



Universiteit Antwerpen

| Faculteit Farmaceutische, Biomedische  
en Diergeneeskundige Wetenschappen

# Design of novel DPP8 and DPP9 inhibitors using cosolvent molecular dynamics simulations

Olivier Beyens, Hans De Winter

# Why are we interested in DPP8/DPP9?

DPP9 inhibition leads to cell death in acute myeloid leukemia (AML) cell lines

**5-Year Survival rate AML**

**31.7%**

**Incidence: 1% of cancer cases (4.1/100,000 py) <sup>1</sup>**

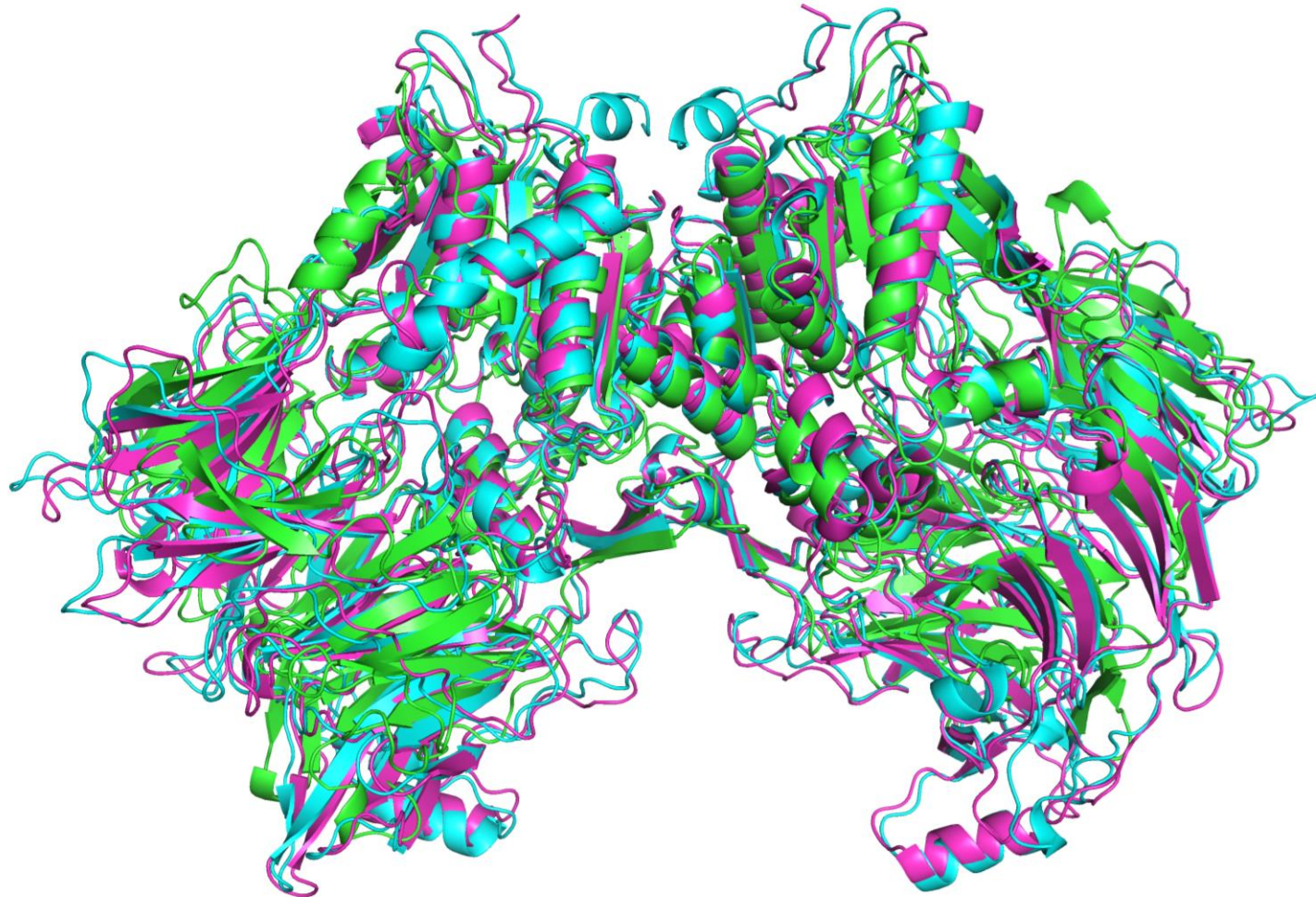
Role DPP8 less clear, selective inhibitor could help elucidate role



**Goal: design novel DPP8/DPP9 inhibitors, preferably selective**

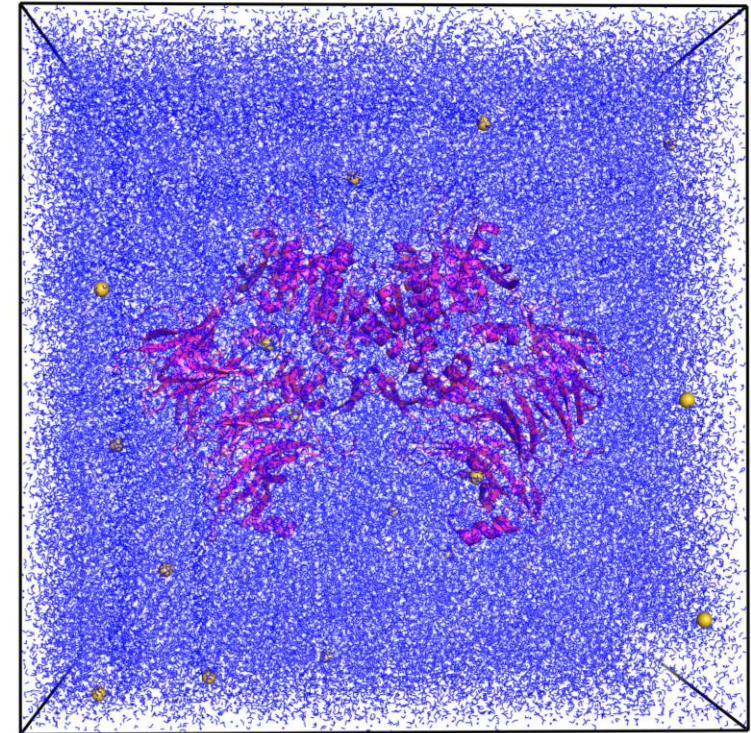
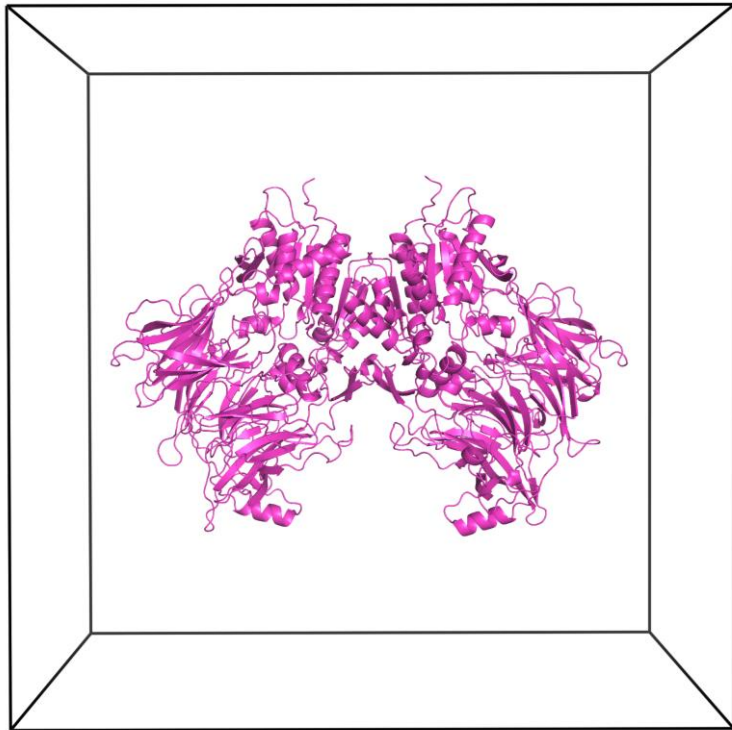
# Why is selectivity difficult?

Overlap of **DPP4**, **DPP8** and **DPP9** :



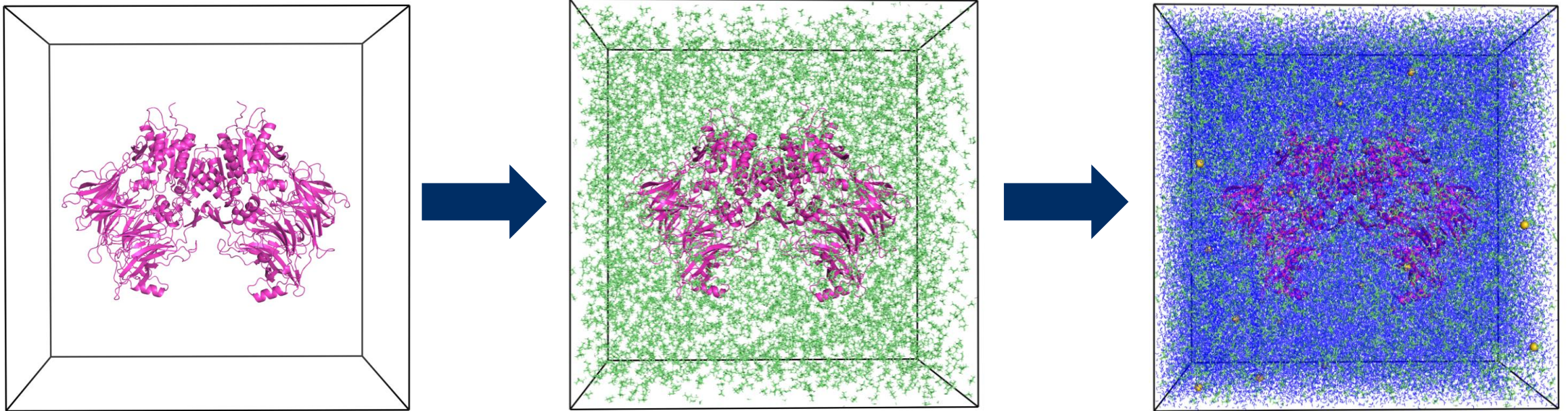
# Our solution: Cosolvent molecular dynamics

## Regular molecular dynamics setup

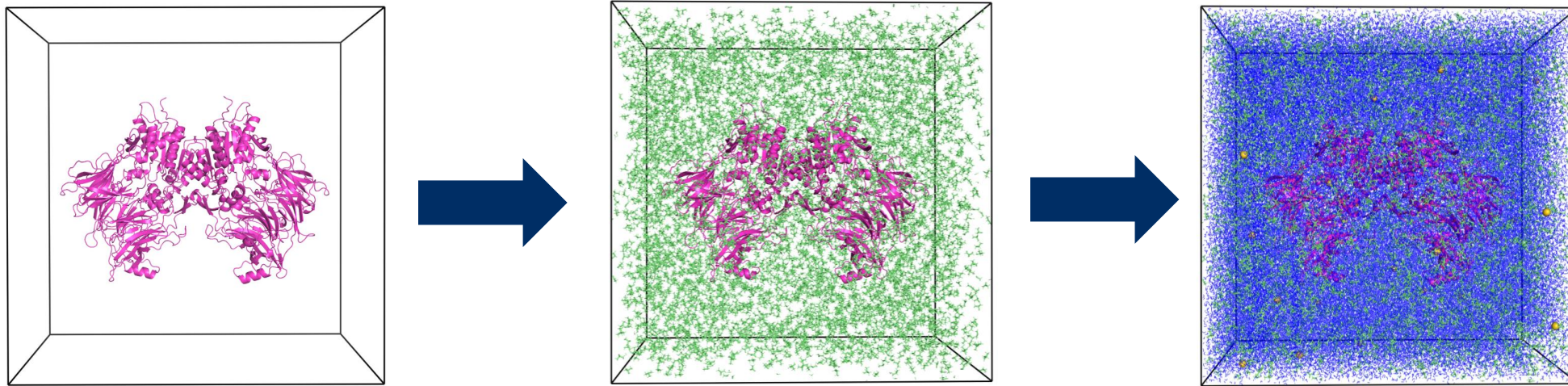


# Our solution: Cosolvent molecular dynamics

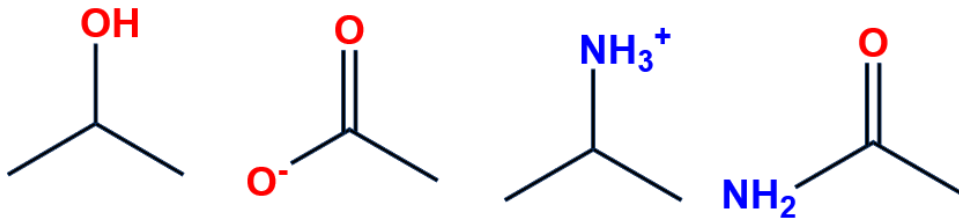
## Cosolvent molecular dynamics setup



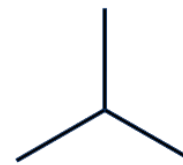
# Cosolvent molecular dynamics simulations



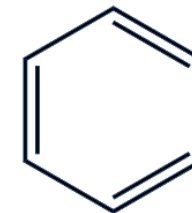
**Hydrophilic mix\***  
*50 x 360 ns = 18  $\mu$ s*



**Hydrophobic + PART**  
*25 x 200 ns = 5  $\mu$ s*

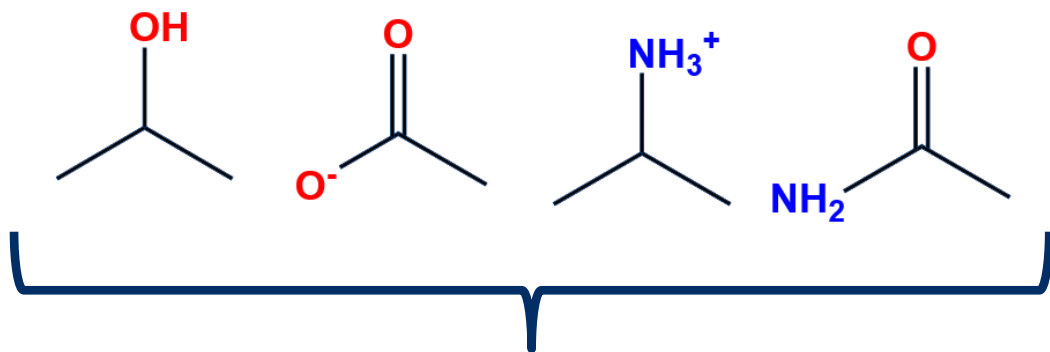


**Aromatic + PART**  
*25 x 200 ns = 5  $\mu$ s*



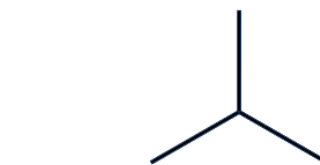
# LUMI: Powerful machine

**Hydrophylic mix**  
 $50 \times 360 \text{ ns} = 18 \mu\text{s}$

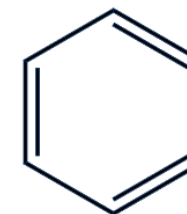


**LUMI-C**

**Hydrophobic + PART**  
 $25 \times 200 \text{ ns} = 5 \mu\text{s}$



**Aromatic + PART**  
 $25 \times 200 \text{ ns} = 5 \mu\text{s}$



**Hortense (VSC Tier 1)**

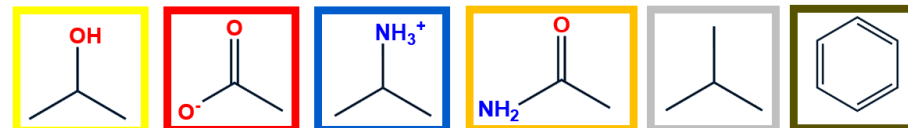
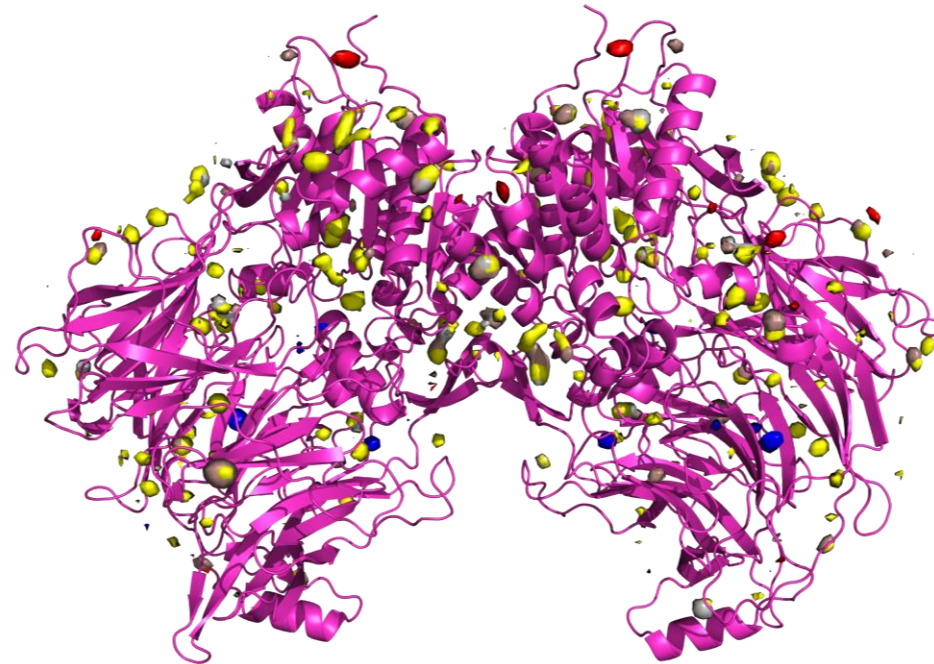
Setup: 1 node per parallel trajectory

Timings:

- DPP4 (366K atoms): 29 ns/day
- DPP8 (468K atoms): 25 ns/day
- DPP9 (419K atoms): 27 ns/day

↔ Previous longest simulation DPP8/9:  $2 \times 200 \text{ ns}^1$

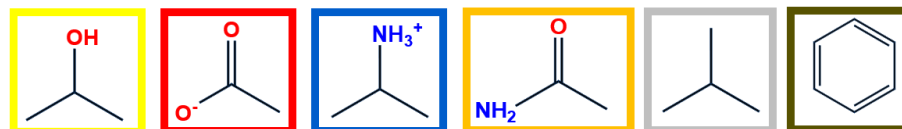
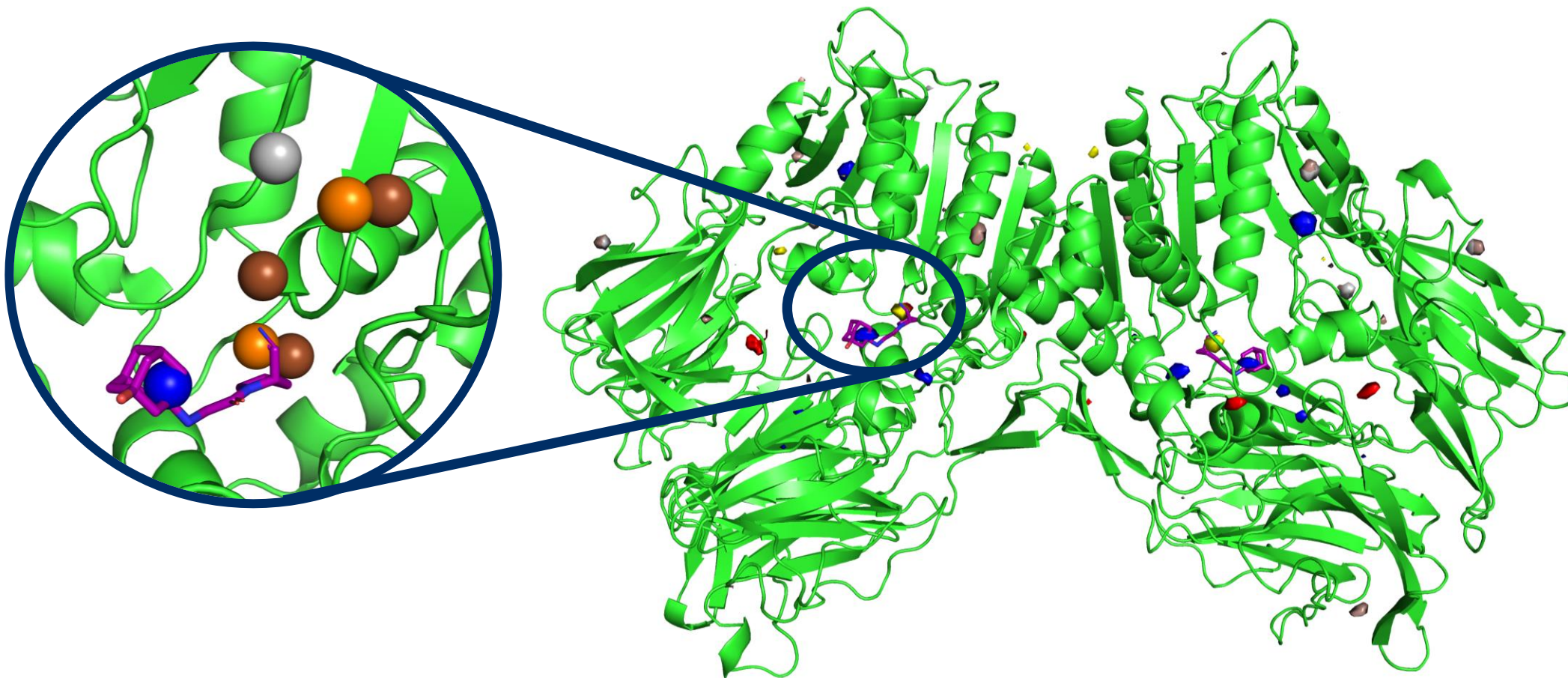
# How can we design new inhibitors?



Cut-offs: all 0.01 Å<sup>-3</sup>

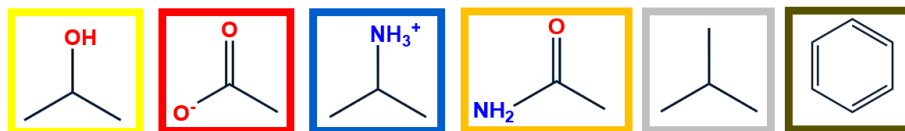
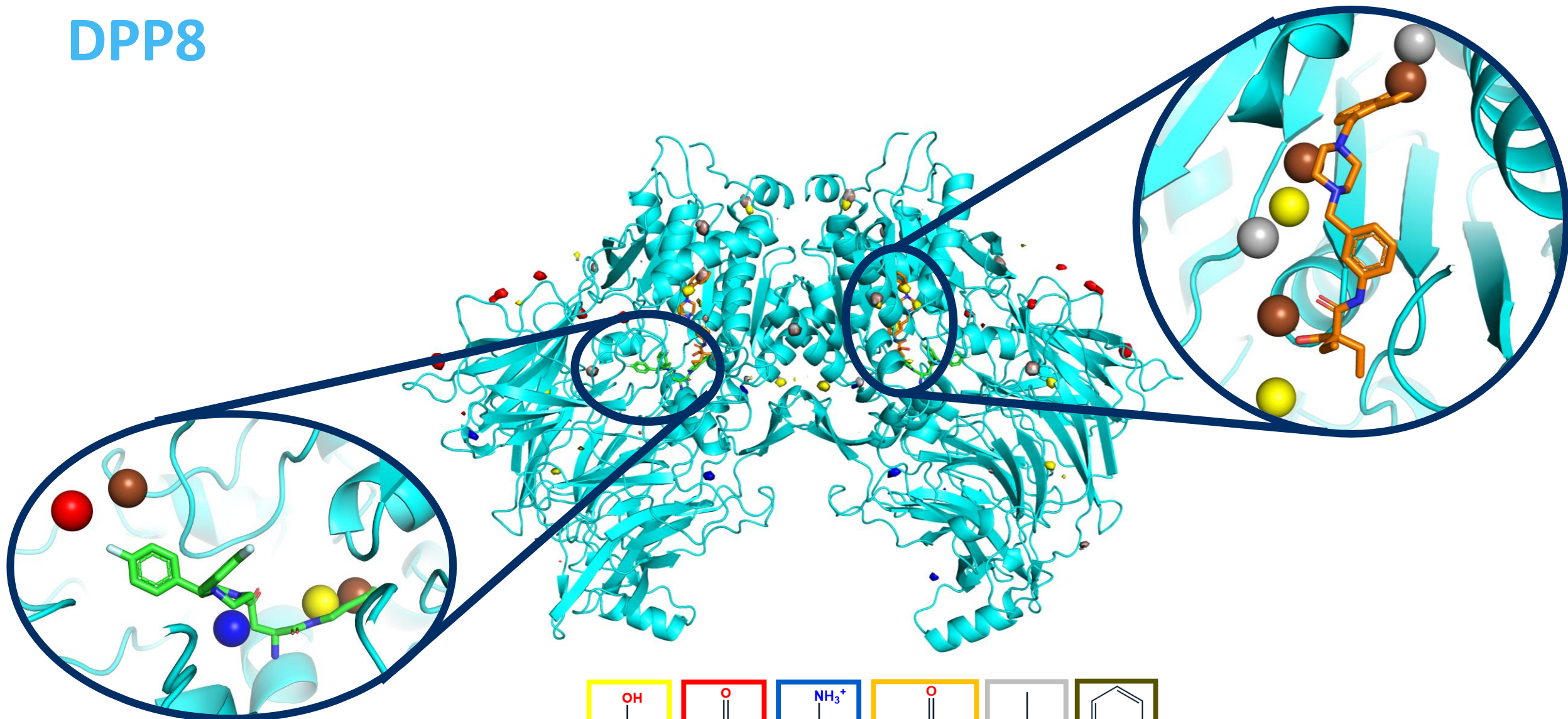


# DPP4



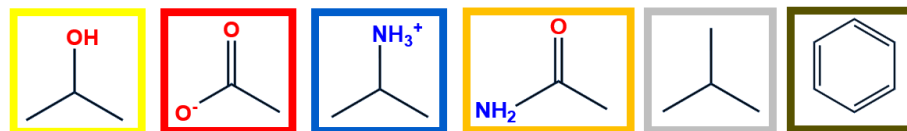
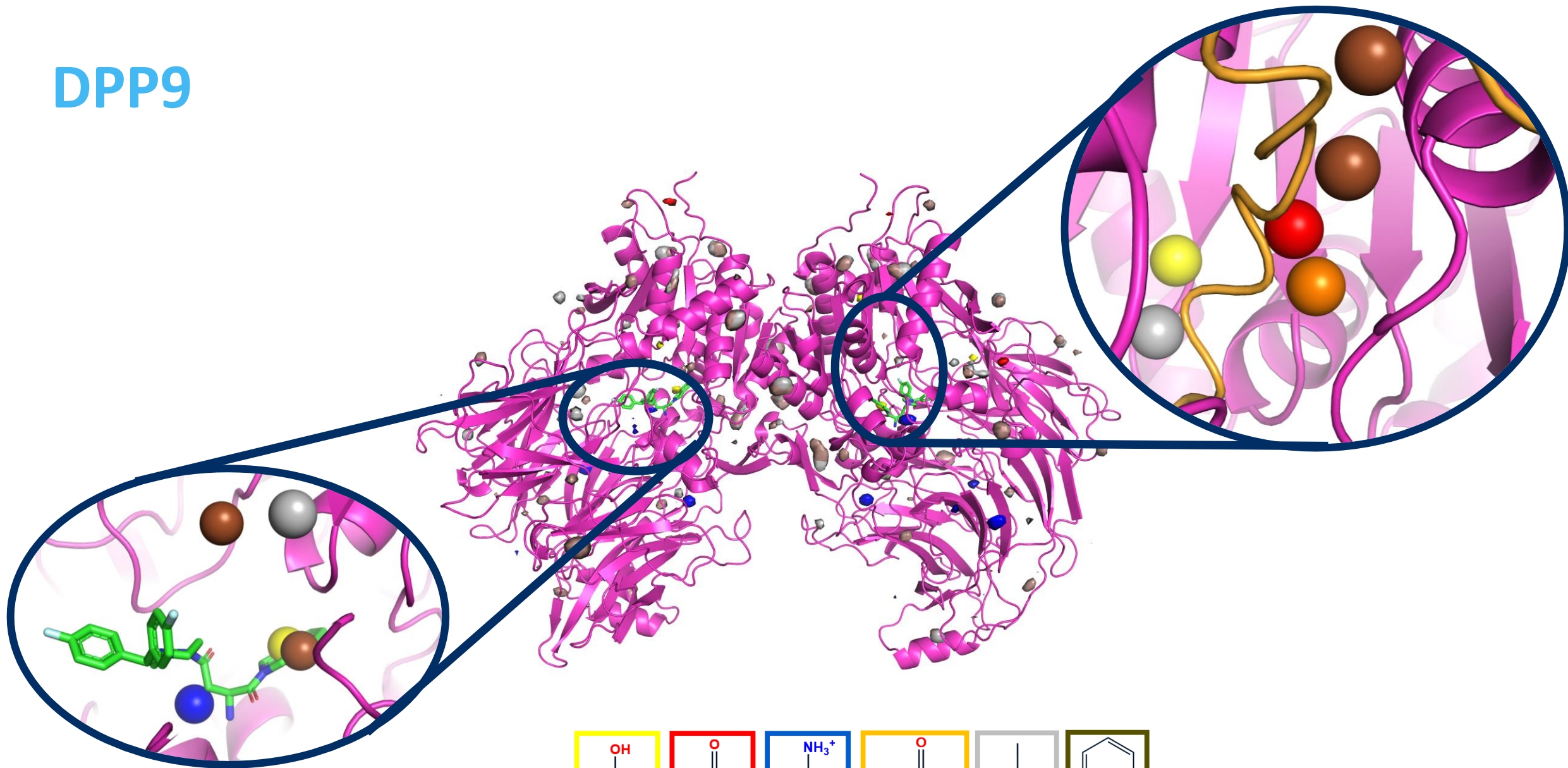
Cut-offs (Å<sup>-3</sup>): 0.03 0.02 0.02 0.02 0.03 0.03

# DPP8



Cut-offs (Å<sup>-3</sup>): 0.03 0.02 0.02 0.02 0.03 0.03

# DPP9



Cut-offs ( $\text{\AA}^{-3}$ ):

0.03

0.02

0.01

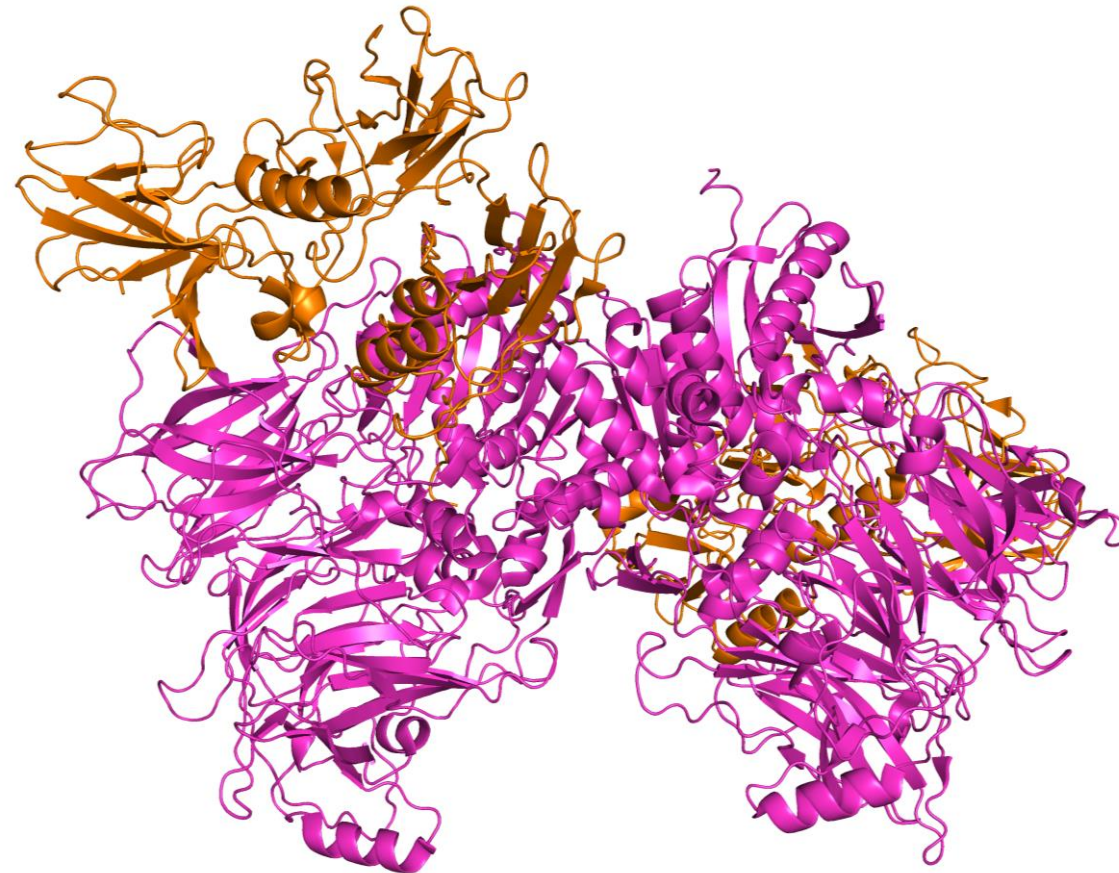
0.02

0.01

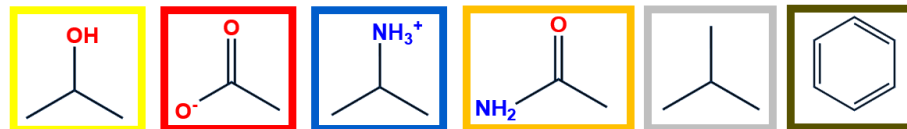
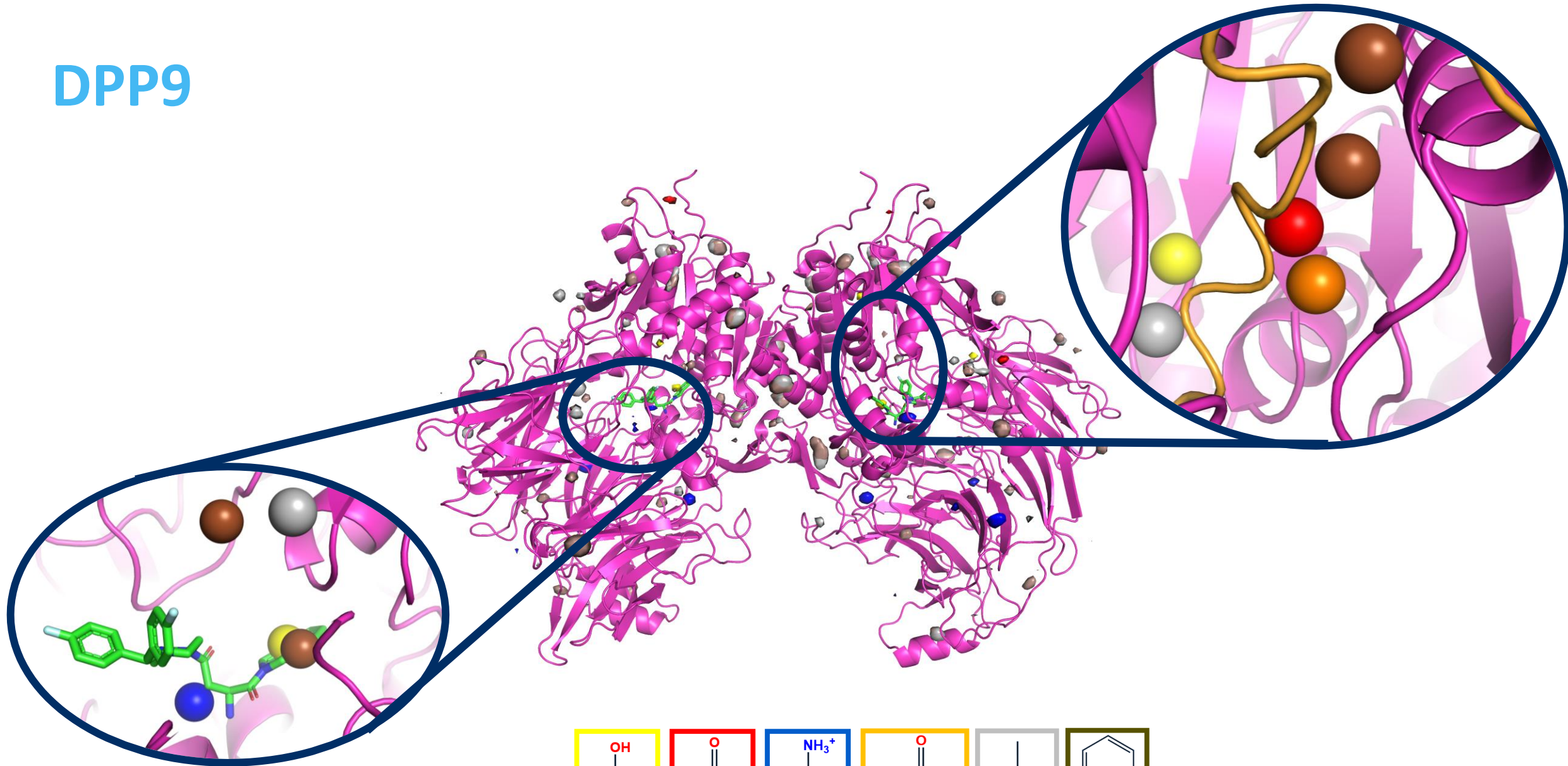
0.01

# Deep dive DPP9

**DPP9** binds the inflammasome sensor **NLRP1** <sup>1</sup>

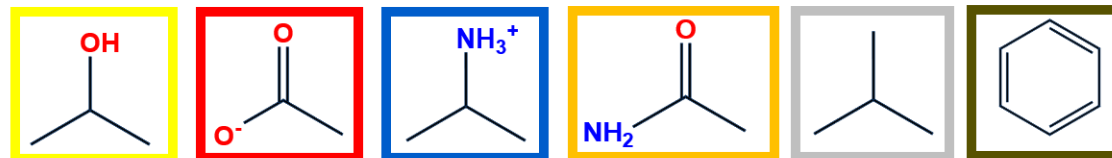
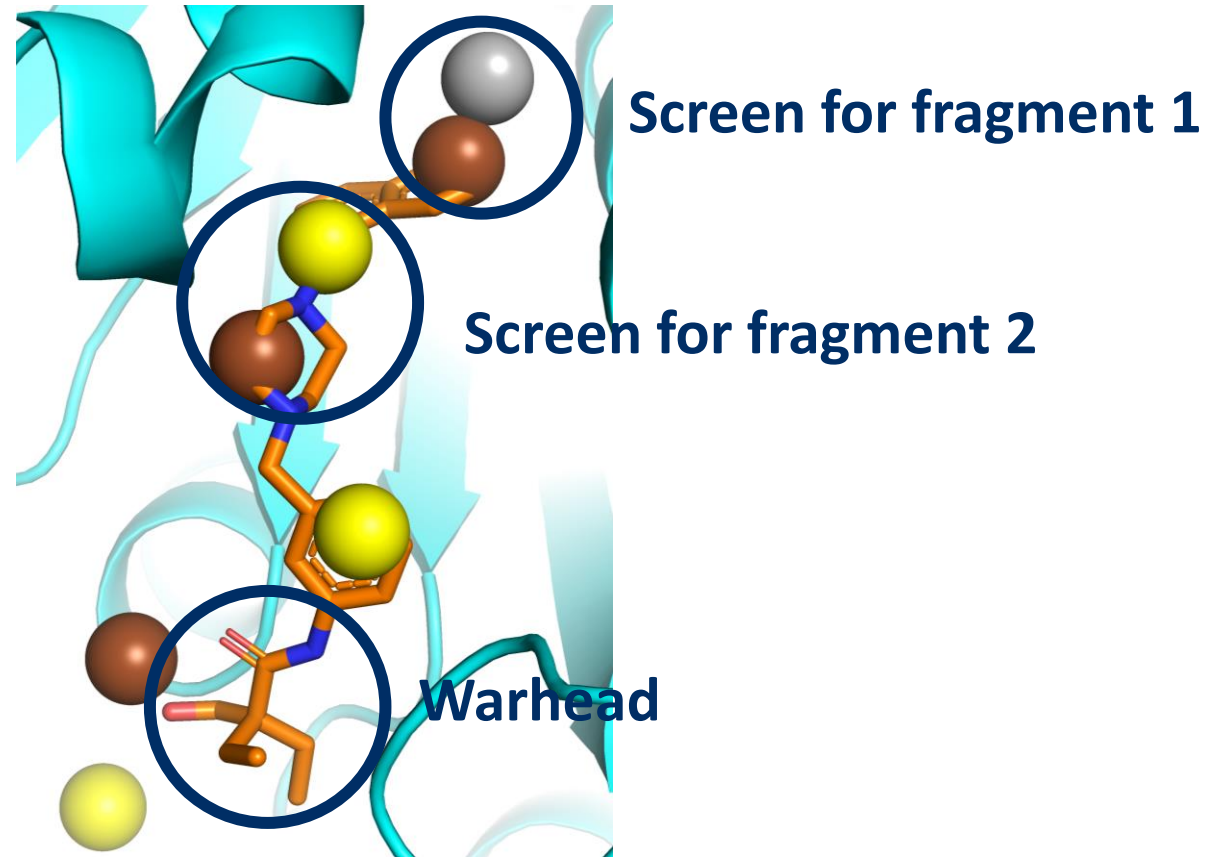


# DPP9



Cut-offs (Å<sup>-3</sup>): 0.03 0.02 0.01 0.02 0.01 0.01

# Fragment linking example



# Conclusion

