Influence of Quinoline Moieties on the Pharmacological Properties and Anticancer Activity of Tetra-aza Pyridinophanes

Sarah Dunn, Nora Del Bosque, Christina Mantsorov, Giridhar Akkaraju, Ph.D., Kayla N. Green, Ph.D., Department of Chemistry and Biochemistry

Abstract

Balance in the human body is crucial for overall health. Properly regulated reactive oxygen species (ROS) play a protective role against diseases but are linked to neurological diseases like **Alzheimer's** when misregulated. Superoxide dismutase (SOD) enzymes neutralize ROS to prevent oxidative damage. In humans, the availability of metal cofactors, such as copper and zinc, influence SOD expression. The Green Group has synthesized a series of potential candidates: 12-membered tetra-aza pyridinophanes (PyN_3) as SOD mimics through substitutions on the 4-position of the pyridine ring.

Misregulation of metal ions has also been connected to **cancer**, with high levels of copper promoting carcinogenesis and cancer growth. Pyridinophane complexes may bind excess copper in cancer cells, slowing their growth. The ongoing aim of this project is developing pyridinophanes as dual characteristics SOD mimic compounds, making them relevant to oxidative stress therapy and potential anti-cancer applications.

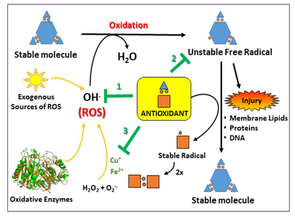
Objective: Synthesizing Dual-Function Ligands for Addressing ROS and Elevated Copper Levels in Diseased Cells

Background and Previous Work

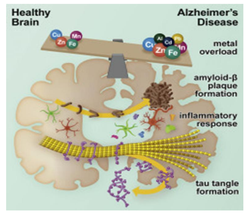
ROS, Metal Ions, and Alzheimer's Disease

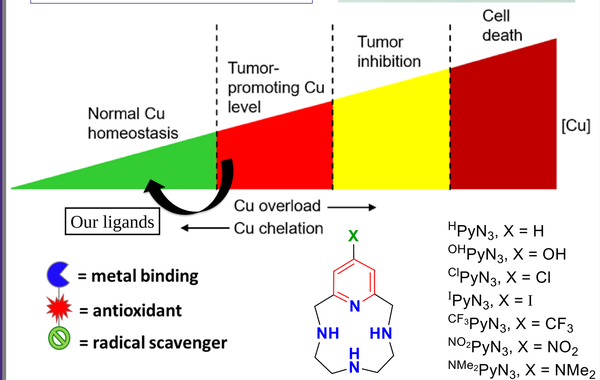
Present antioxidant and metal chelator therapeutics combat oxidative stress through mechanisms such as quenching ROS, donating hydrogen atoms to stabilize radicals, and chelating transition metals to prevent their involvement in harmful processes, including Aβ formation and ROS generation through redox cycling of transition metal ions.

ROS



Metal Ion Imbalance





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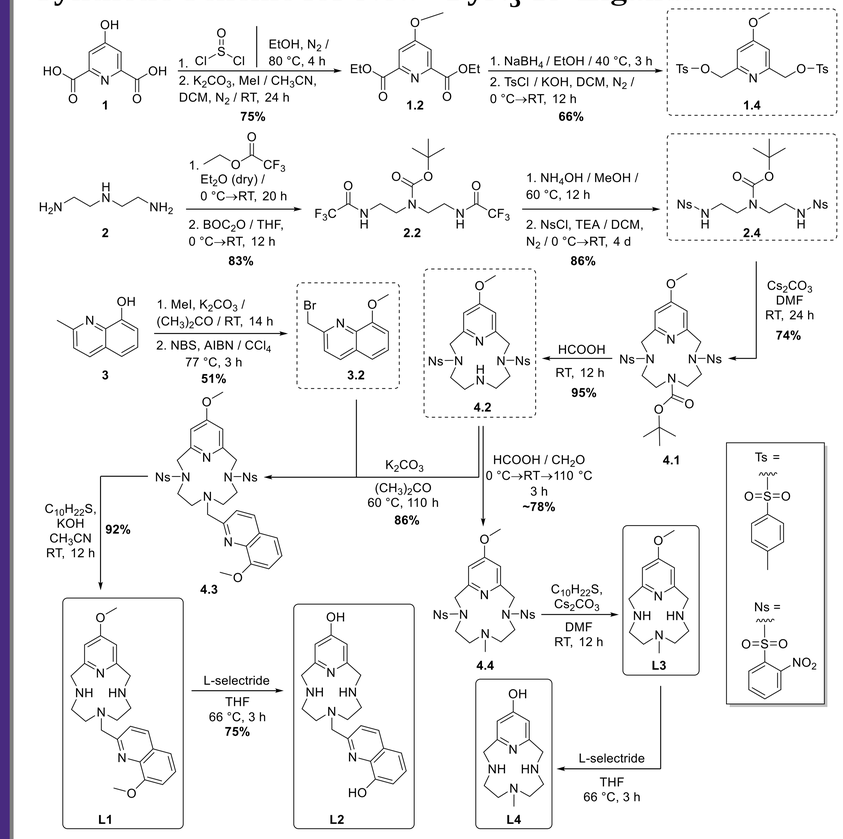
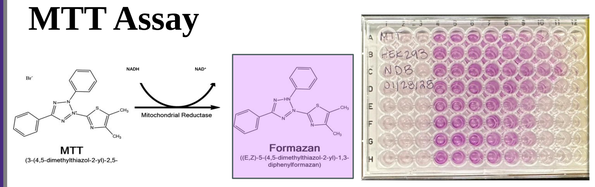
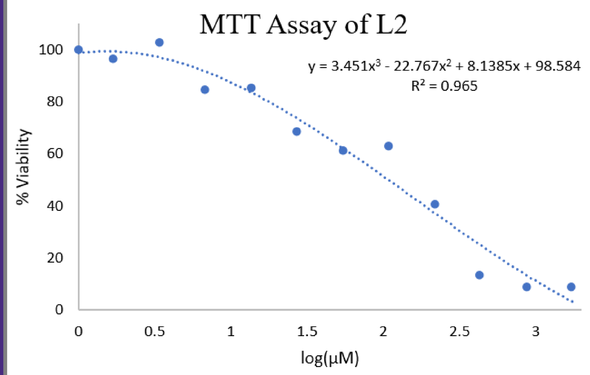
Synthetic Scheme for New $^{R}PyN_3$-R' Ligands



MTT Assay

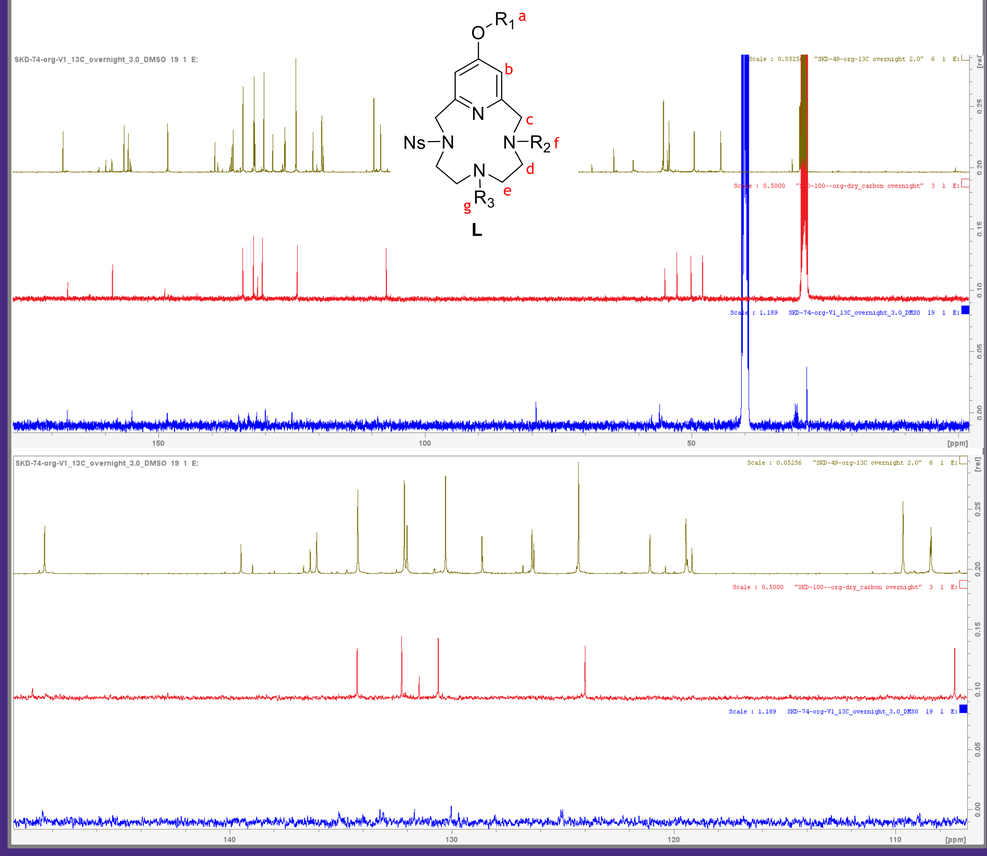




Observations:

- Good working therapeutic window
- L2 is the most cytotoxic.

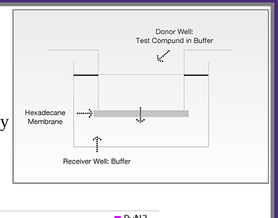
Characterization: ^{1}H NMR

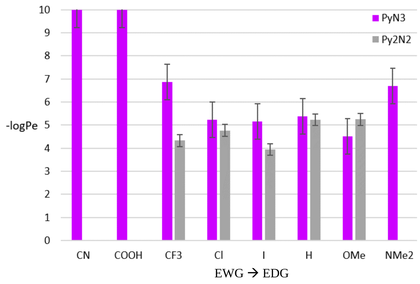


PAMPA Assay

Parallel artificial membrane permeability assay (PAMPA)

- Widely used in pharmaceutical industry as high throughput permeability assay to predict oral absorption.
- Useful for early drug screening.

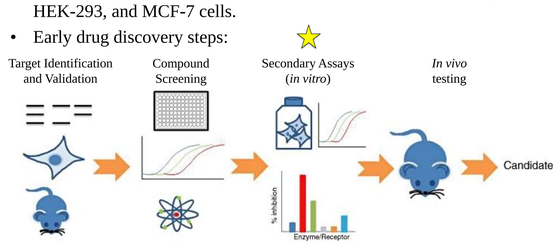




Ligand Name	P_e Value (10^{-6} cm/s)	$-\log P_e$ Value	% Acc	% Don	% Memb
OH-PyN_3	< 0.01	N/A	Not Tested	Not Tested	Not Tested
CN-PyN_3	0.00	10.00	0	96.7	3.2
COOH-PyN_3	0.00	10.00	0	98.4	1.7
NMe_2-PyN_3	0.22 ± 0.11	6.69 ± 0.21	0.36	95.79	3.80
CF_3-PyN_3	0.66 ± 0.38	6.87 ± 1.75	0.94	89.46	9.40
Cl-PyN_3	6.07 ± 2.10	5.24 ± 0.17	9.1	88.7	2.3
I-PyN_3	7.04 ± 0.66	5.15 ± 0.04	10.9	89.1	0.00
OMe-PyN_3	31.58 ± 11.48	4.52 ± 0.15	37.0	59.7	3.3

Future Directions

- Continued characterization of novel PyN_3-Q ligands to complete the PAMPA and MTT assay series with diversely substituted compounds.
- Optimization of current synthesis and additional ligands.
- Continue *in vitro* biological assays on cancer cell lines, including HeLA, HEK-293, and MCF-7 cells.
- Early drug discovery steps:



Acknowledgements

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