Honours Projects 2016

Gold(III) DNA Cross-Linking Agents

Supervisor: Dr M. P. Akerman

It is well established that some metal-based anti-cancer agents, particularly those based on platinum(II), inhibit tumour cell growth by cross linking the DNA duplex. Preliminary research within the Akerman research group has shown that Au(III) chelates with *cis*-chloride substituents, as shown in the figure below, have potential as DNA cross-linking agents and therefore chemotherapeutics. However, their poor aqueous solubility has limited their potential application and has made mechanism of action elucidation challenging. The first stage of the project will therefore centre on increasing aqueous solubility of the chelates through the addition of water solubilising groups such as ethanol. In the second stage of the project, the likely mechanism of action will be elucidated.

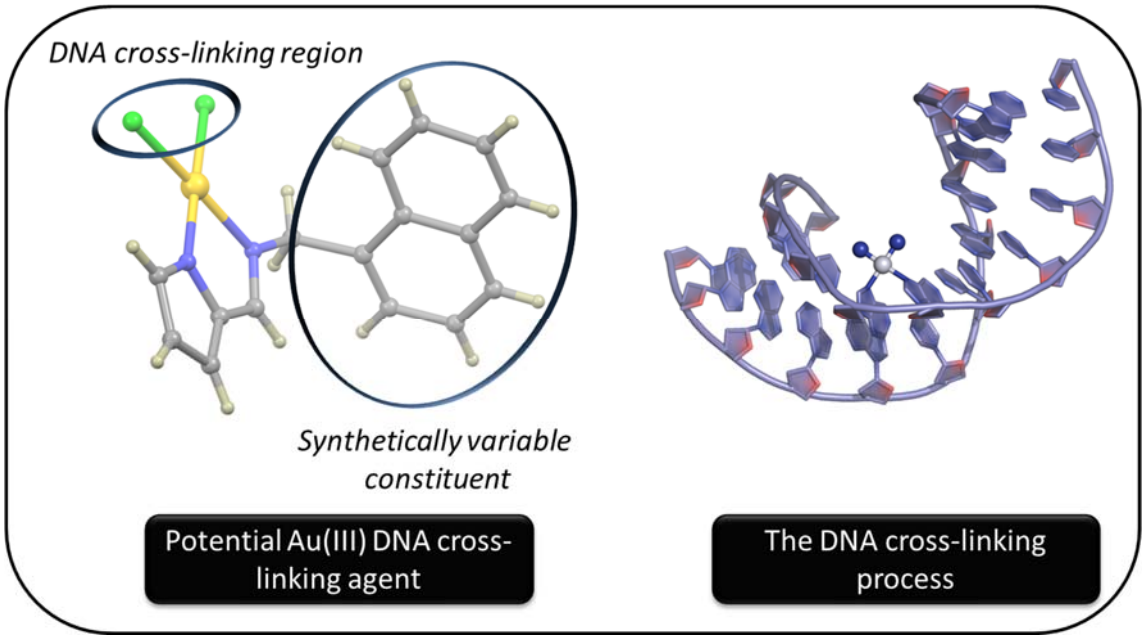


Figure 1: [Left] *Identification of potential DNA cross-linking site and the synthetically variable component that will allow for the tuning of aqueous solubility. [Right] General representation of DNA cross-linking by a metal-based chemotherapeutic agent.*

The key aspects of this project are as follows:

- Ligand synthesis.
- Synthesis of a suitable gold(III) salt.
- Coordination of the ligands to gold(III).
- Full spectroscopic characterisation of the ligands and metal chelates (NMR, UV/vis and IR spectroscopy as well as X-ray crystallography).

- Physical measurements (octanol/water partition coefficients, GSH stability and DNA-binding affinity)
- Screening of the compounds against various human cancer cell lines.
- Potential investigation of the substitution kinetics of the chloride groups with biologically relevant ligands.

Formation, Characterization and DNA Binding Studies of Novel Oxovanadium Compounds with Nucleosides

Supervisor: Dr. I. N. Booysen

Oxovanadium compounds have been shown to exhibit a wide range of biological activities which include anti-tumour and antibacterial activities as well as insulin enhancing capabilities for the treatment of diabetes mellitus [**1**, **2**]. Recent developments are geared towards the utilization of biocompatible ligands which may facilitate biodistribution and solubility in the blood stream of the formulated oxovanadium therapeutic agents [**3**, **4**]. Thus in this research study, the coordination behaviour of nucleosides (see **Figure 1**) towards the acidic $[V^{IV}O]^{2+}$ and $[V^{V}O_2]^{+}$ cores will be explored. Beside the important biological functions of nucleosides, the interest behind these compounds stems from their analogues' profound anticancer and antiviral activities [**5**, **6**].

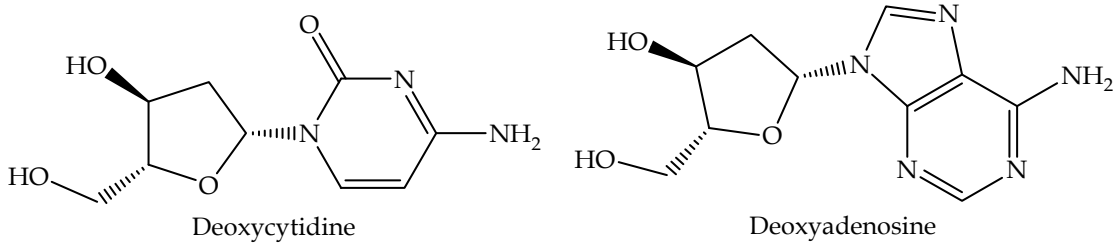


Figure 1: *Structures of two nucleosides: deoxycytidine and deoxyadenosine.*

The formulated oxovanadium compounds will be synthesized by experimental preparative techniques, and will be spectroscopically characterized. Structural elucidations of the respective metal complexes will be confirmed *via* elemental analysis and X-ray structure determinations. In addition, the metallic compounds will be subjected to DNA binding studies.

References:

[1] D. Rehder, Inorg. Chem. Commun. 6 (2003) 604.

[2] A.M. Evangelou, Crit. Rev. Oncol. Hemat. 42 (2002) 249.

[3] I.N. Booysen, T. Hlela, T.I.A. Gerber, O.Q. Munro, M.P. Akerman, Polyhedron 53 (2013) 8.

[4] I.N. Booysen, T. Hlela, M.P. Akerman, B. Xulu, Polyhedron 85 (2015) 144.

[5] J. Wu *et. al*, Eur. J. Med Chem. 63 (2013) 739.

[6] L.P. Jordheim *et. al*, *Nature Reviews Drug Discovery* 12 (2013) 447.

Quantum Dot M(II) Terpyridine nanoconjugates, {M = Ru or Pt}: Potential dual diagnostic and therapeutic agents

Supervisors: Dr. I. N. Booysen, Dr. D. Reddy

Quantum dot-based nanoconjugates have shown potential as novel diagnostic agents for *in vitro* and *in vivo* imaging [**1**]. These diagnostic capabilities of quantum dots (QDs) are largely ascribed to their excellent photochemical properties which can be optimized through altering their size and shape as well by formulating core-shell QDs [**2**]. Hence inherently, quantum dot constituents could potentially allow diagnostic imaging of cancer tumours *via* fluorescence microscopy while transition metal complex constituents may enforce therapeutic treatment of cancers. The interest in the inclusion ruthenium- or platinum terpyridine complexes stems from the discovery of the first ruthenium anticancer drug, NAMI A, *trans*-[$Ru^{III}Cl_4$(DMSO)(Im)](ImH) {ImH = imidazole} which are currently under Phase II clinical trials while various platinum compounds are well established chemotherapeutic agents [**3**].

Thus, this research study will entail the synthesis and spectroscopic characterization of CdSe quantum dots as well as M(II) Terpyridine {M = Ru or Pt} complexes. In addition, the nanofabrication of the quantum dot M(II) terpyridine nanoconjugates. Electronic properties and size distribution of the CdSe QDs and their nanoconjugates will be probed *via* emission- and UV-Vis spectroscopy. The formation of the nanoconjugates will be confirmed by powder X-ray diffraction and Transmission Electron Microscopy (TEM).

References:

[1] T.R. Pisanic II, Y. Zhang, T.H. Wang, *Quantum dots in diagnostics and detection: principles and paradigms*, Analyst, 2014, 139, 2968.

[2] D. Vasudevan, R.R. Gaddam, A. Trinchi, I. Cole, *Core–shell quantum dots: Properties and Applications*, Journal of Alloys and Compounds, 2015, 636, 395.

[3] K.D. Mjos, C. Orvig, *Metallodrugs in Medicinal Inorganic Chemistry*, Chemical Reviews. 2014, 114, 4540.

Formation and DNA Binding Studies of Novel Diamide Ruthenium Compounds with *Bis*-Heterocyclic Ligands

Supervisors: Dr. I.N. Booysen and Dr S. Sithebe

The concerted efforts in the isolation of new analogues of NAMI A, *trans*-[$RuCl_4$(DMSO)(Im)](ImH) {ImH = imidazole} are due to its potent anti-metastatic cancer activity [**1**]. Recent developments are geared towards the utilization of biocompatible ligands which may facilitate biodistribution and solubility in the blood stream of the formulated ruthenium anticancer agents [**2**]. Thus, the coordination behaviour of biologically relevant, *bis*-heterocyclic ligands (see Figure 1) will be explored towards the *trans*-$[Ru(PPh_3)_2]^{2+}$ core.

The formulated ruthenium compounds and their free-ligands will be synthesized by experimental preparative techniques, and will be analysed by elemental analysis, infrared and electronic spectroscopy, ^{13}C and ^{1}H NMR spectroscopy, molar conductivity measurements, electroanalytical methods, computational modelling calculations and X-ray structure determinations. In addition, the metallic compounds will also be subjected to DNA binding studies.

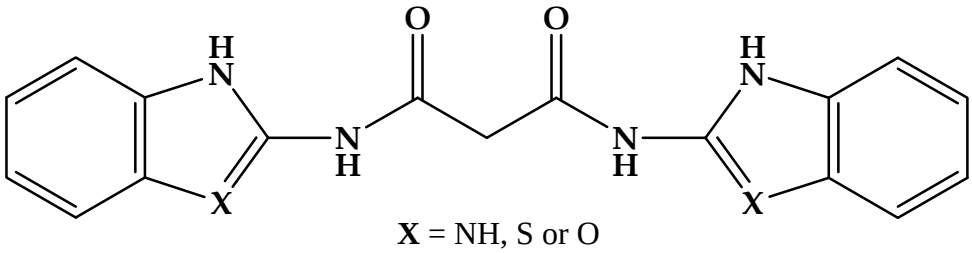


Figure 1: *Generic structure of the bis-heterocyclic ligands.*

References:

[1] J.B. Aitken, S. Antony, C.M. Weekley, B. Lai, L. Spiccia, H.H. Harris, *Metallomics*, 2012, **4**, 1051.

[2] S. Medici, M. Peana, V. M. Nurchi, J.I. Lachowicz, G. Crisponi, M.A. Zoroddua, *Coord. Chem. Rev.*, 2014, http://dx.doi.org/10.1016/j.ccr.2014.08.002.

An Environmentally Friendly Synthetic Route to 1,4 – Dihydropyridines

Supervisor: Dr. V. Jeena

1,4-Dihydropyridines(DHPs) are an important and privileged class of heterocyclic scaffolds of low molecular weight in medicinal chemistry, providing important ligands for biological receptors. The first synthesis of these molecules was carried out by Arthur Rudolf Hantzsch in 1882, through a multicomponent reaction between 2 equivalents of a β-ketoester, aldehydes, and NH_4OAc in the presence of hydrochloric acid as a catalyst.

Our approach to these 1,4-dihydropyridines is to use the Hantzsch procedure above, however, making use of environmentally friendly solvents and reagents. The project will also aim to synthesize commercially available *Nifedipine* (**Figure 1**), using a Hantzsch process, which is currently being used to treat high blood pressure and is on the World Health Organizations (WHO) list of most valuable drugs.

Figure 1: A box of Nifedipine tablets

An Environmentally Friendly Synthetic Route to 3,4-dihydropyrimidin-2(1*H*)-ones

Supervisor: Dr. V. Jeena

3,4-dihydropyrimidin-2(1*H*)-ones are an important and privileged class of heterocyclic scaffolds of low molecular weight in medicinal chemistry, providing important ligands for biological receptors. The first synthesis of these molecules was carried out by Pietro Biginelli in 1891, through a multicomponent reaction between ethyl acetoacetate, aldehydes, and urea in the presence of an acid catalyst.

Our approach to these 3,4-dihydropyrimidin-2(1*H*)-ones is to use the Biginelli procedure above, however, making use of environmentally friendly solvents and reagents. The project will also aim to synthesize *Monastrol* (**Figure 1**) using the developed Biginelli process. This interesting compound has been shown to block the mitosis process of cancer cells and, therefore, is an exciting alternative cancer treatment and consequently, we would like to synthesize it in our laboratories.

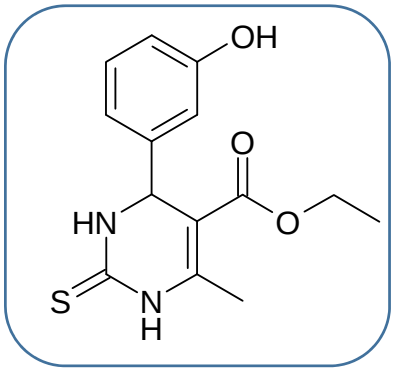
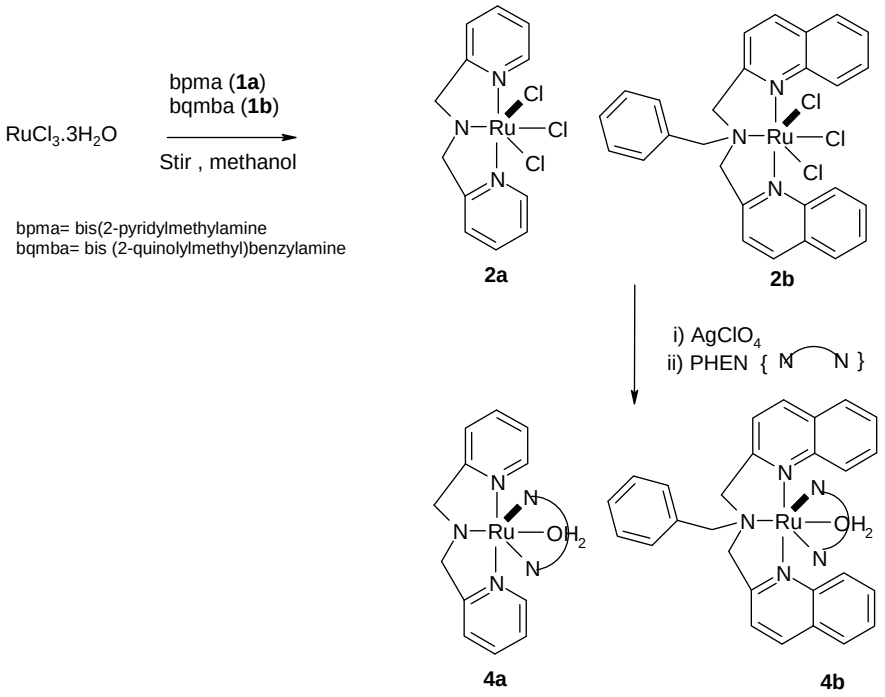


Figure 1: Monastrol = Mitosis Inhibitor = Potential cancer antagonist

Synthesis and Kinetic Study of Ruthenium(II) Monoaqua Complexes with a *Bis*(2-pyridylmethyl)amine or *Bis*(2-quinolylmethyl)benzylamine Ligand

Supervisors: Dr. A. Mambanda and Prof. D. Jaganyi

Ruthenium complexes with polypyridyl ligands are known to be excellent DNA intercalators. This can be helpful in the treatment of cancers (1-3). Some of the complexes can chemically cut out DNA at specific base sequences.



Aims:

- To synthesize and characterize two Ru(II) complexes of the type [Ru(**bpma**/**bqmba**)(NN)$(OH_2)]^{2+}$; NN = phenthroline. **bqmba** is synthesized starting from 2- quinolylmethyl chloride hydrochloride and benzylamine.
- To carry out kinetics studies of these complexes to determine the influence of the tridentate (NNN) ligands on the reactivity of the complexes.

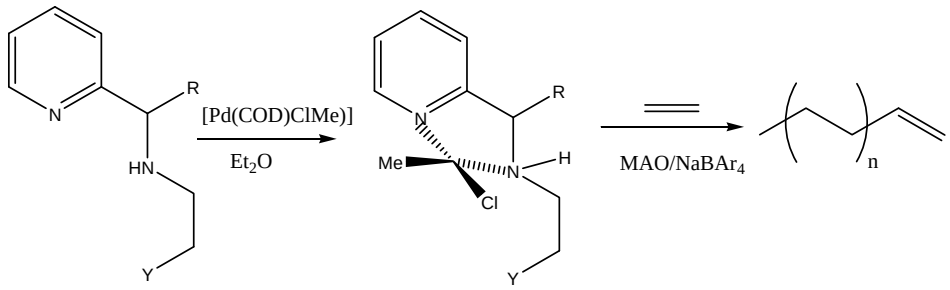
References

[1] I. Greguric, J. R. Aldrich-Wright, and J. G. Collins, J. Am. Chem. Soc., **1997**, 119, 3621.
[2] Y. Xiong, et al, J. Chem. Soc., Dalton Trans., **1999**, 19.
[3] F. M. Foley, F. R. Keene, and J. g. Collins, J. Chem. Soc., Dalton Trans., **2001**, 2968.
[4] Rodríguez et al, Inorg. Chem., **2001**, 40, 4151

Ethylene Oligomerization and Polymerization Reactions Catalyzed By Nitrogen-Donor Palladium(II) Complexes

Supervisor: Dr. S. O. Ojwach

Transition metal catalyzed olefin transformation reactions have played a significant role in the petrochemical, fine chemical and pharmaceutical industries.[1] For example the conversion of lighter α-olefins (C_2-C_8) to higher α-olefins (C_{10}-C_{20}), fine and bulk chemicals used in the manufacture of plastics, detergents, plasticizers, adhesives, pharmaceutical products is currently receiving much attention. As a result, the development of homogenous catalysts that would add value to these α-olefins is of great importance.[2-4] Homogeneous single-site transition metal catalysts offer several advantages over the well-established heterogeneous catalysts. Most notable is the ease of control of product properties in addition to understanding the mechanisms involved in such reactions. It is on this premise that this project seeks to develop effective catalysts for the oligomerization or polymerization of ethylene using palladium(II) complexes of potential hemi-labile (amino)pyridine ligands (Scheme 1).



Y = $N(Et)_2$, OCH_3, OH; R = Me, H
Ar = Ar = 3,5-$(CF_3)_2C_6H_3$)

Scheme 1

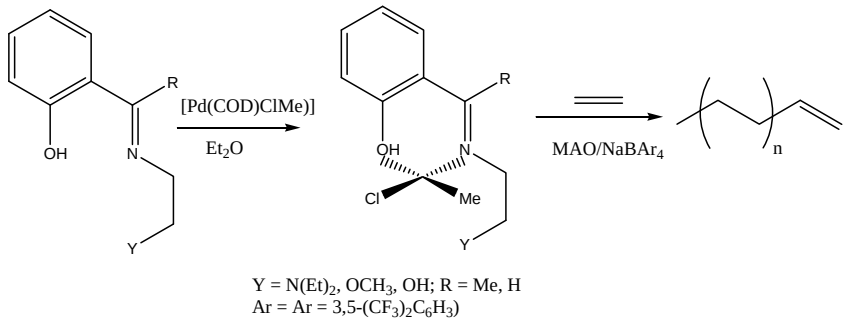
References

1. Rix, F. and Brookhart, M., *J. Am. Chem. Soc.*, **1995**, *117*, 1137.
2. Ittel, S. D.; Johnson, L. K.; Brookhart, M. *Chem. Rev.* **2000**, *100*, 1169.
3. Ojwach, S.O., Guzei, I. A., Bernade, L.L., Mapolie, S.F., Darkwa, J., *Organometallics*, **2009**, *28*, 2127.
4. G. S. Nyamato, S. O. Ojwach and M. P. Akerman, *Organometallics*, 2015, DOI:10.1021/acs.organomet.5b00860.

Ethylene Oligomerization and Polymerization Reactions Catalyzed By Hemi-labile Nitrogen-Oxygen Donor Palladium(II) Complexes

Supervisor: Dr. S. O. Ojwach

Late transition metal complexes have been used as catalysts in a number of organic transformations, including ethylene oligomerization and polymerization reactions[1, 2] since the seminal work of Brookhart *et al.*[3] on the use of a-diimine ligands in the development of a-olefin oligomerization catalysts. One strategy that has been adopted for the design of stable and more active catalysts for ethylene oligomerization and polymerization has been in the use of ''hemi-labile ligands'', pioneered by Jeffrey and Rauchfuss in 1979.[4] In one such report, hemilabile ligands based on bidentate P,O-ligands were found to influence both the selectivity and stability of transition metal catalysts.[5] We thus aim to prepare potential hemi-labile palladium complexes of N^O ligands and investigate their ability to catalyze ethylene oligomerization and polymerization reactions (Scheme 1).



Scheme 1: Syntheses of palladium complexes and ethylene oligomerization reactions

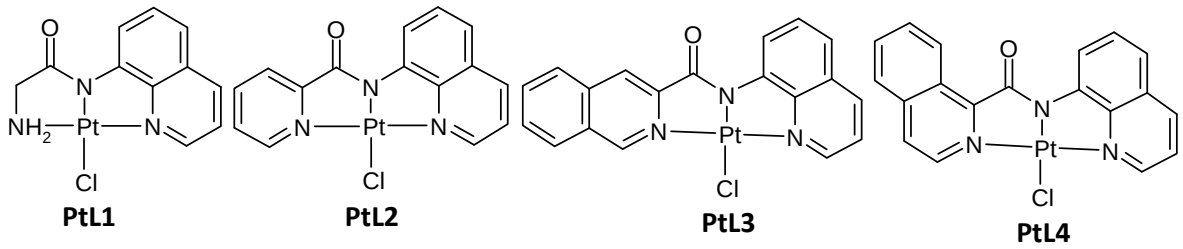
References

1. Ittel, S. D.; Johnson, L. K.; Brookhart, M., Chem. Rev. **2000**, 100, 1169-1204.
2. McGarrigle, E. M.; Gilheany, D. G., Chem. Rev. **2005**, 105, 1563-1602.
3. Johnson, L. K.; Killian, C. M.; Brookhart, M., J. Am. Chem. Soc. **1995**, 117, 6414-6415
4. Jeffrey, J. C.; Rauchfuss, T. B., Inorg. Chem. **1979**, 18, 2658-2666.
5. Mecking, S.; Keim, W., Organometallics **1996**, 15, 2650-2656.

A Kinetic and Mechanistic study of Platinum(II)- Quinoline Carboxamide Complexes with Azole Nucleophiles

Supervisors: Ms. T. Papo and Prof. D. Jaganyi

Since the discovery of the anti-proliferation activity of cisplatin in the 1960s[1], the search for platinum based anti-cancer drugs with better efficacy and lower toxicity has been going on. In order to design more drugs with specific kinetic and thermodynamic properties, we have to understand the factors controlling the reactivity of these complexes. It has been shown that structural modifications of the non-labile chelate ligand can produce significant changes in the substitution reactions of Pt(II) complexes.[2] The reactivity of these complexes is controlled by the σ-donor and π-acceptor effect of the ligand backbone.[3] To further extend our understanding on the role played by π-back-bonding, substitution reactions of four mononuclear Pt(II) complexes (**PtL1**, **PtL2**, **PtL3** and **PtL4**), comprising a carboxamide ligand will be investigated with azole nucleophiles in solution.



Scheme 1: Structures of the Pt(II) complexes to be studied.

References:

1. B. Rosenberg, L. Van Camp and T. Krigas, *Nature*, 1965, **205**, 698
2. (a) M. R. Plutino, L. M. Scolaro, R. Romeo and A. Grassi, *Inorg Chem*, 2000, **39**, 2712
   b) R. Romeo, M. R. Plutino, L. M. Scolaro, S. Stoccoro and G. Minghetti, *Inorg Chem*, 2000, **39**, 4749
3. P. Ongoma and D. Jaganyi, *Dalton Trans*, 2012, **41**, 10724

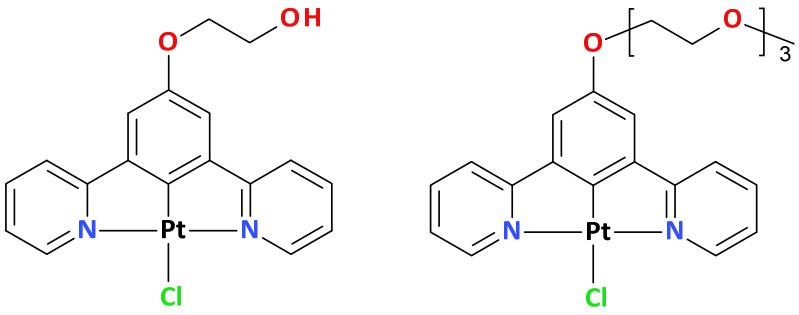
Neutral N^C^N Terdendate Luminescent Platinum(II) Complexes: Synthesis, Photophysical Properties and Mechanistic Studies

Supervisor: Dr. D. Reddy

Whilst interest in the development of platinum-based drugs continues to grow, d^8 platinum(II) complexes have also attracted attention for their interesting luminescence properties. In particular, a fast emerging field is the use of luminescent platinum(II) complexes as luminescent labels for bio-imaging.

Platinum complexes offer several advantages over the more widely used fluorescent organic labels, in that (i) there is a wide emission colour tenability by choice of the ligands, (ii) there is better stability towards photo- and chemical degradation and (iii) the emission lifetimes are several orders longer that those of classic organic fluorophores.

In this project, the incumbent student will synthesize and fully characterize two platinum(II) complexes (*Figure 1*).



PtL¹Cl **PtL²Cl**

Figure 1: Chemical structures of the neutral platinum complexes to be investigated

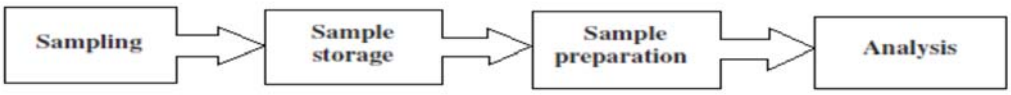
The synthesized complexes will subsequently be photophysically characterized and the kinetics of chloride substitution will be investigated by a detailed mechanistic study.

The candidate student will gain experience in inorganic synthesis, modern characterization techniques and in the area of photophysical and mechanistic studies and the accompanying techniques. In addition, you will be exposed introductory computational chemistry in an effort to explain the findings of your kinetic study. In addition, there is a distinct possibility of publishing your findings in a peer-reviewed journal.

Method development/modification for pesticides analysis in PMB area

Supervisor: Dr. P. Sibiya

Pesticides have major contribution to the quality of life as they are used for the protection of food crops against pests and diseases. On the other hand, their improper usage has some disadvantages as it leads to potential harmful side effects to humans and other animals. The leaching run-off from agricultural and forest lands as well as the residue from the industrial wastewater treatment are mainly responsible for water contamination by pesticides. The effective use of pesticides requires knowledge of their distribution and persistence in the environment. This knowledge is obtained by the collection and analysis of water, soil and air samples to assess their distribution patterns during application and also to evaluate the environmental fate of the pesticides after application. The process of obtaining accurate results in organic pollutants measurement requires a series of steps whereby each of them is critical to the validity of data. These steps are shown in the following scheme.



Sample preparation is done to transfer the analyte from the matrix to a suitable medium for introduction into the analytical instrument for analysis. It involves pre-concentration and removal of interferences and other operations that allow accurate determination of the analyte. Organic pollutants are usually present in very low concentrations in water therefore a pre-concentration step is required for their detection and quantification. Also as the samples might have complex and many matrix components, hence a clean-up step is normally required to separate the analyte from the matrix. The successful use of extraction and clean up methods depends on the ability to choose the right combination of operational conditions. Therefore in this work the solid phase extraction (SPE) will be used due to its ability to pre concentrate and clean up the sample. SPE and liquid/liquid extraction methods will be optimised and then used for the extraction of pesticides in water samples. GC-MS or HPLC-MS will be used for the detection and quantification. The samples will be taken around PMB area.

Aims of the project

- To develop/modify SPE and LLE extraction methods for extraction of pesticides in water and compare their extraction efficiency.
- To apply the modified methods on real water samples in order to identify the pesticides present in water and determine their concentrations.

References

1. Kratochvil B., Peak J. (1989). Analytical methods for pesticides and plant growth.
2. Tuzimski T. (2011). Multidimensional Chromatography in Pesticides Analysis. 460-463.

Method development/modification for pharmaceuticals analysis in PMB area

Supervisor: Dr. P. Sibiya

Pharmaceutical compounds are substances found in prescription medicines and they are consumed by humans for treatment and prevention of diseases. The major sources of pharmaceutical contaminants in the environment are domestic and hospital discharges, veterinary applications and industrial waste streams. Most of these discharges find their way into wastewater treatment plants where they get degraded and thereafter released into the natural water systems. Due to the increase in the pharmaceuticals uptake, even though their levels are found to be low in aquatic environment, they are regarded as an environmental concern because they could have an ecological and human health effect. There is therefore a need to monitor these compounds in the environment. In this project the SPE and liquid/liquid extraction methods will be optimised and then used for the extraction of pharmaceutical compounds in water samples. GC-MS or HPLC-MS will be used for detection and quantification. The samples will be taken around PMB area.

Aims of the project

- To develop/modify SPE and LLE extraction methods and compare their extraction efficiency.
- To apply the modified methods on real water samples for in order to identify the pharmaceutical compounds present in water and determine their concentration.

References

1. Birnbaum L.S., Fenton S.E. (2003). Environ Health Perspect 111:389-394.

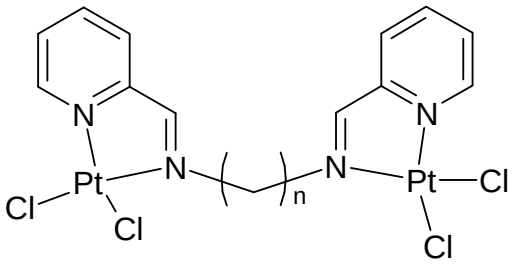
Synthesis of Binuclear Platinum(II) Complexes of *N,N'*-{1, n}-alkanediyl-bis(pyridinyl-2-methanimine) Ligands and Their Reactivity with Thiourea Nucleophiles

Supervisors: Mr. M. K. Sitati and Prof. D. Jaganyi

Isolation of allylpalladium and ortho-palladated complexes in the 1960's[1] motivated the development of binuclear palladium complexes due to their use in organic transformations. The field is versatile including areas such as organic synthesis, catalysis, material-science, and chemotherapy[2] just to name but a few.

Dinuclear organometallic compounds are unique because their reactivity is different from their mononuclear counterparts.[3] Metal-metal interactions enable accessibility to more oxidation states for binuclear complexes[4] which also result to increased reaction rates or yield transformation rates.[5] Distance between the two metal centres and their orientation relative to each other may account for observed reactivity.[6] The nature of ligand plays an important role on the behaviour of the metal. The rigidity and the bulk imposed by nitrogen ligands have been the subject of several studies, especially the class of rigid α-diimine ligands such as bis(aryl)acenaphthene (bian).[7] The α-diimine ligands combine good π-acceptor and π-donor properties and as a result can stabilize low and high oxidation state transition metals.[8] Additionally, these types of ligands' electronic and steric properties can easily be tuned.

In this study, we report the synthesis of a variety of [*N,N'*{1, n}-alkanediyl-bis(pyridinyl-2-methanimine)] ligands {n = 2 (L1), 3 (L2), 5 (L3), 6 (L4)} and their tetrachloro-platinum(II) complexes. Since these complexes are potential anticancer agents, understanding the mechanism of action of these complexes with human cells is important. Thus, this work reports for the first time the synthesis of the platinum(II) metal complexes and their reactivity with biorelevant thiourea nucleophiles viz; TU, MTU, DMTU. The complexes to studied using biological nucleophiles are given in Scheme 1.



n = 2, 3, 4, 5

Scheme 1

References

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2. T. Ikariya, K. Murata, R. Noyori, Org. Biomol. Chem. 4 (2006) 393.
3. (a) Z. Wang, S. Teo, L.L. Koh, T.S.A. Hor, Organometallics 23 (2004) 3603; (b) S. Barlow, D. O'Hare, Chem. Rev. 97 (1997) 637.
4. B.-H. Xia, H.-X. Zhang, C.-M. Che, K.-H. Leung, D.L. Phillips, N. Zhu, Z.-Y. Zhou, J. Am. Chem. Soc. 125 (2003) 10362.
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7. R. van Asselt, E.E.C.G. Gielens, R.E. Rulke, K. Vrieze, C.J. Elsevier, J. Am. Chem. Soc. 116 (1994) 979.
8. R. Chen, S. Mapolie, J. Mol. Cat. A: Chem. 193 (2003) 33.

The Role of Terminal and Bridging Ligands on the Reactivity of Binuclear Arene-Ruthenium Complexes

Supervisors: Mr. M. K. Sitati and Prof. D. Jaganyi

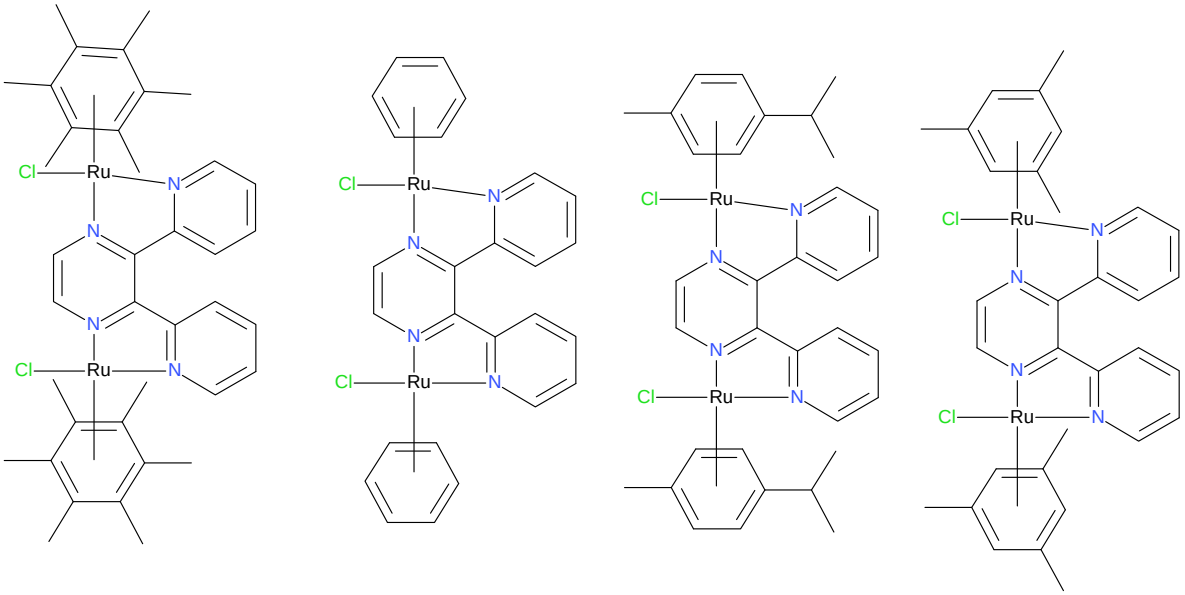
As an alternatives to platinum anti-cancer agents, ruthenium compounds are most promising.[1] The ligand exchange kinetics of metal complexes in aqueous solution, which seem to be crucial for the anticancer activity though different in orders of magnitude for platinum(II) and ruthenium(II) complexes but is similar.[2]

Ruthenium is attractive particularly because many ruthenium compounds are not very toxic and some ruthenium compounds have been shown to be quite selective for cancer cells.[3,4] The specificity is believed to be due to the ability of ruthenium to mimic iron in binding to biomolecules. As cancer cells overexpress transferrin receptors to satisfy their increased demand for iron, ruthenium-based drugs (containing the iron homologue ruthenium) may be delivered more efficiently to cancer cells.[5,6]

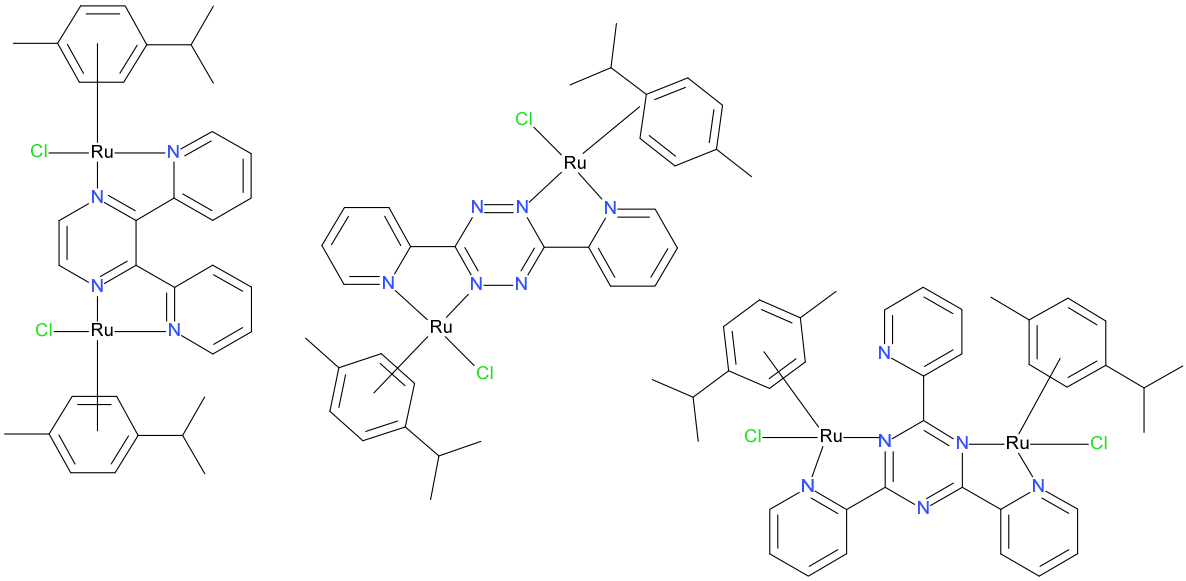
The greatest explanation for the flourishing design of arene-ruthenium based anticancer drugs are the amphiphilic properties of the arene ruthenium unit, provided by the hydrophobic arene ligand counterbalanced by the hydrophilic metal centre, and the synthetic diversity of the arene ligand, which is an excellent scaffold for the coupling of organic segments for targeted chemotherapy.[7] Another critical feature is the hydrolysis of Ru–X bonds to give R-OH_2, while the arene– ruthenium bond is robust the corresponding aqua complex will exist over a range of pH, but for pH > p*K*a the hydroxo complex formed by deprotonation will be predominant. Since hydroxide is a less labile ligand than water, it will not so easily be displaced by biomolecular targets. It's worth noting that *para*-cymene and derivatives inhibit metastasis.[8]

In the studies presented below, arene-ruthenium binuclear complexes with different variations of ligands have been synthesised and characterised. Because of the potential of the complexes to be applied in cancer treatment, understanding their mechanism of action with human cells is important. Thus, this work reports for the first time the kinetic and mechanistic study of arene-ruthenium binuclear complexes with biorelavant thiourea nucleophiles viz; TU, DMTU, TMTU. The structures of the complexes to be studied are given in Scheme 1.

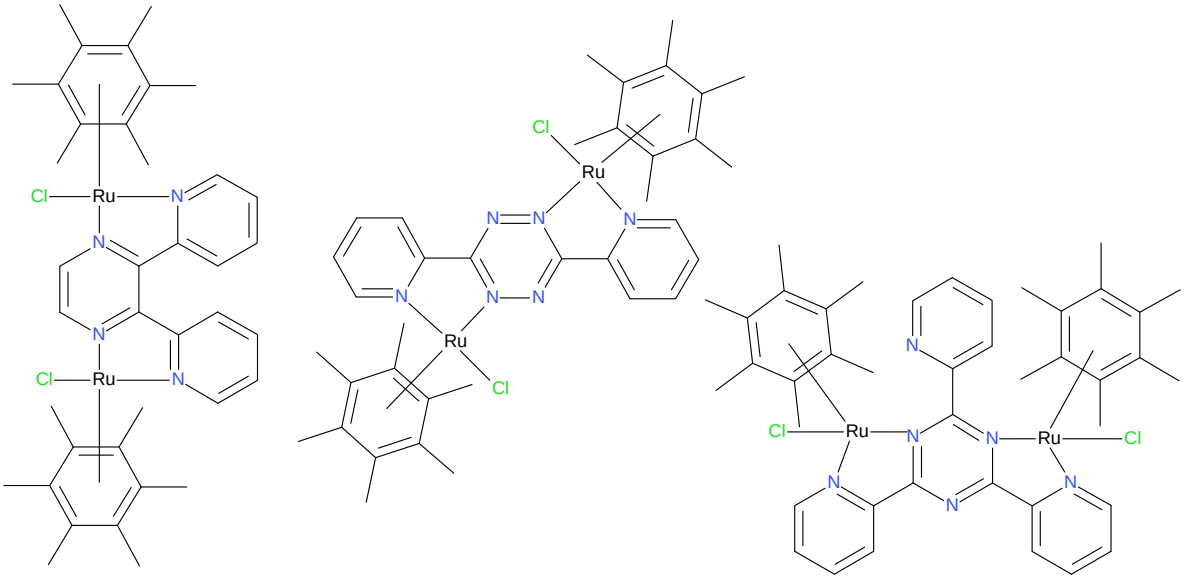
Study 1



Study 2



Study 3



Note: *For this project, a student will only need to select one of the three studies.*

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Base Free Suzuki-Miyaura Acylation Reactions: An Efficient Procedure For the Synthesis of Ketones

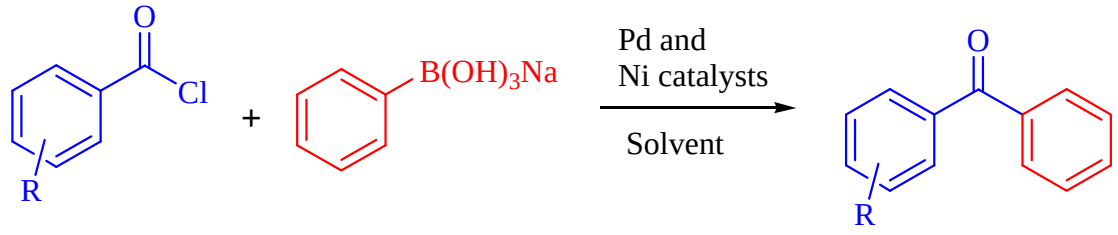
Supervisor: Dr. S. Sithebe

Ketones are organic compounds containing a carbonyl functionality bonded to two hydrocarbon groups. Ketones constitutes an important building blocks in many natural products as well as biological active pharmaceutical compounds.[1] A number of approaches, to introduce acyl functionalities, have been exploited and well documented in the literature.[2,3] Traditionally, the introduction of acyl functionalities has been introduced through Friedel-Craft Acylation reaction of both substituted and un-substituted aromatic rings. However this method suffers from a number of limitations such as low yields, harsh reaction conditions and low regioselectivities to mention just a few.

Beside, other methods, to prepare ketones, such as nucleophilic addition of organometallic compounds to carboxylic acid derivatives, have also been successfully used. The low yields, large amount of by-products as well as drastic reaction conditions have limited the use of these methods.[4]

The Suzuki-Miyara cross coupling of organoboron compounds and carboxylic acid derivatives is well known to introduce an acyl functionality with high regioselectivities and high yields, but the reaction conditions employed often requires three equivalent of base and are conducted at high temperatures.

The aim of this project is to develop a cheap, convenient and a base free Suzuki-Miyaura procedure for the synthesis of ketones at room temperature (**Scheme 1**).



R = NO_2, H, CH_3, Br

Scheme 1

References

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Phytochemistry of *Euphorbia* Species

Supervisor: Prof. F. R. van Heerden

Many drugs are developed from natural products, i.e. compounds isolated from plants, marine organisms or microorganisms. Examples of drugs developed from plants are morphine, aspirin (acetylsalycilic acid) and taxol, a very effective anticancer drug. The plant family Euphorbiaceae, to which *Euphorbia* belongs, has a large number species in South Africa. *Euphorbia* species are normally associated with the skin irritation caused by the skin-irritant properties of the white latex of the plant. Apart from the irritant properties, compounds like ingenol, isolated from the African *Euphorbia tirucalli*, has a number of biological properties.

In this project a *Euphorbia* species will be collected form the UKZN Botanical Garden. The plant will be extracted and from the extracts, compounds will be isolated and the structures determined. If a clean compound is isolated, the compound will be tested for anti-HIV activity.

You will get experience in:

- Extraction of plant material
- Purification of compounds by chromatography
- Structural determination of complex organic compounds
- Techniques used will be TLC, column chromatography, radial chromatography, HPLC, LC-MS, NMR.

Investigation of the Reaction of Rooperol with Hypochlorous Acid

Supervisors: Prof. F. R. Van Heerden and Dr. B. A. Xulu

Many South Africans believe that the African potato (AP), *Hypoxis hemerocallidea*, also known as *Hypoxis rooperi* of the family Hypoxidaceae possess both nutritional and medicinal value. It is widely used as an immune booster for the treatment of various ailments such as the treatment of urinary diseases, prostate hypertrophy, and internal cancer. The main constituent in the AP believed to exhibit the antioxidant properties is rooperol (Figure 1). Structurally, rooperol resembles known strong antioxidants including resveratrol, quercetin, piceatannol and nordihydroguaiaretic acid. However, there is an astonishing absence of information in literature for the reactions of rooperol with biologically relevant oxidants such as hypochlorous acid (HOCl) which are released during inflammatory response.

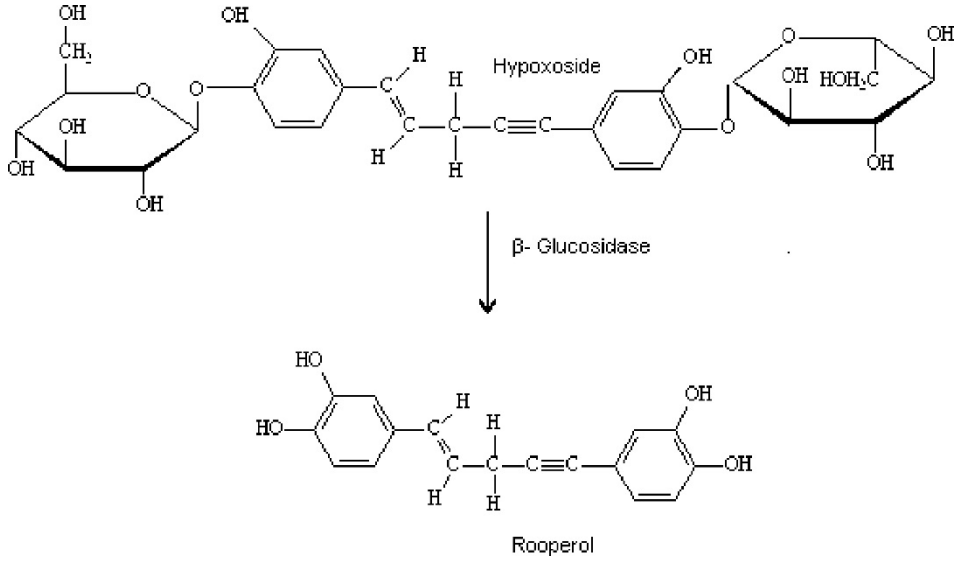

Figure 1: The structures of hypoxoside and rooperol

In this project, the student will isolate hypoxoside from the *H. hemerocallidea* and then synthesize rooperol from it as per Figure 1. This will be followed by the characterization of the products of the reaction of rooperol with HOCl. The identity of these products will offer insight into the antioxidant mechanism of rooperol. The analytical techniques to be employed include UV-Vis, Stopped flow, NMR, MS/MS.

Reaction of *trans*-resveratrol with hypochlorous acid (HOCl)

Supervisor: Dr. B. A. Xulu

Resveratrol (3, 4, 5-trihydroxy-trans-stilbene) is a natural phytoalexin found in grapes and has antioxidant properties. It has attracted interest as a wine constituent that may reduce heart disease. The reaction of resveratrol with proinflammatory oxidants such as hypochlorous acid (HOCl) at physiological pH conditions has been explored by Zhou *et al*. Surprisingly, they obtained very low yields of chlorinated products (1 – 6.5 %). We believe that the main reason for these low yields was the ineffectiveness of the ethyl acetate extraction used in their study. The purpose of our study is to investigate the products of this reaction in aqueous media which we believe will result in much higher yields. Our preliminary UV-Vis experiments have shown the formation of a new species around 324 nm which we believe to be a resveratrol chlorinated at 1 position.

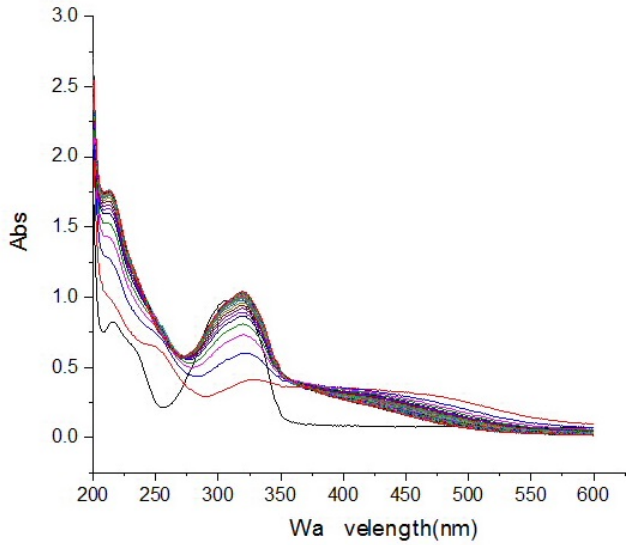

Figure 1: Chlorinated product formation from the reaction of resveratrol with HOCl

In this study we will measure the rate constants for the disappearance of resveratrol and the formation of the chlorinated product(s) using the UV-Vis and the stopped flow techniques. We will then determine the molar absorptivity of the chlorinated product and use it to calculate the yield. The identity of the product(s) will further be characterised by NMR and MS/MS.