



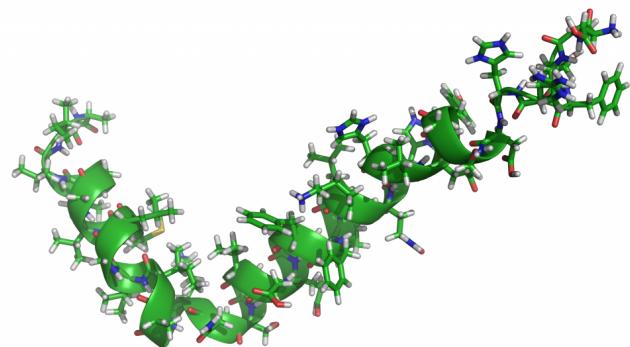
# Enhancing the therapeutic potential of heterocyclic ligands for treating Alzheimer's disease

NISHANTH SADAGOPAN

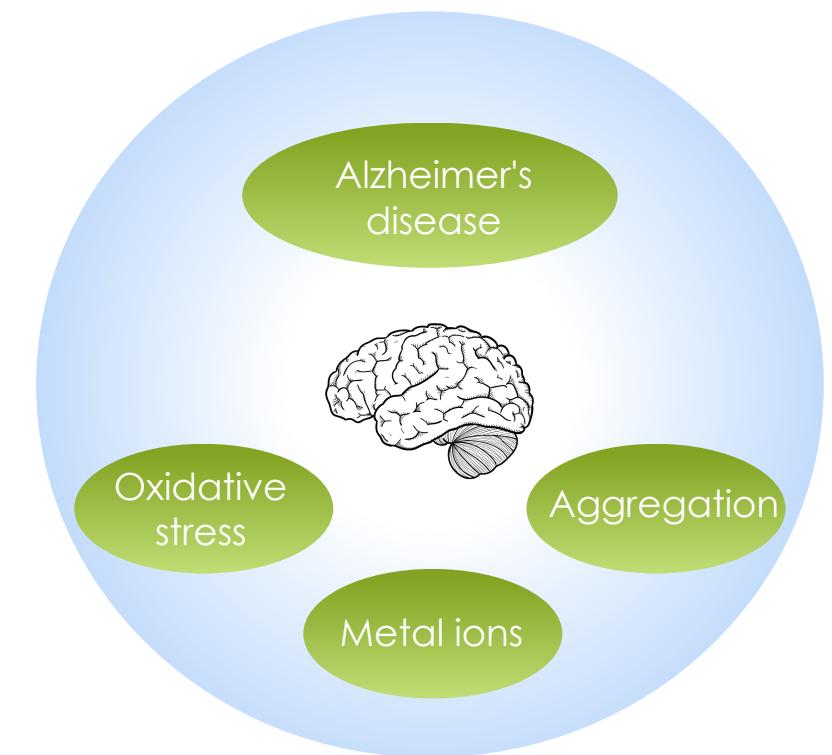
DEPARTMENT OF CHEMISTRY & BIOCHEMISTRY

# Alzheimer's Disease

- ▶ Affects over 5 million people
- ▶ Currently no approved treatments
- ▶ Hallmarks:
  - ▶ Oxidative stress
  - ▶ Metal dysregulation
  - ▶ Protein aggregation

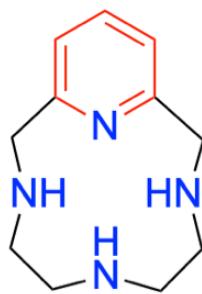


Amyloid Beta Peptide

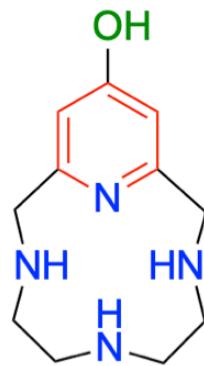


# Functionality of Green Group Macrocyclic Ligands

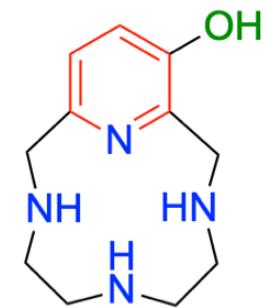
- ▶ Green Group heterocyclic library
  - ▶ Metal chelating nitrogen centers
  - ▶ Antioxidant pyridine rings
  - ▶ Radical scavenging hydroxyl groups



L1



L2



L3



L4

# Parameters Assessing Blood Brain Barrier Permeability Potential

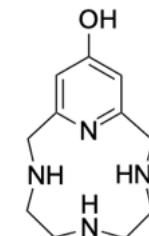
- ▶ Molecular weight (MW)
- ▶ Calculated logarithm of the octanol-water partition coefficient (clogP)
- ▶ H-bond donors & H-bond acceptors (HBD & HBA)
- ▶ Polar surface area (PSA)
- ▶ Logarithmic ratio of the concentration between the brain and blood (logBB)

Compound	MW	clogP	HBA	HBD	Number of Lipinski Violations	PSA (Å)	logBB
Lipinski's Rules & Other Parameters	≤ 500	≤ 5.0	≤ 10	≤ 5	≤ 1	≤ 90	> 3.0 (readily); ≤ -1.0 (poorly)

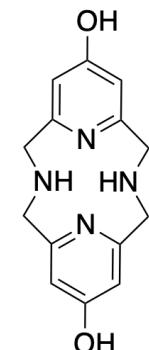
# BBB Computational Study of L2 and L4

**Table 1. Values of L2 and L4 (MW, clogP, HBA, HBD, Number of Lipinski Violations, PSA, logBB)**

Compound	MW	clogP	HBA	HBD	Number of Lipinski Violations	PSA (Å)	logBB
L2	222.3	-0.5	5	4	0	69.2	-0.961
L4	272.3	0.38	6	4	0	90.29	-1.140
Lipinski's Rules & Other Parameters	≤ 500	≤ 5.0	≤ 10	≤ 5	≤ 1	≤ 90	> 3.0 (readily); ≤ -1.0 (poorly)



L2

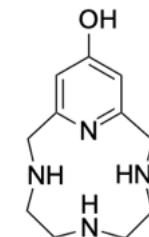


L4

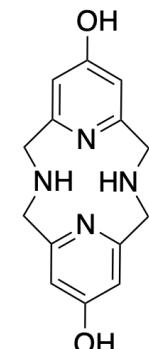
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L2



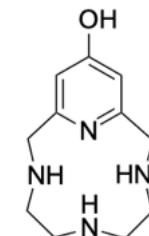
L4

# BBB Computational Study of L2 and L4

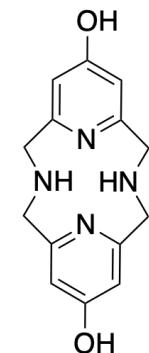
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$$\text{logBB} = (-0.0148 \times \text{PSA}) + (0.152 \times \text{clogP}) + 0.139$$



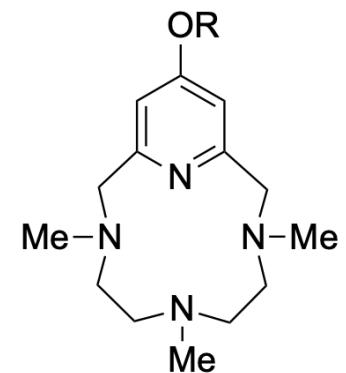
L2



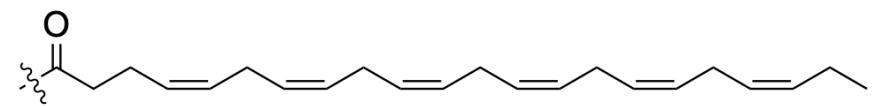
L4

## Project Goal: Increase BBB Permeability of Macrocycles

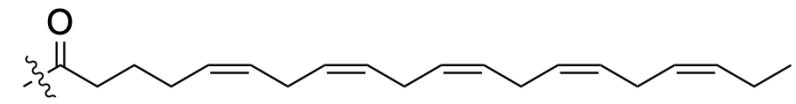
- ▶ Focus on L2
- ▶ Fatty acid appendage:
  - ▶ Increased lipophilicity
- ▶ Methylation
  - ▶ Decreased polar surface area



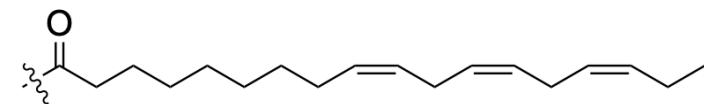
R =



**Docosahexaenoic acid (DHA)**



**Eicosopentaenoic acid (EPA)**

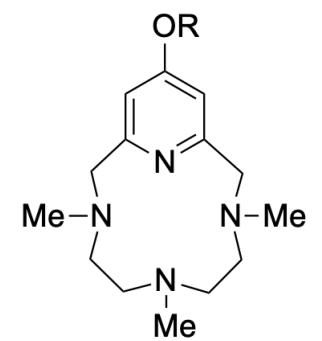


**Alpha-linolenic acid (ALA)**

# BBB Computational Study of Methylated-L2 with Fatty Acids

**Table 3. Values of Me-L2 with Fatty Acids (MW, clogP, HBA, HBD, Number of Lipinski Violations, PSA, logBB)**

Compound	MW	clogP	HBA	HBD	Number of Lipinski Violations	PSA (Å)	logBB
L2	222.3	-0.5	5	4	0	69.2	-0.961
Me-L2 with DHA	574.4	7.44	6	0	2	48.38	0.554
Me-L2 with EPA	548.8	6.92	6	0	2	48.38	0.475
Me-L2 with ALA	524.4	6.73	6	0	2	48.38	0.446
<b>Lipinski's Rules &amp; Other Parameters</b>	≤ 500	≤ 5.0	≤ 10	≤ 5	≤ 1	≤ 90	> 3.0 (readily); < -1.0 (poorly)

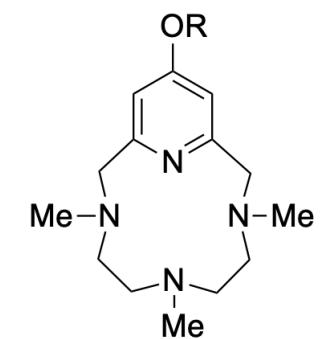


R = DHA, EPA, ALA

# BBB Computational Study of Methylated-L2 with Fatty Acids

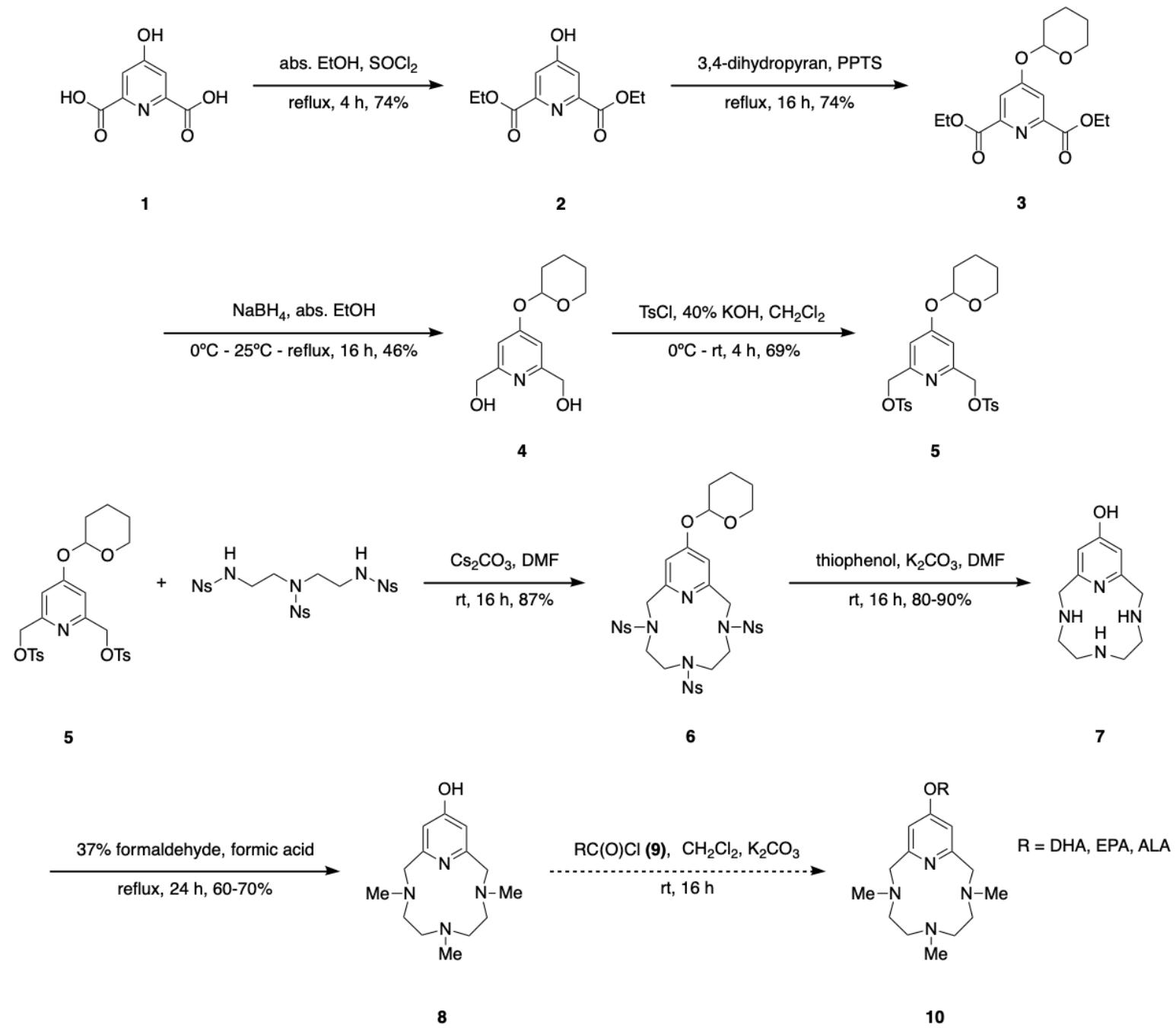
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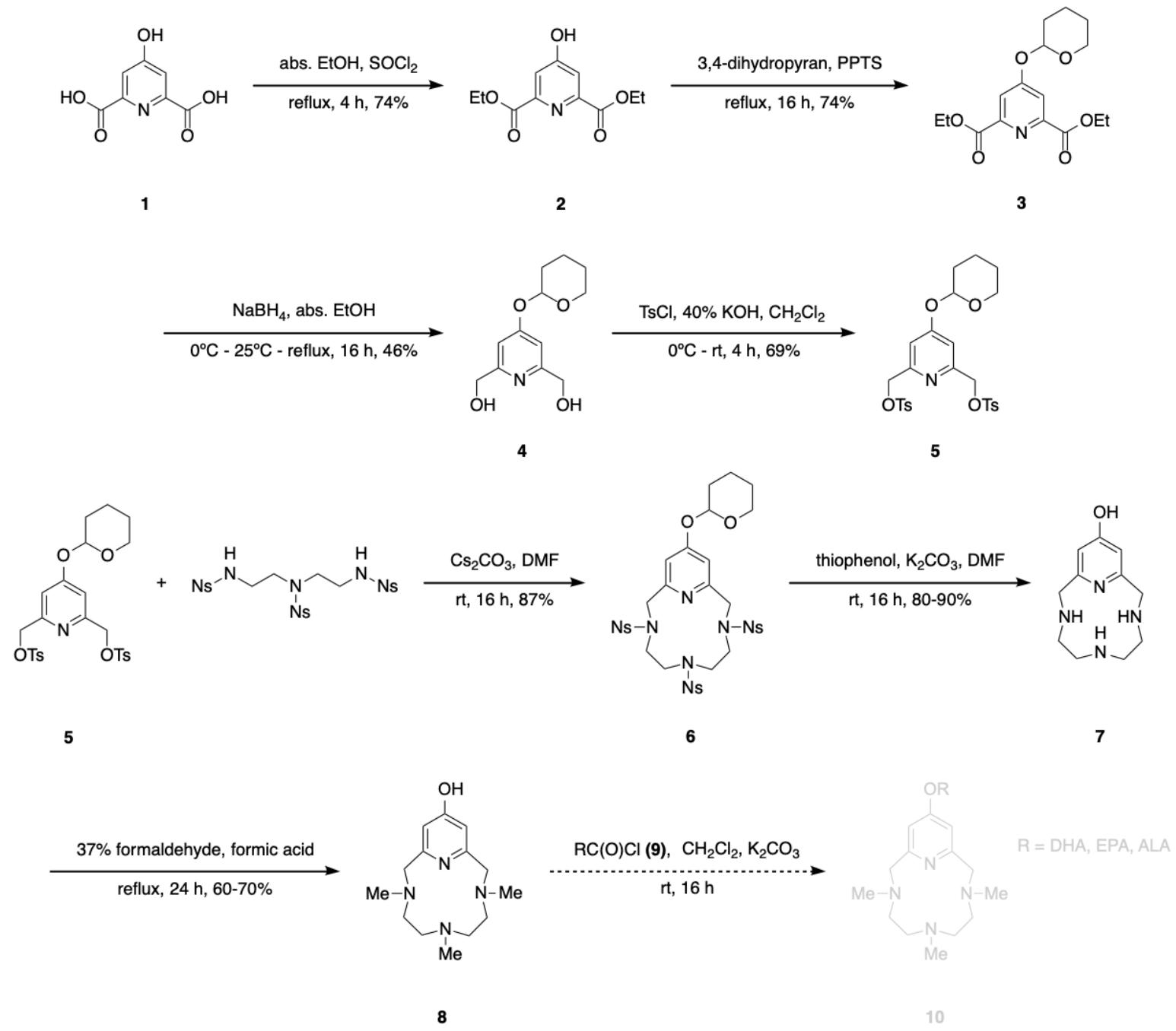


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# Synthetic Pathway and Results

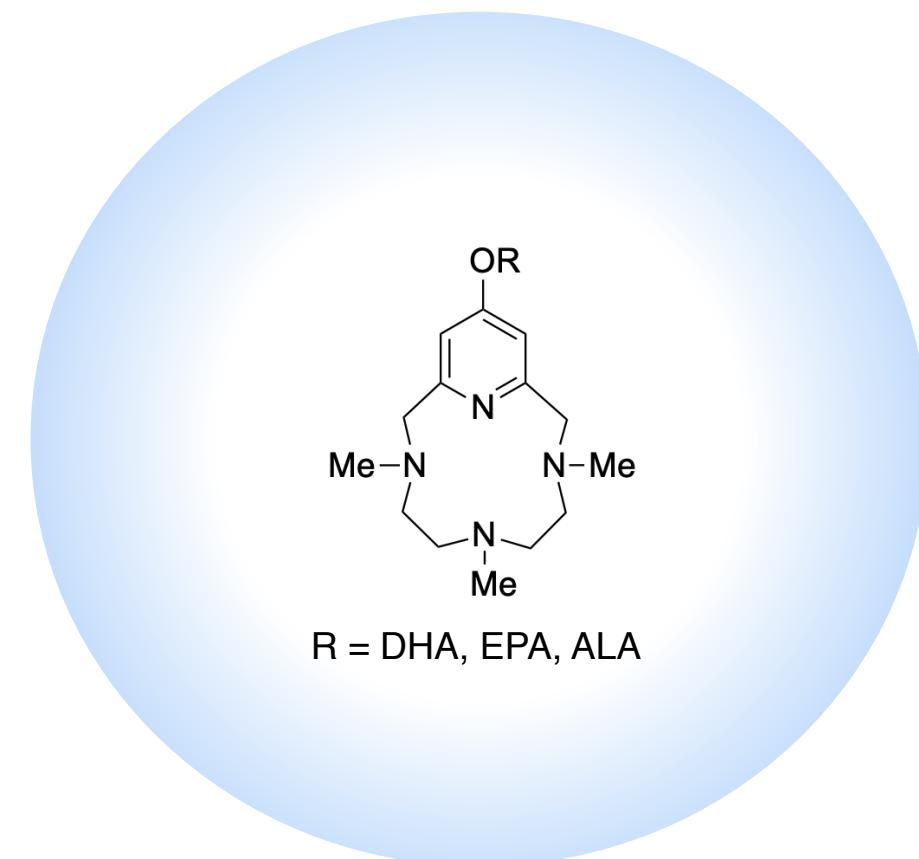


# Synthetic Pathway and Results



# Conclusions, Future Work, and Impact

- ▶ Conclusions
  - ▶ Computational analyses
  - ▶ Omega-3 fatty acid appendage
- ▶ Future Work
  - ▶ Finish synthesis of target molecule
- ▶ Impact
  - ▶ Enhance BBB permeability of ligands
  - ▶ Deliver therapeutics patients with AD



# Acknowledgements

► Special thanks to all of the members of our team!

- Dr. Kayla Green      ► Tim Schwartz
- Dr. Sugam Kharel    ► Katie Smith
- Kristof Pota           ► Emily Hoffer
- Magy Mekhail          ► Nam Nguyen
- David Freire           ► Diandria Veals
- Chelsea Miller



## Resources & Funding

