Amination of N3-Alkylamide Quinazolinones

Daniel Tolas, Yen-Po Huang, Haleigh Rzonca, Dr. Kelly Kim

UNIVERSITY of WASHINGTON TACOMA

INTRODUCTION

Trypanosomiasis:

Caused by the protist *Trypanosoma Cruzi.*

Transmission and Distribution

the transmission of *Trypanosoma cruzi* the protist responsible for Chagas disease, from an infected Triatominae to a human is not easy. The parasite that causes the disease is found in the feces of infected Triatominae. The Triatominae generally defecates on or near a person while it is feeding on their blood, usually when the person is sleeping. Transmission of the parasite happens when excrement is accidentally rubbed into the bite wound or into a mucous membrane (for example, the eye or mouth), and the parasite enters the body.[1]

Figure 1: Triatominae (kissing Bug).[2]

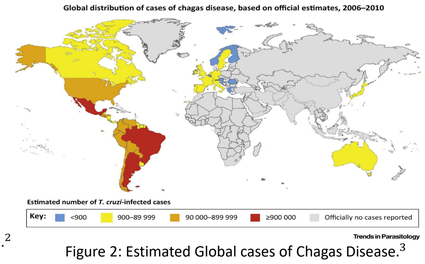


Figure 2: Estimated Global cases of Chagas Disease.[3]

The world Health Organization (WHO) lists chagas disease as a Neglected Tropical disease and with the help of organizations Like the Drugs for Neglected Diseases Initiative (DNDi), have provided new avenues with their Open Synthesis Network (OSN) allowing Researches to collaborate on projects surrounding lesser-known Diseases like chagas disease.

Chagas Disease Pathology

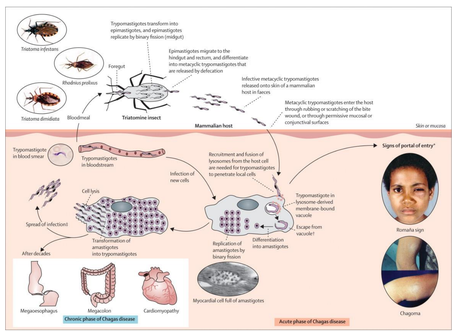


Figure 3: Chagas Disease Symptoms and Progression.[4]

Treatment

The drugs Nifurtimox and Benznidazole are currently the only drugs available to treat Chagas Disease but are meant only to treat Chagas disease in its acute phase; there are no prescriptions available to treat the chronic stage of this disease.

TABLE 2
CDC Treatment Guidelines

Benznidazole	Age 0-11 y: 5-7.5 mg/kg/d po divided twice daily for 60 d	Age 12+ y: 5-7 mg/kg/d po divided twice daily for 60 d	
Nifurtimox	Age ≤ 10 y: 15-20 mg/kg/d po divided into 3 or 4 doses for 90 d	Age 11-16 y: 12.5-15 mg/kg/d po divided into 3 or 4 doses for 90 d	Age 17+ y: 8-10 mg/kg/d po divided into 3 or 4 doses for 90 d
Contraindications to treatment: breastfeeding infants, severe renal/hepatic disease.			

Source: CDC. 2013.[18]

Figure 4: CDC Chagas disease treatment guidelines.[5]

OBJECTIVE

Research Goal #1: establish pathway to bioactive quinazolinone.
Research Goal #2: prepare derivatives of the bioactive quinazolinone based on the amination step.

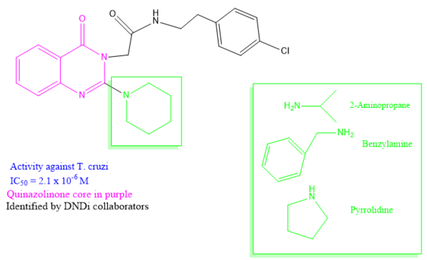
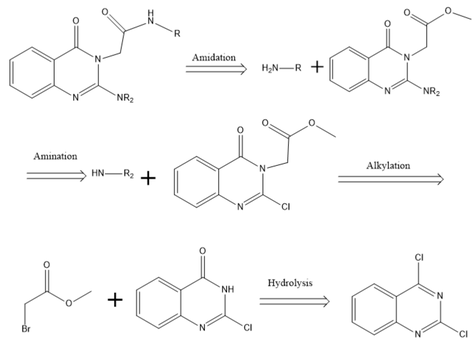
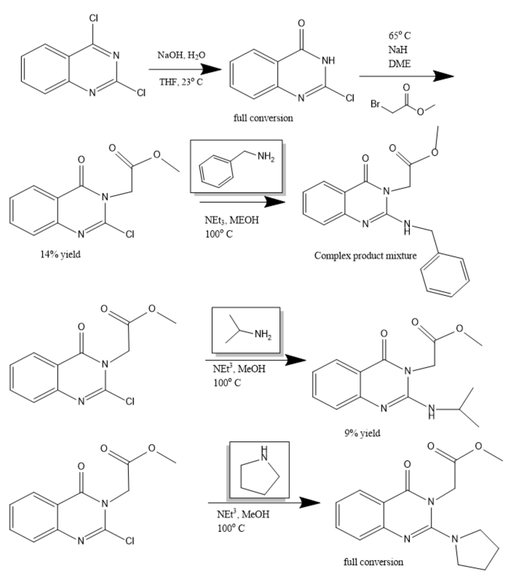


Figure 5: DNDi and OSN Research objective.[6]

Retrosynthesis



Forward Synthesis



RESULTS

- Peaks between 7-9ppm correspond to H atoms on the quinazolinone core.
- Peaks around 2ppm and 3.5ppm correspond to those of the pyrrolidine.
- Peaks at 4.8 and 3.8 correspond with the two Alkyl groups on the methyl ester.

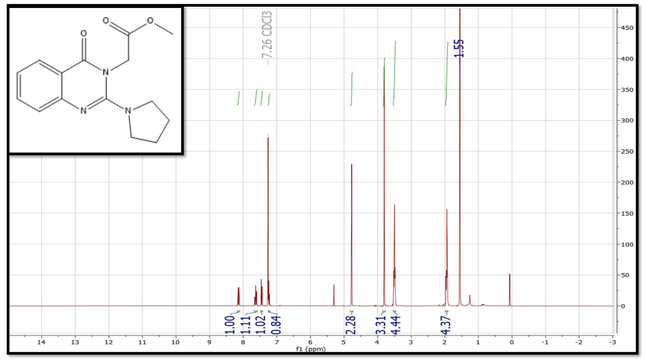


Figure 6: 1H NMR from compound EXP3-2S, 300MHz, CDCl3.

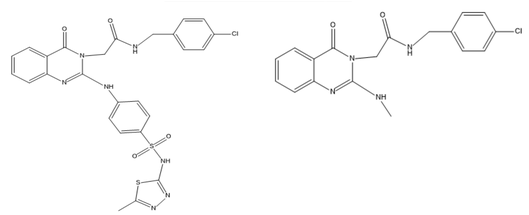
CONCLUSIONS & FUTURE DIRECTIONS

Based on our groups results we can conclude that the current synthesis pathway to the bioactive quinazolinone are valid. Furthermore with regards to the amination of the bioactive quinazolinone scaffold, 2^0 amines performed better than 1^0 amines given the NMR Data providing evidence of a successful amination and the full conversion of the starting material with the Pyrrolidine when compared to the lower yields of the 2-amino propane and the benzylamine.

Amines for further consideration.
- Cyclic amines like imidazole based on the success of pyrrolidine.
- Methylamine confirm conclusions on 1^0 Amines
- Sulfamethizole: approved as an antibiotic.

Optimize Amination Methods.
- Solvent, Temperature, Time >8hrs.
- Increase the equivalence of amine to quinazolinone scaffold.
- Perform amination at an earlier stage of the bioactive quinazolinone synthesis.

- **Future Amination Targets**



ACKNOWLEDGEMENTS

Thanks to the Drugs for Neglected Diseases initiative for investing time and resources into researching neglected diseases and creating the Open Synthesis Network, allowing undergraduate students like those at UWT to collaborate in a research program with real life implications in the development of drugs for neglected diseases like Chagas. Furthermore, a special thanks to Dr. Kim, Yen-Po Huang, Haleigh Rzonca, the UWT Lab Staff, and the UW Seattle NMR Facility managers.

DNDi Drugs for Neglected Diseases initiative

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OSN DNDi Open Synthesis Network

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