

Synthesis of palladium complexes and their antimalarial properties

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Degree Project in Subject, 2024
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BSc, 30 hp



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Syntes av palladium-komplex och malariamedicin

En av de sjukdomar som påverkar flest människor årligen är malaria. Malaria sprids av myggor som bär på parasiten och när de biter en människa överförs parasiten till människan. Vanliga symptom vid en malariainfektion är lätt feber, frossa och huvudvärk. Dessa symptom kan bli allvarigare om personen är gravid, ett barn mindre än fem år gammalt, eller har HIV eller AIDS, eftersom sådana personer tillhör riskgrupper och därför är känsligare och drabbas hårdare. Malaria måste botas genom medicin men kan förebyggas genom att ta medicin innan, under och efter vistelse i ett land med malaria. Det är därför mycket viktigt att kunna diagnostisera malaria och dela ut nödvändig medicin vid minsta misstanke om smitta. Malaria är huvudsakligen spritt i Afrika men även i Asien, och beroende på var du befinner dig kan du stöta på olika typer av parasiten. Beroende på vilken parasit som smittat kan valet av medicin vara avgörande, då allt fler parasiter är resistent mot ett eller flera malarialäkemedel. Det är därför mycket viktigt att hitta nya läkemedel som kan användas i kampen mot malaria. Målet med denna rapport var därför att syntetisera metallkomplex som förväntas ha aktivitet mot malaria.

Abstract

Malaria is a well-known disease and affects large regions around the world. Medicines used for treatment already exist, but due to increasing resistance and unpleasant side effects it has become critical to develop new drug candidates. Several palladium complexes were synthesised and studied to understand their properties for treating malaria. The ligands and the complexes were synthesised and characterized using several spectroscopic methods, i.e ^1H NMR, UV-Vis and FTIR. The NMR, IR and UV-VIS spectra give evidence that the product was obtained. The variation of reaction conditions give purer results when done under reflux. Twelve new palladium complexes have been synthesised and characterized.

Keywords: Chloroquine, Malaria, Organometallic medicine, Palladium, Quinolines

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1. List of abbreviations

WHO	World Health Organisation
NMR	Nuclear Magnetic Resonance
IR	InfraRed
UV-VIS	UltraViolet-VISible spectrometry
CQ	Chloroquine
COD	Cyclooctadiene
DCM	DiChloroMethane
DMF	DiMethyl
DMSO	DiMethylSulfOxide
TLC	Thin Layer Chromatography

2. Introduction

Malaria is one of the deadliest diseases in today's day and age, and it is caused by vector-borne parasites, where mosquitoes are the primary vector. Other ways to contract the parasitic disease is through used syringe needles and blood transfusions, although they are less common. Malaria can affect everyone and is spread over 85 different countries. In 2022, the World Health Organisation, WHO, estimated that the number of malaria cases were 249 million with a death toll of 608 000 casualties. The largest number of malaria cases are in Africa, 94%, and it is also the region that reaps the most casualties, 95%. It is most common in countries with a tropical climate and the strain of the parasite differs regarding region. In total, there are five different types of malaria parasites that affect humans, and those are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*. The two deadliest ones are *P. falciparum*, found in Africa, and *P. vivax*, which is mainly found in other regions with malaria. (1)

Malaria affects people differently and thus makes a few groups more vulnerable to the disease. Those with higher risk of having severe symptoms are children under five, pregnant women, travellers, and those with HIV or AIDS. Severe symptoms may vary but a few are as listed; fatigue, confusion, seizures, difficulty breathing, jaundice and abnormal bleeding. Those who are pregnant may also have a premature delivery and/or lower birth weight. People outside of these groups are more likely to develop lighter symptoms such as; febrile fever, chills and headache. These symptoms are common to a lot of different diseases and cause misdiagnosis. It is also one of the reasons that malaria has managed to mutate itself and gained resistance against medicine. Besides this, medicines are important since it prevents symptoms from getting more severe and life threatening, but is also necessary to be cured. (1, 2, 3)

Malaria can also be prevented by taking precautionary measures and thus avoiding the disease. Firstly, one can use insecticide-treated nets (ITNs) and indoor residual spraying (IRS). However, this is less effective than hoped since they either do not do enough to keep mosquitoes away or for the lack of available insecticides. These options have caused new behaviors among mosquitoes, along with resistance against the insecticides. Secondly, one can prevent a malaria infection by taking chemoprophylaxis, and this is taken before entering an area where malaria exists. Another similar precautionary measurement is chemotherapies, but it is dependent on the fact that more people take the medicine regardless of symptoms or not. These chemotherapies are given during different seasons and

at different times. Thirdly, there are vaccines that were introduced in 2021 by WHO and were tested on children. It showed reducing cases in malaria and two WHO-approved malaria vaccines now exists. (1)

There is a wide range of different medicines one can take when exposed to malaria, because different strains may react differently to different chemicals. The first example is of *P. falciparum* and artemisinin, where artemisinin is very effective *against P. falciparum*. However, this may not work all the time since artemisinin resistance has started to surface around Eritrea, Rwanda, Uganda and Tanzania. Another similar example is *P. vivax* and chloroquine, but since most regions where malaria exists have developed a resistance to this drug it is important to know if that particular strain is resistant. (1)

In order for a region to be deemed free of malaria, the region must have three consecutive years with no cases. When working with elimination of malaria the procedure is very important and doctors are urged to prescribe more medicine even if it is not certainly malaria. This since some people have partial immunity and can carry the parasitic disease but remain asymptomatic. (1)

2.1 Antimalarial medicines

Malaria has been treated for long before people knew of medicines and diseases. The first substance thought to cure malaria was quinine, which is found in the bark of Cinchona trees. It can be found in the Andes and was used by native Americans. Quinine was isolated from the bark in 1820, but the first attempts to design new synthetic antimalarial drugs came a hundred years later. One of the then synthesised substances was chloroquine, but this substance was first thought to be toxic. Once tests proved it to be more desirable than quinine it became widely popular. Chloroquine, or CQ, had less side effects than quinine but was also more effective upon further analysis. However, chloroquine has since lessened in effectiveness due to the parasite having mutated and gained resistance. The main thought regarding reasons for the rise of resistance created is that it is due to overuse and incomplete treatments. Today chloroquine can only be used to treat malaria in a very select few regions. (4, 5, 6)

Due to resistance of chloroquine the search for a cure for malaria is highly sought after. Other derivatives originating from chloroquine have been developed and amongst them are 4-aminoquinoline and amodiaquine. However, the latter creates a harmful metabolite and is therefore no

longer in use. Aside from that, they also do not have the desired effectiveness and side effects. 4-aminoquinolines are otherwise the most studied when it comes to potential future antimalarials. (4, 5)

A different way to treat malaria is with folate antagonists since the parasite itself must synthesise folates. The parasite would not be able to create the essential folates to survive if the enzyme was inhibited. Proguanil and pyrimethamine-sulfadoxine are both folate antagonists by being competitive inhibitors, and the latter has a synergistic effect since the two molecules inhibit different enzymes. If pyrimethamine-sulfadoxine is used it is important that both are non-compromised or the effectiveness will be deteriorated. The biggest problem with these are the wide resistance against them, resulting in the enzymes no longer having the same sensitivity towards the drugs. (4, 5)

Aside from chloroquine, there is one other largely used antimalarial named artemisinin. Artemisinin is found in sweet wormwood and is considered the most effective antimalarial drug in current use. Additional derivatives of artemisinins are artemether, artesunate and dihydroartemisinin. However, this natural product is much more expensive due to extraction processes from the plant. Aside from this some resistance towards artemisinin has been found. (4, 5)

2.2 Metal based antimalarial medicines

Bio-organometallic chemistry was first introduced 1985 and was explained as metals bonded to biomolecules or biologically active molecules. The main purpose was to use both the organic and inorganic properties of the complexes synthesised to gain further effectiveness. The first widely known complex of this kind is ferroquine, which has a ferrocene core that is bonded to two amine nitrogens in the lateral side chain of chloroquine. This was done in 1994 and this molecule has since started going through a drug trial. What is known about the complex is that it has been effective against strains of malaria that are resistant against chloroquine as well as non-resistant strains. Furthermore, it has shown similar effectiveness and activity which is essential. The mechanism for how this antimalarial drug works is uncertain, but it is expected to work in a manner similar to chloroquine. Chloroquine builds up in the vacuole of the parasite and due to the naturally acidic nature of it, chloroquine is able to increase the pH of the vacuole because of its basic properties. (4, 5, 6)

Since the introduction of bio-organometallic chemistry additional complexes have been synthesised and studied. A range of different metals have been used as the central atom and a few examples are

triphenylphosphine gold(I) and $[\text{Rh}(\text{CQ})\text{Cl}_2]_2$. (4, 5) In this report, palladium complexes will be in focus and different derivatives of quinolines have been used as a ligand. To characterize and verify the identity of the new complexes, Nuclear Magnetic Resonance, NMR, was used in combination with Infrared and Ultraviolet-Visible spectroscopy.

3. Materials and Methods

3.1. Chemicals

The chemicals used for this experiment were purchased from Sigma Aldrich. The starting materials (7-(chloro)quinolin-4-yl)ethane-1,2-diamine and (7-methoxyquinolin-4-yl)ethane-1,2-diamine were synthesized according to literature (2). All solvents were from VWR and/or Sigma Aldrich. The experiments were done under inert atmosphere using Schlenk techniques.

3.2. Method

3.2.1 Synthesis of 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol, L1

(7-(chloro)quinolin-4-yl)ethane-1,2-diamine (504,51 mg, 2,41 mmol) was dissolved in ethanol (20 ml). To remove all air, nitrogen was bubbled into the solution (45 minutes). Salicylaldehyde (0,4 ml, 3,75 mmol) was then added dropwise into the solution. The mixture was stirred (30 minutes) so a precipitate was produced. The precipitate was suction-filtered and washed with ethanol. The yellow powder was then measured and weighed (472,17 mg, 1,50 mmol, 63% Yield).

¹H NMR (Methanol, 500 MHz) δ 8,43 (s, 1H), 8,38 (d, 1H), 8,09 (d, 1H), 7,80 (d, 1H), 7,41 (dd, 1H), 7,28 (m, 2H), 6,84 (m, 2H), 6,68 (d, 1H), 4,60 (s, 2H), 3,97 (td, 2H), 3,79 (t, 2H), 1,35 (s, 1H), 1,31 (s, 1H) ppm.

IR 3200 (br), 3000 (w), 1600 (s), 1580 (s) cm⁻¹

3.2.2 Synthesis of 4-fluoro- 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol, L2

(7-(chloro)quinolin-4-yl)ethane-1,2-diamine (619,5 mg, 2,75 mmol) was dissolved in ethanol (20 ml). Fluoro-salicylaldehyde (355,9 mg, 2,54 mmol) was then added under nitrogen. The solution was stirred and refluxed overnight. The precipitate was suction filtered and washed with ethanol. The yellow powder was then measured and weighed (778,45 mg, 2,26 mmol, 89% Yield).

¹H NMR (Acetonitrile, 500 MHz) δ 13,16 (s, 1H), 8,47 (d, 2H), 8,38 (d, 2H), 7,90 (m, 4H), 7,42 (dd, 2H), 7,09 (m, 4H), 6,89 (dd, 2H), 6,62 (d, 2H), 6,17 (s, 1H), 3,94 (ddd, 4H), 3,74 (q, 4H), 3,37 (q, 12H), 2,62 (s, 3H), 1,14 (t, 17H) ppm

3.2.3 Synthesis of 4-chloro-2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol, L3

(7-(chloro)quinolin-4-yl)ethane-1,2-diamine (501,6 mg, 2,26 mmol) was dissolved in ethanol (50 ml). Separately, chloro-salicylaldehyde (444,9 mg, 2,84 mmol) was also dissolved in ethanol (30 ml) and both solutions were put in a water bath (45°C). The solutions were then added together and were continued to be heated in a water bath (45 °C) for an hour. The reaction was stirred overnight at room temperature. The precipitate was suction-filtered and washed with water and diethyl ether. The yellow powder was then measured and weighed (547,49 mg, 1,52 mmol, 67% Yield).

¹H NMR (CDCl₃, 500 MHz) δ 10,94 (s, 1H), 9,88 (s, 1H), 9,25 (s, 1H), 9,19 (s, 1H), 8,52 (m, 2H), 8,10 (m, 2H), 8,05 (m, 2H), 7,94 (d, 2H), 7,89 (m, 2H), 7,65 (d, 1H), 7,56 (d, 1H), 7,49 (m, 3H), 7,35 (m, 3H), 7,23 (m, 5H), 7,04 (d, 2H), 6,97 (m, 2H), 6,85 (d, 1H), 4,56 (m, 2H), 4,24 (t, 2H), 3,99 (m, 7H), 3,76 (d, 2H), 2,68 (s, 2H), 2,31 (d, 1H), 2,25 (s, 2H), 2,12 (s, 2H), 1,36 (s, 2H), 1,28 (s, 5H), 0,91 (dd, 3H), 0,86 (s, 2H), 0,11 (m, 7H), 0,09 (s) ppm

3.2.4 Synthesis of 4-bromo-2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol, L4

(7-(chloro)quinolin-4-yl)ethane-1,2-diamine (516,7 mg, 2,46 mmol) was dissolved in ethanol (50 ml). Separately, bromo-salicylaldehyde (556,68 mg, 2,77 mmol) was also dissolved in ethanol (30 ml) and both solutions were put in a water bath (45°C). The solutions were then added together and were continued to be heated in a water bath (45 °C) for an hour. The reaction was stirred overnight at room temperature. The precipitate was suction filtered and washed with water and diethyl ether. The pale yellow powder was then measured and weighed (901,16 mg, 2,20 mmol, 89% Yield).

¹H NMR (CDCl₃, 500 MHz) δ 12,86 (s, 1H), 10,95 (s), 9,44 (s 2H), 9,19 (s 2H), 8,65 (d, 3H), 8,49 (s, 2H), 8,05 (m, 8H), 7,95 (t, 4H), 7,77 (d, 2H), 7,48 (m, 4H), 7,35 (m, 8H), 7,22 (m, 6H), 6,94 (m, 5H), 6,78 (d, 3H), 6,52 (d, 3H), 6,32 (d, 2H), 6,23 (s, 2H), 4,54 (d, 3H), 4,23 (t, 4H), 3,96 (m, 13H), 3,76 (m, 4H), 1,28 (m, 10H), 0,90 (dd, 4H), 0,86 (s, 2H), 0,11 (m, 6H), 0,09 (s) ppm

3.2.5 Synthesis of 4-iodo-2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol, L5

(7-(chloro)quinolin-4-yl)ethane-1,2-diamine (545,5 mg, 2,46 mmol) was dissolved in ethanol (50 ml). Separately, iodo-salicylaldehyde (734,5 mg, 2,96 mmol) was also dissolved in ethanol (30 ml) and both solutions were put in a water bath (45°C). The solutions were then added together and were continued to be heated in a water bath (45 °C) for an hour. The reaction was stirred overnight at room temperature. The precipitate was suction filtered and washed with water and diethyl ether. The pale yellow powder was then measured and weighed (1767,14 mg, 3,91 mmol, 159% Yield). The amount collected is too much to be all product.

3.2.6 Synthesis of 2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol, L6

(6-methoxyquinolin-4-yl)ethane-1,2-diamine (526,9 mg, 2,58 mmol) was dissolved in ethanol (50 ml). Separately, salicylaldehyde (0,5 ml, 4,69 mmol) was also dissolved in ethanol (30 ml) and both solutions were put in a water bath (45°C). The solutions were then added together and were continued to be heated in a water bath (45 °C) for an hour. The reaction was stirred overnight at room temperature. The solvent was then evaporated with rotary evaporation and the liquidus residue was collected. The sticky amber-colored product was put under vacuum and then weighed (481,0 mg, 4,0 mmol, 155% Yield). The amount collected is too much to be all product.

¹H NMR (DCM, 500 MHz) δ 13,16 (s, 1H), 9,95 (d, 1H), 8,43 (m, 2H), 7,89 (d, 1H), 7,60 (m, 2H), 7,32 (m, 3H), 7,01 (m, 5H), 6,57 (d, 1H), 5,36 (m, 2H), 3,98 (d, 2H), 3,77 (d, 2H) ppm.

3.2.7 Method A Pd(2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol)₂ complex, 1A

The ligand (396,8 mg, 1,26 mmol) was added and dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was purged of all air and nitrogen was pumped through. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (325,82 mg, 1,14 mmol) was added together with dichloromethane. The mixture was stirred for 10 minutes while cooled and stirred overnight at room temperature. Thereafter the

precipitate was suction-filtered and washed with dichloromethane. The orange red precipitate was then measured (323,48 mg, 0,44 mmol, 69%).

The product (183,7 mg, 0,24 mmol) was then added into a mixture of ethanol (20 ml) and sodium bisulfite-saturated water (30 ml). It was then stirred for two hours at room temperature. Afterwards the precipitate was filtered and washed with water. The yellow precipitate was then measured (100,86 mg, 0,13 mmol, 55%).

¹H NMR (DMSO, 500 MHz) δ 8,41 (d, 2H), 8,22 (d, 2H), 8,08 (s, 1H), 7,98 (s, 2H), 7,77 (s, 2H), 7,42 (d, 2H), 7,24 (m, 4H), 6,85 (d, 2H), 6,78 (d, 2H), 6,56 (t, 2H), 4,05 (d, 4H), 3,76 (q, 4H), 1,24 (s, 1H) ppm

3.2.8 Method A Pd(4-fluoro- 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl) imino)methyl)phenol)₂ complex, 2A

The ligand (231,79 mg, 0,67 mmol) was added and dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was purged of all air and nitrogen was pumped through. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (460,0 mg, 1,61 mmol) was added together with dichloromethane. The mixture was stirred for 10 minutes while cooled and stirred overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The orange red precipitate was then measured (438,73 mg, 0,55 mmol, 82%).

¹H NMR (DMSO, 500 MHz) δ 8,40 (s, 1H), 8,25 (s, 1H), 8,18 (s, 1H), 7,93 (s, 1H), 7,81 (s, 1H), 7,54 (s, 1H), 7,39 (d, 2H), 7,20 (s, 1H), 7,07 (s, 1H), 6,87 (s, 1H), 6,71 (s, 1H), 5,99 (s, 1H), 5,63 (s, 1H), 5,51 (s, 1H), 5,11 (s, 1H), 4,23 (s, 1H), 4,01 (s, 2H), 3,70 (s, 2H), 2,30 (s, 1H), 2,16 (d, 2H), 1,99 (s, 1H), 1,69 (s, 1H), 1,54 (s, 1H), 1,24 (s, 1H), 1,08 (s, 1H), 0,86 (s, 1H) ppm.

3.2.9 Method A Pd(4-chloro- 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl) imino)methyl)phenol)₂ complex, 3A

The ligand (387,1 mg, 1,07 mmol) was added and dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was purged of all air and nitrogen was pumped through. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached,

[Pd(COD)Cl₂] (325,82 mg, 1,14 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The orange red precipitate was then measured (323,48 mg, 0,43 mmol, 80%).

3.2.10 Method A Pd(4-bromo- 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl) imino)methyl)phenol)₂ complex, 4A

The ligand (386,1 mg, 0,95 mmol) was added and dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was purged of all air and nitrogen was pumped through. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (481,52 mg, 1,69 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The orange-cinnamon-colored precipitate was then measured (640,71 mg, 0,70 mmol, 82%).

¹H NMR (DMSO, 500 MHz) δ 6,33 (s, 1H), 2,93 (s, 1H), 2,60 (d, 1H), 1,28 (s, 2H), 0,90 (m, 2H), 0,87 (s, 1 H), 0,10 (m 2H) ppm.

3.2.11 Method A Pd(4-iodo- 2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl) imino)methyl)phenol)₂ complex, 5A

The ligand (472,7 mg, 1,05 mmol) was added and dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was purged of all air and nitrogen was pumped through. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (424,25 mg, 1,48 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The cinnamon-colored precipitate was then measured (468,55 mg, 0,46 mmol, 88%).

¹H NMR (DMSO, 500 MHz) δ 9,96 (s), 7,73 (dd), 7,61 (m), 7,61 (s), 7,10 (t), 7,01 (d), 6,90 (d), 5,48 (s), 4,92 (s), 4,09 (d), 3,36 (q), 2,30 (s), 2,12 (d), 2,00 (s), 1,99 (s, 1H), 1,36 (s), 1,25 (m), 0,90 (d), 0,11 (s) ppm.

3.2.12 Method A Pd(2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino) methyl)phenol)₂ complex, 6A

The ligand (160,3 mg, 0,49 mmol) was dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was kept under nitrogen and stirred for an hour. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (103,24 mg, 0,36 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and stirred then overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The yellow precipitate was then measured (133,98 mg, 0,18 mmol, 71%).

3.2.13 Method A Pd(4-fluoro-2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino) methyl)phenol)₂ complex, 7A

The ligand (152,2 mg, 0,47 mmol) was dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was kept under nitrogen and stirred for an hour. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (230,29 mg, 0,81 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction-filtered and washed with dichloromethane. The yellowish-brown precipitate was then measured (146,33 mg, 0,19 mmol, 79%).

3.2.14 Method A Pd(4-chloro-2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol)₂ complex, 8A

The ligand (150,5 mg, 0,42 mmol) was dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was kept under nitrogen and stirred for an hour. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (214,2 mg, 0,75 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction-filtered and washed with dichloromethane. The yellow precipitate was then measured (170,57 mg, 0,21 mmol, 99%).

¹H NMR (DMSO, 500 MHz) δ 10,22 (s, 13H), 9,46 (s, 1H), 9,08 (m, 9H), 8,83 (s, 3H), 8,71 (d, 14H), 7,55 (s, 1H), 7,10 (s, 1H), 6,45 (s, 14H), 5,65 (m, 2H), 5,41 (s, 2H), 4,90 (d, 3H), 3,94(s, 1H), 2,75 (s,1H) ppm

3.2.15 Method A Pd(4-bromo-2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino) methyl)phenol)2 complex, 9A

The ligand (115,1 mg, 0,29 mmol) was dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was kept under nitrogen and stirred for an hour. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (185,42 mg, 0,65 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction-filtered and washed with dichloromethane. The greenish cinnamon-colored precipitate was then measured (117,2 mg, 0,13 mmol, 90%).

3.2.16 Method A Pd(4-iodo-2-(((2-((6-methoxyquinolin-1-yl)amino)ethyl)imino) methyl)phenol)2 complex, 10A

The ligand (137,9 mg, 0,31 mmol) was dissolved in dichloromethane (30 ml) and triethylamine (0,4 ml). The solution was kept under nitrogen and stirred for an hour. The solution was cooled with an acetone dry ice bath and when the temperature -78°C was reached, [Pd(COD)Cl₂] (154,00 mg, 0,54 mmol) was added together with dichloromethane. The mixture was stirred for 60 minutes while cooled and then stirred overnight at room temperature. Thereafter the precipitate was suction filtered and washed with dichloromethane. The light orange precipitate was then measured (31,14 mg, 0,03 mmol, 20%).

¹H NMR (DMSO, 500 MHz) δ 10,21 (s, 1H), 8,31 (s, 1H), 7,85 (s, 1H), 7,77 (s, 1H), 7,60 (s, 1H), 7,49 (s, 1H), 7,31 (s, 1H), 5,98 (s, 1H), 5,63 (s, 1H), 5,32 (d, 2H), 5,11 (d, 1H), 3,89 (s, 2H), 3,75 (s, 2H), 2,94 (s, 1H), 2,31 (s, 4H), 1,99 (s, 1H), 1,70 (s, 1H), 1,57 (s, 1H), 1,46 (s, 1H), 1,24 (d, 5H), 1,12 (s, 2H), 0,86 (s, 1H) ppm.

3.2.17 Method A Pd(7-chloro-N-(2-((pyridin-3-ylmethylene)amino)ethyl) quinolin-4-amine)Cl₂ complex, 11A

The ligand (160,5 mg, 0,48 mmol) and [Pd(COD)Cl₂] (142,3 mg, 0,50 mmol) were dissolved in dichloromethane (30 ml). The mixture was stirred for two hours at room temperature. Thereafter the precipitate was suction-filtered and washed with dichloromethane. The pearl white-colored precipitate was then measured (189,36 mg, 0,25 mmol, 51%).

3.2.18 Method A Pd(N-(2-(((1H-imidazol-5-yl)methylene)amino)ethyl)-7-chloroquinolin-4-amine)Cl₂ complex, 12A

The ligand (150,35 mg, 0,47 mmol) and [Pd(COD)Cl₂] (129,26 mg, 0,45 mmol) was dissolved in dichloromethane (30 ml). The mixture was stirred for one hour at room temperature. Thereafter the precipitate was suction-filtered and washed with dichloromethane. The sandy-colored precipitate was then measured (172,49 mg, 0,23 mmol, 49%).

¹H NMR (Methanol, 500 MHz) δ 7,24 (s 1H), 5,93 (s, 1H), 5,53 (d, 2H), 4,11 (s, 1H), 3,83 (s, 2H), 3,76 (s, 1H), 3,70 (s, 1H), 3,33 (s, 5H), 2,68 (s, 1H), 2,30 (s, 1H), 1,30 (s, 1H) ppm

3.2.19 Method B Pd(2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl) imino)methyl)phenol)₂, 1B

The ligand was extracted from column chromatography (Ethyl Acetate:Methanol, 1:1). The ligand (104,1 mg, 0,32 mmol) was then dissolved in DCM (30 ml), triethylamine (0,4 ml) and THF (6,0 ml). The solution was heated up to 60°C before [Pd(COD)Cl₂] (90,62 mg, 0,32 mmol) was added. Once the metal complex was added the mixture was heated to 74°C and left to stir overnight. The yellow precipitate was then dried and washed with DCM (2x10ml). The product was measured and weighed (36,56 mg, 0,05 mmol, 30%).

¹H NMR (DMSO, 500 MHz) δ 8,54 (s, 1H), 8,40 (d, 1H), 8,37 (s, 1H), 8,31 (s, 1H), 8,24 (d, 1H), 8,15 (d, 1H), 7,95 (s, 1H), 7,78 (d, 1H), 7,76 (d, 1H), 7,33 (m, 1H), 4,04 (d, 2H), 3,89 (s), 3,69 (d, 2H) ppm

IR 3200 (br), 2900 (w), 1610 (m), 1580 (m) cm⁻¹

3.2.20 Method B Pd(4-fluoro-2-(((2-((7-(chloro)quinolin-4-yl)amino) ethyl)imino)methyl)phenol)₂, 2B

The ligand (118,5 mg, 0,34 mmol) was dissolved in DCM (30 ml), triethylamine (0,4 ml) and THF (6,0 ml). The solution was heated to 60°C before the [Pd(COD)Cl₂] (93,31 mg, 0,33 mmol) was added. Once the metal was added the mixture was heated to 74°C and left to stir overnight. No precipitate was formed and the solution was dried. The yellow precipitate was then measured and weighed (129,83 mg, 0,16 mmol, 95%).

3.2.21 Method B Pd(4-chloro-2-(((2-((7-(chloro)quinolin-4-yl)amino) ethyl)imino)methyl)phenol)₂, 3B

The ligand (105,0 mg, 0,29 mmol) was dissolved in DCM (30 ml), triethylamine (0,4 ml) and THF (6,0 ml). The solution was heated up to 60°C before [Pd(COD)Cl₂] (83,1 mg, 0,29 mmol) was added. Once the metal was added, the mixture was heated to 74°C and left to stir overnight. The yellow precipitate was then dried and washed with DCM (2x10ml). The product was measured and weighed (26,51 mg, 0,03 mmol, 22%).

¹H NMR (DMSO) δ 10,21 (s, 1H), 8,40 (d, 2H), 8,20 (d, 1H), 7,92 (s, 1H), 7,78 (s, 1H), 7,41 (d, 1H), 7,26 (d, 2H), 6,88 (d, 1H), 6,73 (s, 1H), 5,32 (d, 1H), 3,98 (s, 2H), 3,71 (s, 2H) ppm.

IR 3289 (br, w), 3228 (br, w), 2931 (w), 1616 (m), 1586 (s), 1456 (s), 1306 (m), 805 (m), 708 (m)cm⁻¹

3.2.22 Method B Pd(4-bromo-2-(((2-((7-(chloro)quinolin-4-yl)amino) ethyl)imino)methyl)phenol)₂, 4B

The ligand (115,9 mg, 0,28 mmol) was dissolved in DCM (30 ml), triethylamine (0,4 ml) and THF (6,0 ml). The solution was heated to 60°C before [Pd(COD)Cl₂] (82,2 mg, 0,29 mmol) was added. Once the metal was added, the mixture was heated to 74°C and left to stir overnight. The orange precipitate was then dried and washed with DCM (2x10ml). The product was measured and weighed (74,50 mg, 0,08 mmol, 57%).

¹H NMR (DMSO) δ 10,22 (s, 1H), 8,39 (d), 8,18 (d), 7,91 (s), 7,78 (s), 7,52 (s), 7,38 (m, 1H), 6,83 (d), 6,71 (d), 5,76 (s), 5,30 (s), 3,97 (s), 3,70 (s) ppm

IR 3289 (br, w), 3228 (br, w), 2931 (w), 1616 (m), 1586 (s), 1456 (s), 1306 (m), 805 (m), 708 (m) cm⁻¹

3.2.23 Method B Pd(4-iodo-2-(((2-((7-(chloro)quinolin-4-yl)amino)ethyl)imino)methyl)phenol)₂, 5B

The ligand (230,4 mg, 0,51 mmol) was dissolved in DCM (30 ml), triethylamine (0,4 ml) and THF (6,0 ml). The solution was heated to 60°C before [Pd(COD)Cl₂] (76,7 mg, 0,27 mmol) was added. Once the metal was added, the mixture was heated to 74°C and left to stir overnight. The orange precipitate was then dried and washed with DCM (2x10ml). The product was measured and weighed (89,31 mg, 0,09 mmol, 35%).

¹H NMR (DMSO) δ 8,39 (d, 1H), 8,19 (m, 1H), 7,88 (s, 1H), 7,79 (s, 1H), 7,45 (m, 3H), 7,04 (s, 1H), 6,70 (m, 2H), 3,96 (s, 2H), 3,84 (s, 1H), 3,69 (d, 2H) ppm.

IR 3289 (br, w), 3228 (br, w), 2931 (w), 1616 (m), 1586 (s), 1456 (s), 1306 (m), 805 (m), 708 (m) cm⁻¹

4. Results and discussion

4.1 Ligand synthesis and mechanism

The ligands used in this experiment were all synthesized from the condensation of a chloroquinoline or methoxyquinoline-based amino derivative and differently substituted salicylaldehydes. The reaction that occurs is a Schiff Base formation (4, 7) where the nitrogen amine substituent of the quinoline, see **Figure 1**, reacts with the aldehyde moiety in the salicylaldehyde to create an imine with water as a byproduct. This reaction is an equilibrium reaction and to further push the reaction forward absolute ethanol was used under nitrogen. In all the reactions excess of salicylaldehyde was used to further push the reaction to the Schiff base product. Two of the ligands synthesised had a yield higher than 100% which is impossible, but due to the excess of salicylaldehyde used in the synthesis it is probable that the ligand is impure and thus is mixed with salicylaldehyde. The ligands used for the methoxyquinoline-based ligands were also synthesised under the same conditions, but were done by supervisor.

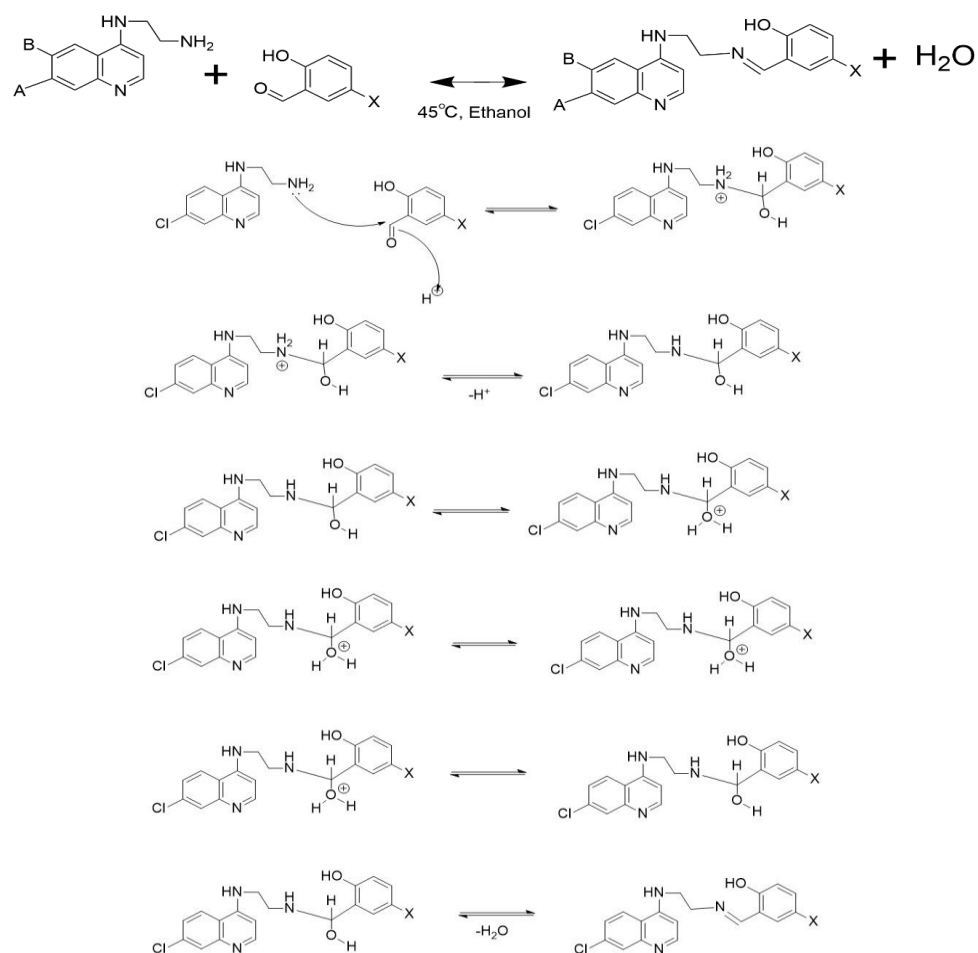
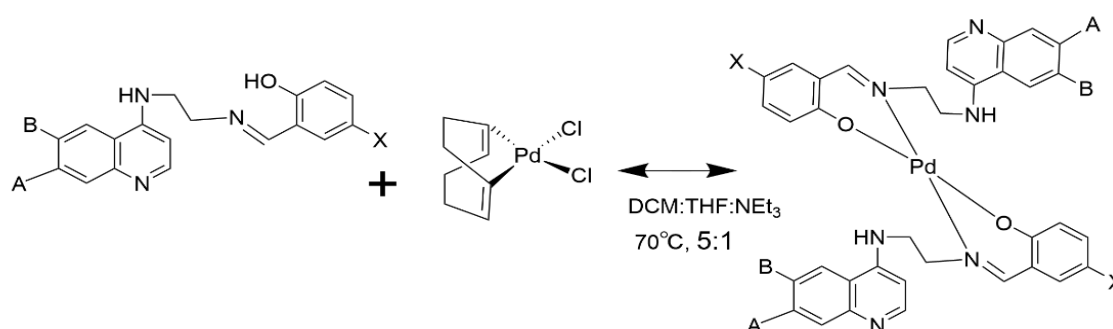


Figure 1, General reaction mechanism of ligand. The letter X is either H, F, Cl, Br or I. Additionally, A or B is present and is not both bound, A is the position of Cl and B is the position of the methoxy-group.

4.2 Complex synthesis and mechanism

The mechanism for the synthesis of the palladium complex assumes that the hydrogen bound to oxygen is the one to leave, if the surroundings are more basic than the pKa of the compound. The reason for this is due to three main points: bond strength, electronegativity and resonance. The bond between a carbon atom and a hydrogen is much stronger than the bond between oxygen and hydrogen. Furthermore, this is due to the electronegativity of the two elements and the larger the difference the more polar the bond will be. This makes the hydrogen more prone to leaving since the more electronegative oxygen is pulling the electrons closer to itself. Finally, there will be a possibility for resonance which stabilizes the ionic state and thus lowers the energy in that bond further. All these points make it most likely for the H on OH to be the most acidic hydrogen. This is the first step in order for the complex to be created, see **Figure 2**. The reaction for methoxyquinolines is the same as for chloroquinolines. (4)



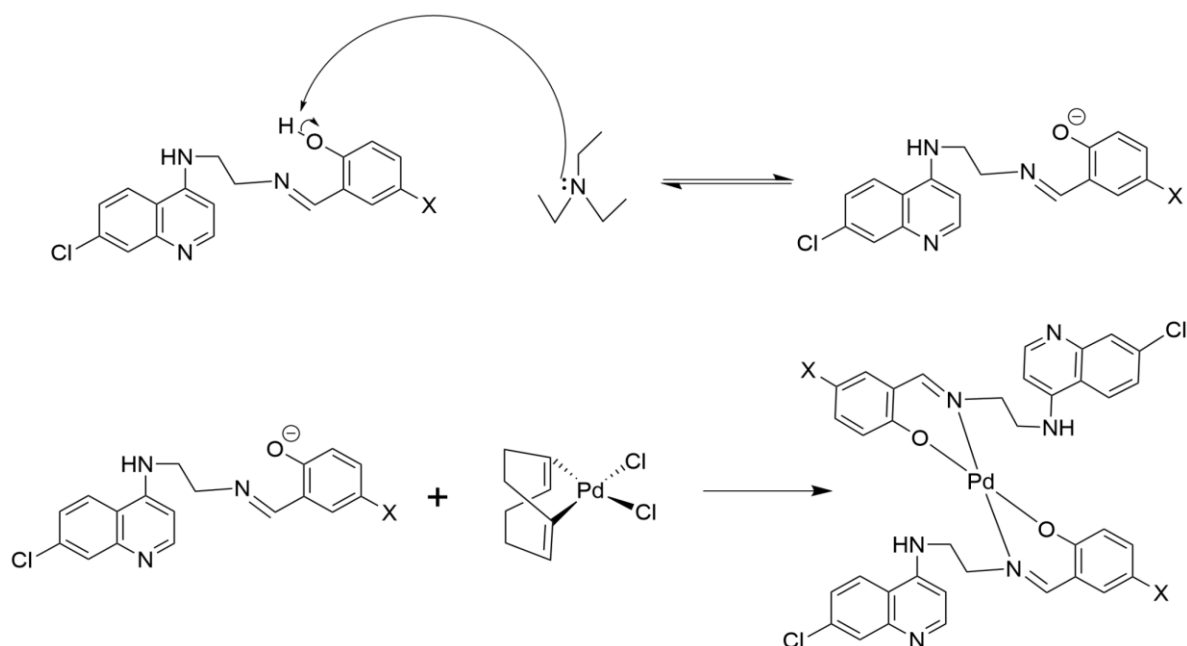


Figure 2, reaction between chloroquinoline ligand and $[Pd(COD)Cl_2]$. The letter X is either H, F, Cl, Br or I. Additionally, A or B is present and is not both bound, A is the position of Cl and B is the position of the methoxy-group.

Afterwards, the reaction can occur in a couple of different ways and speculations can only be done without doing a kinetic study. For complexes with 16 valence electrons, associative reactions are more common, in other words the nucleophile binds to the metal and creates an 18-electron intermediary. If this would be the case the next step would be which of the already bound ligands (compounds) would leave the metal first. This can either be one of the chlorides or one of the bonds to cyclooctadiene (COD), consequently the next bond to be broken can also be either of them. The ligand will first bind to the metal with the oxygen and the second bond from the same ligand will happen before the second ligand reacts. However, what can be expected is that the time it takes for the second ligand to bind is expected to be faster due to Banzhaf's law, since the first ligand has overcome the highest energy barrier. (8)

The starting metal complex is a palladium (II) complex and therefore has a square planar geometry. This is due to the crystal field splitting that occurs between the metal and its ligands. Furthermore, this can be explained by palladium being a d^8 metal once it is in the $Pd(II)$ oxidation state, and the interactions between the ligand and metal's orbitals. Palladium (II) does most commonly bind to four

ligands and have a total of 16 electrons shared by the metal and its ligands. This makes the most favorable geometry to be square planar, the reason for this is that the $d_{x^2-y^2}$ orbital is in the plane of all bonds and thus has a higher energy level due to the interactions between electrons. This makes the orbital much higher in energy in comparison to all the other orbitals which have less overlap with the bonds due to their geometry, see **Figure 3**. The plane that has the least amount of overlap is the d_{zx} and d_{zy} and will thus have the lowest energy in the crystal field splitting. **Figure 3** also shows the crystal field splitting for a complex with tetrahedral geometry, which would be preferable if the metal was palladium (0). Furthermore, the total energy for a square planar geometry has a lower energy if only 16 electrons are put into the orbitals than if it would have been in the tetrahedral geometry. The light gray line in **Figure 3** is the representation of the d-orbitals in their ground state when no bonds are present. (8)

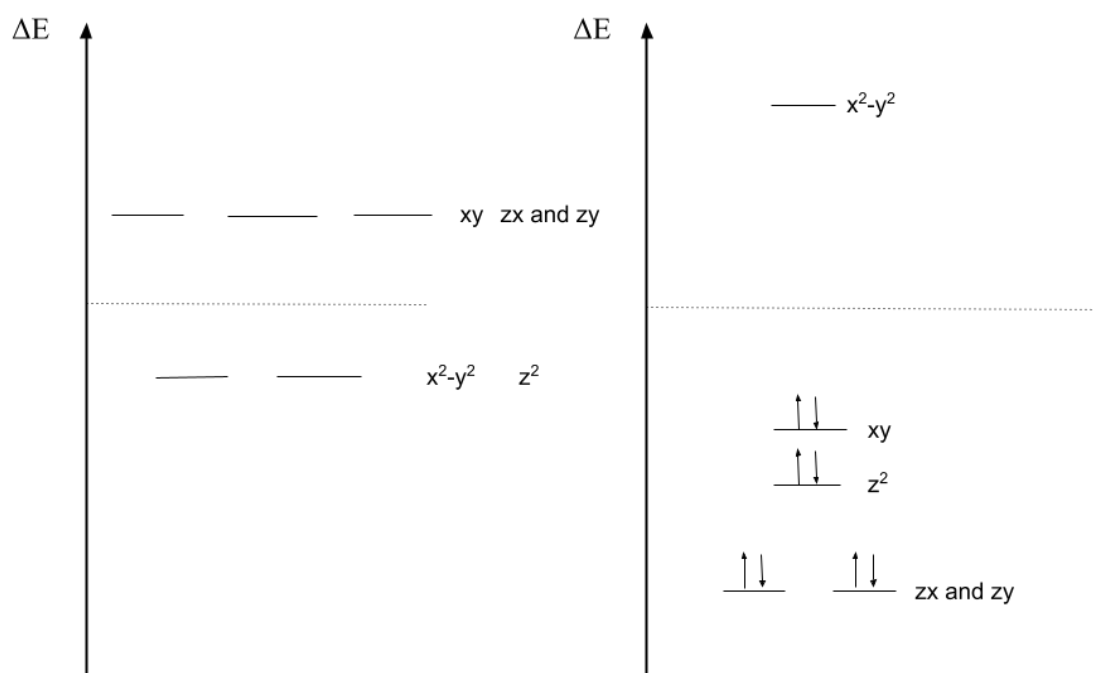
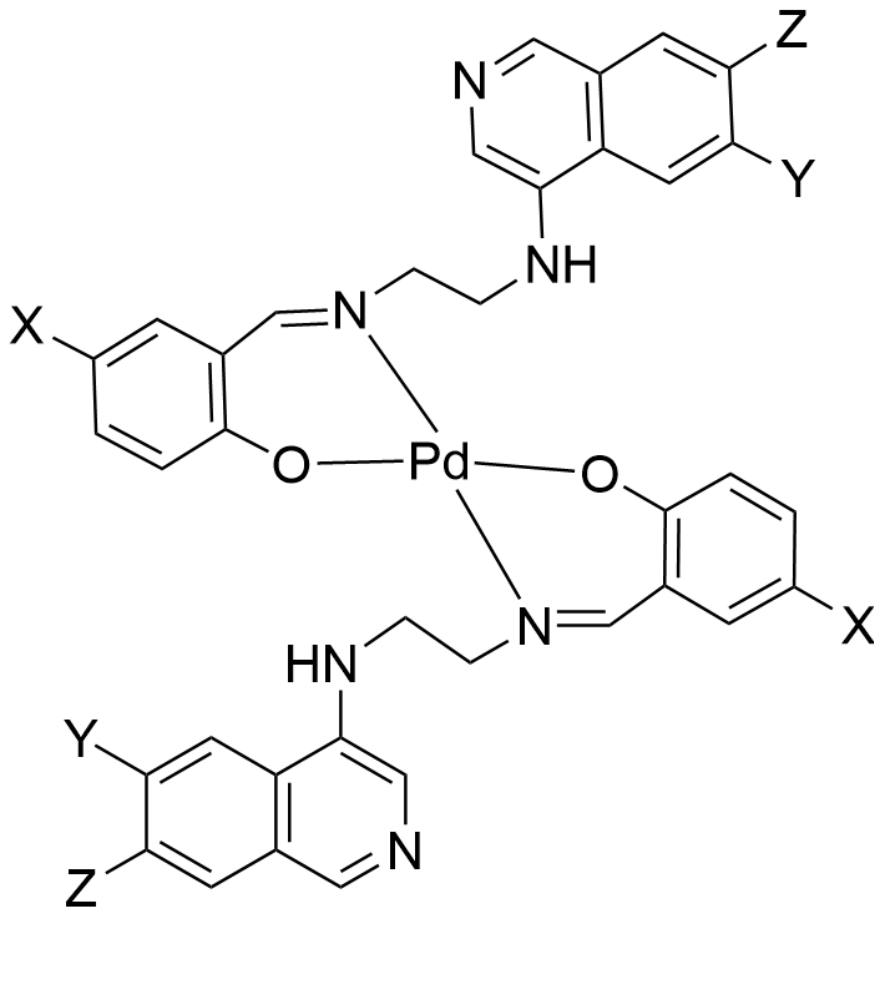


Figure 3, crystal field splitting for tetrahedral (left) and square planar (right) geometry.

In the following pages in this report the individual complexes and ligands will be discussed, therefore a table has been made to easier follow. The general structure of the complex is drawn with three varying bonds. The atom in Z position is where either chloro is bound or hydrogen, while Y is where hydrogen or a methoxy group is located. Another changing atom is X and will vary between the

halogens or hydrogen. The complexes and their ligands can be seen in **Table 1**. For complex **11A** and **12A** their structure can be seen in the **Appendix** in **Table 2**, along with a more detailed table of each of the ligands.

Table 1, Summary of complexes described in this thesis.

1A/B X:H, Y:H, Z:Cl (L1)	
2A/B X:F, Y:H, Z:Cl (L2)	
3A/B X:Cl, Y:H, Z:Cl (L3)	
4A/B X:Br, Y:H, Z:Cl (L4)	
5A/B X:I, Y:H, Z:Cl (L5)	
6A X:H, Y:MeO, Z:H (L6)	
7A X:F, Y:MeO, Z:H (L7)	
8A X:Cl, Y:MeO, Z:H (L8)	
9A X:Br, Y:MeO, Z:H (L9)	
10A X:I, Y:MeO, Z:H (L10)	

4.2 Solubility

Solubility tests were done to understand the physical properties of the complexes. This will ease the choice of preferable solvent used in the NMR, UV-VIS, and FTIR measurement later. The complexes with the same starting quinoline, either chloro- or methoxy-quinoline, are assumed to have the same solubility. Therefore, it seems that the derivatives of salicylaldehyde did not affect the solubility. Two complexes with the chloroquinoline base were tested, these were **1A** and **4A**. Furthermore, **1A** was hard to dissolve in water, ethanol, acetone, acetonitrile, DCM and heptane. The complex could be seen floating on the solvent and did not interact with the solvent at all. The samples were partially soluble in a couple of solvents but the solubility was so low that the solutions were not suitable for analysis.

Among those solvents were benzene, cyclohexane and DMF. Thus, further solvents were tested to find a solvent appropriate for analysis and recrystallization. Suitable solvents were pyridine and DMSO, but the latter would still have trouble dissolving larger amounts and would lead to precipitation. Due to these observations on solubility the analysis of the synthesised complexes were difficult. For some solvents, the solubility of the complexes increased upon heating, for example DMF and benzene. However, the NMR machine used were not able to heat our samples while under analysis.

The solubility of **4A** differed from **1A**, however they were synthesized under different temperatures and using different purification steps. This could explain the differences in solubility since **1** was purified in an additional step and thus **4A** probably contains impurities. A few solvents were tested and amongst them water and DCM did not dissolve the complex. Those solvents that partly dissolved the complex were acetone, acetonitrile and methanol. Additionally, the complex was could be dissolved in DMF, pyridine and DMSO. No other solvents were tested for this complex and the analysis cannot be fully compared to the extensive analysis on solvability for **1A**.

Furthermore, the complexes with pyridine and imidazole, **11A** and **12A**, were also tested, but the tests were not as broad as prior testings. These complexes were not able to be dissolved in acetone and acetonitrile. They did however dissolve in water, methanol, DMSO and pyridine.

Additionally, tests were performed on a methoxy-based quinoline and more specifically complex **8A**. The complex was insoluble in water, but methanol, acetonitrile, THF, DCM and acetone had partial solubility. It was, however, fully soluble in DMF, DMSO and pyridine.

Since all the complexes were soluble in pyridine, this solvent was used to crystallise the complexes. The complex was dissolved in pyridine and after the solution was heated, DCM was added. The mixture was allowed to cool to room temperature before it was placed in the freezer, -17 °C. Some crystals were formed in a few of the vials but no analysis was done on them due to lack of time. So, to further analyse the complexes three spectroscopic analytical methods were used - UV-Vis, IR and NMR.

4.3 UV-VIS

In order to be able to draw conclusions by UV-Vis spectroscopy, spectra were obtained for the ligand, starting metal complex and the product complex. By comparing them to each other, it is possible, but not certain, to draw conclusions on whether the product contains either ligand or starting metal. All of the compounds were dissolved in DMSO and DMSO was used as a blank. To further minimize errors, the same cuvette was used for every measurement and all the points of measurements were below one in absorbance for best results.

Firstly, the ligand L3, can be seen on **Figure 4** and has one absorbance maximum at 345 nm. The complex, **3A**, also has this peak, but the peak has shifted to a higher wavelength, which could happen due to the metal being bound to the ligand. Them having the same peak suggests the presence of the ligand in the complex. Thus, the metal complex used as starting material, $[\text{Pd}(\text{COD})\text{Cl}_2]$, should also be compared to the complex, since the metal has a similar peak to the ligand but also has an additional peak at 400 nm. The same peak, 400 nm, is present in the complex but, like the ligand-based peak at 245 nm it has shifted to a higher wavelength. What can be said is that a new compound has been created as evidenced by the additional peak at 475 nm that is not present in the reactants. Since only the ligand and starting metal complex, $[\text{Pd}(\text{COD})\text{Cl}_2]$, were used for the reaction along with solvents it is very likely that the complex contains multiple or single ligands and metals. Therefore, there is a high chance that complex **3A** consists of both the ligand and the starting metal, but for a more certain conclusion, IR and NMR is needed.

The UV-Vis spectra of the different palladium complexes were compared to each other to see the similarities and differences between them. The shift in the peaks from the ligand and the metal is visibly not the same in all of them, as discussed above. The only difference between the complexes is the hydrogen or halide bound to the salicyl group, thus likely being the main reason for the differences in shift. The size of the shift to longer wavelengths grows the further down the halogen group one goes. Halides are electron drawing and could therefore affect the electron densities for the salicyl group, causing it to absorb light differently, see **Appendix** and **Figure 17**.

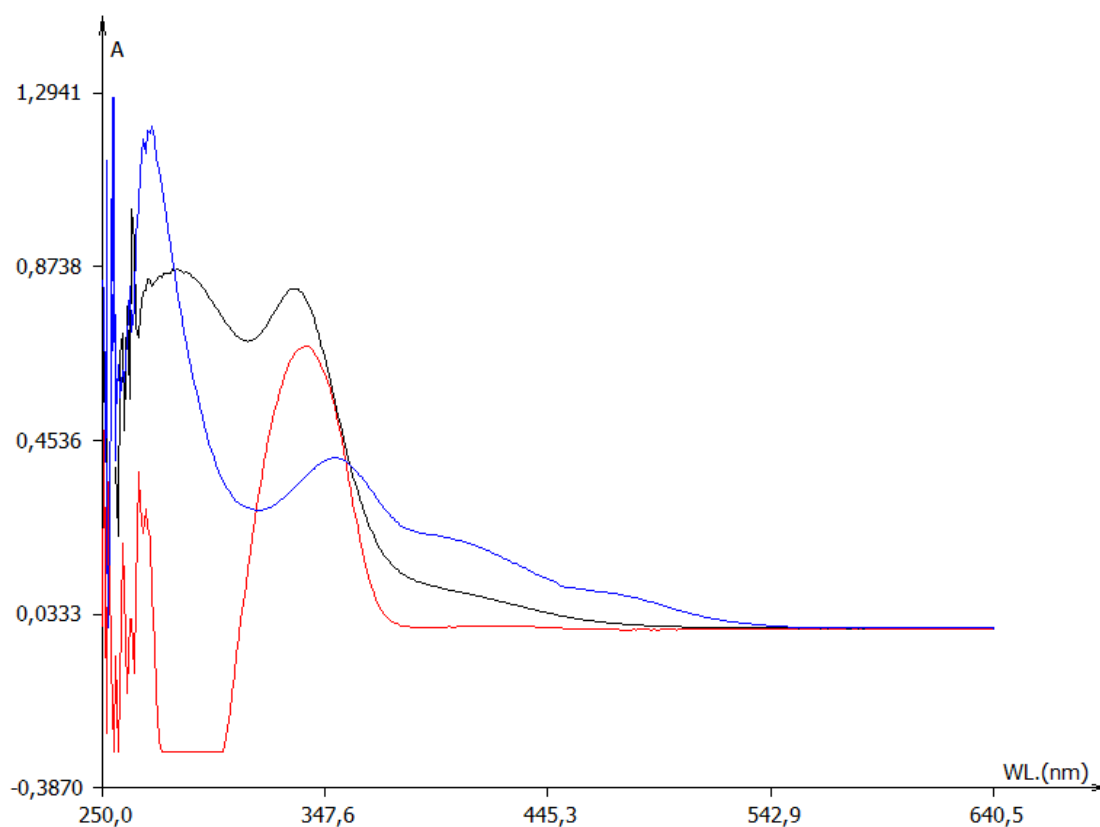


Figure 4, UV-VIS spectrums for ligand L3 (red), metal (black) and complex **3A** (blue).

4.4 IR

IR, or infrared spectroscopy, is used to determine and verify different functional groups and compounds. These functional groups can be bonds of high energy such as double bonds or those with high polarity. The compounds in this experiment are expected to have peaks at certain wavenumbers and by verifying that, it makes it possible to determine the nature of the complex. At 1600 cm^{-1} imines are visible due to the double bond between carbon and nitrogen, see **Figures 5-9**. This proves the presence of the synthesized ligand in the sample since no other imine can be present. Another peak is the one at 1580 cm^{-1} which corresponds to the quinoline, therefore it should be present in both the ones with a chloroquinoline and methoxyquinoline base. This peak seems to be a little higher than 1580 cm^{-1} but the small shift of a few wavenumbers may be due to the chloro- or methoxy group, see **Figure 5-9**.

If the reaction did not go as expected and only one ligand is bound to the metal, an additional peak at 1700 cm^{-1} can be visible. This peak corresponds to a metal halide interaction and would suggest the chlorides not having left the complex. Another possibility is that the quinoline of the ligand coordinates to the metal by the quinoline nitrogen, in which case an IR band should be visible at 1680 cm^{-1} . Neither of these possibilities seem to be true since they cannot be seen in **Figure 5-9**.

The ligand and metal should have similar IR spectra and the biggest difference seen between **Figure 5** and **Figure 6** is the intensity of a few of the peaks. For example, the ligand has a few clear bands that belong to the salicylaldehyde, $1740\text{-}1720\text{ cm}^{-1}$, and the starting quinoline, $3330\text{-}3250\text{ cm}^{-1}$. The peak corresponding to the salicylaldehyde is the carbon oxygen double bond, which more specifically corresponds to an aldehyde. For the starting quinoline, the peak listed is one for aliphatic primary amines, the bond between carbon and nitrogen. These are mostly impurities in the ligand but are not as visible in the final complex. The complex therefore seems to have little of the starting reactants present in the complex. Otherwise, the ligand and complexes both have peaks at 1580 and 1600 cm^{-1} which confirms the presence of the quinoline and imine.

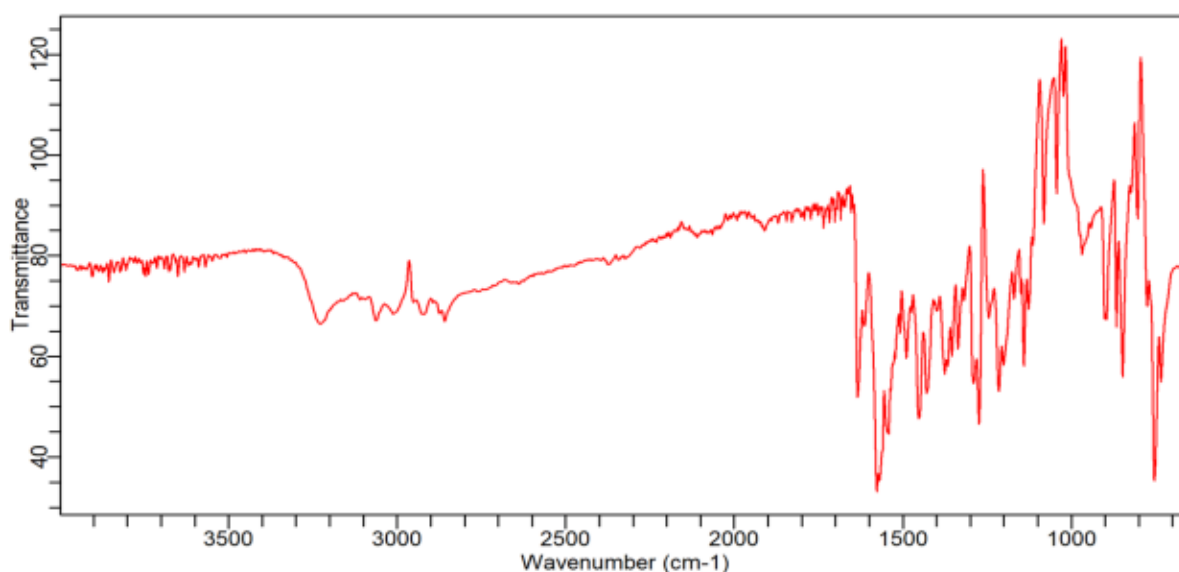


Figure 5, IR spectrum for L1.

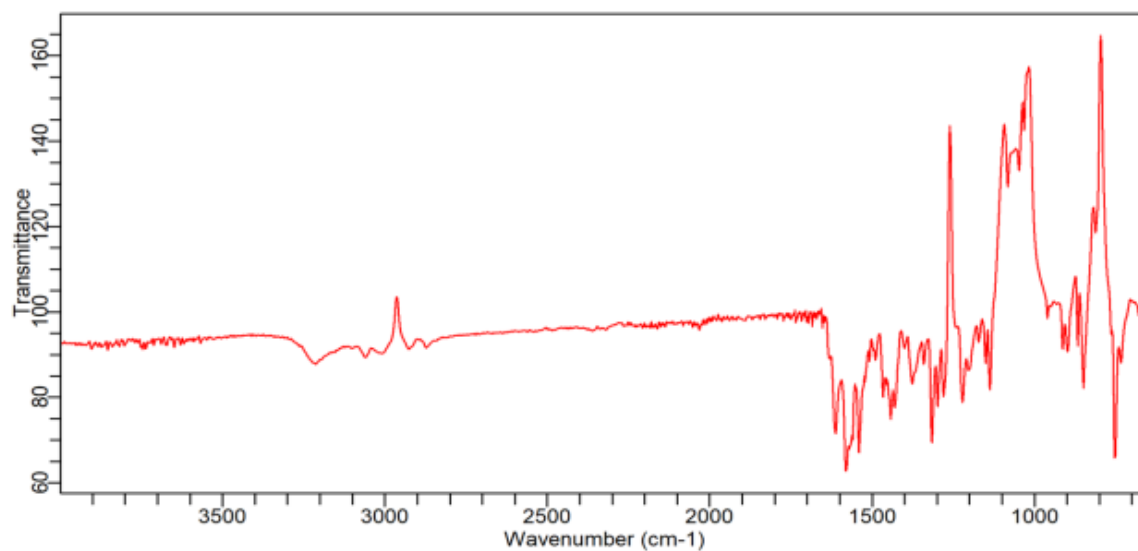


Figure 6, IR spectrum for **1B**.

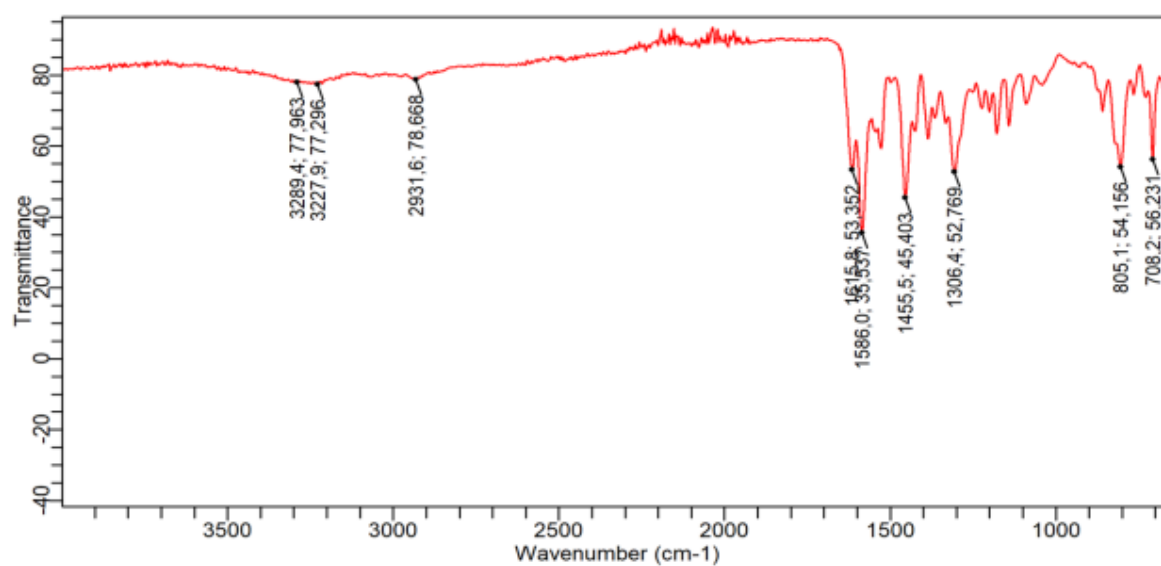


Figure 7, IR spectrum for **3B**.

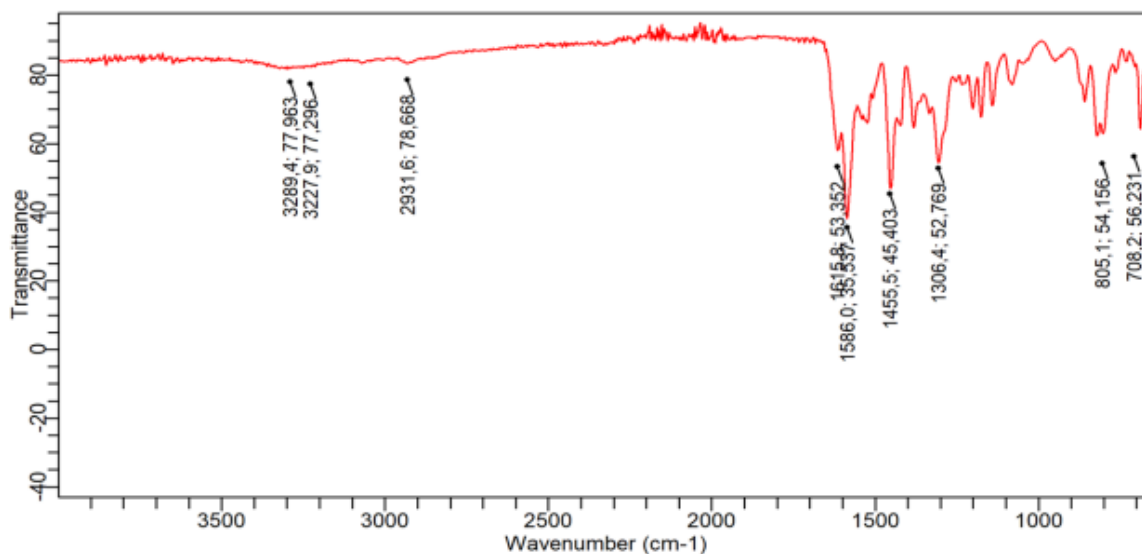


Figure 8, IR spectrum for **4B**.

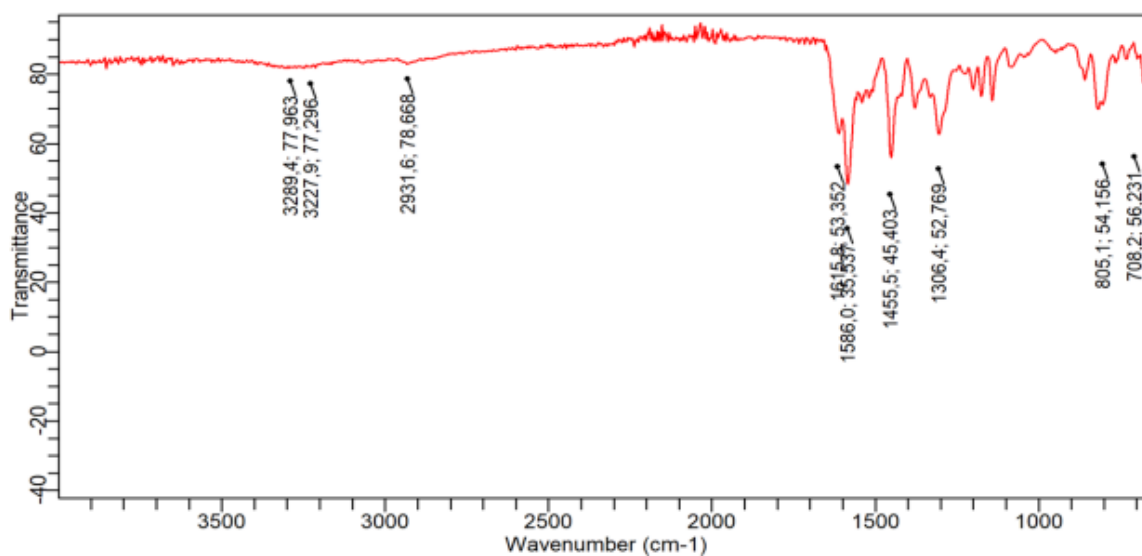


Figure 9, IR spectrum for **5B**.

4.5 NMR

A recurring problem that was met was with NMR readings, since many of the complexes synthesised with Method A were impure. Therefore, another method was introduced, Method B, where the complex synthesis was done under heat. Hence, only four complexes and their NMR spectra will be

discussed while the other spectra can be seen in the **Appendix**, see **Figures 28-44**. Additionally, the NMR spectra of some ligands will be discussed and compared to the complex.

By comparing the ligand to the complex, it was possible to tell whether the reaction was successful. Two of the main peaks to look for are the peak at 13 ppm and the peak at 10 ppm. The absence of a 10 ppm peak suggests that there is no salicylaldehyde present nor a salicylaldehyde complex. This peak is visible in the ligand, see **Figure 10**, but disappears once the complex has been formed, see **Figure 12**. Salicylaldehyde being used in excess is the main reason for why it shows up in the ligand, otherwise it should not be visible in that one either. However, since the ligand, salicylaldehyde and the starting metal complex all are dissolved in DCM it can be removed by washing the precipitate formed from the complex synthesis with DCM. The lack of solubility in DCM for the complex makes it possible to get a mostly pure NMR of it. This was however not possible for the complexes **6-10** since some of them partly dissolved in DCM which was used during synthesis. Furthermore, the same problem was met with complexes **11** and **12**.

The other peak at 13 ppm is the hydrogen in the OH on the salicylic group once the ligand has been created. Thus, the presence of a peak at 13 ppm proves that the ligand has been formed, see **Figure 10**. However, the absence of this peak suggests that the ligand no longer is present in its original state. The other hydrogens in the ligand are still visible, see **Figure 11**, and if these two possibilities both are true, then the ligand is present in another form, i.e. it is coordinated to the metal.

Other peaks that can be used for identifying the complex and ligand are the peaks at 8,4, 4 and 3,7 ppm. The peak at 8,4 will be different depending on whether the salicylaldehyde is bound to the ligand or not, see **Figures 10** and **12**. This peak corresponds to the arene hydrogen bound to the carbon next to the imine, and once the ligand is bound it will have a higher shift. The other two points mentioned above are the methylene hydrogens between the two nitrogens linking the quinoline part of the ligand to the salicylaldehyde moiety. The hydrogens are present and can be seen in **Figure 13, 14 and 15** but only **Figure 14, 4B**, is the one where the integration is not two.

There are many different impurities in the NMR spectra and a few to discuss are methanol, at around 3,30 ppm, and water, at around 4,9 and 1,2 ppm. The water peak at 4,9 ppm is for HDO is most likely due to impurities in the NMR solvent, in this case DMSO. These peaks are most likely leftover solvents that were not dried out properly before the NMR spectra were recorded. The complexes were

dissolved in DMSO and a residual solvent peak is visible in the NMR spectra shown below, see **Figures 12, 13, 14 and 15** at 2,4 ppm.

To compare the NMR spectra of all the ligands to each other, the spectra were stacked together, see **Figure 11**. Shown in the figure is the ligands L6-L10, and they all have a few things in common. When looking at them they all seem to share the peaks around the aromatic region between 8,5 to 7 ppm. None of the ligands seem to have the 13 ppm peak, which is problematic, but still have the aromatic peaks so it is possible the ligands have reacted with each other. The complexes can both be compared to the ligands but also the expected number of hydrogens. Thus, should the aromatic region consist of eight hydrogens, 9-7 ppm, see **Figure 13 and 15**. This is the case for **3B** and **5B**, see **Figure 13 and 15**, that all have eight hydrogens present in the aromatic region. Furthermore, the total number of hydrogens present is 15 hydrogens, and this correlates to the number of hydrogens in the figures for **3B** and **5B**. The number of hydrogens for **1B** seems to be 14 but theoretically it should be 16. In **Figure 16** all hydrogens have been illustrated and H_{G,H,I,J} is visible in **Figures 12, 13 and 14** at 4 and 3,7 ppm.

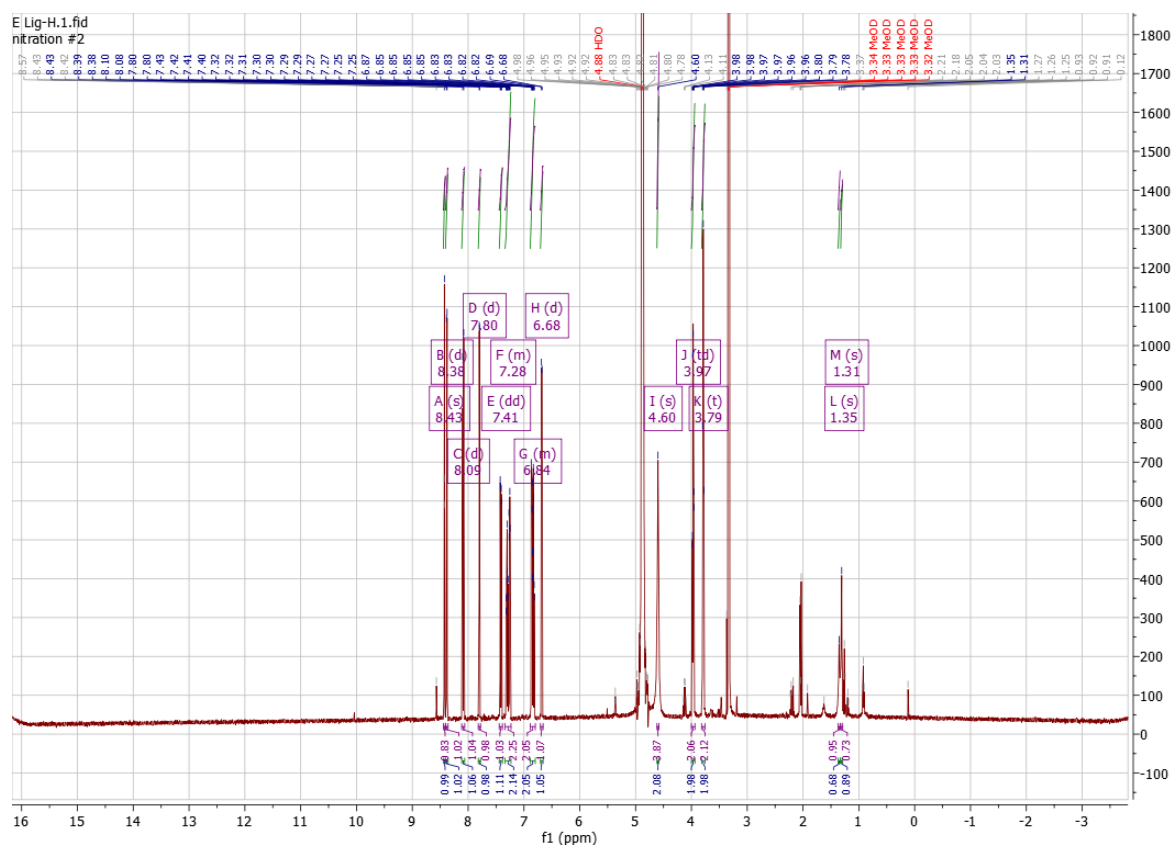


Figure 10, NMR for L1 in methanol.

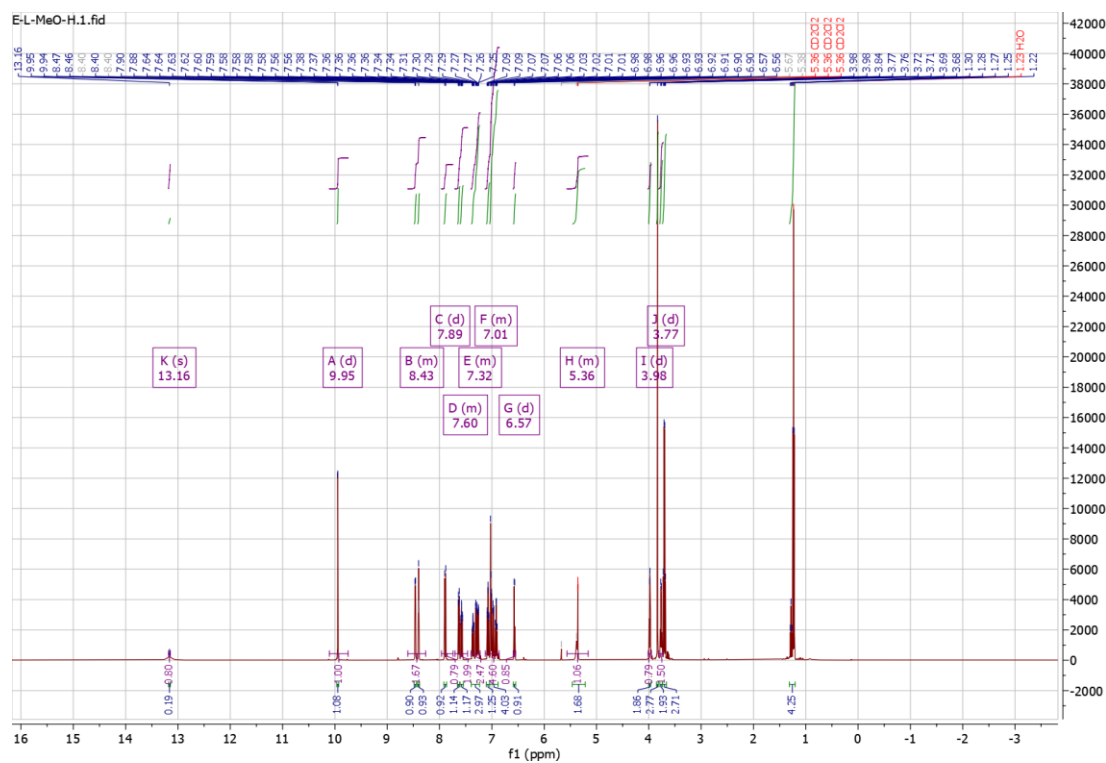


Figure 10, NMR for L6 in DCM.

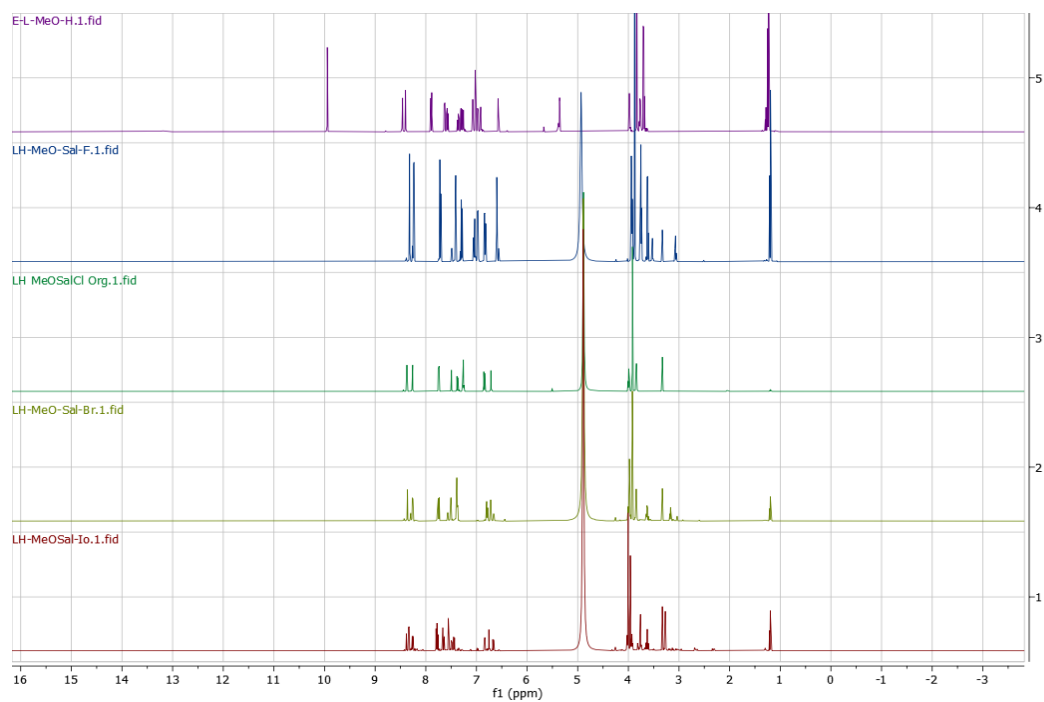


Figure 11, all methoxyquinoline ligands. Top to bottom; L6, L7, L8, L9 and L10.

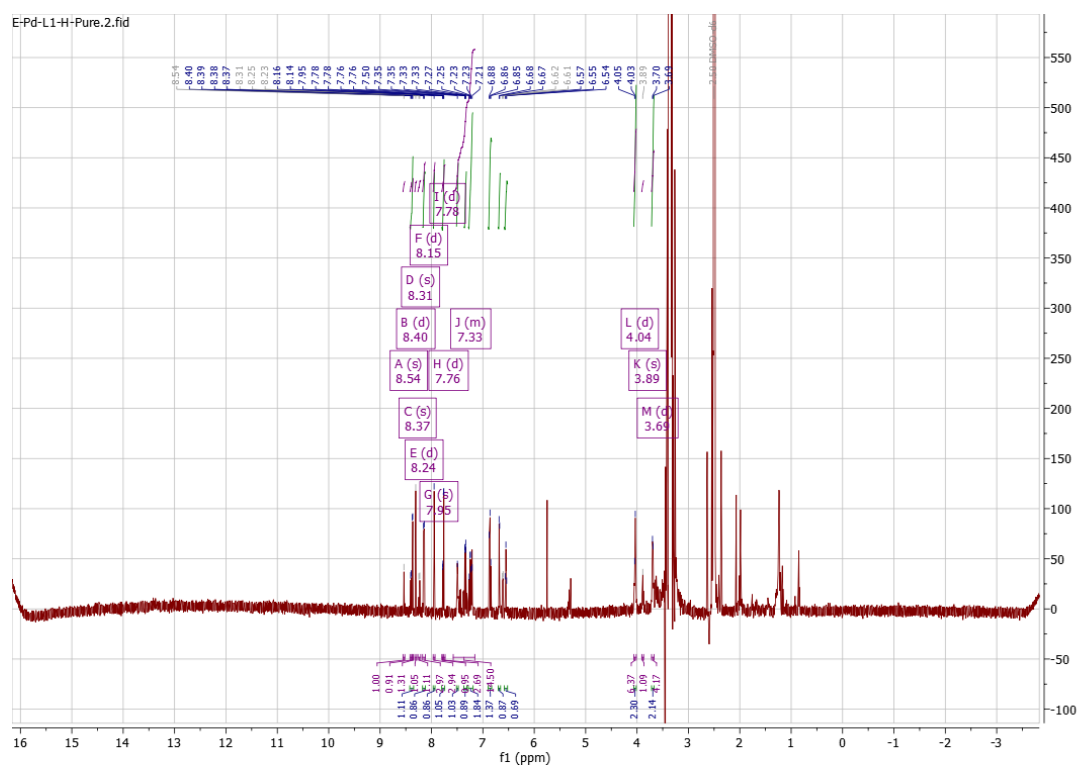
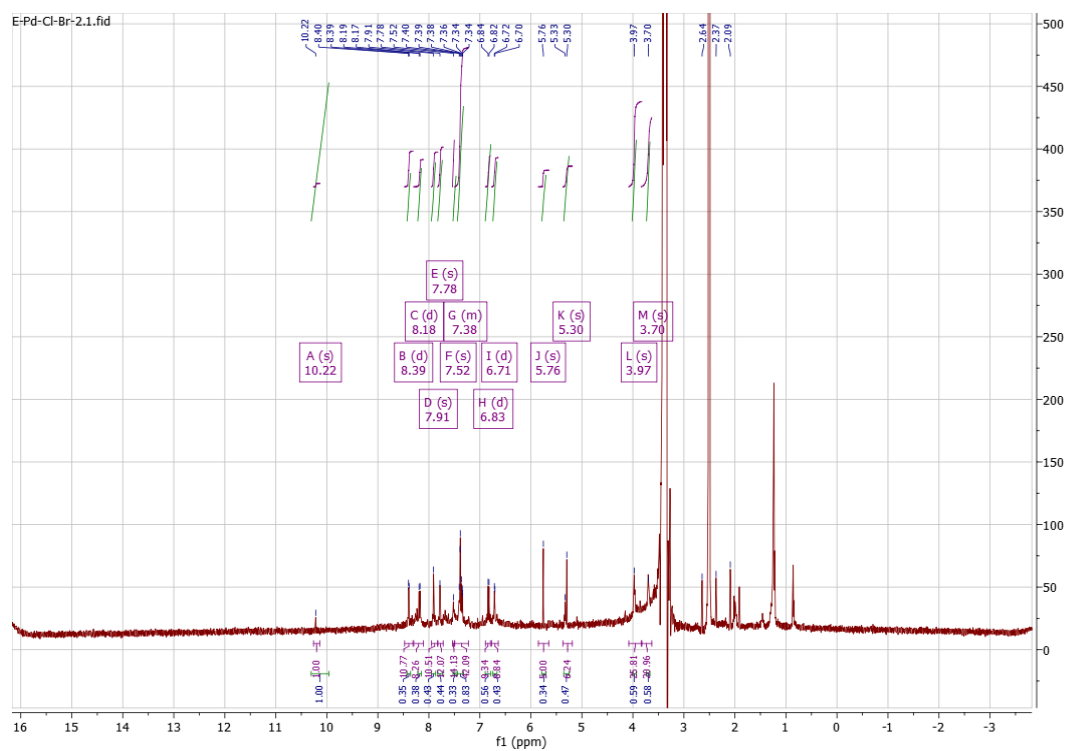
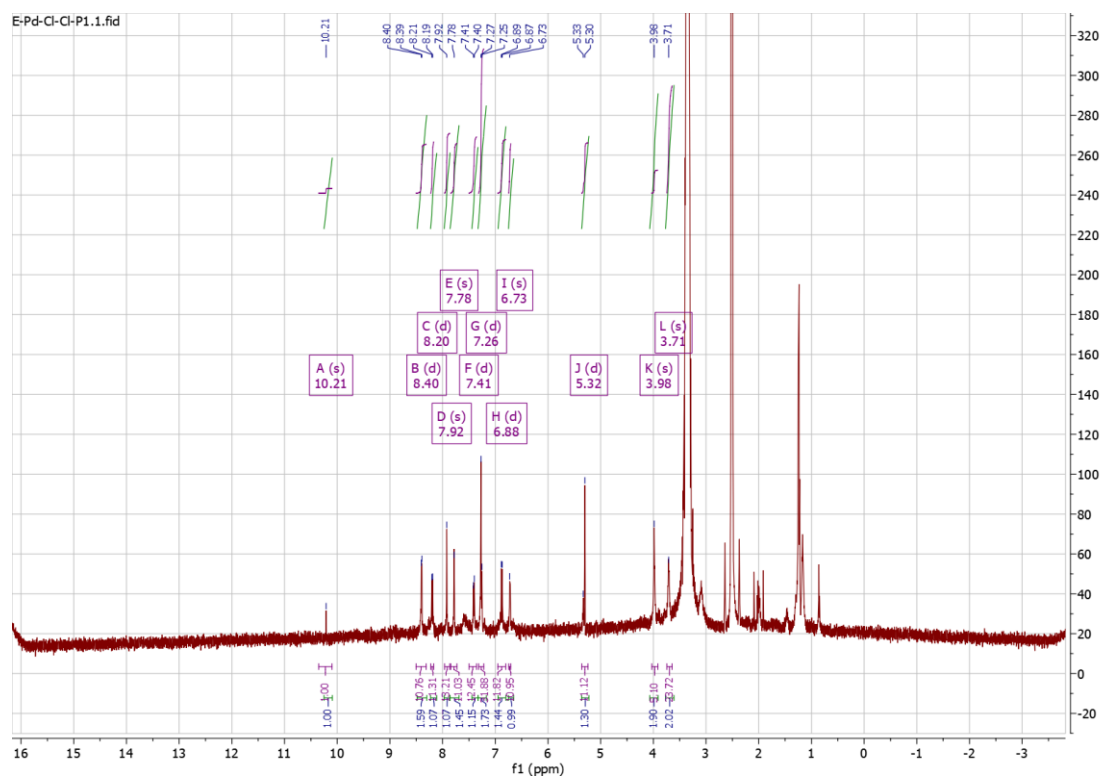


Figure 12, NMR for **1B** in DMSO.



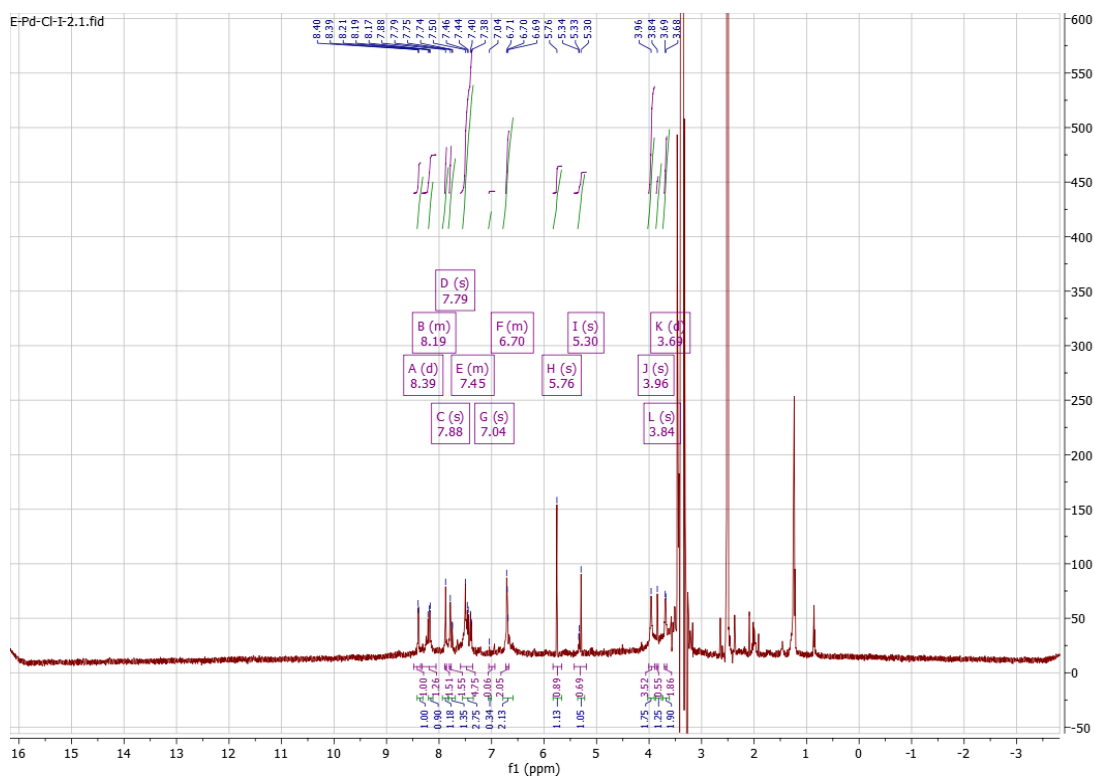


Figure 15, NMR for **5B** in DMSO.

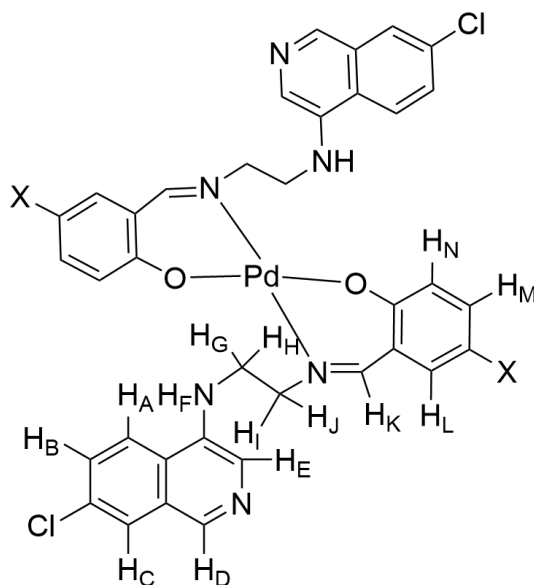


Figure 16, general structure of complexes **1B**, **3B**, **4B** and **5B** with their hydrogens marked.

The formation of a complex was able to be observed by the change in colour once the metal was introduced to the ligand. The ligands with chloroquinoline were in most cases a very light yellow or

pale colour, but once the orange yellow metal was added, the solution changed colour and a precipitate was created. Furthermore, the same happened with the methoxyquinolines, but the starting ligand was different shades of dark orange or brownish orange.

The change in colour and the fact that a precipitate forms over time is pointing to a reaction taking place and to confirm the presence of the desired palladium product complex, an NMR spectrum was recorded. Since the new complex was not soluble in DCM, it was used to wash away possible residues of the starting ligand and metal since they were dissolved in DCM. This would remove the 13 ppm peak that otherwise would correspond to the OH-group on the ligand and if the spectra did not have it but still had the other aromatic hydrogens it would indicate the formation of the desired complex. The complexes themselves had a range of different colours, but all stemmed from some shade of yellow or orange.

4.6 Purification

The goal of this study was to synthesise possible complexes that can be used to treat malaria, and therefore it is important that the substance is pure when it is tested. Hence, a large part of this study was aimed to synthesise pure complexes in varying degrees. One of the larger problems with the complexes synthesised were their solubility or rather lack of. Consequently, many problems arose when it was to be analysed since NMR needs the sample to be soluble to get a reading. A hypothesis for the lack of solubility was the presence of impurities in the ligand and thus also the complexes. This led to extensive testing of different ways to purify both the ligand and the complex.

To synthesise the ligand, an excess of salicylaldehyde was used in relation to the starting chloroquinoline. However, the precipitate that was assumed to be the ligand contained a lot of salicylaldehyde as well. This gives an NMR spectrum with a high 10 ppm peak which corresponds to the OH-group on the salicylaldehyde and proves that salicylaldehyde was also present in the ligand. This crude mixture also had peaks corresponding to the aromatic hydrogens and was therefore used for synthesis of the complexes. Contrary to what was expected, the NMR spectra of the complex was too complex to obtain any real conclusions. This was the case for all the complexes analysed and a hypothesis was that the excess salicylaldehyde present in the crude ligand may have coordinated to the metal instead or together with the ligand, thus creating more NMR signals than what was expected.

To test that theory, the ligand L1 was purified with column chromatography and a similar procedure was used as a reference⁴. The ligand was separated firstly by TLC to see what the optimal eluent would be for the column chromatography. First, only ethyl acetate was used and proved to create three different sections of separation, but two of the sections were barely moving so another one was done where the polarity was increased. The second one was done in methanol and ethyl acetate, in a one-to-one ratio, and had a clearer distinction of the two sections. Since salicylaldehyde was assumed to be the bigger problem for the complex synthesis, the column was eluted with only ethyl acetate at first. A yellow band could be observed and was assumed to be the salicylaldehyde, while another much darker yellow line moved very slowly. The first yellow band was collected and proved to be the salicylaldehyde in the previous TLC test. The eluent was then changed to the methanol and ethyl acetate mixture, which made the darker yellow band move. When checked with TLC the mixture still had small amounts of salicylaldehyde, but the line on the TLC was very faint. The fractions containing the same band were then dried and the purified ligand was then used for the complex synthesis. This was done with Method B, under heat, and gave no salicylaldehyde peak, see **Figure 12**.

Another factor that could have made the synthesis problematic is the procedure used. Instead of letting the reaction occur at -78 °C, the starting metal complex and the ligand L1 were heated together. The idea was that it would make the metal and its existing ligands to leave and the new ligand to bind. This was firstly tested for with L1 and gave the product of **1B**, which gave a clearer NMR to analyse and was repeated for L2, L3, L4 and L5. The original procedure used only DCM but due to its low boiling point, 39,6°C, THF was added to heat the mixture further. Triethylamine was still present to deprotonate OH on the salicylic group of the ligand and was therefore also present when the solution was heated to 74 °C. The reaction was run overnight since no precipitate was formed after two hours; the colour had however changed from a deep reddish orange to an orange with hints of red. The day after a yellow precipitate had formed and was washed with DCM, to remove eventual starting materials. This was done for all the complexes with the ligands previously mentioned, but the one with fluoro, **2B**, did not form a precipitate and was left for an additional day under heat. However, it still had not formed a precipitate and was analysed with NMR, but it showed too many peaks to draw any conclusions from it.

Triethylamine was used to deprotonate the ligand to enable the phenolate oxygen to coordinate to the palladium atom, thus being a base in this reaction. However, triethylamine could be exchanged for another base if necessary and the more basic it would be in comparison to the ligand the better. An

example for a compound would be sodium hydride which is a much stronger base than triethylamine and would more easily deprotonate the OH-group on the salicylic part of the ligand.

5. Conclusions

In total there were 12 new complexes synthesised with varying purity, and they were all characterized by NMR. Additionally, UV-VIS and IR spectra were obtained for the four complexes with more pure NMR. During synthesis all complexes changed colour and ended up with different shades of yellow, orange and brown, which was different from the starting colour of pale yellow or pale orange. Finally, all complexes were able to dissolve in pyridine and DMSO.

6. Future aspects

The experiment was focused on the synthesis of possible antimalaria substances, but the compounds properties have not been tested. Additionally, further analysis should be done for the complexes such as x-ray diffraction. This was not possible to be done within the time limit since crystals had not been formed at the time. However, the complementary reaction for the chloroquinolines was not crystallised and could be further investigated. Another aspect to investigate is other potential complexes that could be used to treat malaria.

7. References

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8. Housecraft, E. Catherine och Sharpe, G. Alan. Inorganic Chemistry. Fifth edition. Storbritannien; Pearson Education Limited, 2018.

8. Appendix

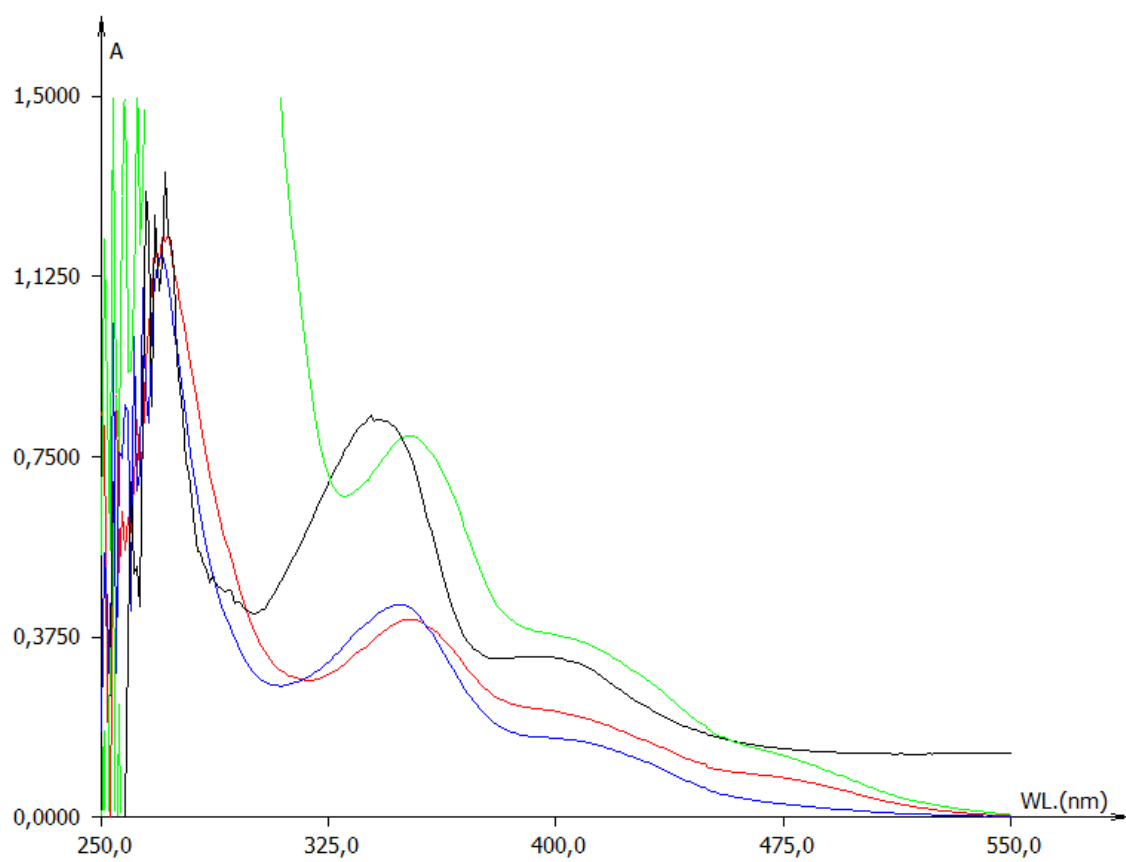


Figure 17, comparison for chloroquinoline complexes; Pd-1X (black), Pd-3X (blue), Pd-4X (red) and Pd-5X (green).

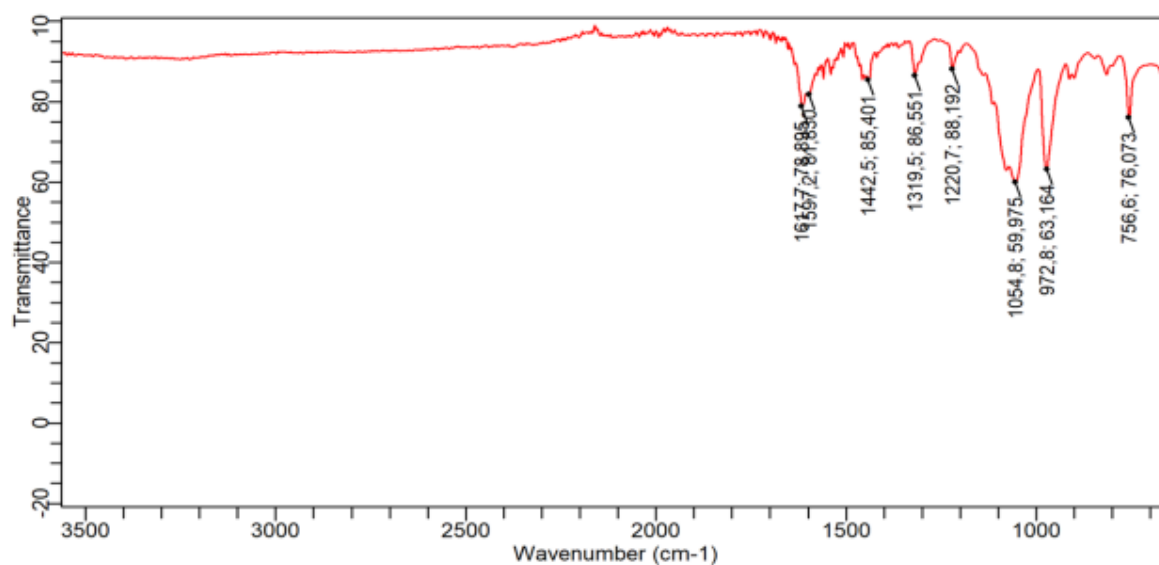


Figure 18, IR for 1A.

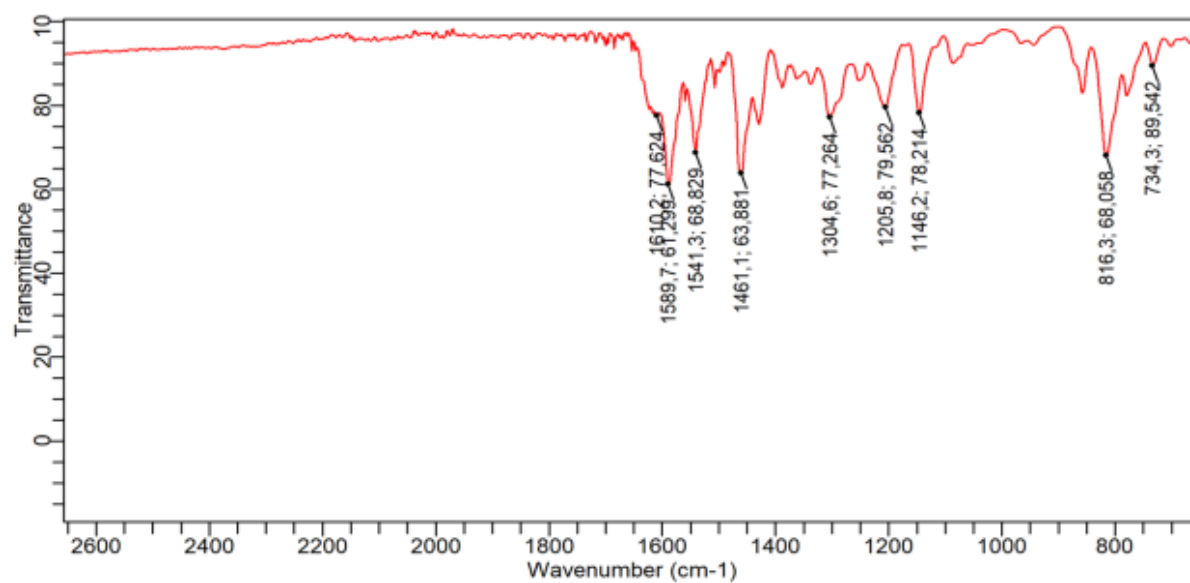


Figure 19, IR for 2A.

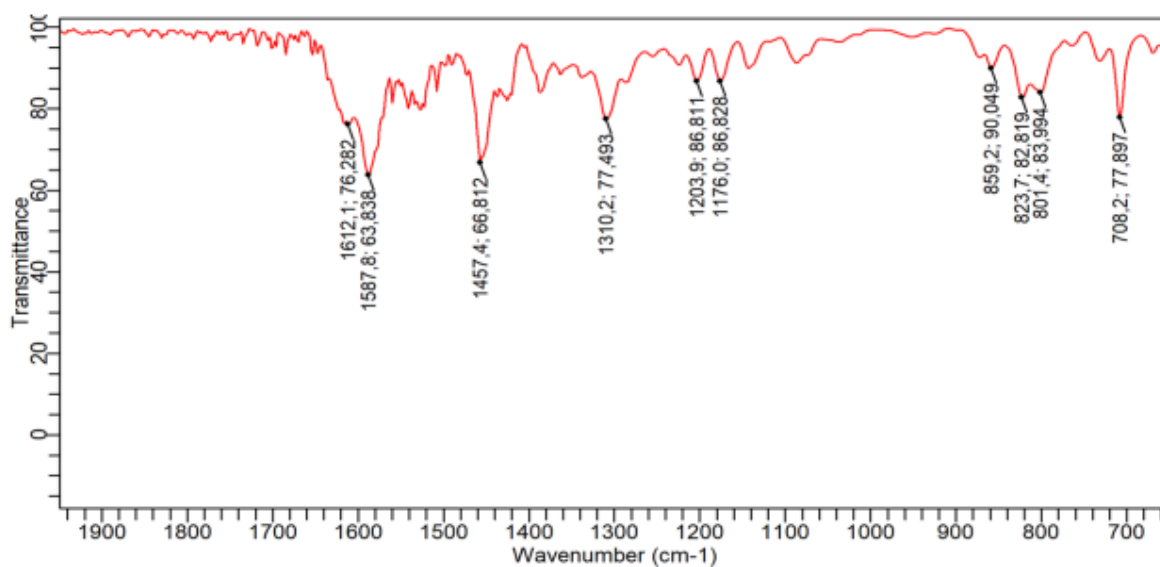


Figure 20, IR for 3A.

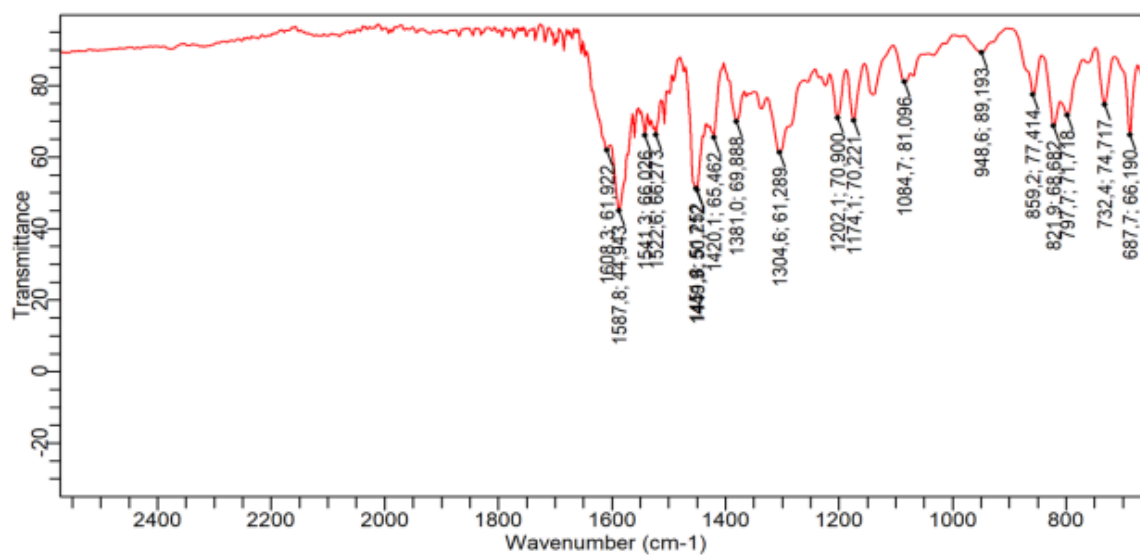


Figure 21, IR for 4A.

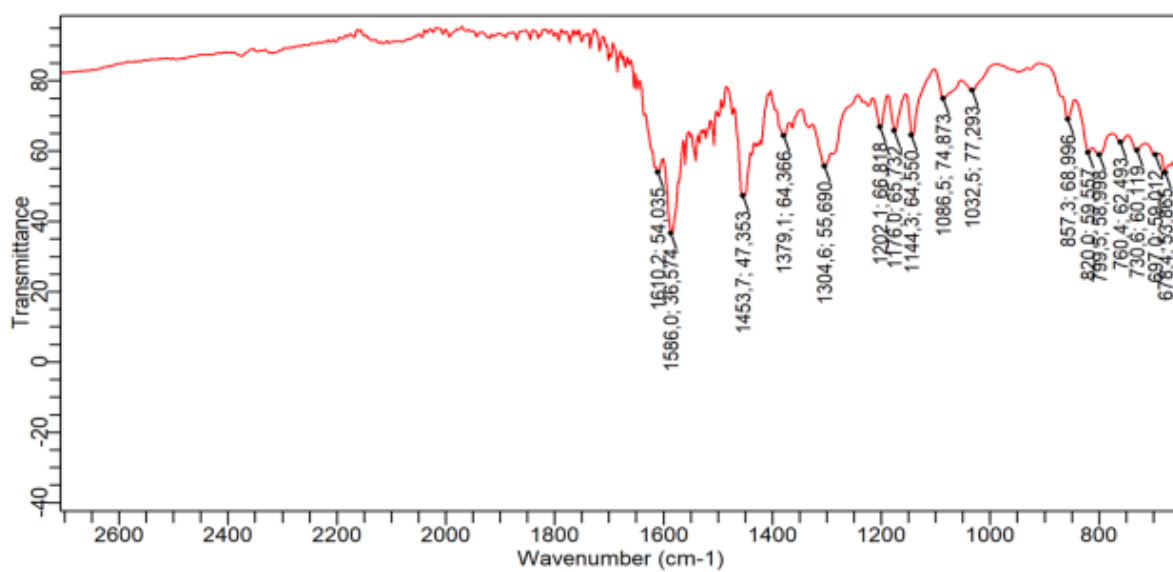


Figure 22, IR for 5A.

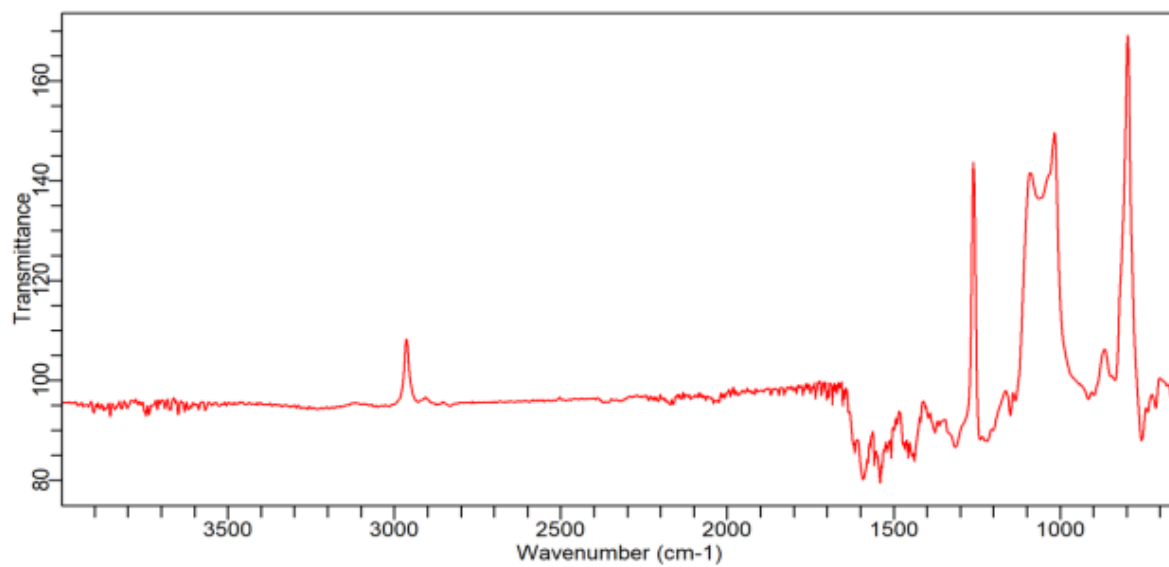


Figure 23, IR for 6A.

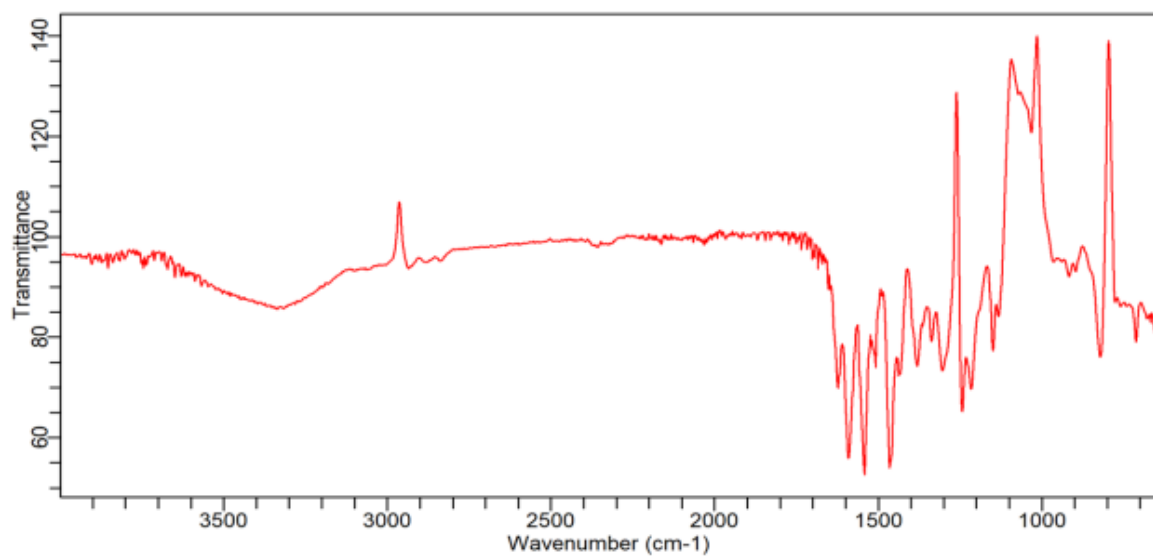


Figure 24, IR for 7A.

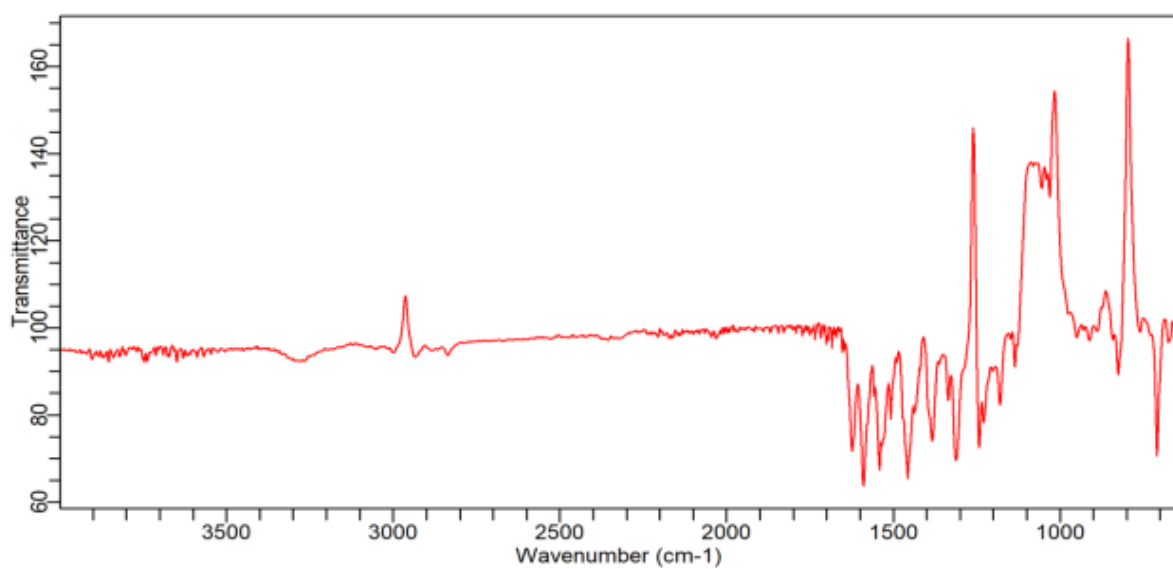


Figure 25, IR for 8A.

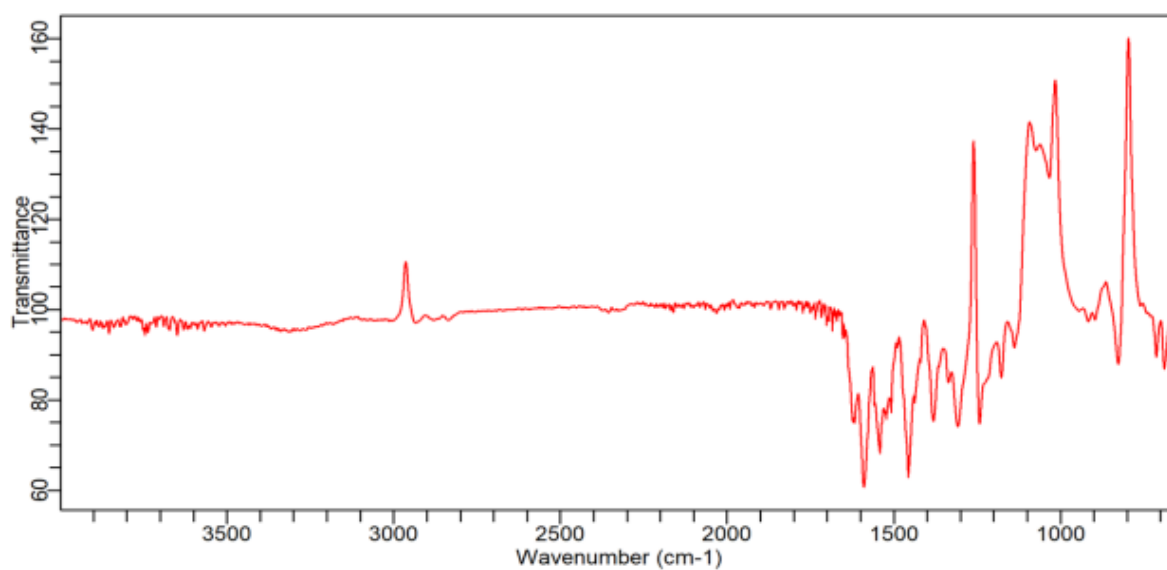


Figure 26, IR for 9A.

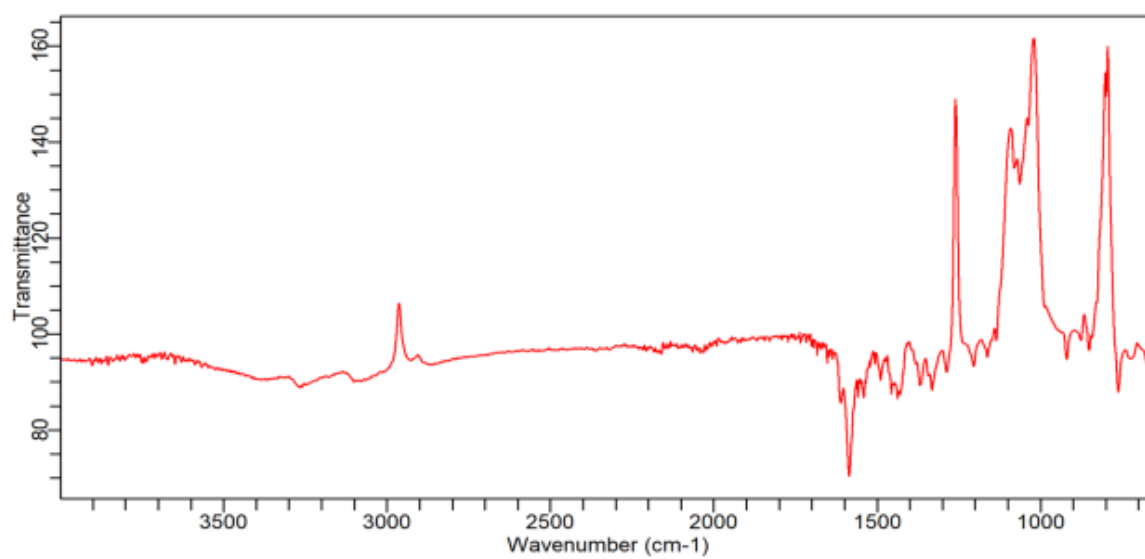


Figure 27, IR for 11A.

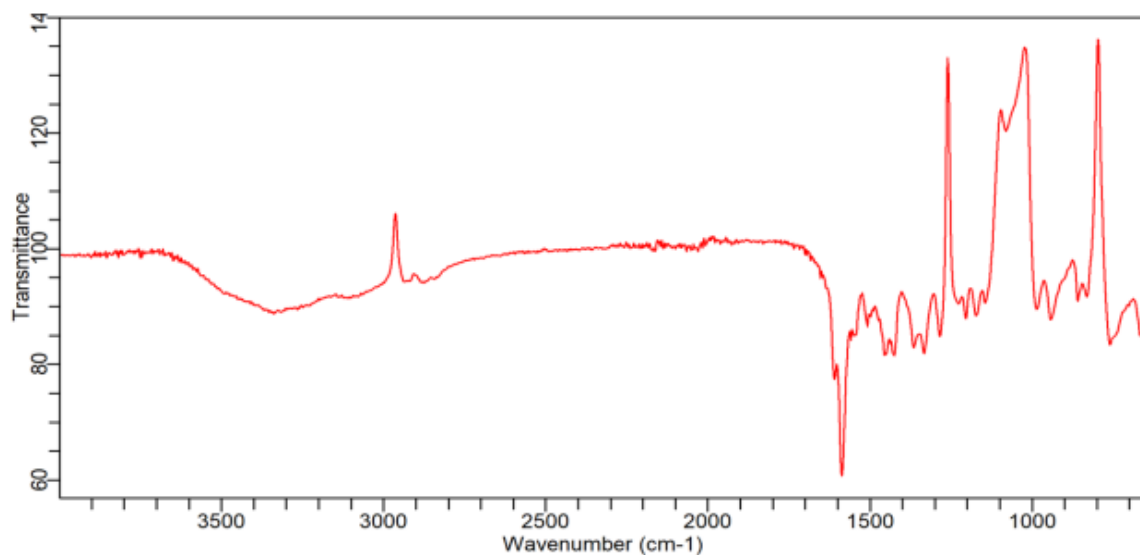


Figure 28, IR for 12A.

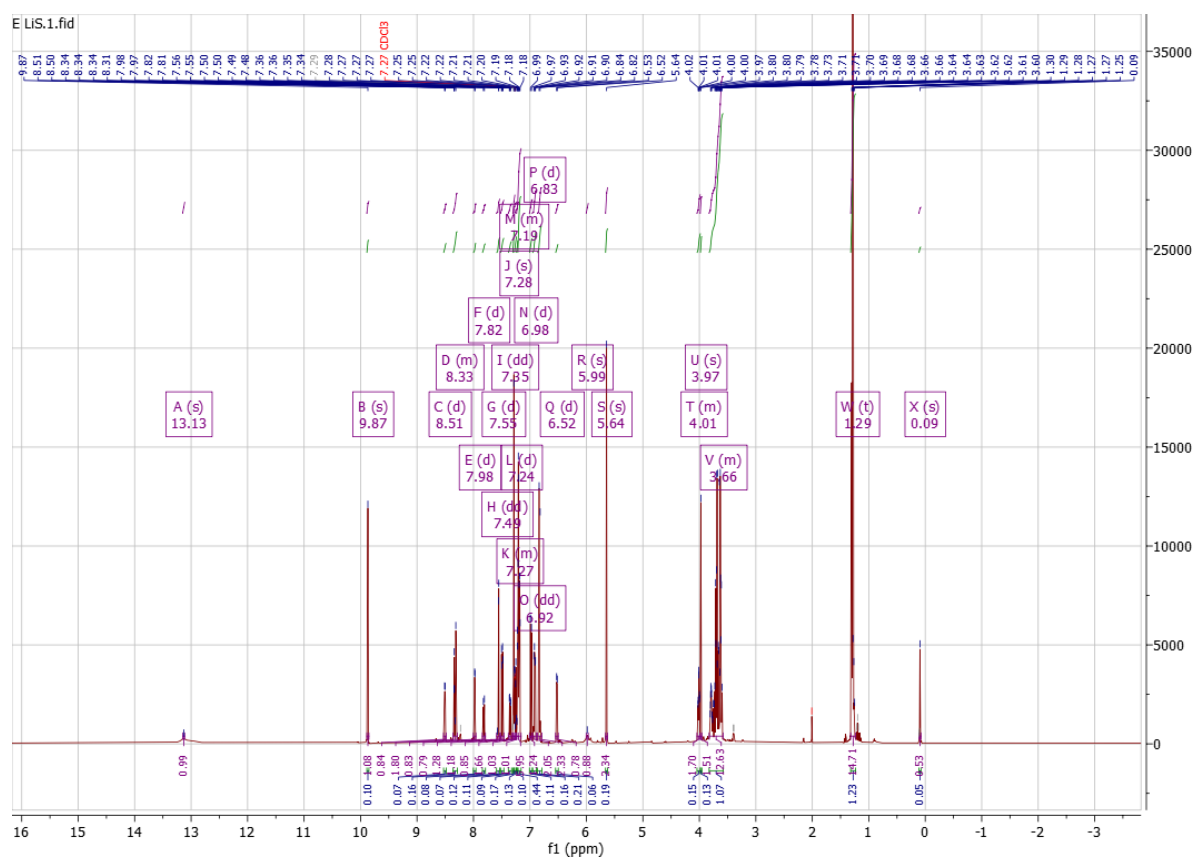


Figure 29, NMR for L1 in chloroform.

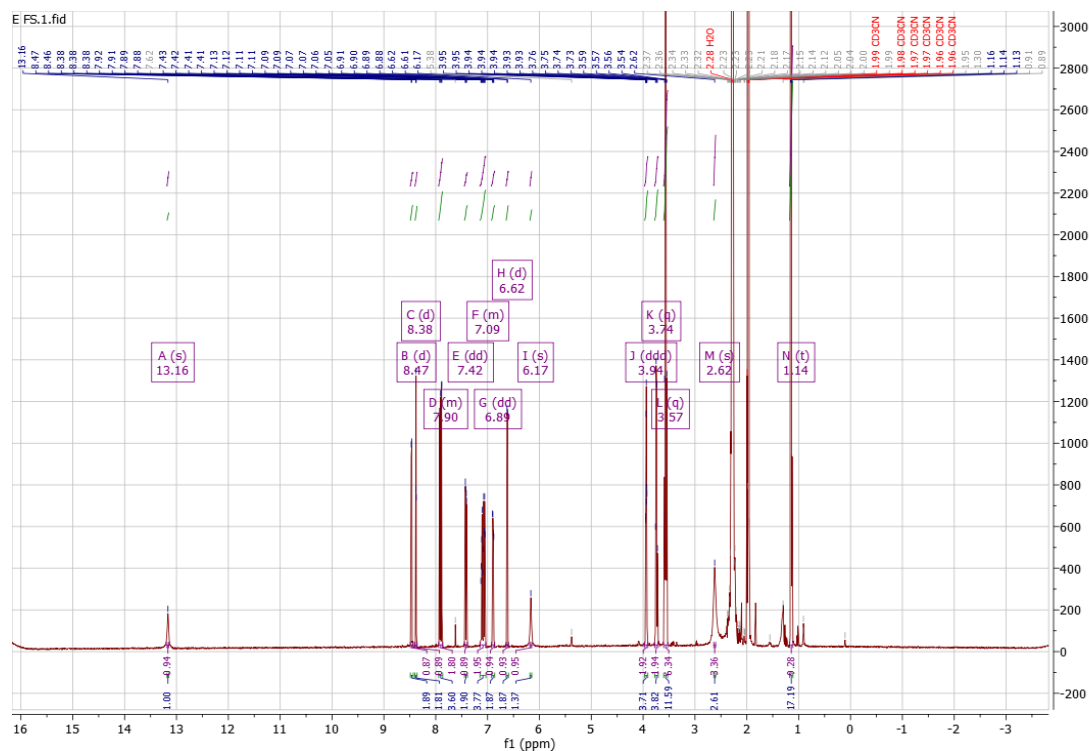
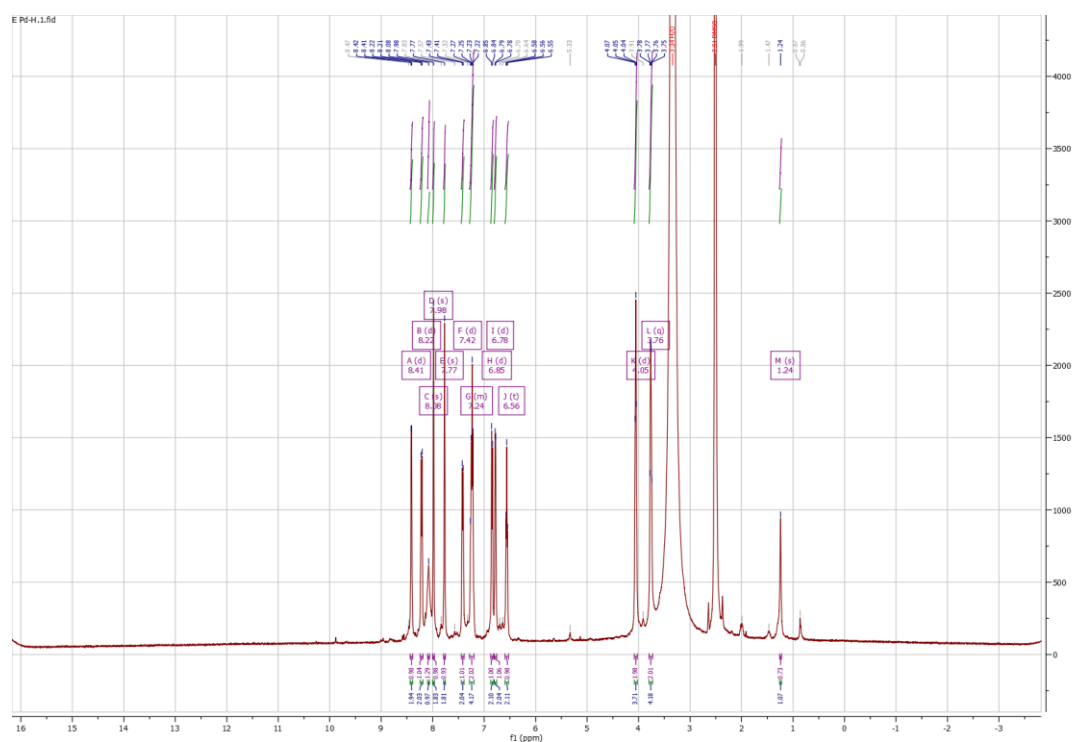
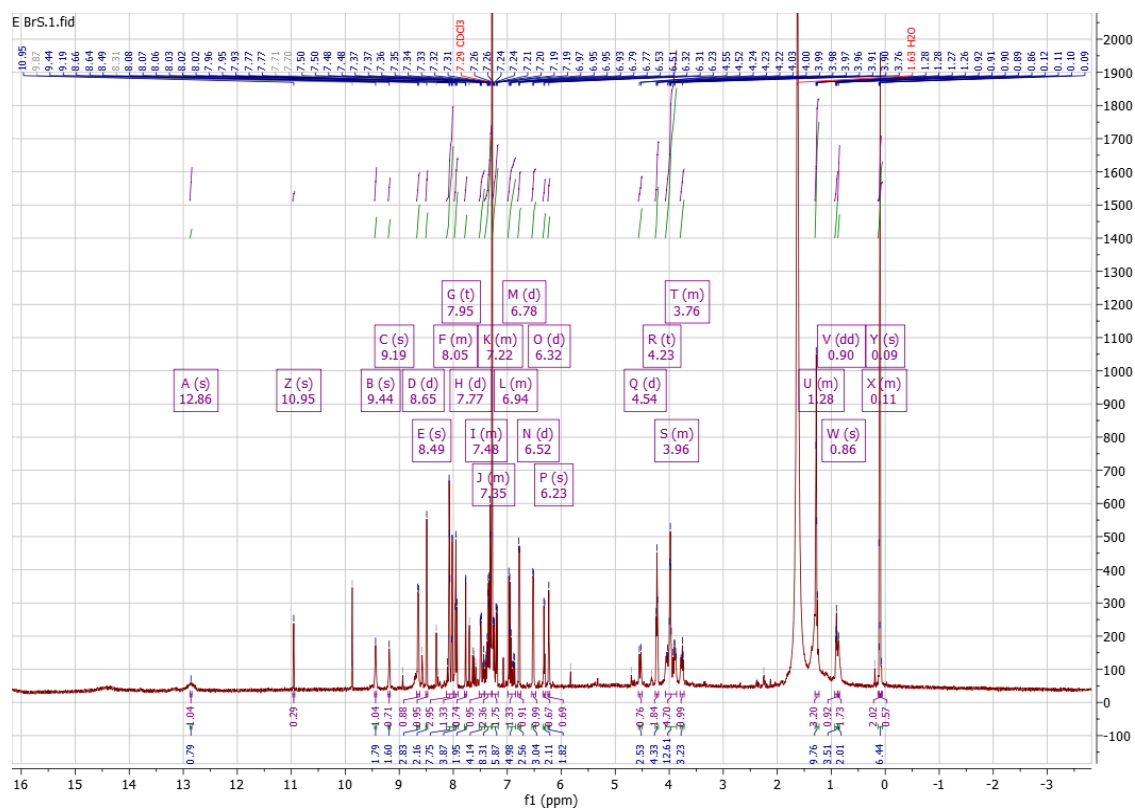


Figure 30, NMR for L2 in acetonitrile.



Figure 31, NMR for L3 in chloroform.



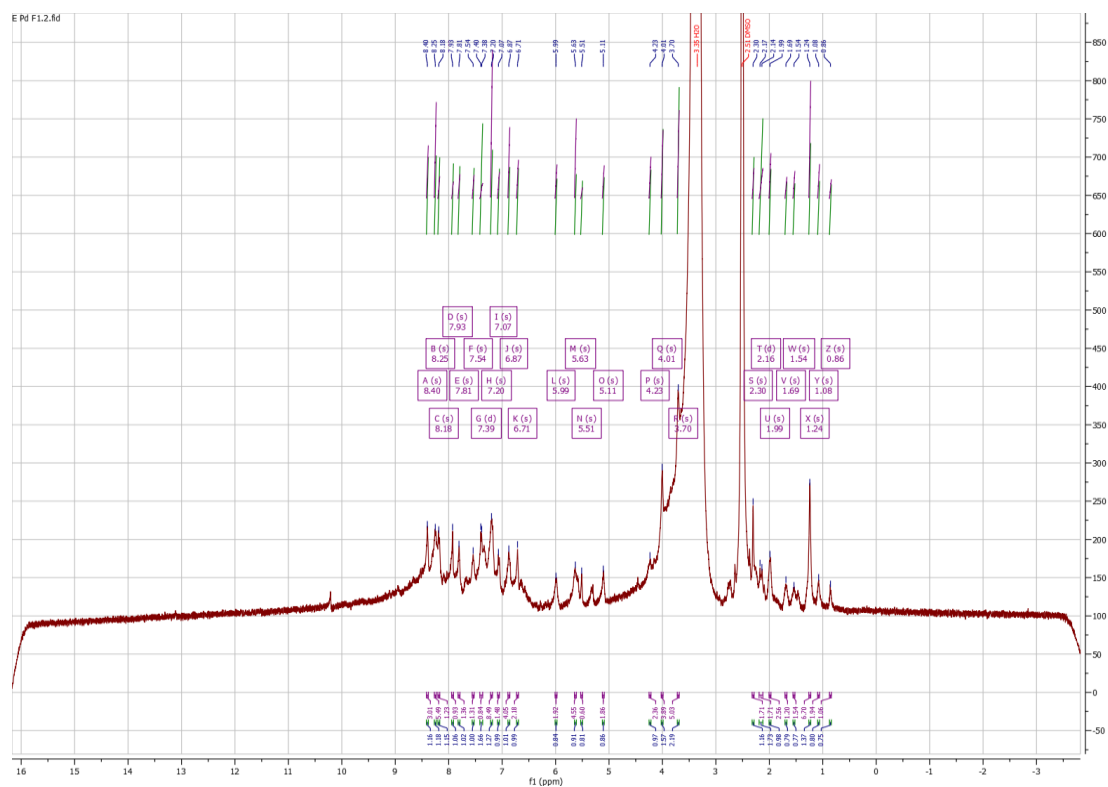


Figure 34, NMR for 2A in DMSO

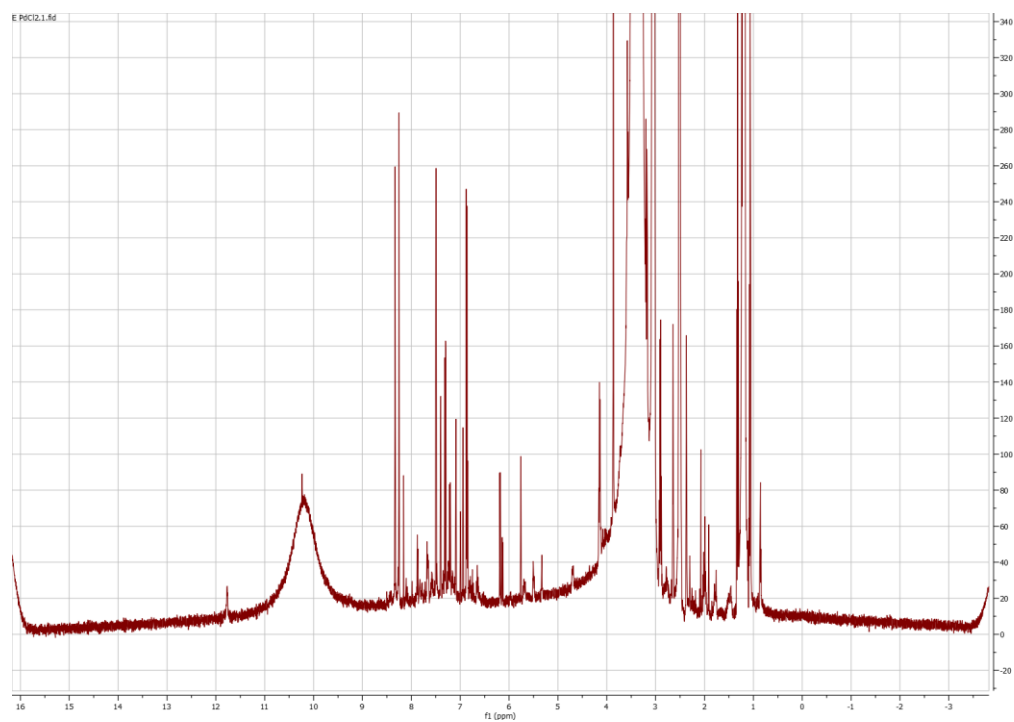


Figure 35, NMR for 3A in DMSO.

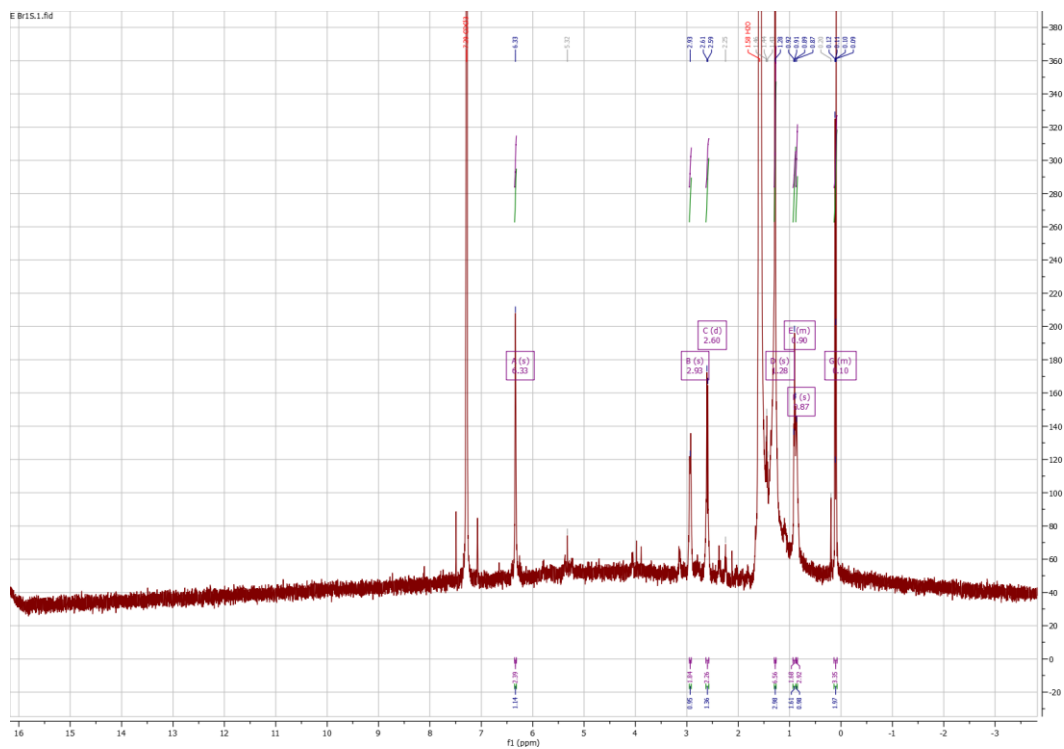


Figure 36, NMR for **4A** in DMSO

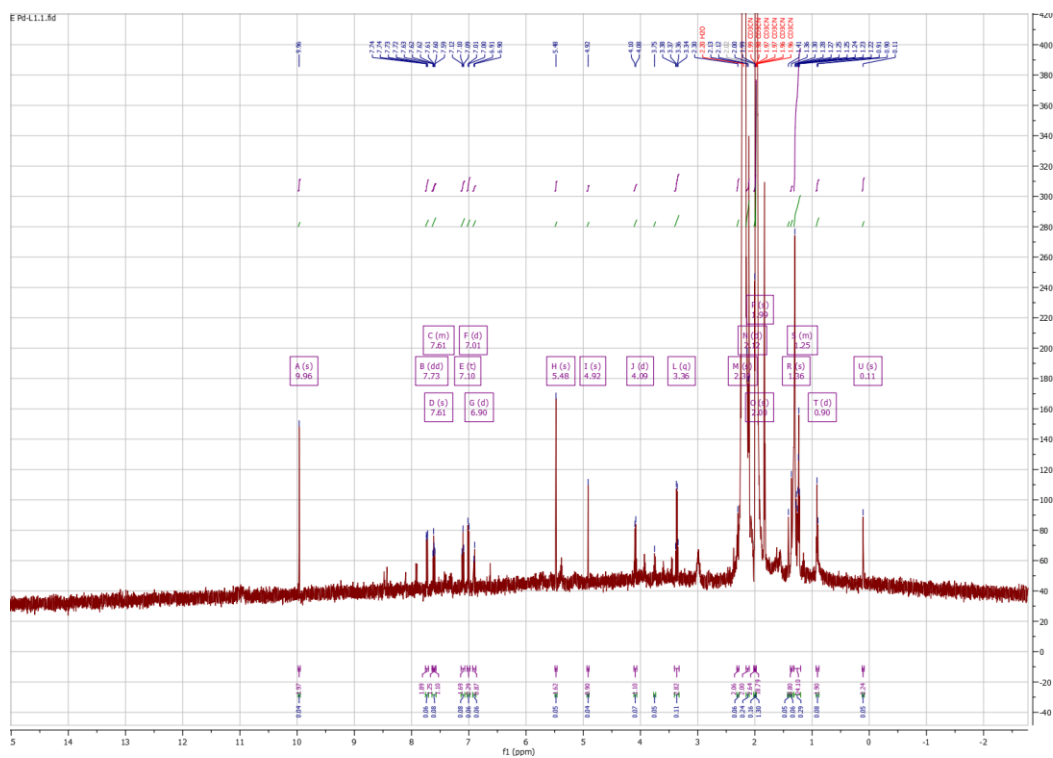


Figure 37, NMR for **5A** in DMSO

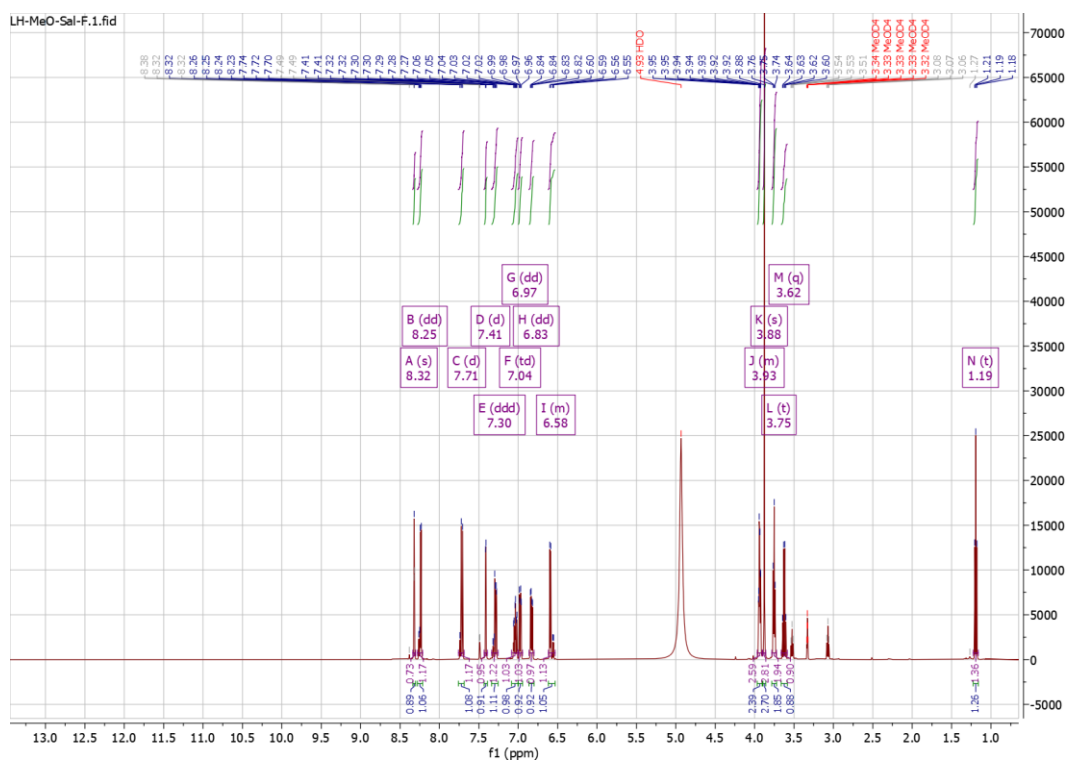


Figure 38, NMR for L7 in methanol.

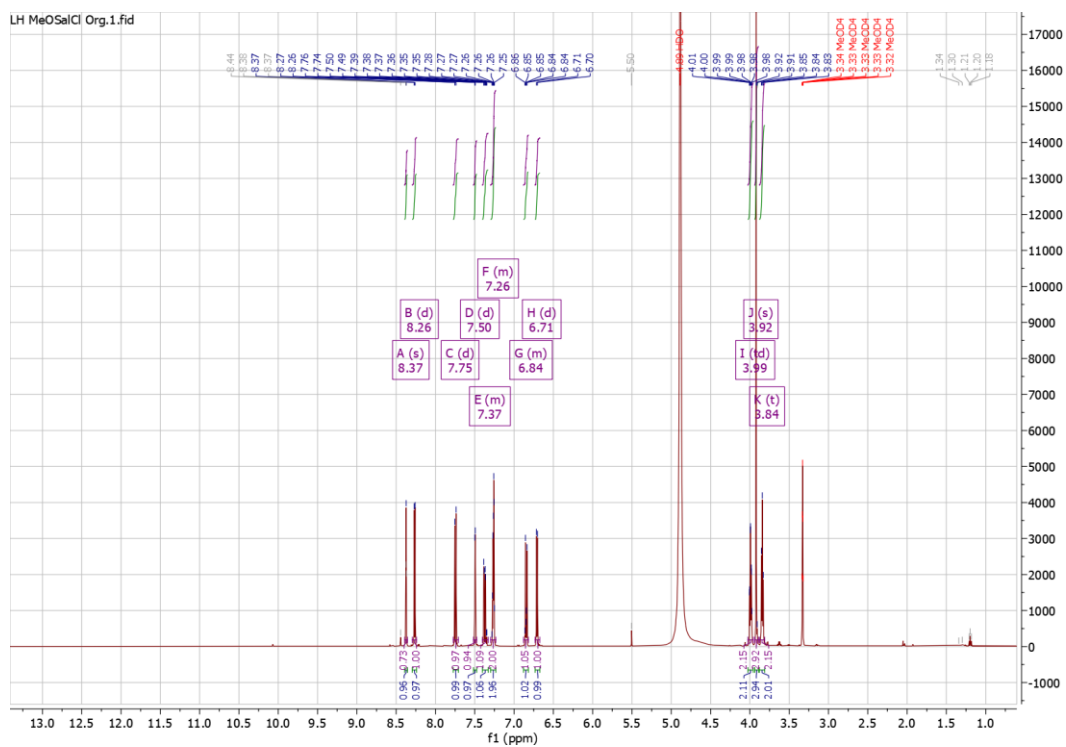


Figure 39, NMR for L8 in methanol.

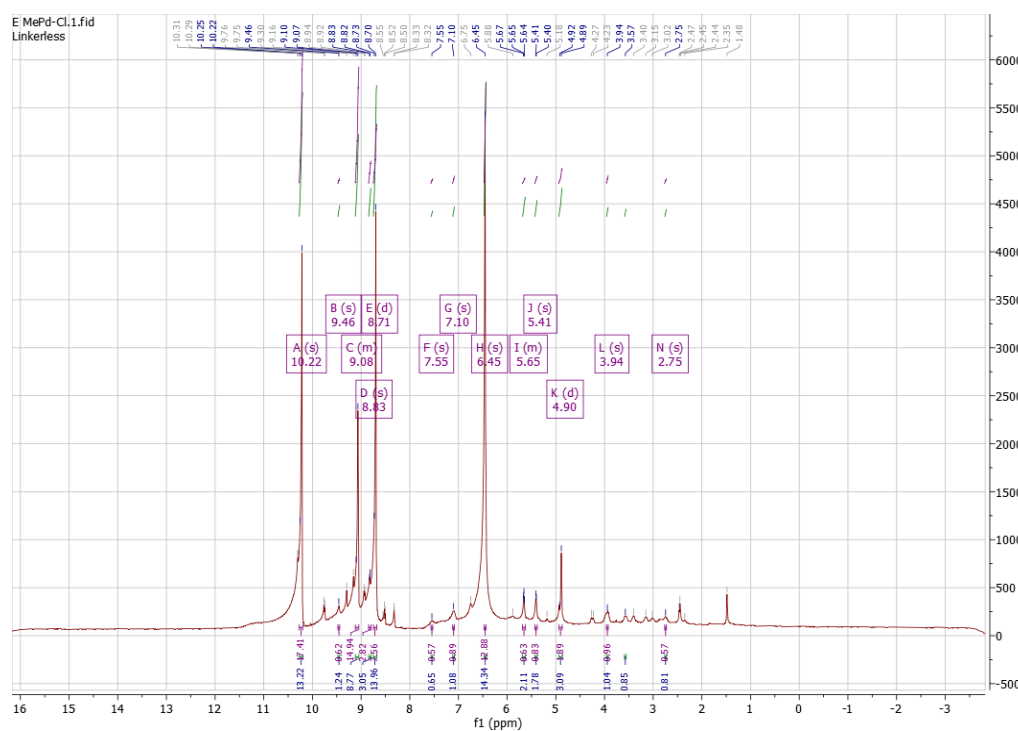


Figure 42, NMR for 7A in DMSO.

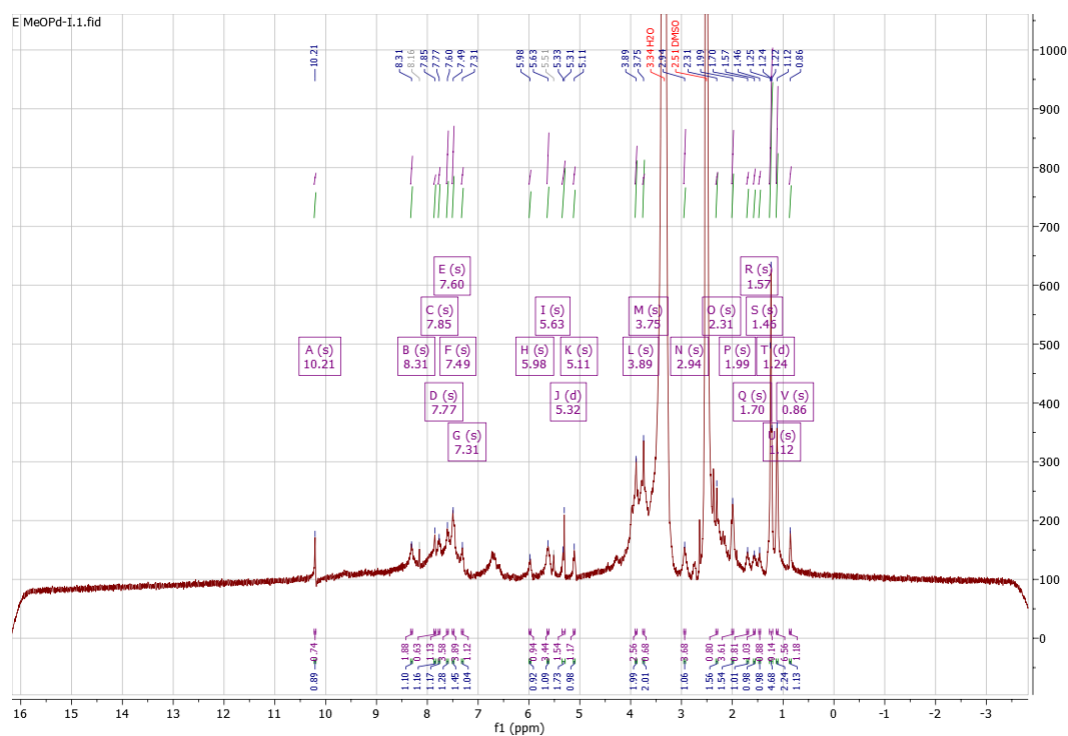


Figure 43, NMR for 10A in DMSO.

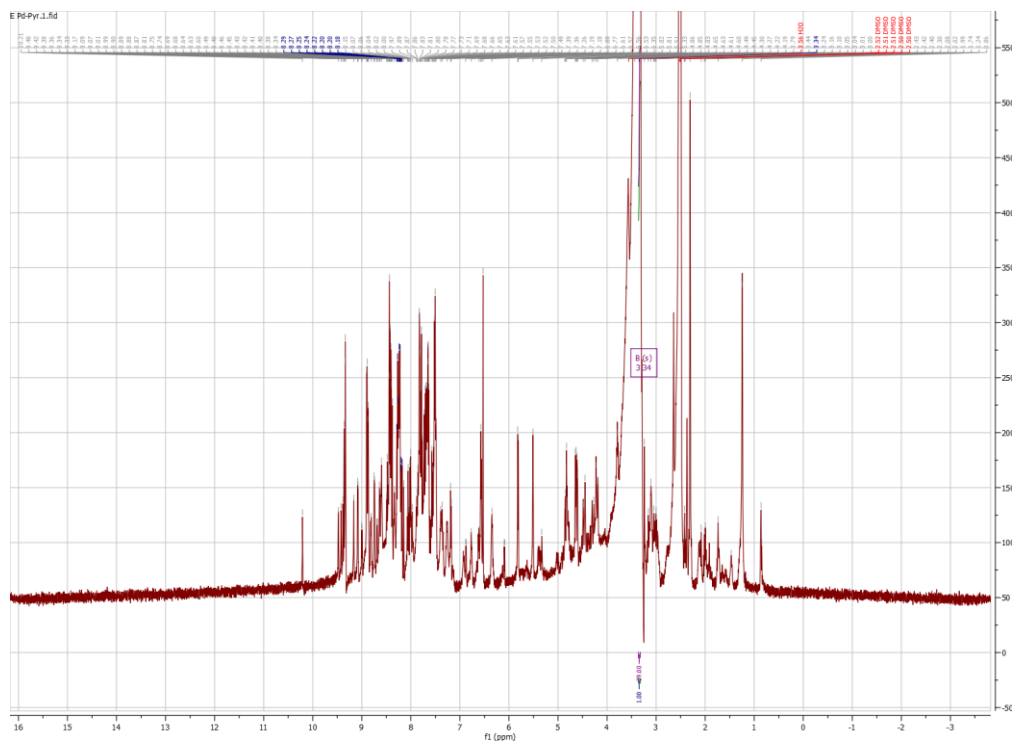


Figure 44, NMR for **11A** in DMSO.

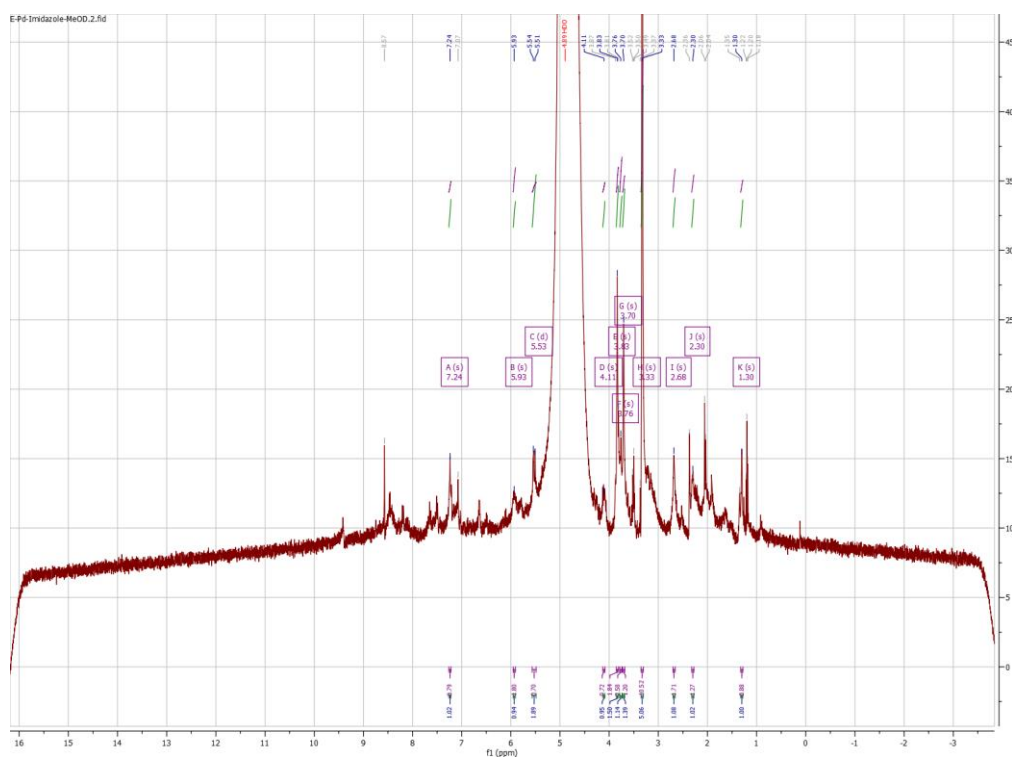
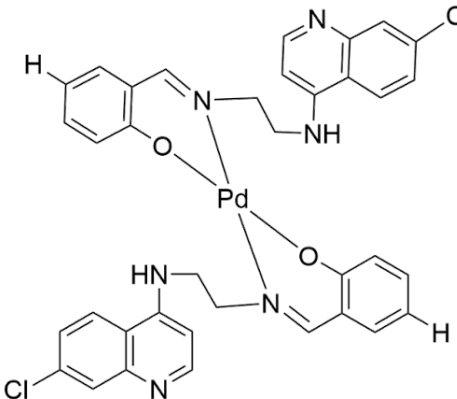
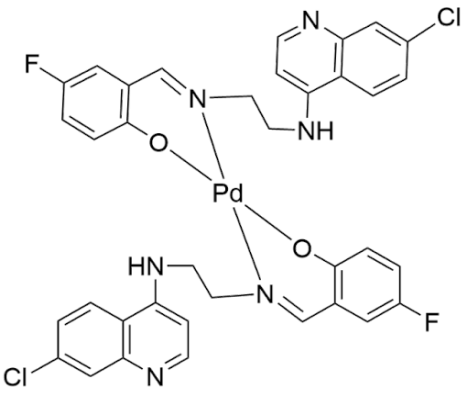
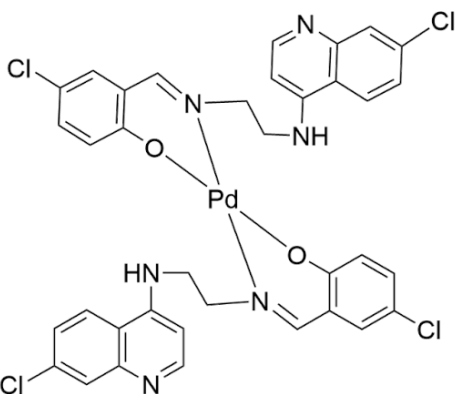
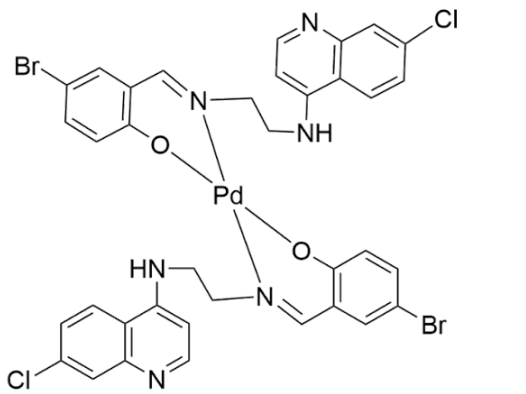
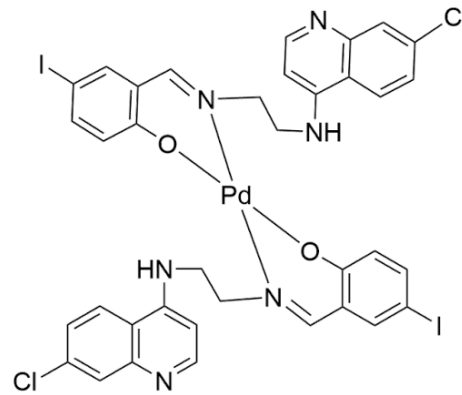
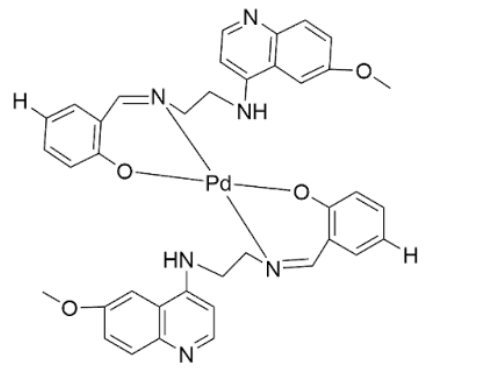
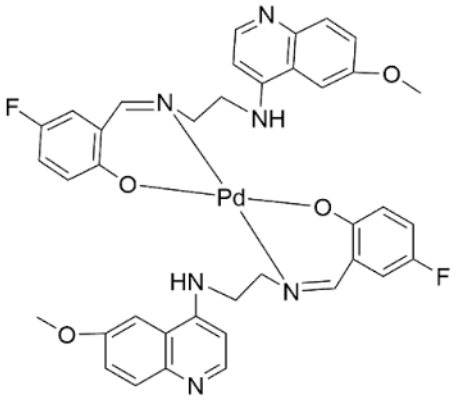
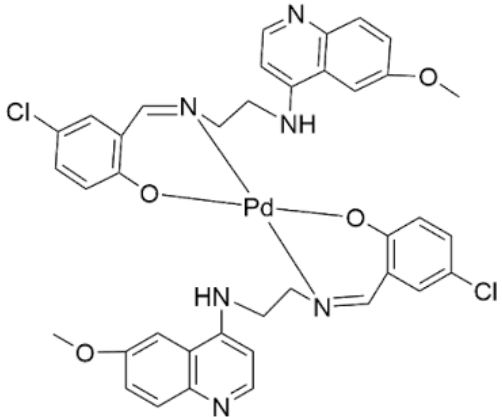
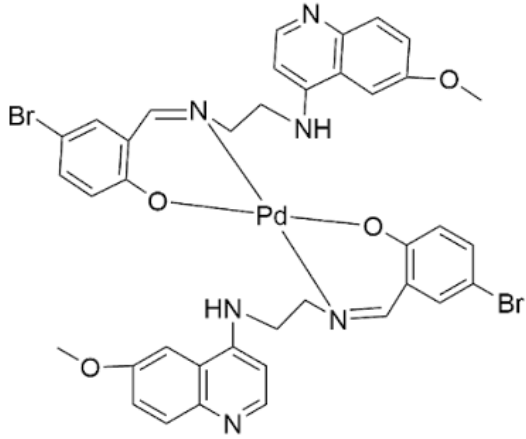


Figure 45, NMR for **12A** in methanol.

Table 2, skeletal structure of all complexes synthesized and the IUPAC name for the ligand. The left column is the nickname given to easier talk about the different ligands.

L1	(Z)-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenol	
L2	(Z)-4-fluoro-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenol	
L3	(Z)-4-chloro-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenol	

L4	(Z)-4-bromo-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenol	
L5	(Z)-4-iodo-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenol	
L6	(Z)-2-(((2-((7-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol	

L7	((Z)-4-fluoro-2-(((2-((7-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol	
L8	(Z)-4-chloro-2-(((2-((7-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol	
L9	(Z)-4-bromo-2-(((2-((7-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol	

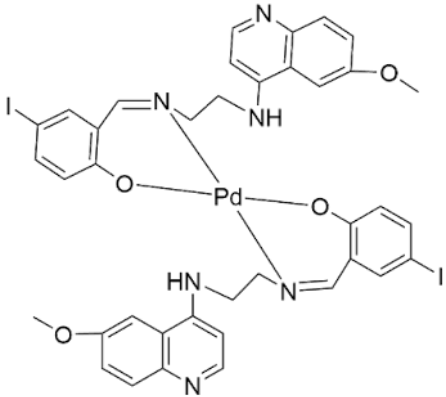
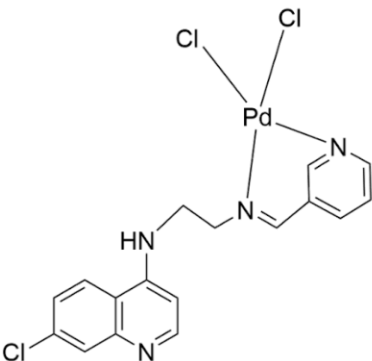
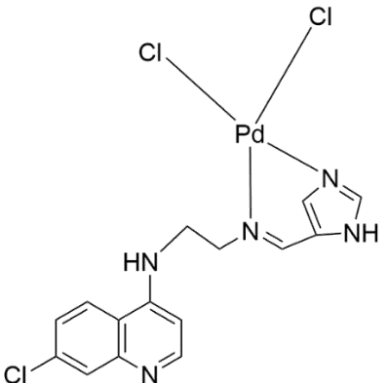
L10	(Z)-4-iodo-2-(((2-((7-methoxyquinolin-1-yl)amino)ethyl)imino)methyl)phenol	
L11	(Z)-7-chloro-N-(2-((pyridin-3-ylmethylene)amino)ethyl)quinolin-4-amine	
L12	(Z)-N-(2-(((1H-imidazol-5-yl)methylene)amino)ethyl)-7-chloroquinolin-4-amine	

Table 3, solvability table of complexes that were tested. Gray means not tested, red means insoluble, yellow means little solvability and green means soluble.

Solvent	Pd-1	Pd-4	Pd-8	Pd-1X	Pd-11
Water	Red	Red	Red	Gray	Green
Methanol	Red	Yellow	Yellow	Gray	Green
Ethanol	Red	Yellow	Gray	Gray	Green
Acetone	Red	Yellow	Yellow	Gray	Red
Acetonitrile	Red	Yellow	Yellow	Gray	Red
DCM	Red	Red	Yellow	Gray	Red
DMF	Red	Green	Green	Gray	Gray
DMSO	Yellow	Green	Green	Green	Green
THF	Red	Gray	Yellow	Red	Gray
Cyclohexane	Red	Gray	Gray	Gray	Gray
Heptane	Red	Gray	Gray	Gray	Gray
Benzene	Red	Gray	Gray	Gray	Gray
Pyridine	Green	Green	Green	Green	Green