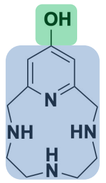
Exploration of Radical Scavenging Reactivity in Substituted Pyridinophane Ligands for Alzheimer's Disease Therapeutics

CHRISTINA MANTSOROV, KATHERINE SMITH, DAVID FREIRE, KRISTOF POTA, Ph.D., MAGY MEKHAIL, Ph.D., and KAYLA N. GREEN, Ph.D.
GREEN RESEARCH GROUP, DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY AT TEXAS CHRISTIAN UNIVERSITY, FORT WORTH, TX USA

INTRODUCTION

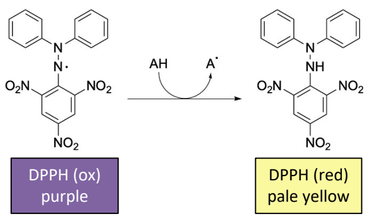
- Reactive oxygen species (ROS): Atoms/molecules that contain unpaired valence electrons and at least one oxygen within their structure.
- Necessary: Natural metabolic byproduct and serve important functions in cellular processes, including homeostasis and cell signaling.
- Mis-regulation: Severe damage to cells and membranes, can lead to neurological diseases like Alzheimer's Disease (AD).
- Radical scavengers: Substances that react with ROS to neutralize them and make them less reactive.
- Natural Antioxidant Sources Include:

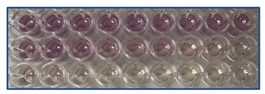


Synthetic Antioxidant $^{OH}PyN_3$

DPPH• ASSAY

DPPH (2,2-diphenyl-1-picrylhydrazyl) Assay: Used to predict antioxidant activity through free radical scavenging capacity.

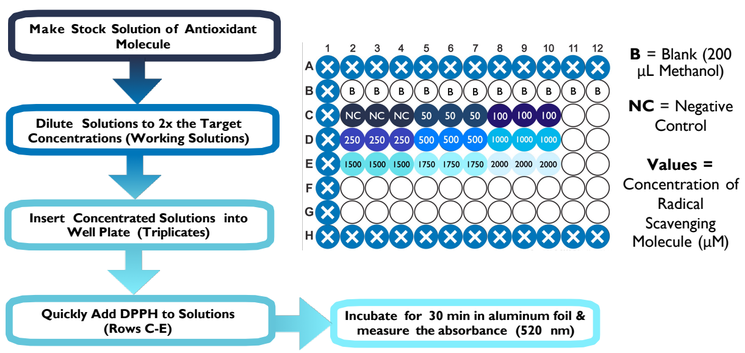




Main Questions to be Addressed:

1. Do the synthetic antioxidant molecules react with DPPH to demonstrate radical scavenging reactivity?
2. IF YES, what is each molecules effect on DPPH at various concentrations?

INITIAL PROCEDURE

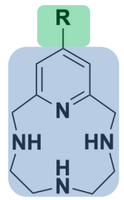


B = Blank (200 µL Methanol)

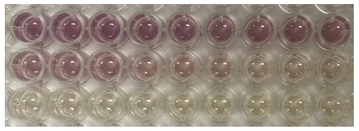
NC = Negative Control

Values = Concentration of Radical Scavenging Molecule (µM)

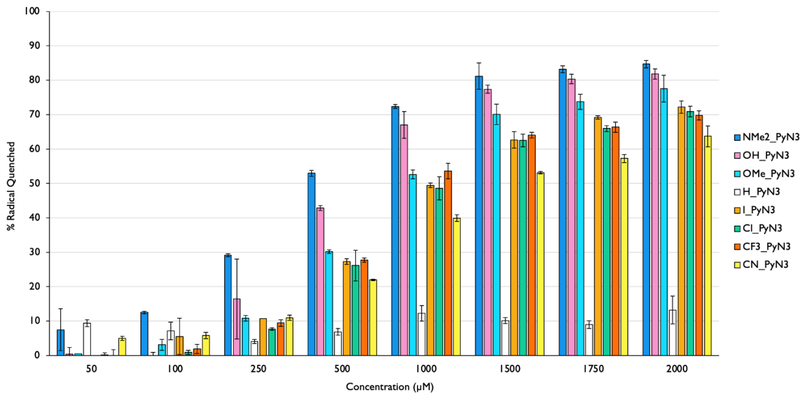
PyN_3 Series



R = NMe_2, OH, OMe, H, I, Cl, CN, CF_3

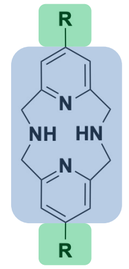


Design Strategy: Pyridine rings are known to stabilize radicals as a result of π-electron delocalization and stabilization of radical species or the captodative effect.

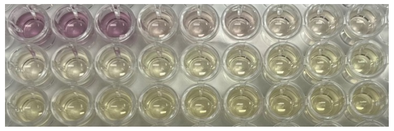


- ✓$^{H}PyN_3$ is a weak radical scavenger
- ✓At high concentrations, the substituted PyN_3 series shows sufficient quenching activity
- ✓Electron-donating R groups show higher levels of scavenging radicals than electron-withdrawing substitutions
- ✓**Conclusion:** Functionalizing the R group on the PyN_3 moiety increases radical scavenging activity compared to the $^{H}PyN_3$ parent molecule

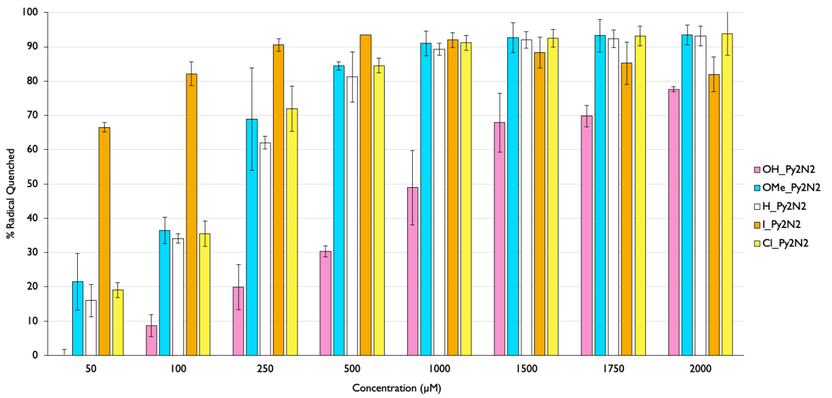
Py_2N_2 Series



R = OH, OMe, H, I, Cl



Design Strategy: PyN_3 moieties have been shown to provide radical scavenging reactivity. Therefore, adding another pyridine to the ligand backbone should increase scavenging ability.



- ✓All Py_2N_2 moieties are strong radical scavengers
- ✓Quenching activity occurs more effectively at lower concentrations compared to the PyN_3 series
- ✓Further studies are needed to understand the impact of pyridine ring substitutions on radical scavenging activity within the Py_2N_2 series
- ✓**Conclusion:** An additional pyridine group with the macrocyclic core increases radical scavenging activity compared to PyN_3 series

FUTURE DIRECTIONS

- Complete the Coumarin Carboxylic Acid (CCA) assays for both series
- TCU Biology Collaborators: Cell studies for cytotoxicity
- Analyze additional Py_2N_2 molecules to understand trends in radical scavenging

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Contacts
@christinamant__
@TCUGreenGroup
c.mantsorov@tcu.edu