Synthetic approaches for quinazolinone amination towards bioactive quinazolinone derivatives

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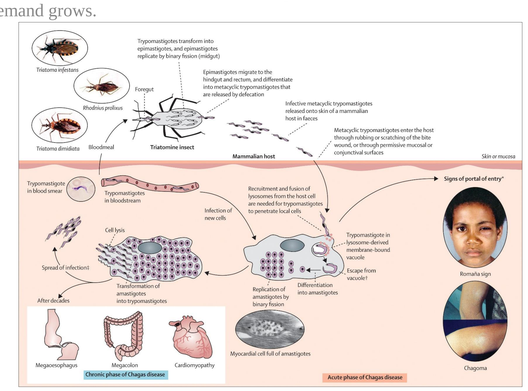
INTRODUCTION

This project revolves around the Quinazolinone molecule as it is being used in the intermediary process of various drug synthesis. A bioactive form of quinazolinone proves promising for the treatment of Chagas disease, a parasitic disease that is affecting as many as 8 million people in central and south America. Around 30-40% of those effected suffer from heart and digestive health conditions. C.D is expected to become an emerging health problem, especially in non-endemic regions due to population growth. This new synthesis provides an alternative to the currently available treatment for Chagas disease (C.D), benznidazole (or nifurtimox), and avoids potential bottleneck of the treatment synthesis if demand grows.



OBJECTIVE

The goal of this project is to improve the yield of the intermediary pathway to get to the bioactive quinazolinone (Figure 1) and to discover any useful products formed from the amination. By testing different aminations of the alkylated scaffold from quinazolinone **2**, such as reacting it with amines of varying degrees of substitution (1° vs. 2°) and aromaticity, or the absence of, in the amination group, the hope is to be able to provide data for future synthesis that utilizes a similar pathway. It is be expected that the more accessible an amine group is for a nucleophilic attack, the better the yield of the pathway would be, 1° amine would be more reactive than 2° amine, and aromatic amines better than aliphatic amines etc. Figures 2~3 show the synthesis of compound **2,** the molecule of interest for this subgroup.

Bioactive Quinazolinone: Synthetic pathway

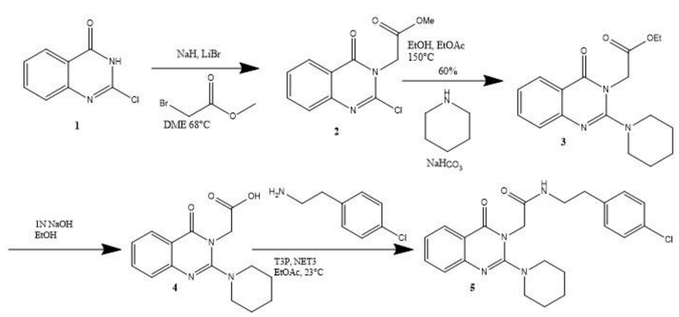


Figure 1. Synthesis of the bioactive quinazolinone target molecule. Researchers at the Drugs for Neglected Diseases initiative discovered its bioactivity. The amination of quinazolinone 2 to quinazolinone 3 is the reaction of interest, amination of the alkylated scaffold, previous findings show that reaction with piperidine results in 60% yield.

METHODS AND MATERIALS

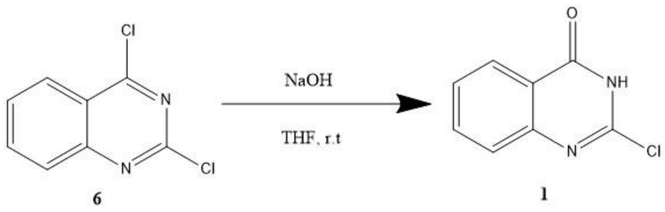


Figure 2. Full conversion, no purification was performed. TLC showed a single spot for the product, NMR showed the aromatic ring peaks, both showed the reaction had proceeded to completion.

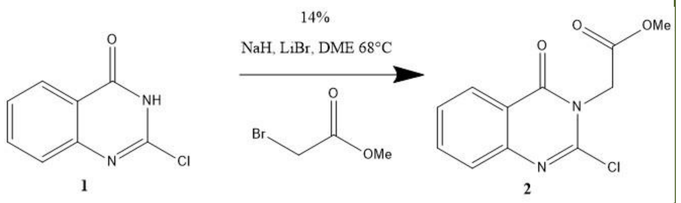
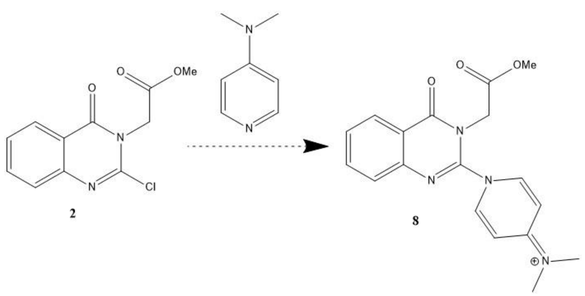


Figure 3. Low yield: 14%, purification via column chromatography. NMR showed the carbonyl peaks, reaction proceeded to completion.

Future direction



Through the work of this subgroup, one can be advised to keep in mind of the inter-reactivity of the reagents. Unintentional reactants such as solvents or other contaminants from lab equipment should be considered and the reagents altered accordingly to minimize frustration or unintended results. However, it is worth noting that for the TLC and column purification of the benzylamine product (figure 5), using DCM as the TLC solvent showed better separation of the crude products, while 2% MeOH/DCM solute has a better result than using 20% Hexanes/Ethyl acetate in column chromatography.

RESULTS

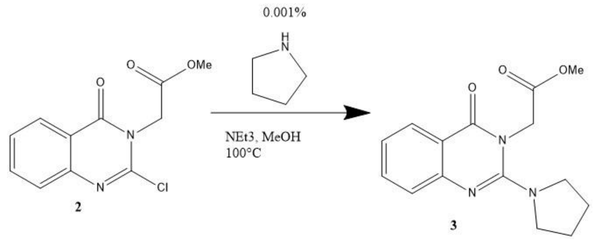


Figure 4. Poor yield: 0.001%, purification through column chromatography. NMR showed additional peaks for pyrrolidine, reaction proceeded to completion.

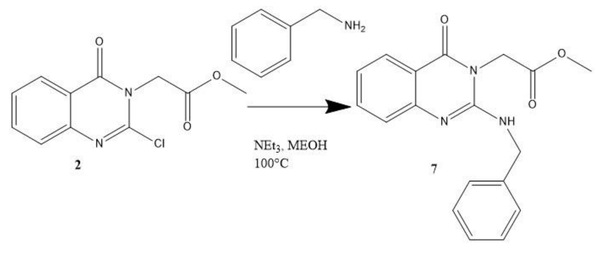


Figure 5. Yield still needs to be determined after removing impurities, purification using column chromatography has been difficult. TLC showed overlapping spots, NMR results were inconclusive.

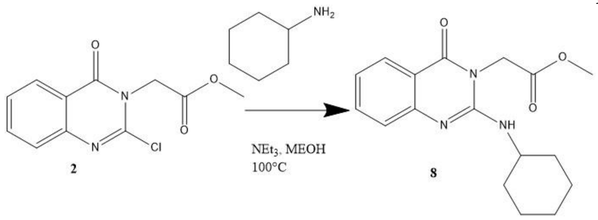


Figure 6. Yield still needs to be determined after removing impurities, NMR results were inconclusive.

Figures 4~6 show the reaction of interest. Neither reaction was able to support the hypothesis of more availability of a nucleophilic attack equates to a higher yield, instead the results support the opposite. Especially so in figure 5 where the workup is more challenging than the other experiments. Some possible explanation for this might be that the amine is too strong of a nucleophilic group that it had unintended reactions with another molecule, it can be suggested that the NMR data could be showing a benzyl alcohol. For future lab sessions, one molecule of interest would be 4-(dimethylamino) pyridine (Figure 7), it would be interesting to see how aromaticity would interact with or perhaps hinder the reactivity with compound **2.**

REFERENCES

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