Synthesizing Piperidine Quinazolinone Derivatives for The Treatment of Chagas Disease

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INTRODUCTION

The protozoan parasite *Trypanosoma cruzi* (T. cruzi) is commonly found in areas of Latin America where poverty is especially prevalent. Transmittance of T. cruzi to humans and animals is caused by insect vectors, this causes the disease known as Chagas.[5] Chagas currently infects over 10 million people, and an additional 100 million are currently living in high-risk areas for transmission. This disease can be largely asymptomatic, however, 30% of those who are chronically infected suffer severe heart and gut tissue damage that can lead to disability and death.[1]

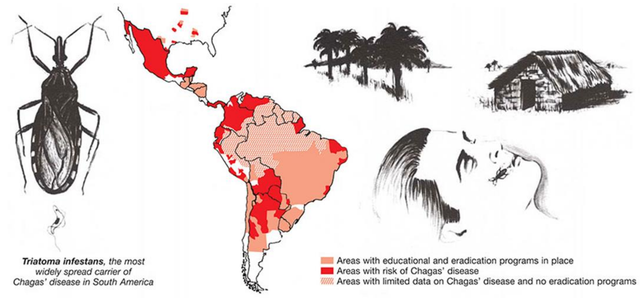


Figure 1: Populations at high risk of developing Chagas' disease [2]

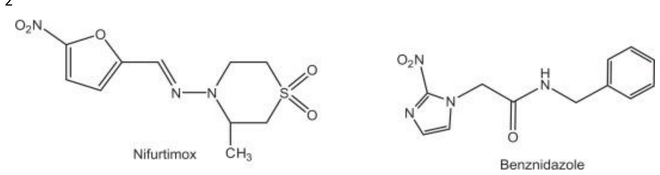


Figure 2: Nifurtimox and Benznidazole are the main treatment options currently.[3]

There is currently no vaccine and the current treatment options pose severe side effects that cause a discontinuation of treatment. Additionally, these treatment options having varying degrees of success. [4]

OBJECTIVE

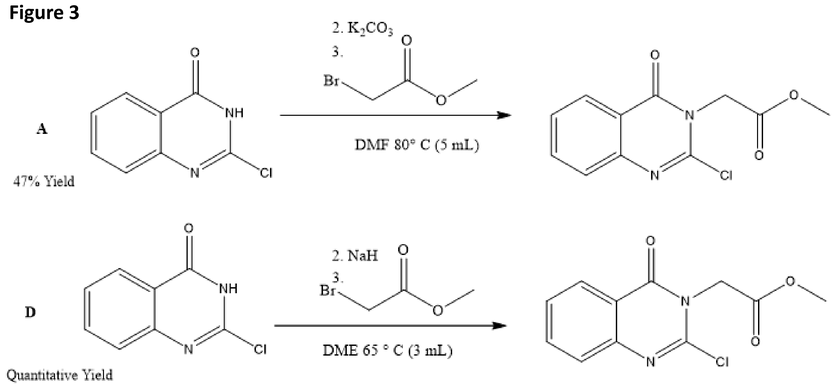
Scheme 1

Scheme 1 represents a retrosynthetic plan for the synthesis of a piperidine and 4-methoxyphenethylamine substituted quinazolinone derivative. This derivative is thought to be synthesizable via N-alkylation, substitution, hydrolysis, and coupling reactions.

METHODS AND MATERIALS

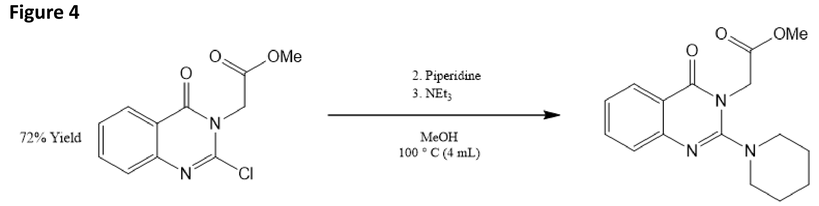
Amine Alkylation

Figure 3



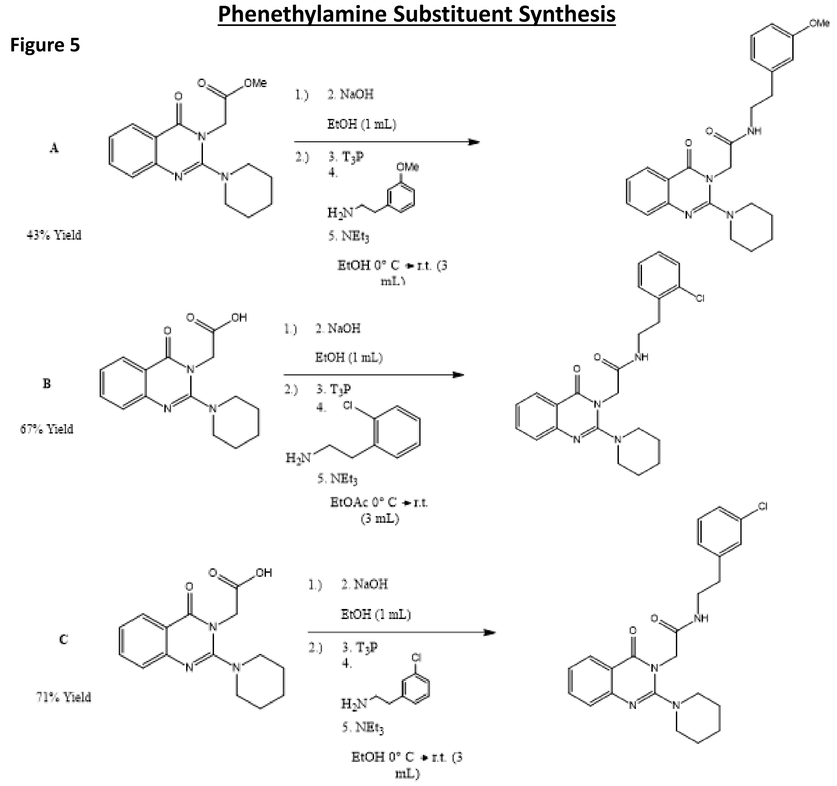
Synthesis of Piperidine Substituted Quinazolinone Derivative

Figure 4



Phenethylamine Substituent Synthesis

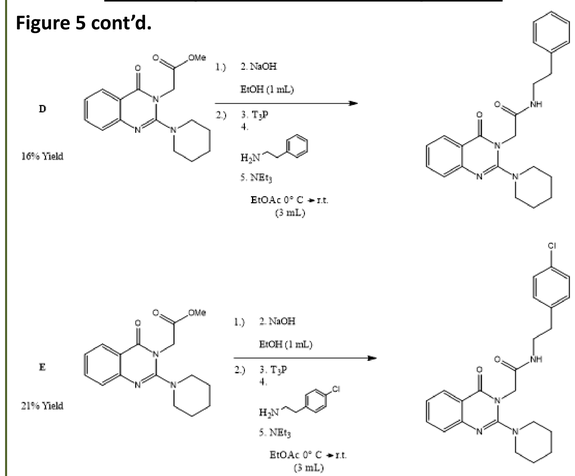
Figure 5



METHODS AND MATERIALS (cont.)

Phenethylamine Substituent Synthesis

Figure 5 cont'd.



All reactions were monitored by TLC.

Upon full conversion of the hydrolysis step, the reaction was acidified to a pH of 2 with 10 drops of 6 N HCl and then placed on a rotary evaporator at 45° C to remove volatiles.

Upon completion of the coupling step, the reaction was then worked up with water twice, followed by sodium bicarbonate and then brine. Confirmation of the product structure was determined by NMR and IR.

RESULTS

Amine Alkylation: Performed under conditions with and without a catalyst. The catalyst, Lithium Bromide, proved to be insignificant in yield production.

Synthesis of Piperidine Substituted Quinazolinone Derivative: Proven to be efficient with piperidine, triethylamine, and methanol (4 mL) at 100° C as it produced a yield of 72%. While under similar conditions, except with the amounts of the starting material, reagents and solvent doubled, the yield decreased to 58%.

Phenethylamine Substituent Synthesis: The final step in our synthesis involved a coupling reaction that was responsible for producing the phenethylamine substituent on the piperidine quinazolinone derivative. As shown in Figure 5, several different phenethylamines were used to create different derivatives

This coupling step was later combined with our hydrolysis step and produced varying levels of success as shown in Figure 5. All our reactions took place under ethyl acetate as the solvent, however reactions (A) and (C) were also done with ethanol as the solvent and saw an increase in yield from 15% to 43%, and from 0% to 71%, respectively.

This research helped provide a solid foundation that now can go through the process of refinement and scaling up to test the clinical utility of these compounds against Chagas disease. Additionally, this work will help us continue to pursue viable synthesis methods to produce these quinazolinone derivatives as well as other derivatives in the future that will hopefully fulfill the medicinal treatment need for Chagas disease.

REFERENCES

1.) Alonso-Padilla J, Rodríguez A. 2014. High Throughput Screening for Anti–Trypanosoma cruzi Drug Discovery. Dumonteil E, editor. PLoS Neglected Tropical Diseases. 8(12):e3259. doi:10.1371/journal.pntd.0003259. [accessed 2021 Aug 28]. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003259.

2.) IAMAT | Chagas Disease. 2021. Iamatorg. [accessed 2022 Jun 6]. https://www.iamat.org/risks/chagas-disease.

3.) Mathew NS, Negi PS. 2019. Plant-derived compounds against protozoan neglected diseases: toward sustainable drug development. Discovery and Development of Therapeutics from Natural Products Against Neglected Tropical Diseases.:241–292. doi:10.1016/b978-0-12-815723-7.00007-9. [accessed 2022 Jun 6]. https://www.sciencedirect.com/science/article/pii/B9780128157237000079.

4.) Wilkinson SR, Kelly JM. 2009. Trypanocidal drugs: mechanisms, resistance and new targets. Expert Reviews in Molecular Medicine. 11. doi:10.1017/s1462399409001252. [accessed 2021 Aug 28]. https://pubmed.ncbi.nlm.nih.gov/19863838/.

5.) CDC - Chagas Disease - Detailed FAQs. 2021. [accessed 2021 Aug 28]. https://www.cdc.gov/parasites/chagas/gen_info/detailed.html#intro.

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