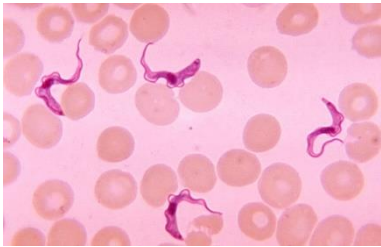# Fragment Hit Follow-up
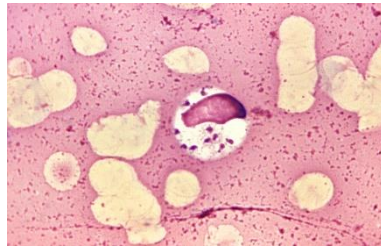
Fredrik Svensson, David Bailey

Phosphodiesterase Inhibitors for Neglected Parasitic Diseases
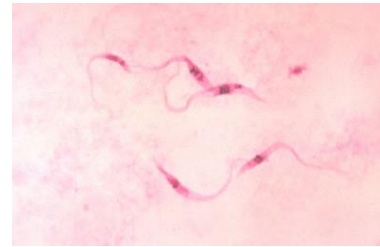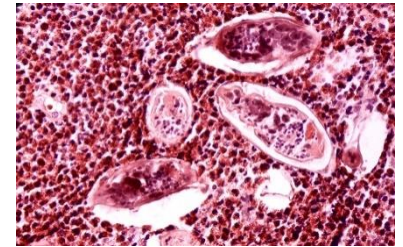

Sleeping Sickness | Leishmaniasis | Chagas Disease | Schistosomiasis
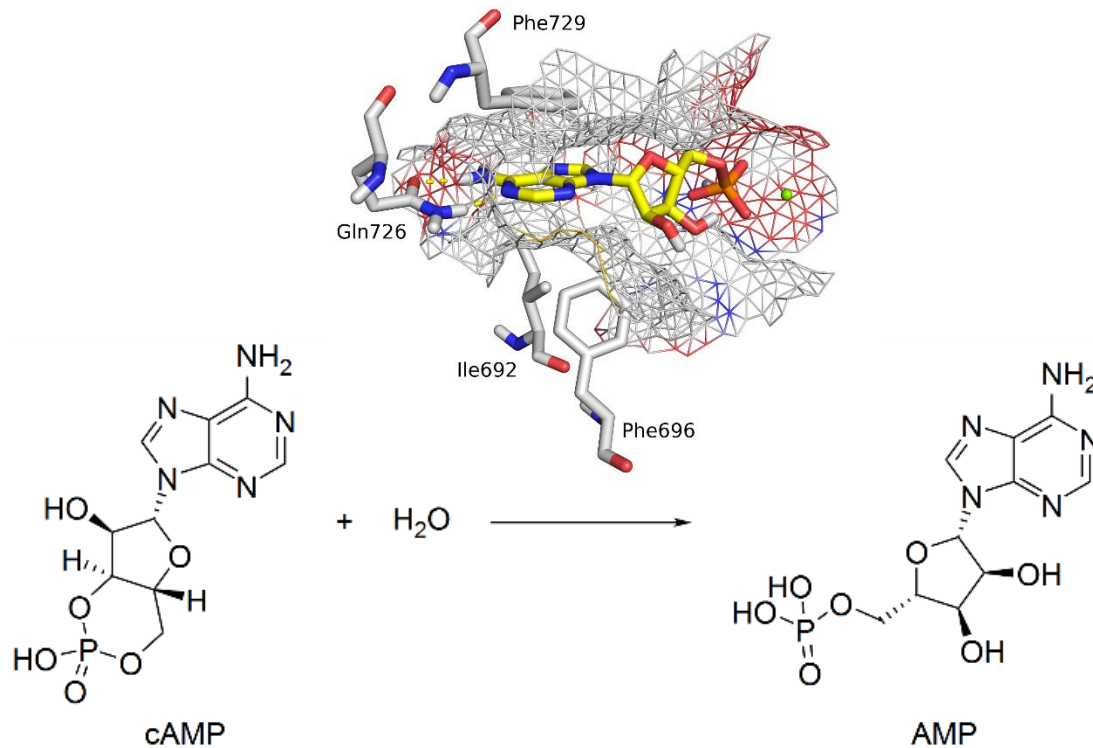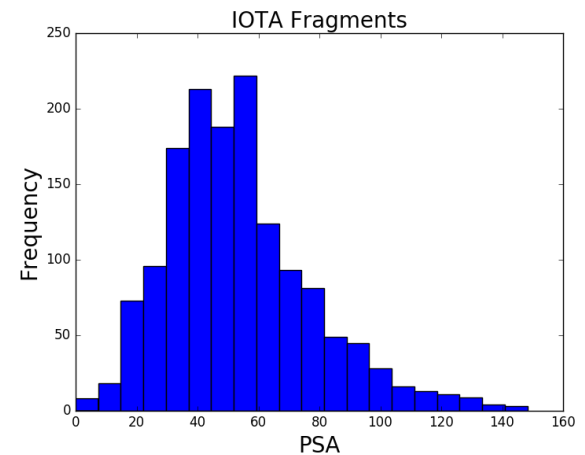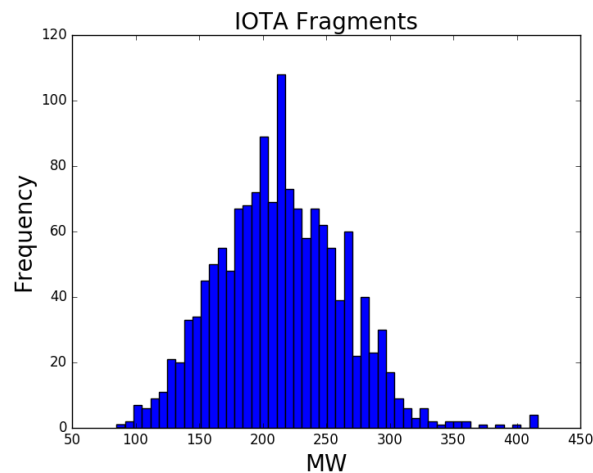
Consortium Partners

Phosphodiesterases

cAMP + H₂O → AMP

PDEs as anti-parasite targets
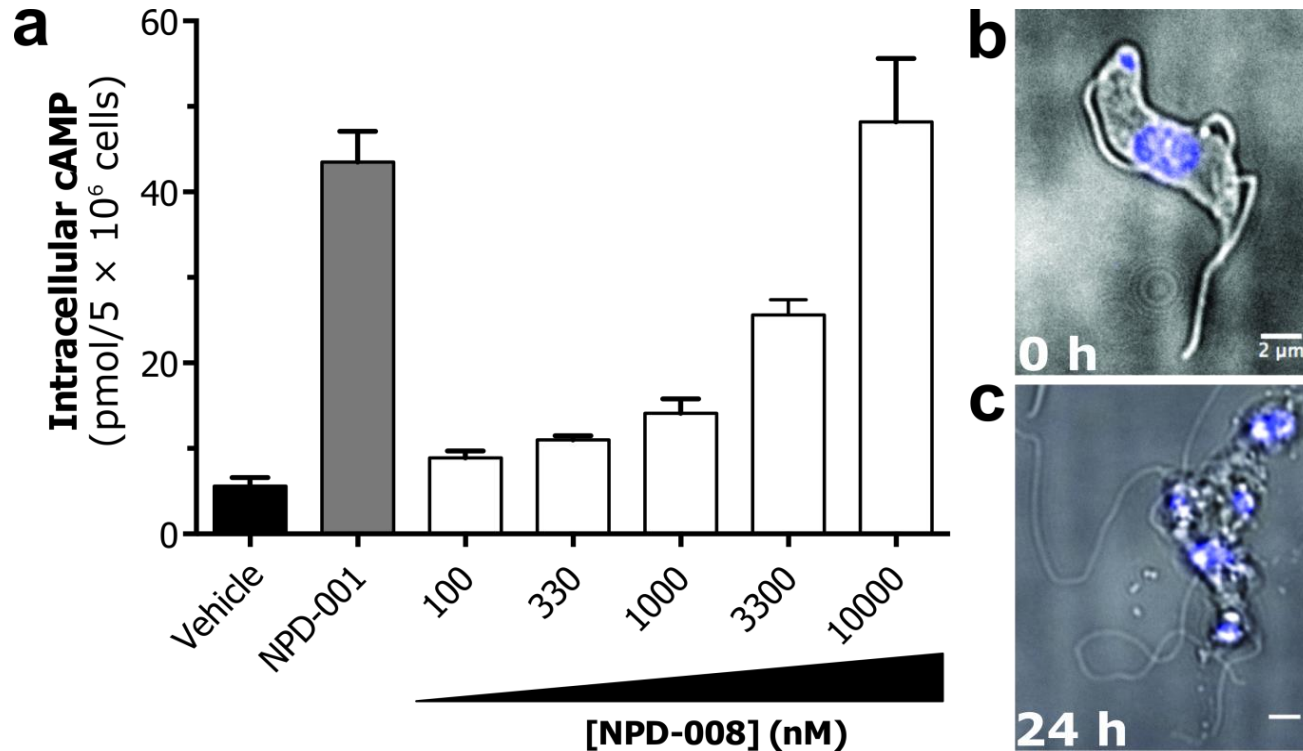
IOTA 1500 Fragment Library

FRET Assay

Primary Screen
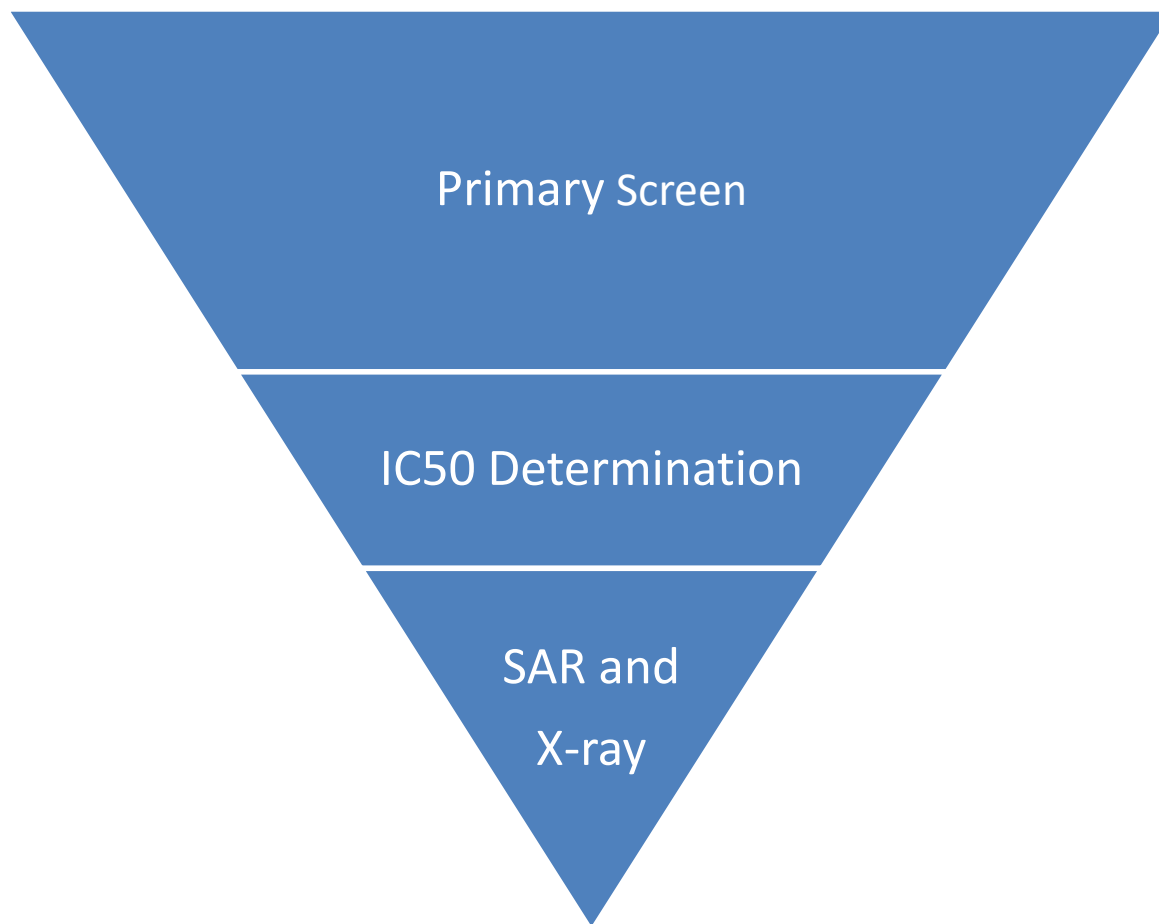
IC50 Determination
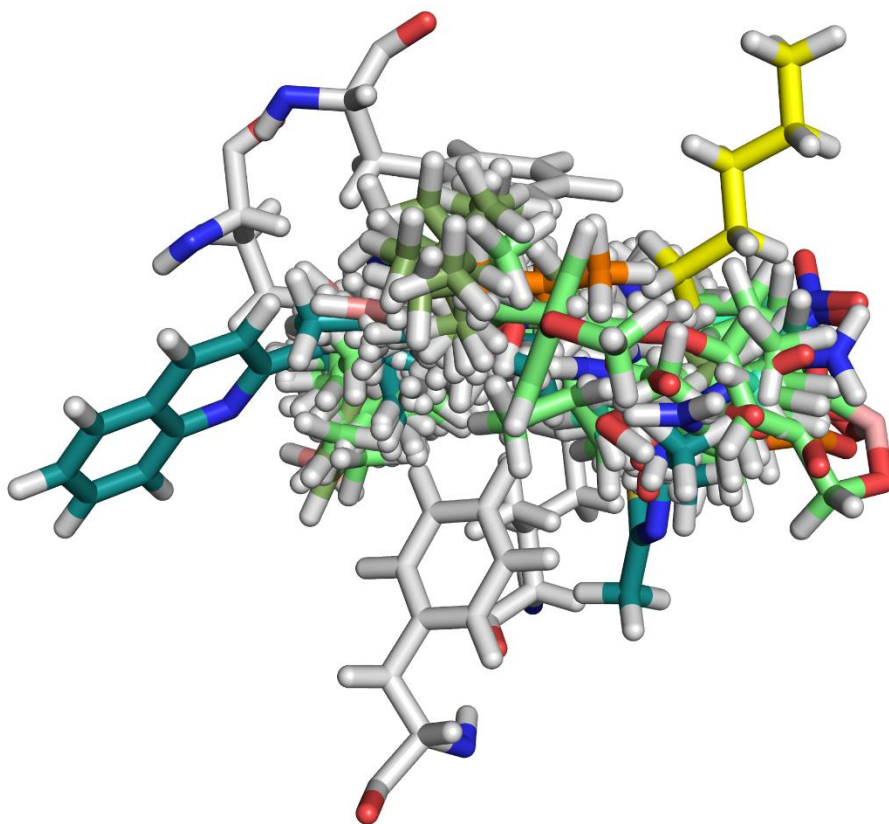
SAR and
X-ray
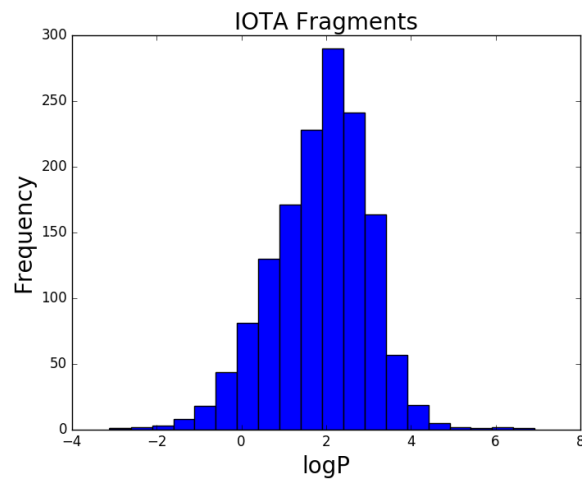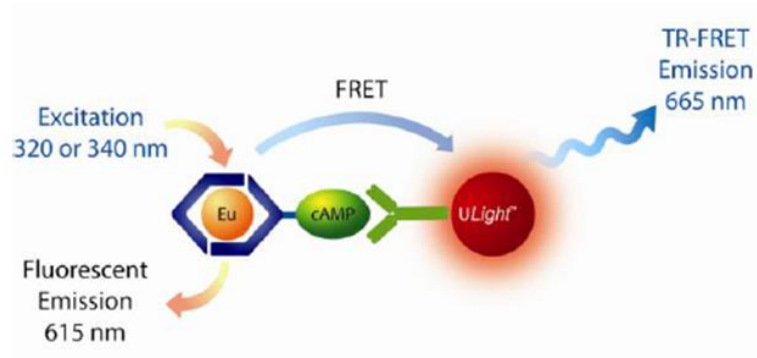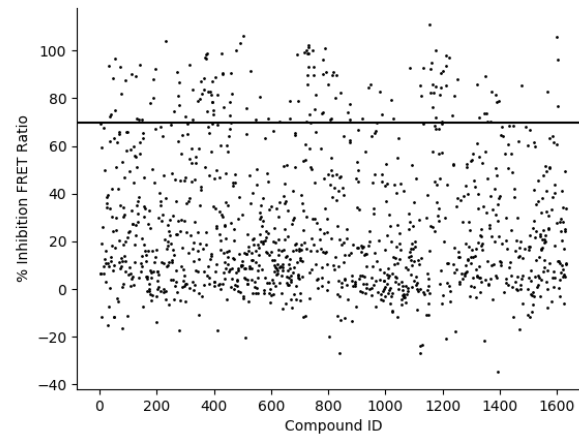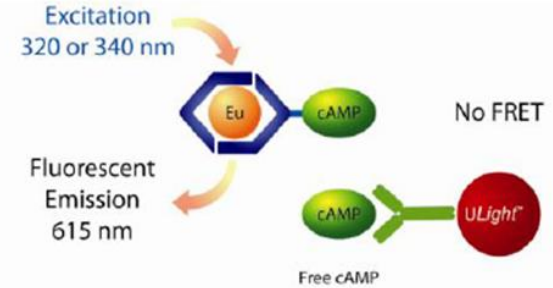
MedChem

Computational Hit Follow-up

- Informatics
- Predicted/calculated properties
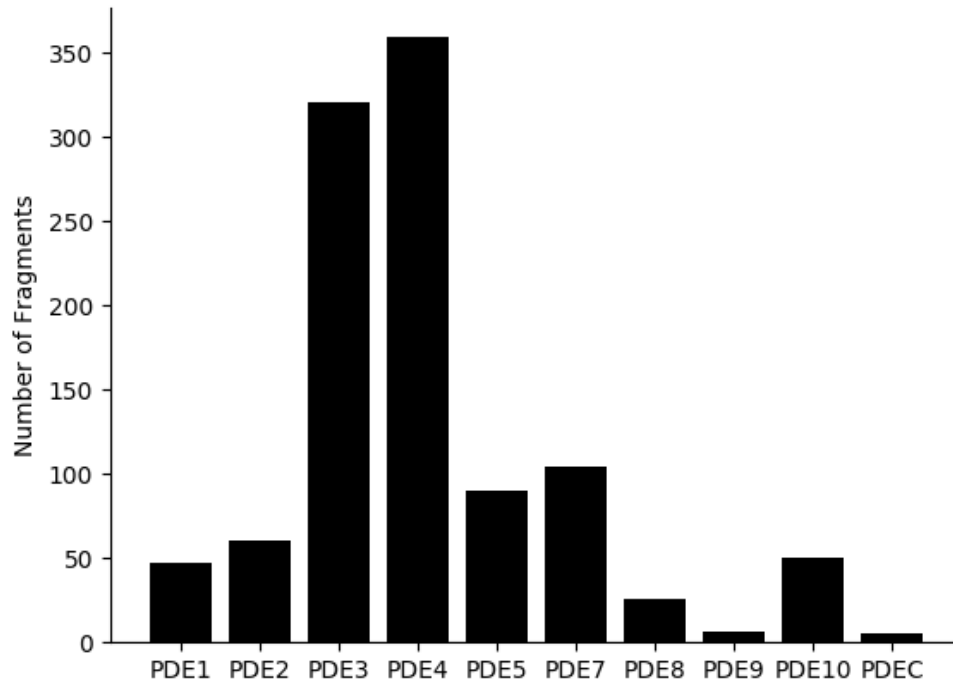- Predicted binding modes

Computational Hit Follow-up

- Informatics
- Predicted/calculated properties
- Predicted binding modes

IOTA

Fragment Binding to PDEs

PDE active fragments

- 906 PDE inhibitory fragments compiled

Computational Hit Follow-up

- Informatics

- Predicted/calculated properties

- Predicted binding modes

IOTA

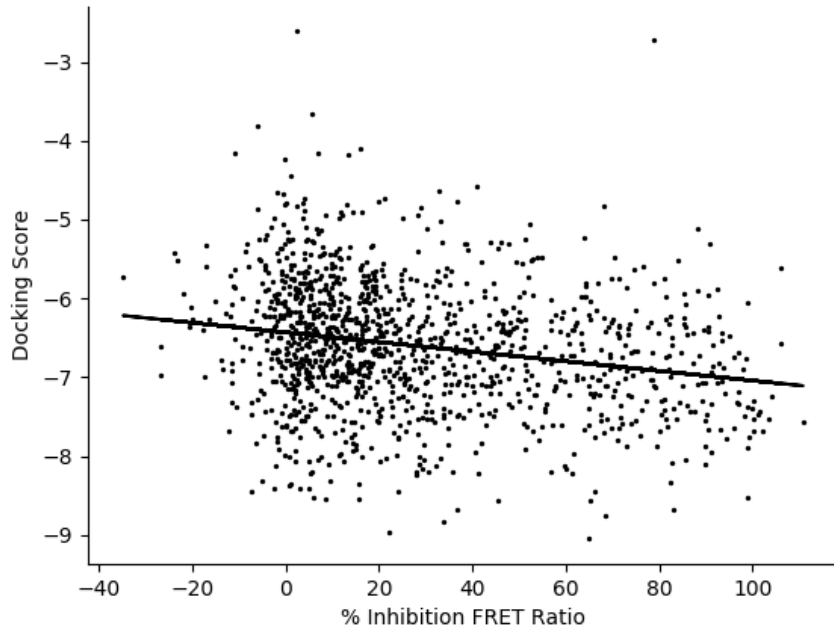# Predicted/Calculated Properties

- LE, LLE
- Physico-chemical properties (QikProp)
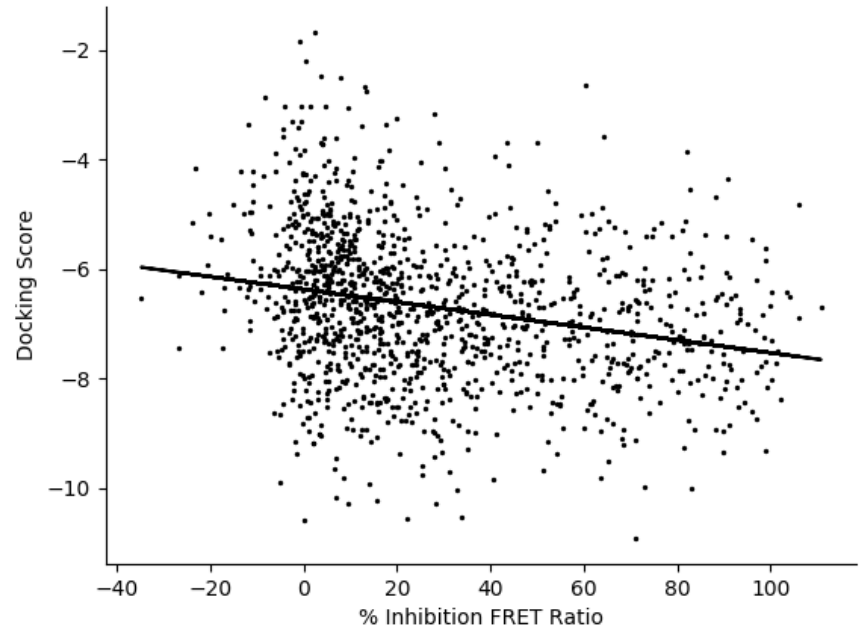- ADME

IOTA

Computational Hit Follow-up

- Informatics

- Predicted/calculated properties

- Predicted binding modes
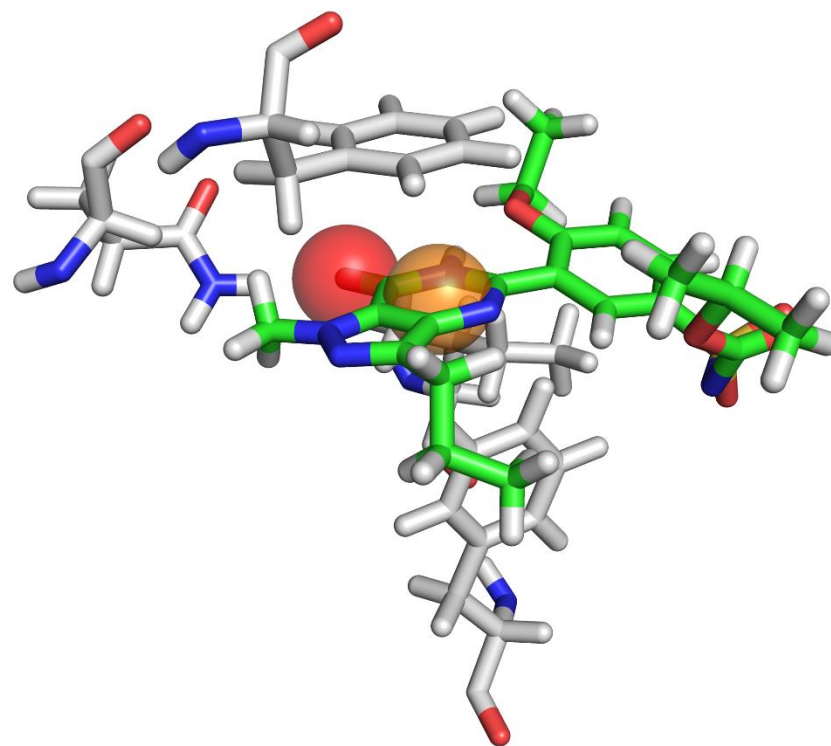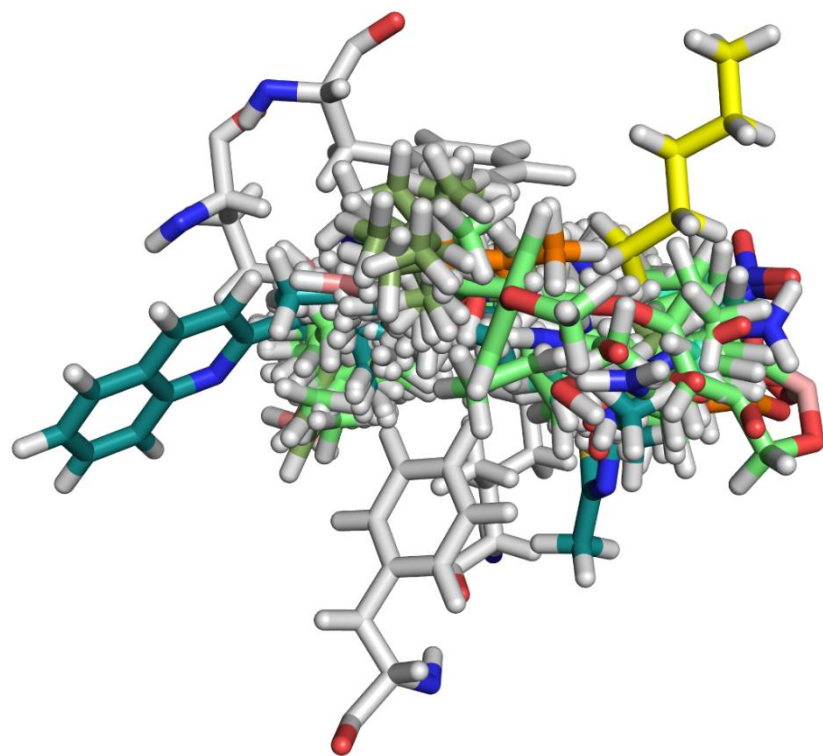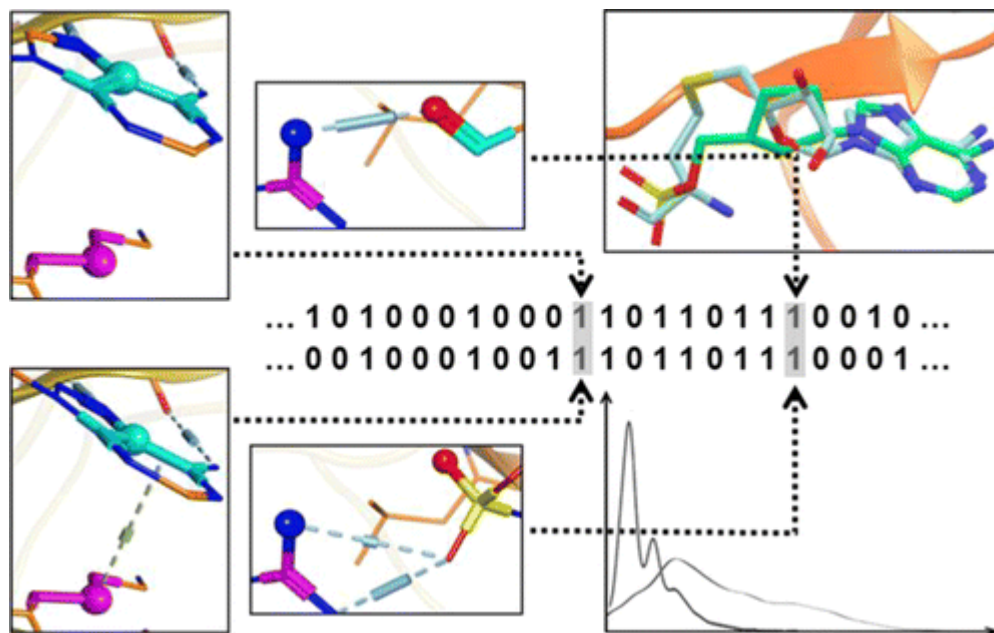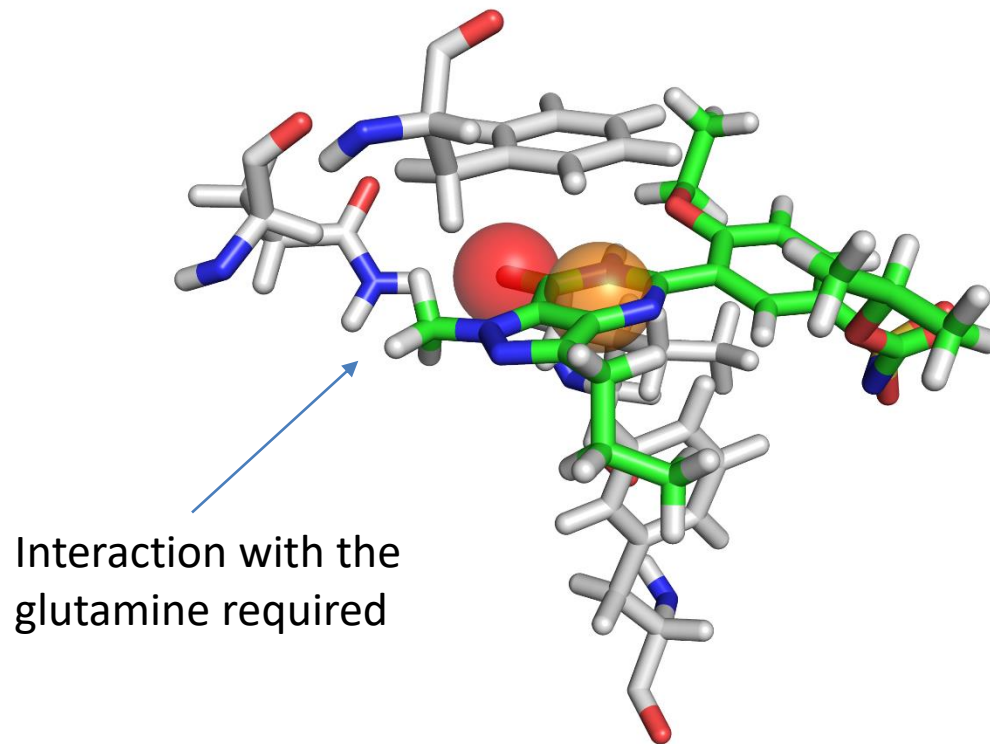
IOTA

Docking - not very promising

Glide SP

Glide XP

PDE Pharmacophore – better

Interaction fingerprints
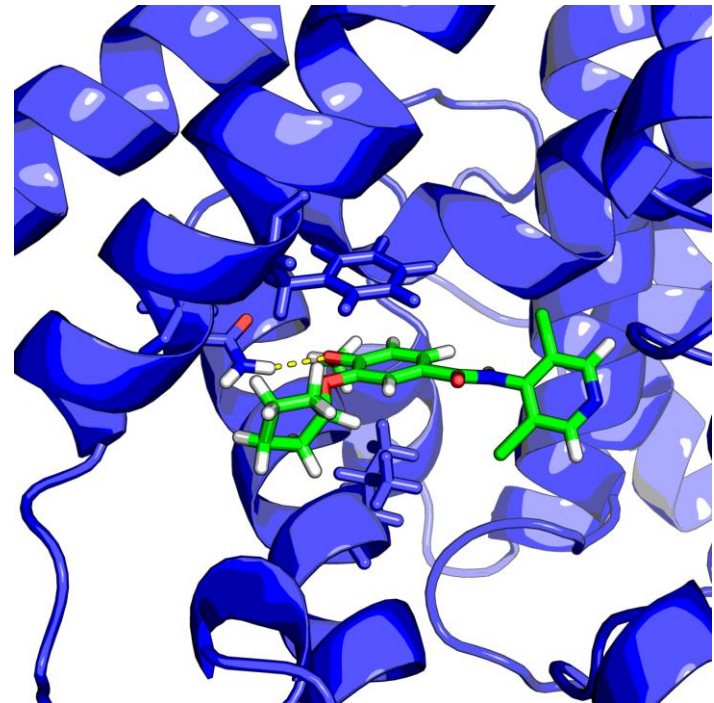
Constrained Docking

Interaction with the
glutamine required

Predicted binding mode

- Promising interactions?
- Good vectors?

IOTA

Decision making

- Computational work only one factor
  - Quality of binding data/orthogonal assays
  - Synthetic accessibility
  - Commercially available analogues
  - Ligand Efficiency

Thank you!

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