Chemistry

Synthesis of Gamma Lactam Analogues of Combretastatin A4

1. **Abstract**

The goal of this research is to access gamma lactam combretastatin A4 analogues. The synthetic route explored to make gamma lactams utilizes beta lactams, the active ring system in penicillin, as precursors. It is hypothesized that gamma lactam combretastatin A4 analogues can be made via cleavage of a certain bond in a beta lactam compound with a strong base, namely Lithium Diisopropylamide (LDA). To make the necessary beta lactams as precursors, specific imines and acid chlorides are necessary. Upon successful synthesis of imine compounds, they will be subjected to the Staudinger cycloaddition method with the appropriate acid chloride to access the respective beta lactams. Imines derived from benzylamine and 3,4,5-trimethoxybenzylamine were recently synthesized and are now ready for further reactivity. The synthesis of the ketene needed for the Staudinger reaction with the imines is currently under investigation.

2. **Description of Research**

Combretastatin A4 is a compound that is isolated from the South African willow tree, *Combretum Caffrum,* this compound is known for bearing key similarities with drugs previously explored such as colchicine, which is used in treating cancer. Each drug has a 3,4,5-trimethoxybenzene as part of the core structure necessary for protein binding.[1] There is strong evidence that the anticancer property exhibited by these compounds is based in their ability to arrest cancer cell growth and development by inhibiting the polymerization of tubulin. Combretastatin A4, however has not been shown to be greatly selective in the cells it attacks, and equally problematic, must be taken at maximum tolerable doses to show effectiveness, also it poses issues of water solubility, and lack of a stable cis over trans conformation. Again, despite the issues at hand, combretastatin A4 serves as a great scaffold for designing many new potential drugs.

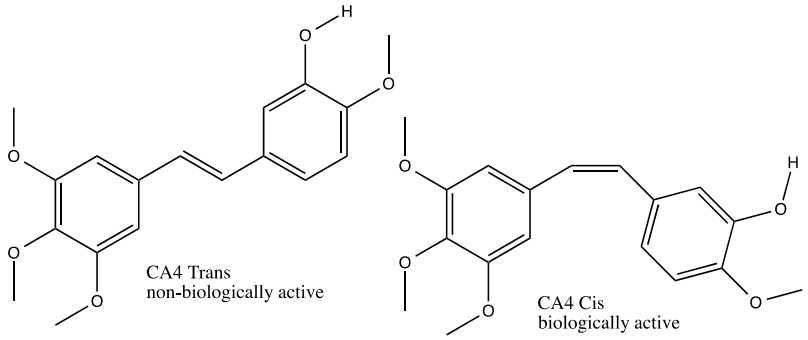

Figure 1. The cis and trans CA4 conformations.

With Gamma lactam combretastatin A4 analogues, this research opens the door to a new variety of combretastatin A4 compounds that my resolve one or more of these key pharmacokinetic issues: stability of the cis form, resistance to metabolism, and maintenance of cytotoxicity are properties of most current consideration. Beta lactam combretastatin A4 analogues have been investigated in other research groups, in many cases with reasonable success.[2]Beta lactams are four membered cyclic amides and gamma lactams are five membered

cyclic amides, five membered rings have been shown to be a good option for medicinal chemist in place of the ethylene bridge on combretastatin A4 and the resemblance of them to the beta lactam is also encouraging.[3] The method used to obtain the beta lactams is the well established Staudinger 2+2 cycloaddition method.[2]Upon synthesis of gamma lactams analogues of combretastatin A4, revisiting the benzylamines with other functional groups, can be examined, a library of gamma lactams can be synthesized to see which contribute to combatting cancer.[4]

3. Synthetic route

There are 3 core phases of this project that must be performed in order:

Synthesis of Imine, Synthesis of beta lactam, Synthesis of gamma lactam.

Phase 1

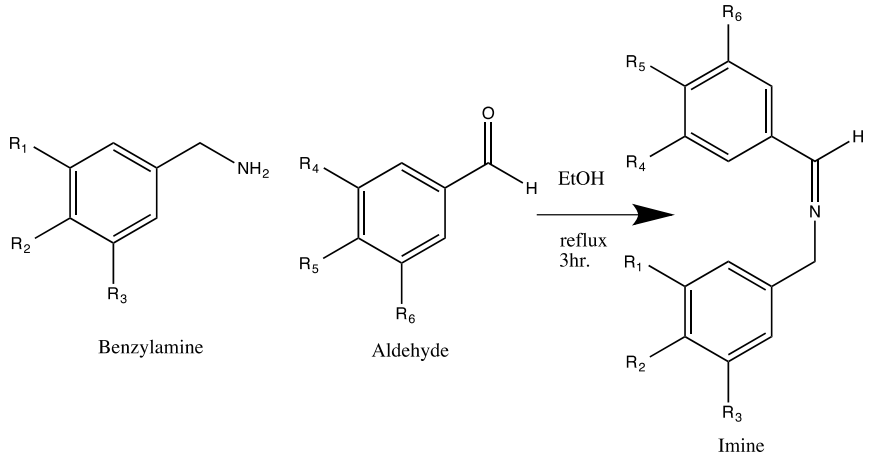

Figure 2. Synthesis of Imine.

Phase 2

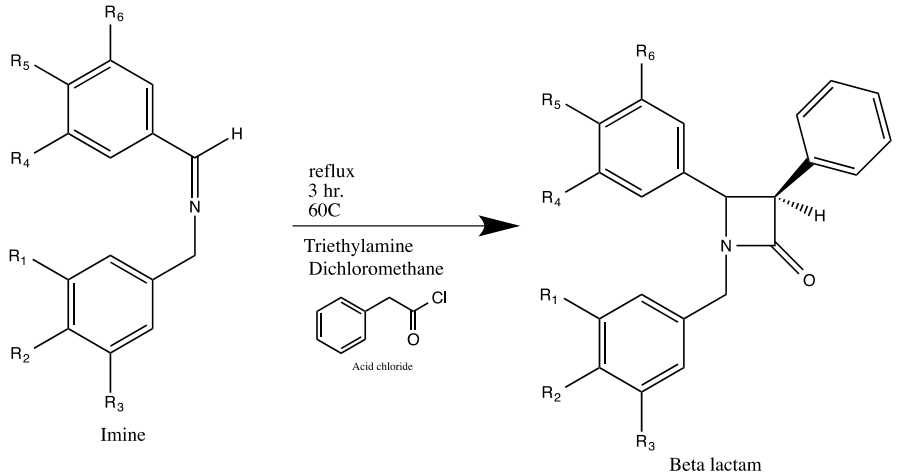

Figure 3. Synthesis of beta-lactam.

Phase 3

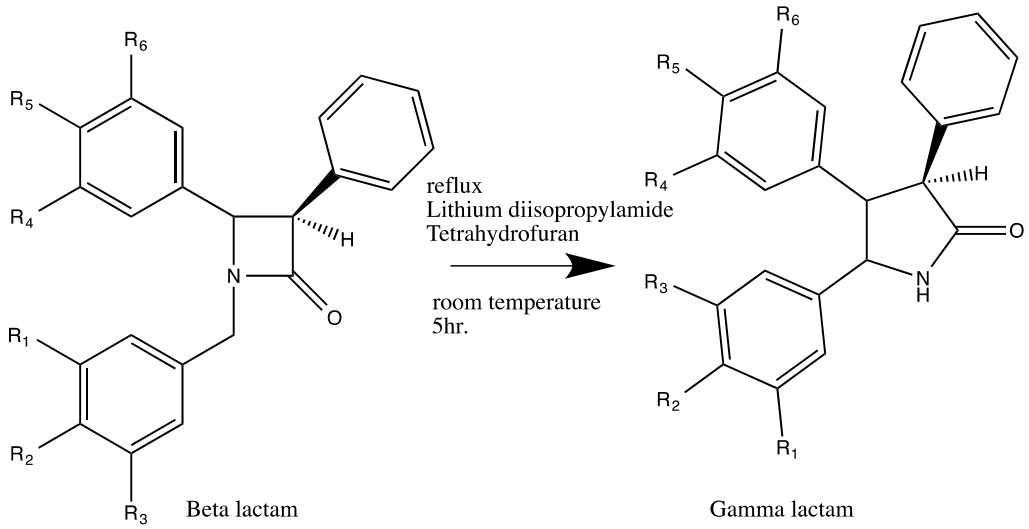

Figure 4. Synthesis of gamma lactam from beta lactam.[5]

4. **Time Period.** The work will take place from August 2014 to May 2015

5. **Budget with Justification**

Lithium Diisopropylamide (LDA)- 100 mL **$37.30**
The only base previously shown in literature
to form gamma lactam from beta lactam.

Diphenylacetylchloride- 25g **$127.50**
Acid chlorides are used to create ketenes
which allow the formation of beta lactams.

3-hydroxy-4 methoxybenzylamine-
hydrochloride (97%)-5g **$126.50**
4-methoxybenzylamine-25g **$41.30**
3,4-dimethoxybenzylamine-25g **$123.30**
these three amines are key precursors in forming
the appropriate imines which are then reacted
with acid chlorides to form
beta lactams.

Total: $455.90

References

1) O'Boyle N.; Carr M.; Greene L.; Et al. Synthesis and Evaluation of Azetidinone Analogues of Combretastatin A-4 as Tubulin Targeting Agents. J. Med. Chem. 2010, 53, 8569-8584.

2) Kamath A.; Joima I. Advances in the chemistry of beta-lactam and its medicinal applications.Tetrahedron. 2012, 68, 10640-10664.

3) Tron G.;Piralie T.; Sorba G.; Et al. Medicinal Chemistry of Combretastatin A4: Present and Future Directions. J. Med Chem. 2006,49, 3033-3044.

4) Jean D.; Fotsch C. Mitigating Heterocycle Metabolism in Drug Discovery. J. Med. Chem. 2012, 55, 6002-6020.

5) Park, J.; Ha J.; Oh, S.; Et al. The stereoselective synthesis of gamma-lactam derivatives through N(1)-C(4) one carbon ring expansion of beta-lactam derivatives. Tetrahedron letters. 2005, 46, 1755-1757.

6. **Are you seeking additional funding from other sources?** Not currently.
7. **Publication outlet.**
   The results will be published in the University of North Carolina at Asheville Journal of undergraduate research, and will be presented to the community at the fall undergraduate research symposium.
8. **Human Subject Form.** No human subjects will be used for this research.