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Accessing Rare Heterocycles from Alkynyl Ethers and Nitrogenous Electrophiles & The Development of Small Molecule Inhibitors Against Naegleria *fowleri* infection

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&

The Development of Small Molecule Inhibitors Against *Naegleria fowleri* infection

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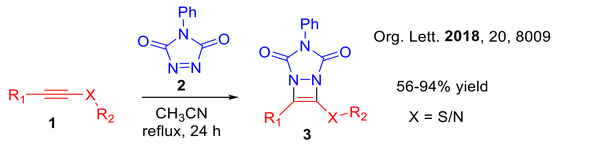
Background

- ❑ *Trypanosoma brucei* is responsible for causing "sleeping sickness" (African Trypanosomiasis) in humans
- ❑ Sleeping sickness is fatal if left untreated.
- ❑ Diazocyclobutenes (DCB, **3**) exhibit potent antitrypanisomal activity.
- ❑ The present study investigates DCBs using alkynyl ethers instead of alkynyl sulfides or ynamines.



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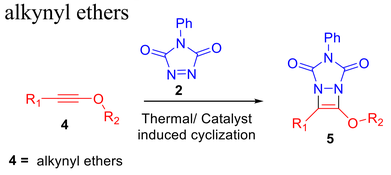
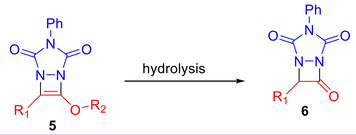
56-94% yield

Project Aims

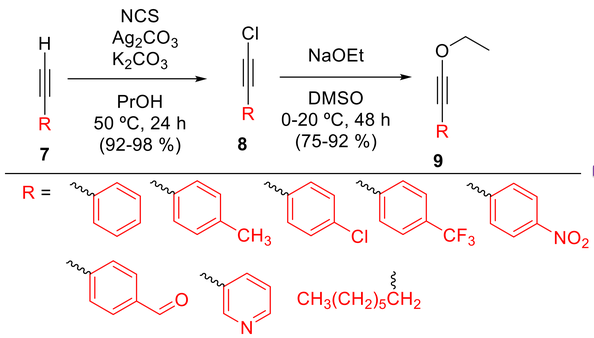
- ❑ Access DCB from phenyltriazolinedione (PTAD, **2**) and alkynyl ethers



- ❑ Access Beta-Lactam from DCB via hydrolysis



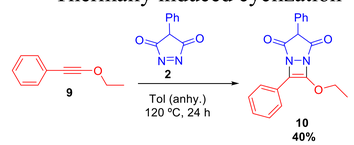
Accessing Alkynyl Ethers



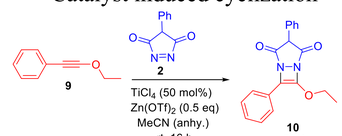
- ❑ Substrate scope investigated so far, however, this would be expanded to include other functional groups in hopes of uncovering more effective molecules.

Accessing DCB

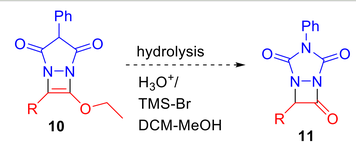
Thermally induced cyclization



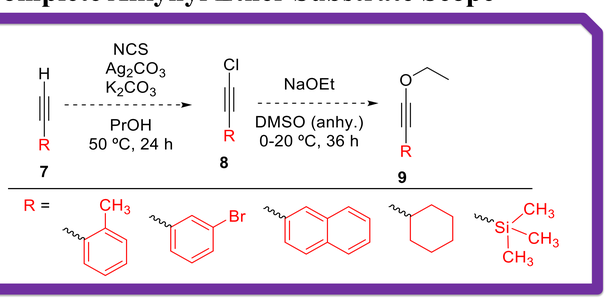
Catalyst induced cyclization



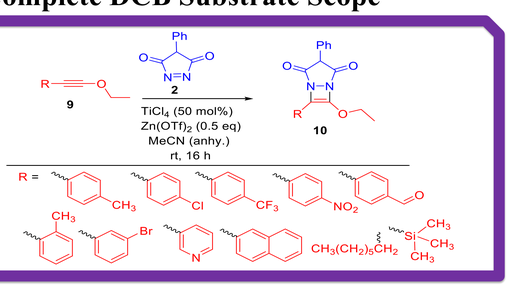
Accessing Beta-Lactam



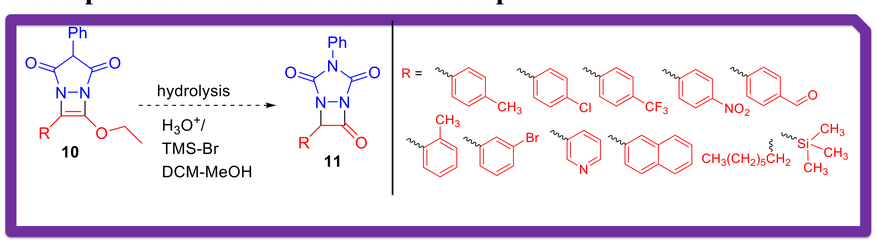
Complete Alkynyl Ether Substrate Scope



Complete DCB Substrate Scope



Complete Beta-Lactam Substrate Scope

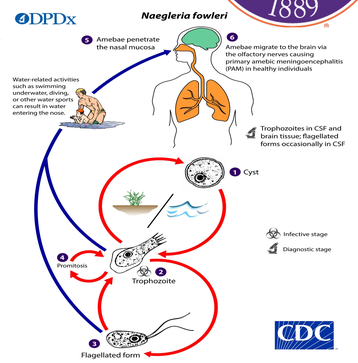


Conclusion

Synthesized molecules will be investigated for their antitrypanosomal activity

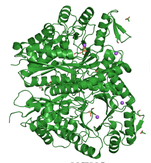
Introduction

- ❑ *Naegleria fowleri* is an amoeba commonly found in warm freshwater (lakes, rivers, and hot springs) and poorly treated water sources.
- ❑ Infection in humans is established when trophozoites from contaminated water enter the nose and travel into the brain.
- ❑ Once infection is established, *Naegleria folweri is* **>95% lethal**. only 5 people have survived infection in North America.

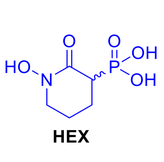


Project Aim

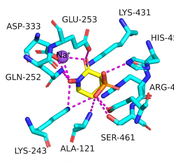
- ❑ *N. fowleri* harbors a single enolase gene (*NfENO)* that plays a crucial role during glycolysis for the survival of the amoeba
- ❑ Our previous study revealed that the human ENO2 phosphonate inhibitor (**HEX**) is a potent inhibitor of *Nf*ENO and is also toxic to the amoebae.
- ❑ The current study explores the structure-activity relationship (SAR) of the HEX scaffold to design new compounds (1-5) guided by favorable binding interactions with the *Nf*ENO active site through molecular modeling



***Nf*ENO**
(PDB 7UGH)



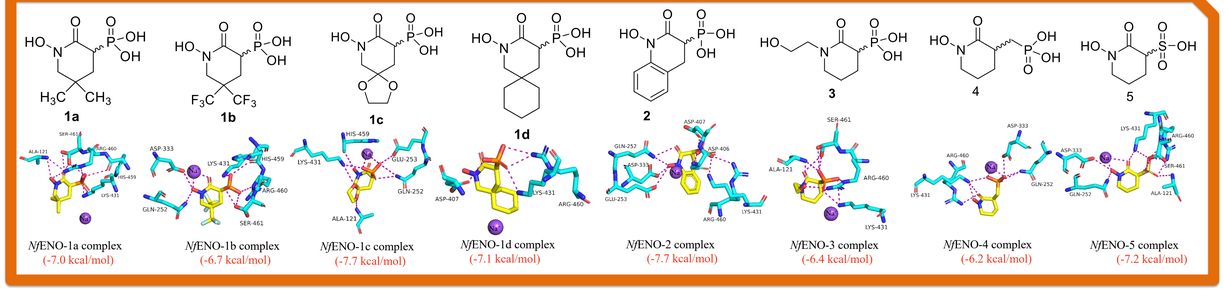
HEX



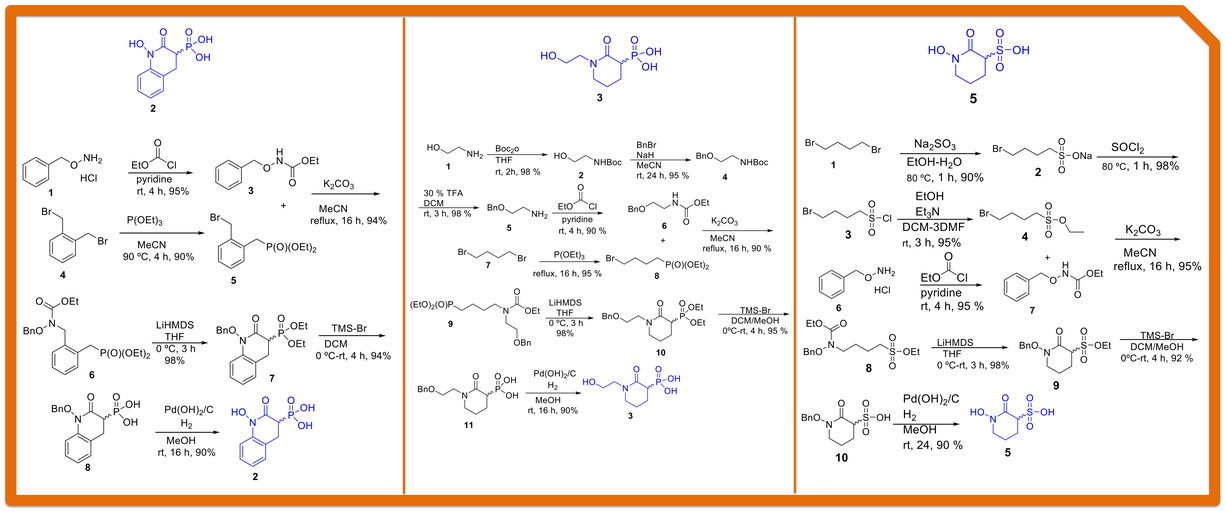
***Nf*ENO-HEX complex**
Binding affinity (-8.9 kcal/mol)

*nf*ENO	IC_{50} (µM)
	0.14 ± 0.04
N. Fowleri	EC_{50} (µM)
	0.21±0.02

New compounds



Synthesis Schemes for compounds 2, 3 and 5



Conclusion

- ❑Small molecule competitive inhibition against *Nf*ENO might impede glucose metabolism in the *N. fowleri* lifecycle stage.
- ❑The *Nf*ENO inhibitors may prove useful for future therapy for *N. fowleri* infections, alone or in concert with other agents.

Acknowledgments

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