%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 4.28 (6H, s, H<sub>i</sub>); 4.47 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 13.29, H<sub>j(Eq)</sub>); 4.56 (3H, d, <sup>2</sup>J<sub>H-H</sub> = 12.75, H<sub>j(Ax)</sub>); 6.82 (2H, s, NH<sub>2</sub>); 7.03 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 9.05, H<sub>g</sub>); 7.31 (1H, dd, <sup>4</sup>J<sub>H-H</sub> = 2.81, <sup>3</sup>J<sub>H-H</sub> = 9.02, H<sub>f</sub>); 7.63 (2H, d, <sup>4</sup>J<sub>H-H</sub> = 2.80, H<sub>d</sub>); 8.55 (1H, d, <sup>4</sup>J<sub>P-H</sub> = 11.11, H<sub>b</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -58.07 (1P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3338.67. **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 50.12 (C<sub>i</sub>); 72.74 (C<sub>j</sub>); 118.90 (C<sub>g</sub>); 120.16 (C<sub>c</sub>); 123.49 (C<sub>e</sub>); 132.37 (C<sub>d</sub>); 132.69 (C<sub>f</sub>); 145.72 (C<sub>b</sub>); 159.10 (C<sub>h</sub>); 174.11 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1592 (C=N), 1630 (C=N). **Elemental analysis** calculated for C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>OCISPtP: C, 28.99; H, 3.13; N, 14.49; S, 5.53%. Found: C, 29.57; H, 3.32; N, 14.13; S, 5.27%. **ESI-MS**: *m/z* 581 (100%, [M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

## 7.4.2. Synthesis of dithiosemicarbazone complexes

## 7.4.2.1. Dithiosemicarbazone Pd(II) complexes

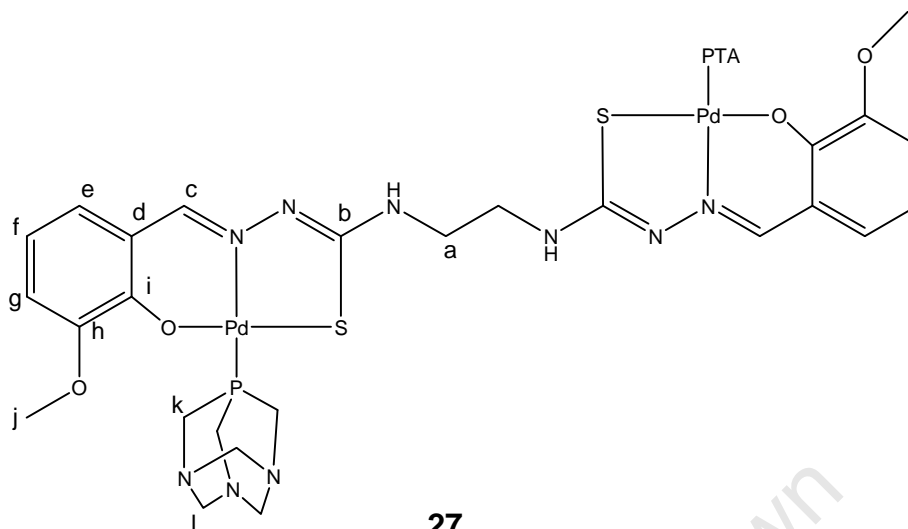
Synthesis of salicylaldiminato dithiosemicarbazone palladium(II) PTA complex



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Salicylaldimine dithiosemicarbazone (0.039 g, 0.093 mmol), triethylamine (0.02 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.086 g, 0.17 mmol) were refluxed in ethanol for 8 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol. The product obtained was a yellow powder (0.067 g, 82%). <sup>1</sup>H NMR (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.40 (4H, s, H<sub>a</sub>); 4.31 (12H, s, H<sub>j</sub>); 4.42 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.19, H<sub>k(Eq)</sub>); 4.57 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.85, H<sub>k(Ax)</sub>); 6.56 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.88, H<sub>f</sub>); 6.89 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 8.15, H<sub>h</sub>); 7.07 (2H, s, NH); 7.23 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 8.55, H<sub>g</sub>); 7.38 (2H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.75, <sup>3</sup>J<sub>H-H</sub> = 7.98, H<sub>e</sub>); 8.31 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 13.15, H<sub>c</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.55 (2P, s, PTA). <sup>13</sup>C{<sup>1</sup>H} NMR (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 45.86 (C<sub>a</sub>); 50.65 (C<sub>j</sub>); 72.59 (C<sub>k</sub>); 115.12 (C<sub>h</sub>); 118.66 (C<sub>d</sub>), 121.42 (C<sub>f</sub>); 133.23 (C<sub>e</sub>); 134.92 (C<sub>g</sub>); 149.08 (C<sub>c</sub>); 162.44 (C<sub>i</sub>); 170.83 (C<sub>b</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1598 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>40</sub>N<sub>12</sub>S<sub>2</sub>P<sub>2</sub>O<sub>2</sub>Pd<sub>2</sub>·2H<sub>2</sub>O: C, 36.93; H, 4.54; N, 17.23; S, 6.57%. Found: C, 36.96; H, 4.63; N, 18.30; S, 6.03%. **ESI-MS**: *m/z* 247 (30%, [M+2H+2Na]<sup>4+</sup>); 941 (50%, [M+H]<sup>+</sup>). **M.p.** 250-254 °C.

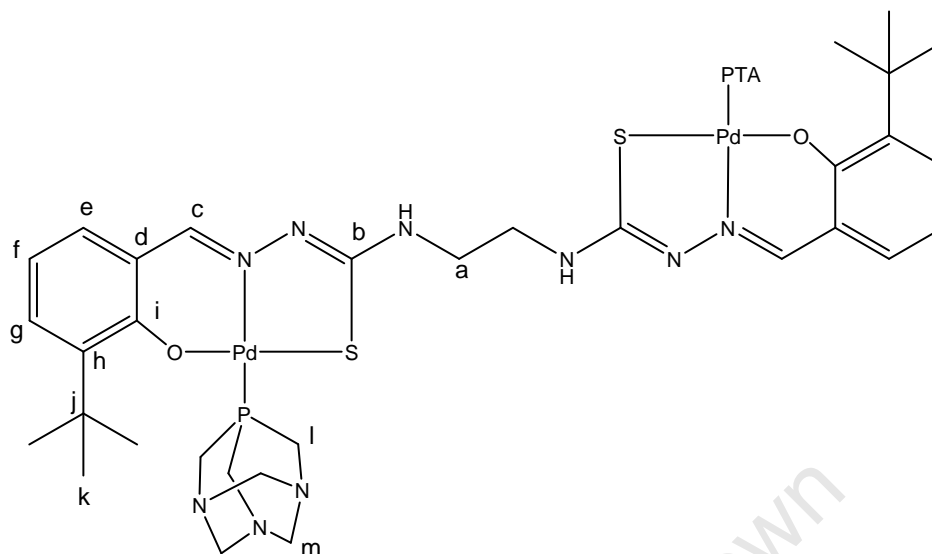
Synthesis of 3-methoxysalicylaldiminato dithiosemicarbazone palladium(II) PTA complex



27

3-Methoxy salicylaldimine dithiosemicarbazone (0.051 g, 0.11 mmol), triethylamine (0.02 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.103 g, 0.21 mmol) were refluxed in ethanol for 8 hours and stirred overnight at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and ether. The product was dried under vacuum and obtained as a yellow-orange powder (0.083 g, 79%). <sup>1</sup>H NMR (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.41 (4H, s, H<sub>a</sub>); 3.77 (6H, s, H<sub>j</sub>); 4.33 (12H, s, H<sub>k</sub>); 4.43 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.22, H<sub>i(Eq)</sub>); 4.56 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.85, H<sub>i(Ax)</sub>); 6.49 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.69, H<sub>f</sub>); 6.89 (2H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.60, <sup>3</sup>J<sub>H-H</sub> = 7.68, H<sub>g</sub>); 7.03 (4H, m, NH, H<sub>e</sub>); 8.29 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 13.17, H<sub>c</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -39.22 (2P, s, PTA). <sup>13</sup>C{<sup>1</sup>H} NMR (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 45.15 (C<sub>a</sub>); 50.10 (C<sub>k</sub>); 56.28 (C<sub>j</sub>); 71.93 (C<sub>l</sub>); 113.42 (C<sub>f</sub>); 114.40 (C<sub>g</sub>), 117.77 (C<sub>d</sub>); 126.04 (C<sub>e</sub>); 148.07 (C<sub>c</sub>); 150.95 (C<sub>h</sub>); 153.12 (C<sub>i</sub>); 170.15 (C<sub>b</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1598 (C=N). **Elemental analysis** calculated for C<sub>32</sub>H<sub>44</sub>N<sub>12</sub>S<sub>2</sub>P<sub>2</sub>O<sub>4</sub>Pd<sub>2</sub>·2H<sub>2</sub>O: C, 37.11; H, 4.67; N, 16.23; S, 6.19%. Found: C, 37.35; H, 4.72; N, 14.95; S, 5.59%. **ESI-MS**: *m/z* 1001 (100%, [M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

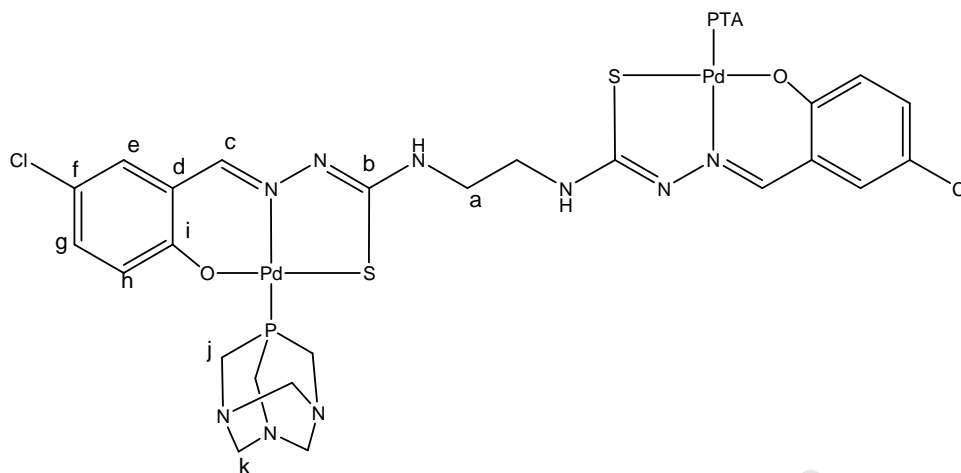
Synthesis of 3-*tert* butylsalicylaldiminato dithiosemicarbazone palladium(II) PTA complex



28

3-*tert* Butyl salicylaldimine dithiosemicarbazone (0.057 g, 0.11 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.105 g, 0.21 mmol) were stirred in ethanol for 72 hours at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product obtained was a yellow-orange powder and dried *in vacuo* (0.075 g, 81%). <sup>1</sup>H NMR (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.46 (18H, s, H<sub>k</sub>); 3.52 (2H, s, H<sub>a</sub>); 4.37 (12H, s, H<sub>l</sub>); 4.47 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.85, H<sub>m(Eq)</sub>); 4.55 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.70, H<sub>m(Ax)</sub>); 6.54 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.58, H<sub>f</sub>); 7.09 (2H, s, NH); 7.30 (4H, m, H<sub>e</sub>, H<sub>g</sub>); 8.33 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 13.47, H<sub>c</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.28 (2P, s, PTA). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1594 (C=N). **Elemental analysis** calculated for C<sub>38</sub>H<sub>56</sub>N<sub>12</sub>S<sub>2</sub>P<sub>2</sub>O<sub>2</sub>Pd<sub>2</sub>: C, 43.39; H, 5.37; N, 15.98; S, 6.09%. Found: C, 44.17; H, 5.46; N, 18.08; S, 5.98%. **ESI-MS**: *m/z* 365 (100%, [M+H+2Na]<sup>3+</sup>); 1052 (10%, [M]<sup>+</sup>). **M.p.** no melting < 300 °C.

Synthesis of 5-chlorosalicylaldiminato dithiosemicarbazone palladium(II) PTA complex

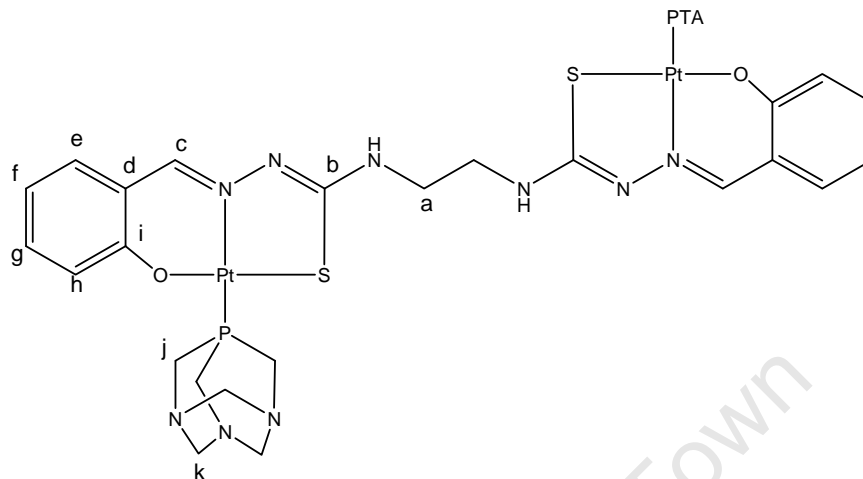


29

5-Chlorosalicylaldimine dithiosemicarbazone (0.045 g, 0.09 mmol), triethylamine (0.02 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.090 g, 0.18 mmol) were refluxed in ethanol for 48 hours. The mixture was allowed to cool to room temperature and the precipitate was filtered using a Büchner funnel. The product washed with ethanol, washed with ether and dried *in vacuo*. The product obtained was a yellow powder (0.077 g, 83%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.42 (4H, s, H<sub>a</sub>); 4.30 (12H, s, H<sub>j</sub>); 4.42 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.12, H<sub>k(Eq)</sub>); 4.57 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.93, H<sub>k(Ax)</sub>); 6.90 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 9.04, H<sub>h</sub>); 7.20 (4H, m, NH, H<sub>g</sub>); 7.47 (4H, d, <sup>3</sup>J<sub>H-H</sub> = 2.83, H<sub>e</sub>); 8.31 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 12.95, H<sub>c</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -39.92 (2P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.454 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 45.02 (C<sub>a</sub>); 49.90 (C<sub>j</sub>); 71.82 (C<sub>k</sub>); 117.10 (C<sub>h</sub>); 119.05 (C<sub>d</sub>), 122.38 (C<sub>f</sub>); 131.75 (C<sub>e</sub>); 132.00 (C<sub>g</sub>); 147.12 (C<sub>c</sub>); 160.36 (C<sub>i</sub>); 170.88 (C<sub>b</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1595 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>38</sub>N<sub>12</sub>S<sub>2</sub>P<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>Pd<sub>2</sub>: C, 35.73; H, 3.79; N, 16.67; S, 6.36%. Found: C, 34.64; H, 4.01; N, 15.11; S, 6.01%. **ESI-MS**: *m/z* 1009 (5%, [M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

## 7.4.2.2. Dithiosemicarbazone Pt(II) complexes

Synthesis of salicyaldiminato dithiosemicarbazone platinum(II) PTA complex

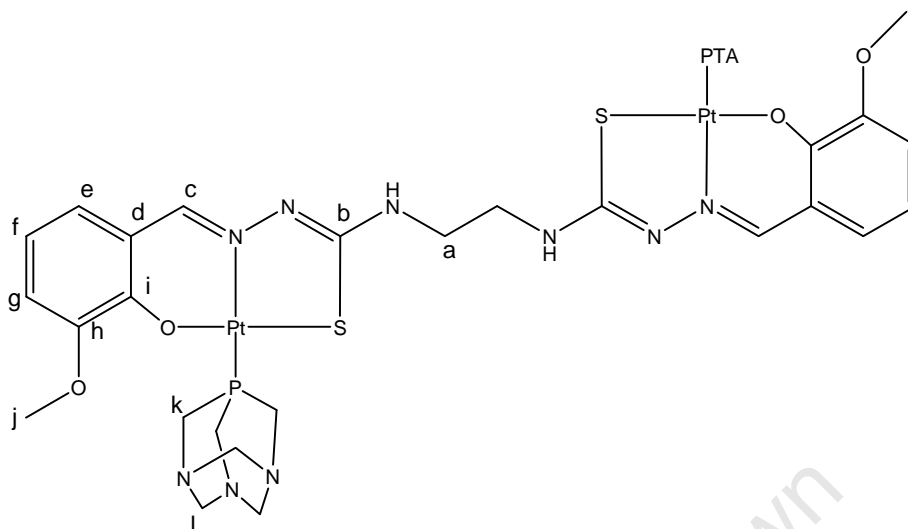


30

Salicyaldimine dithiosemicarbazone (0.070 g, 0.167 mmol), triethylamine (0.04 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.191 g, 0.329 mmol) were refluxed in ethanol for 5 hours and stirred overnight at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product obtained was a yellow powder (0.141 g, 83%). **<sup>1</sup>H NMR** (399.952 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.52 (4H, s, H<sub>a</sub>); 4.29 (12H, s, H<sub>j</sub>); 4.48 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.06, H<sub>k(Eq)</sub>); 4.57 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.78, H<sub>k(Ax)</sub>); 6.69 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.25, H<sub>f</sub>); 7.04 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 8.50, H<sub>h</sub>); 7.29 (2H, s, NH); 7.38 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.62, H<sub>g</sub>); 7.57 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.85, H<sub>e</sub>); 8.67 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 11.19, H<sub>c</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -61.47 (2P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3329.69. **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 45.97 (C<sub>a</sub>); 50.27 (C<sub>j</sub>); 72.84 (C<sub>k</sub>); 116.09 (C<sub>h</sub>); 119.01 (C<sub>d</sub>), 121.64 (C<sub>f</sub>); 133.15 (C<sub>e</sub>); 134.71 (C<sub>g</sub>); 147.46 (C<sub>c</sub>); 160.58 (C<sub>i</sub>); 172.45 (C<sub>b</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1599 (C=N), 1635 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>40</sub>N<sub>12</sub>O<sub>2</sub>S<sub>2</sub>Pt<sub>2</sub>P<sub>2</sub>·5H<sub>2</sub>O: C, 29.82; H, 4.17; N, 13.93; S, 5.31%. Found: C, 29.96; H, 3.63; N, 13.93; S, 5.17%. **ESI-MS**: *m/z* 1117 (100%, [M]<sup>+</sup>). **M.p.** no melting < 300 °C.



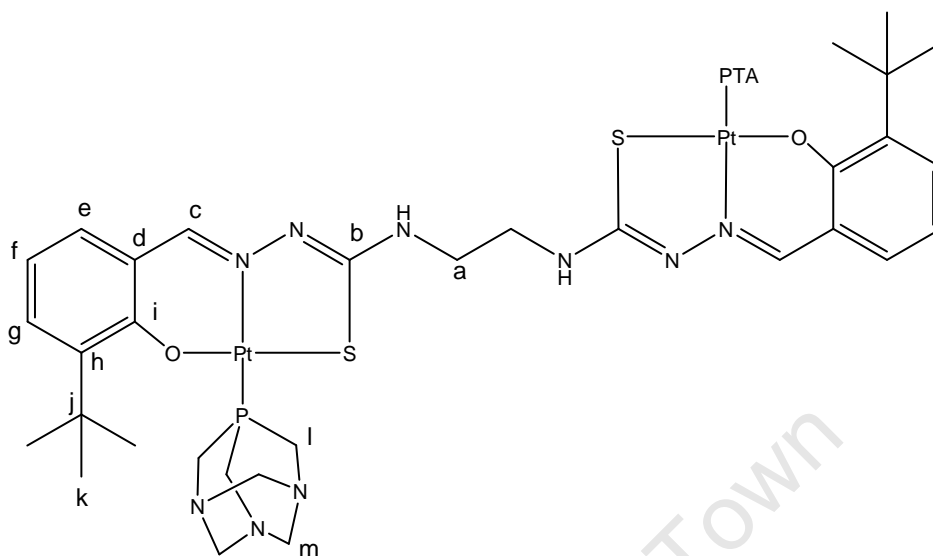
Synthesis of 3-methoxysalicylaldiminato dithiosemicarbazone platinum(II) PTA complex



## 31

3-Methoxy salicylaldimine dithiosemicarbazone (0.081 g, 0.171 mmol), triethylamine (0.05 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.196 g, 0.338 mmol) were refluxed in ethanol for 5 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product was obtained as a yellow powder (0.175 g, 95%). **<sup>1</sup>H NMR** (399.952 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.52 (4H, s, H<sub>a</sub>); 3.84 (6H, s, H<sub>j</sub>); 4.31 (12H, s, H<sub>k</sub>); 4.50 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 13.02, H<sub>i(Eq)</sub>); 4.57 (6H, d, <sup>2</sup>J<sub>H-H</sub> = 12.72, H<sub>i(Ax)</sub>); 6.62 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.83, H<sub>f</sub>); 7.02 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 7.78, H<sub>g</sub>); 7.19 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 8.16, H<sub>e</sub>); 7.29 (2H, s, NH); 8.65 (2H, d, <sup>4</sup>J<sub>P-H</sub> = 11.18, H<sub>c</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -60.18 (2P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3321.44. **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 45.16 (C<sub>a</sub>); 49.40 (C<sub>k</sub>); 56.23 (C<sub>j</sub>); 72.07 (C<sub>i</sub>); 113.56 (C<sub>f</sub>); 114.37 (C<sub>g</sub>); 118.047 (C<sub>d</sub>); 125.58 (C<sub>e</sub>); 146.35 (C<sub>c</sub>); 150.93 (C<sub>h</sub>); 151.07 (C<sub>i</sub>); 171.63 (C<sub>b</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1596 (C=N), 1619 (C=N). **Elemental analysis** calculated for C<sub>32</sub>H<sub>44</sub>N<sub>12</sub>O<sub>4</sub>Pt<sub>2</sub>P<sub>2</sub>S<sub>2</sub>: C, 32.65; H, 3.77; N, 14.28; S, 5.45%. Found: C, 31.44; H, 3.98; N, 13.13; S, 4.90%. **ESI-MS**: *m/z* 1177 (100%, [M]<sup>+</sup>). **M.p.** no melting < 300 °C.

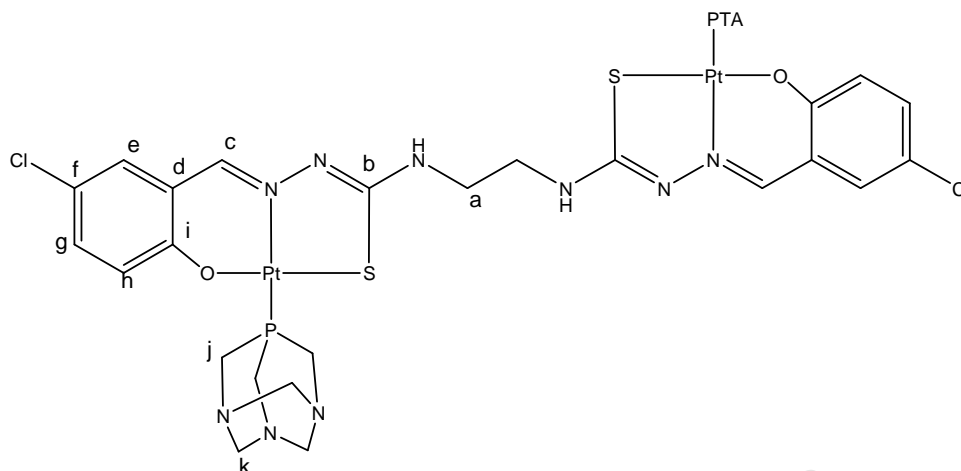
Synthesis of 3-tert butylsalicylaldimino dithiosemicarbazone platinum(II) PTA complex



## 32

3-tert Butyl salicylaldimine dithiosemicarbazone (0.090 g, 0.170 mmol), triethylamine (0.05 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.196 g, 0.338 mmol) were stirred in ethanol for 5 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product obtained was a yellow amorphous solid (0.166, 86%). **FT-IR** (KBr): ( $\nu_{max}$ , cm<sup>-1</sup>) 1594 cm<sup>-1</sup> (C=N). **Elemental analysis** calculated for C<sub>38</sub>H<sub>56</sub>N<sub>12</sub>S<sub>2</sub>P<sub>2</sub>O<sub>2</sub>Pt<sub>2</sub>: C, 37.13; H, 4.59; N, 13.68; S, 5.22%. Found: C, 38.04; H, 4.61; N, 13.76; S, 4.99%. **M.p.** no melting < 300 °C.

Synthesis of 5-chlorosalicylaldiminato dithiosemicarbazone platinum(II) PTA complex



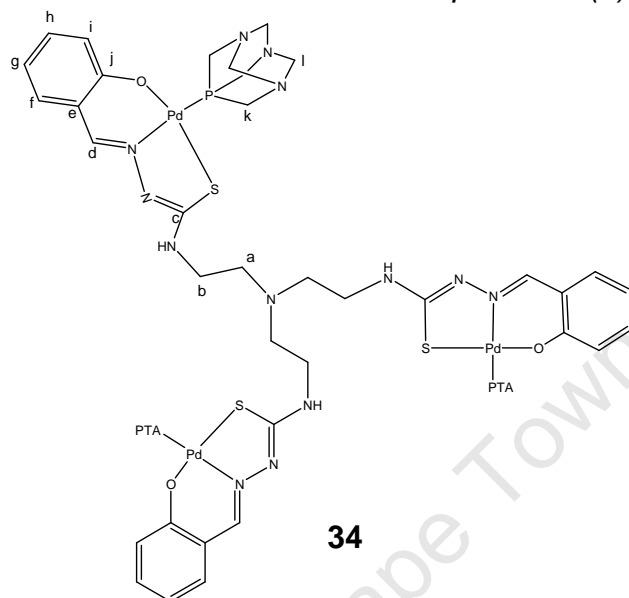
33

5-Chlorosalicylaldimine dithiosemicarbazone (0.086 g, 0.177 mmol), triethylamine (0.05 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.206 g, 0.355 mmol) were refluxed in ethanol for 5 hours. The precipitate was filtered using a Büchner funnel and the product washed with ethanol and diethyl ether. The product obtained was a yellow powder (0.167 g, 79%). **<sup>1</sup>H NMR** (399.952 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.55 (4H, s, H<sub>a</sub>); 4.31 (12H, s, H<sub>i</sub>); 4.50 (6H, d, <sup>2</sup>*J*<sub>H-H</sub> = 13.82, H<sub>k(Eq)</sub>); 4.58 (6H, d, <sup>2</sup>*J*<sub>H-H</sub> = 12.69, H<sub>k(AX)</sub>); 7.07 (2H, d, <sup>3</sup>*J*<sub>H-H</sub> = 9.09, H<sub>h</sub>); 7.26 (2H, s, NH); 7.35 (2H, dd, <sup>4</sup>*J*<sub>H-H</sub> = 2.70, <sup>3</sup>*J*<sub>H-H</sub> = 8.91, H<sub>g</sub>); 7.64 (2H, d, <sup>4</sup>*J*<sub>H-H</sub> = 2.84, H<sub>e</sub>); 8.64 (2H, d, <sup>4</sup>*J*<sub>P-H</sub> = 10.99, H<sub>c</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -61.60 (2P, s, PTA), <sup>1</sup>*J*<sub>Pt-P</sub> = 3343.30. **FT-IR** (KBr): (*v*<sub>max</sub>, cm<sup>-1</sup>) 1595 (C=N), 1631 (C=N). **Elemental analysis** calculated for C<sub>30</sub>H<sub>38</sub>N<sub>12</sub>O<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>Pt<sub>2</sub>P<sub>2</sub>·6H<sub>2</sub>O: C, 27.85; H, 3.89; N, 12.99; S, 4.95%. Found: C, 27.58; H, 3.14; N, 11.58; S, 4.65%. **ESI-MS**: *m/z* 1117 (100%, [M-Cl]<sup>+</sup>); 1187 (30%, [M+H]<sup>+</sup>). **M.p.** no melting < 300 °C.

## 7.4.3. Synthesis of trithiosemicarbazone complexes

## 7.4.3.1. Trithiosemicarbazone Pd(II) complexes

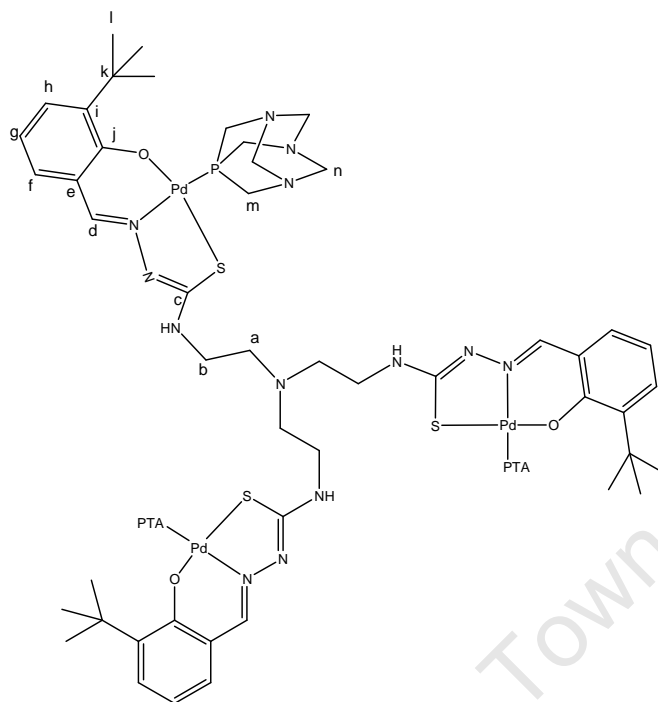
Synthesis of salicylaldiminato trithiosemicarbazone palladium(II) PTA complex



Salicylaldimine trithiosemicarbazone (0.044 g, 0.06 mmol), triethylamine (0.03 cm<sup>3</sup>) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.0951 g, 0.19 mmol) were refluxed in ethanol for 16 hours and stirred for an additional 24 hours at room temperature. The precipitate was filtered using a Büchner funnel and the product washed with cold ethanol. The product obtained was a yellow powder (0.083 g, 87%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.72 (6H, m, H<sub>a</sub>); 3.33 (6H, m, H<sub>b</sub>); 4.28 (18H, s, H<sub>k</sub>); 4.41 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 13.27, H<sub>I(Eq)</sub>); 4.55 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 12.69, H<sub>I(Ax)</sub>); 6.55 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 6.84, H<sub>h</sub>); 6.92 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 8.27, H<sub>f</sub>); 7.04 (3H, s, NH); 7.26 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.94, H<sub>g</sub>); 7.39 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 7.91, H<sub>i</sub>); 8.31 (3H, d, <sup>4</sup>J<sub>P-H</sub> = 12.99, H<sub>d</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.55 (3P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 44.48 (C<sub>b</sub>); 50.67 (C<sub>k</sub>); 54.08 (C<sub>a</sub>); 72.66 (C<sub>i</sub>); 115.17 (C<sub>h</sub>), 118.80 (C<sub>e</sub>); 121.51 (C<sub>f</sub>); 133.30 (C<sub>g</sub>); 135.05 (C<sub>j</sub>); 149.09 (C<sub>d</sub>); 162.52 (C<sub>j</sub>); 171.15 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1598 (C=N). **Elemental analysis** calculated for C<sub>48</sub>H<sub>66</sub>N<sub>19</sub>S<sub>3</sub>O<sub>3</sub>Pd<sub>3</sub>P<sub>3</sub>·8H<sub>2</sub>O: C, 35.81; H, 5.13; N, 16.54; S, 5.97%. Found: C, 35.58; H, 4.77; N, 16.67; S, 4.70%. **ESI-MS**: *m/z* 1466 (25%, [M+H]<sup>+</sup>). **M.p.** 245-247 °C (with decomposition).



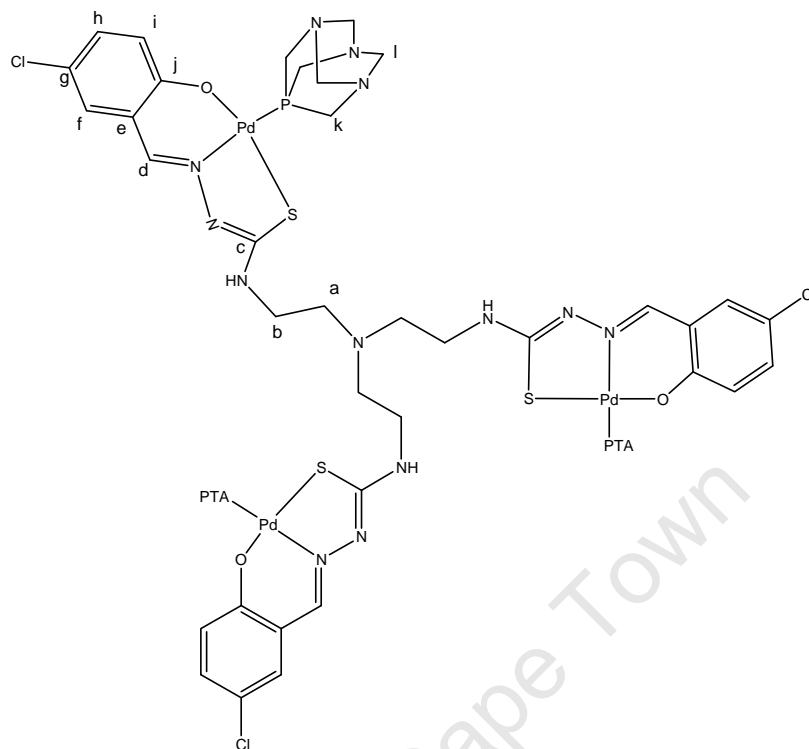
Synthesis of 3-*tert* butylsalicylaldiminato trithiosemicarbazone palladium(II) PTA complex



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3-*t*-Bu salicylaldimine trithiosemicarbazone (0.082 g, 0.965 mmol) was dissolved in MeOH (25 cm<sup>3</sup>). Triethylamine (0.04 cm<sup>3</sup>) was added to the solution and stirred for 5 minutes. (0.142 g, 0.289 mmol) *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] was then added and the solution was stirred for 48 hours at room temperature. The yellow precipitate was filtered using a Büchner funnel and washed with cold methanol and diethyl ether. The product was dried *in vacuo*. The product was obtained as a yellow powder (0.099 g, 62%). <sup>1</sup>H NMR (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.43 (27H, s, H<sub>l</sub>); 2.75 (6H, s, H<sub>a</sub>); 3.41 (6H, s, H<sub>b</sub>); 4.33-4.54 (36H, m, H<sub>m</sub>, H<sub>n</sub>); 6.46 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.54, H<sub>g</sub>); 7.21 (9H, m, NH, H<sub>f</sub>, H<sub>h</sub>); 8.26 (3H, d, <sup>4</sup>J<sub>P-H</sub> = 13.44, H<sub>d</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.468 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -40.11 (3P, s, PTA). <sup>13</sup>C{<sup>1</sup>H} NMR (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 29.82 (C<sub>i</sub>); 35.66 (C<sub>k</sub>); 44.73 (C<sub>b</sub>); 51.48 (C<sub>m</sub>); 53.85 (C<sub>a</sub>); 72.31 (C<sub>n</sub>); 114.39 (C<sub>g</sub>), 118.60 (C<sub>e</sub>); 130.06 (C<sub>f</sub>); 133.76 (C<sub>h</sub>); 139.17 (C<sub>j</sub>); 149.95 (C<sub>d</sub>); 161.14 (C<sub>j</sub>); 169.41 (C<sub>c</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1594 (C=N), 1624 (C=N). ESI-MS: *m/z* 1634 (30%, [M]<sup>+</sup>); 818 (70%, [M+2H]<sup>2+</sup>). M.p. decomposes at 274 °C.

Synthesis of 5-chlorosalicylaldiminato trithiosemicarbazone palladium(II) PTA complex

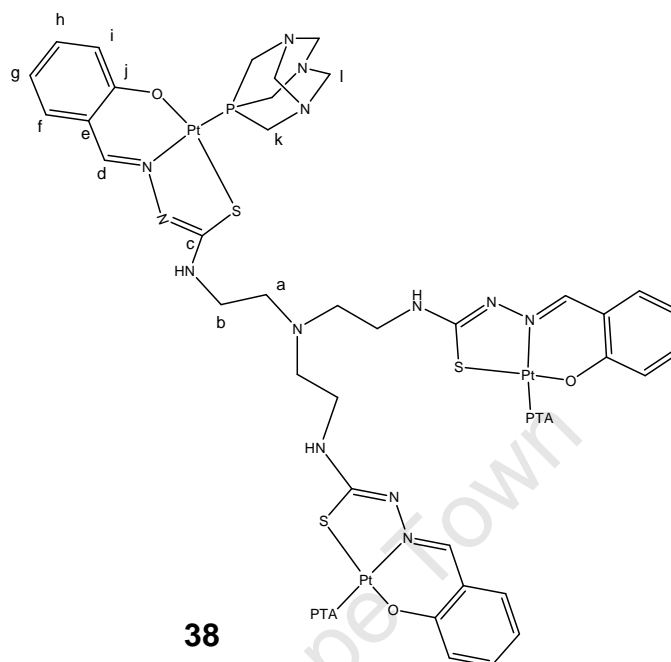


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5-Chlorosalicylaldimine trithiosemicarbazone (0.097 g, 0.124 mmol), sodium acetate (0.030 g, 0.362 mmol) and *cis*-[Pd(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.178 g, 0.362 mmol) were refluxed in ethanol for 48 hours. The mixture was cooled to room temperature and the precipitate filtered, washed with ethanol and diethyl ether then dried *in vacuo*. The product obtained was a yellow powder (0.164 g, 84%). **<sup>1</sup>H NMR** (300.077 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.78 (6H, s, H<sub>a</sub>); 3.38 (6H, s, H<sub>b</sub>); 4.27 (18H, s, H<sub>k</sub>); 4.41 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 12.81, H<sub>l(Eq)</sub>); 4.55 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 12.32, H<sub>l(Ax)</sub>); 6.89 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 8.95, H<sub>i</sub>); 7.20 (6H, m, H<sub>h</sub>, NH); 7.39 (3H, d, <sup>4</sup>J<sub>H-H</sub> = 2.74, H<sub>f</sub>); 8.19 (3H, d, <sup>4</sup>J<sub>H-H</sub> = 12.92, H<sub>d</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.472 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -36.32 (3P, s, PTA). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 43.93 (C<sub>b</sub>); 49.90 (C<sub>k</sub>); 52.80 (C<sub>a</sub>); 71.82 (C<sub>i</sub>); 117.08 (C<sub>i</sub>); 119.02 (C<sub>e</sub>); 122.35 (C<sub>g</sub>); 131.73 (C<sub>f</sub>); 131.99 (C<sub>h</sub>); 147.16 (C<sub>d</sub>); 160.35 (C<sub>j</sub>); 170.69 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1597 (C=N). **Elemental analysis** calculated for C<sub>48</sub>H<sub>63</sub>N<sub>6</sub>O<sub>3</sub>S<sub>3</sub>Pd<sub>3</sub>P<sub>3</sub>Cl<sub>3</sub>: C, 36.75; H, 4.05; N, 16.97; S, 6.13%. Found: C, 35.12; H, 4.03; N, 16.00; S, 5.40%. **ESI-MS**: *m/z* 1569 (10%, [M]<sup>+</sup>); 785 (90%, [M+2H]<sup>2+</sup>). M.p. 241-246 °C (with decomposition).

## 7.4.3.2. Trithiosemicarbazone Pt(II) complexes

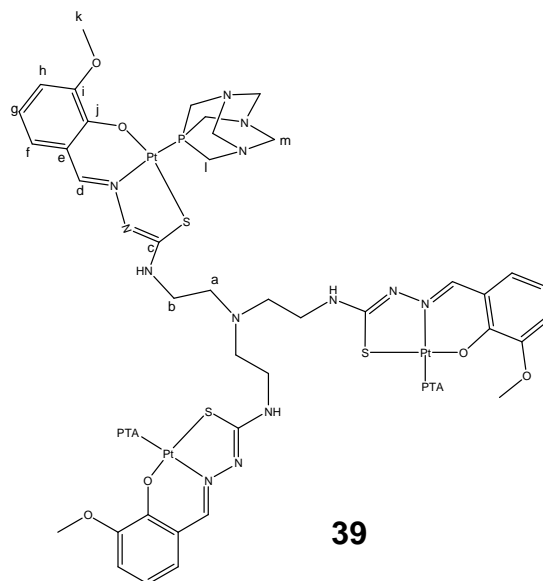
## Synthesis of salicylaldiminato trithiosemicarbazone platinum(II) PTA complex



Salicylaldimine trithiosemicarbazone (0.074 g, 0.109 mmol), triethylamine (0.05 cm<sup>3</sup>) and *cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.185 g, 0.319 mmol) were refluxed in methanol for 6 hours and stirred for an additional 12 hours at room temperature. The precipitate was collected using a Büchner funnel and the product washed with methanol and diethyl ether. The product was obtained as a yellow-orange amorphous solid (0.078 g, 41%). **<sup>1</sup>H NMR** (399.953 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.70 (6H, m, H<sub>a</sub>); 3.33 (6H, m, H<sub>b</sub>); 4.15 (18H, s, H<sub>k</sub>); 4.36 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 13.11, H<sub>I(Eq)</sub>); 4.44 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 12.78, H<sub>I(Ax)</sub>); 6.60 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.25, H<sub>h</sub>); 6.98 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 8.49, H<sub>f</sub>); 7.10 (3H, s, NH); 7.32 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.22, H<sub>g</sub>); 7.46 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 8.31, H<sub>i</sub>); 8.57 (3H, d, <sup>4</sup>J<sub>P-H</sub> = 11.20, H<sub>d</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (161.903 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -61.49 (3P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3348.80. **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 44.80 (C<sub>b</sub>); 50.19 (C<sub>k</sub>); 53.92 (C<sub>a</sub>); 72.79 (C<sub>i</sub>); 115.66 (C<sub>h</sub>), 118.77 (C<sub>e</sub>); 121.29 (C<sub>f</sub>); 132.68 (C<sub>g</sub>); 134.29 (C<sub>j</sub>); 147.06 (C<sub>d</sub>); 160.58 (C<sub>j</sub>); 172.32 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1599 (C=N). **Elemental analysis** calculated for C<sub>48</sub>H<sub>66</sub>N<sub>19</sub>S<sub>3</sub>O<sub>3</sub>Pt<sub>3</sub>P<sub>3</sub>: C, 33.29; H, 3.84; N, 15.37; S, 5.55%. Found: C, 33.07; H, 4.07; N, 15.35; S, 4.69%. **ESI-MS**: *m/z* 1731 (50%, [M]<sup>+</sup>). **M.p.** 231-233 °C

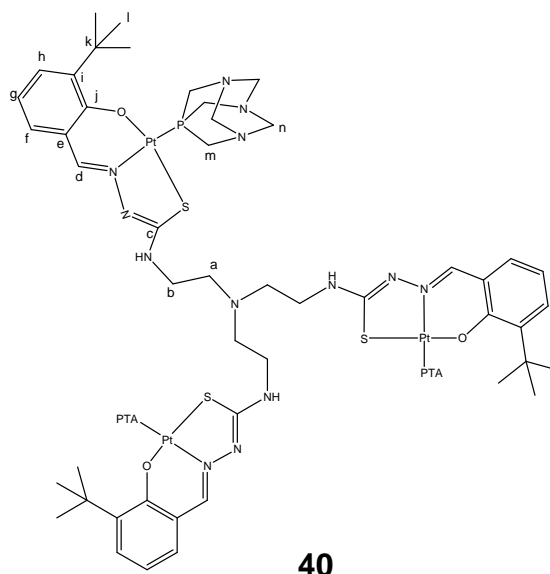


Synthesis of 3-methoxysalicylaldiminato trithiosemicarbazone platinum(II) PTA complex



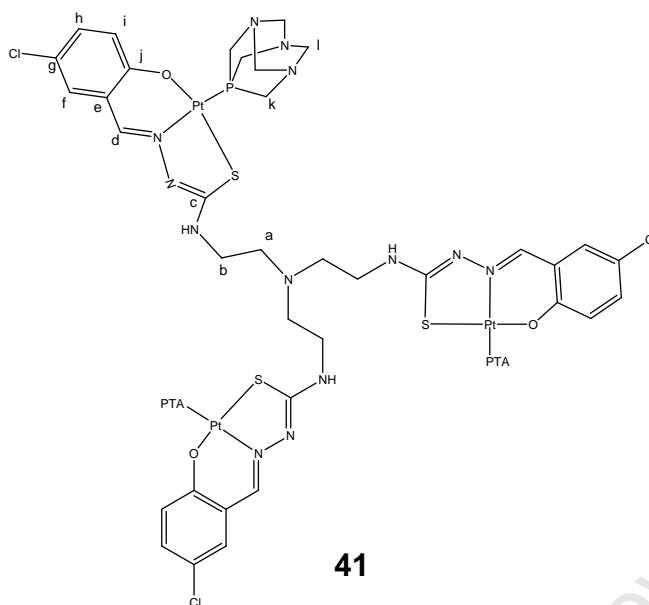
3-Methoxysalicylaldimine trithiosemicarbazone (0.164 g, 0.213 mmol) in methanol (25 cm<sup>3</sup>) was heated in a round bottom flask. To this, triethylamine (0.10 cm<sup>3</sup>) was added and the solution stirred for 5 minutes. *Cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.368 g, 0.633 mmol) in hot de-ionised water (25 cm<sup>3</sup>) was added to the solution and the resulting mixture was refluxed for 6 hours and stirred for an additional 12 hours at room temperature. Upon cooling a yellow precipitate was observed and filtered using a Büchner funnel. The product washed with methanol and diethyl ether and dried *in vacuo*. The product obtained was a yellow powder (0.054 g, 14%). <sup>1</sup>H NMR (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.72 (6H, t, <sup>3</sup>J<sub>H-H</sub> = 6.37, H<sub>a</sub>); 3.42 (6H, m, H<sub>b</sub>); 3.80 (9H, s, H<sub>k</sub>) 4.24 (18H, s, H<sub>l</sub>); 4.48 (18H, s, H<sub>m</sub>); 6.50 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.79, H<sub>g</sub>); 6.86 (3H, s, NH); 6.95 (3H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.50, <sup>3</sup>J<sub>H-H</sub> = 7.65, H<sub>h</sub>); 7.07 (3H, dd, <sup>4</sup>J<sub>H-H</sub> = 1.55, <sup>3</sup>J<sub>H-H</sub> = 8.24, H<sub>f</sub>); 8.51 (3H, d, <sup>4</sup>J<sub>P-H</sub> = 11.22, H<sub>d</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.468 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -56.90 (3P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3333.81. <sup>13</sup>C{<sup>1</sup>H} NMR (75.451 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 44.09 (C<sub>b</sub>); 49.52 (C<sub>l</sub>); 53.13 (C<sub>a</sub>); 56.23 (C<sub>k</sub>); 72.01 (C<sub>m</sub>); 113.67 (C<sub>g</sub>), 114.14 (C<sub>h</sub>); 118.04 (C<sub>e</sub>); 125.55 (C<sub>f</sub>); 146.09 (C<sub>d</sub>); 150.98 (C<sub>i</sub>); 154.49 (C<sub>j</sub>); 171.51 (C<sub>c</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1592 (C=N), 1631 (C=N). **Elemental analysis** calculated for C<sub>51</sub>H<sub>72</sub>N<sub>19</sub>O<sub>6</sub>S<sub>3</sub>Pt<sub>3</sub>P<sub>3</sub>: C, 33.63; H, 3.98; N, 14.61; S, 5.28%. Found: C, 32.03; H, 4.05; N, 13.79; S, 4.65%. **ESI-MS**: *m/z* 1821 (44%, [M]<sup>+</sup>); 912 (10%, [M+2H]<sup>2+</sup>). **M.p.** 237-241 °C (with decomposition).

Synthesis of 3-tert butylsalicylaldiminato trithiosemicarbazone platinum(II) PTA complex



3-<sup>t</sup>Bu salicylaldimine trithiosemicarbazone (0.085 g, 0.010 mmol) was dissolved in MeOH (25 cm<sup>3</sup>). Triethylamine (0.04 cm<sup>3</sup>) was added to the solution and stirred for 5 minutes. *Cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.167 g, 0.289 mmol) was then added and the solution was stirred for 48 hours at room temperature. The yellow precipitate was filtered using a Büchner funnel and washed with methanol and diethyl ether. The product was dissolved in DCM and filtered by gravity. The solvent was evaporated and the product dried *in vacuo*. The product was isolated as a yellow powder (0.069 g, 38%). <sup>1</sup>H NMR (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 1.45 (27H, s, H<sub>i</sub>); 2.71 (6H, s, H<sub>a</sub>); 3.40 (6H, s, H<sub>b</sub>); 4.27 (18H, s, H<sub>m</sub>); 4.44 (18H, m, H<sub>n</sub>); 6.53 (3H, t, <sup>3</sup>J<sub>H-H</sub> = 7.58, H<sub>g</sub>); 7.07 (3H, s, NH); 7.30 (6H, d, <sup>3</sup>J<sub>H-H</sub> = 7.75, H<sub>f</sub>, H<sub>h</sub>); 8.58 (3H, d, <sup>4</sup>J<sub>P-H</sub> = 11.35, H<sub>d</sub>). <sup>31</sup>P{<sup>1</sup>H} NMR (121.468 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -60.76 (3P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3340.49. <sup>13</sup>C{<sup>1</sup>H} NMR (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 30.02 (C<sub>i</sub>); 35.95 (C<sub>k</sub>); 44.70 (C<sub>b</sub>); 51.27 (C<sub>m</sub>); 53.88 (C<sub>a</sub>); 72.64 (C<sub>n</sub>); 115.47 (C<sub>g</sub>), 119.13 (C<sub>e</sub>); 130.09 (C<sub>f</sub>); 133.74 (C<sub>h</sub>); 139.51 (C<sub>i</sub>); 148.21 (C<sub>d</sub>); 159.25 (C<sub>j</sub>); 171.31 (C<sub>c</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1594 (C=N), 1628 (C=N). **Elemental analysis** calculated for C<sub>60</sub>H<sub>90</sub>N<sub>19</sub>O<sub>3</sub>S<sub>3</sub>Pt<sub>3</sub>P<sub>3</sub>·4CH<sub>2</sub>Cl<sub>2</sub>: C, 34.32; H, 4.41; N, 11.88; S, 4.29%. Found: C, 34.28; H, 5.23; N, 16.25; S, 4.82%. **ESI-MS**: *m/z* 1900 (60%, [M]<sup>+</sup>); 951 (100%, [M+2H]<sup>2+</sup>). **M.p.** 259 – 264 °C (with decomposition).

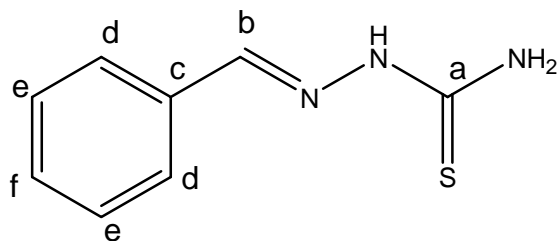
Synthesis of 5-chlorosalicylaldiminato trithiosemicarbazone platinum(II) PTA complex



5-Chlorosalicylaldimine trithiosemicarbazone (0.158 g, 0.202 mmol) in ethanol (25 cm<sup>3</sup>) was heated in a round bottom flask. To this, triethylamine (0.10 cm<sup>3</sup>) was added and the solution stirred for 5 minutes. *Cis*-[Pt(PTA)<sub>2</sub>Cl<sub>2</sub>] (0.347 g, 0.598 mmol) in hot de-ionised water (25 cm<sup>3</sup>) was added to the solution and the resulting mixture was refluxed for 3 hours and stirred for an additional 12 hours at room temperature. A dark yellow precipitate was obtained and filtered using a Büchner funnel. The product washed with ethanol and diethyl ether and dried *in vacuo*. The product obtained was a dark yellow powder (0.196 g, 54%). **<sup>1</sup>H NMR** (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.71 (6H, t, <sup>3</sup>J<sub>H-H</sub> = 6.10, H<sub>a</sub>); 3.39 (6H, m, H<sub>b</sub>); 4.23 (18H, s, H<sub>k</sub>); 4.43 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 13.48, H<sub>l(Eq)</sub>); 4.51 (9H, d, <sup>2</sup>J<sub>H-H</sub> = 12.75, H<sub>l(Ax)</sub>); 6.99 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 9.07, H<sub>i</sub>); 7.12 (3H, m, NH); 7.27 (3H, dd, <sup>4</sup>J<sub>H-H</sub> = 2.80, <sup>3</sup>J<sub>H-H</sub> = 9.02, H<sub>h</sub>); 7.52 (3H, d, <sup>4</sup>J<sub>H-H</sub> = 2.79, H<sub>f</sub>); 8.53 (3H, d, <sup>4</sup>J<sub>H-H</sub> = 11.04, H<sub>d</sub>). **<sup>31</sup>P{<sup>1</sup>H} NMR** (121.467 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) -58.19 (3P, s, PTA), <sup>1</sup>J<sub>Pt-P</sub> = 3341.09. **<sup>13</sup>C{<sup>1</sup>H} NMR** (75.451 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 43.95 (C<sub>b</sub>); 49.27 (C<sub>k</sub>); 53.06 (C<sub>a</sub>); 71.93 (C<sub>l</sub>); 118.07 (C<sub>i</sub>), 119.20 (C<sub>e</sub>); 122.50 (C<sub>g</sub>); 131.49 (C<sub>f</sub>); 131.62 (C<sub>h</sub>); 145.28 (C<sub>d</sub>); 158.27 (C<sub>j</sub>); 172.36 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1596 (C=N), 1628 (C=N). **Elemental analysis** calculated for C<sub>48</sub>H<sub>63</sub>N<sub>19</sub>O<sub>3</sub>S<sub>3</sub>Pt<sub>3</sub>P<sub>3</sub>Cl<sub>3</sub>: C, 31.42; H, 3.46; N, 14.51; S, 5.24%. Found: C, 30.19; H, 3.95; N, 13.65; S, 4.94%. **ESI-MS**: *m/z* 1835 (30%, [M]<sup>+</sup>); 918 (55%, [M+2H]<sup>2+</sup>). M.p. 250-254 °C.

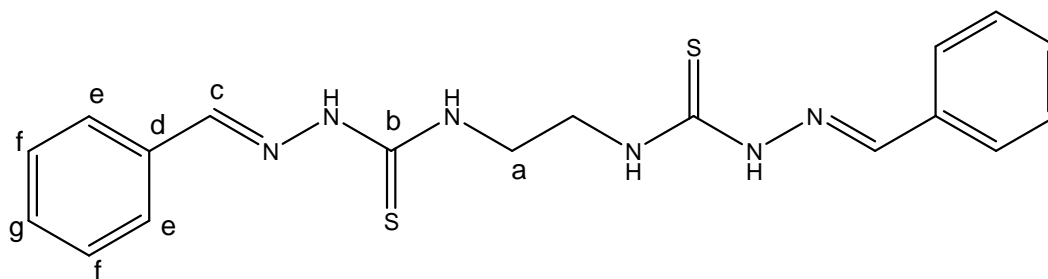
## 7.5. Synthesis of benzaldehyde thiosemicarbazones

Synthesis of benzaldehyde monothiosemicarbazone<sup>12</sup>



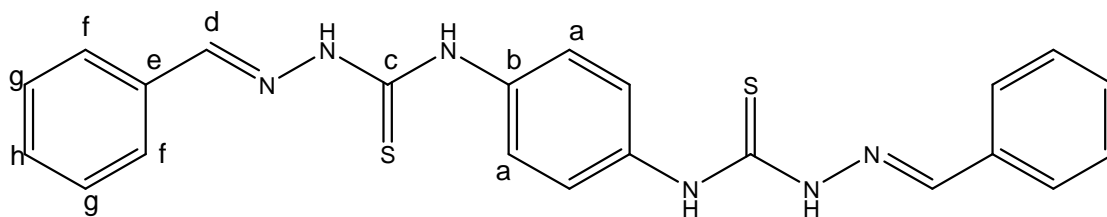
42

Thiosemicarbazide (0.231 g, 2.530 mmol) was added to MeOH (25 cm<sup>3</sup>), to this benzaldehyde (0.26 cm<sup>3</sup>) was added and the mixture refluxed for 5 hours and stirred for an additional 12 hours at room temperature yielding a clear solution. The volume of MeOH was reduced to half of its original volume and water was added to precipitate the product. The product was filtered using a Büchner funnel, washed with water and dried *in vacuo*. The product obtained was a white powder (0.453 g, 93%). **<sup>1</sup>H NMR** (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 7.39 (3H, m, H<sub>e</sub>, H<sub>f</sub>); 7.76 (2H, m, H<sub>d</sub>); 7.87 (1H, s, NH<sub>2</sub>); 8.05 (2H, br s, NH<sub>2</sub>, H<sub>b</sub>); 11.31 (1H, s, NH). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 127.69 (C<sub>e</sub>); 129.06 (C<sub>d</sub>); 130.25 (C<sub>f</sub>); 134.56 (C<sub>c</sub>); 142.73 (C<sub>b</sub>), 178.40 (C<sub>a</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1591 (C=N); 871 (C=S). **Elemental analysis** calculated for C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>S: C, 53.60; H, 5.06; N, 23.44; S, 17.88%. Found: C, 54.76; H, 5.37; N, 24.31; S, 18.10%. **M.p.** 160-162 °C; Lit: 167-169 °C.

Synthesis of non-rigid benzaldehyde dithiosemicarbazone<sup>13</sup>

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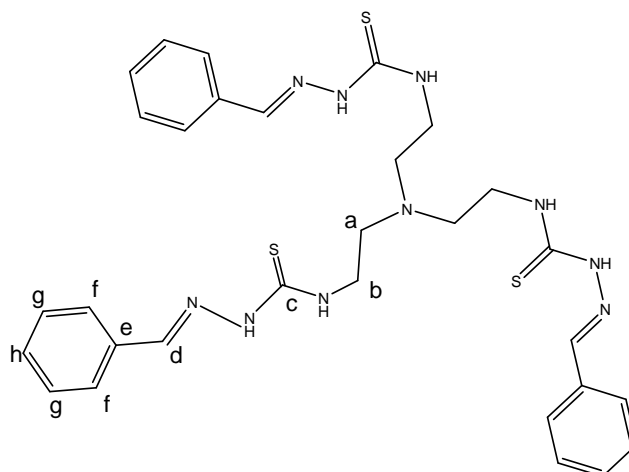
Ethane-1,2-dithiosemicarbazide (0.122 g, 0.586 mmol) was added to MeOH (25 cm<sup>3</sup>). Benzaldehyde (0.12 cm<sup>3</sup>) was added to this and the suspension refluxed for 24 hours and stirred for an additional 16 hours at room temperature yielding a white solid. The product was filtered on a Büchner funnel, washed with MeOH and diethyl ether and then dried *in vacuo*. The product was obtained as a white powder (0.154 g, 68%). <sup>1</sup>H NMR (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 3.87 (4H, s, H<sub>a</sub>); 7.37 (6H, m, H<sub>f</sub>, H<sub>g</sub>); 7.79 (4H, m, H<sub>e</sub>); 8.06 (2H, s, H<sub>c</sub>); 8.61 (2H, s, -C<sub>a</sub>NH-); 11.45 (2H, s, -NHN=). <sup>13</sup>C{<sup>1</sup>H} NMR (100.600 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 44.00 (C<sub>a</sub>); 127.79 (C<sub>e</sub>); 129.07 (C<sub>f</sub>); 130.27 (C<sub>g</sub>); 134.60 (C<sub>d</sub>); 142.86 (C<sub>c</sub>), 178.01 (C<sub>b</sub>). FT-IR (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1599 (C=N); 884 (C=S). **Elemental analysis** calculated for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>S<sub>2</sub>: C, 56.42; H, 5.24; N, 21.86; S, 16.67%. Found: C, 55.96; H, 5.54; N, 21.99; S, 16.45%. **M.p.** 211-213 °C; Lit: 212 °C.

*Synthesis of rigid benzaldehyde dithiosemicarbazone*

45

Benzene-1,4-dithiosemicarbazide (0.140 g, 0.544 mmol) was added to MeOH (25 cm<sup>3</sup>). Benzaldehyde (0.11 cm<sup>3</sup>) was added to this and the suspension refluxed for 24 hours and stirred for an additional 12 hours at room temperature yielding a white solid. The product was filtered using a Büchner funnel, washed with MeOH and diethyl ether and then dried in vacuo. The product was obtained as a white powder (0.215 g, 91%). **<sup>1</sup>H NMR** (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 7.76 (6H, m, H<sub>g</sub>, H<sub>h</sub>); 7.92 (4H, s, H<sub>a</sub>); 8.24 (4H, m, H<sub>f</sub>); 8.52 (2H, s, H<sub>d</sub>); 10.38 (2H, s, -C<sub>b</sub>NH-); 12.06 (2H, s, -NHN=). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 125.92 (C<sub>a</sub>); 128.05 (C<sub>g</sub>); 129.06 (C<sub>f</sub>); 130.46 (C<sub>h</sub>); 134.43 (C<sub>e</sub>); 136.62 (C<sub>b</sub>); 143.30 (C<sub>d</sub>), 176.43 (C<sub>c</sub>). **FT-IR** (KBr): (ν<sub>max</sub>, cm<sup>-1</sup>) 1600 (C=N); 860 (C=S). **Elemental analysis** calculated for C<sub>22</sub>H<sub>20</sub>N<sub>6</sub>S<sub>2</sub>: C, 61.08; H, 4.66; N, 19.43; S, 14.38%. Found: C, 60.48; H, 5.07; N, 19.71; S, 14.38%. **ESI-MS**: *m/z* 455 (100%, [M+Na]<sup>+</sup>). **M.p.** 262-265 °C.

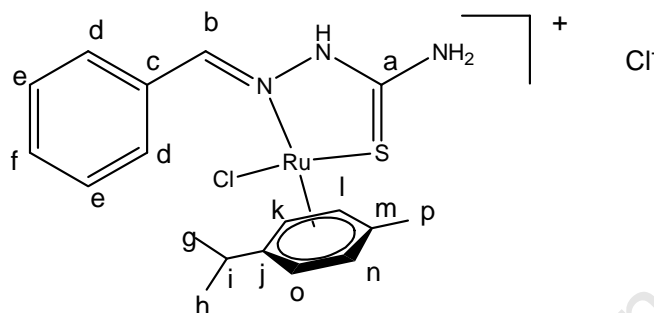
## Synthesis of non-rigid benzaldehyde trithiosemicarbazone



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Trithiosemicarbazide (0.211 g, 0.572 mmol) was added to EtOH (25 cm<sup>3</sup>), to this benzaldehyde (0.17 cm<sup>3</sup>) was added and the mixture refluxed for 12 hours and stirred for an additional 12 hours at room temperature. Water was added to precipitate the cream product, which was then filtered using a Hirsch funnel and washed with water. The product was then dried *in vacuo*. The product obtained was a cream powder (0.193 g, 53%). **<sup>1</sup>H NMR** (300.066 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 2.70 (6H, m, H<sub>a</sub>); 3.45 (6H, m, H<sub>b</sub>); 7.38 (9H, m, H<sub>g</sub>, H<sub>h</sub>); 7.73 (6H, s, H<sub>i</sub>); 8.04 (3H, s, H<sub>d</sub>); 8.37 (3H, m, -C<sub>b</sub>NH-); 11.38 (3H, s, -NHN=). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.577 MHz, DMSO-*d*<sub>6</sub>): (δ, ppm) 42.16 (C<sub>b</sub>); 53.03 (C<sub>a</sub>); 127.59 (C<sub>g</sub>); 129.14 (C<sub>f</sub>); 130.24 (C<sub>h</sub>); 134.62 (C<sub>e</sub>); 142.47 (C<sub>d</sub>), 177.58 (C<sub>c</sub>). **FT-IR** (KBr): (*v*<sub>max</sub>, cm<sup>-1</sup>) 1634 (C=N); 873 (C=S). **Elemental analysis** calculated for C<sub>30</sub>H<sub>36</sub>N<sub>10</sub>S<sub>3</sub>·4½H<sub>2</sub>O: C, 50.47; H, 6.35; N, 19.62; S, 13.47%. Found: C, 50.07; H, 6.59; N, 23.03; S, 15.47%. **ESI-MS**: *m/z* 633 (100%, [M]<sup>+</sup>). **M.p.** 156-160 °C.

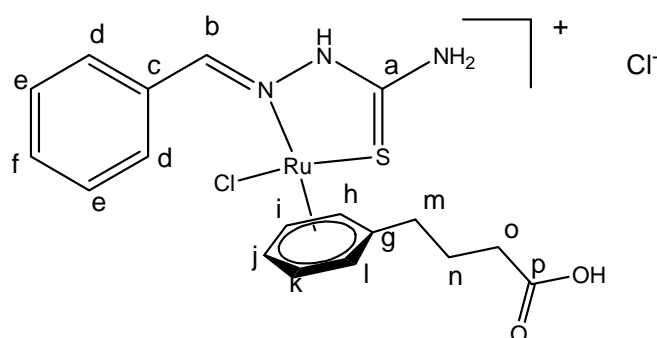
## 7.6. Synthesis of arene-ruthenium(II) TSC complexes

7.6.1. Synthesis of mononuclear ( $\eta^6$ -arene)ruthenium(II) TSC complexesSynthesis of ( $\eta^6$ -*p*-cymene)Ru(II) monothiosemicarbazone

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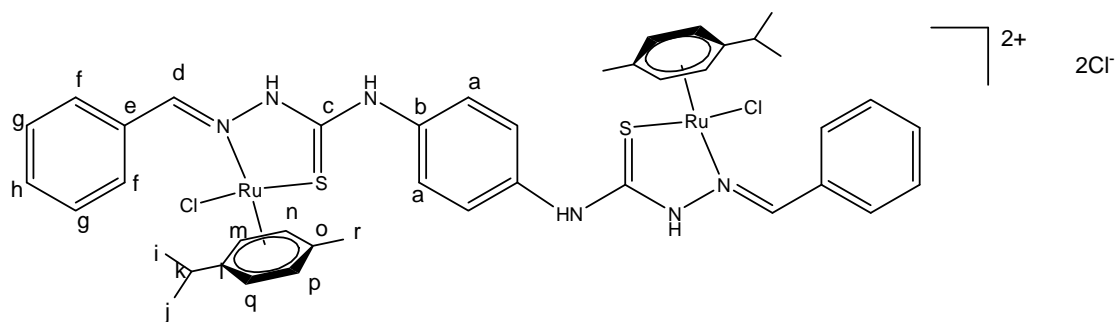
Benzaldehyde monothiosemicarbazone (0.092 g, 0.513 mmol) in MeOH (25 cm<sup>3</sup>) was stirred at ambient temperature. To this, [Ru( $\eta^6$ -*p*-cymene)( $\mu$ -Cl)Cl]<sub>2</sub> (0.157 g, 0.257 mmol) was added, and the dark orange solution stirred for 24 hours at room temperature. After this period, the clear orange-red solution is reduced to less than one-quarter of the original volume. The solution was added dropwise to diethyl ether (90 cm<sup>3</sup>) to precipitate an orange product. The product was washed with diethyl ether, which was removed *in vacuo* yielding the desired product (0.155 g, 62%). **<sup>1</sup>H NMR** (400.200 MHz, CDCl<sub>3</sub>-*d*): ( $\delta$ , ppm) 1.07 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 6.81, H<sub>g</sub>); 1.13 (3H, d, <sup>3</sup>J<sub>H-H</sub> = 6.94, H<sub>h</sub>); 2.05 (3H, s, H<sub>p</sub>); 2.61 (1H, m, H<sub>i</sub>); 4.64 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.72, H<sub>n</sub>); 4.80 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.82, H<sub>k</sub>); 4.88 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.79, H<sub>o</sub>); 5.41 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.79, H<sub>l</sub>); 7.57 (4H, m, H<sub>e</sub>, H<sub>f</sub>, -NNH); 8.15 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 6.99, H<sub>d</sub>); 9.05 (1H, s, H<sub>b</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.600 MHz, CDCl<sub>3</sub>-*d*): ( $\delta$ , ppm) 18.57 (C<sub>p</sub>); 21.39 (C<sub>g</sub>); 23.05 (C<sub>h</sub>); 30.73 (C<sub>i</sub>); 81.35 (C<sub>k</sub>); 82.41 (C<sub>o</sub>); 87.79 (C<sub>l</sub>); 88.78 (C<sub>n</sub>); 103.85 (C<sub>m</sub>); 127.84 (C<sub>j</sub>); 128.86 (C<sub>e</sub>); 130.54 (C<sub>d</sub>); 131.78 (C<sub>f</sub>); 133.34 (C<sub>c</sub>); 161.65 (C<sub>b</sub>); 177.54 (C<sub>a</sub>). **FT-IR** (KBr): ( $\nu_{max}$ , cm<sup>-1</sup>) 1618 (C=N); 875 (C=S). **Elemental analysis** calculated for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>SRuCl<sub>2</sub>: C, 44.54; H, 4.77; N, 8.66; S, 6.60%. Found: C, 44.22; H, 4.82; N, 7.69; S, 6.07%. **ESI-MS**: *m/z* 414 (100%, [M-H-2Cl]<sup>+</sup>). **M.p.** 177-181 °C.



Synthesis of ( $\eta^6$ -C<sub>6</sub>H<sub>5</sub>C<sub>3</sub>H<sub>6</sub>COOH)Ru(II) monothiosemicarbazone

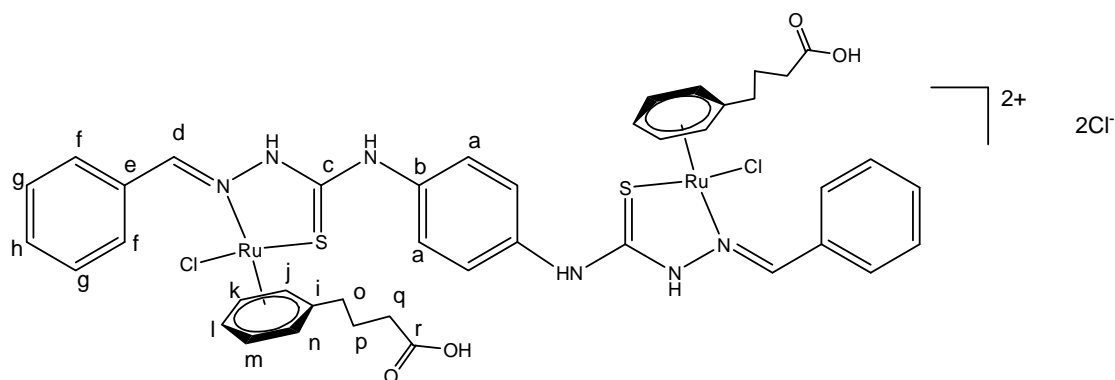
50

Benzaldehyde monothiosemicarbazone (0.105 g, 0.584 mmol) was dissolved in DCM (20 cm<sup>3</sup>). [Ru( $\eta^6$ -C<sub>6</sub>H<sub>5</sub>C<sub>3</sub>H<sub>6</sub>COOH)( $\mu$ -Cl)Cl]<sub>2</sub> (0.196 g, 0.292 mmol) was added and the dark orange mixture stirred for 10 hours at room temperature. After this period, the solid obtained was filtered, washed with diethyl ether and dried under vacuum giving rise to a red powder (0.225 g, 75%). **<sup>1</sup>H NMR** (400.200 MHz, CD<sub>3</sub>OD-*d*<sub>4</sub>): ( $\delta$ , ppm) 1.81 (2H, qn, H<sub>n</sub>); 2.37 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.14, H<sub>o</sub>); 2.44 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 7.09, H<sub>m</sub>); 5.09 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.84, H<sub>h</sub>); 5.17 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.89, H<sub>i</sub>); 5.29 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.72, H<sub>j</sub>); 5.43 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.85, H<sub>i</sub>); 5.57 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.77, H<sub>k</sub>); 7.71 (3H, m, H<sub>e</sub>, H<sub>f</sub>); 8.24 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 5.86, H<sub>d</sub>); 8.81 (1H, s, H<sub>b</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.600 MHz, CD<sub>3</sub>OD-*d*<sub>4</sub>): ( $\delta$ , ppm) 24.36 (C<sub>n</sub>); 32.13 (C<sub>m</sub>); 32.48 (C<sub>o</sub>); 81.25 (C<sub>k</sub>); 83.14 (C<sub>l</sub>); 86.65 (C<sub>j</sub>); 88.36 (C<sub>h</sub>); 89.24 (C<sub>i</sub>); 106.25 (C<sub>g</sub>); 128.63 (C<sub>e</sub>); 130.17 (C<sub>d</sub>); 131.77 (C<sub>f</sub>); 133.47 (C<sub>c</sub>); 162.35 (C<sub>b</sub>); 174.98 (C<sub>p</sub>); 177.82 (C<sub>a</sub>). **FT-IR** (KBr): ( $\nu_{max}$ , cm<sup>-1</sup>) 1698 (C=O); 1601 (C=N); 871 (C=S). **Elemental analysis** calculated for C<sub>18</sub>H<sub>21</sub>O<sub>2</sub>N<sub>3</sub>SRuCl<sub>2</sub>: C, 41.94; H, 4.11; N, 8.15; S, 6.22%. Found: C, 41.25; H, 4.13; N, 6.46; S, 5.51%. **ESI-MS**: *m/z* 444 (100%, [M-H-2Cl]<sup>+</sup>). **M.p.** decomposes at 163 °C.

7.6.2. Synthesis of dinuclear ( $\eta^6$ -arene)ruthenium(II) TSC complexesSynthesis of ( $\eta^6$ -*p*-cymene)Ru(II) dithiosemicarbazone

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Benzene-1,4-dithiosemicarbazone (0.114 g, 0.263 mmol) was added to MeOH (25 cm<sup>3</sup>). To this, [Ru( $\eta^6$ -*p*-cymene)( $\mu$ -Cl)Cl]<sub>2</sub> (0.1618 g, 0.264 mmol) was added and the dark orange suspension stirred for 24 hours at room temperature. After the 24 hour period a clear red solution is obtained. The solvent was evaporated and DCM added to the contents of the flask. Diethyl ether (90 cm<sup>3</sup>) was added to precipitate an orange product. The product was washed with diethyl ether which was removed *in vacuo* yielding an orange powder (0.187 g, 68%). <sup>1</sup>H NMR (400.200 MHz, CDCl<sub>3</sub>-*d*): (δ, ppm) 1.09 (6H, d, <sup>3</sup>J<sub>H-H</sub> = 6.74, H<sub>i</sub>); 1.15 (6H, d, <sup>3</sup>J<sub>H-H</sub> = 6.82, H<sub>j</sub>); 2.07 (6H, s, H<sub>r</sub>); 2.64 (2H, m, H<sub>k</sub>); 4.69 (2H, m, H<sub>p</sub>); 4.82 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 5.39, H<sub>m</sub>); 4.92 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 4.86, H<sub>q</sub>); 5.41 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 5.67, H<sub>n</sub>); 7.58 (12H, m, H<sub>a</sub>, -NNH, H<sub>g</sub>, H<sub>h</sub>); 8.19 (4H, d, <sup>3</sup>J<sub>H-H</sub> = 6.44, H<sub>f</sub>); 9.04 (2H, s, H<sub>d</sub>); 10.66 (2H, s, -C<sub>b</sub>NH). <sup>13</sup>C{<sup>1</sup>H} NMR (100.600 MHz, CDCl<sub>3</sub>-*d*): (δ, ppm) 18.65 (C<sub>r</sub>); 21.40 (C<sub>i</sub>); 23.14 (C<sub>j</sub>); 30.76 (C<sub>k</sub>); 81.91 (C<sub>m</sub>); 82.66 (C<sub>q</sub>); 87.93 (C<sub>n</sub>); 88.88 (C<sub>p</sub>); 103.97 (C<sub>o</sub>); 124.35 (C<sub>a</sub>); 124.48 (l); 128.90 (C<sub>g</sub>); 130.61 (C<sub>f</sub>); 131.80 (C<sub>h</sub>); 133.49 (C<sub>e</sub>); 135.28 (C<sub>b</sub>); 161.45 (C<sub>d</sub>); 175.97 (C<sub>c</sub>). FT-IR (KBR): (ν<sub>max</sub>, cm<sup>-1</sup>) 1614 (C=N); 869 (C=S). **Elemental analysis** calculated for C<sub>42</sub>H<sub>48</sub>N<sub>6</sub>S<sub>2</sub>Ru<sub>2</sub>Cl<sub>4</sub>·½CH<sub>2</sub>Cl<sub>2</sub>: C, 46.94; H, 4.54; N, 7.73; S, 5.90%. Found: C, 46.43; H, 4.69; N, 7.05; S, 5.78%. **ESI-MS**: *m/z* 945 (85%, [M-5H-4Cl+2Na]<sup>+</sup>). **M.p.** decomposes at 224 °C.

Synthesis of  $(\eta^6\text{-C}_6\text{H}_5\text{C}_3\text{H}_6\text{COOH})\text{Ru(II)}$  dithiosemicarbazone

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Benzene-1,4-dithiosemicarbazone (0.082 g, 0.189 mmol) was added to MeOH (25 cm<sup>3</sup>). To this,  $[\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{C}_3\text{H}_6\text{COOH})(\mu\text{-Cl})\text{Cl}]_2$  (0.122 g, 0.182 mmol) was added and the orange suspension stirred for 16 hours at room temperature. After this time, a clear deep red solution is observed. The solution was filtered by gravity into a round-bottom flask and the solution was concentrated to less than one-quarter of the original volume. Excess diethyl ether was added to the remaining solution to precipitate the product. The orange solid was filtered using a Hirsch funnel, washed with diethyl ether and dried *in vacuo* yielding an orange powder (0.179 g, 89%). **<sup>1</sup>H NMR** (400.200 MHz, CD<sub>3</sub>OD-*d*<sub>4</sub>): (δ, ppm) 1.81 (4H, qn, H<sub>p</sub>); 2.30 (8H, m, H<sub>o</sub>, H<sub>q</sub>); 4.99 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 5.73, H<sub>j</sub>); 5.04 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 6.14, H<sub>n</sub>); 5.13 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 5.63, H<sub>l</sub>); 5.28 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 6.06, H<sub>k</sub>); 5.40 (2H, t, <sup>3</sup>J<sub>H-H</sub> = 5.87, H<sub>m</sub>); 7.42 (4H, s, H<sub>a</sub>); 7.57 (6H, m, H<sub>g</sub>, H<sub>h</sub>); 8.14 (4H, d, <sup>3</sup>J<sub>H-H</sub> = 5.48, H<sub>f</sub>); 8.90 (2H, s, H<sub>d</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR** (100.600 MHz, CD<sub>3</sub>OD-*d*<sub>4</sub>): (δ, ppm) 25.35 (C<sub>p</sub>); 33.19 (C<sub>o</sub>); 33.60 (C<sub>q</sub>); 82.66 (C<sub>m</sub>); 84.69 (C<sub>n</sub>); 88.06 (C<sub>l</sub>); 89.52 (C<sub>j</sub>); 90.19 (C<sub>k</sub>); 100.94 (C<sub>i</sub>); 125.10 (C<sub>a</sub>); 129.68 (C<sub>g</sub>); 131.36 (C<sub>f</sub>); 132.59 (C<sub>h</sub>); 135.22 (C<sub>e</sub>); 137.00 (C<sub>b</sub>); 164.86 (C<sub>d</sub>); 170.61 (C<sub>r</sub>); 174.77 (C<sub>c</sub>). **FT-IR** (KBr): ( $\nu_{\text{max}}$ , cm<sup>-1</sup>) 1727 (C=O); 1600 (C=N); 845 (C=S). **Elemental analysis** calculated for C<sub>42</sub>H<sub>44</sub>N<sub>6</sub>S<sub>2</sub>O<sub>4</sub>Cl<sub>4</sub>Ru<sub>2</sub>: C, 45.65; H, 4.01; N, 7.61; S, 5.80%. Found: C, 45.60; H, 4.49; N, 7.03; S, 5.67%. **ESI-MS**: *m/z* 495 (100%, [M-2Cl-CO<sub>2</sub>]<sup>2+</sup>). **M.p.** decomposes at 158 °C.

## 7.7. X-ray crystallography

### 7.7.1. X-ray data of compound 20

$C_{18}H_{27}N_6OSPPd$ ,  $M = 512.89 \text{ g mol}^{-1}$ , Triclinic,  $P\bar{1}$ ,  $a = 9.4573(4)$ ,  $b = 12.3185(5)$ ,  $c = 18.6788(7) \text{ \AA}$ ,  $\alpha = 92.746(2)$ ,  $\beta = 104.015(2)$ ,  $\gamma = 94.481(2)^\circ$ ,  $V = 2099.81(15) \text{ \AA}^3$ ,  $T = 173.2 \text{ K}$ ,  $Z = 4$ . A total of 14900 reflections were collected giving 7684 unique reflections ( $R_{int} = 0.0541$ ) for the compound. Data for the structure was collected on a Nonius Kappa-CCD diffractometer using graphite monochromated  $MoK\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). The temperature was controlled by using an Oxford Cryostream cooling system (Oxford Cryostat). The strategy for the data collections was evaluated using the Bruker Nonius "Collect" program. Data were scaled and reduced using DENZO-SMN software.<sup>14</sup> An empirical absorption correction was applied by using the program SADABS.<sup>15</sup> The structure was solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97<sup>16</sup> refining on  $F^2$ . Packing diagrams were produced using the program PovRay and graphic interface X-seed.<sup>17</sup>

### 7.7.2. X-ray data of compound 49

$C_{19}H_{26}Cl_2N_3ORuS$ ,  $M = 516.46 \text{ g mol}^{-1}$ , Monoclinic,  $C2/c$ ,  $a = 16.366(3)$ ,  $b = 11.063(2)$ ,  $c = 26.328(5) \text{ \AA}$ ,  $\alpha = 90.00$ ,  $\beta = 104.21(3)$ ,  $\gamma = 90.00^\circ$ ,  $V = 4621.0(15) \text{ \AA}^3$ ,  $T = 293(2) \text{ K}$ ,  $Z = 8$ . A total of 12730 reflections were collected giving 6097 unique reflections ( $R_{int} = 0.1130$ ) for the compound. The data were measured using a Stoe Image Plate Diffraction system using graphite monochromated  $MoK\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). The structure was solved by direct methods using the program SHELXS-97.<sup>16</sup> The refinement and all further calculations were carried out using SHELXL-97.<sup>16</sup>

## 7.8. Biological studies

### 7.8.1. *In vitro* cytotoxicity studies

The compounds were evaluated against the oesophageal cancer cell-line, *WHCO1*. These cells were derived from biopsies of primary oesophageal

squamous cell carcinomas (oesophageal cancer cells of South African origin)<sup>18</sup> and kindly provided by Professor Rob Veale (University of Witwatersrand, South Africa). IC<sub>50</sub> determinations were carried out using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. 3000 cells were seeded per well in 96-well plates. Cells were incubated at 37 °C under 5% CO<sub>2</sub> (24 hours), after which aqueous DMSO solutions of each compound (10 µl, with a constant final DMSO concentration of 0.2%) were plated at various concentrations. After a 48 hour incubation period, MTT (10 µl) solution was added to each well. After further 4 hour incubation, solubilisation solution (100 µl) was added to each well, and plates were incubated overnight. Plates were read at 595 nm using a BioTek microplate reader.

### 7.8.2. *In vitro* antiparasitic studies

Cultures of *T. vaginalis* T1 strain were grown in 5 ml completed TYM Diamond's media in a 37 °C incubator for 24 hours. 100 mM stocks of the compounds were made by dissolving in DMSO and these were screened against the T1 strain of *T. vaginalis*. Untreated and inoculated cells with 5 µl DMSO were used as the controls. 5 µl of the 100 mM stock solutions of the compounds were further inoculated to a final concentration of 100 µM. Results were calculated based on counts utilising a hemocytometer after a 24 hour period. For IC<sub>50</sub> values, the 100 mM stock solutions were added at 80 µM, 60 µM, 40 µM and 20 µM final concentrations.

### 7.9. References

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