Investigation of Suzuki-Miyara Coupling as a Synthetic Route Towards the Development of Novel Alzheimer's Disease Therapeutics

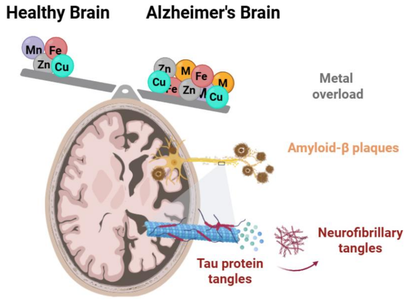
Killian Lyon, Jack Bonnell, Davis Wagnon, Kayla N. Green

Department of Chemistry & Biochemistry - Texas Christian University

Abstract

Alzheimer's Disease (AD) is a neurodegenerative terminal disease that affects 11% of Americans who are 65+ years old. The progression of AD has been associated with the **dysregulation of reactive oxygen species (ROS)** via multiple mechanisms, resulting in oxidative stress and neuronal damage. One of the focuses of the Green Lab at TCU is the development of PyN_3 pyridinophanes that act as antioxidants to counter the effects caused by unregulated ROS. While most compounds synthesized within the lab both have antioxidant characteristics and activate the Nrf2 pathway, they face the **issue of having poor permeability to the Blood Brain Barrier (BBB)**, making them unable to deliver the therapeutic effects to the diseased neurons. To counter this deficit, the series of molecules proposed herein aim to **increase the lipophilicity of the base PyN_3** molecules while maintaining or increasing their antioxidant potential. In pursuit of these aims, we aimed to utilize **Suzuki-Miyara-like carbon-carbon bond formation** to add aromatic, lipophilic, antioxidant moieties to the para position of the parent PyN3 molecule. Computational studies including the **BOILED-Egg plot** were used to identify these synthetic targets for probable BBB permeability with the goal of highlighting a new route in drug synthesis to increase the delivery of active compounds to target tissues past the BBB.

What Causes Neurodegenerative Disease?



Iron and Copper generate ROS causing:

- Direct killing of neurons
- Amyloid-β plaque build up
- Damage to metal-binding proteins

Parent PyN_3 Design

Characteristics:

1) Suppresses free radicals with self-stabilization
2) Binds to unregulated metals cations, preventing free radical formation

Challenge:

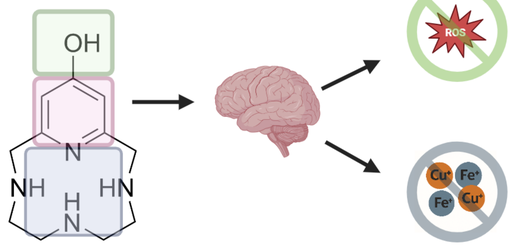
- Unable to pass through the Blood Brain Barrier

Motivation for Future Pyridinophanes Derivatives

Antioxidant Radical Scavenger

Free Radical Stabilization

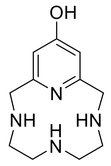
Metal Chelation Binding



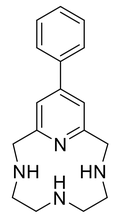
Introduction to Novel Compound: Phenyl-PyN_3 via Suzuki-Miyara Coupling

OH-PyN_3

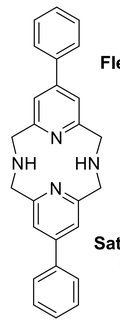
(Parent Molecule)

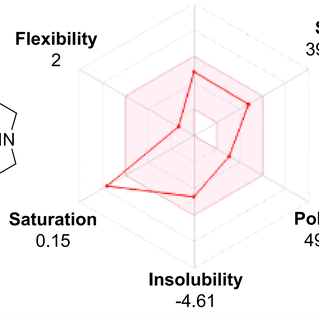


Phenyl-PyN_3



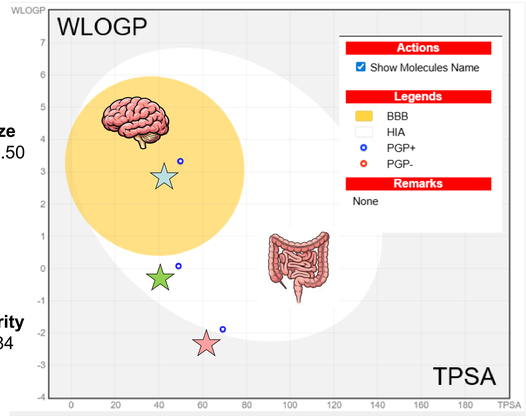
Phenyl-Py_2N_2





SwissADME BOILED-Egg Plot:

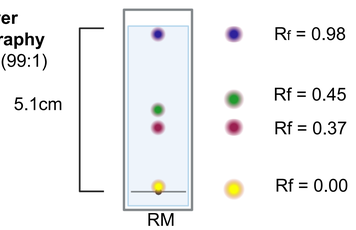
- Predicts the ability of molecular compounds to cross into the Blood Brain Barrier
- Analyzes molecule based on two qualities:
  - WLOGP – lipophilicity
  - TPSA – topological polar surface area
- PGP – Efflux Pump within BBB
  - PGP+ means molecule actively gets pumped out of BBB
  - PGP- means molecule remains in the brain once originally transported across BBB

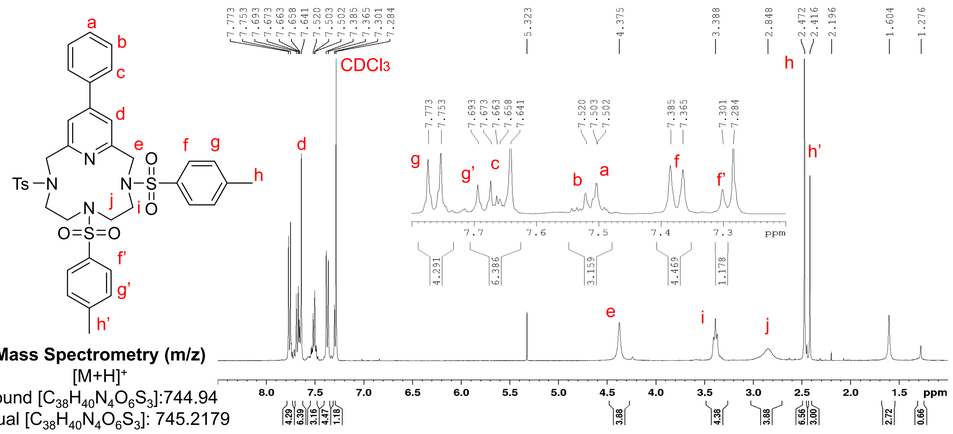


Phenyl Coupling Reaction Analysis

- Sample of Ph-PyN_3 (Tosylated)
- Yield by Mass Percent: 96%
- Characterization Methods:
  - Mass Spectrometry
  - ^{1}HNMR
  - ^{13}CNMR
  - DEPT-135
  - COSY-4SW
  - HSQC

Thin Layer Chromatography
DCM:MeOH (99:1)





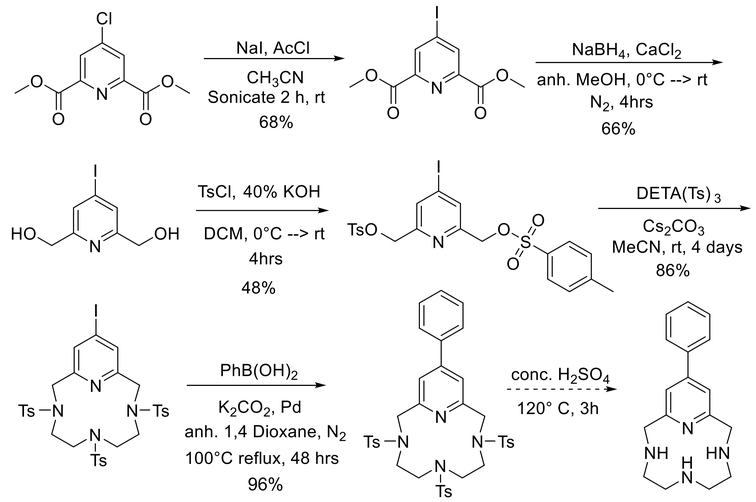
Mass Spectrometry (m/z)

$[M+H]^+$

Found $[C_{38}H_{40}N_4O_6S_3]$:744.94

Actual $[C_{38}H_{40}N_4O_6S_3]$: 745.2179

Synthetic Methods



- Each intermediate was isolated as white/tan solids and characterized by ^{1}H NMR.
- Steps 1-4 are well established at the multigram Scale
- Step 5 was initially run at a milligram scale and has since been raised to multigram scale with 20% catalytic load.

Future Directions

1. **Obtain final product of Ph-PyN_3 and Ph-Py_2N_2**
2. **Full characterization: ^{1}H, ^{13}C NMR; MS; pK_a, log β (Cu^{2+}, Mn^{2+}, Fe^{2+}, Zn^{2+})**
3. **Measure Permeability: PAMPA (BBB) and Caco-2 (Intestinal) Models**
4. **Metalate with Cu(II): Evaluate SOD Activity**
5. **Determine HT-22 (neuronal cell) protection against ROS**
6. **Evaluate Nrf2 Activity**

Acknowledgements

BOILED EGG PLOT - Daina, A.; Michielin, O.; Zoete, V. *SwissADME*. http://www.swissadme.ch (accessed 2026-03-10).

Alzheimer's Demographic (Abstract) - Alzheimer's Association. *2025 Alzheimer's Disease Facts and Figures.* Alzheimer's Dement. **2025**, *21* (5).

ROS Destruction (Abstract) - Barnham, K. J.; Masters, C. L.; Bush, A. I. *Neurodegenerative Diseases and Oxidative Stress.* Nat. Rev. Drug Discov. **2004**, *3*, 205–214.

Select Graphics produced using - BioRender