

# Synthesis of Quinazolinone Derivatives for use in Biological Testing

Grant Hobby, Matthew Fisher, Carter McCormick and Dr. Kelly Kim

## INTRODUCTION

### Chagas Disease

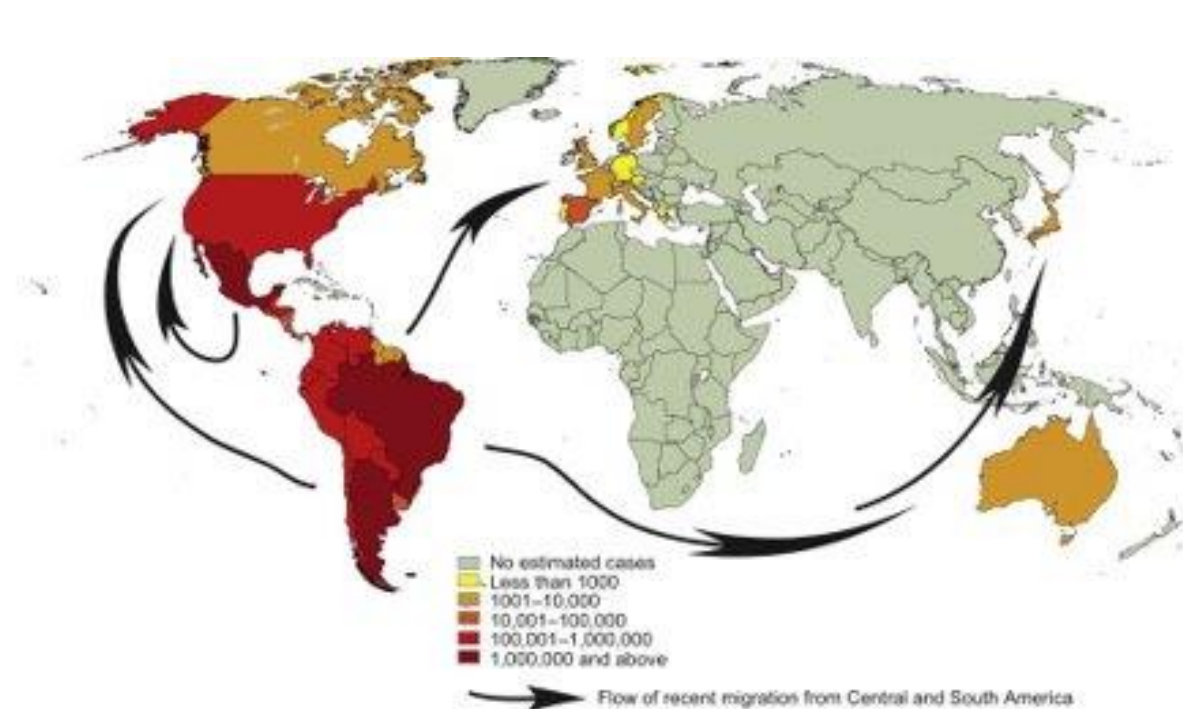
Chagas disease, was discovered in 1909 by Brazilian physician Carlos Chagas. Approximately more than 300,000 people in the United states are infected with the parasite *Trypanosoma cruzi*, most of which contracted the parasite in Latin America<sup>2</sup>. Mexico, Central America and South America are estimated to have 8 million infected individuals. This results in about 20,000 deaths per year worldwide<sup>1</sup>.

### Transmission



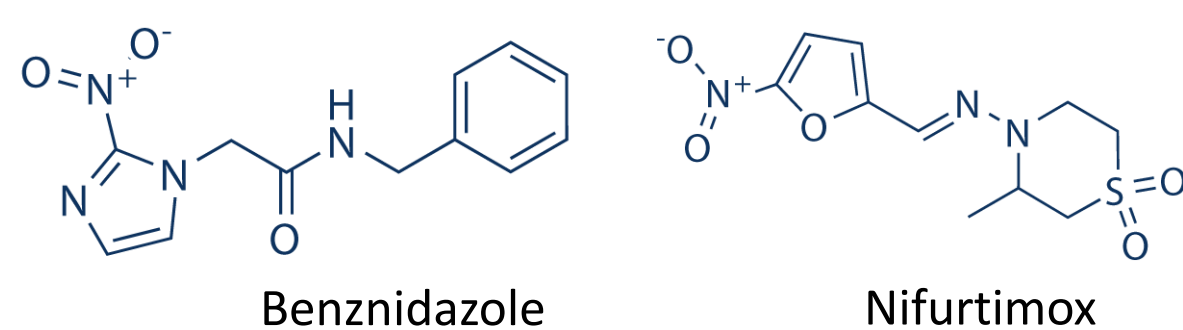
**Figure 1.** Chagas disease is spread by the Triatominae (kissing bug) acting as a vector. It feeds on blood around the mouth leaving behind its feces carrying *T.cruzi*, entering the body through the wound or other openings such as the eyes<sup>2</sup>.

### Affected area



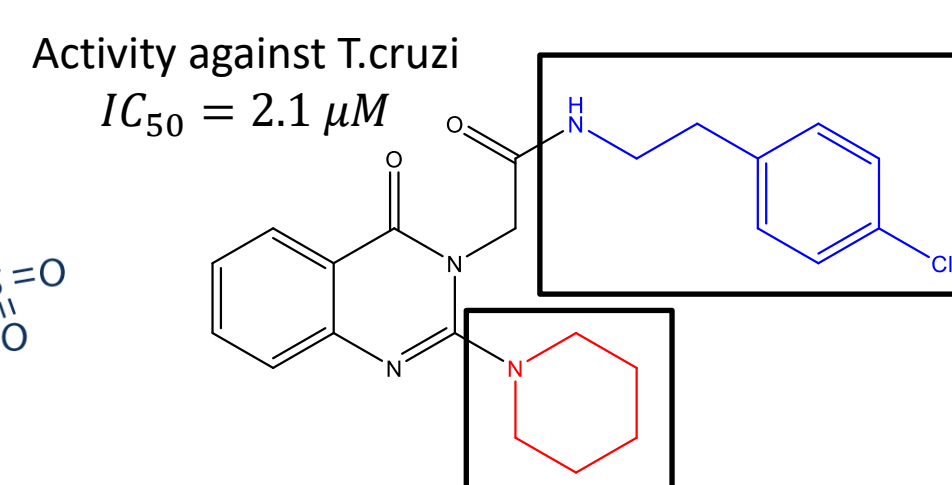
**Figure 2.** Chagas is primarily distributed within the Americas. However due to its mode of infection we see higher infection rates in less developed regions of the Americas<sup>2</sup>.

### Current Treatments



**Figure 4.** Benznidazole and Nifurtimox are currently the only treatments for Chagas disease. Their toxic effects and ineffectiveness in long term treatment make them weak candidates in treating Chagas disease<sup>3</sup>.

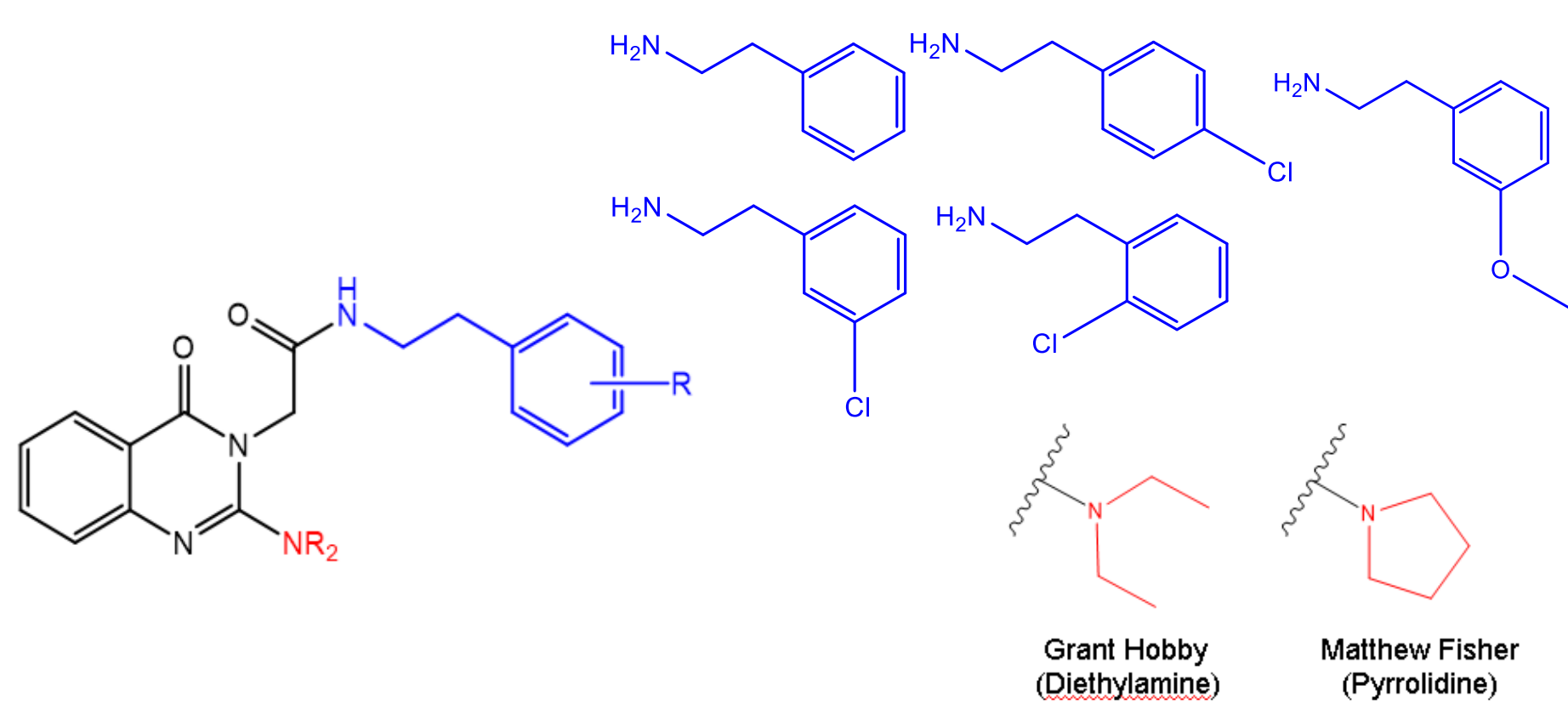
### Quinazolinones



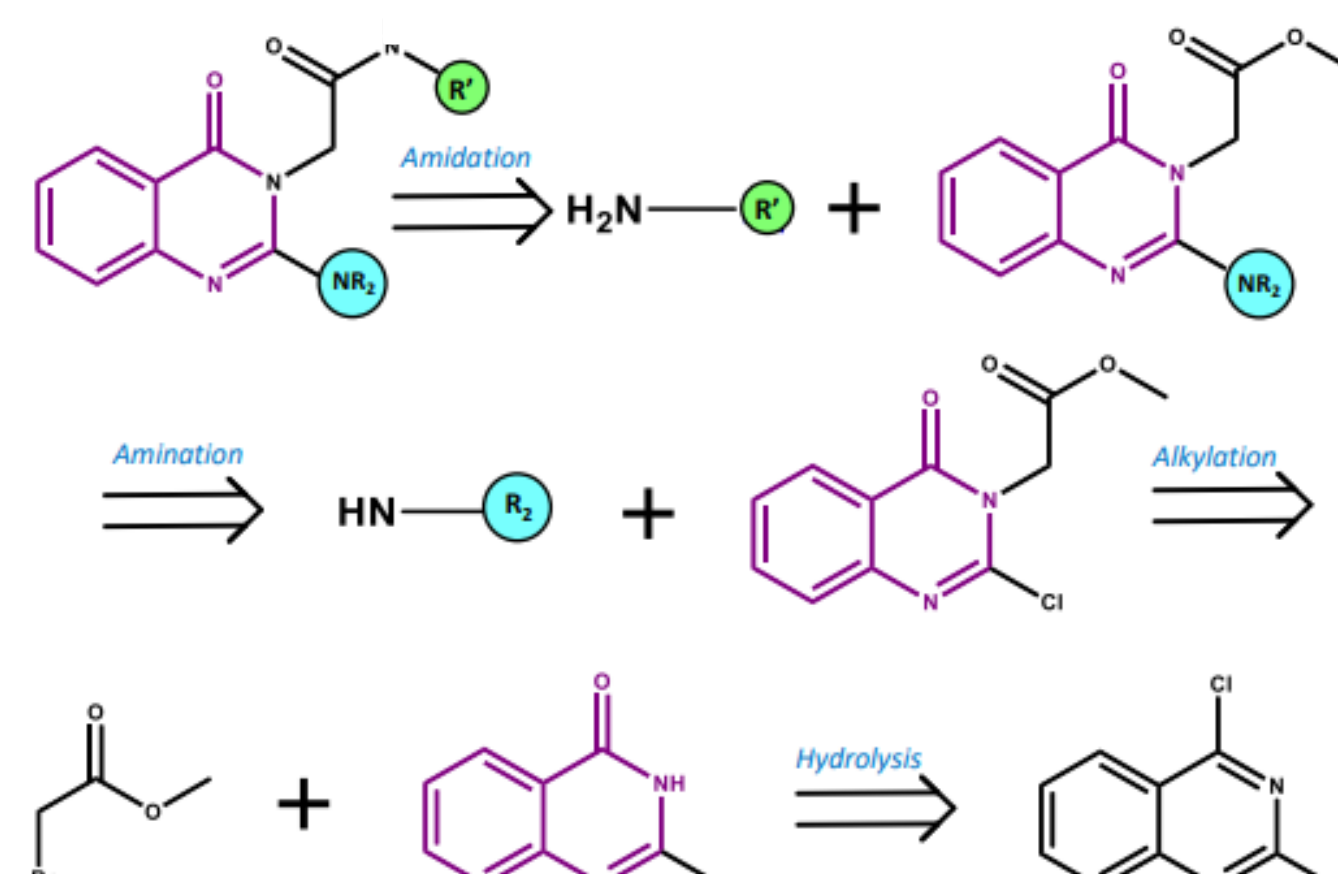
**Figure 5.** Quinazolinone shown by DNDi researchers to have bioactivity against the *T.cruzi* parasite

### Objective

The Goal of this research was to establish and optimize the synthetic pathways of the following quinazolinone derivatives for biological testing.

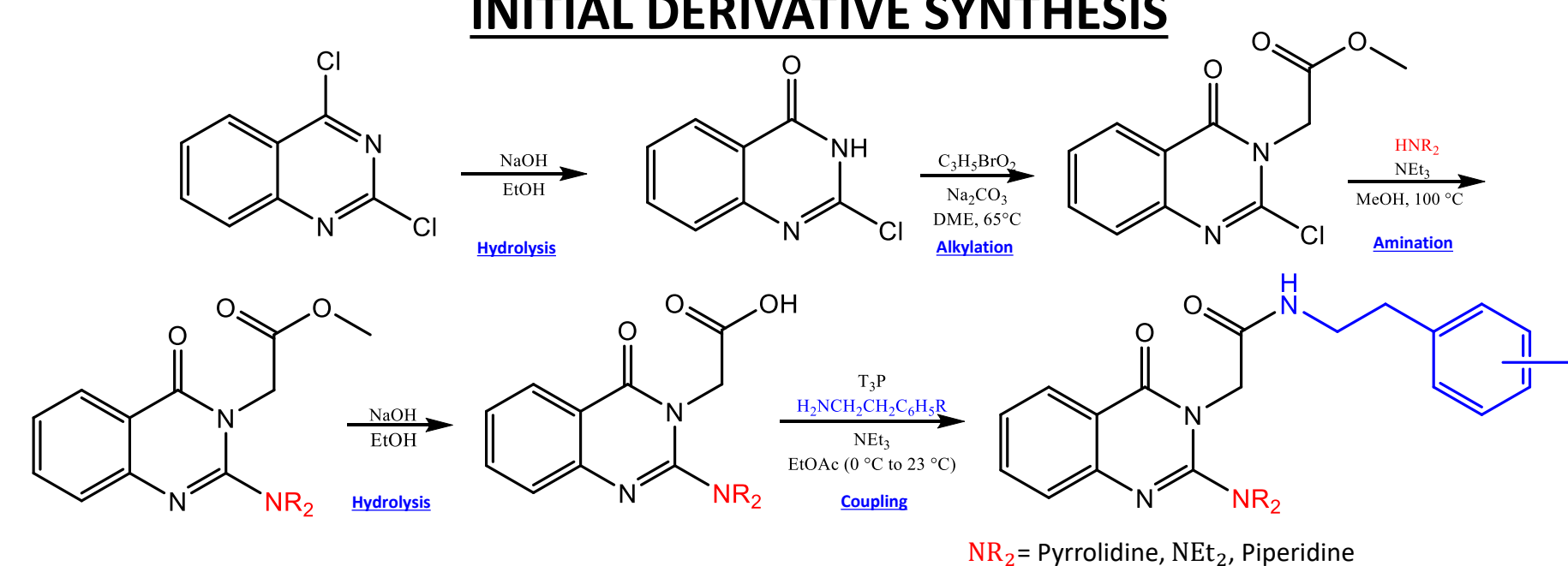


## ESTABLISHED RETROSYNTHESIS

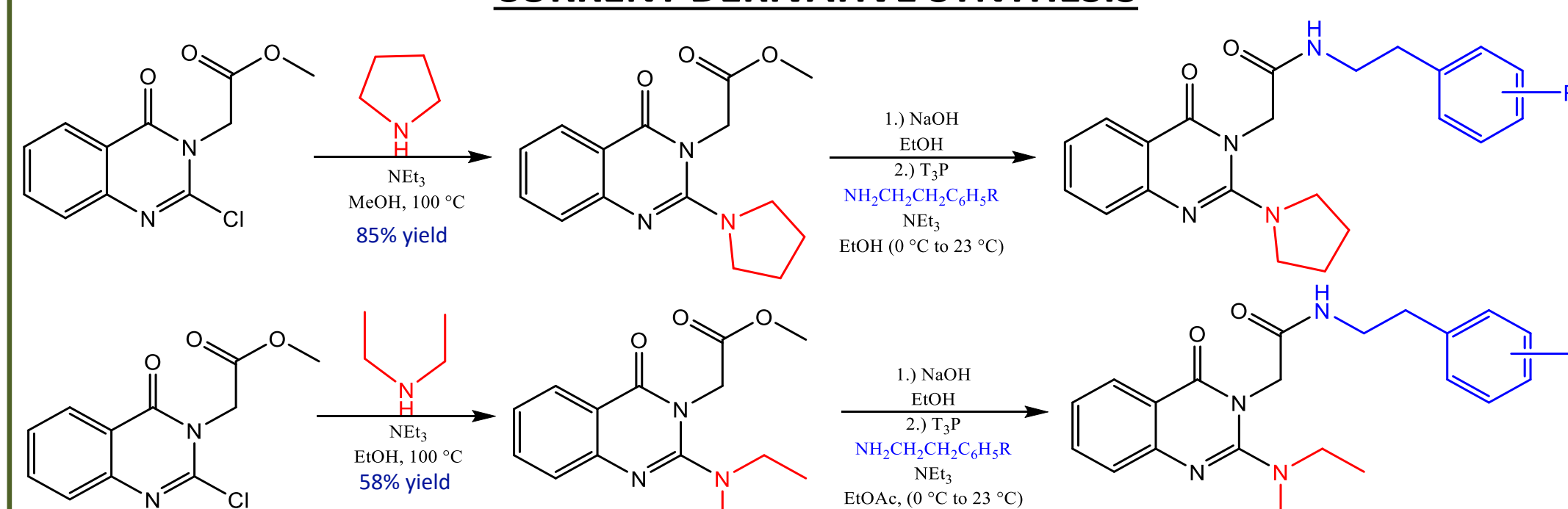


**Figure 6.** Retrosynthesis of the chlorinated scaffold starting material created by Alex Pursel and Jason Comber

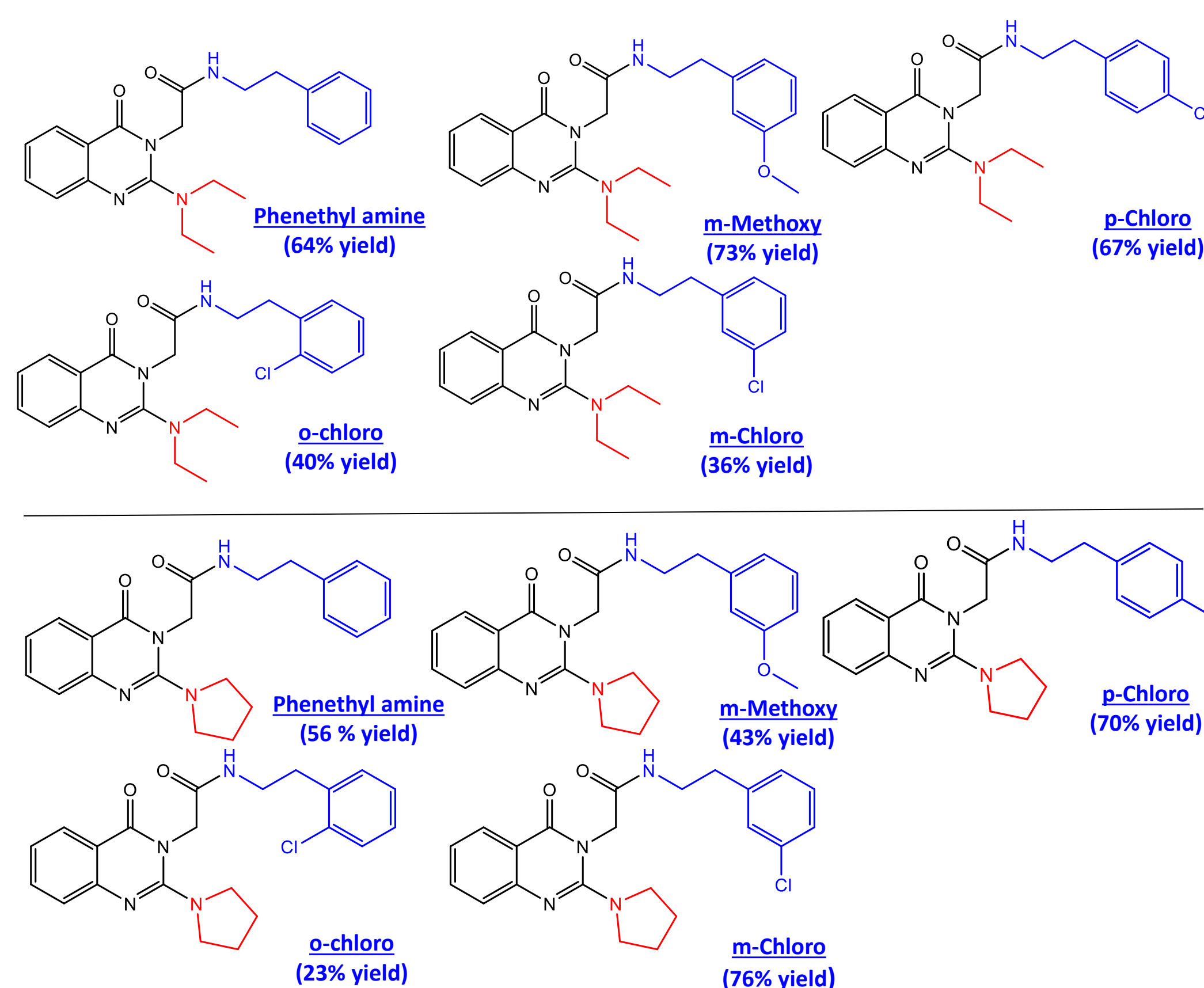
## INITIAL DERIVATIVE SYNTHESIS



## CURRENT DERIVATIVE SYNTHESIS

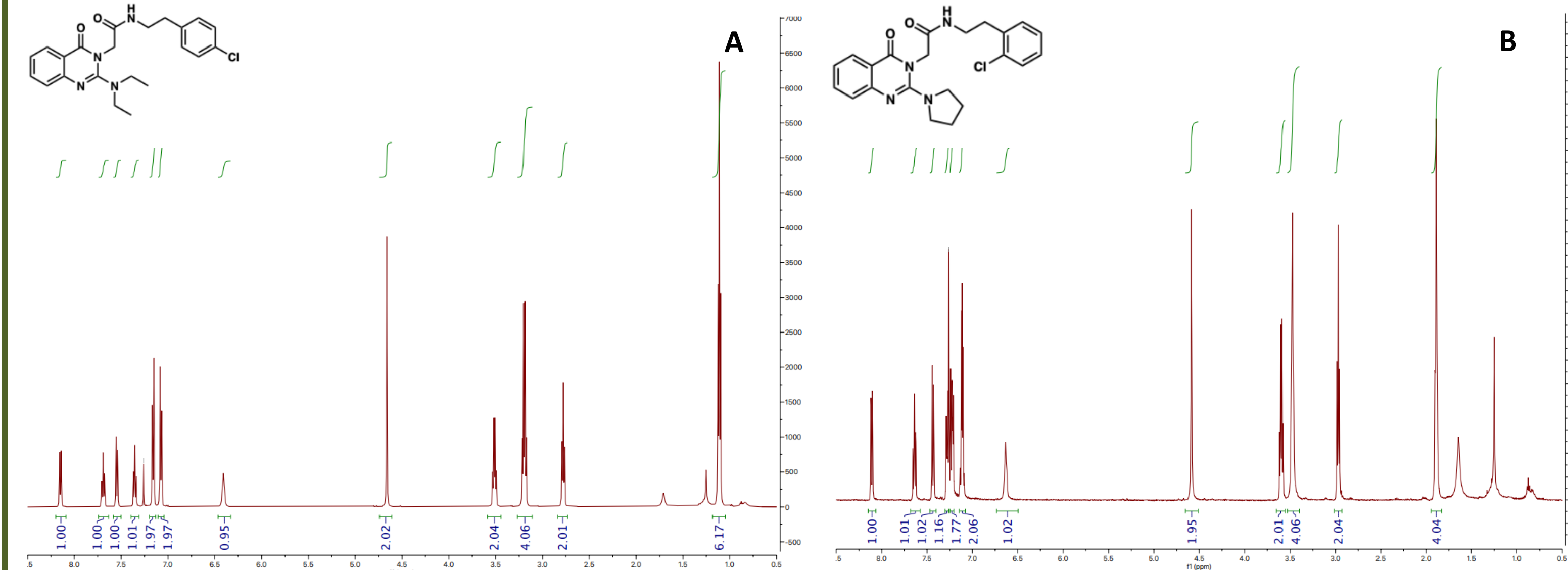


## SYNTHESIZED DERIVATIVES



## SPECTRAL DATA

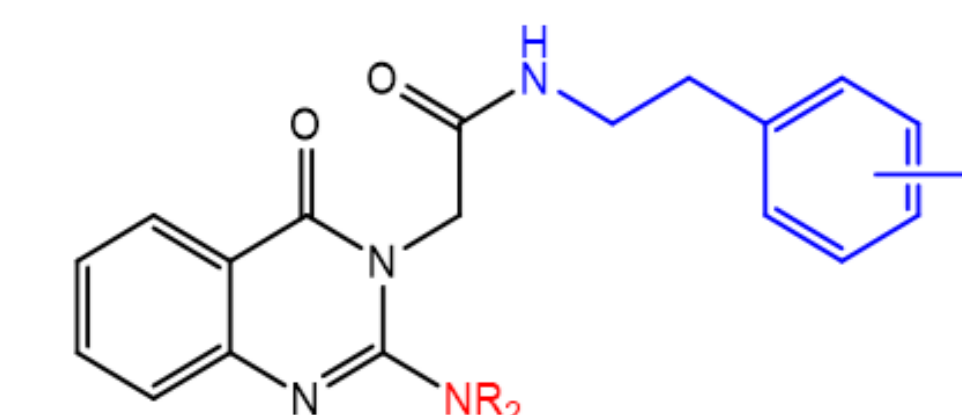
CDCl<sub>3</sub> 300 MHz HNMR spectrum



**Figure 7.** HNMR in CDCl<sub>3</sub> of the p-chloro diethylamine derivative and o-chloro pyrrolidine derivative

## FUTURE DIRECTIONS

- Continue to further optimize reaction conditions to improve yields.
- Further exploration of the amination reaction
- Pursue more derivatives
- Vary the amine
- Vary the phenethylamine linker



The Structure highlighted in red represent the amine group. The Structure highlighted in blue represent the Phenethylamine linker. Other arrangements of amine groups and phenethylamine linkers may offer higher levels of bioactivity

## CONCLUSIONS

- Optimized synthetic route to quinazolinone derivatives.
- Yields can be improved through the one-pot, two-step protocol.
- Changing out sodium hydride for sodium carbonate improved the ease of the alkylation set-up without impacting yield.
- A lighter acidification in the hydrolysis work-up improved yields
- Synthesized Diethyl amine and pyrrolidine derivatives.
- Using different solvents for amination, pyrrolidine methanol created the highest yields, and diethylamine had higher yields with ethanol.
- Switching solvent for pyrrolidine's coupling reaction to ethanol instead of ethyl acetate increased yields. Diethylamine had high yields using ethyl acetate

## REFERENCES

1. Rodriguez, PLOS Negl. Trop. Dis. 2014, 8, e3259
2. Center for Disease Control [internet]. 2022. Atlanta (GA). Center for Disease Control; [cited 2022 Jun 4]. Available from: <https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html>
3. Rodriguez A. 2021. 300K Americans may live with a chronic, deadly disease transmitted by the 'kissing bug.' What is Chagas and why are doctors missing it?[internet]. 2022. McLean (VA). USA Today; [cited 2022 Jun 4]. Available from: <https://www.usatoday.com/story/news/health/2021/06/19/kissing-bug-chagas-disease-doctors-may-missing-cases-study-finds/7636755002/>

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