Synthesis of Silver Compounds with Potential Anti-Cancer Activity

Silver(I) Complexes with Xylyl-Substituted Heterocyclic Thiones and Selones

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Summary

Silver has been used since ancient times as a way to combat bacterial infections. Before the introduction of modern antibiotics, silver was mainly used for its bactericidal properties. However, silver also exhibits cytotoxicity towards cancer cells, which would provide a safer treatment for those with this illness. Within this project, four different silver complexes have been synthesized with a saturated pyrimidine 6-membered ring. These complexes also contain a thione or selone functional group within the ligand, as well as 2,6- xylyl, otherwise known as dimethylbenzene. The general formula of the ligand is SypmXyE, where E is either sulfur or selenium. The ligand is reacted with silver (I) perchlorate and silver (I) tetrafluoroborate, with a formula of [Ag(SpymXyE)2]+X, where X is perchlorate or tetrafluoroborate. All four compounds have been fully characterized using 1H- and 13C-NMR data, IR data, melting point, and x-ray crystallization.

Research Question

Can a silver based compound [Ag(SpymXyE)2] be developed that could affect cancer cell activity?

Introduction

In the past few years, diseases such as cancer have been more prevalent. In a recent study, it was estimated that in 2018, more than 1.9 million people would be diagnosed with cancer. While many causes can be prevented, such as smoking, the use of tanning beds and unhealthy nutrition, there is no effective cure for the disease. This problem is overshadowed by the many side effects of common drugs used now. Some side effects include thrombocytopenia, swelling, alopecia, lymphedema and sleep and attention problems. These side effects can reduce the quality of life for many cancer patients. With the overwhelming impact that cancer has in our society, many researchers have focused on finding an alternative to common anti-cancer drugs, without the harmful side effects. A promising solution has been found in silver.

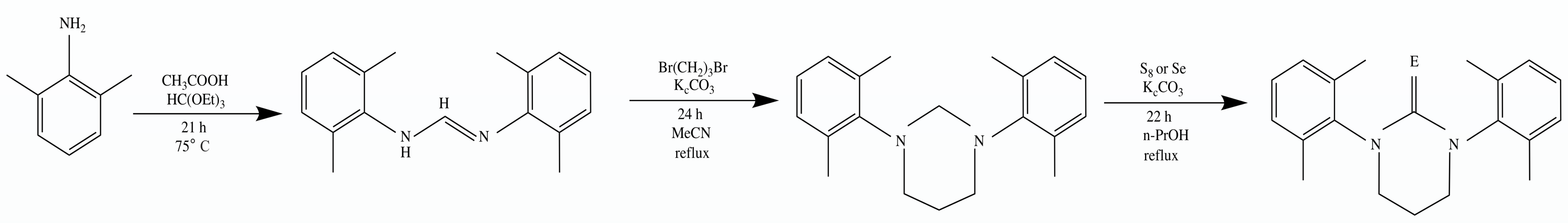
Silver has been used for many medical conditions, mostly before it was known that microorganisms and bacteria were the main cause of most infections. Colloids of silver were the first widely used antibacterial compound before the introduction of antibiotics in the 1940s. Silver has been continued as a treatment in many forms, including silver foil for wound dressings, silver for wound antisepsis, and silver nitrate drops for eye problems. However, the continued use of silver can cause argyria, which is when silver deposits in the skin. A way to prevent these types of conditions and to provide a more dependable medication is by the use of silver nanoparticles. Silver nanoparticles kill bacteria by deactivating enzymes, causing the cell to stop reproducing, and by structurally changing the cell membrane. The bactericidal impact of silver has been studied on various bacteria, including *E. Coli*, *V. cholera*, and *S. typhus*. It was found that the nanoparticles disperse themselves throughout the cell and may sometimes attach themselves to the cell membrane or penetrate the bacteria itself. They are safe for human contact, and it is difficult for bacteria to become resistant to it, which has boosted their popularity. A common form of silver nanoparticles is as a silver N-heterocyclic carbene.

Carbenes are molecules which contain a divalent carbon atom. They were first created in 1963 and have grown in popularity in inorganic chemistry since their introduction. N-heterocyclic carbenes, which were first isolated and characterized in 1991, are molecules which contain one carbene and at least one nitrogen atom within the carbene structure. They are commonly used as ligands for transition-metal based compounds. By combining silver with an NHC, the resulting compound can release silver more slowly and safely.

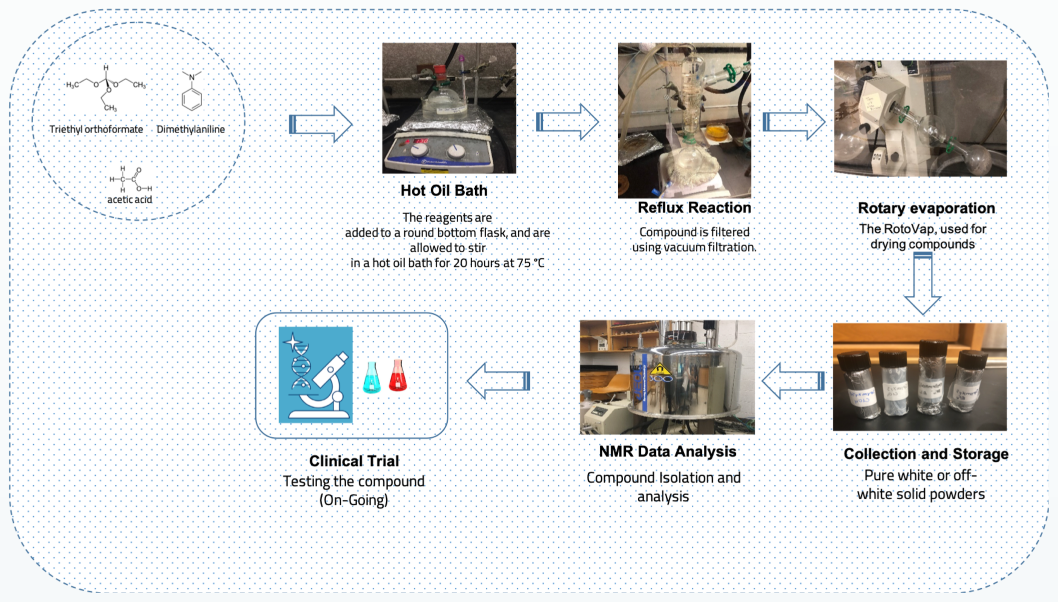
In order to create the silver NHC, two common methods are employed. The first method is known as green synthesis. By adding an extract of the stem to silver nitrate and incubating it, silver nanoparticles were created. The silver nanoparticles were added to cells, and a method knows as Trypan blue exclusion was used to examine the cell death caused. Second method to achieve the silver NHC is by the reaction of a salt with silver compound. Silver oxide is a common method for creating silver nanoparticles due to the ease of access. Many studies have been done on imidazole salts. Imidazole is an aromatic heterocycle and has non-adjacent nitrogen atoms. In this study, saturated dimethylbenzene pyrimidine salts are used in conjunction silver tetrafluoroborate and silver perchlorate to create 6-membered silver nanoparticles.

In this study, N-heterocyclicthiones (NHTs) and selones (NHSes) are used as reagents and constituents. They are both very commonly found in amino acids and enzymes within the body. Sulfur and selenium are important elements, found in proteins. Additionally, by adding sulfur to an NHC, electron dense granules are formed which can negatively impact the health of the cell. By combining the helpful benefits of sulfur, selenium, silver, and N-heterocyclic carbenes, this study hopes to achieve a solution to the cancer drug problem.

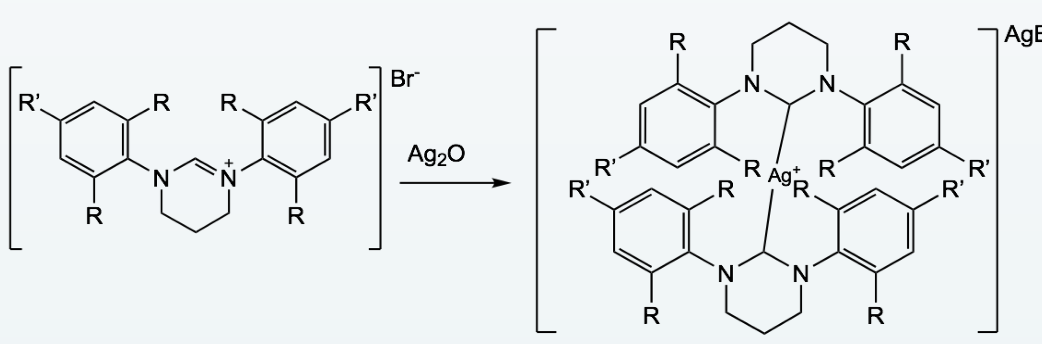
Synthesis of SpymXyE Ligand



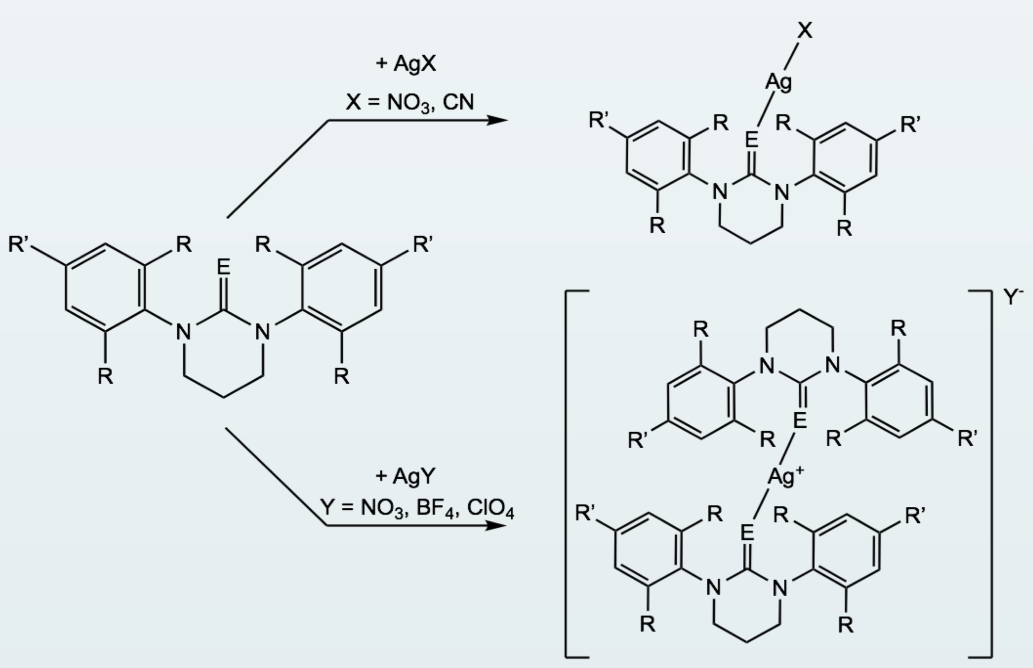
Research Plan



Carbene Coordination



Synthesis of Silver(I) Complexes



Research Execution Method

1) Formamidine

Triethyl orthoformate is added to Dimethylaniline along with a few drops of acetic acid, which is used as a catalyst. By reacting an amine derivative and an orthoester of formic acid under a high temperature, the xylyl formamidine can be created. The reagents are added to a round bottom flask, and are allowed to stir in a hot oil bath for 20 hours at 75 °C. Afterwards, the compound is filtered using vacuum filtration.

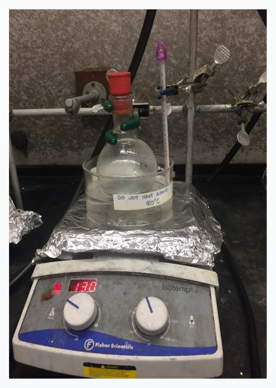


Fig A: Hot Oil Bath

2) Intermediate Salt

The xylyl formamidine is added to potassium carbonate and 1,3-dibromopropane in a round bottom flask. The potassium carbonate acts as a base, and removes the hydrogen bonded to the nitrogen. This allows for 1,3-dibromopropane to form the rest of the ring. This reaction is allowed to reflux for 24 hours. The salt solution is evaporated down.

Fig B: Reflux Reaction

3) Silver Compound

The ligand can then be utilized to create silver compounds. In this study, both silver(I) tetrafluoroborate and silver(I) perchlorate have been used, with identical procedures. The ligand is measured out into a 4-dram vial, along with 10 mL of acetonitrile. In another 1-dram vial, the silver salt is pre-dissolved in a few drops of deionized water. The silver solution is then transferred to the 4-dram vial. The solution is stirred for 22 hours.

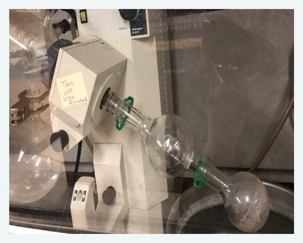


Fig C: The RotoVap, used for drying compounds

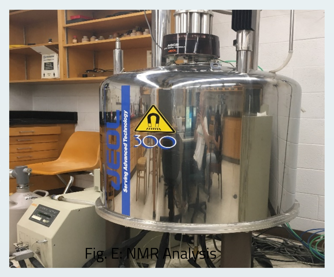
4) Final extraction and storage

Throughout the whole procedure, great care is taken to ensure that the solution and silver compounds have the least exposure to light as possible. This can be achieved by turning off lights and wrapping vials in aluminum foil. After stirring, the compound is then concentrated to almost dryness (0.5 mL) using the vacuum line or rotary evaporator. In order to improve yield, 10 mL diethyl ether is added to the vial. After collecting as much of the compound off of the sides of the vial, the compound is filtered by vacuum filtration and dried in vacuo for 24 hours.

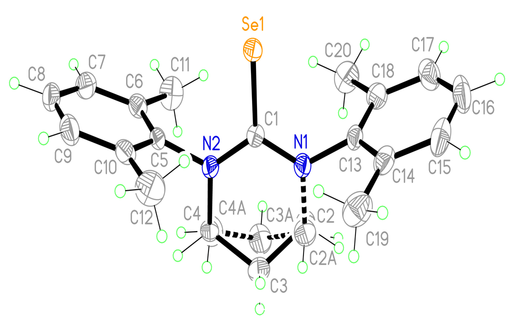
Fig. D: Pure white or off-white solid powders

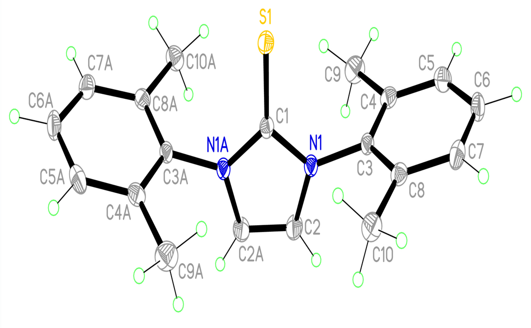
5) NMR Characterization

Final compounds are characterized by NMR, IR, elemental analysis and crystallization. Stored under least exposure to light as possible.



Molecular Structures





Selenium Ligand **Sulfur Ligand**

Yield Data Calculations

Yield Calculations for [Ag(SpymXyS)2BF4]:

$$0.0229 \cdot \frac{1\text{ mol A}}{194.664\text{g A}} \cdot \frac{1\text{ mol P}}{1\text{ mol A}} \cdot \frac{843.613\text{g P}}{1\text{ mol A}} = 0.099$$

$$0.0798 \cdot \frac{1\text{ mol B}}{324.486\text{g B}} \cdot \frac{1\text{ mol P}}{2\text{ mol B}} \cdot \frac{843.613\text{g P}}{1\text{ mol P}} = 0.1$$

$$\text{First Trial: } \frac{0.026}{0.099} = 26\text{ percent yield}$$

$$\text{Second Trial: } \frac{0.069}{0.099} = 70\text{ percent yield}$$

Yield Calculations for [Ag(SpymXyS)2ClO4]:

$$0.083g \cdot \frac{1\text{ mol A}}{324.486\text{g A}} \cdot \frac{1\text{ mol P}}{1\text{ mol A}} \cdot \frac{846.292\text{g P}}{1\text{ mol P}} = 0.219$$

$$0.028g \cdot \frac{1\text{ mol B}}{207.32\text{g B}} \cdot \frac{1\text{ mol P}}{1\text{ mol B}} \cdot \frac{856.292\text{g P}}{1\text{ mol P}} = 0.1156$$

$$\text{First Trial: } \frac{0.06}{0.1156} = 52\text{ percent yield}$$

$$\text{Second Trial: } \frac{0.0838}{0.1156} = 72.5\text{ percent yield}$$

Yield Calculations for [Ag(SpymXySe)2ClO4]:

$$0.082g \cdot \frac{1\text{ mol A}}{371.38\text{g A}} \cdot \frac{1\text{ mol P}}{1\text{ mol A}} \cdot \frac{950.07\text{g P}}{1\text{ mol P}} = 0.2$$

$$0.023g \cdot \frac{1\text{ mol B}}{371.38\text{g B}} \cdot \frac{1\text{ mol P}}{1\text{ mol B}} \cdot \frac{950.07\text{g P}}{1\text{ mol P}} = 0.1$$

$$\text{First Trial: } \frac{0.03}{0.1} = 30\text{ percent yield}$$

Yield Calculations for [Ag(SpymXySe)2BF4]:

$$0.083g \cdot \frac{1\text{ mol A}}{371.38\text{g A}} \cdot \frac{1\text{ mol P}}{1\text{ mol A}} \cdot \frac{937.44\text{g P}}{1\text{ mol P}} = 0.2$$

$$0.022g \cdot \frac{1\text{ mol B}}{194.664\text{g B}} \cdot \frac{1\text{ mol P}}{1\text{ mol B}} \cdot \frac{937.44\text{g P}}{1\text{ mol P}} = 0.1$$

$$\text{First Trial: } \frac{0.06}{0.1056} = 56.6\text{ percent yield}$$

- Four silver complexes (two perchlorate complexes and two tetrafluoroborate complexes) were characterized using NMR, IR and melting point data.
- Each were synthesized using either sulfur or selenium. Yields were improved by adjusting the procedure until yields were above 50 percent
- All NMR data was shown to be pure, thereby showing that all compounds are ready for biological studies against cancer cells.

Conclusion

Successfully crystallized the compound and analysis that shows that the resulting compound includes the 6 ring format as originally designed. Researches showed immense potential .

The next steps are to put the compounds through through cell studies. Apart from being cost effective compound using silver instead of platinum compound approved for some cancer treatments. Additionally, more work on other ligands, such as the saturated and unsaturated imidazolium ligand can be looked at.

I would like to continue the research to find more ways to synthesize the compound and increase yield. Since there are various other silver complexes, it would be useful to analyze the effect of other compounds, such as silver nitrate and study the biological activity (e.g., anticancer properties) of all the silver complexes.

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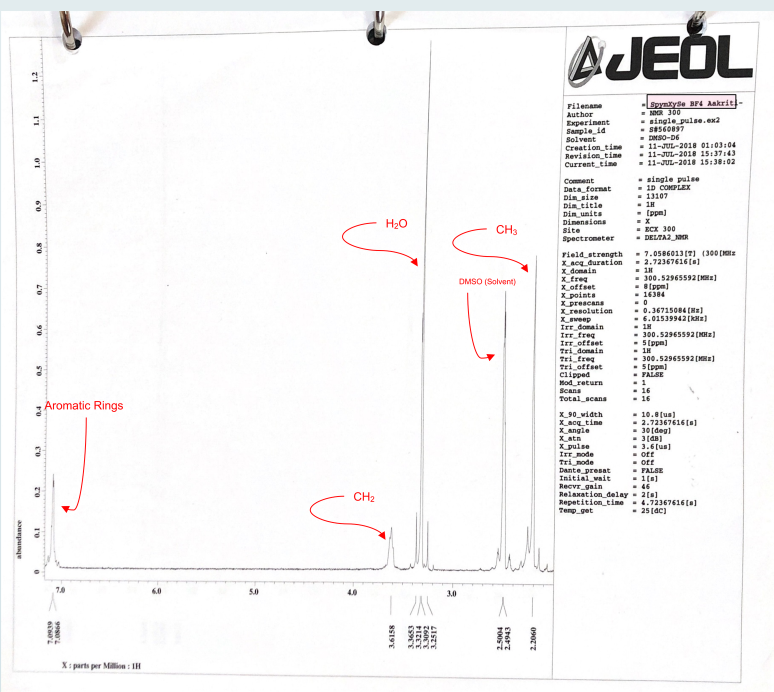
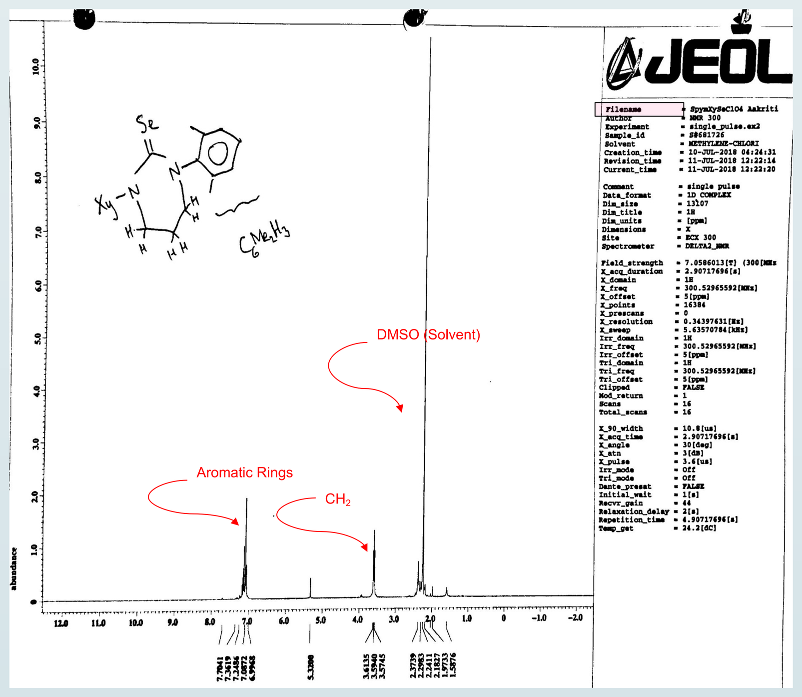
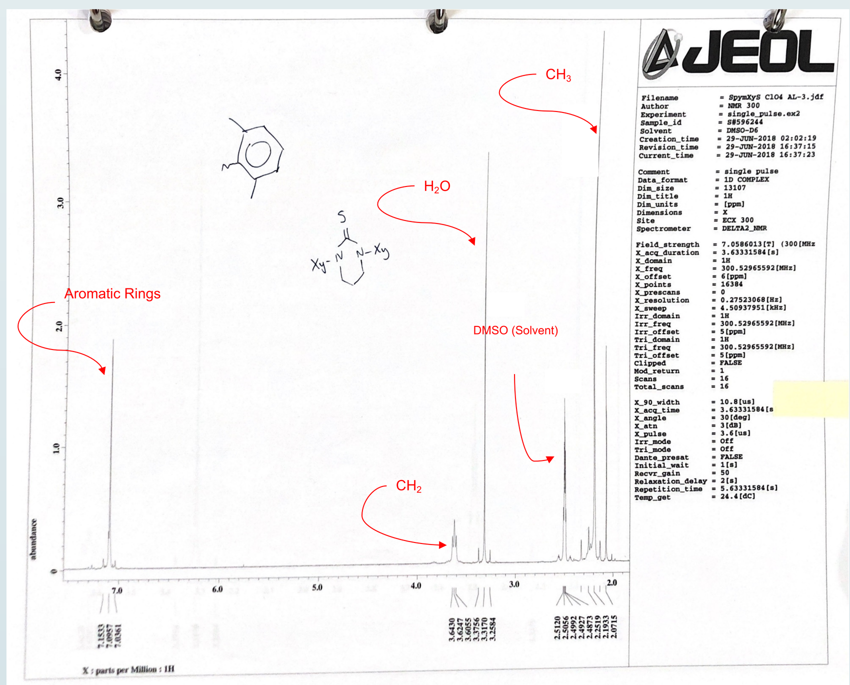
- DR Group

NMR Data Analysis







All pictures and charts are taken by Aakriti Lakshmanan