ROS Breakdown By Catalase Macrocyclic Ligand Mimics

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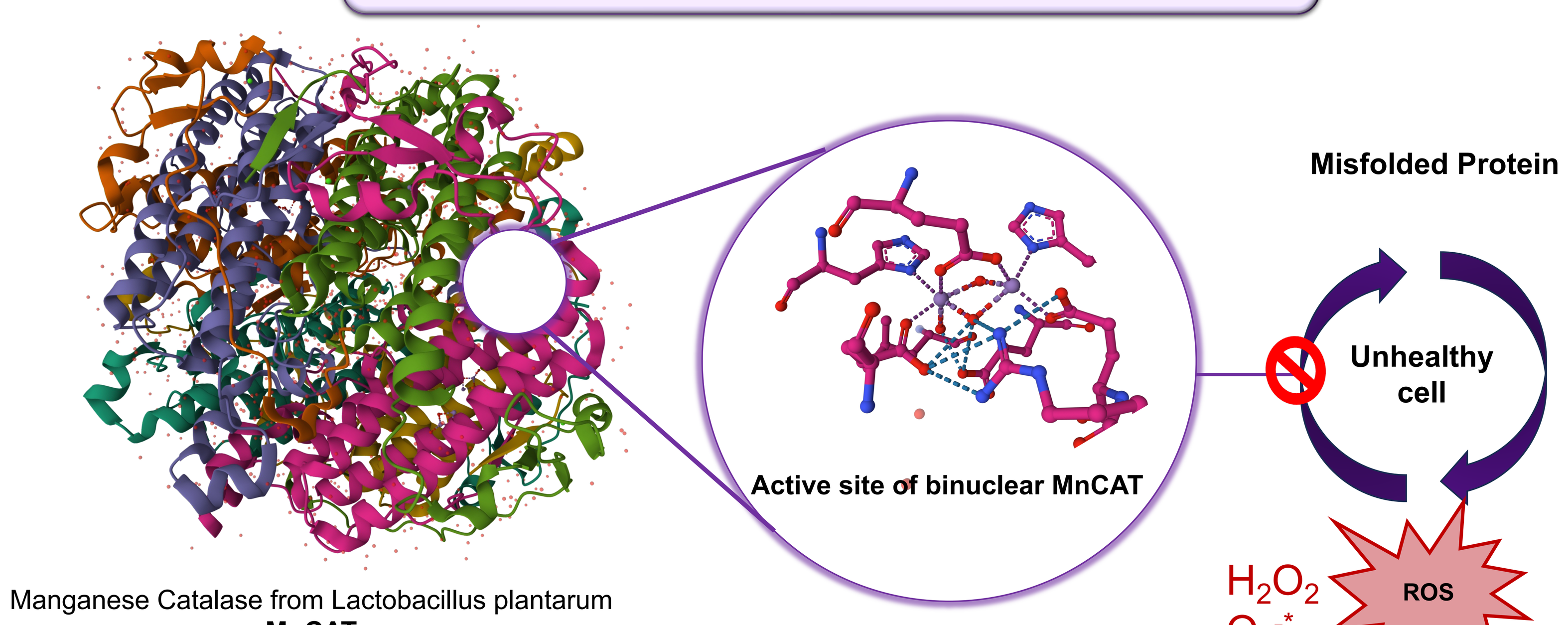
Background

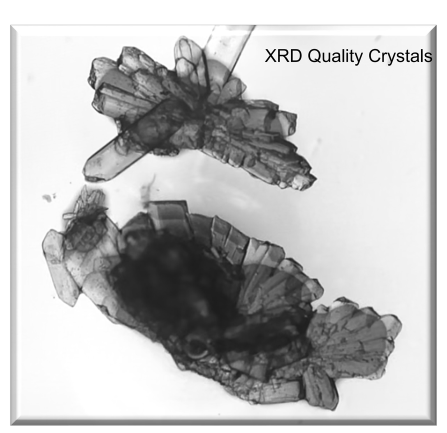
Neurodegenerative Disease
- Destroy motor neurons
- Alzheimer's, Parkinson's, Huntington's
- Caused by misfolded proteins

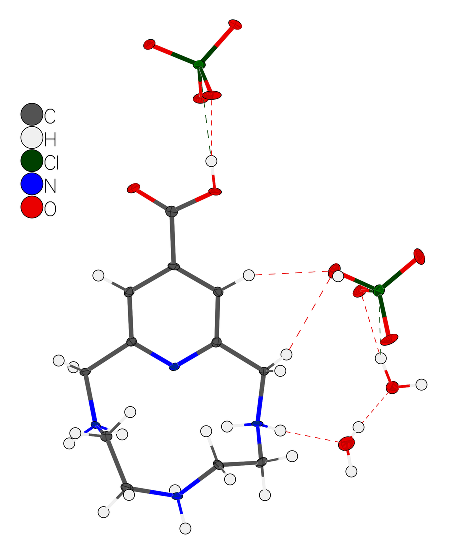
Current Therapeutics
- Nonspecific targeting
- Premature release behavior
- Low therapeutic efficacy

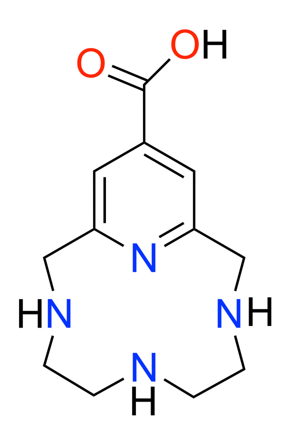
Approach



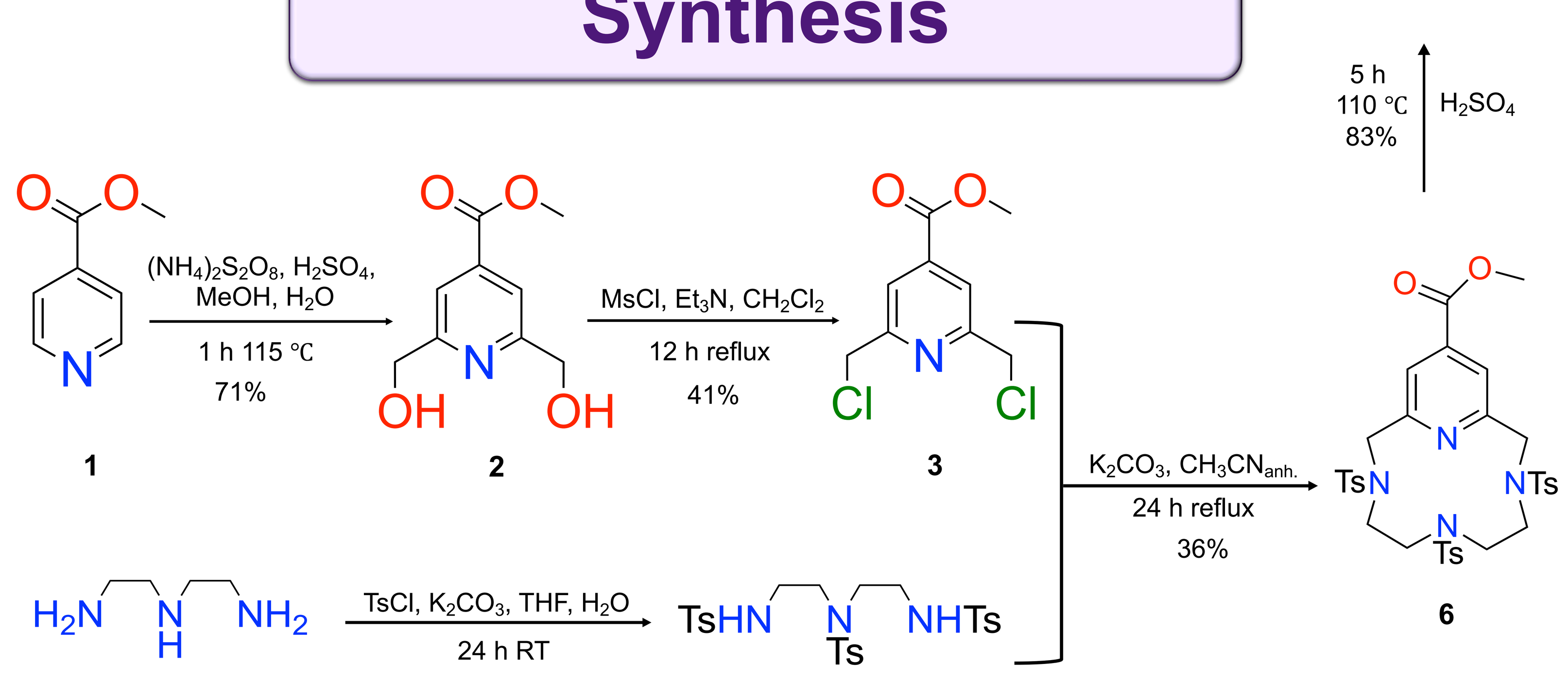
Manganese Catalase from Lactobacillus plantarum
MnCAT




Reciprocal lattice from crystalline solid of L1

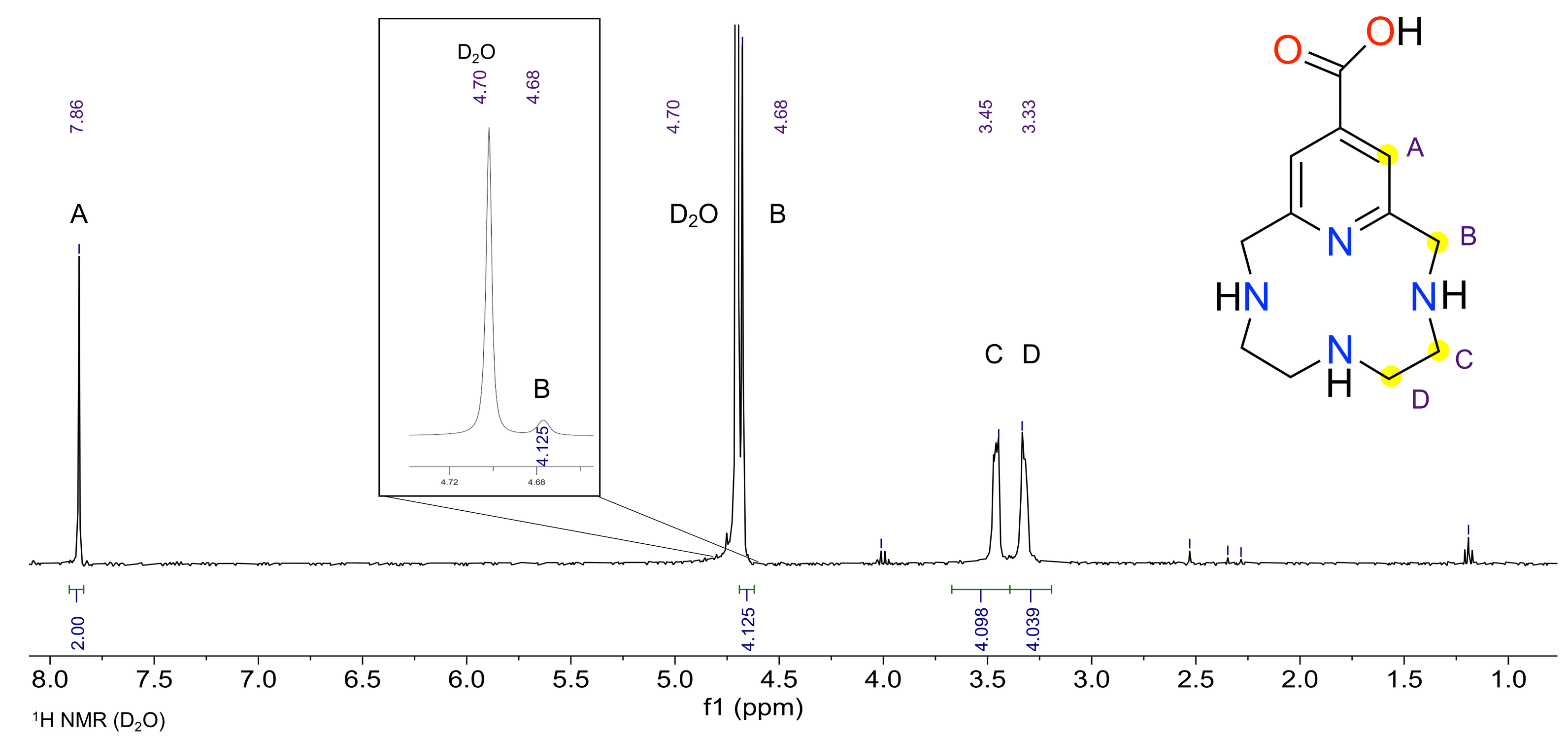

L1·3HCL

Synthesis



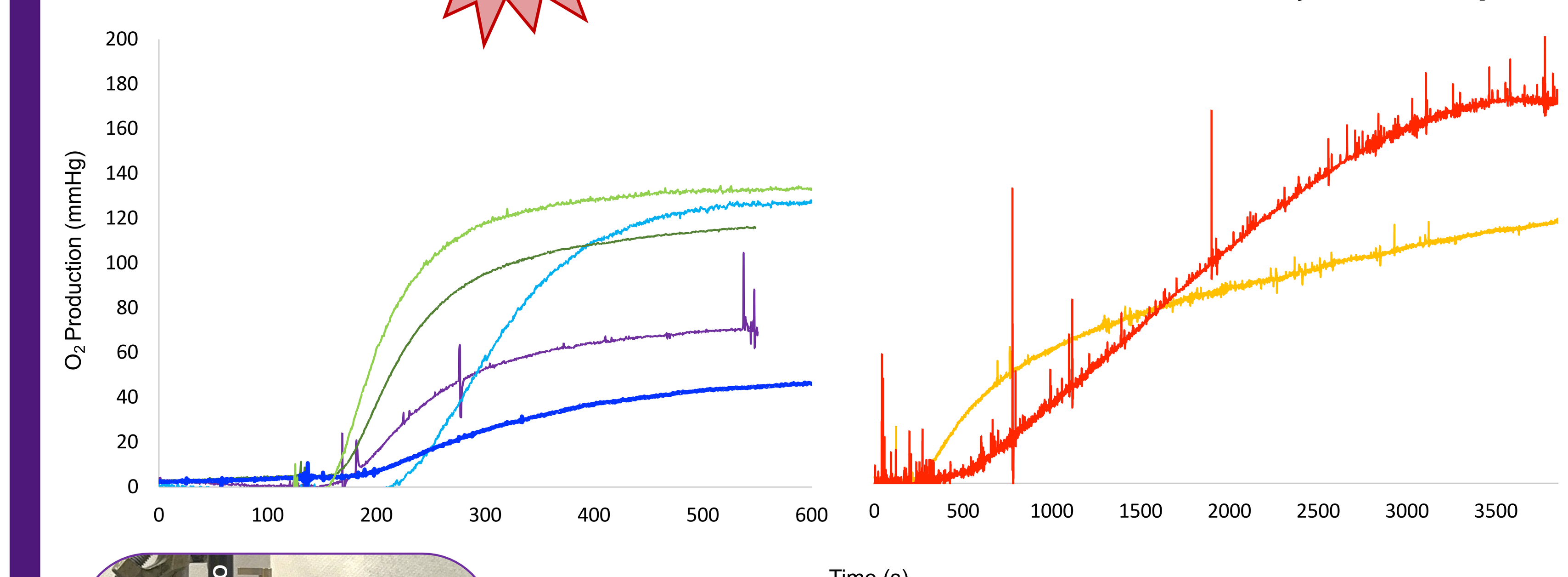
Research Goal
- Synthesize **L1** to mimic the activity of catalase
- Combine with an unhealthy cell to decrease ROS levels
- Test O_2 production from ligand metal complex after H_2O_2 addition
- Calculate the ligand mimic's turnover number
- Compare reactivity to ligand library

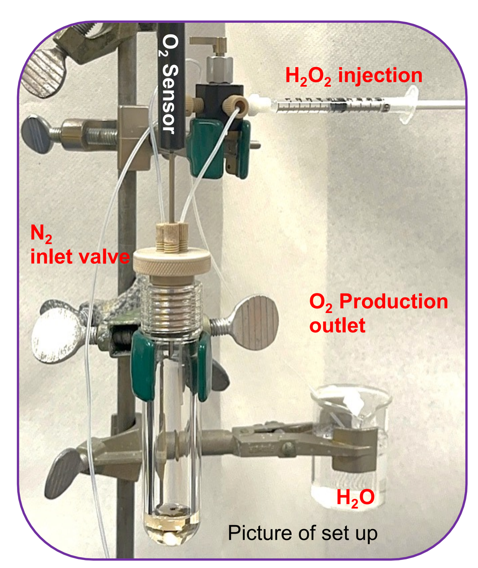
Characterization



O_2 Production

$$MnCl_2 + L + 2H_2O_2 \xrightarrow{Mn + L} 2H_2O + O_2 \qquad TON = \frac{\text{mole of } O_2 \text{ produced}}{\text{mole of Metal complex}}$$

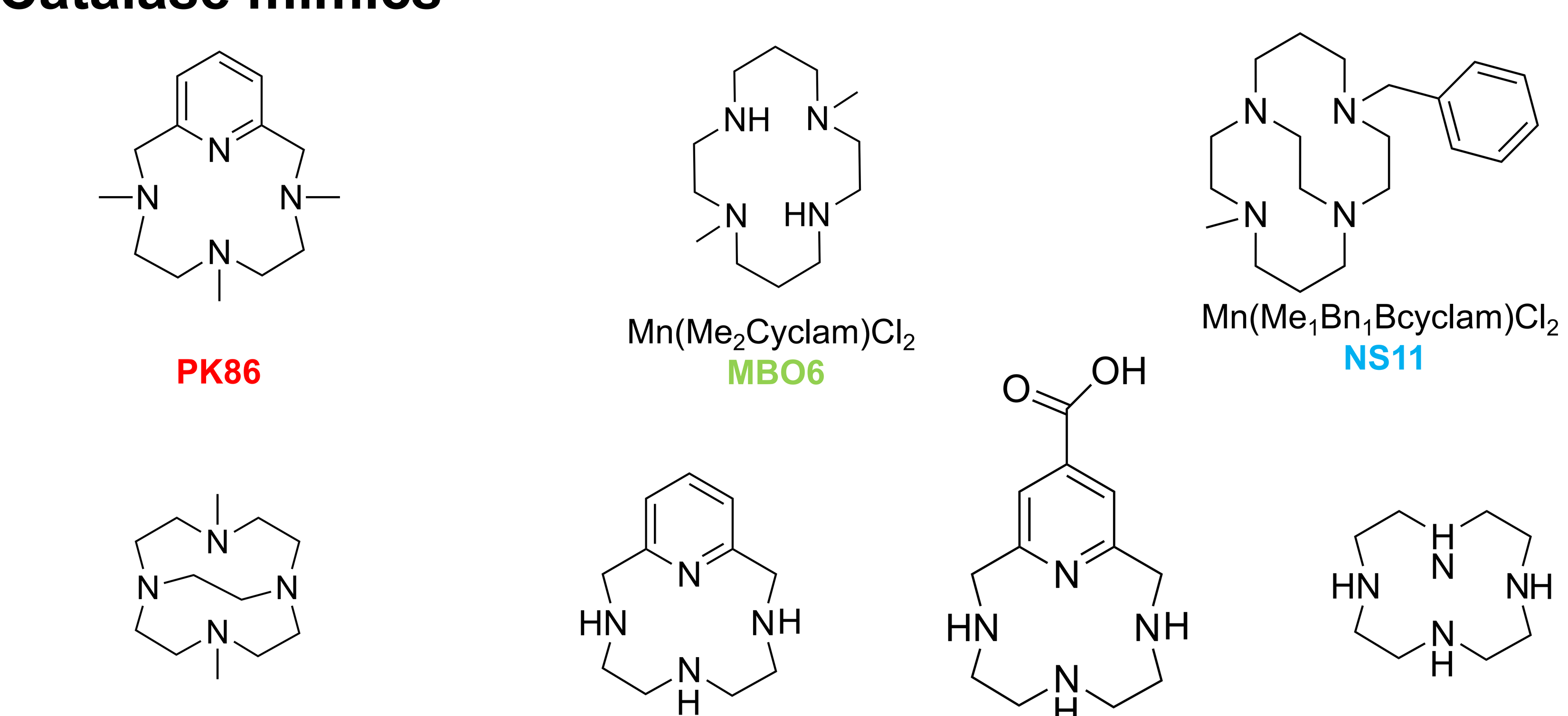




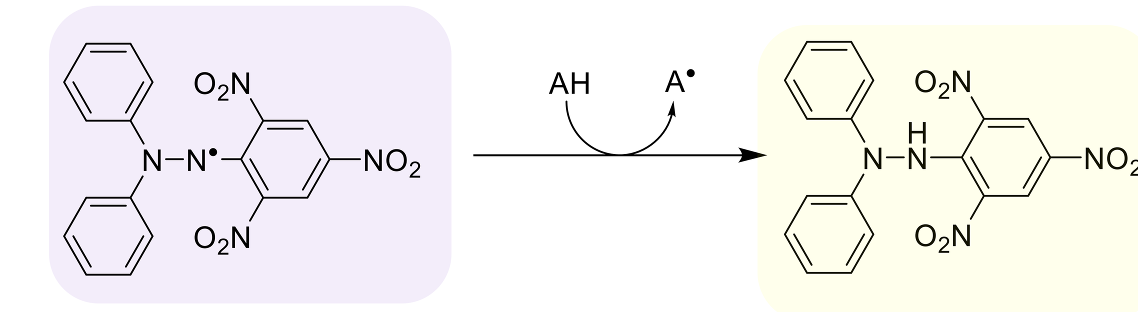
INCREASING TON

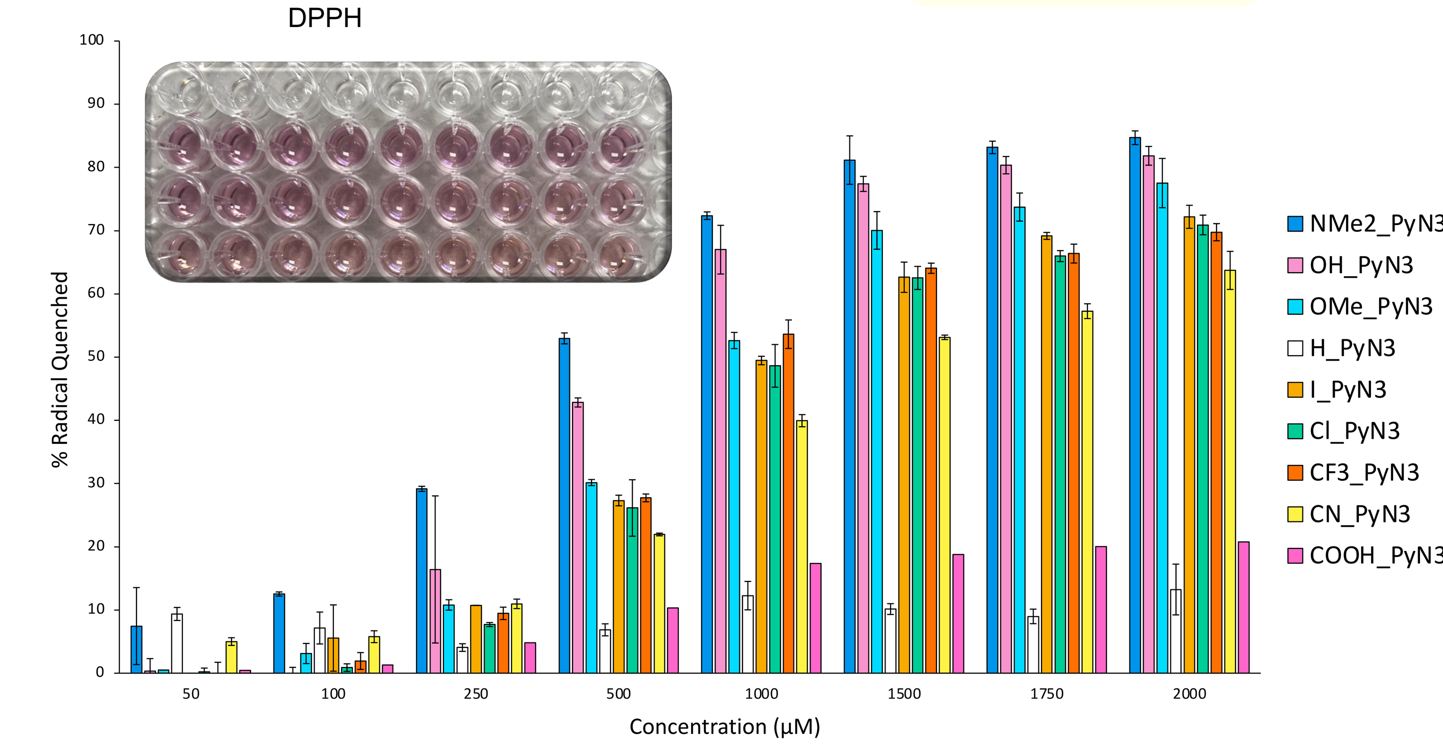
Compound	Avg. TON	% yield
PK86	41.36(2.1)	83.76%
MBO6	30.70(0.6)	62.71%
NS11	29.34 (1)	59.42%
ANO6	28.25(6.8)	57.21%
Pyclen	23.24(0.5)	47.06%
L1	**16.52(0.9)**	**31.74%**
Cyclen	11.09(1.4)	22.45%

Catalase mimics


PK86
Mn(Me_2Cyclam)Cl_2 MBO6
Mn(Me_1Bn_1Bcyclam)Cl_2 NS11
Mn(Me_2Bcyclen)Cl_2]PF_6 AN06
PyN_3 Pyclen
$^{COOH}PyN_3$
N_3 Cyclen

Radical scavenging ability





DPPH Assay data collected by Christina Mantsorov

Permeability

Table 1. PAMPA analysis of PyN_3 molecules.

Ligand Name	P_e Value (10^6 cm/s)	$-logP_e$ Value	% Acc	% Don	% Memb
$^{OH}PyN_3$	< 0.01	ND	ND	ND	ND
$^{CN}PyN_3$	0.00	10.00	0	96.7	3.2
L1	0.00	10.00	0	98.4	1.7
$^{NMe2}PyN_3$	0.22 ± 0.11	6.69 ± 0.21	0.36	95.79	3.80
$^{CF3}PyN_3$	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

ND = Not Detected

Conclusion

In conclusion, **L1** was successfully synthesized and added to the ligand library. The O_2 production from the addition of H_2O_2 was tested with the reactivity being compared to the ligand library. In the future, we hope to enhance **L1** permeability by covalent attachment to a nitrogen-glucosamine quantum dot in collaboration with the Naumov group in the TCU physics department.

Acknowledgements

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1. Martínez-Camarena, Á., et al. (2022). Chemical Communications **58**(32): 5021-5024.

NIH National Institutes of Health
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