Impacts of Indole Moiety Location on Pyridinophane Activity

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Abstract

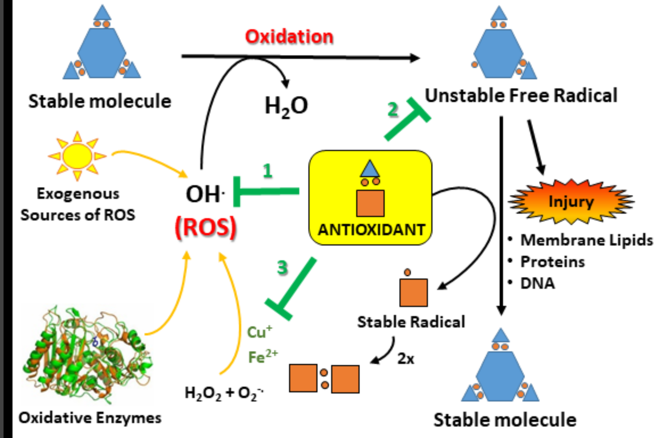
Pyridinophane molecules have recently been shown to have both antioxidant and pharmacological properties suitable for therapeutic applications targeting neurodegenerative disease (ND), including Alzheimer's. We have synthesized derivatives of the parent molecules with substitutions on the pyridine ring (**L1**) or on the 'side' of the macrocycle (**L2**) designed to increase the antioxidant activity beyond that of the parent molecule in hopes of producing a molecule suitable for pharmacological testing in animal models. The lab is currently working towards substituting on the 'bottom' of the macrocycle (**L3**) to characterize and compare substitutions at each of the three positions.

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]



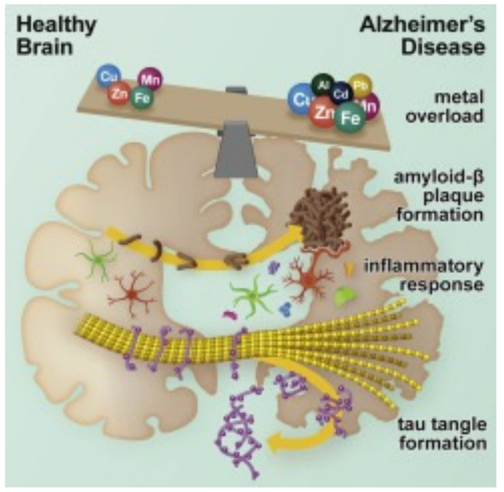
Examples of Antioxidant Properties of Therapeutics to date

(1) Quench ROS

(2) Donate H· species

(3) Chelate Transition Metals

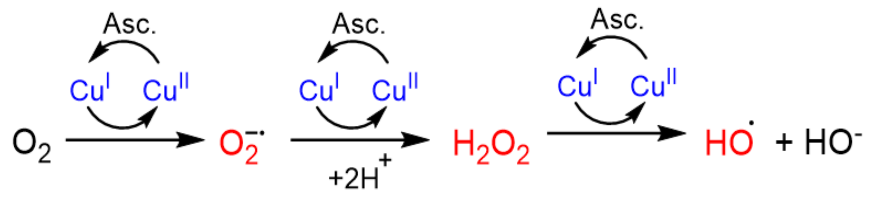
Transition Metal Ion Imbalance[2]



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

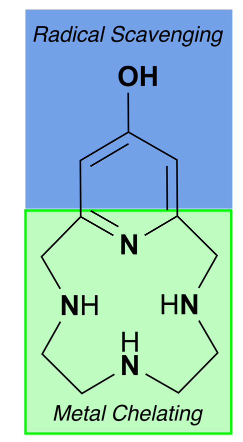
Antioxidant Pyridinophane

Reactive Properties

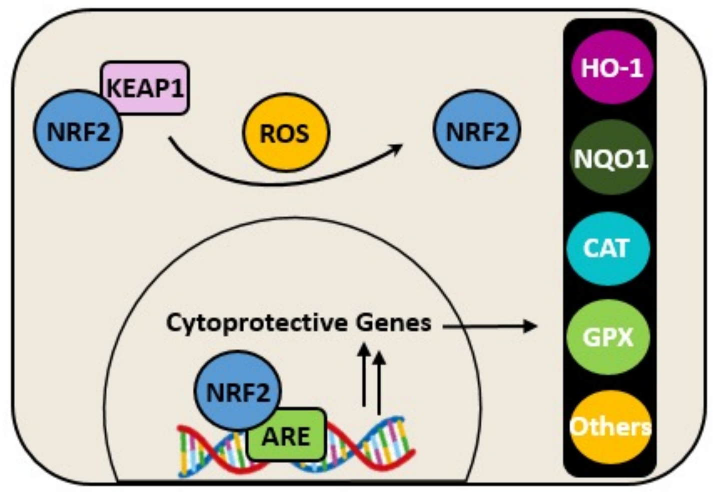
a) Radical Scavenger
   - Inherent Activity

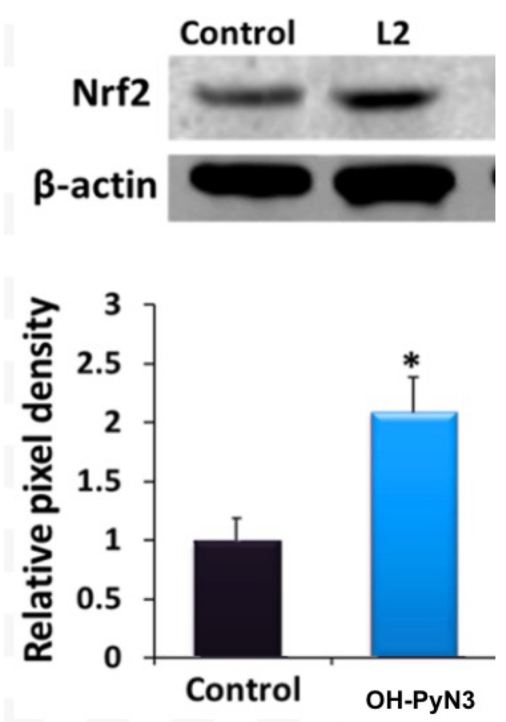
b) Metal Chelator (log β) = 19.16
   - Stops Redox Cycling

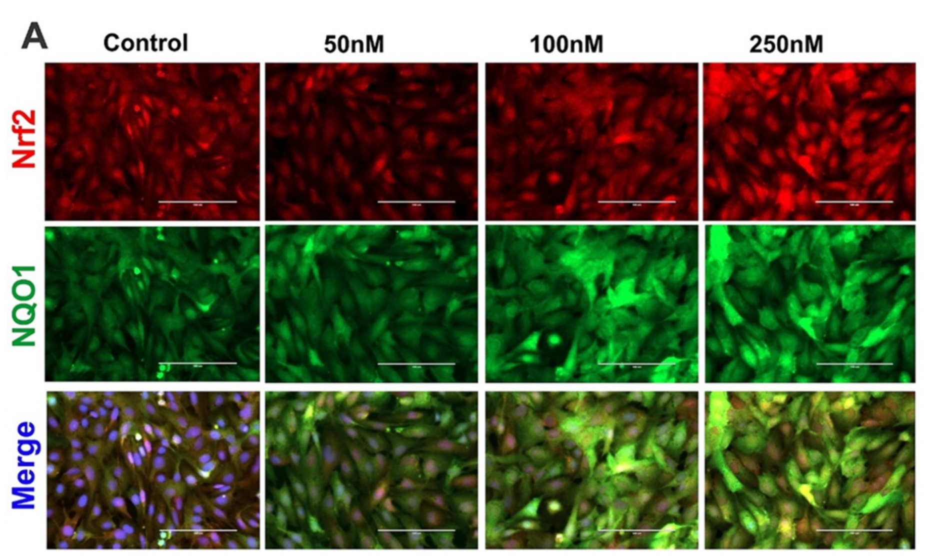
c) Nrf2 activation
   - Catalytic Activity



$^{OH}PyN_3$







Exposure to $^{OH}PyN_3$:

1) Nrf2 Activation

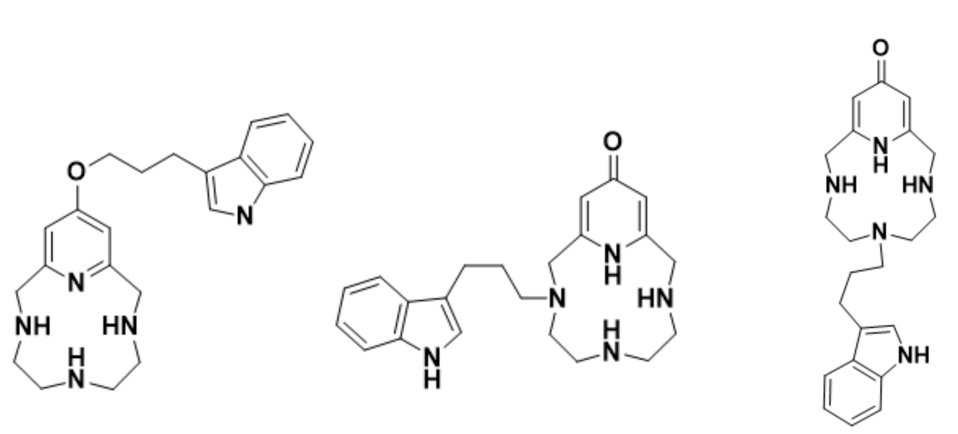
2) Cytoprotective Gene Expression

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	clog P	HBA	HBD	PSA (Å)	log BB	-log P_e	log D	Caco-2
$^{OH}PyN_3$	222	-0.34	5	4	68.7	-0.93	>8	ND	ND
Lipinski's Rules, Other Parameters	≤ 450	≤ 5.0	≤ 10	≤ 5	≤ 90	>3 BBB+, <-1 BBB-	-log P_e < 5.4 (CNS+) -log P_e > 5.7 (CNS-)		



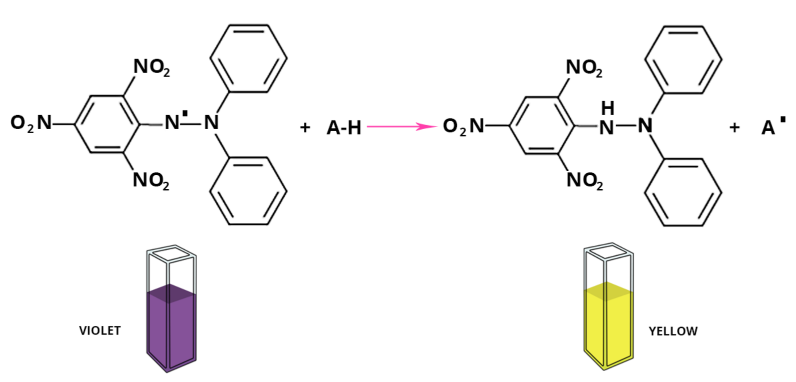
L1 L2 L3
In Progress

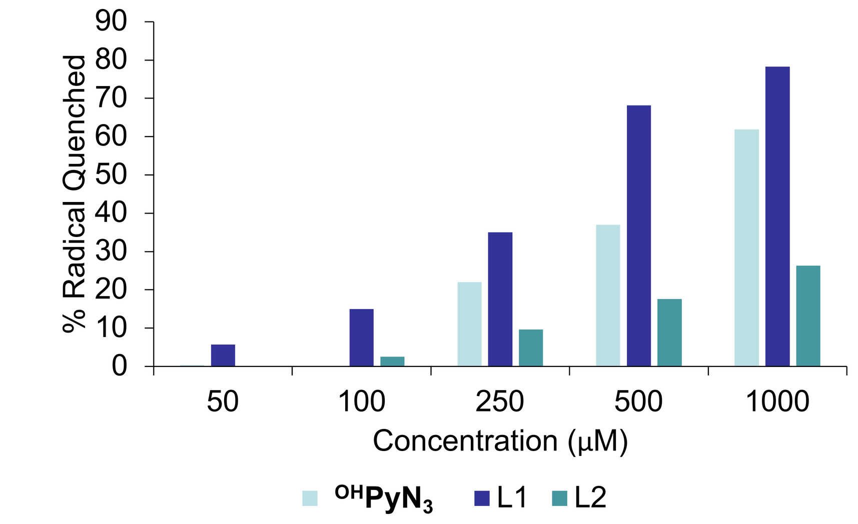
Hypothesis: Installing a indole moiety will retain the properties of the parent but improve permeability and other pharmacological properties.

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:





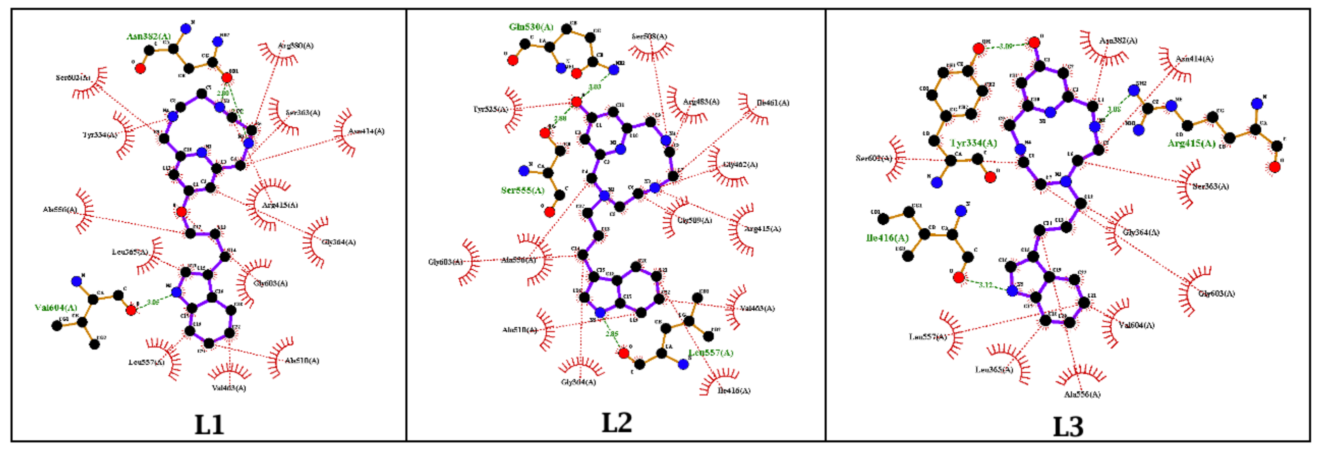
BBB Permeability – Lipinski's Parameters

	MW	clog P	HBA	HBD	PSA (Å)	log BB	-log P_e	Log D	Caco-2
L1	379.508	1.9	5	4	48.45	-0.57	6.08 ± 0.33	-0.71 ± 0.04	8.29×10^{-8}
L2	378.501	-0.6	6	3	70.5	-0.996	6.04 ± 0.12	0.58 ± 0.07	3.0×10^{-6}

Metal Chelating – Protonation Constants & Chelating Equilibrium Quotients

	Equilibrium quotient	$^{OH}PyN_3$	L1	L2
Cu(II)	[ML]/([M][L])	19.16	19.821(3)*	>19

Nrf2 Activation – Docking Computation Predictions with Keap1



	Nrf_2	L1	L3	L2
Tyr 334	✓	✓	✓	-
Ser 363	✓	✓	✓	-
Arg 380	✓	✓	-	-
Asn 382	✓	✓	✓	-
Arg 415	✓	✓	✓	✓
Arg 483	✓	-	-	-
Ser 508	✓	-	-	-
Tyr 525	✓	-	-	-
Tyr 572	✓	-	-	✓

Upon synthesis, we plan to characterize **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