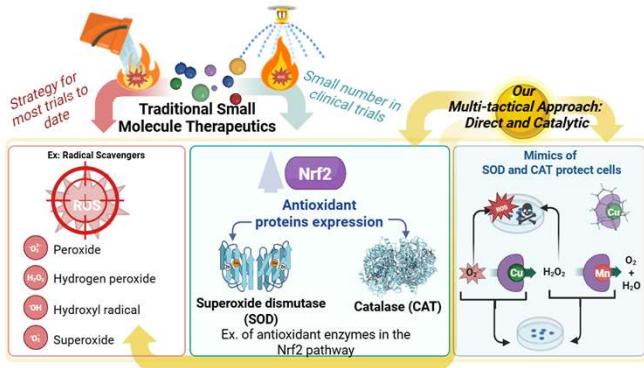


# BOILED-eggs and the Blood-Brain Barrier: How BOILED-egg Modeling Can Predict Permeability of Pyridine Macroyclic Molecules to Combat Alzheimer's Disease

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## INTRODUCTION



- Chronic exposure to reactive oxygen species (ROS) leads to neurological diseases.
  - Ex: Alzheimer's Disease
  - Macrocycles have shown promise in targeting ROS.
- Problem to be addressed:** Increasing BBB permeability of antioxidant molecules.

## WORKFLOW



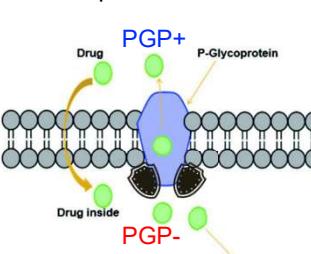
## BOILED-EGG MODEL

### What is this BOILED-egg?

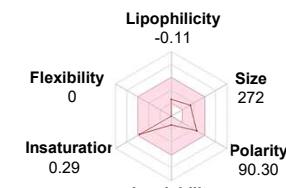
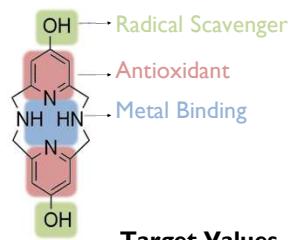
A model that predicts BBB permeability and GI absorption based on lipophilicity and polarity

Y-axis: fat solubility

X-axis: polar surface area



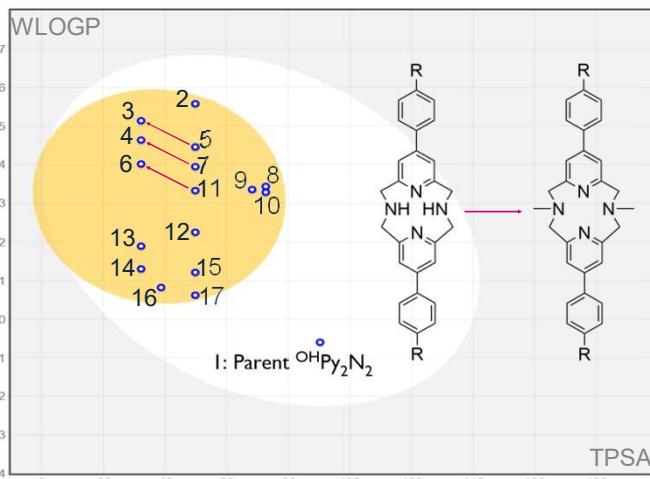
## RESULTS



### Target Values

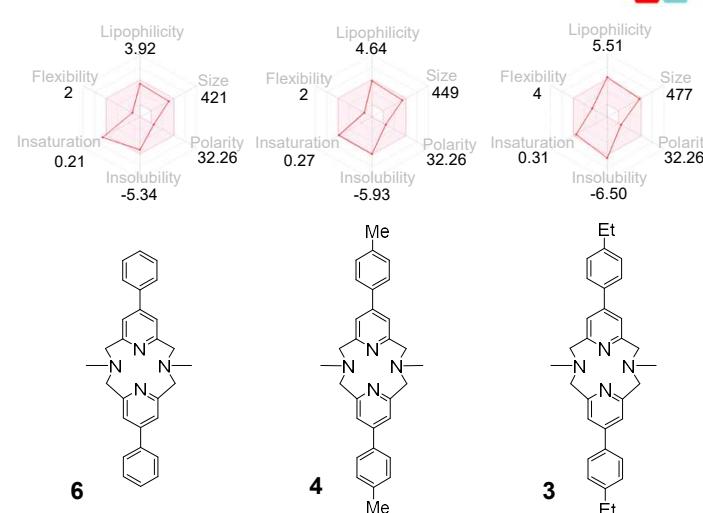
Lipophilicity: 5  
Size (g/mol): 150  
Polarity ( $\text{\AA}^2$ ): 20  
Insolubility (mol/L): 0  
Insaturation: 1  
Flexibility: 0

**Design Strategy:**  
 $\text{OH}\text{Py}_2\text{N}_2$  properties must be improved to obtain BBB permeability

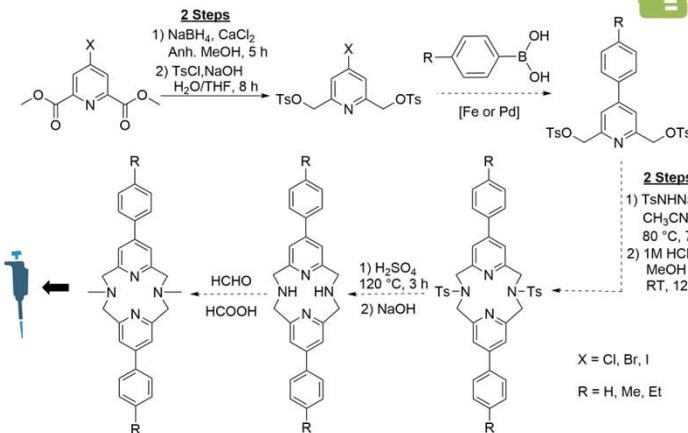


- |  |  |  |
|--|--|--|
| $\text{I: Parent } \text{OH}\text{Py}_2\text{N}_2$ | $\text{1 } \text{R}_1=\text{OH}, \text{R}_2=\text{H}$<br>$\text{2 } \text{R}_1=\text{i-PrPh}, \text{R}_2=\text{H}$<br>$\text{3 } \text{R}_1=\text{PhEt}, \text{R}_2=\text{Me}$<br>$\text{4 } \text{R}_1=\text{PhMe}, \text{R}_2=\text{Me}$<br>$\text{5 } \text{R}_1=\text{PhEt}, \text{R}_2=\text{H}$<br>$\text{6 } \text{R}_1=\text{Ph}, \text{R}_2=\text{Me}$<br>$\text{7 } \text{R}_1=\text{PhMe}, \text{R}_2=\text{H}$<br>$\text{8 } \text{R}_1=\text{PhOH}, \text{R}_2=\text{Me}$ | $\text{9 } \text{R}_1=\text{MeOPh}, \text{R}_2=\text{H}$<br>$\text{10 } \text{R}_1=\text{CH}_2\text{PhOH}, \text{R}_2=\text{Me}$<br>$\text{11 } \text{R}_1=\text{Ph}, \text{R}_2=\text{H}$<br>$\text{12 } \text{R}_1=\text{i-Pr}, \text{R}_2=\text{H}$<br>$\text{13 } \text{R}_1=\text{I}, \text{R}_2=\text{Me}$<br>$\text{14 } \text{R}_1=\text{Me}, \text{R}_2=\text{Me}$<br>$\text{15 } \text{R}_1=\text{I}, \text{R}_2=\text{H}$<br>$\text{16 } \text{R}_1=\text{N,N-DMA}, \text{R}_2=\text{Me}$<br>$\text{17 } \text{R}_1=\text{Me}, \text{R}_2=\text{H}$ |
|--|--|--|

## TARGET MOLECULES



## FUTURE DIRECTIONS



## ACKNOWLEDGMENTS

**SwissADME Tool:**  
Daina, A.; Michelin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetic Properties and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* 2017, 7, 42717.

**BOILED-Egg Model:**  
Daina, A.; Zoete, V. A BOILED-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem* 2016, 11 (11), 1117–1121.

**P-Glycoprotein Model:**  
Ahire ED, Kshirsagar SJ. Efflux Pump Inhibitors: New Hope in Microbial Multidrug Resistance? Role of Efflux Pump Inhibitors in multidrug resistance protein (P-gp). *Community Acquir Infect* 2022;9.