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

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INTRODUCTION

Strategy for most trials to date — **Traditional Small Molecule Therapeutics**

Small number in clinical trials

Our Multi-tactical Approach: Direct and Catalytic

Ex: Radical Scavengers — RUS
- Peroxide O_2^-
- Hydrogen peroxide H_2O_2
- Hydroxyl radical $\cdot OH$
- Superoxide O_2^-

Nrf2 — **Antioxidant proteins expression**
Superoxide dismutase (SOD) — Catalase (CAT)
Ex. of antioxidant enzymes in the Nrf2 pathway

Mimics of SOD and CAT protect cells
Cu H_2O_2 Mn $O_2 + H_2O$
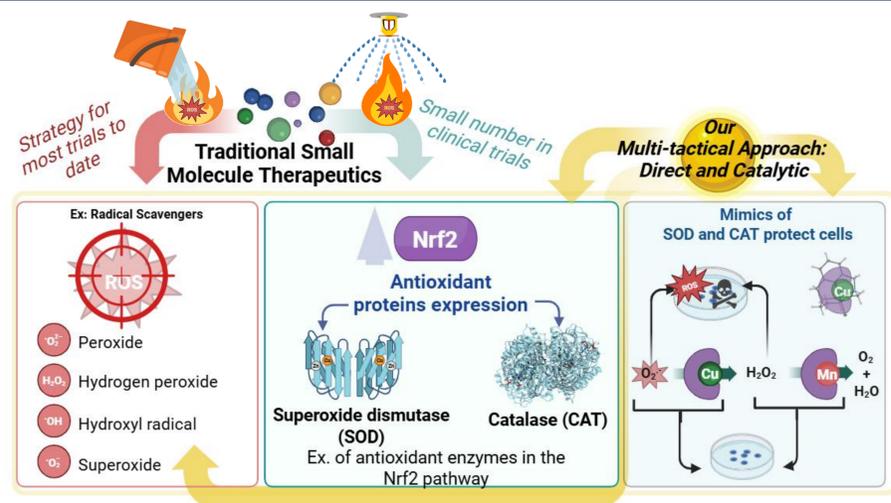
- Chronic exposure to reactive oxygen species (ROS) leads to neurological diseases.
- Ex: Alzheimer's Disease
- Macrocycles have shown promise in targeting ROS.
  Problem to be addressed: Increasing BBB permeability of antioxidant molecules.

WORKFLOW

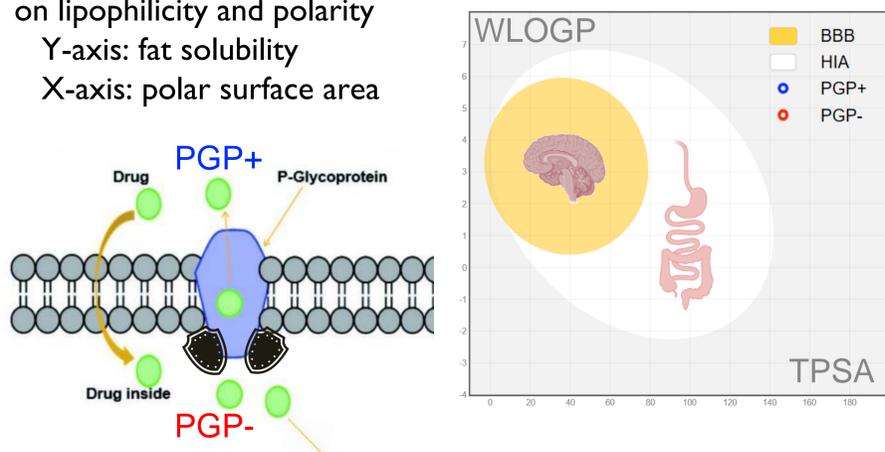CD → **SwissADME** SwissDrugDesign → beaker → pipette
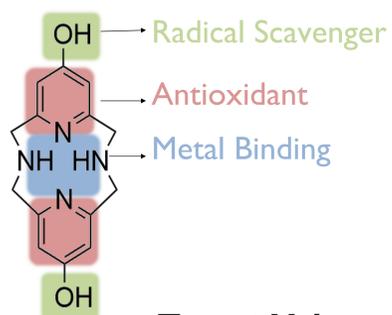
BOILED-EGG MODEL

What is this BOILED-egg?
A model that predicts BBB permeability and GI absorption based on lipophilicity and polarity
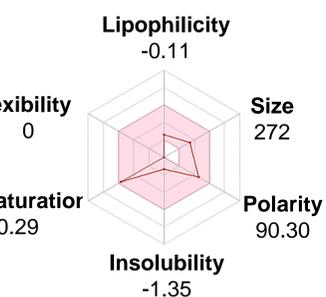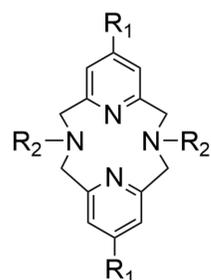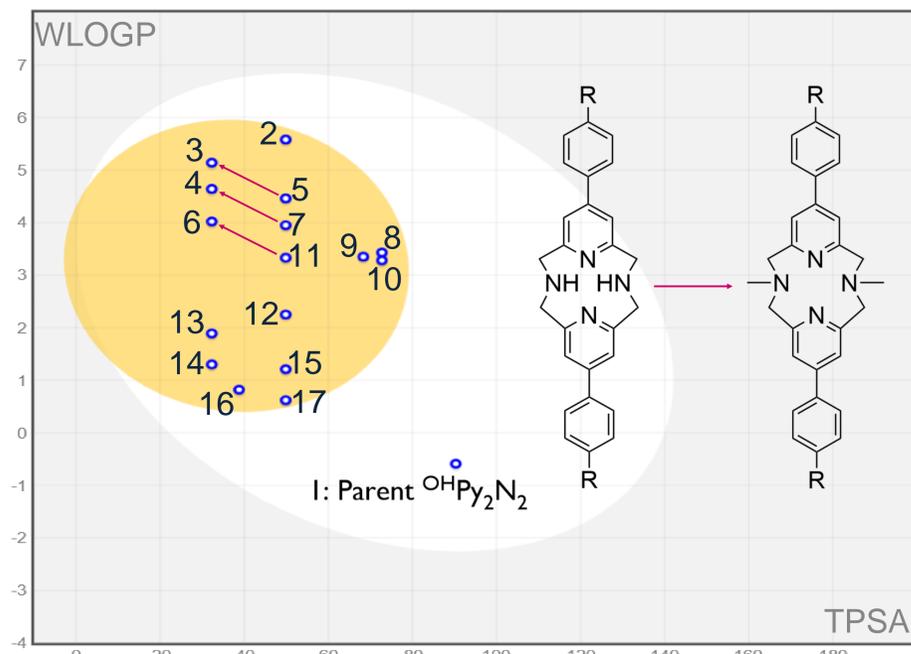- Y-axis: fat solubility
- X-axis: polar surface area

WLOGP vs TPSA
- BBB
- HIA
- PGP+
- PGP-

PGP+ Drug — P-Glycoprotein — Drug inside — PGP-

RESULTS

OH — Radical Scavenger
NH HN — Antioxidant — Metal Binding
OH

Target Values
Lipophilicity: 5
Size (g/mol): 150
Polarity (Å^2): 20
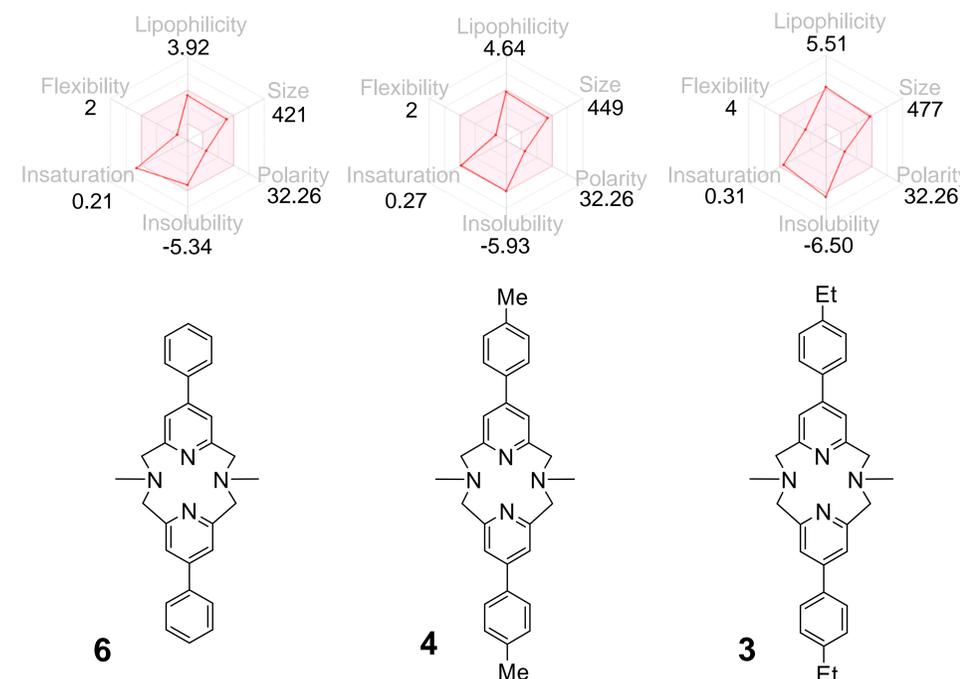Insolubility (mol/L): 0
Insaturation: 1
Flexibility: 0

Radar chart:
- Lipophilicity -0.11
- Size 272
- Polarity 90.30
- Insolubility -1.35
- Insaturation 0.29
- Flexibility 0

Design Strategy:
$^{OH}Py_2N_2$ properties must be improved to obtain BBB permeability

WLOGP vs TPSA scatter plot
Points: 3, 2, 4, 5, 6, 7, 11, 9, 8, 10, 13, 12, 14, 15, 16, 17
1: Parent $^{OH}Py_2N_2$

	R$_1$=OH, R$_2$=H		9 R$_1$=MeOPh, R$_2$=H
1	R$_1$=OH, R$_2$=H	9	R$_1$=MeOPh, R$_2$=H
2	R$_1$=i-PrPh, R$_2$=H	10	R$_1$=CH$_2$PhOH, R$_2$=Me
3	R$_1$=PhEt, R$_2$=Me	11	R$_1$=Ph, R$_2$=H
4	R$_1$=PhMe, R$_2$=Me	12	R$_1$=i-Pr, R$_2$=H
5	R$_1$=PhEt, R$_2$=H	13	R$_1$=I, R$_2$=Me
6	R$_1$=Ph, R$_2$=Me	14	R$_1$=Me, R$_2$=Me
7	R$_1$=PhMe, R$_2$=H	15	R$_1$=I, R$_2$=H
8	R$_1$=PhOH, R$_2$=Me	16	R$_1$=N,N-DMA, R$_2$=Me
		17	R$_1$=Me, R$_2$=H

TARGET MOLECULES

Molecule 6:
- Lipophilicity 3.92
- Size 421
- Polarity 32.26
- Insolubility -5.34
- Insaturation 0.21
- Flexibility 2

Molecule 4:
- Lipophilicity 4.64
- Size 449
- Polarity 32.26
- Insolubility -5.93
- Insaturation 0.27
- Flexibility 2

Molecule 3:
- Lipophilicity 5.51
- Size 477
- Polarity 32.26
- Insolubility -6.50
- Insaturation 0.31
- Flexibility 4

FUTURE DIRECTIONS

2 Steps
1) NaBH$_4$, CaCl$_2$, Anh. MeOH, 5 h
2) TsCl, NaOH H$_2$O/THF, 8 h

2 Steps
1) TsNHNa, CH$_3$CN 80 °C, 7 d
2) 1M HCl MeOH RT, 12 h

[Fe or Pd]

1) H$_2$SO$_4$ 120 °C, 3 h
2) NaOH

HCHO / HCOOH

X = Cl, Br, I
R = H, Me, Et

ACKNOWLEDGMENTS