LUND UNIVERSITY

Metals in medicine

-a cure for malaria?

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Bachelor thesis

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2015-10-31, Lund University

Contents

Introduction

This bachelor project was about investigating new synthetic routes for metal complexes that are potential anti-malarial agents. The testing for anti malarial activity is to be carried out after the end of this project. The focus will thus be on presenting the laboratory work that was achieved; some synthetic strategies that can be used and further developed and some that should be avoided when synthesizing these kinds of metal complexes.

It is believed that four different metal complexes with potential anti-malaria activity were successfully synthesized, of which two were pure and two needs further purification.

This report describes the synthesis and structures of for the ligands **L' L**^{1}, **HL**^{2} and **HL**^{3} that were used in the attempted syntheses to form the different complexes. The routes for making the complexes **(1) – (5)** are thought to have been successful (complex **(3)** was an intermediate) and the desired complexes **(6) – (10)** could not be synthesized.

Metal drugs

Metal-containing drugs are a relatively new field in medicine, and today it is uncommon for a drug to contain any metal. There are, however, a few exceptions; Sodium aurothiomalate is a gold-containing drug used for treating rheumatoid arthritis, and the drug cisplatine, which contains platinum, is used in cancer treatment.

When a pathogenic organism has developed resistance to a drug the drug needs to be modified to overcome the resistance. One way of modification could be the addition of a metal. Since so few drugs today contains metal they could indeed be modified by adding one. It is therefore not unlikely that more and more metal containing drugs will be synthesized and tested in the future.

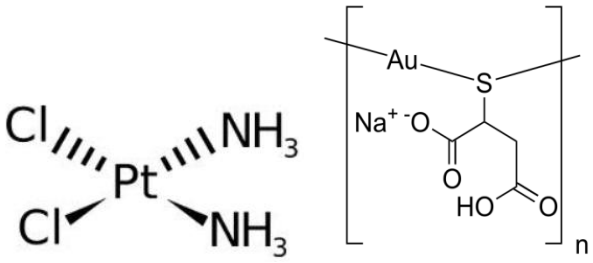

Figure 1. Examples of metal containing drugs, the anti-cancer agent cis-platin (left) and rheumatoid treatment sodium aurothiomalate (right).

Malaria

A parasitic disease

Malaria is caused by protozoan parasites of the genus *Plasmodium.* Five types are known to infect humans; *Plasmodium falciparum, Plasmodium vivax, Plasmodium malarie, Plasmodium ovale* and *Plasmodium knowlesi*.[1] The lifecycle of the parasite is quite complex. It begins with a mosquito biting a vertebrate host (i.e. a human). From the mosquito´s saliva so called sporozoites are released into the blood and transported to the liver where they invade liver cells and produce merozoites. After several days the liver cells burst, releasing thousands of merozoites that invade red blood cells. Inside the red blood cells they digest hemoglobin, using its amino acids as building blocks to develop new merozoites through asexual reproduction. Eventually the cells burst, releasing a new wave of merozoites to invade new red blood cells. This cycle goes on and on, and every time it reaches the step of bursting blood cells the infected vertebrate develops flue like symptoms like fever, vomiting and joint pain. Some merozoites develop further into gametocytes, which can be either male or female. When a mosquito bites the host the gametocytes can be taken up and multiply through sexual reproduction in the mosquito´s gut. If the mosquito already carries a strain of gametocytes these two will mate, giving rise to a new strain of parasites. The offspring will undergo several transformations and is eventually developed to sporozoites, which can enter a host via a mosquito bite and complete the life cycle.[2] Since *Plasmodium* parasites are able to reproduce sexually they have a much larger diversity in their gene pool compare to bacteria, and are therefore more likely to develop drug resistance.

The WHO World Malaria Report from 2014 states that there has been great progress in the fight against malaria during the 21th century. According to the report the mortality rate has decreased by 47 % globally and 54 % in the WHO African Region between 2000 and 2013, which is believed to be an effect of increased political commitment and expansion of global malaria investments. These two factors have lead to improvement in mosquito control, diagnostic testing and treatment with artermisinin-based combination therapies (ACT:s). However, the report also states that parasite resistance to drugs is of great concern, and that malaria is still responsible for 430 000 child deaths each year. [3] Since more and more parasites develop resistance to drugs that are now used it is crucial to come up with new drugs to overcome the resistance.

Malaria drugs

As mentioned, the parasite digests red blood cells to use their amino acids for growth and reproduction. When doing so the iron in the hemoglobin gets oxidized from Fe^{2+} to Fe^{3+}. The oxidized heme is called ferric heme and is poisonous for organisms, since it can react with various parts of the cell. The human body protects itself from this by using an enzyme that the malaria parasite does not have. Instead the parasite has a different way of protecting itself

[1] Warrell, D. A. *Oxford Text Book of Medicine*, Fifth edition. 7.8.2 Malaria. Latest Update - November **2011**
[2] Greenwood, B. M.; Fidock, D. A.; Kyle, D. E.; Kappe, S. H. I.; Alonso, P. L.; Collins, F. H.; Duffy J. *Clin. Invest.,* **2008**, 1136, 32.
[3] *World Malarial Report 2014*, World Health Organization, Geneva, **2014**

from the ferric heme; the hemoglobin is digested in an organelle called the food vacuole, and in this vacuole the poisonous ferric heme gets crystallized into a non-toxic substance called hemozoin. Some successful malaria drugs have this heme crystallization as a target. These types of drugs enter the vacuole, accumulate and prevent the formation of hemozoin. The parasite then dies from poisoning by ferric heme.

One example is the drug chloroquine (Figure 2), which was discovered in 1934 and widely used since WWII. It is a quite hydrophobic molecule and can therefore enter the food vacuole through the hydrophobic vacuole membrane wall, and since the food vacuole is highly acidic the chloroquine gets protonated. This makes it a lot more hydrophilic and prevents it from exiting the vacuole through the membrane wall. Within the vacuole chloroquine interacts with the iron(III) in ferric heme and thereby prevents the formation of hemozoine.

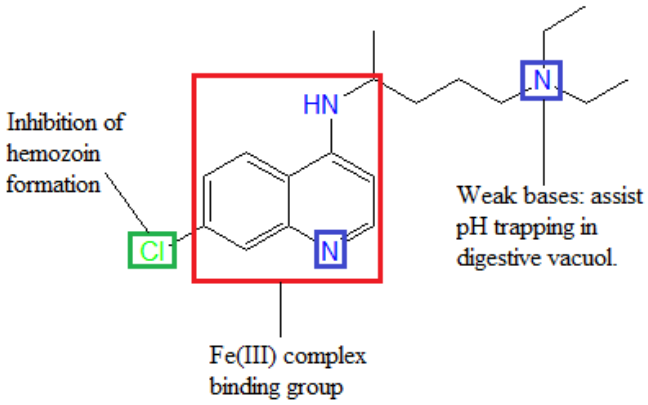

Figure 2. Structure and active sites in the anti malaria drug chloroquine. Adapted from Glans (2012).[4]

Due to massive global use of choloquine most of the malaria parasites today have developed some or complete resistance against chloroquine. It is believed that this is caused by a mutation in a transport protein, which makes the protein more hydrophilic. The protein can then interact with the protonated and hydrophilic cholorioquine[5,6], which then gets transported out of the food vacuole.

In order to overcome this resistance a huge number of modified chloroquine molecules have been synthesized. Biot *et al* linked the chloroquine to a ferrocene, creating the molecule ferroquine (Figure 3).[7] Ferroquine overcomes the chloroquine resistance and has now completed Phase IIb clinical trials.[8] It is therefore most interesting to come up with new similar, metal-containing molecules to test for anti-malaria activity.

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[4] Glans L. *Organometallic complexes with antimalarial properties*, Doctoral Thesis, Lund University, Sweden, **2012**.
[5] Hyde, J. E. *FEBS Journal,* **2007**, 274, 4688
[6] Lakshmanan, V.; Bray, P. G.; Verdier-Pinard, D.; Johnson, D. J.; Horrocks, P.; Muhle, R. A.; Alakpa, G. E. Hughes, R. H.; Wars, S. A.; Krogstad, D. J.; Sidhu, A. B. S.; Fidock, D. A. *EMBO J* **2005**, 24, 2294
[7] Biot, C.; Dive, D.; *Medical Organometallic Chemistry,* eds Jaouen G and Meltzer-Nolte N, Springer, **2010**, pp. 155-194
[8] https://clinicaltrials.gov/ct2/show/NCT00988507?term=ferroquine&rank=1 , updated June 27 **2011**

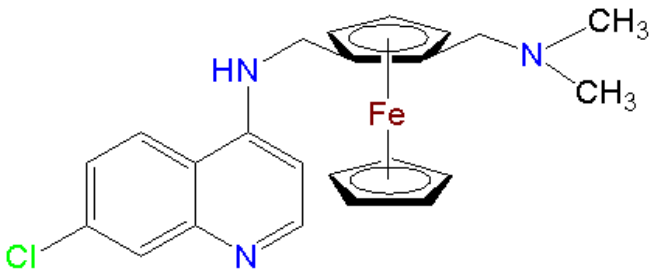


Figure 3. Picture of ferroquine.

Other malaria drugs

According to the WHO World Malaria Report from 2014 artemisine and its semisynthetic derivatives are the most important malaria drugs today, but growing resistance to these makes it important to come up with new drugs. Except the emerging resistance, a major drawback with artemisinin is that it is synthesized by modifying extracted plant material, which makes it highly expensive compare to chloroquinoline.[9] The full of action mechanism of artemisinin is a subject of debate.[3]

The oldest, and still an effective malaria drug, is quinine. It is found in the bark of the Cinchona tree, which is native to the Andes, and still today the tree remains the only economically practical source of quinine. A drawback with this drug is that it exhibits many unpleasant side effects, which is a motivation to come up with alternatives. Quinine is almost only used to for treatment when no other drugs work and the patent risks dying from the malaria infection. As can be seen on the structure, chloroquine resembles quinine.

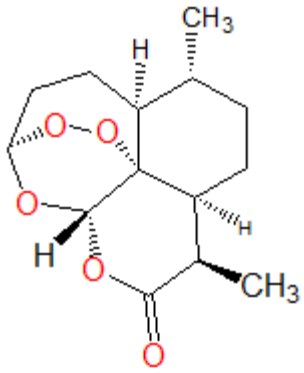


Figure 4. Structure of the anti-malaria agent artemisinin.

[9] Eastman, R. T.; Fidock, D. A. *Nat. Rev.Microbiol.,***2009**, 7, 864.

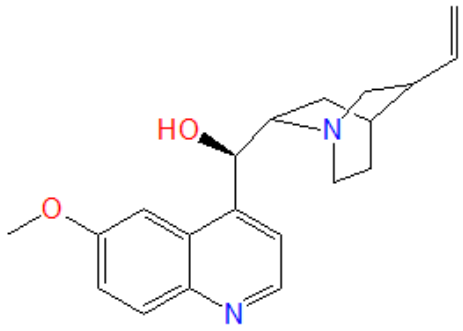


Figure 5: Structure of the anti-malaria quinine. The newer drug chloroquine resembles of this molecule.

Tuberculosis

Tuberculosis (TB) is a disease caused by various strains of mycobacteria, which typically infect the lungs. This leads to chronic cough, bleeding lungs and fever. One third of the world's population is believed to be or have been infected with TB, however not all these cases lead to any symptoms. An infection can however develop to active disease with the mentioned symptoms and 9 million people had active TB in 2013, of which 1.5 million died of the disease[10].

There are different types of drugs against TB, which needs to be combined to for effective treatment. One of these drugs is pyrazinamide (PZA). It is never taken on its own, but still it is an important drug for the treatment of TB since it is used in combination with other drugs. TB causes most problems for poor people in development countries like the WHO African Region because the lack of sufficient hygiene and AIDS makes it more likely to develop active TB. Since both malaria and tuberculosis causes problems in the same areas it would be useful to have a drug that can be used to treat both diseases. The ligand $\mathbf{L^1}$ was synthesized and used in the synthesis of some metal complexes. As can be seen when looking at its structure, it both has a part resembling of chloroquine and a part for anti-TB activity (PZA).

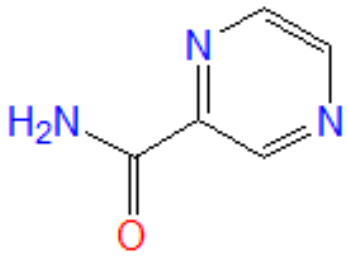


Figure 6. Pyrazinamide, a drug used in combination with other drugs in the treatment of tuberculosis.

The ultimate result for this project would be to synthesize a drug that would overcome the chloquine resistance of malaria due to the addition of a metal, and also work as a treatment for tuberculosis when combined with other TB drugs.

[10] WHO Global Tuberculosis report **2014,** World Health Organization, Geneva, 2014

Complexes

General

The metals ruthenium (Ru), rhodium (Rh) and rhenium (Re) were used in the attempts of making the metal complexes along with the ligands $\mathbf{L^1}$, $\mathbf{HL^2}$ and $\mathbf{HL^3}$ which are presented in Figure 7. All ligands were synthesized by the precursor **L'**. $\mathbf{L^3}$ is a reduced form of $\mathbf{L^2}$ and was used only in a few unsuccessful experiments. In all the synthetic attempts with $\mathbf{HL^2}$ and $\mathbf{HL^3}$ a base was used to deprotonate the desired ligand into $[\mathbf{L^2}]^-$ or $[\mathbf{L^3}]^-$, to make them able to coordinate to the metal. The base was either triethylamine or KOH. All three ligands are bidentate, meaning that they interact with the metal from two different sites of the ligand; bidentate can roughly be translated at "two toothed", meaning that the ligand "bites" from two directions.

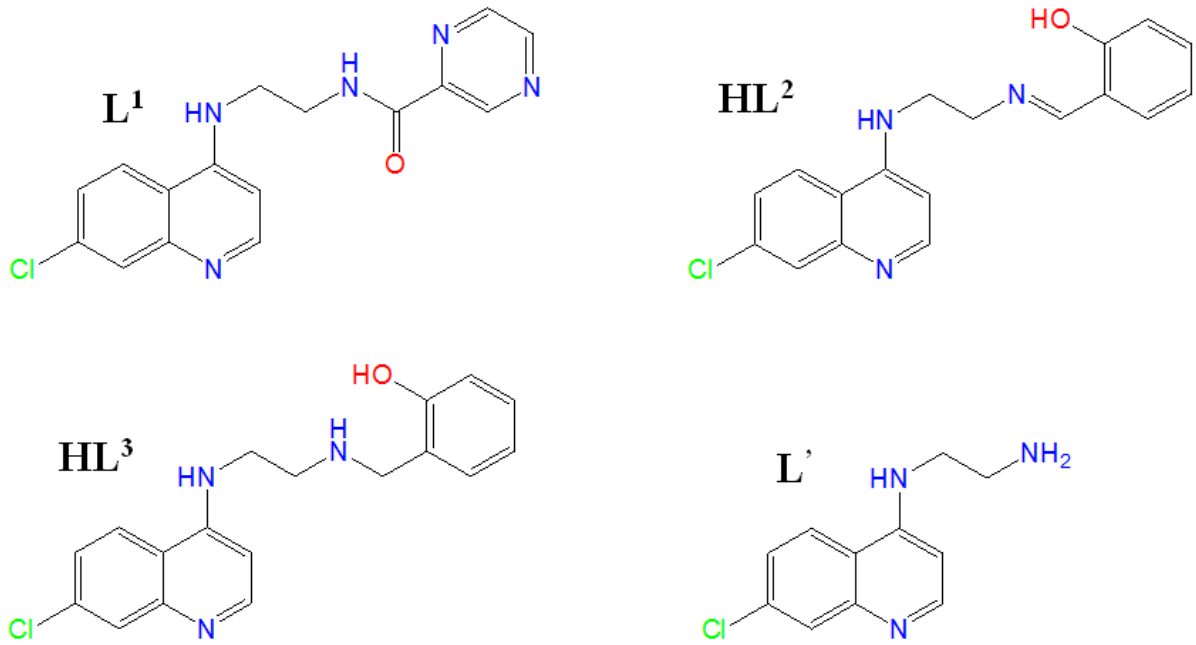


Figure 7. Chemical structures of the ligands L^1, HL^2 and HL^3. The synthesis of all ligands started from L'.

So, what reason is there for a complex to actually form? The main answer to the question could be described by the so called *chelate effect*: When a bidentate ligand interacts with the metal in a solution the metal loses two monodentate ligands (Figure 8). Thus one molecule has been taken up and two released, which gives the net change of one molecule. The entropy of mixing is therefore increased, making the Gibbs free energy of the mixture lower. This should favor the reaction and drive it towards a state where the bidentate ligand interacts with the metal and the monodentate ligands have gone into solution. The chelate effect is thus an entropic effect.

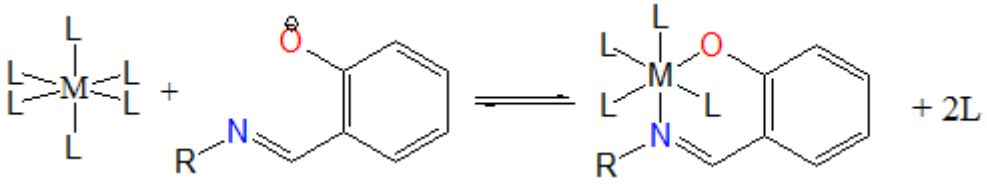


Figure 8. A metal complex consisting of solely monodentate ligands reacts with a bidentate ligand. The entropy increases as one molecule is taken up at the same time as two are released from the metal.

Previous work

Previous syntheses of metal complexes that have potential anti-malaria activity have been carried out by the Nordlander Group of Lund Univerity. A large amount of work is described by Glans[3], while other results have not yet been published. The complexes **(1) – (11)** that are presented in this bachelor thesis differ from the previous complexes because they are not based on half sandwiched structure. Figure 5 shows examples of previous synthesized half sandwich complexes containing the ligands $\mathbf{L^1}$ and $\mathbf{HL^2}$, the same ligands that were used in this bachelor project. The complexes containing ruthenium and osmium are presented by Glans[3], while the other four have not yet been published.

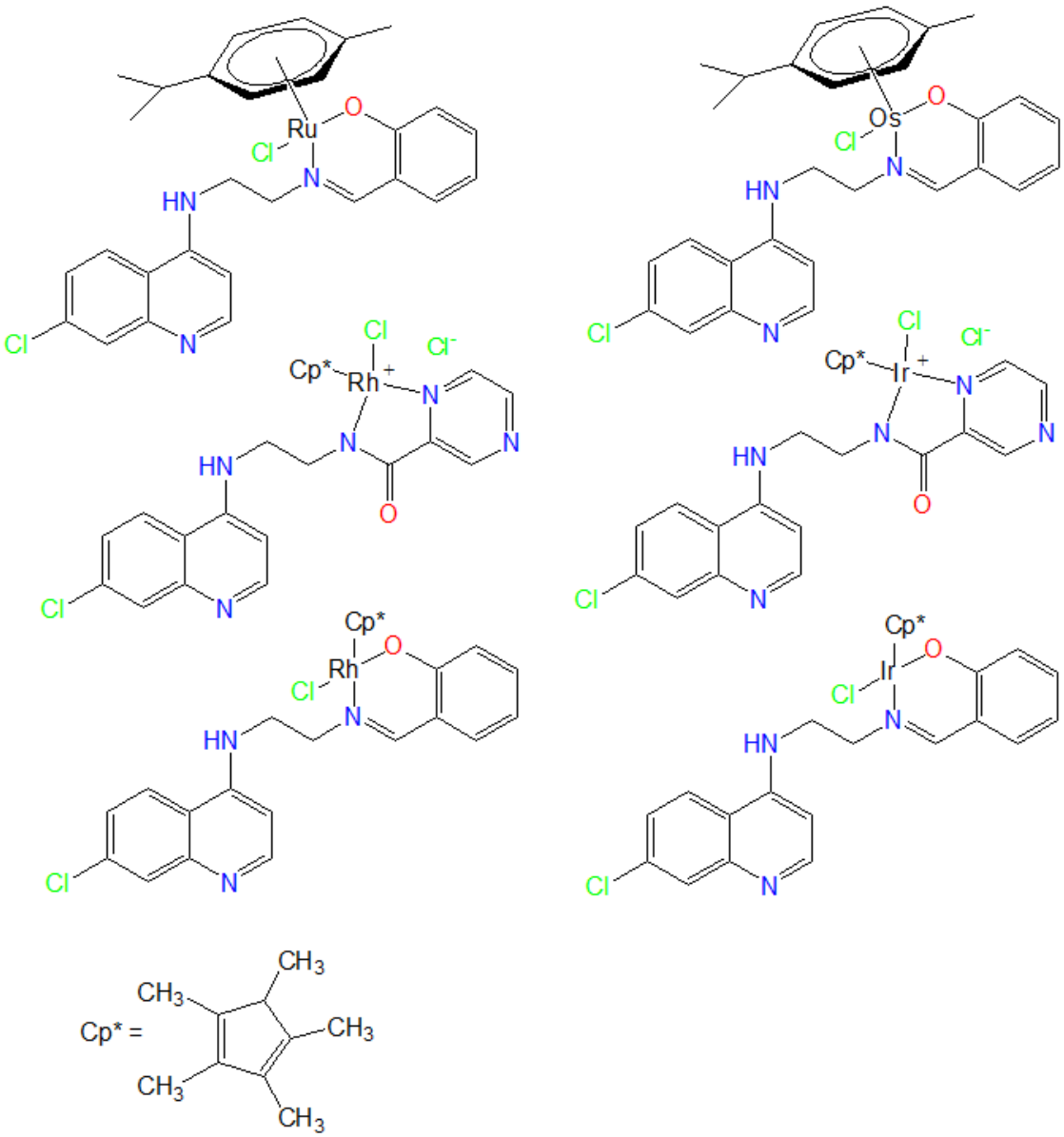


Figure 9. Examples of half sandwich complexes of L^1 and L^2 already synthesized in the Nordlander Group.

Ruthenium

Two ruthenium starting materials were used: $RuCl_2(DMSO)_4$, where ruthenium has the oxidation number 2, and $RuCl_3$ x H_2O, where ruthenium is in the +3 as oxidation state.

It was attempted to react both **L**[1] and **HL**[2] with $RuCl_2(DMSO)_4$ under various conditions in order to form new metal complexes. Likely complexes to form during these reactions are **$RuCl_2(DMSO)_2$L**[1] and **RuCl(DMSO)$_3$L**[2], but others are also possible. It was also attemped to react **HL**[2] with $RuCl_3$,

A ligand similar to **HL**[2], containing two Schiff-base nitrogens, had previously been synthesized and used in a ruthenium(III) complex.[11] There are also examples of ruthenium(II) complexes with DMSO and a ligand containing two Schiff bases in the reported by Khan et. Al.[12] (Figure 10). However, all these examples includes ligands with two Schiff bases, while H**L**[2] contains only one and **L**[1] none.

It was however not attempted to synthesize the complex to the lower left in Figure 10 since it seemed that all the products containing ruthenium were insoluble in most solvents and was therefore hard to analyze.

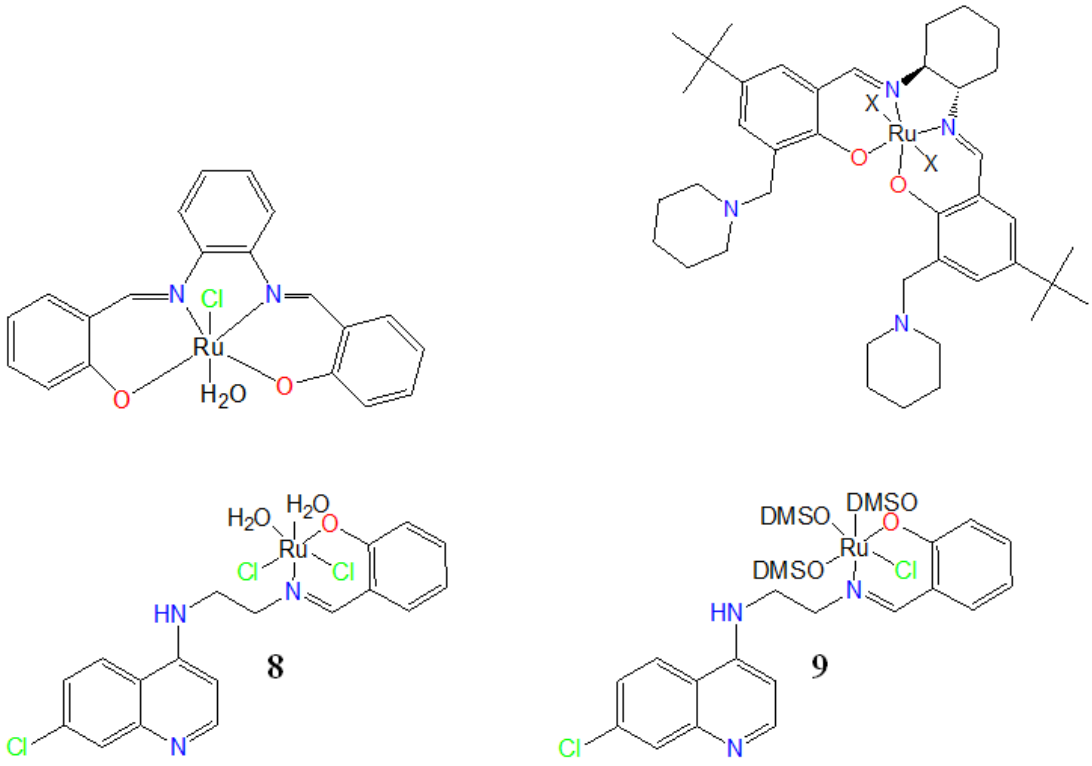


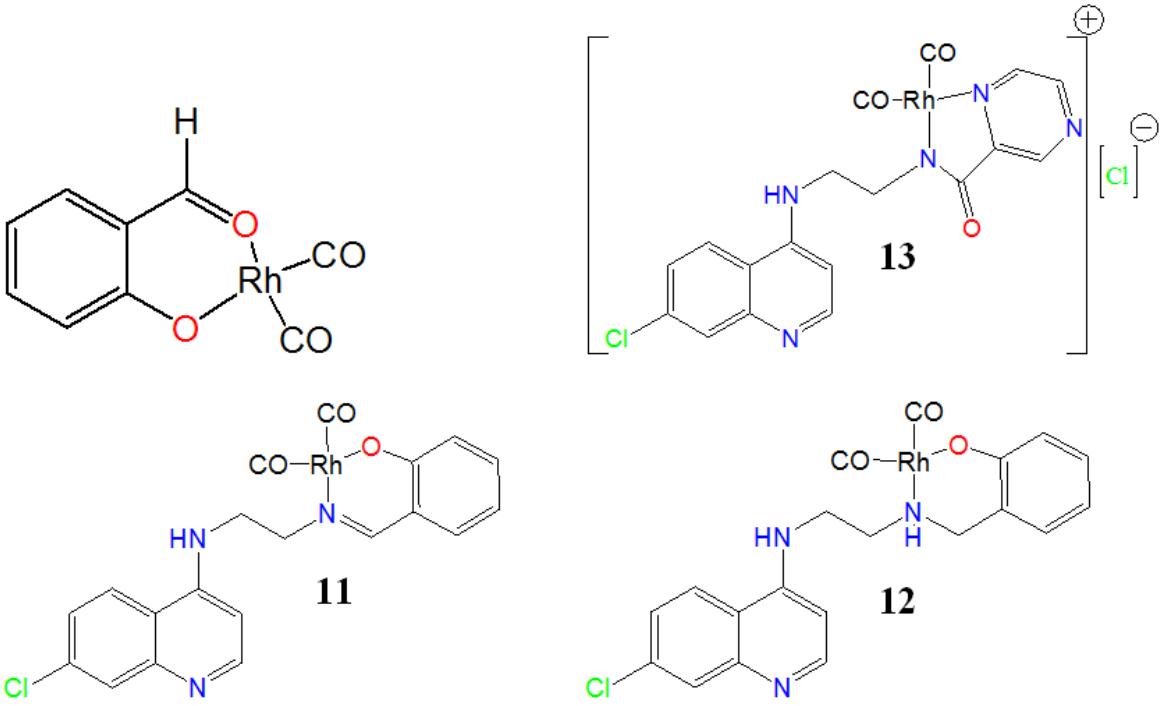
Figure 10. A complex with Ru(III) synthesized by Khan *et al* (upper left) and a complex with Ru(II) synthesized by Chatterjee *et al* (upper right) in comparison to complexes with L[2] that was likely to form during the reactions with Ru(III) and Ru(II). X in the upper right complex is DMSO.

[11] Chatterjee, D.; Mitra, A. *Journal of Coordination Chemistry* **2004** 57:3 175-182

[12] Khan, N. H.; Pandya, N.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Bajaj, H. C.; Pandya, J.; Gupte, A. *Spectrochimica Acta Part A 74* **2009** 113–119

Rhodium

Three rhodium starting materials were used: $RhCl_3xH_2O$, where rhodium has the oxidation number 2, the dimer $[Rh(COD)Cl]_2$, where rhodium is in the +1 oxidation state and COD stands for cyclo-octadien, and $Rh(CO)_3Cl$ where rhodium has +3 as oxidation state. $Rh(CO)_3Cl$ were obtained by treating $RhCl_3xH_2O$ with DMF and it was then used in attempts of synthesizing new metal complexes. **$[Rh(CO)_2]L^2$** and **$[Rh(CO)L^1]Cl$** are possible products of this reaction. This route has been successfully carried out to form similar metal complexes by Oro *et. Al.*[13] (Figure 10). In addition some **HL^2** was reduced by $NaBH_4$ to form **HL^3** which also was reacted in the same way. A probable complexes to form by these reaction is **$[Rh(CO)_2]L^3$**. The conversion of **HL^2** into **HL^3** was confirmed by ^{1}H-NMR spectroscopy, and the conversion was made in order to avoid possible hydrolysis of the ligand



Figur 11. Example of a salicealdehyde-Rh(I) complex synthesized by Oro *et al* which was synthesized by treating $RhCl_3$ with DMF followed by addition of a bidentate ligand (upper left) in comparison to complexes with L^1 (upper right), HL^2 (lower left) and HL^3 (lower right) that was likely to form during similar reactions in DMF. Since rhodium has the oxidation state of +1 the complexes are square planar.

[13] Valderrama, M.; Oro, L. A. *Journal of Organometallic Chemistry* **1981**, *218*, 241.

The most effort in this project was spent on attempts to synthesize new metal complexes by reacting $\mathbf{L^1}$ and $\mathbf{HL^2}$ with the dimer $[Rh(COD)Cl]_2$. The idea was to split the dimer $[Rh(COD)Cl]_2$ into two monomers and add a stoichiometric amount of equivalent ligand. $\mathbf{[Rh(COD)L^1]^+}$ and $\mathbf{Rh(COD)L^2}$ are complexes that are likely to form by this reaction. Similar complexes to $\mathbf{Rh(COD)L^2}$ have been synthesized by *Saed et Al*[14] by reacting the ligand and $Rh_2(COD)_2Cl_2$ in DCM and adding a solution of KOH in water, and this strategy was attempted with $\mathbf{L^2}$. Comparison of the complexes is shown in Figure 11.

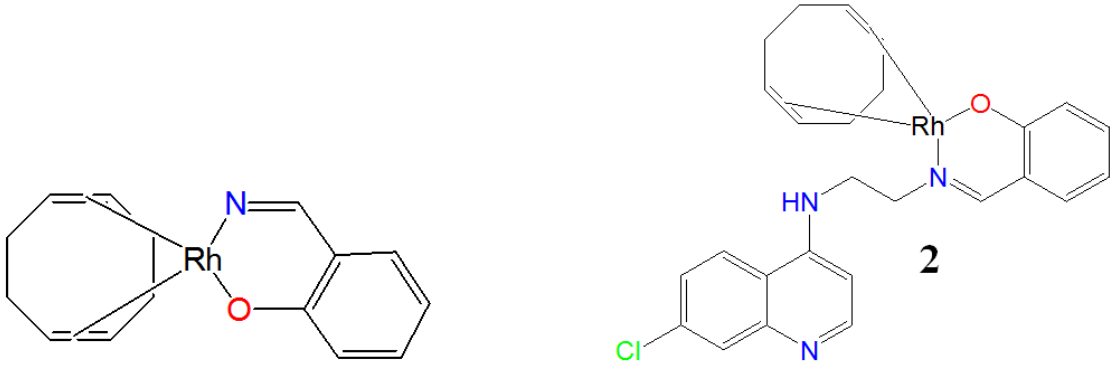


Figure 12. Comparison of a complex synthesized by Saed *et al* (left) and a complex that would likely form when L^2 is reacted with $[Rh(COD)Cl]_2$ (right).

Metroni et. Al.[15] reported that similar complexes to $\mathbf{[Rh(COD)L^1]^+}$ (see Figure 12) can be made by reacting the ligand and Rh-dimer in MeOH without the addition of base, and then add NH_4PF_6 to precipitate the product. A combination of the two methods of Saed *et al* and Meteroni *et al* was used in the attempt to synthesize complexes that likely have the structure. $\mathbf{[Rh(COD)L^1]^+}$and $\mathbf{Rh(COD)L^2}$. Since no NH_4PF_6 was available $AgPF_6$ was used instead.

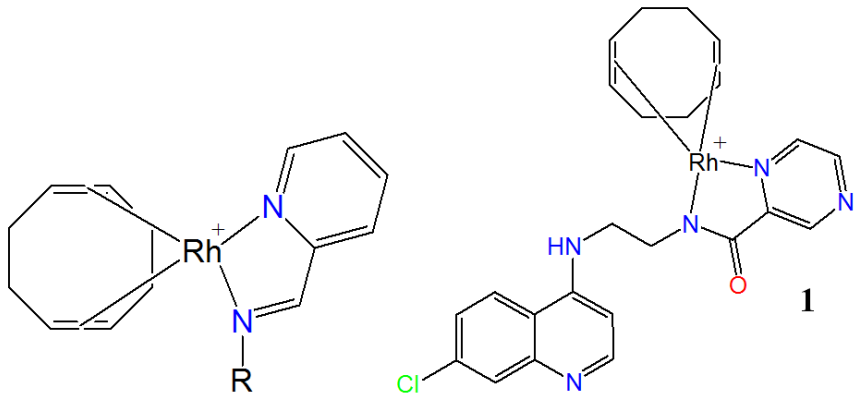


Figure 13. Comparison of the type of molecules reported by Meteroni et. Al. and the desired complex (1) $(Rh(COD)L^1)^+$ that we attempted to synthesize.

[14] Saeed, I.; Shiotsuki, M.; Masuda, T.; *Journal of Molecular Catalysis A*: Chemical 254 **2006** 124–130

[15] Zassinovich, G.; Camus, A.; Mestroni, G. *Journal of Organometallic Chemistry, 133* **1977** *377-384*

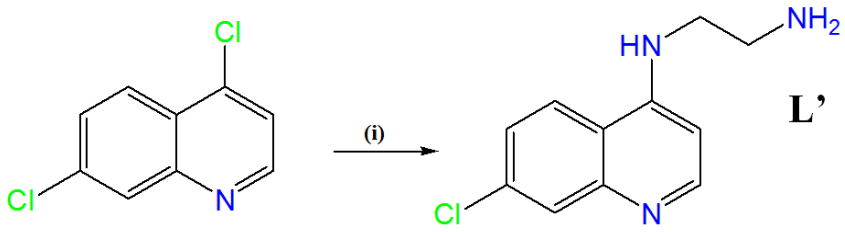
Rhenium

The starting material for the attempted rhenium reactions $Re(CO)_5Br$, which was obtained by treating the dimer $(Re(CO)_5)_2$ with Br_2 following a standard procedure[16] and an attempt was made to form the complexes **$Re(CO)_3BrL^1$** and **$Re(CO)_4L^2$** by reacting $Re(CO)_5Br$ with **L^1** or **L^2**.

Results and discussion

Ligand synthesis

L' was synthesized following the procedure used in the Nordlander Group, except 5 equivalents of ethylene diamine was used instead of two. Increasing the amount of ethylene diamine made the solution less viscous and easier to handle. The reaction led to the formation of a white byproduct that was insoluble in DCM and partly soluble in water. This had to be filtered of before the washing steps were done with the separation funnel, otherwise the funnel would clog. The byproduct was probably formed when the **L'** reacted with 4,7-dichloroquinoline, forming N,N'-di(7-chloroquinoline-4-yl)ethane-1,2-diamine. This structure was however not confirmed, since the byproduct was insoluble in the solvents used for ^{1}HNMR analysis. Due to the formation of byproduct, the overall yield was only 23.1 %.



Scheme 1. Synthesis of L'. Reagents and conditions: i) $NH_2(CH_2)_2NH_2$ 5 eq, 80 °C for 1 hour and 130 °C for 12 hours.

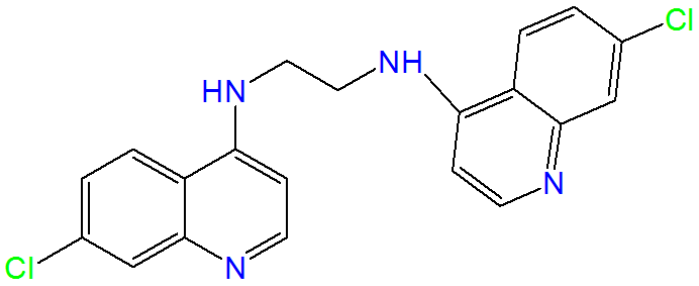


Figure 14. Proposed structure of the byproduct that forms during the synthesis of L'. The structure of the byproduct was not confirmed.

The three ligands **L^1**, **HL^2** and **HL^3** were synthesized according to Scheme 2, 3 and 4. The synthesis of and **HL^2** had previously been described[3] while **L^1** and **HL^3** has been synthesized

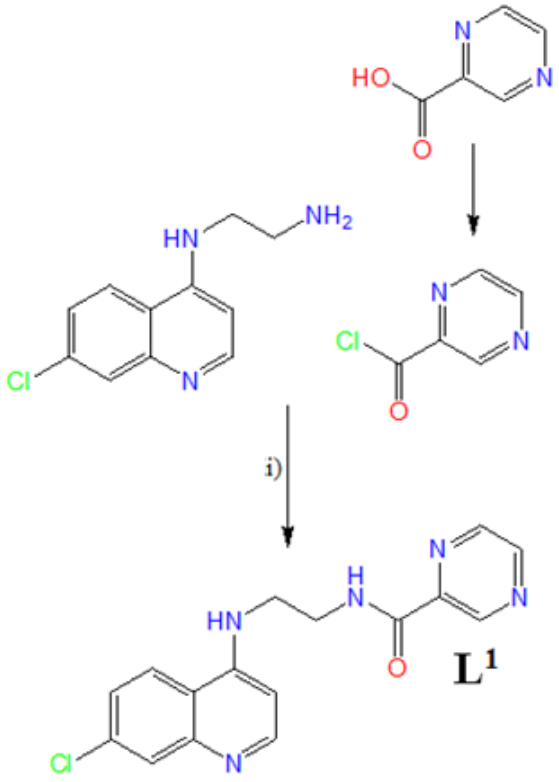
[16] Angelici, R. J. *Inorganic Synthesis vol 28*, **1990** , ISBN 0-471-52619-3, also http://onlinelibrary.wiley.com/doi/10.1002/9780470132593.ch42/summary;jsessionid=0A27676D0DCE0DA842F06051E806240C.f03t01 Jan 2015.

in our laboratory (unpublished work). Good yields were obtained for all three ligands (**L**[1] 89.7 %, , **HL**[2] 85.6%, **HL**[3] 87.3%).

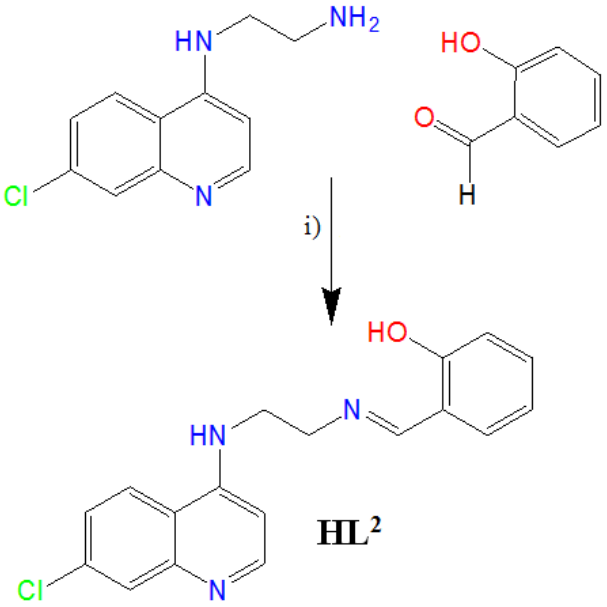
The first step in the synthesis of **L**[1] (Scheme 2) was to make pyrzinoic acid chloride by reacting pyrzinoic acid with thionyl chloride. This had already been made by a lab worker, but since the acid chloride was purple it had to be purified, which was done by sublimation. This yielded a white powder of pyrzinoic acid chloride, which was suspended in DCM at 0 °C and a suspension of **L'** was added dropwise. The low temperature and slow addition of **L'** was to prevent unwanted side reactions.

When **HL**[2] first was synthesized it was realized that a small amount of the salicylaldehyde did not reacted, as could be seen in the ^{1}H-NMR spectrum. The unreacted aldehyde could easily be removed by putting the product under vacuum on the Shlenk line and heating to 80 °C for 4 h, but that left some unreacted **L'** in the product. It was therefore decided to use some excess of aldehyde to make sure that all **L'** was converted to **HL**[2], and always heat the product to 80 °C under vacuum before the purity was checked by ^{1}H-NMR. Two reactions were done following this procedure and both yielded the desired product in high yield (89.7 %) without any impurities.

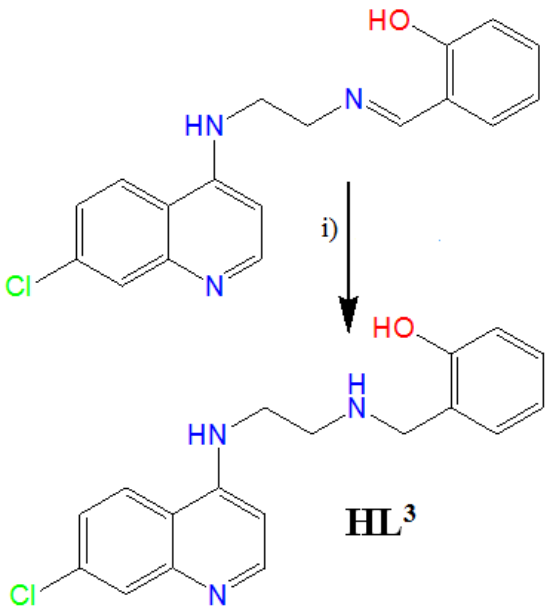
HL[3] is a reduced form of **HL**[2], which was made in one step by reacting **HL**[2] with $NaBH_4$. ^{1}H-NMR of H**L**[3] showed that all reactants had been consumed, which means that any loss of product must be due to the washing step. The washing was made in order to remove the side products $NaBH_3$ and NaOH. **HL**[3] was only used in one unsuccessful experiment due to lack of time.



Scheme 2. Conditions for the synthesis of L[1]. i) DCM, 0 °, 1 h and then washing with hexane.



Scheme 3. Conditions for the synthesis of HL^2 i) EtOH, reflux overnight followed by removal of excess aldehyde at 80 C^o, vacuum 2-4 h.



Scheme 4. Conditions for the synthesis of HL^3 i) $NaBH_4$, MeOH, 25°C, 10 min.

Ruthenium complexes

Since it seemed that all the products containing ruthenium were insoluble in most solvents only a few reaction were made with this metal. In total 7 different reactions were carried out, but the tested combinations of $RuCl_2(DMSO)_4$ or $RuCl_3xH_2O$ with $\mathbf{L^1}$ or $\mathbf{HL^2}$ always lead to a product that was always a blackish solid that could not be analyzed by NMR. It could therefore not be said if any of the desired complexes **(6)**, **(7)**, **(8)**, or **(9)** ($\mathbf{RuCl_2(DMSO)_2L^1}$, $\mathbf{(RuCl_3xH_2O)L^1}$, $\mathbf{RuCl_1(DMSO)_3L^2}$ and $\mathbf{RuCl_1(DMSO)_3L^2}$) were obtained. TLC indicated that some reactions had occurred, but since it was not possible to tell what the outcome had been it was decided to focus on other metals instead of Ru. TLC indicated that usually three different products + the starting materials remained after the reactions, but these were hard to distinguish. For example, when preparative TLC was made during an attempted synthesis of **(6)** ($\mathbf{RuCl_2(DMSO)_2L^1}$) the product could not be analyzed by ^{1}H-NMR due to insufficient solubility. It was not soluble in water, MeOH, acetone, benzene or DMSO.

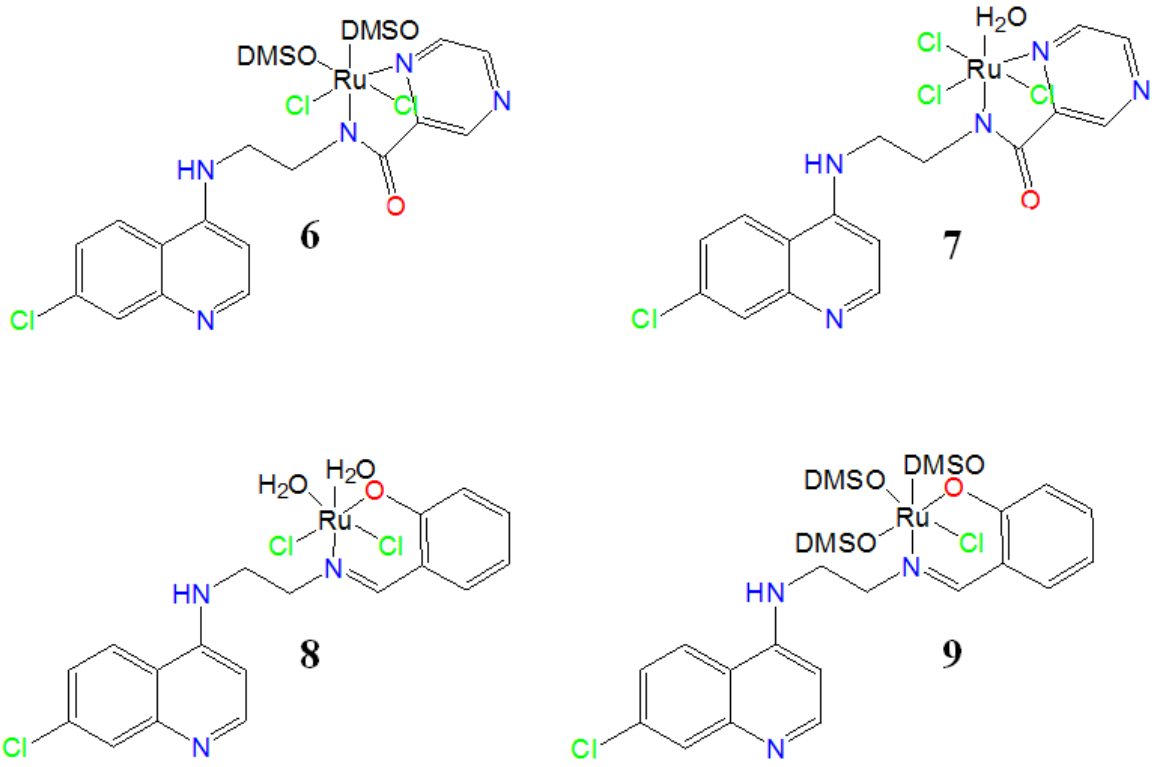
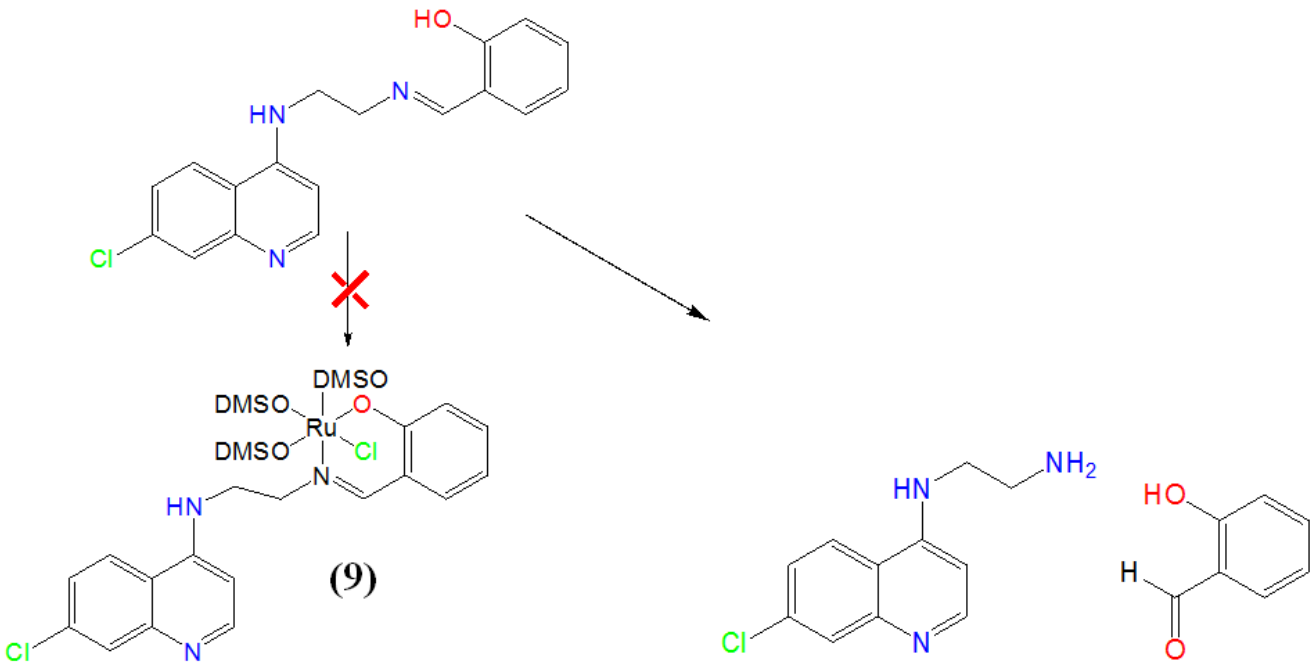


Figure 15. The desired ruthenium complexes $RuCl_2(DMSO)_2L^1$ (upper left) , $(RuCl_3xH_2O)L^1$ (upper right), $RuCl_1(DMSO)_3L^2$ (lower left). None of these complexes were successfully synthesized and characterized. Note: all possible isomers are not represented in the picture.

In the attempted synthesis of **RuCl(DMSO)$_3$L^2** the ^{1}H-NMR showed a very distinct peak at 9 ppm, which corresponds to an aldehyde proton. An explanation for this peak is that the ligand has been hydrolyzed, forming the amine and aldehyde from which it was synthesized (Scheme 5). Hydrolytic cleavage of Shiff bases by Ru(II) has been documented by Sakanya *et. Al.*[17] and Mahalingam *et. Al*[18], which unfortunately was discovered *after* the attempted reactions had been carried out. The experiments in this project, along with the results of Sakanya *et. Al*. and Mahalingam *et. Al*. concludes that it is not possible to attach **HL^2** to Ru(II) without causing hydrolysis, and it seems best to put the effort on different experiments in order to come up with a useful anti malaria agent. In comparison to the successful synthesized ruthenium complex by *Khan et. Al*. it seems that a ligand needs to have at least 2 Schiff-base nitrogens in order to not be hydrolyzed by Ru(II).



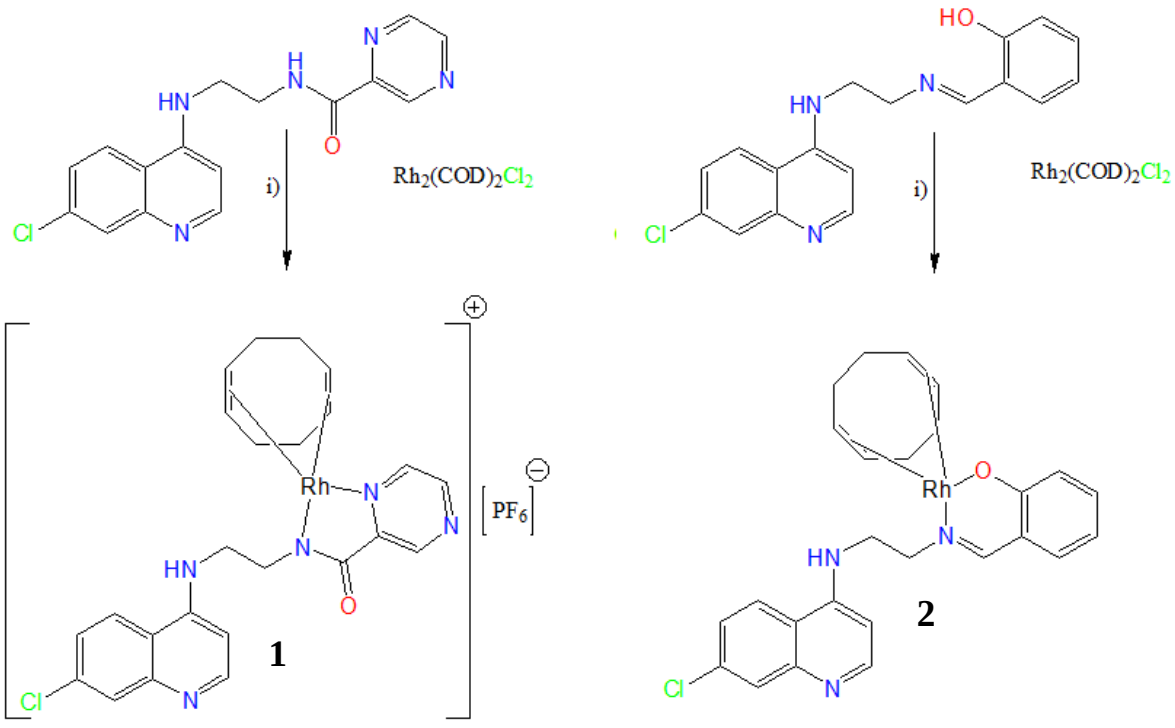
Scheme 5. Attempted synthesis of complex (9). Reagents and conditions: (i) 1 eq $RuCl_2(DMSO)_4$, MeOH. This rout was confirmed to not work. Different stereoisomers for the desired product are not represented.

[17] Sakanya, D.; Evans, R. M.; Zeller, M.; Natarajan, K. *Polyhedron* 26 **2007** 4314–4320
[18] Mahalingam, V.; Chitrapriya, N.; Fronczek, F. R.; Natarajan, K. *Polyhedron* 29 **2010** 3363–3371

Rhodium complexes

Lots of effort was made in the attempt synthesizing **[Rh(COD)L^1]$^+$ (1)** and **Rh(COD)L^2 (2)** using $(Rh(COD)Cl)_2$ as starting materials, since Meteroni *et. Al.* have reported very similar complexes. One attempt was also made to synthesize **Rh(COD)L^3 (11)**. As in the case with ruthenium the solubility of the product remained an issue: it was not soluble in common deuterated solvents used for NMR. It was however realized that it could be dissolved in a mixture of 70:30 $CDCl_3$:MeOH-d4. The mixture also contained TMS as reference. For comparison, the ^{1}H-NMR spectra of the starting materials was measured in the same solvent mixture.

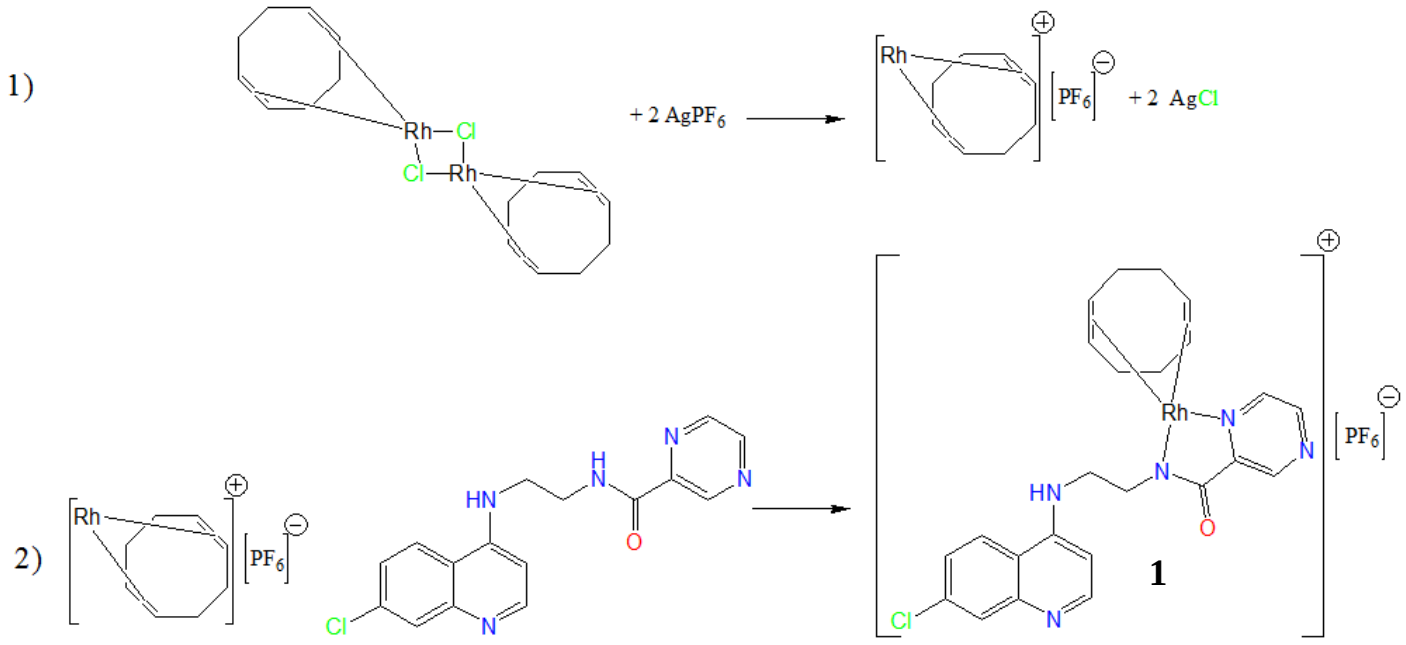
It was seen that no product **(1, Rh(COD)L^1**), was formed when the reaction was carried out in DCM or MeOH at -80 °C, but that some was formed when the same reaction was run at room temperature. The amount of product formed was determined by comparing the size of the peaks corresponding to starting material and the size of the peaks corresponding to product in the ^{1}H-NMR spectra. It was realized that more activation energy was needed for complete conversion of starting material to product. The reaction was then carried out in refluxing MeOH (10 % product), refluxing EtOH (60% product) and refluxing DMF (no NMR result). It was reasoned that the high activation energy was needed to break the dimer bonds in $(Rh(COD)Cl)_2$ in order to make it react. To investigate this 0.9 eq AgPF6 was added to a reaction mixture of 0.5 eq $Rh_2(COD)_2Cl_2$ and 1 eq **L^1** or 1 eq **HL^2** in MeOH. Even though the reactions were run at room temperature almost all the starting materials was converted to product. The same experiments were then repeated using 1.1 eq $AgPF_6$, and all the starting materials was converted, forming either crystals of **1** (blood red) or **2** (dark yellow). The ^{1}H-NMR spectra for **2** was not fully clean and the product needs further purification, and spectra of **1** indicated that it was pure. Scheme 6 shows the successful routes used for the syntheses.



Scheme 6. Probably successful syntheses of the complexes [L^{1}Rh(COD)][PF_6] (1) and L^{2}Rh(COD) (2). i) DCM, RT, 10 min ii) addition of 1.1 eq $AgPF_6$ in MeOH, mixing at RT overnight.

The fully reaction that likely yields **1**, [**L**^{1}**Rh(COD)][PF$_6$]**, is described in Figure 11: The silver ions react with the dimer to form AgCl, which is the precipitate that is seen in the reaction mixture. While the dimer is split free nothing prevents the ligand from interact with it, and a metal complex can form. Any silver ion could be used, but the advantage of $AgPF_6$ (in comparison to for example $AgNO_3$) is that the hexaflourophosphate ion makes crystal formation of the product more likely to occur. Crystal formation is important since good quality crystals are needed for x-ray crystallography.

Regrettably the yields were not calculated for these two complexes, and the synthetic route was not optimized due to lack of time. About 40 mg reactant was used, and to get sufficient ^{1}H-NMR spectra 10 mg is needed, so one can assume that the yields were 25% at the very least, but probably much higher since all reactant seemed to have reacted when interpreting the NMR spectra. It is possible that the route could have been simplified, for example by mixing all the reactants at once and using a shorter reaction time. The presumable successful synthesis was carried out by first dissolving $(Rh(COD)Cl)_2$ and **L**^{1} or **HL**^{2} in DCM and then add a solution of 1.1 eq $AgPF_6$ in MeOH. Due to lack of time no simplification of the routes were tested, and no further attempt to synthesize **(11)** was made.



Scheme 7. The assumed complete reaction in the synthesis of 1, [L^{1}Rh(COD)][PF$_6$].

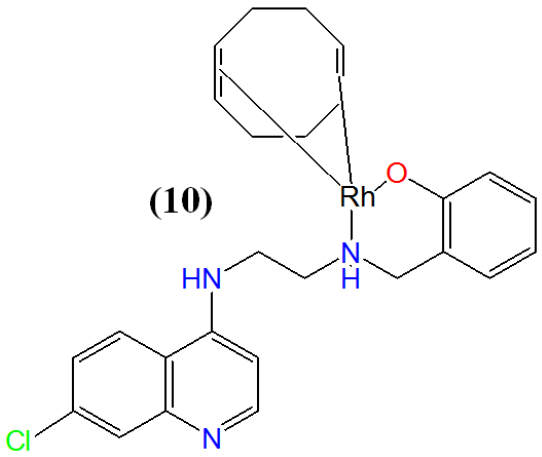
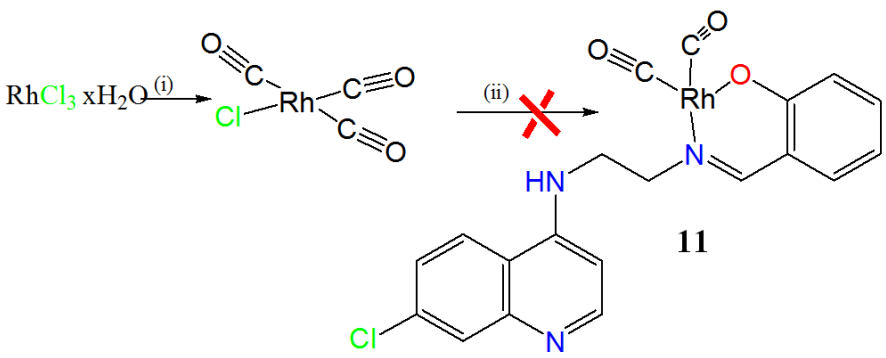


Figure 16. Structure of the complex 10, the L^3 equivalent of complex 2. Synthesis of 10 was not attempted to due to lack of time.

The synthesis of **(11)**, **($Rh(CO)_3Cl$) L^2**, was attempted in a number of ways, since a similar compound have been described by Oro *et. Al*. As described in this paper, $RhCl_3xH_2O$ was refluxed in DMF to form $Rh(CO)_3Cl$. The color of the mixture went from red to amber, indicating $Rh(CO)_3Cl$ had formed. **L^2** was then added to the solution was stirred for 1 h before water was added to make the product precipitate. Since it did not precipitate the pH was adjusted to 10 and the solution was left in the freezer overnight, and a small amount of precipitate was formed. The solution was then centrifuged and a red-brown powder was obtained. It was insoluble in water, MeOH, $CDCl_3$ and DMSO, so no ^{1}HNMR could be performed.

The same experiment was repeated without adjusting the pH, since it was believed that this might hydrolyze the ligand **HL^2**. The red-brown precipitate that was collected after centrifugation could now be dissolved in MeOD. ^{1}H-NMR showed an aromatic compound with only four different shifts in the aromatic region, indicating that the ligand had been cleaved despite the neutral pH. It was reasoned that the C=N bond in **L^2** had been hydrolyzed as in the case with the Ru(II), and that **L'** was in the supernatant and salicylaldehyde in the precipitate. To confirm this the supernatant was also analyzed. A small amount of an unknown aromatic compound plus some aldehyde was found. No conclusion can be drawn from this data, but the fact that the spectrum of the precipitate did not contain as many signals as expected for the ligand indicate that **L^2** had been cleaved.

The same experiment was repeated once again under water free conditions, to prevent any hydrolysis during the synthesis. All glass ware was dried in an oven over night, dry DMF was used and EtOAc (70 mL) was used to form the precipitate. One advantage was that the density of EtOAc is 0.9 kg/L, which made sedimentation much faster compared to when water was used. When EtOAc had been added the opaque mixture was left in the fridge over the weekend and the supernatant could then be decanted from the precipitate. Again the ^{1}H-NMR only showed 4 different peaks corresponding to the same molecule in the aromatic region, indicating that **HL^2** had been hydrolyzed despite the water free environment in which the reaction was performed.



Scheme 8. Atempted synthesis of complex 11. Reagents and conditions: (i) DMF, 154 ° C, 1 hour, (ii) L^2, DMF, room temp, 1 hour. This route did not give the desiered product.

In a last attempt**,** **HL**^{2} was reduced to **HL**^{3}, using $NaBH_4$, and the same experiment was repeated using this new ligand in an attempt to form **Rh(CO)$_2$L**^{3}, complex **12**. EtOAc was used to precipitate the product of the reaction, but not enough could be collected to run ^{1}H-NMR despite that 100 mL EtOAc was used and the mixture was stored in the freezer over weekend to get as much precipitate as possible. It was then decided to not attempt any more reactions that included DMF as a solvent. The mayor drawback with DMF is its high boiling point of 154 °C; the solvent is hard to remove *in vacuo* and the product is easier obtained by precipitation, which in this case showed to be a bit to challenging.

Due to lack of time it was not tested to reflux $RhCl_3xH_2O$ in DMF to form $Rh(CO)_3Cl$ and then react it with **L**^{1}, which might have given complex **13**.

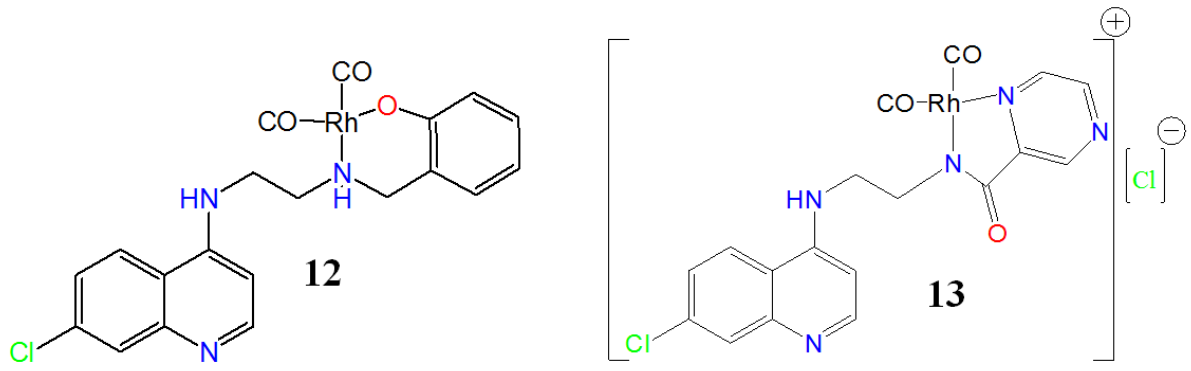


Figure 17. Rh(CO)$_2$L^3 (complex 12) that was not successfully synthesized and [Rh(CO)$_2$L^1][Cl] (complex 13) that was not attempted to synthesize due to lack of time.

Rhenium complexes

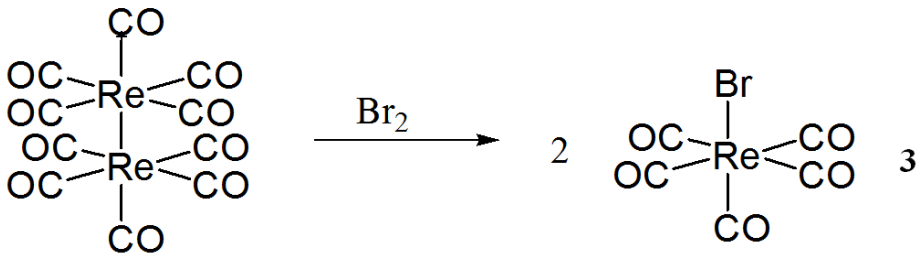
Two rhenium complexes **$Re(CO)_3BrL^1$ (4)** and **$Re(CO)_4L^2$ (5)** is believed to have been synthesized, using $Re(CO)_5Br$ **(3)** as starting the material. The exact molecular formula of these were not determined due to lack of time, but there are good reasons to believe that they formed: no trace of the staring material $Re(CO)_5Br$ could be seen by IR spectroscopy, but instead new carbonyl peaks appeared. This indicates that all the starting material was consumed, and therefore that the product was formed. KBr was used since **4** and **5** were not soluble in DCE or DCM, solvents which were used for IR analysis. The spectra of **3** in KBr showed peaks corresponding to CO at 1964, 2035 and 2060. The supposed product **$L^1Re(CO)_3Br$** showed signals at 2019, 1903, 1884, 1602 and 1565. Since none of the signals from the starting material remains it is most likely that **L^1** has coordinated with the metal. The product when **HL^2** was reacted with **3** showed strong IR signals at 2010, 1906, 1882 and 1592. Again the same argument applies; The signals have changes in comparison to the starting material, so it is likely that the ligand has coordinated.

The 1H-nmr of **4** agrees with the proposed formulation, peaks of **L^1** was shifted in such a way that it indicates coordination of Re through the oxygen and nitrogen of **L^1**.

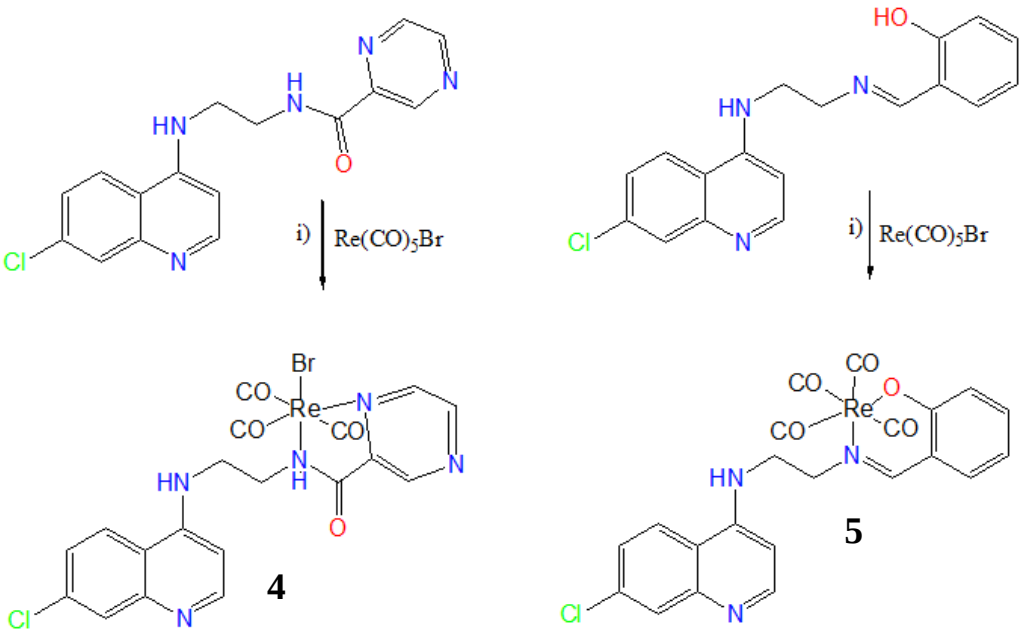
No ^{1}H-NMR could be obtained of **$Re(CO)_4L^2$** due to low solubility in common deuterated solvents. It was not determined if rhenium coordinated to the lone pair of the Schiff base nitrogen, which is drawn in Scheme 10. One way to have done this would have been to take IR spectra of the ligands **L^1** and **HL^2** and compare with those of the product. If rhenium is coordinated to the amide nitrogen in complex **4** the N=O stretching frequency would probably be affected, so if the corresponding signals for this bond differs between **L^1** and complex **4** it would be indicated that the proposed structure in Scheme 10 is correct.

If the metal is coordinated to the Schiff base nitrogen in complex **5** it would probably change the C=N stretching frequency in **HL^2**, so a change at this signal would confirm the proposed structure. However, it might be hard to observe the C=N signal in **HL^2** since the quinoline part of the molecule also has IR absorption in the same region. One can also look for changes in the region in which the O-H bond of the alcohol part of **HL^2** gives rise to signals.

The reason why one the complex with **L^1** is thought to have a bromine coordinated to the metal while the complex with **$[L^2]^-$** does not is because of the oxidation state of Re(I). If one assumes that Re does not change its oxidation number the bromine needs to be kept to forma a neutral complex when **L^1** is coordinated, since **L^1** is a neutral ligand. **$[L^2]^-$** on the other hand is a charged ligand, and the thus the bromine needs to leave in order for Re(II) to keep its oxidation state. This reasoning assumes however that the complexes are neutral. It is possible that they instead are charged, so that **4** has the formula **$[Re(CO)_4L^1]^+$**$[Br]^-$ and **(5)** the formula **$[Re(CO)_4L^2Br]^-$[$[Et_3NH]^+$**. Since the complexes were much less soluble in water than DMSO it is however believed that they are neutral. Crystallography or mass spectrometry are examples of methods that could be used in order to determine this.



Scheme 9. Synthesis of $Re(CO)_5Br$ (complex 3) from $[Re(CO)_4]_2$ (3). 1 eq Br_2, dried DCM, N_2 atmosphere.



Scheme 10. Synthesis of the complexes $L^1Re(CO)_3Br$ (4) and $Re(CO)_4L^2$ (5). Conditions for Complex 4: i) DCE, reflux 48 hours. Conditions for Complex 5: i) 1.5 eq Et_3N, DCE ii) reflux 48 hours.

Conclusions

Ruthenium complexes

None of the desired complexes **6 – 9** (**$RuCl_2(DMSO)_2L^1$** , **$(RuCl_3xH_2O)L^1$** , **$RuCl_1(DMSO)_3L^2$** or **$(RuCl_2xH_2O)L^2$**) could successfully be synthesized. It was realized that Ru(II) hydrolyses Schiff bases such as **HL^2**, and that these two molecules cannot be combined to form a metal complex. Overall, reactions of **L^1** or **HL^2** with ruthenium tend to form black, insoluble solids that are hard to characterize. Since they not seem to be soluble in anything it is not likely that they would be able to penetrate a malaria parasites food vacuole. It would also be challenging to administrate a drug based on these complexes and measure the anti-malaria activity in vitro, and it is therefore unlikely that they would work as anti-malaria agents.

Rhodium complexes

The complexes **1** and **2** (**$[Rh(COD)L^1][PF_6]$** and **$Rh(COD)L^2$**) were successfully synthesized by splitting the $Rh(COD)Cl_2$ dimer using $AgPF_6$. The synthesis gave pure **1** while **2** needs further purification. Even though these to complexes might not work as anti-malaria agents the synthetic route could still be valuable. It is likely that more complexes with similar ligands, **$Rh(COD)L^x$**, can be made by using this strategy. New metal complexes like these might be useful in medicine, or as catalysts in chemical reactions.

Rhenium complexes

Two rhenium complexes **4** and **5** (**$Re(CO)_3BrL^1$** and **$Re(CO)_4L^2$**) is believed to have been synthesized. The exact characterization and coordination of these was not made due to lack of time, and the yields were also not calculated. However, it was confirmed that rhenium carbonyl complexes that include **L^1** or **HL^2** can be synthesized following the described route, and it is most likely that other similar ligands also can be used to make up these kinds of complexes.

Experimental

All chemicals were used as received unless anything else is noted. The ^{1}H-NMR spectra were recorded on a Varian Inova 500 spectrophotometer at 500 MHz and the IR spectra recorded on a Nicolet Avatar 360 FT-IR instrument.

Successful experiments

N-(7-chloroquinoline-4-yl)ethane-1,2-diamine (L')

4-7-dichloroquinoline (4.62 g, 23 mmol) and ethylene diamine (4670 µl, 70 mmol, 3 eq) were heated to 80 °C for one h before heating to 130 °C overnight. The resulting slurry was diluted with DCM (1000 mL), filtered and the filtrate was washed with water, 5% $NaHCO_3$, again with water and finally brine before drying over $MgSO_4$ and concentrated *in vacuo* yielding **L'** as an off-white solid (1190 mg, 23.1 % yield). H^{1}-NMR: 2.80(t 2H), 3.24(q, 3H), 6.48(d 1H), 7.22(t 1H) 7.43(1H dd)

N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine, (L^1)

Pyrzinoic acid chloride was purified by sublimation and 142 mg (2mmol) was suspended at 0 °C in DCM (10 mL) in a two necked flask fitted with an additional funnel. 7-chloro-4,quinoline)ethylamine, **L'**, (416 mg, 2 mmol, 1 eq) was suspended in DCM and added dropwise during 1 h via the addition funnel. A pink precipitate formed which was filtered of and washed with hexane to yield $\mathbf{L^1}$. (614 mg, 89.7% yield). ^{1}H-NMR (DMSO –d6): 3.64(q 2H) 3.72(q 2H) 7.01(d 1H) 8.56(d 1H), 8.72(t 1H), 8.87(d 1H), 9.16(d 1H), 9.26(t 1H).

N-(-2((2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL^2)

N-(7-chloroquinoline-4-yl)ethane-1,2-diamine, **L'**, (198 mg, 1 mmol) and salicylaldehyde (97 µL, 1.1 mmol, 1.1 eq) were refluxed in EtOH (10 mL) over night, concentrated *in vacuo* and put under vacuum at 80 °C for 4 hours to yield $\mathbf{HL^2}$ as a yellow powder (260 mg, 85.6% yield. ^{1}H-NMR: ($CDCl_3$/MeOH-d4, 70:30): 3.68(t 1H) 3.30 (t 1H), 3.88(t 2H) 6.45(d 1H) 6.82 (t 1H) 6.89(d 1H), 7.15(dd 1H), 7.27 (d 1H) 7.29(t 1H), 7.32 (s 1H), 7.76(d 1H), 7.81(d 1H), 8.37(d H1), 9.00(s 1H),

N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine (HL^3)

$\mathbf{HL^2}$ (126 mg, 0.4 mmol) and $NaBH_4$ (30 mg, 0.8 mmol, 2 eq) were dissolved in MeOH (40 mL) at 25 °C, stirred for 10 min, concentrated *in vacou*, dissolved in DCM, washed 3 times with water and concentrated *in vacuo* to yield $\mathbf{HL^3}$ as an agar colored (yellow-beige) powder (110 mg, 87.3% yield). . ^{1}H-NMR: ($CDCl_3$) showed that the product was pure, but the shift signals were not saved properly and therefore not collected.

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-hapto-4-cyclooctadien-rhodium hexaflourophosphate, (1)

L^1 (22 mg, 70 µmol) and $[Rh(COD)Cl]_2$ (17 mg, 35 µmol, 0.5 eq) were dissolved in DCM (2 mL) and stirred at 25° C for 30 min. $AgPF_6$ (19 mg, 77 µmol, 1.1 eq) was dissolved in MeOH (1 mL) and added to the DCM solution, which instantly made a dark red precipitate form. The solution was stirred at 25°C overnight, filtered through a 0.45 µm propylene filter and concentrated *in vacuo* to yield **[Rh(COD)L^1][PF_6]** as blood red crystals. No yield was calculated. ^{1}H-NMR ($CDCl_3$/MeOH-d4, 70:30): 3.43(t 2H), 3.31(s 1H), 3.62(t 2H), 4.10(s 1H), 4.41(s 2H) 7.78(d 1H), 7.62(d 1H), 7.68 (s 1H), 7.73(d 1H), 8.17(d 1H), 8.19 (s, 1H), 8.83(d 1H), 9.21(s 1H)

η- 2-(N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine) (hapto-4-cyclooctadien-rhodium (2)

HL^2 (23 mg, 70 µmol) and $[Rh(COD)Cl]_2$ (17 mg, 35 µmol) were dissolved in DCM (3 mL) and stirred at 25° C for 30 min. $AgPF_6$ (19 mg, 7.7 mmol, 1.1 eq) was dissolved in MeOH (1 mL) and added to the DCM solution which instantly made a dark red precipitate form. Et_3N (12µL, 100 µmol, 1.5 eq) was added and the mixture was stirred overnight, washed with water and concentrated *in vacuo* to yield **Rh(COD)L^2** as dark yellow crystals. No yield was calculated. The product did not generate a clear ^{1}H-NMR spectra in $CDCl_3$/MeOH-d4 70:30 or DMSO-d6, but it indicated that the product had formed.

Reniumpentacarbonylbromid (3)

$Re_2(CO)_{10}$ (200 mg, 3 mol) was dissolved in dry DCM (5 mL) in a dried schlenk tube under N_2. The solution was titrated with Br_2 (approximately 10 µL) until it changed from colorless to brown by using a syringe that penetrated the septa of the schlenk tube. The solution was concentrated on the schlenk line at 30 °C to yield $Re(CO)_5Br$ as white crystals. No yield was calculated. IR (KBr): 1964, 2035, 2060.

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-tris-carbonyl--bromo-renium (4)

L^1 (22 mg, 70 µmol) and $Re(CO)_5Br$ (24 mg, 70 µmol, 1 eq) were refluxed in DCE for 4 hours and an IR specra was taken of the solution and compared with a spectra for pure DCE. No change were observed and the mixture was refluxed for 48 hours which made an orange-yellow precipitate form that was filtered of to yield **$Re(CO)_3BrL^1$**. No yield was calculated. IR (KBr): 2019, 1903, 1884, 1602, 1565. ^{1}H-NMR ($CDCl_3$/MeOH-d4, 70:30): 2.53(t 1H), 3.62(t 1H), 3.70(s 1H, 3.88 (t 1H), 3.90(s 2H) 6.64(t 1H), 7.65(s 1H), 8.00(d 1H), 8.25(t 1H), 8.89(t 1H), 9.18(s 1H),

η -2-(N- N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine) tris-carbonyl--bromo-renium **(5)**

HL^{2} (21 mg, 70 µmol), $Re(CO)_5Br$ (24 mg, 70 µmol, 1 eq) and Et_3N (11 µL, 100 µmol, 1.5 eq) were refluxed in DCE for 4 hours and an IR specra was taken of the solution and compared with a spectra of pure $Re(CO)_5Br$ in DCE. No change were observed and the mixture was refluxed for 48 hours which made a green-yellow precipitate to form that was filtered of and washed with DCM:MeOH 80:20 to yield **$Re(CO)_4L^2$**. No yield was calculated. IR (KBr): 2010, 1906, 1882, 1592, weak: 1611, 1536, 1445. No sufficient NMR data was obtained due to low solubility.

Examples of unsuccessful experiments

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-ruthenium-dichloro-di-(dimethylsulphoxide) **(6)**

L^{1} (47 mg, 140µmol) and $RuCl_2(DMSO)_4$ (71 mg, 140 µmol, 1 eq) was refluxed in 50:50 MeOH/DCM overnight and concentrated on a rotor vap, yielding a blackish solid that was almost insoluble in common solvents. It was purified by prep TLC (70:29:1 DCM/MeOH/Et_3N) but no sufficient NMR results were obtained due to low solubility in $CDCl_3$, D_2O, d-DMSO, d-benzene and d-MeOH.

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-ruthenium-trichloride-monohydrate **(7)**

L^{1} (50 mg, 150 µmol), $RuCl_3xH_2O$ (82 mg, 150 µmol, 1 eq) and NaOH (10 mg, 250 µmol, excess) were refluxed in MeOH for 2 hours, yielding a black precipitate that was not soluble in any of the solvents in the lab.

η -2-(N- N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine)-ruthenium- dichloride-dihydrate **(8)**

HL^{2} (32 mg, 99 µmol), $RuCl_3xH_2O$ (53 mg, 99 µmol) and Et_3N (28 µl, 200 µmol) was stirred in MeOH (20 mL) for 3 hours at room temperature. The reactants did not dissolved and the MeOH was evaporated, water (20 mL) and and Et_3N (28 µl, 200 µmol) was added and the mixture was refluxed for 1 h and then stirred at room temperature over night. The mixture went from brown to blackish. TLC (MeOH and a few drops Et_3N as eluent) indicated that reaction had occurred but no NMR was made due to bad solubility.

η -2-(N- N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine)-ruthenium-tetra-(dimethylsulphoxide)-chloride **(9)**

HL^2 (24 mg, 72 µmol), $RuCl_2(DMSO)_4$ (35 mg, 72 µmol) and Et_3N (20 µl, 140 mmol, 2 eq) were mixed in MeOH overnight. The mixture went from yellow to amber in 10 minutes and amber to black in 2 hours. TLC (99:1 MeOH/Et_3N) indicated that reaction had occurred, the solution was concentrated *in vacuoto* to yield a black solid. No sufficient NMR results were obtained due to bad solubility, but hydrolysis of **HL^2** was indicated.

η -2-(N- N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine)-rhodium-dichloride-hydrate **(11)**

$RhCl_3xH_2O$ (22 mg, 84 µmol) was dissolved in DMF (7 ml), refluxed for 1 h and cooled to ambient temperature before **HL^2** (27 mg, 84 µmol, 1 eq) was added and the mixture stirred for 2 h. It was then diluted with water and stored in a refrigerator overnight, centrifuged at 400 rpm for 30 min, the supernatant removed, water added, again centrifuged for 10 min and the yellow pellet collected and dried *in vacuo* and analyzed by ^{1}H-NMR. Too small amount of the product was collected to get a clear spectra, but it indicated that hydrolysis of **HL^2** had occurred.

η -(2-N-(-2((2-hydroxyphenyl)methylamino)ethyl)-7-chloroquinolin-4-amine)-rhodium-dichloride-hydrate **(12)**

$RhCl_3xH_2O$ (25 mg, 96 µmol) was dissolved in DMF (7 ml), refluxed for 1 and cooled to ambient temperature before **HL^3** (27 mg, 84 µmol, 1 eq) was added and the mixture stirred for 2 h. EtOAc (100 mL) was added and the mixture stored in a refrigerator over the weekend yielding a yellow precipitate that was collected. Not enough could be collected to get an useful ^{1}H-NMR spectrum.

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-hapto-4-cyclooctadien-rhodium chloride **(1)**

HL^1 (55 mg, 170 µmol) and [$Rh(COD)Cl]_2$ (41 mg, 85 µmol, 0.5 eq) was dissolved in DCM (4 ml) and stirred at 25°C over night. TLC (DCM/MeOH 80:20) showed that no reaction had occurred.

η -2-(N-(7-chloroquinoline-4-yl)ethane-1,-amino-2-amido-pyrazine)-hapto-4-cyclooctadien-rhodium **(2)**

HL^2 (28 mg, 87 µmol) and $[RhCl(COD)]_2$ (22 mg, 44 µmol, 2 eq) was dissolved in DCM (4 mL), KOH (15 µg, excess) in water (5 mL) was added and the suspension stirred at 25 °C for 6 hours before the aqueous phase was removed and the organic phase dried with $MgSO_4$ and concentrated *in vacuo*. ^{1}H-NMR indicated hydrolysis of **HL^2** and the formation of some unknown product.

Populärvetenskaplig sammanfattning

Det här kandidatarbetet gick ut på att syntetisera ett antal olika ämnen som i efterhand ska testas för att se om de kan användas i en malariamedicin. Arbetet fokuserade således på att beskriva sjukdomen malaria, olika ämnen som skulle kunna fungera som medicin och slutligen hur dessa ämnen kan tillverkas. Det innehåller dessutom beskrivningar av några tillvägagångssätt som inte fungerar vid tillverkning av de här ämnena.

Malaria är en sjukdom som orsakas av en parasit (en encelligt eukaryot) som via myggstick kommer in i människan. I kroppen bryter den ner röda blodkroppar, vilket leder till symptom såsom feber och smärta, och i värsta fall kan en malariainfektion leda till döden. När malariaparasiten bryter ner hemoglobin ifrån de röda blodkroparna frisätts haem, ett järninehållande ämne som är en del av hemoglobin och som är giftigt för parasiten. Detta sker i en så kallad födovakuol, en speciell blåsa i parasiten som fungerar som dess mage. I födovakuolen klumpas haemet ihop till en ogiftig, fast form.

Klorokin är en gammal malariamedicin verkar genom att tränga in i födovakuolen och hindra att järnet klumpar ihop sig, vilket leder till att parasiten dör av haemförgiftning. Tyvärr har många parasiter på senare år utvecklat en födovakuol med en cellvägg som gör att klorokinet transporteras ut så fort det kommer in, vilket gör parasiterna klorokinresistenta. Det finns idag även en annan typ av medicin, artemesinin, men parasiterna börjar utveckla resistans mot den också. Enligt Världshälsoorganisationen är ett av de största problemen med malaria att parasiterna utvecklar resistens, och det är därför viktigt att utveckla nya mediciner.

Ämnena som tillverkades under kandidatarbetet påminner om klorokin men innehöll också en metall, vilket förhoppningsvis ska göra att de fungerar på parasiter med en utvecklad födovakuol. Det finns idag ett nyutvecklat ämne som heter ferrokin, vilket påminner om en klorokinmolekyl som är kopplad till en järnatom. Ferrokin kan döda malariaparasiter även om de har en utvecklat klorokinresistans, men ämnet är så pass ny att det ännu inte används som medicin eftersom det fortfarande forskas på det. Detta visar dock att en gammal icke-fungerande medicin kan fungera igen om den görs om så att den innehåller en metall.

Att en medicin innehåller metall är en ganska ny idé, det finns idag endast ett fåtal mediciner som gör det. Eftersom det förmodligen finns så mycket nytt att upptäcka är det därför ett spännande område att utforska inom kemin.

Under arbetet testades att sammanfoga metallerna rutenium, rodium och renium men några organiska molekyler som påminner om klorokin. Resultatet blev att totalt fyra olika molekyler som inte tidigare har gjorts tillverkades: Två som innehöll rodium och två som innehöll renium. Dessa kommer förhoppningsvis att kunna testas för att se om de biter på malariaparasiter med klorokinresistans. Inga fungerande sätt att tillverka specifika molekyler som innehöll rutenium hittades. En anledning till detta är att rutenium kunde bilda många olika föreningar på en gång då det reagerades med en organisk molekyl. Dessutom katalyserade rutenium nedbrytandet av vissa molekyler som metallen var tänkt att bilda föreningar med.

Acknowledgments

Erik Ekengard, for being an educating, patient and always positive supervisor

Ebbe Nordlander, for letting me work in this exciting research group

All of the other members in the Nordlander group, for support and advices in the laboratory.

Mike Richmond for valuable input on Rhenium complexes.

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