Synthesis of KLVFF-Pyclen for Alzheimer's Disease Treatment

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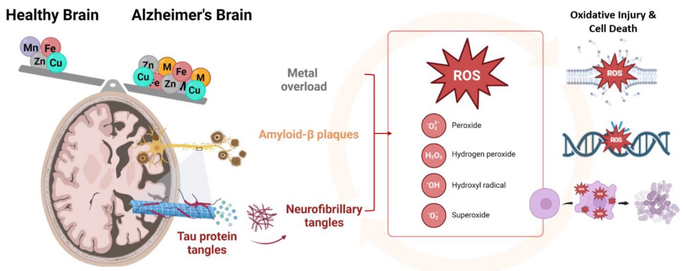
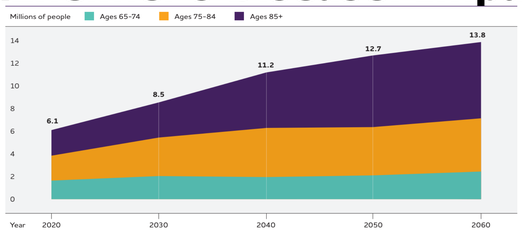
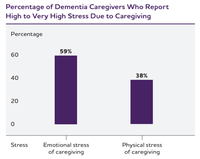
Introduction

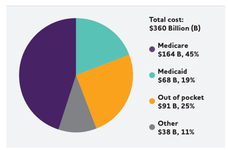
- Alzheimer's Disease (AD): Progressive, neurodegenerative disorder impacting millions.
- Treatments to date have largely focused on slowing the progression of symptoms.
- Hallmarks of disease progression include:



Alzheimer's Disease: Impact







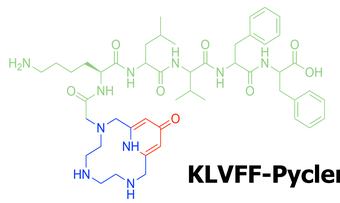
- Figures from *2024 Alzheimer's Disease Facts and Figures*
- AD imposes both a significant personal and economic cost to the health of patients and families
- 13 million expected to have AD by 2050
- Research funding spent on AD research cannot meet the demand

Rationale Design Strategy

- Small peptides have been shown to prevent the formation of amyloid-beta plaques.

Proposed: Chimera molecule composed of plaque preventing KLVFF peptide with a macrocycle that has been shown to both reduce the effects of reactive oxygen species (ROS) and bind transition metal ions.

Goal: Three-pronged approach for the treatment of AD through prevention of amyloid plaques, ROS, and mis-regulated transition metal ions.



KLVFF-Pyclen

= radical scavenger

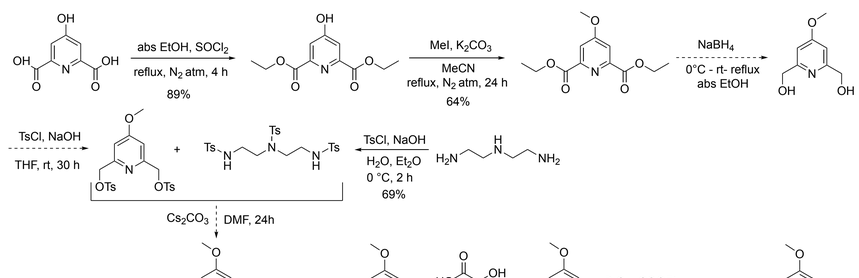
= metal chelator

= amyloid plaque inhibitor

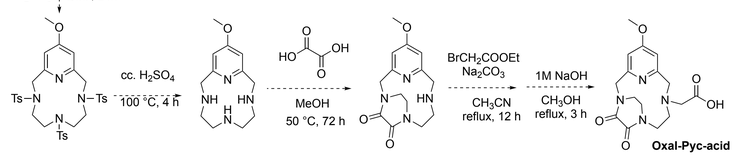
Future Testing

- PAMPA Assay
- DPPH Assay
- CACO-2 Assay
- Metabolic Stability

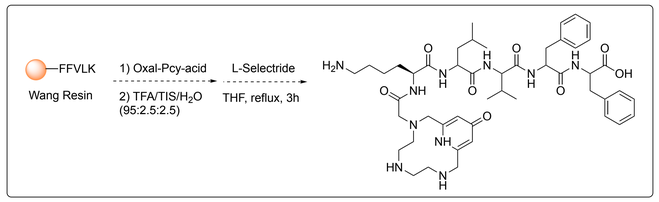
Proposed Synthetic Scheme for Pyclen-KLVFF



Cyclization

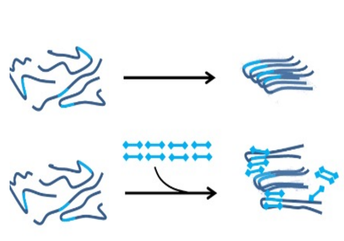


Solid Phase Synthesis and Cleavage from Resin



Advantages of KLVFF

- KLVFF has been shown to disrupt amyloid beta protein aggregation through interacting with regions of the amyloid beta protein
- KLVFF is amino acids 16-20 of the amyloid beta protein, allowing it to disrupt interactions in aggregation
- KLVFF has also been shown to pass the blood brain barrier through RAGE receptors, which are over expressed in AD



References

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- Huang, Q. *et al. ACS Omega* **2019**, *4(2)*, 4233-4242.
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- 2024 Alzheimer's Disease Facts and Figures. *J. Alzheimer's Assc.* **2024**, *20,5*, 3708-3738.

Acknowledgments

- TCU SERC Grant
- TCU Department of Chemistry & Biochemistry