

# Synthesis and Characterization of Novel Iminopyridinium Platinum (II) Coordination Complexes as Potential Chemotherapeutic Drugs.

By

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## Abbreviations

$\delta$	Chemical shift
$^{\circ}\text{C}$	Degrees Celsius
$^{13}\text{C}\{^1\text{H}\}$	Proton-decoupled $^{13}\text{C}$
$^1\text{H}$	Proton
br	Broad
$\text{CDCl}_3$	Deuterated chloroform
coe	Cyclooctene
CTR1	Copper transporter protein
DNA	Deoxyribonucleic acid
EA	Elemental Analysis
FT-IR	Fourier Transform – Infrared
Hz	Hertz
IR	Infrared
J	Coupling constants
m	Multiplet
mg	Milligram(s)
Min	Minutes
mL	Millilitre (s)
mm	Millimoles
mM	Millimolar
mp	Melting point
NMR	Nuclear magnetic resonance
OCT	Organic cation transporter
ov	Overlapping
ppm	Parts per million
q	Quartet
RT	Room temperature
s	Singlet
t	Triplet

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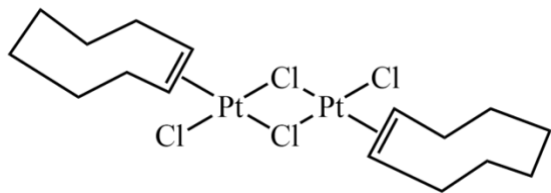
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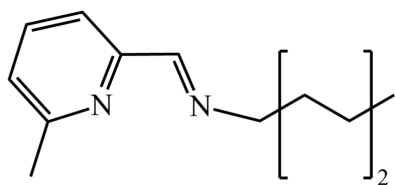
## List of Compounds and Metal Complexes

**Table 1:** Synthesized starting material, ligands, and complexes.



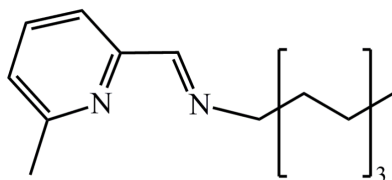
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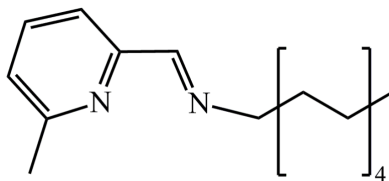
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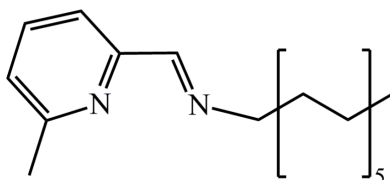
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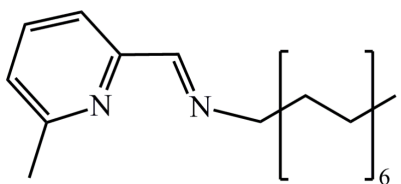
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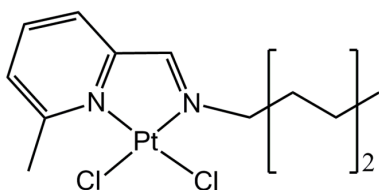
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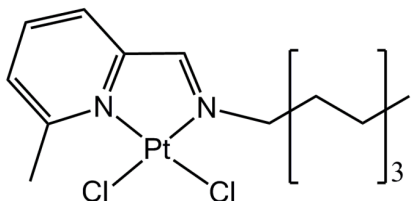
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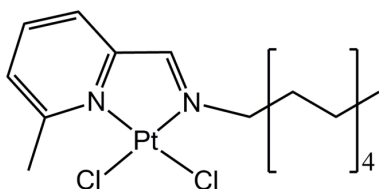
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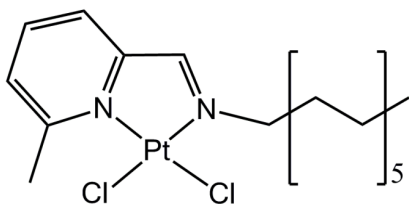
**Dichloro-[(6-methylpyridin-2-yl)methylene]octan-1-amine platinum (II) C2**

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**Dichloro-[(6-methylpyridin-2-yl)methylene]decan-1-amine platinum (II) C3**

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**Dichloro-[(6-methylpyridin-2-yl)methylene]dodecan-1-amine platinum (II) C4**

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## **Abstract**

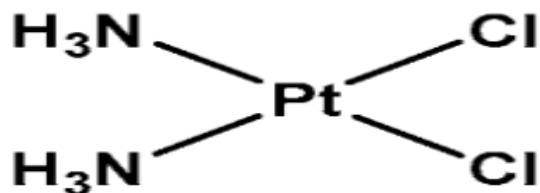
This study focuses on the synthesis and characterization of five novel iminopyridinium ligands using an appropriate alkyl amine and 6-methyl-2-pyridinecarboxaldehyde. Synthesis of four platinum (II) complexes were achieved by chelating the appropriate ligand to  $[\text{PtCl}_2(\eta^2\text{-coe})]_2$  (coe = cis-cyclooctene). The ligands were characterized using  $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$  nuclear magnetic resonance (NMR) and Fourier-Transformed Infrared spectroscopy (FT-IR). The complexes were characterized using  $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$  NMR and FT-IR spectroscopy and melting point analysis. An X-ray diffraction study was performed on dichloro-[(6-methylpyridin-2-yl)methylene]hexan-1-amine] platinum (II). Elemental analysis was also conducted on **C1** and **C2**, however the data was inconclusive. Prospective work includes acquiring a more conclusive elemental analysis on all complexes and conducting bioactivity and cytotoxicity test on the synthesized complexes.

## **Introduction**

### *Cancer*

Cancer is a disease characterized by the uncontrollable proliferation and anomalous motility of somatic cells due to abnormalities in the genetic expression.<sup>1</sup> These genetic mutations can either occur naturally or via prolonged exposure to radiation, carcinogens, or social habits such as pollution, poor diet or smoking.<sup>1,2</sup> Cancer occurs based on the genetic dominance of oncogenes or the inactivation of tumor suppressor genes (TSGs).<sup>1</sup> The normal function of TSGs include homeostatic control of apoptosis and regulation of the cellular cycle. In the events where both alleles of TSGs are recessive, they lose the capability to suppress proliferation. This genetic expression is responsible for the hereditary form of cancer.

Due to the variety of mechanistic pathways in which cancer can develop, it is estimated that there was approximately 1600 deaths per day due to cancer in the United States of America.<sup>3</sup> In addition to the severe and debilitation physiological symptoms of cancer, it also has a widespread financial and social impact. In 2012, Canada spent over 7.5 billion dollars on cancer care.<sup>4</sup> The social impacts of cancer include feelings of isolation, issues with employment, strains on relationships and decreased ability to engage in certain forms of leisure activities.<sup>5</sup> Each patient and their social networks have different experiences, but the commonality is often times a decrease in the quality of life. It is important to note that the impacts of cancer vary based on many factors including the age, health, financial status, social network of the patient and the type and stage of the cancer. Due to the prevalence, physiological, social, and financial implications on patients, the search for more detailed pre-emptive measures and treatment options which can alleviate the negative side-effects on the patient's health is becoming increasingly important.

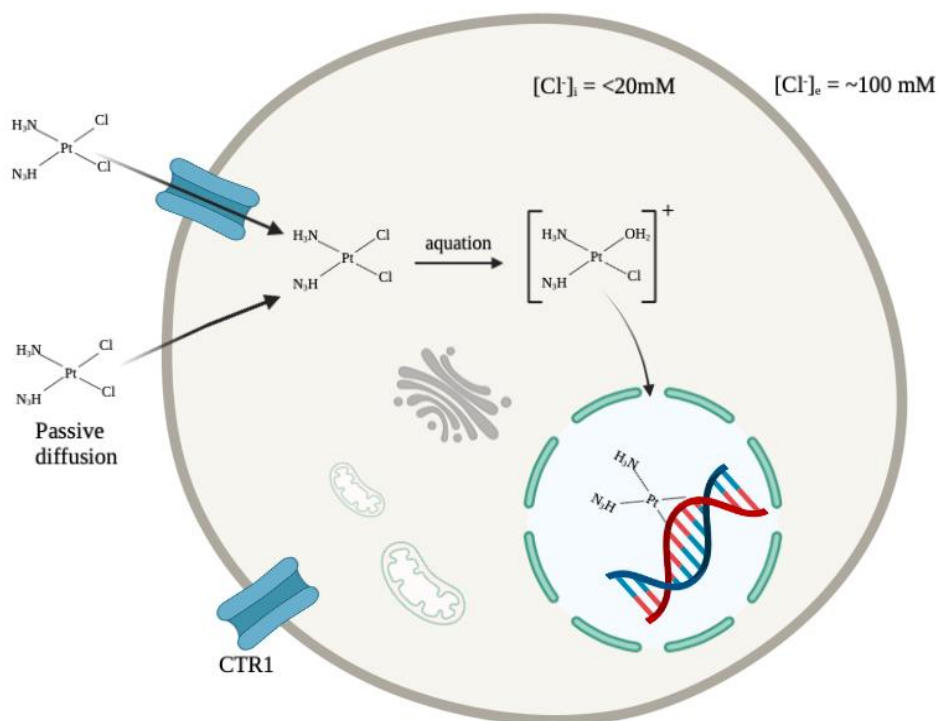


**Figure 1:**Chemical structure of cisplatin.

Metal complexes have been used in medicine for many years. The most successful treatment for cancer is the use of a platinum coordination complex called cisplatin (Figure 1).<sup>6,7</sup> Cisplatin (*cis*-diamminedichloroplatinum) was first synthesized in the early 1840's by Michele Pyrone. Cisplatin is a square planar, d<sup>8</sup> coordination complex which has two amine groups and two chlorine atoms coordinated to a central platinum atom.<sup>7-10</sup> In the 1960s, Rosenberg was examining the implications of electric fields on the cellular division of *Escherichia coli* (*E. coli*) bacteria. For this study he placed the bacteria in an ammonium buffer solution and applied an electrical current using platinum electrodes.<sup>11</sup> The preliminary conclusion of this experiment was that the electrical field did inhibit further cell division in *E. coli*. However, future studies showed that the *cis*-diamminedichloroplatinum was synthesized and this was the molecule responsible for the inhibition of cellular division in *E. coli*. Rosenberg theorized that cisplatin could be used to inhibit the proliferation of cancerous cells. This theory was based on the knowledge that the cellular division observed in *E. coli* exhibits similar characteristics to the rapid growth of cancer cells.<sup>11</sup> The complex underwent clinical trials and was approved in 1978 by the Food and Drug Administration (FDA), as an anticancer drug.<sup>6</sup>

### *Cisplatin Binding to Biomolecules*

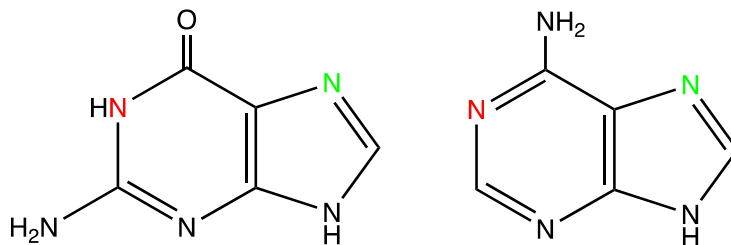
Cisplatin is administered to patients in an intravenous saline solution.<sup>8,12,13</sup> The chloride composition of the blood stream is relatively high with concentrations averaging >100 mM in the plasma.<sup>14</sup> Due to the high concentration, the propensity of cisplatin to lose the chloride ligands is extremely low. Therefore, cisplatin will retain its neutrality and chemical composition in the blood stream. Then cisplatin is transported into tumor cells by either simple passive diffusion across the plasma membrane or by facilitated diffusion through membrane proteins such as copper transporter protein, CTR. Intracellular chloride concentration is between >20 mM (varies depending on the cell type).<sup>14</sup> The intra-cellular chloride concentration is maintained by the electroneutral cation-chloride co-transporters, which are energized by the sodium-potassium pump. Once cisplatin enters the cytoplasm, it undergoes aquation as chloride ligands are replaced with water ligands, facilitated by low cytosolic chloride concentration and resulting in the formation of mono-aquated or diaquated species as seen in Figure 2.<sup>7,9,13</sup>



**Figure 2:** Schematic diagram of the mechanism of action of cisplatin.

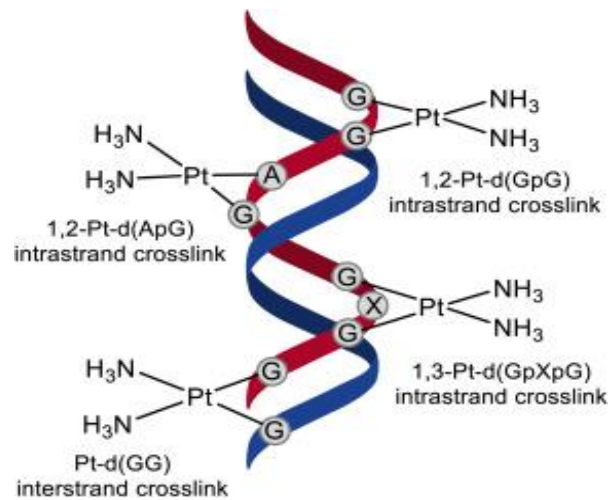
The hydrolyzed cisplatin molecules are converted to cationic molecules which are more electrophilic and can react with nucleophilic biomolecules such as proteins and nucleic acids.<sup>15,16</sup> Even though the hydrolyzed cisplatin can bind to other biomolecules, the main target is nucleophilic sites located on DNA. Cisplatin can coordinate to the nitrogenous bases in DNA resulting in the formation of cisplatin-DNA adducts with the N7 position of the purine bases adenine and guanine.<sup>6,8,13,15–17</sup> Coordination to the N7 position of guanine is more favourable than coordination to any other nitrogen atom in guanine and adenine. The N1 atom of guanine is protonated compared to the N1 in adenine which has a lone pair. The delocalization of the electron density present at the N7 position is reduced by the presence of the proton at the N1 position in guanine.<sup>15</sup> This causes increased localization of electron density at the N7 position making it a stronger nucleophilic site for the binding of cisplatin. The presence of the lone pair at the N1

position of adenine gives the opposite effect resulting in reduced nucleophilicity.<sup>15</sup> The N1 and N7 of the two purine bases is seen in Figure 3.



**Figure 3:** Chemical structures of the purine bases of DNA: guanine (left) and adenine (right). The N1 atoms are red and the N7 atoms are green.

The platinum atom can react with purine bases on the same strand to form an intra-strand crosslink, or it can coordinate to purine bases on opposite strands resulting in the formation of inter-strand crosslinks as seen in Figure 4.<sup>18</sup> The 1,2-intrastrand crosslink occurs when adjacent purine bases are coordinated by a cisplatin molecule. It is the most common and occurs approximately 80% of the time, while the 1,3-intrastrand crosslink is rarer, occurring less than 10% of the time.<sup>19</sup> The inter-strand crosslinks account for ~2% of crosslinks and occur when the platinum coordinates to purine bases on opposite strands.<sup>19</sup> The implications of the formation of crosslinks in the DNA strand include the formation of distortions or kinks in the helical molecule. This results in major interferences in replication, transcription, and it can hinder DNA repair.<sup>20</sup> If a cell is unable to repair the DNA distortion, it leads to damage of the genetic material and eventual apoptosis of the tumor cells. The cellular pathways that result in apoptosis are considered intrinsic or extrinsic.<sup>15,18,21</sup> Cisplatin induces cell death via the extrinsic pathway that is initiated when ligands bind to tumor necrosis factors and results in the formation of death-inducing signalling complex.<sup>6,18</sup>



**Figure 4:** Formation of intra-stand crosslinks between cisplatin and DNA.<sup>6</sup>

### *Toxicity of Cisplatin*

Cisplatin has proven effective against many different types of cancers such as testicular, ovarian, colon, lung, and some sarcomas.<sup>9,15,16,20,22</sup> It is sometimes used to treat hematological cancers in children.<sup>12</sup> Despite its effectiveness, cisplatin is known for its adverse side effects. These include but are not limited to nephrotoxicity, ototoxicity, hepatotoxicity, neurotoxicity, alopecia, and anorexia.<sup>6,15</sup> It is estimated that a cancer patient being treated with any of the platinum containing anti-cancer drugs may experience any of the approximately 40 known side effects.<sup>13</sup> Cytotoxicity of cisplatin and its derivatives is due to reduced selectivity against cancerous versus normal cells.

The dose limiting side effect of cisplatin is nephrotoxicity. Cisplatin can affect the renal system inducing acute renal failure, hypomagnesemia, hypocalcaemia, erythropoietin deficiency, abnormalities in electrolyte composition etc.<sup>12,18,23</sup> Cisplatin induced nephrotoxicity is seen in up to 90% of all patients.<sup>24</sup> When administered, cisplatin is removed from the circulation by

glomerular filtration and tubular secretion in the kidney.<sup>6,13,15</sup> CTR1 facilitates the transport of cisplatin across cellular membrane is highly expressed in the kidney, and *in vitro* studies showed that downregulation of CTR1 in kidney cells was associated with low cisplatin uptake<sup>6,18</sup>. Accumulation of cisplatin in the kidney increases the propensity of chemical interactions with glutathione and the positively charged, aquated cisplatin specie accumulates in negatively charged mitochondria.<sup>6,7,15,18</sup> This results in symptoms such as fluctuations in ion concentration, chronic renal failure, hypocalcaemia, and renal tubular acidosis among other kidney related symptoms.<sup>12</sup>

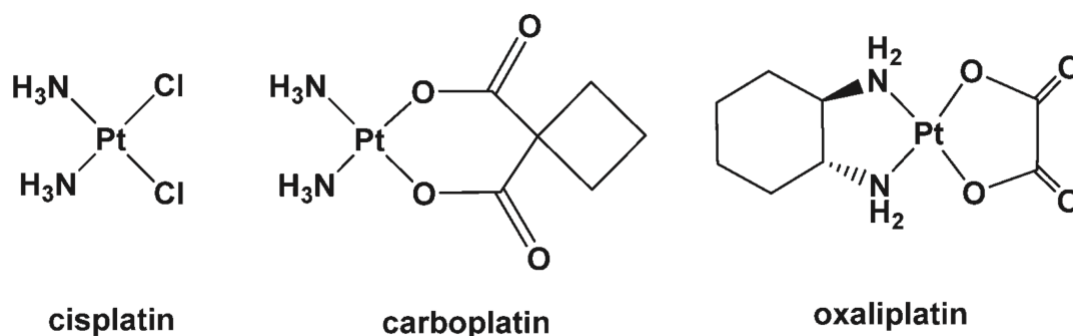
Neurotoxicity is also a very common side effect in cancer patients. It is characterized by issues with the peripheral nervous system such as motor function impairment, convulsions, paraesthesia, and speech impediments.<sup>15</sup> Cisplatin's main target in the nervous system is the cells of the dorsal root ganglia that are responsible for bringing information from the peripheral nervous system to the spinal cord.<sup>15,21,25,26</sup> Cisplatin can enter sensory neurons via CTR1 and organic cation transporter proteins (OCT2) on dorsal ganglia cells. Cisplatin will bind to the purine bases in the DNA of the dorsal ganglia cells resulting in the formation of kinks in the DNA strand.<sup>6,15</sup>

### *Cisplatin Analogues*

Even though cisplatin has proven effective against various types of cancers, it is limited by its toxic effects on non-target biological processes. Synthesis of cisplatin analogues such as oxaliplatin and carboplatin was done to create cancer drugs that can target a variety of cancer types but also have reduced toxic effects.<sup>6,15,21,27</sup> Cisplatin structure activity relationship (SAR) is built on the fact that the molecule is a square planar, *cis* coordination complex with a platinum centre with a +2 oxidation state. Additionally, the molecule must be charge neutral with two anionic ligands and two amine ligands.<sup>11,28</sup>

The trans isomer of cisplatin (transplatin) has been synthesized and its biological activity tested. It was shown that transplatin was more reactive towards biomolecules and because of this increased rate of reactivity, the administered concentration was depleted before it could react with the target compounds.<sup>29</sup> The high kinetic instability of transplatin has deemed it therapeutically inactive.<sup>19,30</sup> Another important SAR includes the use of labile anionic ligands. If the leaving group is too reactive, there is an increase kinetic instability, and the complex can undergo unfavourable chemical interactions before it reaches the site of action. Additionally, if the leaving group is not reactive, there is a decreased propensity of complex-DNA interactions which governs the mode of action and effectiveness of cisplatin.<sup>29</sup> These SAR are being considered when making new platinum (II) chemotherapeutic drug as the aim is to increase the effectiveness of the drug but decrease the toxicity. This is achieved by altering the leaving groups and the non-leaving groups (in cisplatin it is the amine ligands).

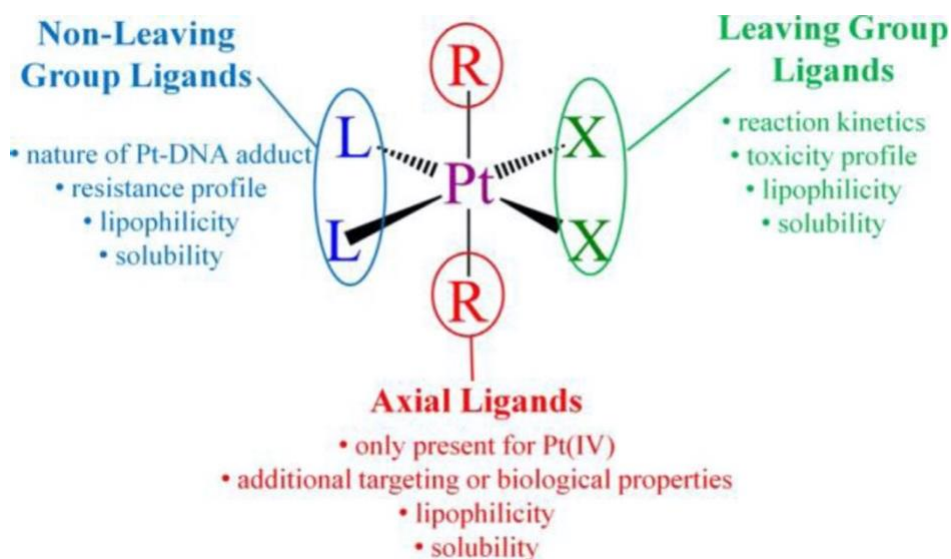
The creation of cisplatin analogues with changes in the leaving group or ligand may result in complexes with greater specificity and fewer side effects.<sup>31</sup> In carboplatin the chloride ligands are replaced with a bidentate 1,1-cyclobutanedicarboxylate ligand. Carboplatin has a reduced toxic effect on various biological systems, has a longer retention half-life and is more stable than cisplatin.<sup>15</sup> In oxaliplatin the carrier ligand is modified to be a bidentate 1,2-diaminocyclohexane



**Figure 5:** Chemical structure of platinum (II) chemotherapeutic compounds approved globally.<sup>13</sup>

ligand and the leaving group is an oxalate ligand. Oxaliplatin has a higher cytotoxic profile than cisplatin, but one of its advantages is that it produces fewer DNA adducts.<sup>32</sup> Other cisplatin derivatives have been approved for utilization in Japan and China. These are lobaplatin and nedaplatin.<sup>7,9,18,33</sup>

As stated, cisplatin (and by extension its analogues) are all platinum (II) compounds. Research has been conducted to assess the possibility of having anti-cancer platinum (IV) drugs. Platinum (IV) compounds are  $d^6$  octahedral complexes, synthesized from the reaction of a platinum (II) complex and ligands.<sup>34,35</sup> These ligands form the axial position of platinum (IV) complexes. In the presence of cancer cells, the axial ligands can react with nucleophiles and leave.<sup>36</sup> This yields the platinum (II) square planar derivative of the platinum (IV) prodrug. Platinum (IV) complexes have far fewer limitations compared to their platinum (II) counterparts, are more stable and less toxic, and are considered acceptable prodrugs.<sup>37</sup> However, their synthesis is challenging.



**Figure 6:** Universal structure of platinum (IV) anti-cancer drugs showing the function of the individual ligands in terms of their structure-activity relations.<sup>38</sup>

## *Ligand and Complex Design*

Modification of the ligands on cisplatin can have will affect the nature of the platinum-DNA adducts and will have a direct correlation with the repair pathways, side-effects, and overall mode of action of the drug.<sup>8</sup> Pyridine-based ring compounds are very widely used in pharmacological applications pertaining to drug design. This heterocyclic ring can occur naturally in compounds such as vitamin B variations, coenzymes such as NADP, NADH and as the precursor to many alkaloids found in plants.<sup>39,40</sup> Approximately 14% of all FDA approved drugs contain a heterocyclic pyridine ring including anti-cancer, anti-diabetic, and anti-inflammatory drugs, among others.<sup>40,41</sup> The desirable characteristics of pyridine rings in medicinal chemistry include their water solubility, high stability, basicity and ability to form hydrogen bonds.<sup>41</sup>

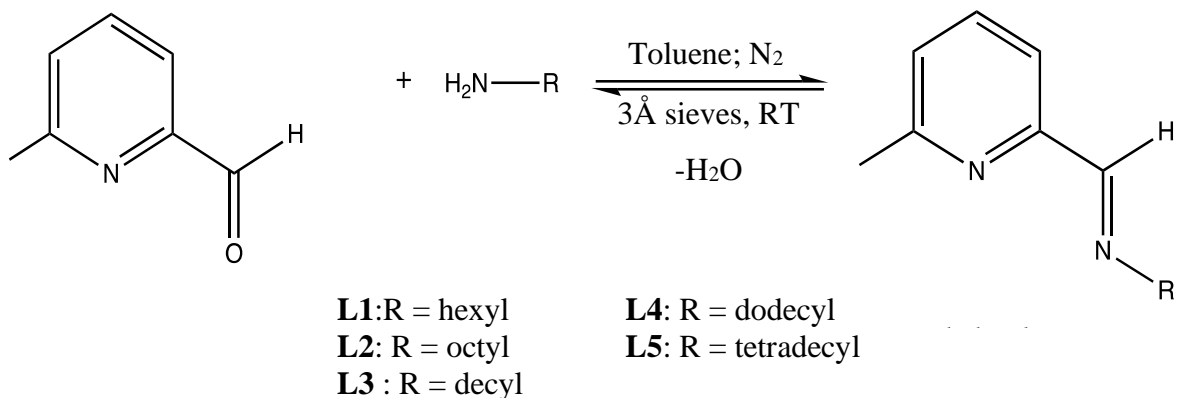
The starting material 6-methyl-2-pyridinecarboxaldehyde has a 2-methylpyridine moiety. 2-Methylpyridine is a stable ligand which is found on picoplatin. Picoplatin is an inorganic platinum (II) chemotherapeutic drug has 2-methylpyridine ligand. This ligand was chosen to increase the steric hindrance around the platinum center which reduces the likelihood of chemical interaction between the molecule and thiol groups.<sup>42</sup> The assumption is that the bioactive properties and the anti-cancer properties of the platinum centre will produce a synergistic effect against cancer cells. Long chain aliphatic R groups were used because alkanes are unreactive and have little bioactivity. The coupled effect of the hydrophobic long alkyl chain and the hydrophilic iminopyridinium platinum portion of the complexes will increase the propensity of the complexes to cross the phospholipid bilayer of cells.

## **Objective**

This study aims to synthesize and characterize a series of novel iminopyridinium ligands, and corresponding iminopyridinium platinum (II) compounds derived from 6-methyl-2-pyridinecarboxaldehyde. This will be a two-step process initiated by the complete synthesis and characterization of the free ligand using 6-methyl-2-pyridinecarboxaldehyde and a long chain aliphatic amine. Characterization of the free ligand will be achieved using FT-IR,  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR. The subsequent step is complexation of the free ligand to a platinum salt. Characterization of these complexes will be achieved using FT-IR,  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectroscopy, melting point analysis, X-ray diffraction, and elemental analysis.

## Results and Discussion

### *Ligand Synthesis and Characterization*



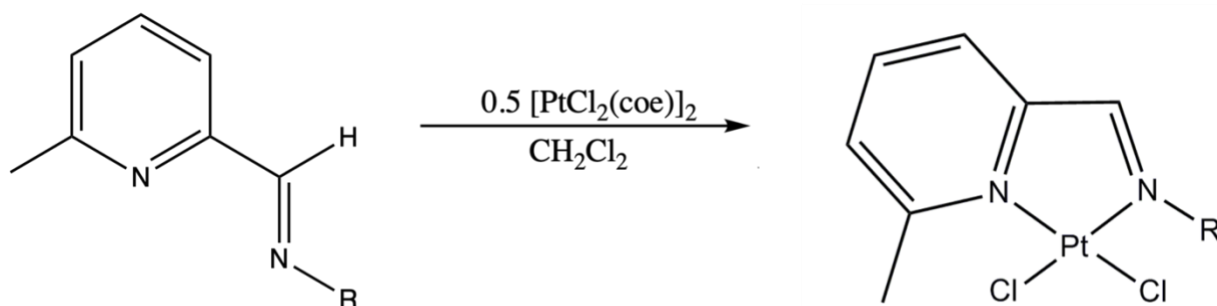
**Scheme 1:** Reaction scheme showing the synthesis of **L1-L5**.

The imines in this study were synthesized via the equimolar reaction of an aldehyde (6-methyl-2-pyridinecarboxaldehyde) and an appropriate amine done in toluene. The reaction mechanism involves the nucleophilic attack of the nitrogen in the amine on the carbonyl carbon of the aldehyde. This is a condensation reaction and water is produced as a by-product. Formation of the imine bond is a reversible reaction and in the presence of oxygen and water the imine bond can be hydrolyzed. Due to the sensitivity of the imine bond, the reaction was conducted in a nitrogen rich atmosphere in a glovebox. To prevent hydrolysis of the imine bond, molecular sieves were added to the reaction to remove water. The addition of the sieves to facilitate water removal resulted in a shift of the equilibrium in favour of the formation of the ligand. Once the reaction is complete, the solvent is removed by vacuum. The relative size of a water molecule is 2.9 Å and 3 Å sieves were used.<sup>43</sup> The size of the sieves was large enough to soak up water molecules and not the solvent, starting material or the iminopyridinium product.

All the ligands that were synthesized were characterized using multinuclear NMR and FT-IR spectroscopy. Since all the ligands synthesized were oily liquids, melting point data was not acquired. Formation of the ligands were confirmed when the peak at 10 ppm resulting from the  $\alpha$  to nitrogen bond (HC-N) in the amine must shift upfield to 8.3 ppm. This peak corresponds to the imine peak (C(H)=N). This peak occurred at 8.34 – 8.35 in **L1-L5**.

FT-IR spectroscopy data was also used to confirm the formation of the imine bond in the ligands. The imine peak for similar complexes have been communicated at  $\sim 1600\text{ cm}^{-1}$  according to other literature.<sup>17</sup> The FT-IR spectra of the isolated ligands showed imine peaks at  $\sim 1650\text{ cm}^{-1}$ . The ligands that were isolated and deemed pure, based on their spectroscopic data, were utilized in the synthesis of the iminopyridinium platinum complexes.

*Iminopyridine platinum (II) complexes: synthesis and characterization*



**C1:** R= hexyl                      **C3:** R= decyl  
**C2:** R= octyl                      **C4:** R= dodecyl

**Scheme 2:** Reaction scheme for the synthesis of the complexes **C1-C4**.

Isolated ligands were reacted with  $\text{Pt}_2[(\text{Cl}_2\text{coe})_2]$  in a 2:1 ratio using dichloromethane as the solvent. The reaction mixture was allowed to stir at room temperature for over 18 hours. Stirring the reaction had many benefits including keeping the concentration and temperature in various parts of the reaction vessel homogenous. Additionally, the solution was stirred to increase

the rate of complexation due to increases in chemical interactions. The reaction was carried out in the nitrogen rich atmosphere of a glovebox to prevent hydrolysis of the ligand before the reaction could proceed to completion. Once the reaction was completed, the reaction mixture was removed from the glovebox and the solvent and by-products removed under vacuum. The yield of the complexes ranged from 53-98%. There was a decrease in yield as the length of the aliphatic chain increased. This was probably due to a decrease in the polarity of the compound. During the clean-up stage, the partitioning to hexane could be greater resulting in reduced yield.

The complexes were characterized using melting points, elemental analysis (EA), x-ray crystallography, multinuclear NMR, and FT-IR spectroscopy. The  $^1\text{H}$  NMR spectra of the complexes had two characteristics that confirmed the formation of the platinum complexes. The first defining feature of the  $^1\text{H}$  NMR is the down-field shift of the  $\text{sp}^2$  imine peak from  $\sim 8.3$  ppm to  $\sim 8.8$  ppm influenced by complexation of the platinum. This de-shielding effect is seen in other studies that have attempted complexation of a ligand to a platinum centre.<sup>17</sup> The second defining feature was the presence of platinum satellite peaks at  $\sim 9.0$  ppm and  $\sim 8.6$  ppm. The coupling constant was approximately 88 Hz, which is consistent with hydrogen-platinum coupling constant in other iminopyridinium compounds.

The presence of those two defining peaks and the lack of the cis-cyclooctene peak at 5.6 ppm, proved that the complexes were pure. Although the cis-cyclooctene (coe) present on the platinum salt is soluble in hexane, on several occasions the coe was retained in the solid despite removal under vacuum. To achieve a pure compound, the complexes were washed in hexane and the solvent and residual coe removed under vacuum. This proved that the complexes were soluble in polar solvents and solubility was achieved in solvents such as dichloromethane, toluene, and acetone.

The  $^{13}\text{C}\{^1\text{H}\}$  NMR of the ligands showed the various chemical environments of the carbons. All the ligands have six  $\text{sp}^2$  hybridized carbons. Five of the  $\text{sp}^2$  carbons originate from the pyridine ring and the additional  $\text{sp}^2$  carbon is the carbon used to form the imine bond. The imine peak in **L1-L5** was consistently seen at 162.0 ppm. The only difference in the ligands is the length of the alkyl chain. The fact that the imine peak did not change, suggests that the alkyl chain does not influence the chemical shift. The imine peak in the complexes were consistently at 169 ppm. This showed a slight downfield shift from the imine peak in the ligand suggesting that the platinum center is a weak electron withdrawing group. FT-IR spectra of the platinum complexes all had a medium peak at 1603-1604  $\text{cm}^{-1}$ . This peak corresponds to the carbon-nitrogen double bond in the imine. This peak showed a 2.8% difference in the IR peak observed in the ligand, which confirms that platinum binding has a slight implication on the stretch/bend motion of the imine peak.

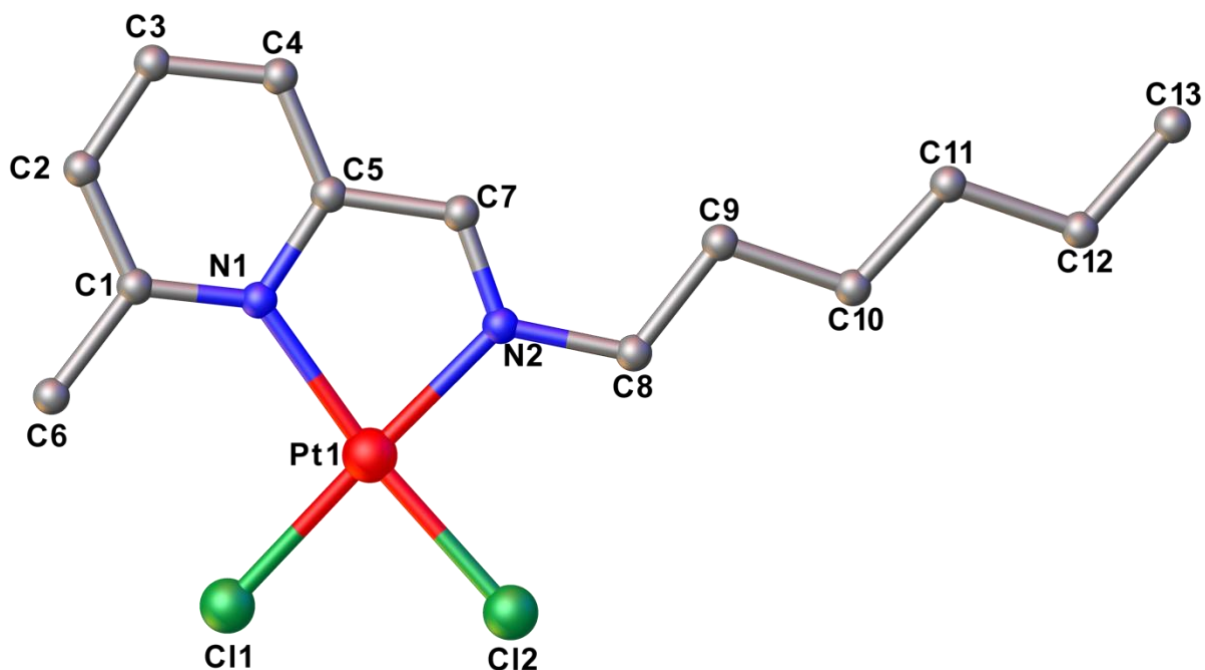
### *Elemental Analysis*

Once the solutions were synthesized and their individual purity confirmed using spectroscopical methods, they were cleaned and sent for elemental analysis (EA). The calculated analysis was done using the ChemDraw software.<sup>23</sup> EA was only conducted for **C1** and **C2**. According to EA data, the **C1** and **C2** were not completely pure and had solvent impurities present. Analysis of **C1** showed that it contained approximately 0.5  $\text{H}_2\text{O}$  and 1.5 DCM molecules per pure solid and analysis of **C2** showed it contained one DCM molecule. This was the lowest ratio of solvent that produced a variation less than 0.5%. This was deemed acceptable as DCM was the solvent utilized in synthesis and clean-up of both molecules and the water could have been introduced from the atmosphere or from solvents used. Fresh samples of **C1** and **C2** were

synthesized and kept in a desiccator under vacuum to ensure complete solvent removal. New EA data was not available at the time of writing.

### *X-ray crystallography*

An x-ray diffraction study was done on the crystals obtained for **C1**. The crystals were grown in a saturated solution of dichloromethane and hexane and stored in at 5°C. This was done to confirm the solid-state structure and to analyze other physical characteristics of the complex. The iminopyridinium ligand coordinated to the platinum complex by a bidentate chelation. The ligand coordinated to the platinum via the nitrogen on the pyridine chain and the imine nitrogen. This is evidenced by the bond angles: N(1)-Pt(1)-N(2), N(1)-Pt(1)-Cl(1), N(2)-Pt(1)-Cl(2) and Cl(1)-Pt(1)-Cl(2) which corresponds to values of 80.50(10)°, 101.68(7)°, 92.77(7)° and 85.63(3)° respectively. This resulted in a distorted square planar geometry around the platinum atom, as demonstrated by the sum of the angles around the bond to be 360.54(27)° and similar literature reported data with similar complexes.<sup>17,45</sup>



**Figure 7:** Molecular structure of dichloro-[(6-methylpyridin-2-yl)methylene]1-hexanamine]platinum (II) **C1**.

The bond angles and length in **C1** were also analyzed. The bond lengths between nitrogen and platinum were 2.071(2)Å and 2.003Å, with the Pt(1)-N(2) bond length being shorter. The Pt(1)-N(2) is notably shorter because the platinum is bonded to the imine nitrogen. The bond angle formed between N(1)-Pt(1)-N(2) is influenced by the chelation of the bidentate iminopyridine ligand, which reduced the size of the bond angle. The crystallographic data also confirmed the carbon-nitrogen bond at C7-N2 is a double bond because the bond length was similar to other C=N reported in the literature.<sup>17,45,46</sup> The bond angle of 1.287Å is like other imine bond lengths reported in similar literature associated with platinum pyridinecarboxaldehydes.<sup>17</sup>

The crystal structure confirmed that the synthesized complex is an analogue of cisplatin. It also confirmed that the two labile chloride ligands were retained during synthesis. Based on the structure of the complex it can be assumed that the complex would have similar structure-activity relationships to cisplatin.

**Table 2:** Bond distances in angstroms (Å) for C1.

<b>Bond</b>	<b>Length (Å)</b>	<b>Bond</b>	<b>Length (Å)</b>
N(1)-Pt(1)	2.071 (2)	N(2)-C(8)	1.472 (4)
N(1)-C(1)	1.357 (4)	C(3)- C(4)	1.386 (5)
N(1)-C(5)	1.373 (4)	C(4) – C(5)	1.385 (4)
Pt(1)- Cl(1)	2.3003 (8)	C(5)-C(7)	1.445 (4)
Pt(1)-N(2)	2.003 (2)	C(8)-C(9)	1.518 (4)
Pt(1)-Cl(2)	2.2856 (7)	C(9)-C(10)	1.525 (4)
C(1)-C(2)	1.399 (4)	C(10)-C(11)	1.525 (4)
C(1) – C(6)	1.498 (4)	C(11)-C(12)	1.523 (5)
C(2)-C(3)	1.376 (5)	C(12)-C(13)	1.521 (5)
N(2)-C(7)	1.287 (4)		

**Table 3:** Crystallographic data collection parameters for dichloro-[(6-methylpyridin-2-yl)methylene]1-hexanamine]platinum (II) (C1).

<b>Bond</b>	<b>Length (Å)</b>
Formula	C <sub>13</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> Pt
Molecular Weight	470.30
Temperature (K)	125.0
Crystal System	monoclinic
Space group	P2 <sub>1</sub> /c
a (Å)	7.6226 (2)
b (Å)	21.1353 (7)
c (Å)	9.5290 (3)
a (°)	90
b (°)	105.0230 (10)
g (°)	90
Volume (Å <sup>3</sup> )	1482.71 (8)
Z	4
ρ <sub>calc</sub> (g cm <sup>-3</sup> )	2.107
m (mm <sup>-1</sup> )	9.808
F(000)	896.0
Crystal size (mm <sup>3</sup> )	0.23*0.08*0.05
Radiation	MoKα (λ = 0.71073)
2θ range for data collection (°)	4.828 to 61
Index range	-10 ≤ h ≤ 10, -30 ≤ k ≤ 30, -13 ≤ l ≤ 13
Reflections collected	73085
Independent reflections	4524 [R <sub>int</sub> = 0.0430, R <sub>sigma</sub> = 0.0157]
Data/restraints/parameters	4524/0/165
Goodness-of-fit on F <sup>2</sup>	1.350
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0199, wR <sub>2</sub> = 0.0414
Final R indexes [all data]	R <sub>1</sub> = 0.0262, wR <sub>2</sub> = 0.0473
Largest difference peak/hole (e Å <sup>-3</sup> )	1.74/-1.33

### *Proposed Structure-Activity Relationship*

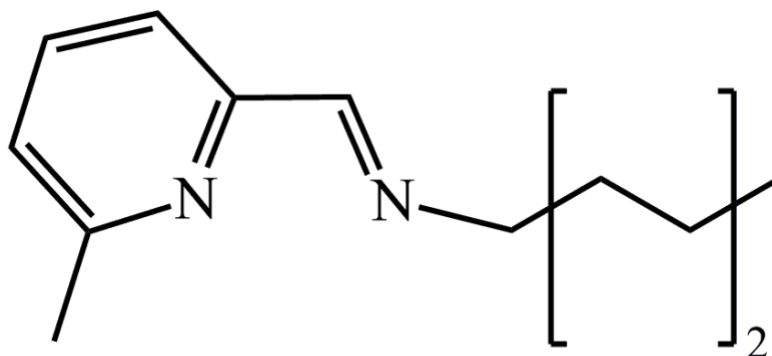
Long chain aliphatic R groups were used because alkanes are unreactive and have little bioactivity. The coupled effect of the hydrophobic long alkyl chain and the hydrophilic iminopyridinium platinum portion of the complexes will increase the propensity of the complexes to cross the phospholipid bilayer of cells. The retention of the labile chloride ligands confirms that **C1** would undergo a similar aquation pathway seen in Figure 2. The crystal structure also corroborates that there was bidentate ligand chelation. It is well known that complexes formed by ligands with an increased denticity are more stable.<sup>47</sup> It can then be theorized that **C1** may be more stable than cisplatin, ignoring any destabilizing potential of the pyridinium ring and the alkyl chain. Stewart et al. (2013)<sup>17</sup> found that increased alkyl chain length intensified the toxicity of the compounds against *Artemia salina* (brine shrimp). They concluded that this may be due to the enhanced penetration of the cellular membrane because of the increasing hydrophobicity and consequent lipophilicity.

## **Experimental**

### *General procedure and methods*

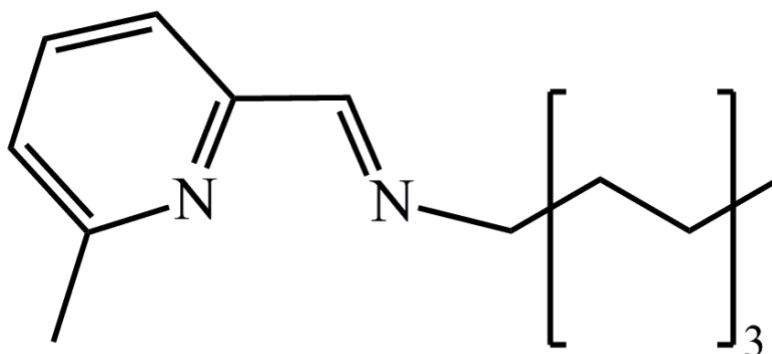
Reagents and solvents required for the following syntheses were acquired from Sigma Aldrich. The starting material, trans-[PtCl<sub>2</sub>(cyclooctene)]<sub>2</sub> ([PtCl<sub>2</sub>(coe)]<sub>2</sub>) was prepared using potassium tetrachloroplatinate and cis-cyclooctene according to a recognized procedure outlined in Shaver et al.<sup>48</sup> Synthesis of the ligands and the complexes were conducted under a nitrogen atmosphere in a MBraun LabMaster glovebox. NMR (nuclear magnetic resonance) spectra was recorded on the Varian Mercury 200 Plus spectrometer and the resulting chemical shifts exhibited by the molecules reported in units of ppm. All chemical shifts were reported with reference to the residual protons present in the deuterated solvent, CDCl<sub>3</sub> at 200 MHz for <sup>1</sup>H and 50.3 for <sup>13</sup>C {<sup>1</sup>H}. Multiplicities were denoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and overlapping (ov). FT-IR spectra were obtained using a Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer and signals reported in units of cm<sup>-1</sup>. Melting point data for the complexes was acquired using a Stuart SP30 mel-temp apparatus. Elemental analyses for carbon, hydrogen and nitrogen were carried out at Centre for Environmental Analysis and Remediation (Saint Mary's University, Halifax, NS). X-ray diffraction study was acquired by Dr. Jason Masuda at Saint Mary's University. The NMR of some of the complexes had peaks at 2.17 and 1.59 ppm due to solvent impurities present in the deuterated chloroform. The presence of the impurity was confirmed by <sup>1</sup>H NMR of just the CDCl<sub>3</sub> which showed these peaks.

Synthesis of (E)-N-((6-methylpyridin-2-yl)methylene)hexan-1-amine **L1**



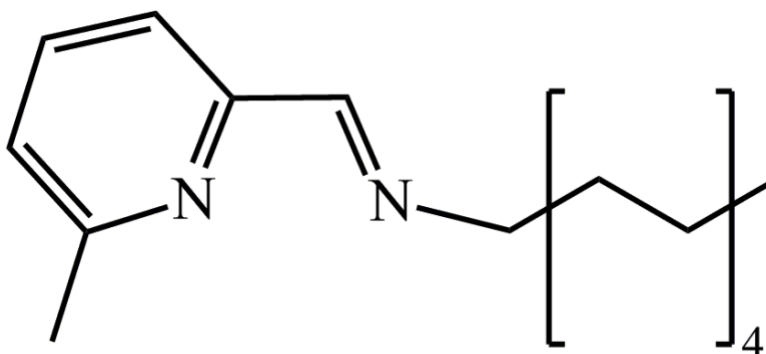
Hexylamine (0.416 g, 4.13 mmol) was bubbled under nitrogen for 5 minutes then capped and brought into a glovebox. 6-Methyl-2-pyridinecarbaldehyde (0.5g, 4.13 mmol) was placed in a scintillation vial. Toluene (10 mL) was added to the hexylamine, and the solution stirred. The hexylamine mixture was added dropwise to the 6-methyl-2-pyridinecarbaldehyde and the mixture stirred. Molecular sieves (3 Å) were added to the vial and the reaction left undisturbed for ~5 days. The solvent was removed under vacuum and the product was collected as a yellow oil. Yield: 28.6 mg (92.4%). NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.35 (s, 1H, C(H)=N) , 7.79 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, Ar), 7.62 (ov dd, 1H, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, Ar) , 7.15 (d, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 1H, Ar), 3.65 (dt, 2H, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, N-CH<sub>2</sub>) , 2.59 (s, 3H, Ar-CH<sub>3</sub>), 1.70 (m, 2H, CH<sub>2</sub>), 1.35-1.27 (ov m, 6H, (CH<sub>2</sub>)<sub>3</sub>) 0.89 (t, <sup>2</sup>J<sub>HH</sub> = 4 Hz, 3H, CH<sub>3</sub>)  
<sup>13</sup>C {<sup>1</sup>H} δ: 162.0 (s, C(H)=N), 158.1 (s), 154.1 (s), 136.7 (s), 124.2 (s), 118.2 (s), 61.6 (s), 31.6 (s), 30.6 (s), 27.0 (s), 24.3 (s), 22.6 (s), 14.1 (s). FT-IR (cm<sup>-1</sup>): 2955 (w), 2927 (w) 2857 (w), 1649 (m, C=N) 1590 (w), 1455 (w), 1325 (w), 985 (w), 791 (s), 640 (s).

Synthesis of (*E*)-*N*-((6-methylpyridin-2-yl)methylene)octan-1-amine **L2**



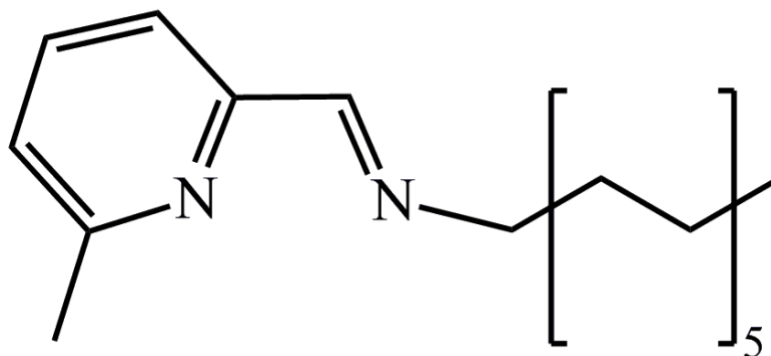
Octylamine (0.536 g, 4.15 mmol) was bubbled under nitrogen for 5 minutes then capped and brought into a glovebox. 6-methyl-2-pyridinecarboxaldehyde (0.5g, 4.13 mmol) was placed in a scintillation vial. Toluene (10 mL) was added to the octylamine, and the solution stirred. The octylamine mixture was added dropwise to the 6-methyl-2-pyridinecarboxaldehyde and the mixture stirred. Molecular sieves (3 Å) were added to the vial and the reaction left undisturbed for ~5 days. The solvent was removed under vacuum and the product was collected as a bright orange oil. NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.34 (s, 1H, C(H)=N), 7.79 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, Ar), 7.62 (t, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, 1H, Ar), 7.17 (d, <sup>3</sup>J<sub>HH</sub> = 8.2 Hz, 1H, Ar), 3.65 (ov dt, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 2H, N-CH<sub>2</sub>), 2.59 (s, 3H, Ar-CH<sub>3</sub>), 1.70 (t, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 2H CH<sub>2</sub>), 1.30 (m, 10H, (CH<sub>2</sub>)<sub>5</sub>), 0.87 (t, <sup>2</sup>J<sub>HH</sub> = 6.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 162.0 (s, C(H)=N), 158.0 (s), 154.1 (s), 136.7 (s), 124.2 (s), 118.2 (s), 61.6 (s), 31.8 (s), 30.7 (s), 29.4 (s), 29.2 (s), 27.3 (s), 24.4 (s), 22.7 (s), 14.1 (s). FT-IR (cm<sup>-1</sup>): 2955 (w), 2924 (w) 2854 (w), 1649 (m, C=N) 1590 (w), 1455 (w), 1375 (w), 790 (s).

Synthesis of (*E*)-*N*-((6-methylpyridin-2-yl)methylene)decan-1-amine **L3**



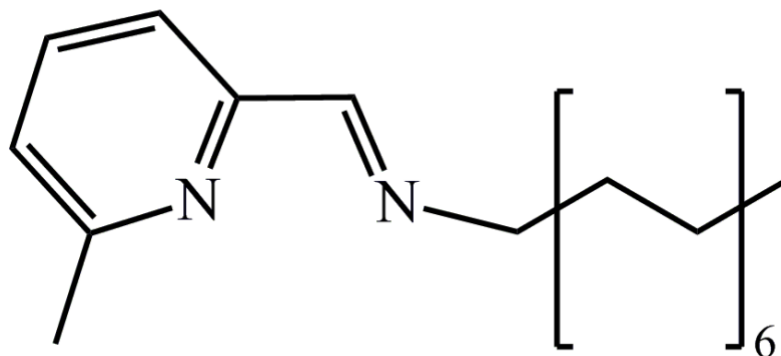
Decylamine (0.646 g, 4.17 mmol) was bubbled under nitrogen for 5 minutes then capped and brought into a glovebox. 6-methyl-2-pyridinecarboxaldehyde (0.505g, 4.11 mmol) was placed in a scintillation vial. Toluene (7 mL) was added to the decylamine, and the solution stirred. The decylamine mixture was added dropwise to the 6-methyl-2-pyridinecarboxaldehyde and then stirred. Molecular sieves (3 Å) were added to the vial and the reaction left undisturbed for ~5 days. The solvent was removed under vacuum and the product was collected as a translucent yellow oil. Yield: 0.682g (64%) NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.34(s,1H, C(H)=N), 7.79 (d, 1H, <sup>3</sup>J<sub>HH</sub>=7.8Hz, Ar), 7.62 (t,1H,<sup>3</sup>J<sub>HH</sub>=7.6Hz, Ar), 7.16 (d,1H,<sup>3</sup>J<sub>HH</sub>=8Hz), 3.65 (ov dt, 2H,<sup>3</sup>J<sub>HH</sub>=7Hz,<sup>3</sup>J<sub>HH</sub> = 7Hz, N-CH<sub>2</sub>), 2.59 (s, 3H, Ar-CH<sub>3</sub>), 1.67 (m, 2H, CH<sub>2</sub>), 1.33–1.25 (ov m, 14H, (CH<sub>2</sub>)<sub>7</sub>), 0.87 (t, <sup>2</sup>J<sub>HH</sub> = 6.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 162.0 (s, C(H)=N), 158.1 (s), 154.1 (s), 136.7 (s), 124.2 (s), 118.2 (s), 61.6 (s), 31.9 (s), 30.7 (s), 29.6 (s), 29.4 (s), 29.4 (s), 29.3 (s), 27.3 (s), 24.4 (s), 22.7 (s), 14.1 (s); FT-IR (cm<sup>-1</sup>): 2923 (w), 2853 (w),1649 (m, C=N) 1590 (w), 1455 (w), 1375 (w), 790 (s).

Synthesis of (E)-N-((6-methylpyridin-2-yl)methylene)dodecan-1-amine **L4**



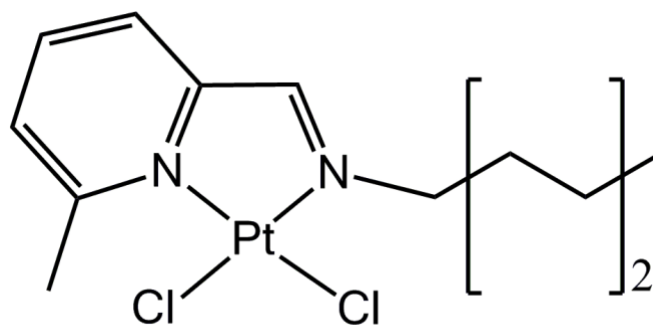
Dodecylamine (0.764 g, 4.12 mmol) was kept in a desiccator under vacuum overnight then capped and brought into a glovebox. In a scintillation vial 6-methyl-2-pyridinecarboxaldehyde (0.503g, 4.14 mmol) was mixed with toluene (5 mL). Toluene (5 mL) was added to the dodecylamine, and the solution stirred. The dodecylamine mixture was added dropwise to the 6-methyl-2-pyridinecarboxaldehyde mixture and the solution stirred. Molecular sieves (3 Å) were added to the vial and the reaction left undisturbed for 7 days. The solvent was removed under vacuum and the product was collected as a bright yellow oil. Yield: 0.923g (78%). NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.34 (s, 1H, C(H)=N), 7.79 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, Ar), 7.62 (t, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, 1H, Ar), 7.17 (d, <sup>3</sup>J<sub>HH</sub> = 7.4 Hz, 1H, Ar), 3.65 (ov dt, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 2H, N-CH<sub>2</sub>), 2.59 (s, 3H, Ar-CH<sub>3</sub>), 1.70 (t, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 2H, CH<sub>2</sub>), 1.30 (m, 18H, (CH<sub>2</sub>)<sub>9</sub>) 0.87 (t, <sup>2</sup>J<sub>HH</sub> = 6.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 162.0 (s, C(H)=N), 158.1 (s), 154.0 (s), 136.8 (s), 124.2 (s), 118.2 (s), 61.7 (s), 31.9 (s), 30.7 (s), 29.7 (s), 29.6 (s), 29.6 (s), 29.6 (s), 29.4 (s), 29.4 (s), 27.3 (s), 24.4 (s), 22.7 (s), 14.1 (s); FT-IR (cm<sup>-1</sup>): 2852 (w), 1649 (m, C=N) 1590 (w), 1455 (w), 790 (s)

Synthesis of (*E*)-*N*-((6-methylpyridin-2-yl)methylene)tetradecan-1-amine **L5**



Tetradecyl amine (0.888 g, 4.16 mmol) was bubbled under nitrogen for 5 minutes then capped and brought into a glovebox. In a scintillation vial 6-methyl-2-pyridinecarbaldehyde (0.506g, 4.18 mmol) was mixed with toluene (5 mL). Toluene (5 mL) was added to the dodecylamine, and the solution stirred. The dodecylamine mixture was added dropwise to the 6-methyl-2-pyridinecarbaldehyde mixture and the solution stirred. Molecular sieves (3 Å) were added to the vial and the reaction left undisturbed for 7 days. The solvent was removed under vacuum and the product was collected as a light orange oil. Yield: 1.254g (95%). NMR Spectroscopic data (in  $\text{CDCl}_3$ ):  $^1\text{H}$   $\delta$ : 8.34 (s, 1H, C(H)=N), 7.79 (d, 1H,  $^3J_{\text{HH}}=7.4$  Hz, Ar), 7.62 (t, 1H,  $^3J_{\text{HH}}=7.8$  Hz, Ar), 7.17 (d, 1H,  $^3J_{\text{HH}}=7.4$  Hz), 3.65 (ov dt, 2H,  $^3J_{\text{HH}}=7\text{Hz}$ ,  $^3J_{\text{HH}}=7$  Hz, N-CH<sub>2</sub>), 2.59 (s, 3H, Ar-CH<sub>3</sub>), 1.70 (m, 2H,  $^3J_{\text{HH}}=7$  Hz, CH<sub>2</sub>), 1.33–1.25 (ov m, 22H, (CH<sub>2</sub>)<sub>11</sub>), 0.87 (t,  $^2J_{\text{HH}}=6.4$  Hz, 3H, CH<sub>3</sub>);  $^{13}\text{C}$  { $^1\text{H}$ }  $\delta$ : 162.0 (s, C(H)=N), 158.1 (s), 154.1 (s), 136.7 (s), 124.2 (s), 118.2 (s), 61.7 (s), 31.9 (s), 30.7 (s), 29.7 (s, 2C), 29.6 (s, 2C), 29.6 (s, 2C), 29.4 (s, 2C), 29.4 (s), 27.3 (s), 24.4 (s), 22.7 (s), 14.1 (s); FT-IR ( $\text{cm}^{-1}$ ): 2921 (s), 2852 (w), 1650 (m, C=N) 1590 (w), 1455 (w), 790 (s)

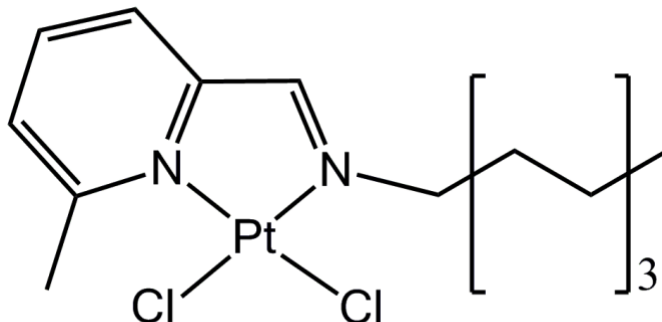
*Synthesis of Dichloro-[(6-methylpyridin-2-yl)methylene]hexan-1-amine] platinum (II) C1*



[PtCl<sub>2</sub>(coe)]<sub>2</sub> (0.100 g) was placed in a clean and dry scintillation vial and covered with a Kimwipe. The vial was placed in a desiccator under vacuum for ~18 hours. The vial was brought into the glovebox and dichloromethane (4mL) was added and the solution stirred to achieve complete dissolution. The **L1** (0.053g, 0.264 mmol) was placed in a separate vial and dichloromethane (4mL) was added. Once dissolution of each complex was achieved, **L1** was added dropwise to the [PtCl<sub>2</sub>(coe)]<sub>2</sub> solution. The mixture was left to stir undisturbed for >18 hours. The product was removed from the glovebox and the solvent removed under vacuum. Clean-up of the solid was achieved by dissolving the solid in a 1:1 hexane and DCM mixture and swirled. The solvent was removed under vacuum. Yield: 0.244g (98%); mp 118.6 – 119.4 °C. NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.81 (s, <sup>3</sup>J<sub>HPt</sub> = 88.6 Hz, 1H, C(H)=N), 7.95 (ov dd, 1H, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, Ar), 7.73 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 6.4 Hz, Ar), 7.45 (ov dd, 1H, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, Ar), 4.06 (t, 2H, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, N-CH<sub>2</sub>), 3.12 (s, 3H, Ar-CH<sub>3</sub>), 1.88 (quint, 2H, <sup>3</sup>J<sub>HH</sub> = 6.2 Hz, CH<sub>2</sub>), 1.29-1.35 (ov m, 6H, (CH<sub>2</sub>)<sub>3</sub>) 0.88 (t, <sup>2</sup>J<sub>HH</sub> = 6 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 169.2 (s, C(H)=N), 167.1 (s), 157.6 (s), 138.8 (s), 131.1 (s), 125.5 (s), 60.7 (s), 31.3 (s), 30.8 (s), 27.9 (s), 26.1 (s), 22.5 (s), 14.0 (s); FT-IR (cm<sup>-1</sup>): 2952 (w), 2917 (w) 2847 (w), 1603 (m, C=N) 1468 (w),

1378 (w), 787 (w), 732 (w). Elemental analysis calcd. For  $\text{PtCl}_2\text{C}_{13}\text{H}_{20}\text{N}_2 \cdot 0.5(\text{CH}_2\text{Cl}_2) \cdot 1.5(\text{H}_2\text{O})$   
(539.76) %: C 33.20, H 4.29, N 5.96; found: C 30.05, H 4.13, N 5.70.

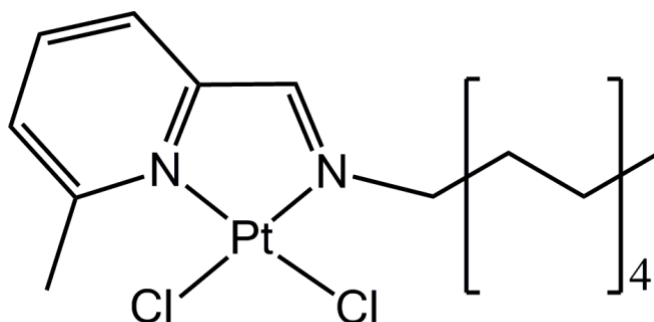
*Synthesis of Dichloro-[(6-methylpyridin-2-yl)methylene]octan-1-amine] platinum (II) C2*



[PtCl<sub>2</sub>(coe)]<sub>2</sub> (0.100 g, 0.133 mmol) was placed in a clean and dry scintillation vial and covered with a Kimwipe. The vial was placed in a desiccator under vacuum for ~18 hours. The vial was brought into the glovebox and dichloromethane (4mL) was added and the solution stirred to achieve complete dissolution. The **L2** (0.061g, 0.262 mmol) was placed in a separate vial and dichloromethane (4mL) was added. Once dissolution of each compound was achieved, **L2** was added dropwise to the [PtCl<sub>2</sub>(coe)]<sub>2</sub> solution. The mixture was left to stir undisturbed for >18 hours. The product was removed from the glovebox and the solvent removed under vacuum. A bright orange powder was collected. The powder was placed in a saturated solution of dichloromethane and hexanes (1:2) at 5°C for 5 days. The solvent was then removed by vacuum filtration through a sintered glass funnel. Bright orange crystalline solids were collected. Yield: 0.204 g (78%); mp 116.1 – 116.8 °C. NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.83 (s, <sup>3</sup>J<sub>HPt</sub> = 85.2 Hz, 1H, C(H)=N), 7.95 (t, <sup>3</sup>J<sub>HH</sub> = 7.7 Hz, 1H, Ar), 7.76 (d, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, 1H, Ar), 7.42 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, Ar), 4.05 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 2H, N-CH<sub>2</sub>), 3.10 (s, 3H, Ar-CH<sub>3</sub>), 1.86 (m, 2H CH<sub>2</sub>), 1.28 (m, 10H, (CH<sub>2</sub>)<sub>5</sub>), 0.85 (t, <sup>2</sup>J<sub>HH</sub> = 6.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 169.0 (s, C(H)=N), 167.3 (s), 157.5 (s), 138.6 (s), 131.1 (s), 125.3 (s), 60.8 (s), 31.7 (s), 30.8 (s), 29.1 (s, 2C), 27.9 (s), 26.4 (s), 22.6 (s), 14.1 (s); FT-IR (cm<sup>-1</sup>): 2918 (m), 2849 (m) 1604 (m, C=N) 1463 (m), 804 (s). Elemental

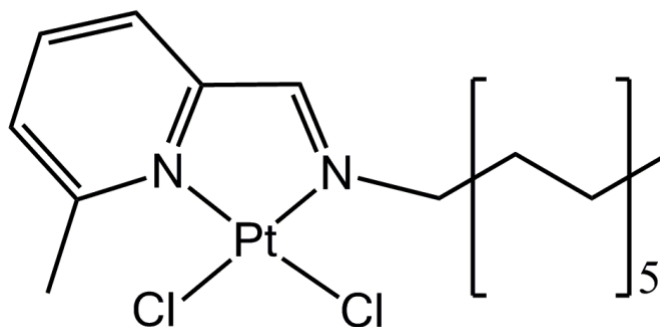
analysis calcd. For  $\text{PtCl}_2\text{C}_{15}\text{H}_{24}\text{N}_2 \cdot 1(\text{CH}_2\text{Cl}_2)$  (583.28) %: C 36.15, H 4.85, N 5.62; found: C 32.5,  
H 4.68, N 5.33

*Synthesis of Dichloro-[(6-methylpyridin-2-yl)methylene]decan-1-amine] platinum (II) C3*



[PtCl<sub>2</sub>(coe)]<sub>2</sub> (0.099 g, 0.132 mmol) was placed in a desiccator under vacuum for ~18 hours. The PtCl<sub>2</sub>(coe)]<sub>2</sub> was brought into the glovebox and dichloromethane (3 mL) was added and the solution stirred to achieve complete dissolution. In a separate vial **L3** (0.074 g, 0.284 mmol) was mixed with and dichloromethane (4mL) was added. Once dissolution of each compound was achieved, **L3** was added dropwise to the [PtCl<sub>2</sub>(coe)]<sub>2</sub> solution. The mixture was left to stir undisturbed for >18 hours. The solvent was removed from the product under vacuum leaving a yellow-orange powder. Once the solvent was removed, dichloromethane (3 mL) and hexanes (~4 mL) was added to the product and the complex was stored at 5°C for a week. The solution was then filtered through a sintered glass funnel and a yellow solid was collected. Yield: 0.197g (62%); mp 108.0 – 108.9 °C. NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.82 (s, <sup>3</sup>J<sub>HPt</sub> = 85.2 Hz, 1H, C(H)=N,) , 7.95 (t, 1H, <sup>3</sup>J<sub>HH</sub> = 7.7 Hz, Ar), 7.74 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 6.6Hz, Ar) , 7.44 (ov dd, 1H, <sup>3</sup>J<sub>HH</sub> = 8.2 Hz, <sup>3</sup>J<sub>HH</sub> = 8.2 Hz, Ar), 4.05 (t, 2H, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, N-CH<sub>2</sub>), 3.11 (s, 3H, Ar-CH<sub>3</sub>), 1.87 (m, 2H, CH<sub>2</sub>), 1.28-1.24 (m, 14H, (CH<sub>2</sub>)<sub>7</sub>), 0.87 (t, <sup>2</sup>J<sub>HH</sub> = 6.5 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 168.7 (s, C(H)=N), 167.4 (s), 157.5 (s), 138.7 (s), 131.1 (s), 125.2 (s), 60.9 (s), 31.9 (s), 30.9 (s), 29.5 (s, 3C), 29.3 (s), 29.2 (s) 28.0 (s), 26.5 (s), 22.7 (s), 14.1 (s); FT-IR (cm<sup>-1</sup>): 2921 (w), 2849 (w), 1637 (m, C=N) 1464 (m).

Synthesis of Dichloro-[(6-methylpyridin-2-yl)methylene]dodecan-1-amine] platinum (II) **C4**



[PtCl<sub>2</sub>(coe)]<sub>2</sub> (0.099 g, 0.132 mmol) was placed in a desiccator under vacuum for ~18 hours. The PtCl<sub>2</sub>(coe)]<sub>2</sub> was brought into the glovebox and dichloromethane (4mL) was added and the solution stirred to achieve complete dissolution. In a separate vial **L4** (0.079 g, 0.274mmol) was mixed with and dichloromethane (4mL) was added. Once dissolution of each compound was achieved, **L4** was added dropwise to the [PtCl<sub>2</sub>(coe)]<sub>2</sub> solution. The mixture was left to stir undisturbed for >18 hours. The solvent was removed from the product under vacuum leaving a bright yellow powder. Once the solvent was removed, dichloromethane (3 mL) and hexanes (~4 mL) was added to the product and the complex was stored at 5°C for a week. The solution was then filtered through a sintered glass funnel and a bright yellow solid was collected. Yield: 0.079g (53%); mp 131.7 – 132.5 °C. NMR Spectroscopic data (in CDCl<sub>3</sub>): <sup>1</sup>H δ: 8.78 (s, <sup>3</sup>J<sub>HPt</sub> = 87.4 Hz, 1H, C(H)=N,) , 7.95 (t, 1H, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, Ar), 7.78 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 6.6 Hz, Ar) , 7.39 (ov dd, 1H, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, Ar), 4.04 (t, 2H, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, N-CH<sub>2</sub>), 3.09 (s, 3H, Ar-CH<sub>3</sub>), 1.86 (m, 2H, CH<sub>2</sub>), 1.23 (m, 18H, (CH<sub>2</sub>)<sub>9</sub>), 0.87 (t, <sup>2</sup>J<sub>HH</sub> = 6.5 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C {<sup>1</sup>H} δ: 168.8 (s, C(H)=N), 167.3 (s), 157.6 (s), 138.7 (s), 131.1 (s), 125.3 (s), 60.8 (s), 31.9 (s), 30.8 (s), 29.6 (s, 2C), 29.6 (s), 29.5 (s), 29.3 (s), 29.2 (s), 28.0 (s), 26.5 (s), 22.7 (s), 14.1 (s). FT-IR (cm<sup>-1</sup>): 2915 (w), 2848 (w), 1600 (m, C=N) 1470 (m), 784.15 (m).

### *X-Ray Crystallography*

Single crystals of  $C_{13}H_{20}Cl_2N_2Pt$  were grown in a solution of 1:1 hexane and dichloromethane at 5°C. A suitable crystal was selected and mounted on a Bruker APEX-II CCD diffractometer. The crystal was kept at 125.0 K during data collection. Using Olex2<sup>49</sup>, the structure was solved with the olex2.solve<sup>49</sup> structure solution program using Charge Flipping and refined with the olex2.refine<sup>49</sup> refinement package using Gauss-Newton minimisation.

## References

- (1) Nenclares, P.; Harrington, K. J. *Medicine* **2020**, *48* (2), 67–72.
- (2) Anand, P.; Kunnumakara, A. B.; Sundaram, C.; Harikumar, K. B.; Tharakan, S. T.; Lai, O. S.; Sung, B.; Aggarwal, B. B. *Pharm. Res.* **2008**, *25* (9), 2097–2116.
- (3) Siegel, R. L.; Miller, K. D.; Fuchs, H. E.; Jemal, A. *CA: A Cancer Journal for Clinicians* **2021**, *71* (1), 7–33.
- (4) Brenner, D. R.; Weir, H. K.; Demers, A. A.; Ellison, L. F.; Louzado, C.; Shaw, A.; Turner, D.; Woods, R. R.; Smith, L. M. *CMAJ* **2020**, *192* (9), E199–E205.
- (5) van Roij, J.; Brom, L.; Youssef-El Soud, M.; van de Poll-Franse, L.; Raijmakers, N. J. H. *Support Care Cancer* **2019**, *27* (4), 1187–1195.
- (6) Qi, L.; Luo, Q.; Zhang, Y.; Jia, F.; Zhao, Y.; Wang, F. *Chem. Res. Toxicol.* **2019**, *32* (8), 1469–1486.
- (7) Zhou, J.; Kang, Y.; Chen, L.; Wang, H.; Liu, J.; Zeng, S.; Yu, L. *Front. Pharmacol.* **2020**, *11*, 343.
- (8) Wilson, J. J.; Lippard, S. J. *Chem Rev* **2014**, *114* (8), 4470–4495.
- (9) Johnstone, T. C.; Wilson, J. J.; Lippard, S. J. *Inorg. Chem.* **2013**, *52* (21), 12234–12249.
- (10) St-Coeur, P.-D.; Adams, M. E.; Kenny, B. J.; Stack, D. L.; Vogels, C. M.; Masuda, J. D.; Morin, P. Jr.; Westcott, S. A. *Transit. Met. Chem.* **2017**, *42* (8), 693–701.
- (11) Johnstone, T. C.; Park, G. Y.; Lippard, S. J. *Anticancer Res.* **2014**, *34* (1), 471–476.
- (12) Astolfi, L.; Ghiselli, S.; Guaran, V.; Chicca, M.; Simoni, E.; Olivetto, E.; Lelli, G.; Martini, A. *Oncol. Rep.* **2013**, *29* (4), 1285–1292.
- (13) Oun, R.; Moussa, Y. E.; Wheate, N. J. *Dalton Trans.* **2018**, *47* (19), 6645–6653.
- (14) Browning, R. J.; Reardon, P. J. T.; Parhizkar, M.; Pedley, R. B.; Edirisinghe, M.; Knowles, J. C.; Stride, E. *ACS Nano.* **2017**, *11* (9), 8560–8578.
- (15) Dasari, S.; Tchounwou, P. B. *Eur. J. Pharmacol.* **2014**, *740*, 364–378.
- (16) Galluzzi, L.; Vitale, I.; Michels, J.; Brenner, C.; Szabadkai, G.; Harel-Bellan, A.; Castedo, M.; Kroemer, G. *Cell Death Dis* **2014**, *5* (5), e1257–e1257.
- (17) Stewart, E. L.; Patterson, A. E.; O'Neill, T.; Li, H.; Flewelling, A.; Vogels, C. M.; Decken, A.; Lloyd, V. K.; Gray, C. A.; Westcott, S. A. *Can. J. Chem.* **2013**, *91* (2), 131–136.
- (18) Miller, R. P.; Tadagavadi, R. K.; Ramesh, G.; Reeves, W. B. *Toxins (Basel)* **2010**, *2* (11), 2490–2518.
- (19) Kishimoto, T.; Yoshikawa, Y.; Yoshikawa, K.; Komeda, S. *Int. J. Mol. Sci.* **2019**, *21* (1), E34.
- (20) Marques, M. P. M. *ISRN Spectroscopy* **2013**, *2013*, 1–29.
- (21) Basu, A.; Krishnamurthy, S. *J. Nucleic Acids* **2010**, *2010*, 201367.
- (22) Brown, A.; Kumar, S.; Tchounwou, P. B. *J Cancer Sci. Ther.* **2019**, *11* (4), 97.
- (23) Higuchi, K.; Yanagawa, T. *PLoS One* **2019**, *14* (4)
- (24) Oun, R.; Moussa, Y. E.; Wheate, N. J. *Dalton Trans.* **2018**, *47* (19), 6645–6653.
- (25) Gorgun, M. F.; Zhuo, M.; Englander, E. W. *Mol. Neurobiol.* **2017**, *54* (10), 7883–7895.
- (26) Haberberger, R. V.; Barry, C.; Dominguez, N.; Matusica, D. *Frontiers in Cellular Neuroscience* **2019**, *13*.
- (27) Muggia, F. M.; Bonetti, A.; Hoeschele, J. D.; Rozencweig, M.; Howell, S. B. *JCO* **2015**, *33* (35), 4219–4226.
- (28) Cleare, M. J.; Hoeschele, J. D. *Bioinorganic Chemistry* **1973**, *2* (3), 187–210.

- (29) Montaña, A. M.; Batalla, C. *Curr. Med. Chem.* **2009**, *16* (18), 2235–2260.
- (30) Coluccia, M.; Natile, G. *Anticancer Agents Med Chem* **2007**, *7* (1), 111–123.
- (31) Makovec, T. *Radiol. Oncol.* **2019**, *53* (2), 148–158.
- (32) Mehmood, R. K.; Parker, J.; Ahmed, S.; Qasem, E.; Mohammed, A. A.; Zeeshan, M.; Jehangir, E. *World J Oncol* **2014**, *5* (3), 97–108.
- (33) Moon, H. H.; Seo, K. W.; Yoon, K. Y.; Shin, Y. M.; Choi, K. H.; Lee, S. H. *World J Gastroenterol.* **2011**, *17* (30), 3510–3517.
- (34) Gibson, D. Multi-Action Pt(IV) *J Inorg. Biochem.* **2019**, *191*, 77–84.
- (35) Gibson, D. *J. Inorg. Biochem.* **2021**, *217*, 111353.
- (36) Wang, Z.; Deng, Z.; Zhu, G. *Dalton Trans.* **2019**, *48* (8), 2536–2544.
- (37) Gabano, E.; Ravera, M.; Osella, D. *Dalton Trans.* **2014**, *43* (26), 9813–9820.
- (38) Johnstone, T. C.; Suntharalingam, K.; Lippard, S. J. *Chem. Rev.* **2016**, *116* (5), 3436–3486.
- (39) Lin, S. X.; Curtis, M. A.; Sperry, J. *Bioorganic & Medicinal Chemistry* **2020**, *28* (24), 115820.
- (40) Ling, Y.; Hao, Z.-Y.; Liang, D.; Zhang, C.-L.; Liu, Y.-F.; Wang, Y. *DDDT* **2021**, *15*, 4289–4338.
- (41) Mohamed, E. A.; Ismail, N. S. M.; Hagra, M.; Refaat, H. *Future Journal of Pharmaceutical Sciences* **2021**, *7* (1), 24.
- (42) Kelland, L. *Expert Opin. Investig. Drugs* **2007**, *16* (7), 1009–1021.
- (43) D'Arrigo, J. S. *American Journal of Physiology-Cell Physiology* **1978**, *235* (3), 109–117.
- (44) Cousins, K. R. *J. Am. Chem. Soc.* **2005**, *127* (11), 4115–4116.
- (45) Conrad, M. L.; Enman, J. E.; Scales, S. J.; Zhang, H.; Vogels, C. M.; Saleh, M. T.; Decken, A.; Westcott, S. A. *Inorganica Chimica Acta* **2005**, *358* (1), 63–69.
- (46) Kesslen, E. C.; Euler, W. B.; Foxman, B. M. *Chem. Mater.* **1999**, *11* (2), 336–340.
- (47) Bowman, D. C. *J. Chem. Educ.* **2006**, *83* (8), 1158.
- (48) Shaver, M. P.; Vogels, C. M.; Wallbank, A. I.; Hennigar, T. L.; Biradha, K.; Zaworotko, M. J.; Westcott, S. A. **2000**, *78*, 9.
- (49) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. a. K.; Puschmann, H. *OLEX2: J. Appl. Cryst.* **2009**, *42* (2), 339–341.

## Appendix A: Supplementary Data

### *A.1 : X-Ray Crystallography*

**Table 4:** Fractional Atomic Coordinates ( $\times 10^4$ ) and Equivalent Isotropic Displacement Parameters ( $\text{\AA}^2 \times 10^3$ ) for **C1**.  $U_{\text{eq}}$  is defined as 1/3 of the trace of the orthogonalized  $U_{ij}$  tensor.

<b>Atom</b>	<b>x</b>	<b>y</b>	<b>z</b>	<b>U(eq)</b>
N1	8241(3)	4076.8(12)	3825(3)	16.6(5)
Pt1	7893.5(2)	4380.0(2)	5801.4(2)	14.70(4)
C1	8477(4)	3492.8(14)	3312(3)	18.7(5)
Cl1	8799.4(14)	3503.6(4)	7237.7(9)	30.83(19)
C2	8722(5)	3415.7(16)	1917(3)	23.3(6)
N2	7438(3)	5196.3(12)	4698(3)	16.6(5)
Cl2	7193.6(12)	4808.2(4)	7791.4(8)	23.38(15)
C3	8711(5)	3922.5(17)	1009(3)	25.3(7)
C4	8400(5)	4518.2(16)	1504(3)	23.3(6)
C5	8159(4)	4576.5(14)	2889(3)	18.4(5)
C6	8447(5)	2912.0(14)	4207(4)	23.6(6)
C7	7718(4)	5180.2(14)	3424(3)	18.7(5)
C8	6981(4)	5792.1(14)	5322(3)	18.4(5)
C9	6826(4)	6376.5(14)	4371(3)	19.5(6)
C10	6550(4)	6955.8(14)	5245(4)	21.1(6)
C11	6336(5)	7571.1(15)	4382(4)	24.1(6)
C12	6127(5)	8148.9(15)	5280(4)	26.2(7)
C13	6175(5)	8767.7(16)	4476(5)	32.6(8)

**Table 5:** Anisotropic Displacement Parameters ( $\text{\AA}^2 \times 10^3$ ) for **C1**. The Anisotropic displacement factor exponent takes the form:  $-2\pi^2[h^2a^2U_{11}+2hka^*b^*U_{12}+\dots]$ .

Atom	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
N1	17.3(11)	17.3(12)	14.5(11)	-0.4(9)	3.0(9)	0.0(9)
Pt1	18.75(6)	11.85(5)	13.66(5)	0.26(3)	4.48(4)	-0.76(4)
C1	20.0(14)	16.2(13)	18.9(13)	-1.1(10)	3.4(11)	0.9(11)
Cl1	56.3(6)	16.8(3)	21.3(3)	5.2(3)	13.7(4)	8.6(3)
C2	27.5(16)	21.1(15)	20.3(14)	-6.6(11)	4.5(12)	1.6(12)
N2	18.9(11)	13.0(11)	17.6(11)	1.5(9)	4.1(9)	-0.4(9)
Cl2	35.7(4)	19.3(3)	17.0(3)	-0.5(3)	10.3(3)	2.5(3)
C3	30.1(17)	31.1(17)	15.1(13)	-4.1(12)	6.5(12)	3.4(14)
C4	30.9(17)	23.0(15)	15.8(13)	-0.7(11)	5.9(12)	-0.6(13)
C5	25.8(15)	15.5(13)	14.1(12)	0.3(10)	5.7(11)	-0.5(11)
C6	32.9(17)	12.8(13)	25.7(15)	-0.9(11)	8.6(13)	2.7(12)
C7	21.8(14)	14.7(13)	17.9(13)	2.3(10)	2.0(11)	-0.1(11)
C8	22.0(14)	15.2(13)	19.3(13)	0.0(10)	7.2(11)	0.3(11)
C9	24.8(15)	14.7(13)	19.1(13)	1.3(10)	6.0(11)	0.5(11)
C10	20.7(14)	17.3(14)	25.7(15)	3.9(11)	6.8(12)	3.7(11)
C11	29.4(16)	16.2(14)	25.9(15)	2.7(11)	5.8(13)	2.2(12)
C12	30.4(17)	15.7(14)	30.0(16)	1.2(12)	3.5(13)	1.6(12)
C13	32.3(18)	16.1(15)	47(2)	4.7(14)	6.4(16)	-1.3(13)

**Table 6:** Bond Lengths for **C1**.

<hr/>		
<b>Atom Atom Length/Å</b>		
<hr/>		
N1	Pt1	2.071(2)
N1	C1	1.357(4)
N1	C5	1.373(4)
Pt1	Cl1	2.3003(8)
Pt1	N2	2.003(2)
Pt1	Cl2	2.2856(7)
C1	C2	1.399(4)
C1	C6	1.498(4)
C2	C3	1.376(5)
N2	C7	1.287(4)
N2	C8	1.472(4)
C3	C4	1.386(5)
C4	C5	1.385(4)
C5	C7	1.445(4)
C8	C9	1.518(4)
C9	C10	1.525(4)
C10	C11	1.525(4)
C11	C12	1.523(5)
C12	C13	1.521(5)

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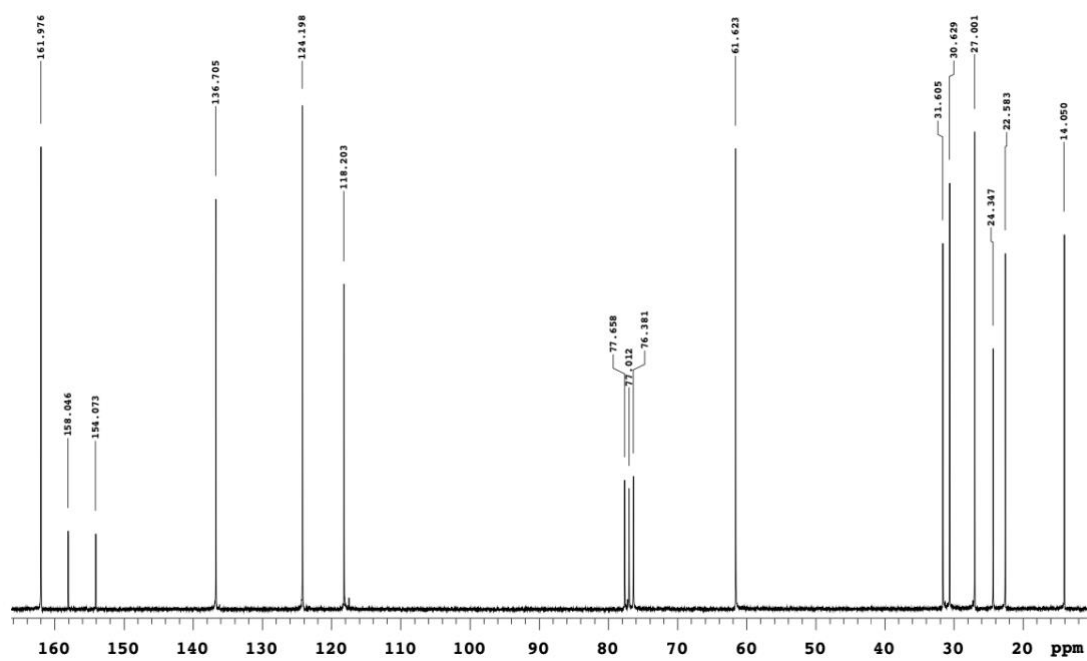
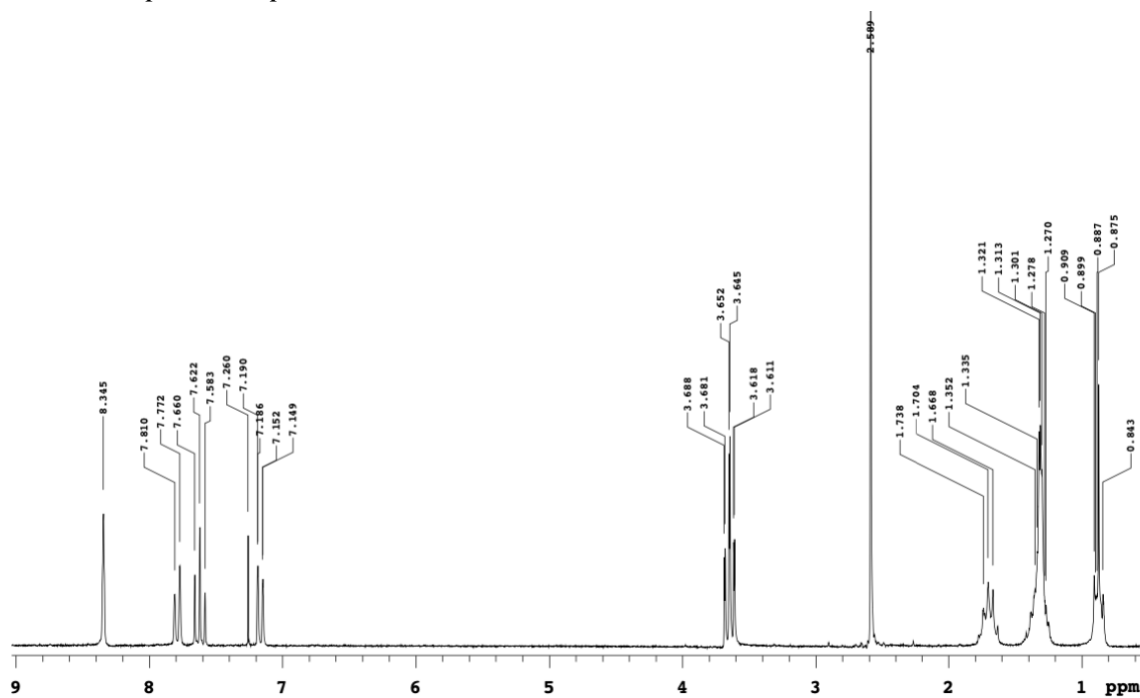
**Table 7:** Bond Angles for **C1**.

<b>Atom</b>	<b>Atom</b>	<b>Atom</b>	<b>Angle/°</b>	<b>Atom</b>	<b>Atom</b>	<b>Atom</b>	<b>Angle/°</b>
C1	N1	Pt1	132.0(2)	C7	N2	C8	121.2(3)
C1	N1	C5	117.0(3)	C8	N2	Pt1	123.51(19)
C5	N1	Pt1	110.94(19)	C2	C3	C4	117.8(3)
N1	Pt1	Cl1	101.68(7)	C5	C4	C3	118.8(3)
N1	Pt1	Cl2	171.77(7)	N1	C5	C4	123.8(3)
N2	Pt1	N1	80.50(10)	N1	C5	C7	115.2(3)
N2	Pt1	Cl1	171.99(8)	C4	C5	C7	121.0(3)
N2	Pt1	Cl2	92.77(7)	N2	C7	C5	117.8(3)
Cl2	Pt1	Cl1	85.63(3)	N2	C8	C9	116.4(2)
N1	C1	C2	120.7(3)	C8	C9	C10	109.1(2)
N1	C1	C6	121.1(3)	C11	C10	C9	113.6(3)
C2	C1	C6	118.1(3)	C12	C11	C10	113.2(3)
C3	C2	C1	121.8(3)	C13	C12	C11	112.8(3)
C7	N2	Pt1	115.1(2)				

**Table 8:** Hydrogen Atom Coordinates ( $\text{\AA}\times 10^4$ ) and Isotropic Displacement Parameters ( $\text{\AA}^2\times 10^3$ ) for **C1**.

<b>Atom</b>	<b>x</b>	<b>y</b>	<b>z</b>	<b>U(eq)</b>
H2	8900.57	3002.29	1588.13	28
H3	8909.79	3866.01	72.72	30
H4	8352.78	4879.92	903.24	28
H6A	9601.1	2875.35	4951.78	35
H6B	8270.94	2537.76	3578.84	35
H6C	7447.37	2943.1	4675.89	35
H7	7638.14	5552.8	2853.05	22
H8A	7919.29	5873.36	6238.29	22
H8B	5810.9	5732.87	5573.93	22
H9A	5785.39	6330.75	3505.25	23
H9B	7944.48	6427.48	4037.99	23
H10A	5454.55	6890.17	5602.03	25
H10B	7603.61	6995.94	6103.26	25
H11A	7412.75	7630.19	3996.69	29
H11B	5256.68	7537.54	3543.6	29
H12A	4960.12	8118.76	5549.15	31
H12B	7117.13	8150.01	6188.12	31
H13A	5877.22	9118.8	5045.77	49
H13B	5285.02	8751.5	3527.46	49
H13C	7391.93	8831.65	4337.41	49

A.2: Selected Spectroscopic Data



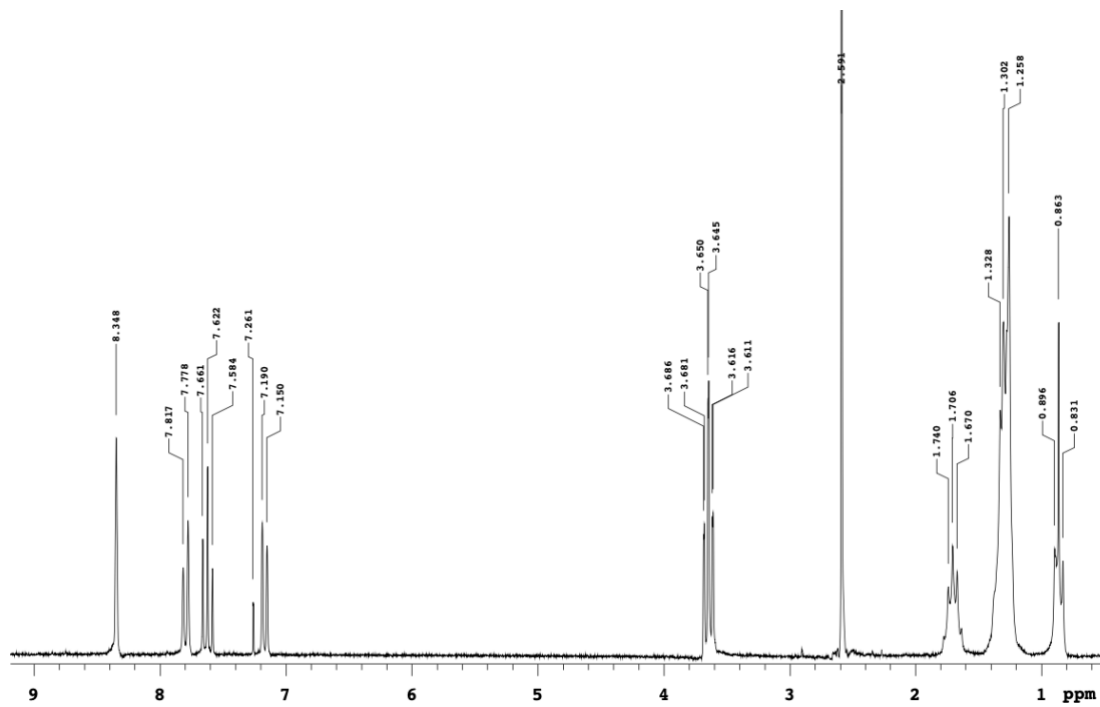


Figure 10:  $^1\text{H}$  proton NMR of L2.

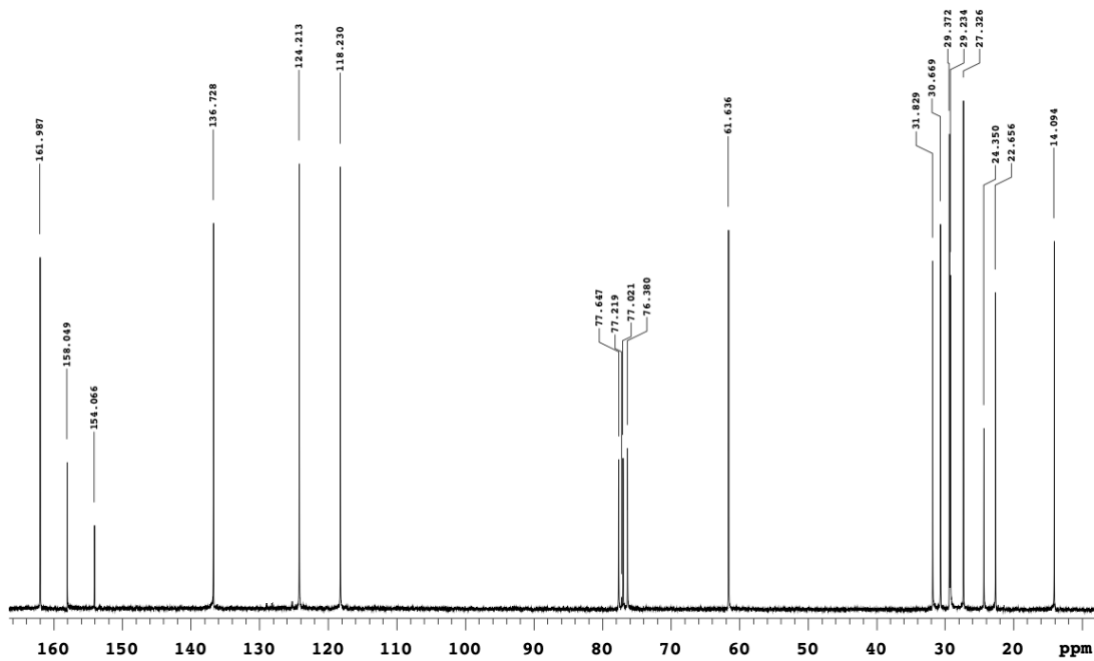


Figure 11:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of L2

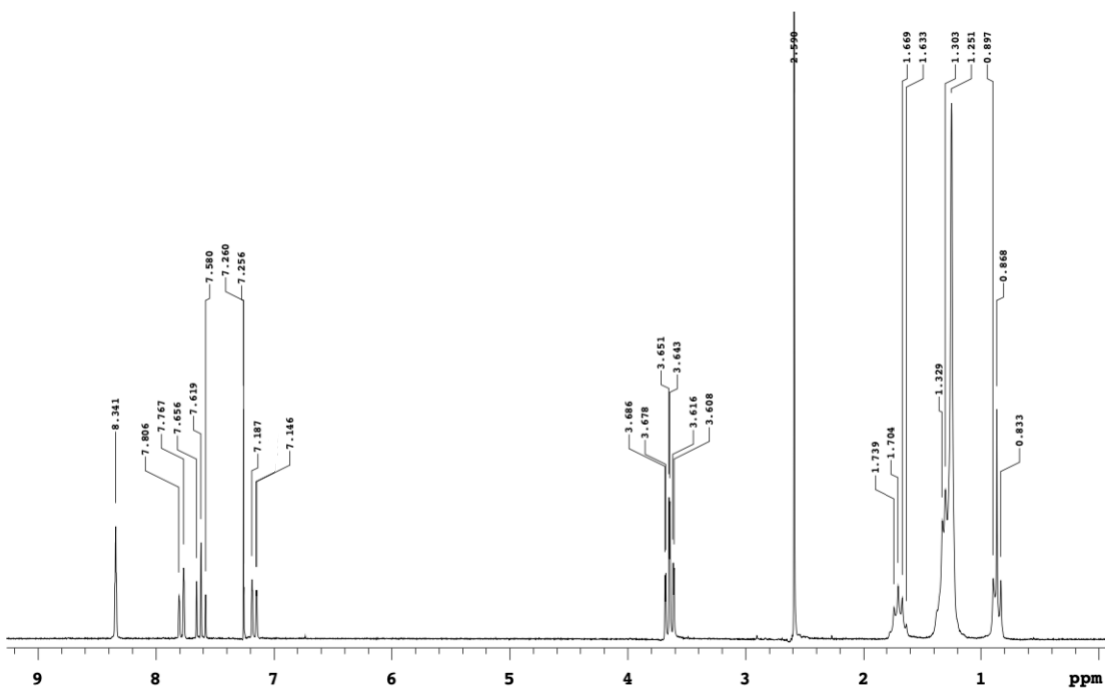


Figure 12:  $^1\text{H}$  proton NMR of L3.

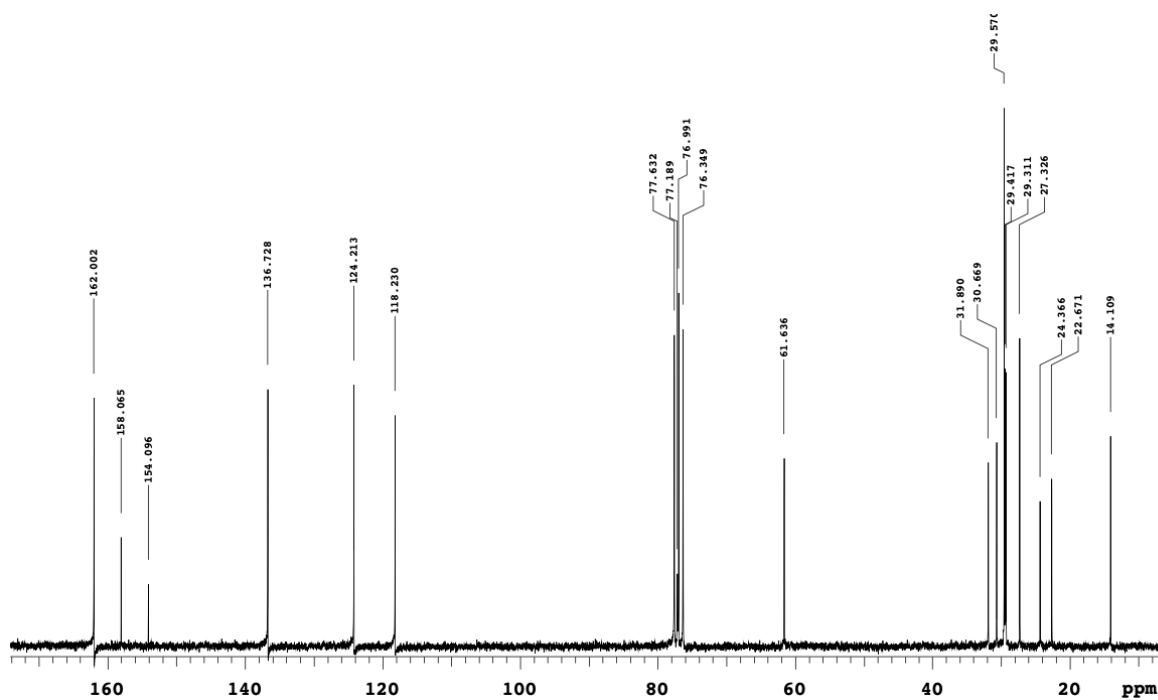


Figure 13:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of L3.

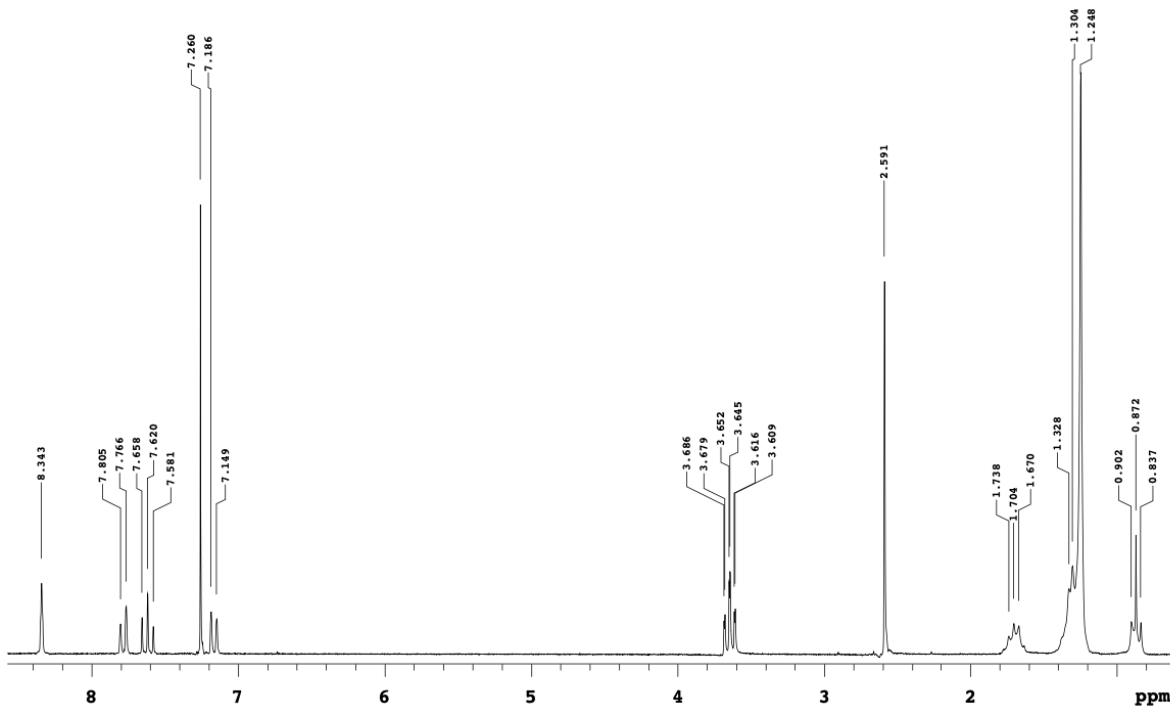


Figure 14: <sup>1</sup>H proton NMR of L4.

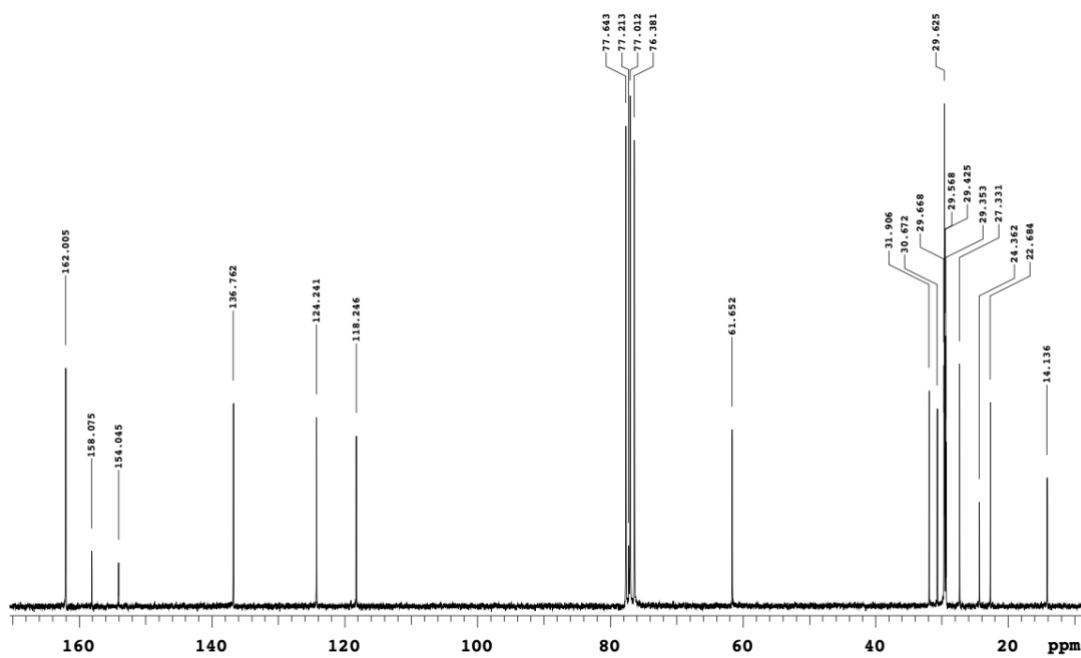


Figure 15: <sup>13</sup>C{<sup>1</sup>H} proton NMR of L4.

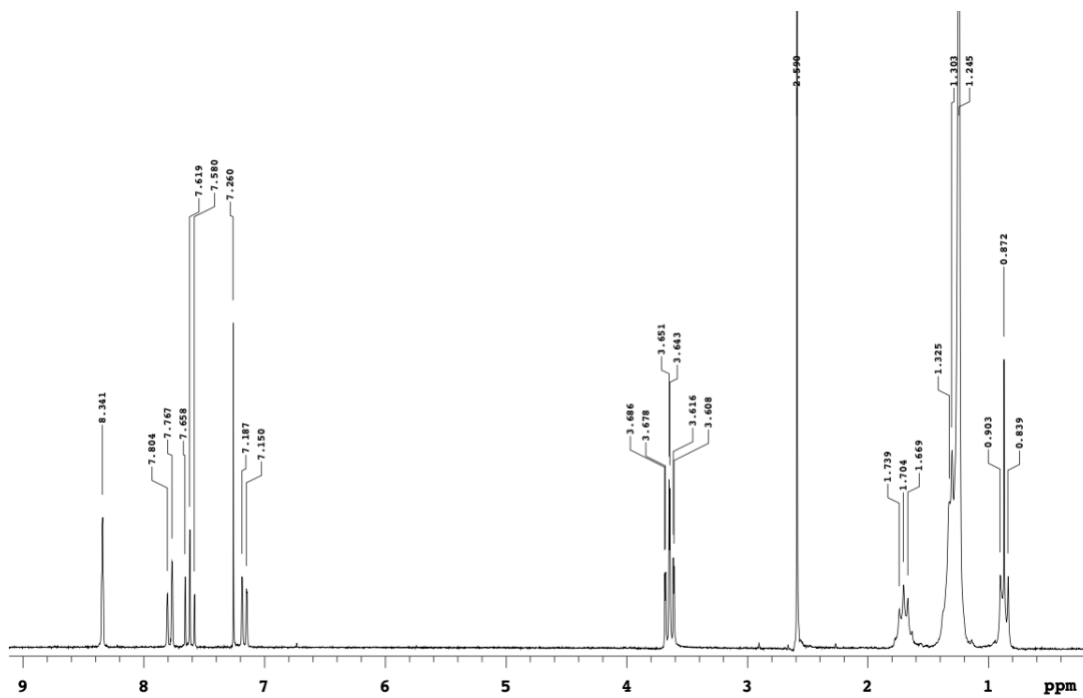


Figure 16:  $^1\text{H}$  proton NMR of L5.

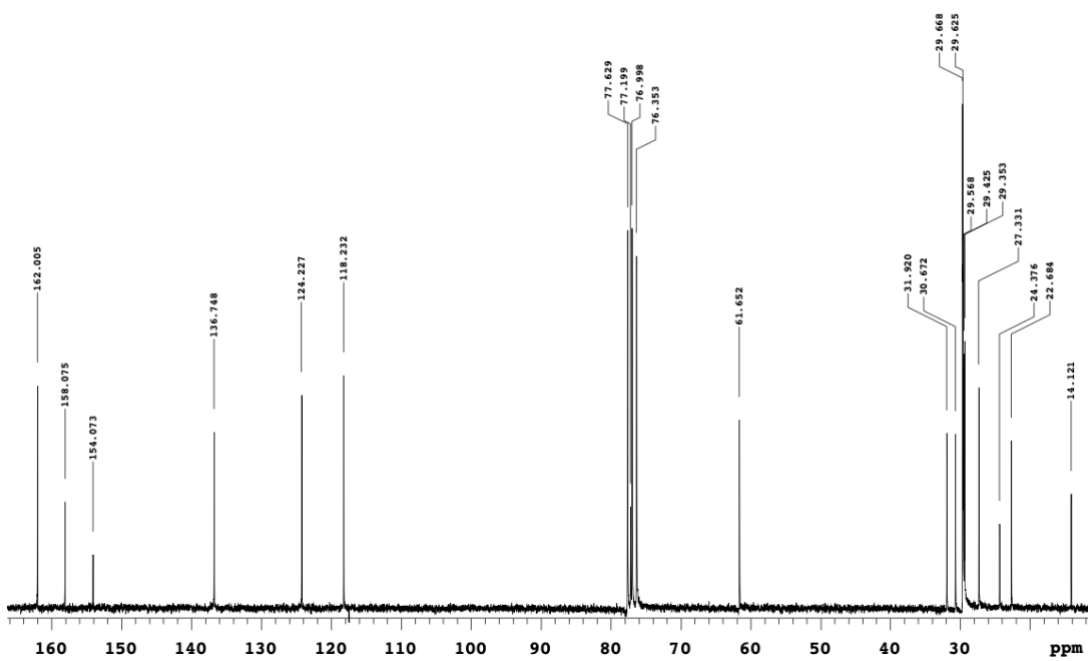


Figure 17:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of L5.

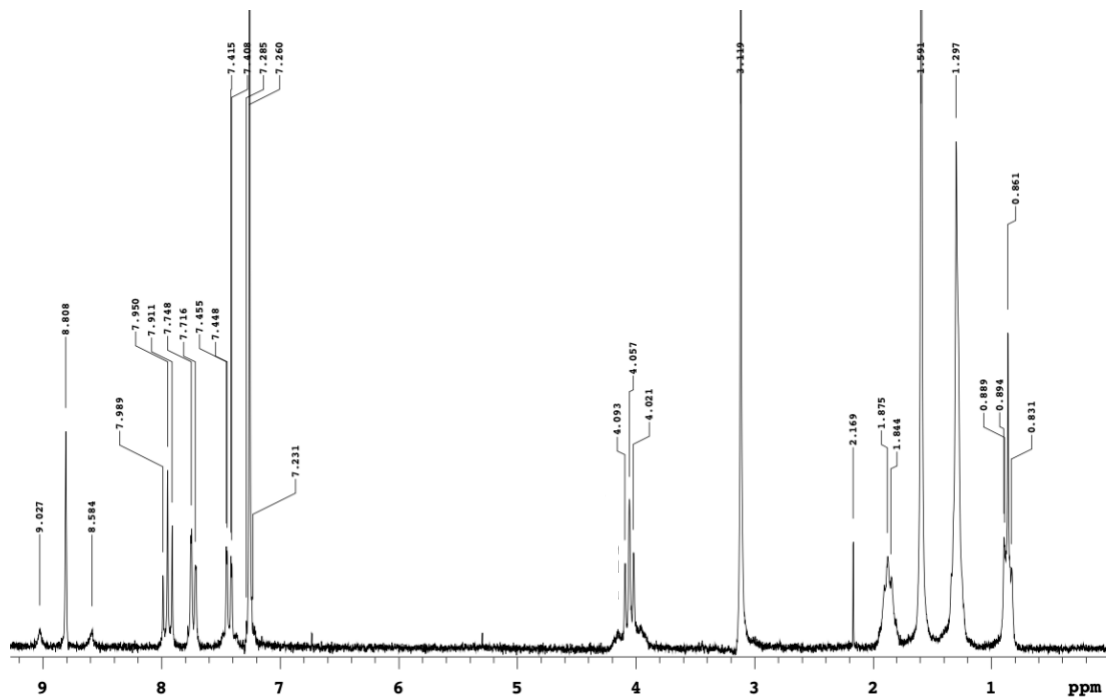


Figure 18:  $^1\text{H}$  proton NMR of C1.

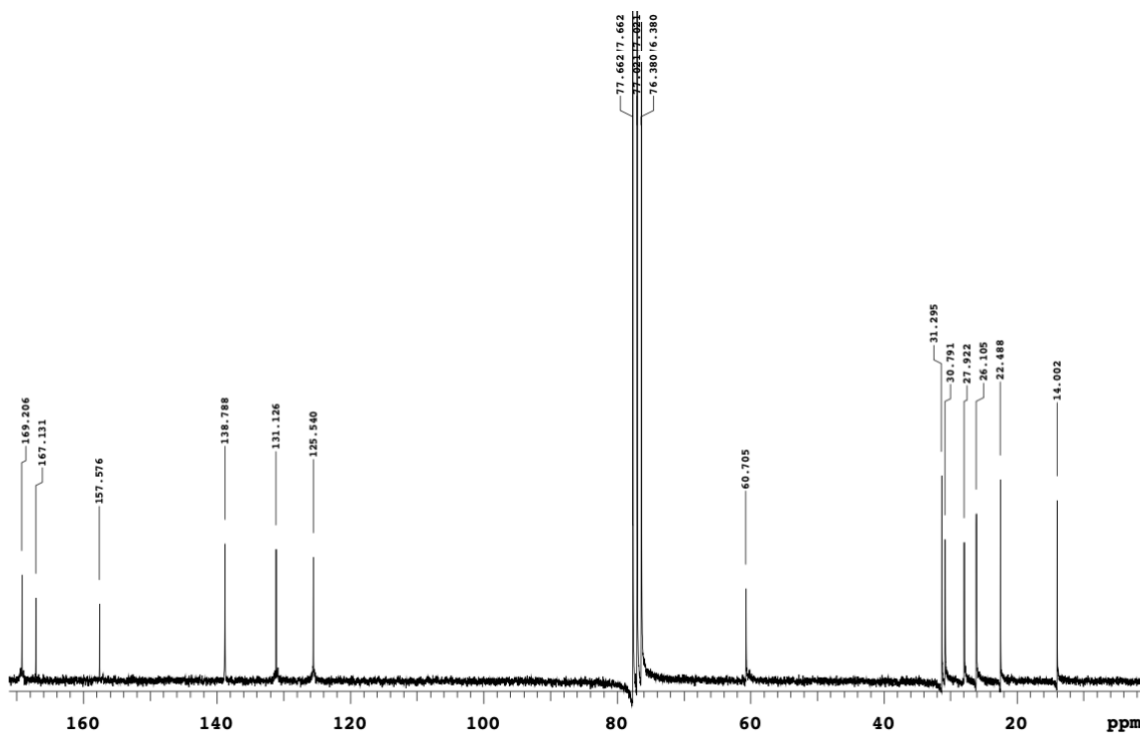


Figure 19:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of C1.

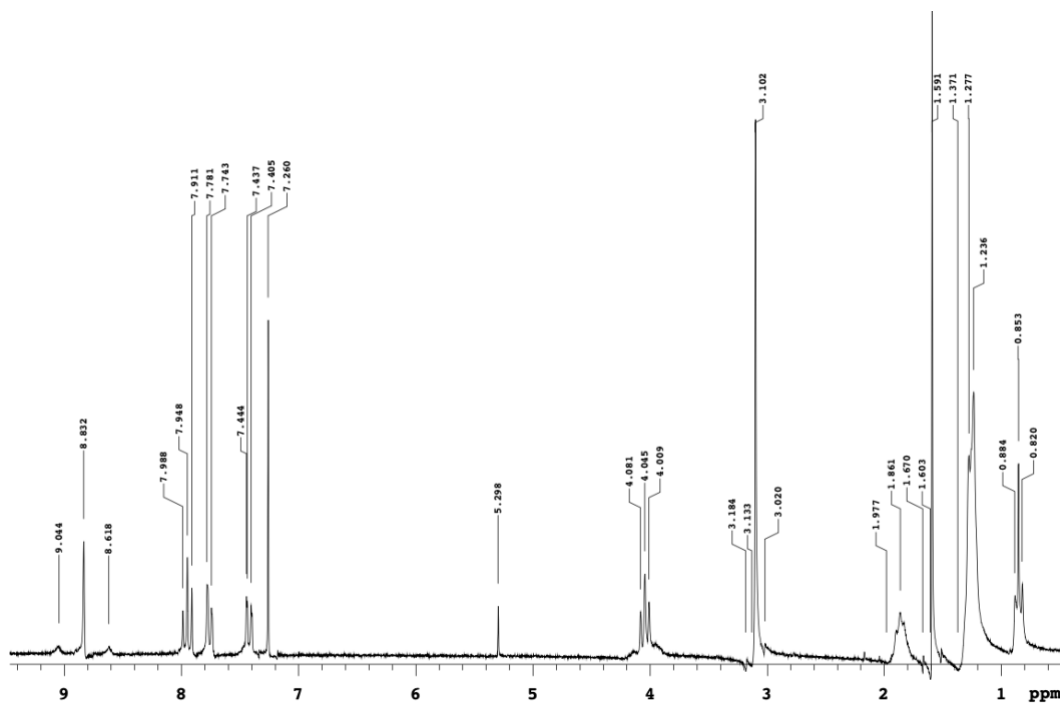


Figure 20:  $^1\text{H}$  proton NMR of C2

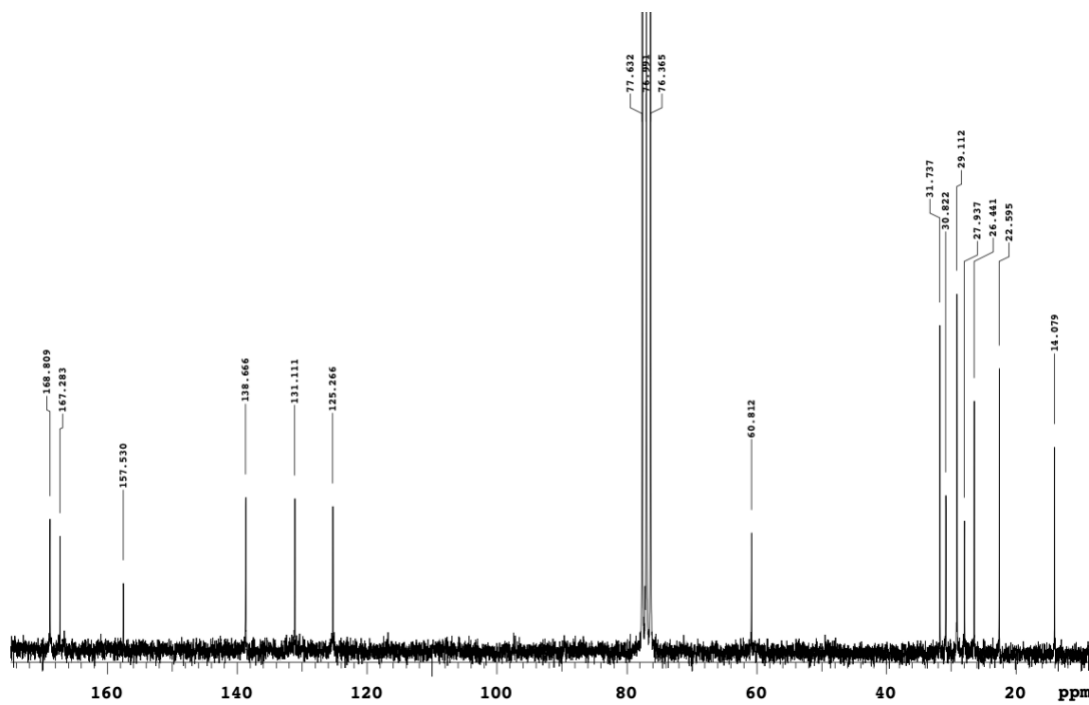


Figure 21:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of C2.

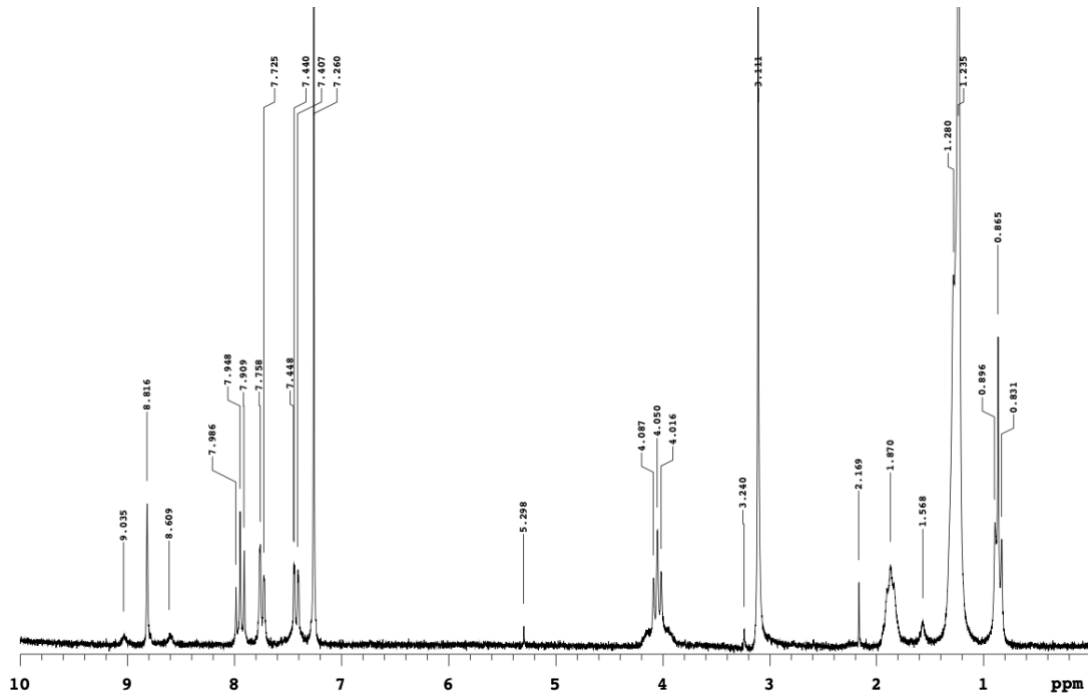


Figure 22:  $^1\text{H}$  proton NMR of C3

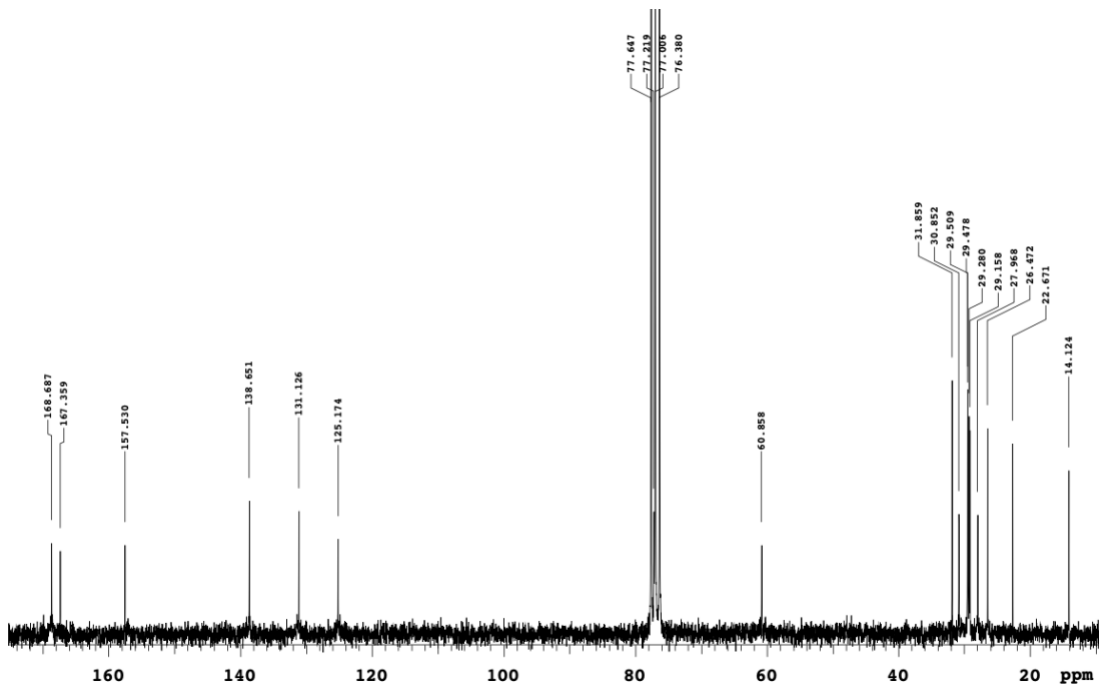


Figure 23:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of C3.

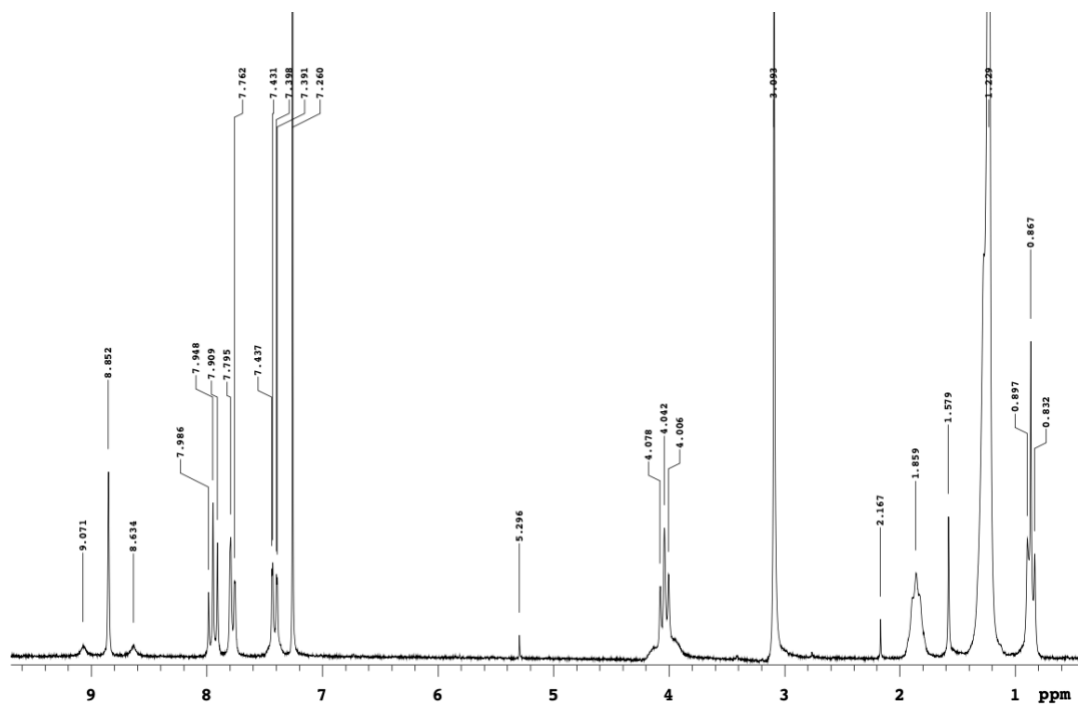


Figure 24:  $^1\text{H}$  proton NMR of C4.

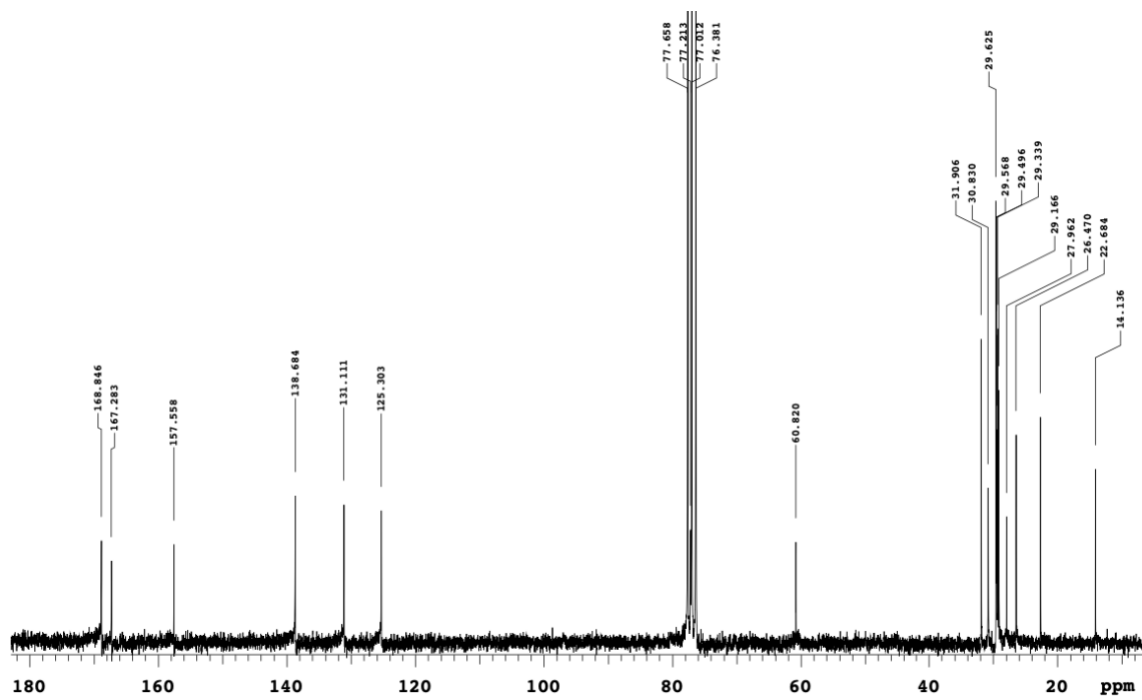


Figure 25:  $^{13}\text{C}\{^1\text{H}\}$  proton NMR of C4.

# Academic Curriculum Vitae

## **Khandra Barrett**

kbarrett@mta.ca • 1-506-688-2765

### **Education:**

- Mount Allison University (2018-present)  
Bachelor of Science, Chemistry (Hons) with a Biochemistry (minor)
- Montego Bay Community College (2016-2018)  
Associate Degree in Natural Sciences  
CAPE Examination Certificate

### **Honours, Awards and Grants**

- Barritt-Marshall Award 2022
- Mount Allison 'Gold A' Award 2022
- George J. De Benedetti Book Prize 2022
- Mount Allison University Deans List 2019-2021
- Murray Sears Award Recipient 2021
- Independent Student Research Grant: Minogue Medical Fund 2021
- Montego Bay Community College Deans' List 2017-2018

### **Research Experience**

- Inorganic Chemistry Student Research Assistant.  
Mount Allison University, Sackville, NB

Successfully synthesized 4 iminopyridinium platinum(II) complexes containing long hydrocarbon chains. These complexes were synthesized then characterized using multinuclear NMR analysis, FT-IR spectroscopy, melting point determination, elemental analysis, and x-ray crystallography.

- Organic Chemistry Student Research Assistant  
Mount Allison University, Sackville, NB

Successfully synthesized the monomer for the polymerization of a novel superconducting polymer. Worked through the experimental synthesis of tetracyano-1,4-dithiin that did not require sodium cyanide.

## Work Experience

- Student Teaching Assistant

Mount Allison University, Sackville, NB

Teacher's assistant for Introductory Chemistry I & II, Inorganic Chemistry, and Introductory Biochemistry II where I provided ancillary support to students in the laboratory aspect of the course. Facilitated the grading of lab assignments for my designated lab groups.

- Assistant Don Thornton House

Mount Allison University, Sackville, NB

Acted as a liaison between students in residence and the Student Life Office. Supervised the residence assistant team by organizing duty shifts. Assisted with the interview, evaluation, and training of incoming resident assistants.

- Organizational Tutor

Mount Allison University, Sackville, NB

Assessing the needs of students and assisted them with them developing good study habits and time management skills.

- Student Health Ambassador

Mount Allison University, Sackville, NB

Monitor outdoor times of students self-isolating. Enforced the COVID-19 protocols on campus and in campus buildings.

- Student Success Course Tutor

Mount Allison University, Sackville, NB

Supervised weekly sessions that provide students with organizational and academic tips to boost academic performance.

- International Orientation Executive Team

Mount Allison University, Sackville, NB

Worked closely with the International Orientation Facilitator in the development and execution of orientation events geared towards incoming international student. Chaired panel discussions on topics related to academics.

- International Centre Summer Coordinator  
Mount Allison University, Sackville, NB

Organized and controlled International Centre's social media platform. Acquired, edited, and updated website content acquisition.

### Experimental Techniques

- Multinuclear NMR, FT-IR (ATR and Nujol), UV/Vis Spectroscopy

Trained in the applicable and appropriate usage of the equipment and software associated with these spectroscopic techniques. Competent in the use, acquisition, manipulation, and analysis of data obtained using these spectroscopic techniques.

- Synthetic Techniques

Proficient in the execution of microscale reactions and reactions requiring inert atmospheres. Competent in the use of procedures such as distillation, centrifugation, and crystallization.

### Computer Skills

- |             |         |
|-------------|---------|
| • Microsoft | • VMD   |
| • Olex      | • Prism |
| • Chemdraw  | • Canva |

### Volunteerism

- International Orientation Facilitator
- International Centre Mentorship Program
- Sappyfest Security and Merch Sales Volunteer
- Covid-19 Vaccination Clinic
- Anti-Racism Response and Education Team student representative
- Relay for life volunteer
- Anti-racism Judicial Panel
- MtA Board of Regents student representative

### Extracurricular Activities

- Black Student Union- Co-president , Former Secretary

The Black Student Union is an organization that acts as a support and resource to all self-identified Black students and allies. My role is to oversee the general operations of the club, lead all general meetings and facilitate the interview process for incoming executive members.

- Chem/Biochemistry Society – VP Chemistry

The CBC society is a faculty club that is responsible for organizing CBC week, arranging help sessions and peer tutoring. I was appointed to the role by a panel of past executive members in consultation with faculty members. My job includes introducing the visiting speakers and assisting with help session for different chemistry courses.

- Mount Allison Student Union – International Student Coordinator

Act as the liaison between international students, the Mount Allison Student Union, and Mount Allison Student Life Office. Chair the International Affairs committee, to assess the needs of international students and make the essential actions to address them. I managed all fundraising events on behalf MASU for the Kavana Wa Kilele Bursary.

- MTA Graduation Executive – Secretary

Responsible for the dissemination of meeting minutes and arrange the booking of spaces for all events. I also serve as a liaison between the current graduating class executives and the incoming graduating class executive.

- MtA Model United Nations - Member

Member of the society, participated in mock discussions. I have attended the McGill Model United Nations conference where I represented Sierra Leone.

## References

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Dr. Stephen Westcott<br/>Professor,<br/>Tier 1 Canada Research Chair<br/>Mount Allison University<br/>Sackville, NB<br/>swestcott@mta.ca<br/>1-506-364- 2372</li> </ul> | <ul style="list-style-type: none"> <li>• Dr. Tyson MacCormack<br/>Associate Professor<br/>Mount Allison University<br/>Sackville, NB<br/>tmaccormack@mta.ca<br/>1-506-364-2</li> </ul> |
|--|--|