

Saba Anjum, Shrikant Nilewar, Kayla N. Green
Department of Chemistry & Biochemistry, Texas Christian University

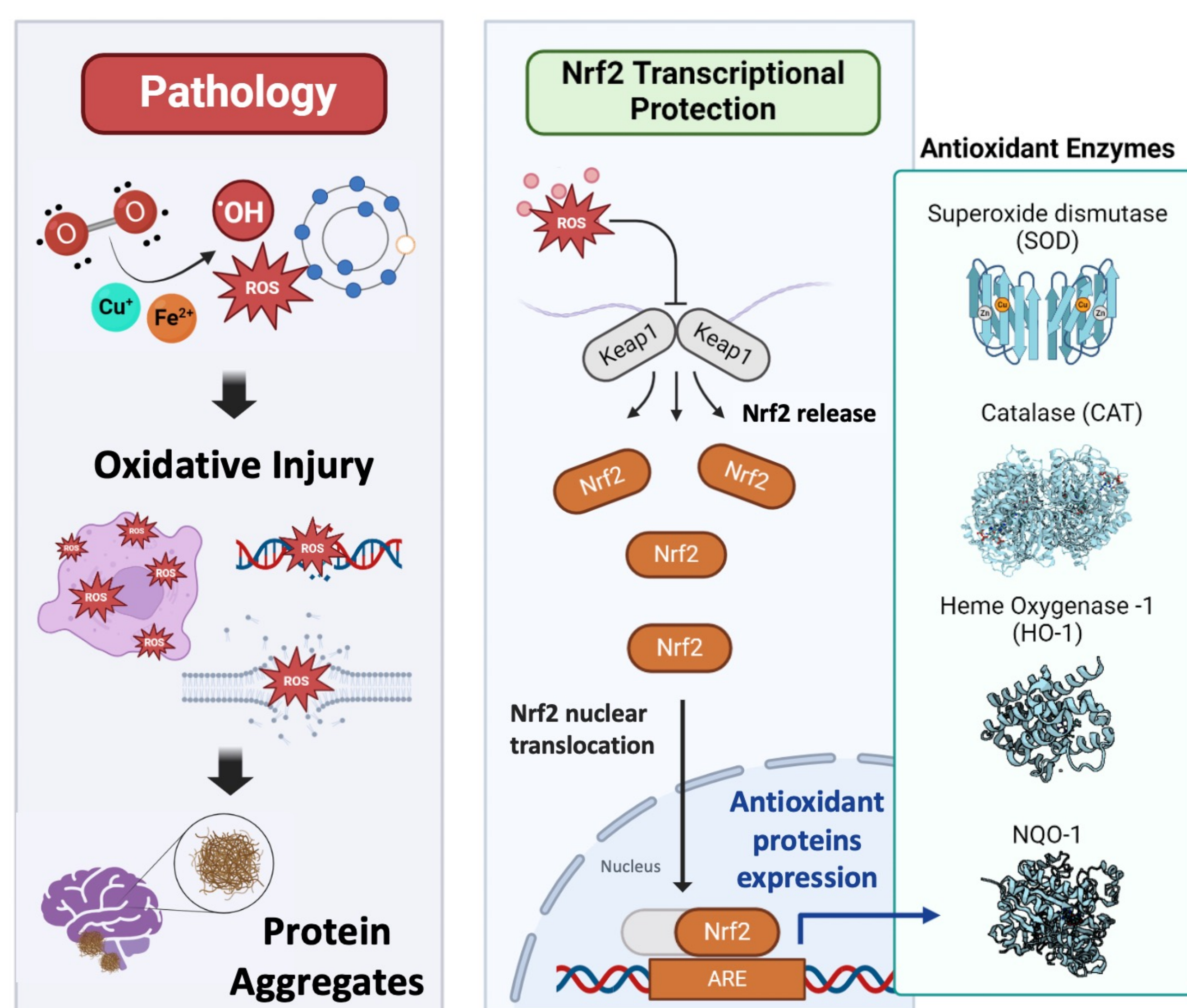
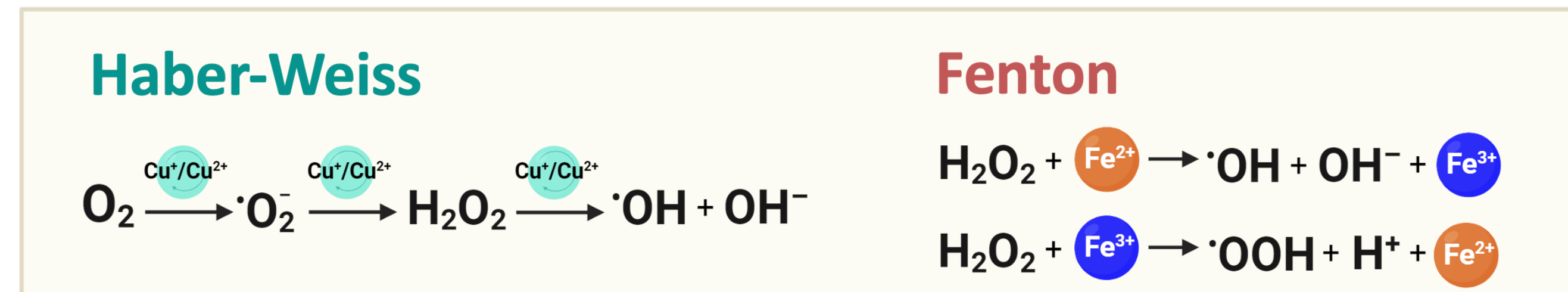
Abstract

Oxidative stress plays a significant role in the development and progression of neurodegenerative diseases, including Alzheimer's, but currently there are no approved drug therapeutics that effectively address oxidative stress in Alzheimer's. The Green Research Group has previously synthesized and reported a pyridine-containing tetra-aza macrocycle, denoted as **L2** herein, which acts as a multifunctional antioxidant agent by targeting oxidative stress directly through radical quenching and metal binding as well as catalytically through activation of the Nrf2 pathway. While preliminary research on **L2** has successfully demonstrated its potent antioxidant capacity in various cell models, its high hydrophilicity results in reduced blood-brain barrier permeability, which is a concern when targeting neurodegenerative diseases. It is hypothesized that employing a prodrug design strategy through the incorporation of a self-immolative linker on **L2** will result in enhanced blood-brain barrier permeability and ideal drug-like behavior while retaining potent antioxidant activity under physiological conditions.

Introduction

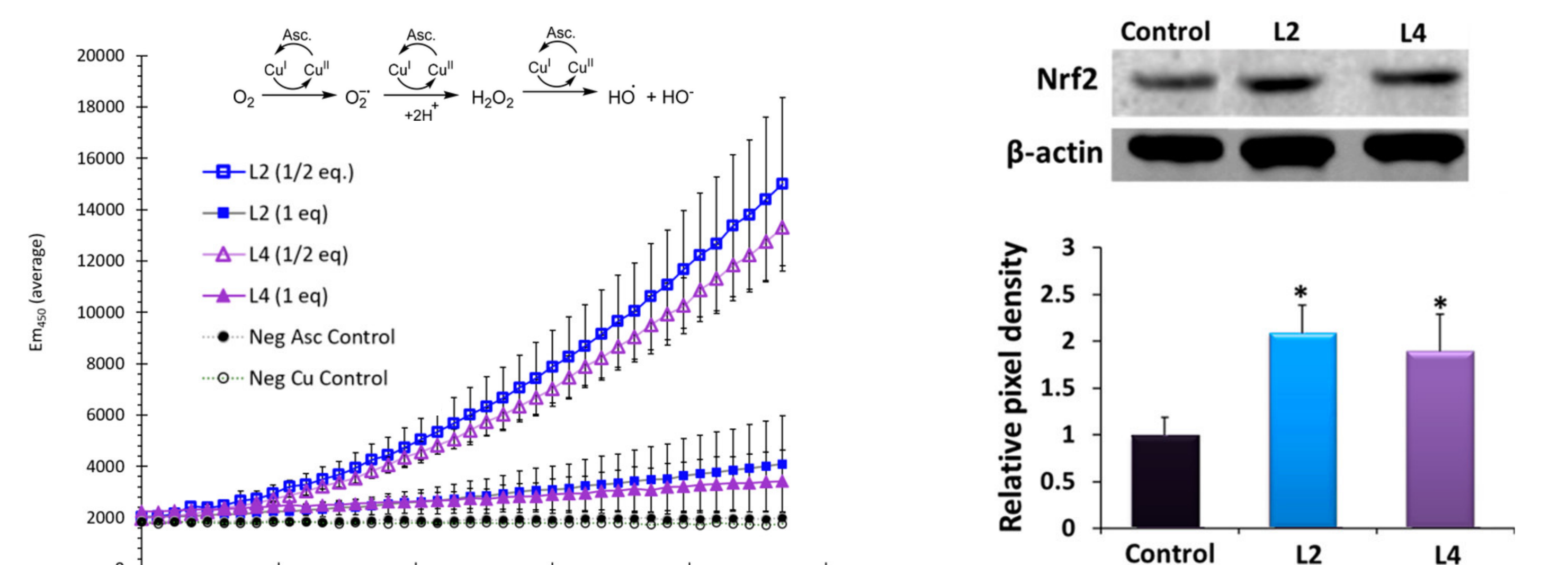
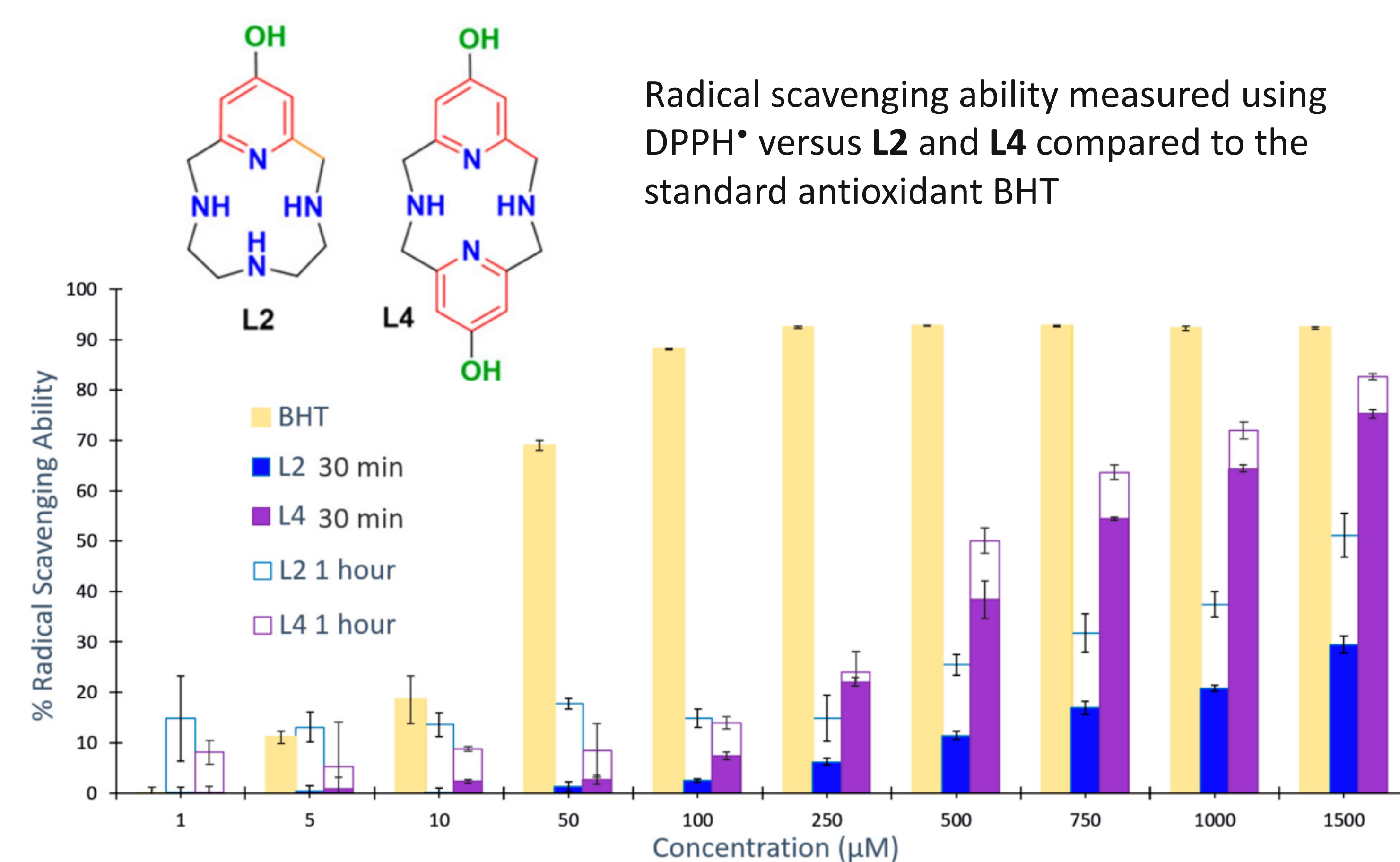
Alzheimer's Disease

- **6+ million** Americans live with Alzheimer's.
- **\$345 billion** were spent in treatments for Alzheimer's patients in 2023.
- **Oxidative stress** is a common feature of Alzheimer's.

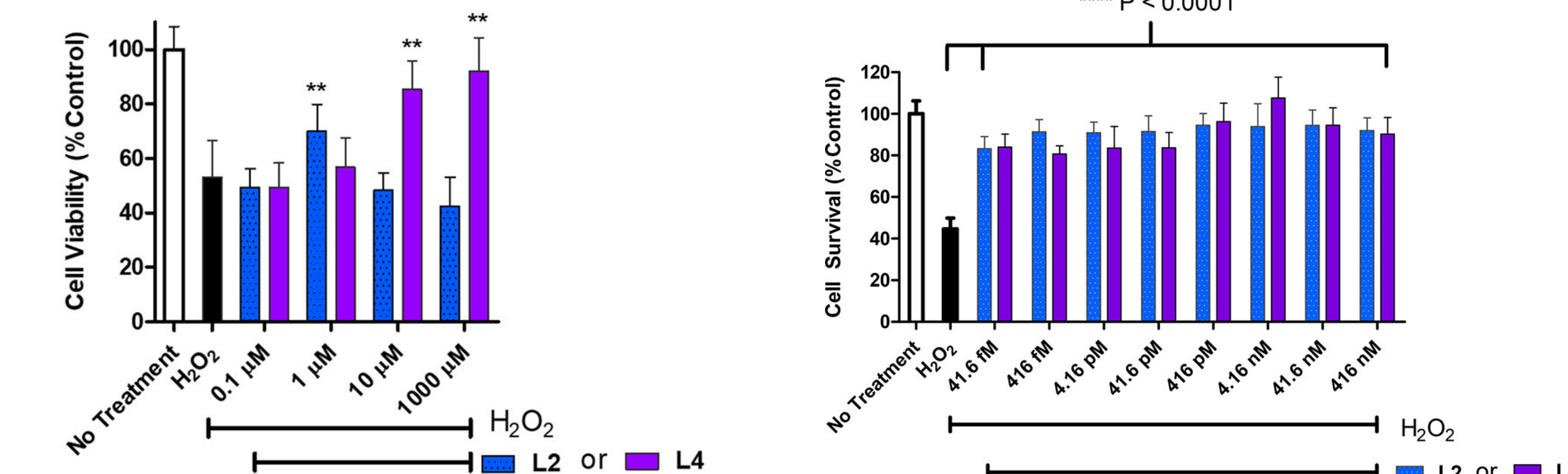


Previous Work

Multi-Target Antioxidant Molecules



Fluorescence intensity of 7-hydroxy-CCA after incubation of CCA and ascorbate with copper(II)



Cytoprotective effects in HT-22 cells measured using WST-8 assay (P < 0.01)

Cytoprotective effects in BV2 microglial cells measured using MTT assay (P < 0.0001)

Table 1. Lipinski's parameter and logBB calculations.

Compound	M.W.	clogP	HBA	HBD	PSA (Å)	logBB
L2	223.3	-1.9	4	3	69.77	-1.182
L4	272.3	-1.08	5	4	93.16	-1.404
L6	438	2.71	7	3	76.14	-0.576

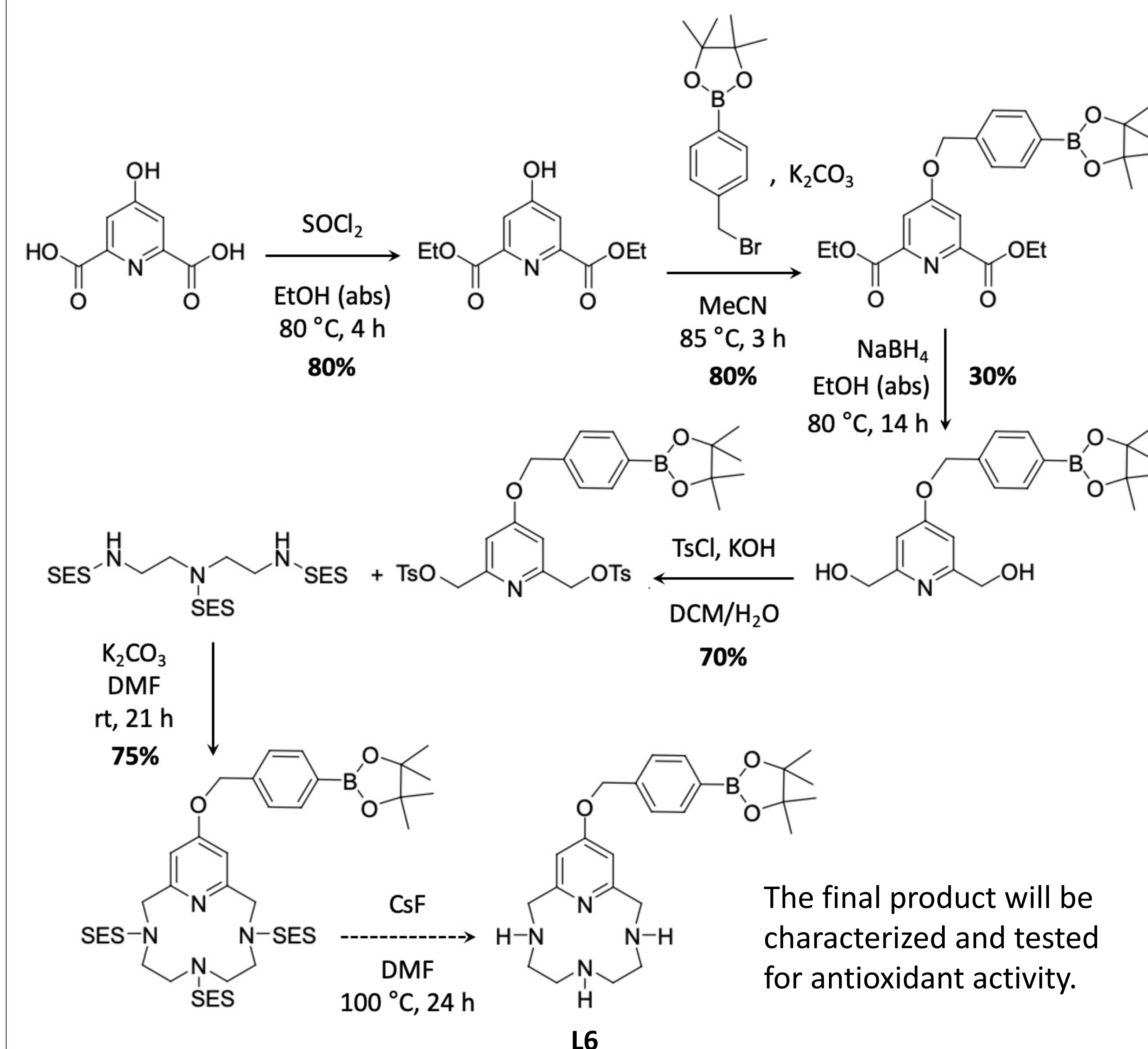
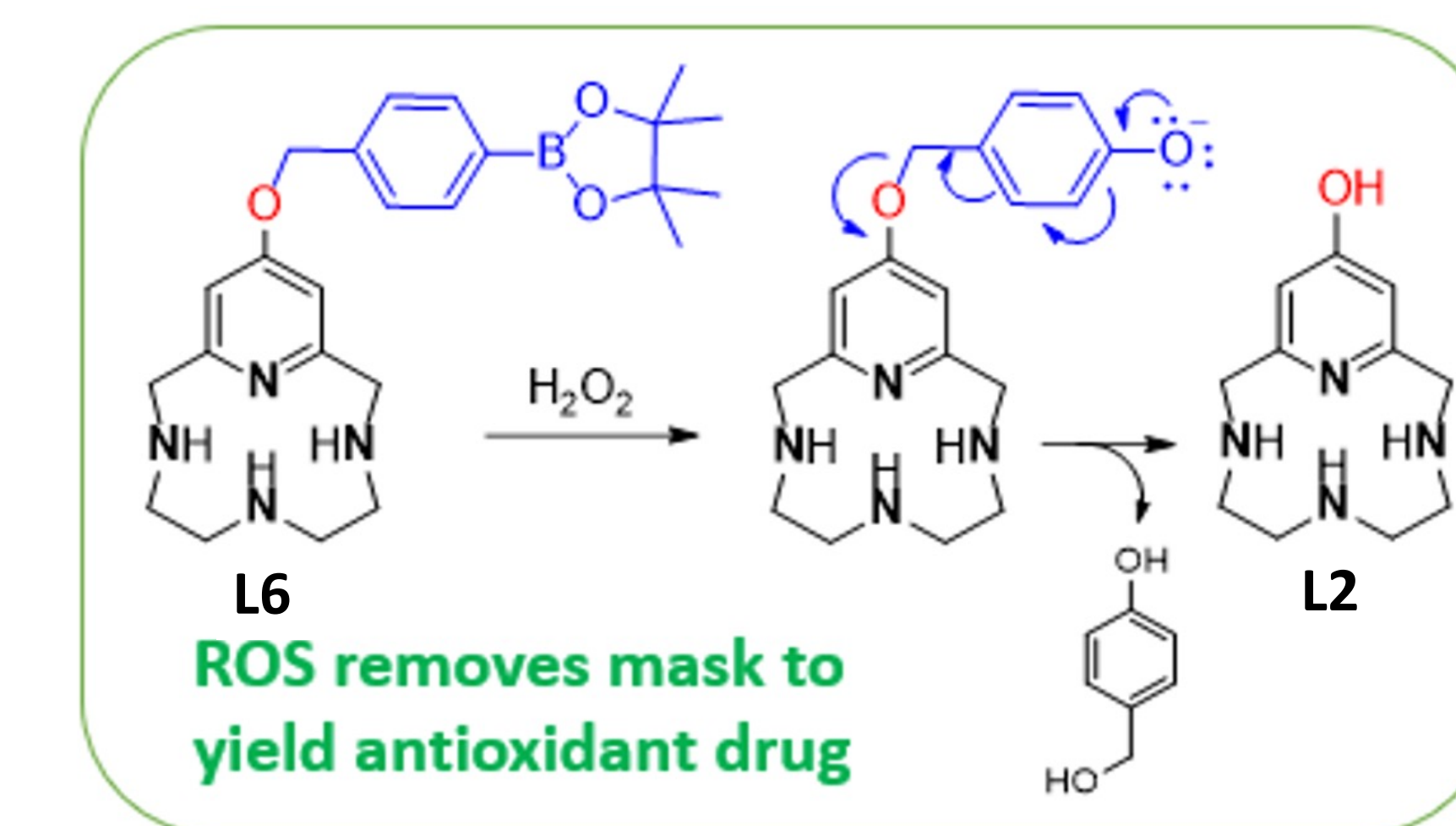
Target values: ≤ 500, ≤ 5.0, ≤ 10, ≤ 5, ≤ 90, > 3.0 (readily); < -1.0 (poorly)

L2 and **L4** lack blood-brain barrier permeability.

Current Work

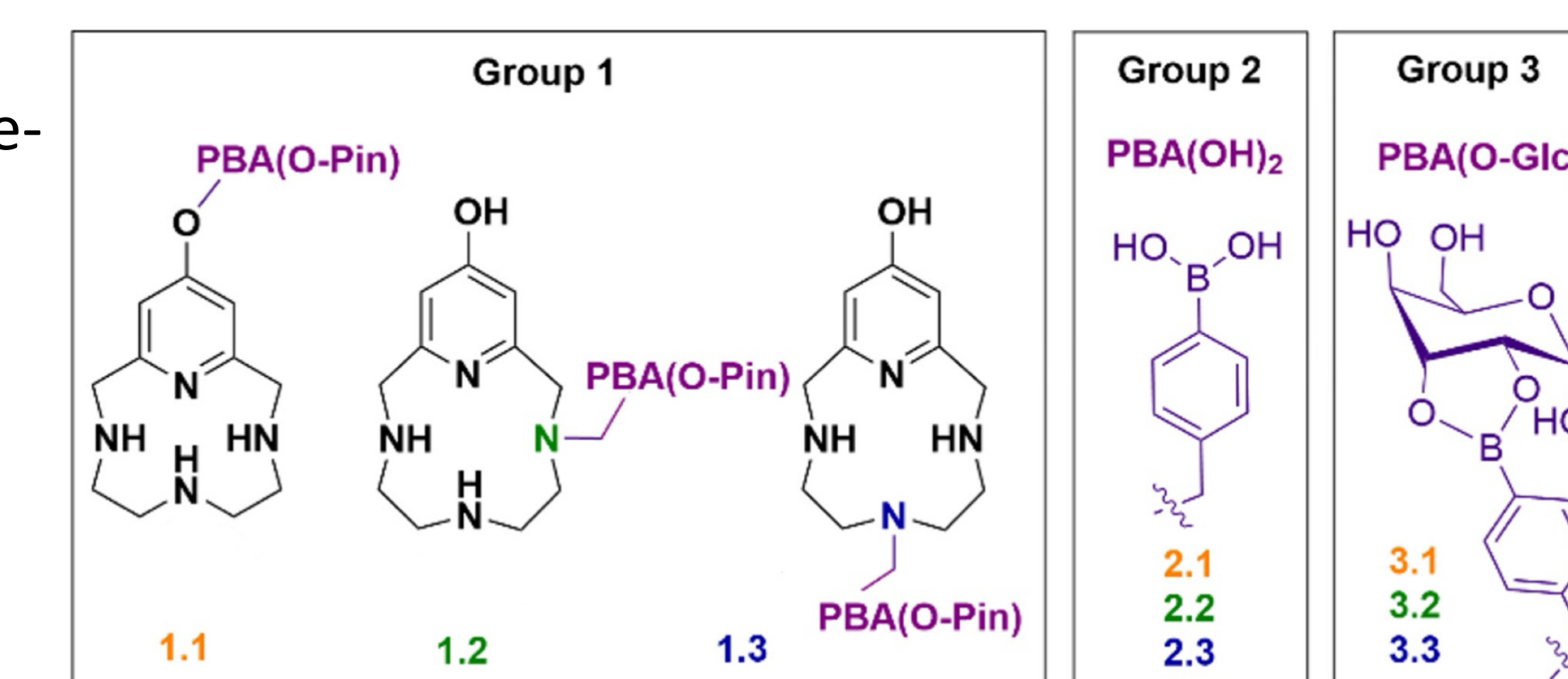
Prodrug Strategy

- ✓ The molecule is reversibly linked to a phenylboronic acid pinacol ester group.
- ✓ The linker will be removed once the molecule encounters ROS, restoring original antioxidant activity.



Future Goals

The lab aims to design and synthesize pyridine-containing tetra-aza macrocycles with different moieties to enhance blood-brain barrier permeability while ensuring antioxidant activity.



Contacts

Saba Anjum, Department of Chemistry & Biochemistry, saba.anjum@tcu.edu

Shrikant Nilewar, shrinilewar@gmail.com

Kayla N. Green, Department of Chemistry & Biochemistry, kayla.green@tcu.edu

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