‘Fine-Tuning’ Potential Alzheimer’s Therapeutics through Pyridinophane Substitution

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Abstract

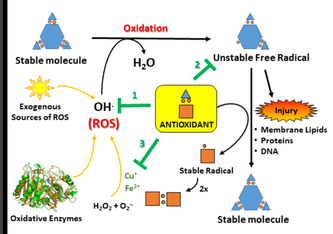
Pyridinophane molecules have recently been shown to have both antioxidant and pharmacological properties suitable for therapeutic applications targeting neurodegenerative diseases, including Alzheimer’s (AD). We are currently synthesizing derivatives of a parent pyridinophane (**P1**), substituting a quinoline moiety on the pyridine ring (**L1**), on the ‘side’ of the macrocycle (**L2**), and on the ‘bottom’ of the macrocycle (**L3**), all of which are designed to increase the antioxidant activity and blood-brain barrier permeability beyond that of the parent molecule in hopes of producing a molecule suitable for pharmacological testing in animal models.

ROS, Metal Ions & Alzheimer's Disease

Alzheimer's Disease[3]

- **6+ million** Americans live with Alzheimer’s
- **$345 billion** in treatments for Alzheimer patients in 2023
- **11 million** Americans provide unpaid care for people with Alzheimer’s
- **18 billion** hours of unpaid care valued at **$339.5 billion**

Proliferation of ROS[1]

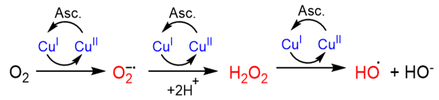


Examples of Antioxidant Properties of Therapeutics to date

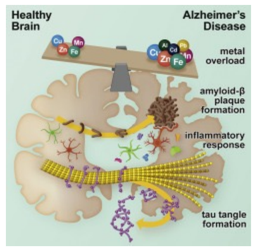
(1) Quench ROS

(2) Donate H· species

(3) Chelate Transition Metals



Transition Metal Ion Imbalance[2]



Binds Metal Ions to Prevent...

(1) Aβ Formation

(2) Generation of ROS through redox cycling of transition metal ions

[1]de Oliveira Silva, E.; Batista, R. Ferulic Acid and Naturally Occurring Compounds Bearing a Feruloyl Moiety: A Review on Their Structures, Occurrence, and Potential Health Benefits. *Comprehensive Reviews in Food Science and Food Safety* **2017**, *16* (4), 580–616.

[2]Huat, T. J.; Camats-Perna, J.; Newcombe, E. A.; Valmas, N.; Kitazawa, M.; Medeiros, R. Metal Toxicity Links to Alzheimer's Disease and Neuroinflammation. *Journal of Molecular Biology* **2019**, *431* (9), 1843–1868.

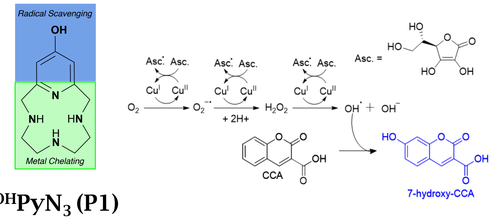
[3]Alzheimer's Association 2023

Antioxidant Pyridinophane

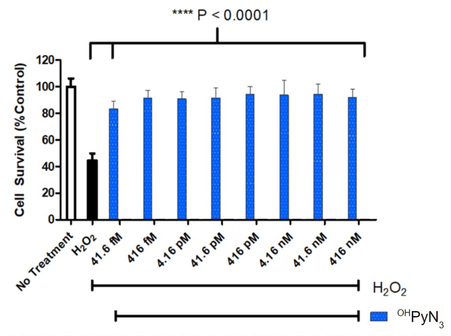
Reactive Properties

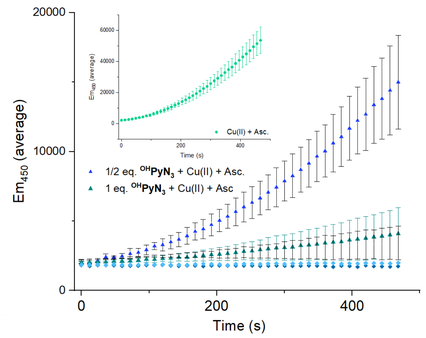
a) Radical Scavenger
- Inherent Activity

b) Metal Chelator (log β = 19.16)
- Stops Redox Cycling



$^{OH}PyN_3$ **(P1)**



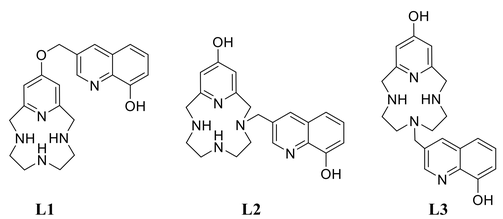


Goal: Determine how substitution impacts reactivity (radical scavenging, metal chelating) and blood-brain barrier permeability.

Rational Design of New Pyridinophanes

Problem: Lipinski’s Parameters and experimental data for $^{OH}PyN_3$ predict poor BBB Permeability

Compound	MW	clogP	TPSA (Å)	GI Absorption	BBB Permeant	Calc. logBB
$^{OH}PyN_3$	222.3	-0.38	69.21	High	No	-0.94

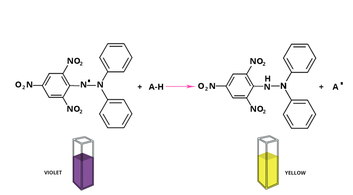


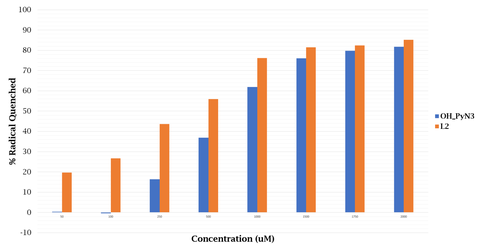
Hypothesis: Installing a quinoline moiety will retain the properties of the parent but improve permeability and other pharmacological properties.

Approach: Multiple points of attachment are possible. Study the impact of each congener to determine the impact of chemical and reactivity properties.

Series Characterization

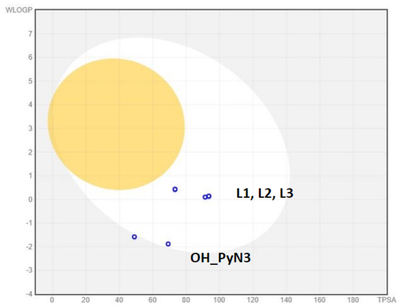
Radical Scavenging - DPPH Assay:





BBB Permeability – Lipinski’s Parameters

Compound	MW	clogP	TPSA (Å)	GI Absorption	BBB Permeant	Calc. logBB
$^{OH}PyN_3$	222.3	-0.38	69.21	High	No	-0.94
L1	379.5	1.23	91.33	High	No	-1.03
L2	379.5	1.03	93.54	High	No	-1.09
L3	379.5	1.05	93.54	High	No	-1.09



WlogP: Water Partition Coefficient
TPSA: Topological Polar Surface Area

Metal Chelating – Chelating Equilibrium Quotients

	Equilibrium quotient	$^{OH}PyN_3$	L2
Cu(II)	[ML]/([M][L])	19.16	21.61

Upon synthesis, we plan to characterize **L1** & **L3** according to the assays above.

Future Goals

The lab aims to continue characterizing ‘series’ of substitutions in the hope of establishing a principle behind substitution location and pyridinophane reactivity.

Acknowledgements

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SciCom Let's Talk Science