MISSIONE 4
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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Integrating computational and biophysical approaches within VITALITY enabling platform for Drug Discovery

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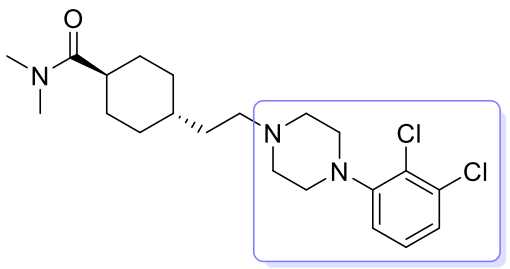
Projects resulting in accessible pipelines for external partners

- Integration of **biophysical experiments** and **binding free-energy calculations** (GSK-3β-D_3 dual-acting compounds)
- Workflows for **database screening integration** in virtual screening (GSK-3β-D_3 dual-acting compounds)
- **Fast shape screening approaches** prioritizing ligand structure and conformation (GSK-3β-D_3 dual-acting compounds and *CysH* project)
- Virtual screening **prioritization through deep learning** (GSK-3β-D_3 dual-acting compounds)
- **Screening of covalent compounds** (*CysH* project)
- Evaluation of ligand **residence time** and **interaction stability** (*CysH* project)

Establishing rapid workflows for DMTA cycles in academic and industrial collaborations

Design of dual-acting compounds targeting D3 receptor and GSK-3β enzymatic activity

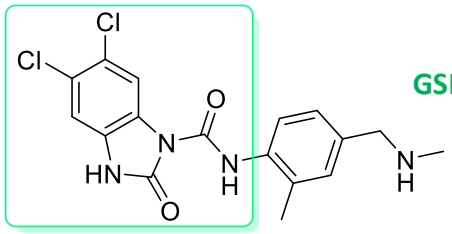
MTDLs concurrent modulation of two targets that contribute to the regulation of the DA signalling pathway and that have both been involved in **bipolar disorder**.



Cariprazine

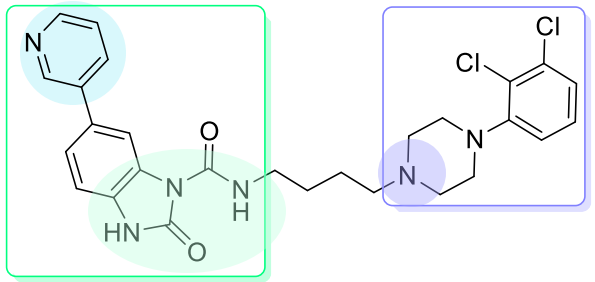
D_3R: EC_{50}= 2.09 nM (70.9% Emax)

D_3R partial agonist



GSK-3β: IC_{50}= 8 nM

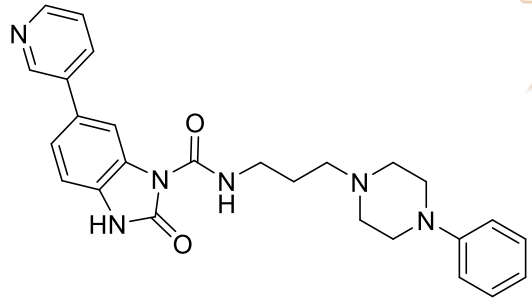
GSK-3β enzyme inhibitor



ARN24161

D_3R: EC_{50}= 10.1 nM (26.3% Eff.)

GSK-3β: IC_{50}= 561 nM



ARN25657

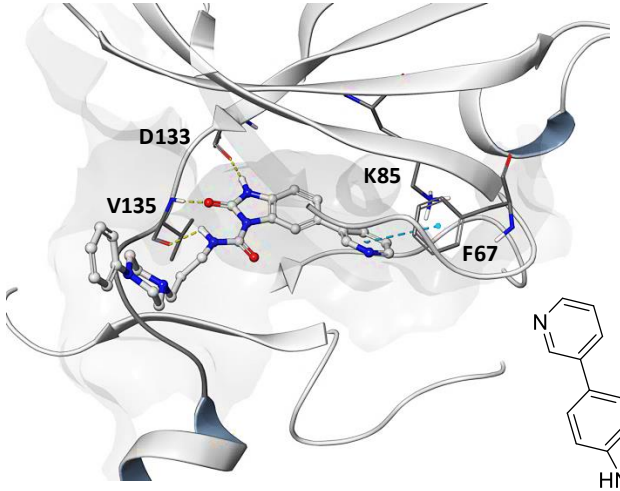
D_3R: EC_{50}= 15.2 nM (37.7% Eff.)

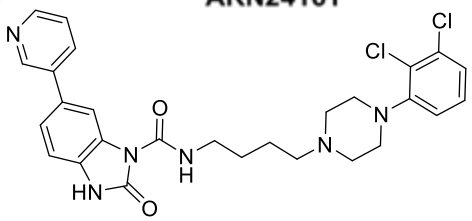
GSK-3β: IC_{50}= 19.7 nM

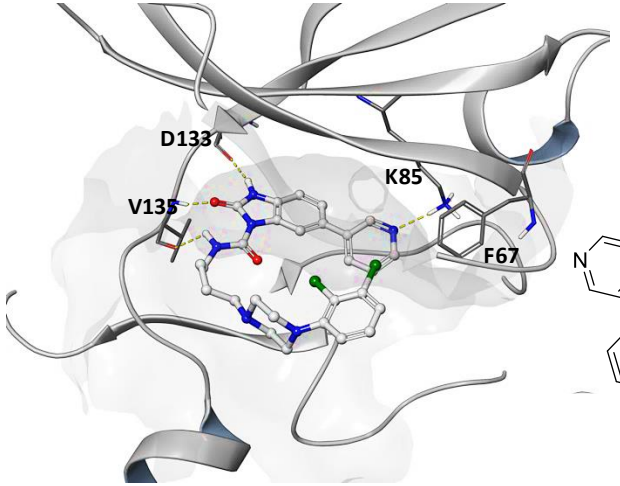
- Piperazine nitrogen is responsible for the salt-bridge formation with $D110^{3.32}$
- Benzo[*d*]imidazole-1-carboxamide portion as GSK-3β hinge binder (D133 e V135)
- 3-pyridil substituent increasing solubility and establishing a contact with K185

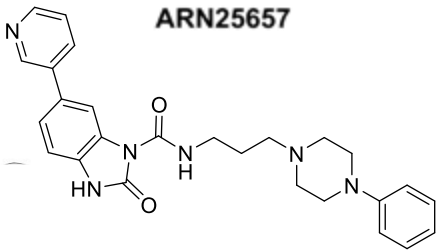
Di Martino R. M. C. et al.,
ChemMedChem. **2020**, 15, 949-54

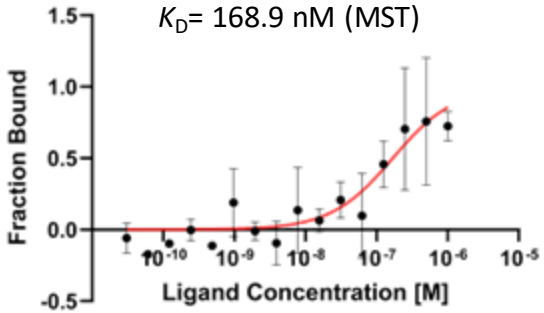
Integrating free-energy simulations and biophysical experiments

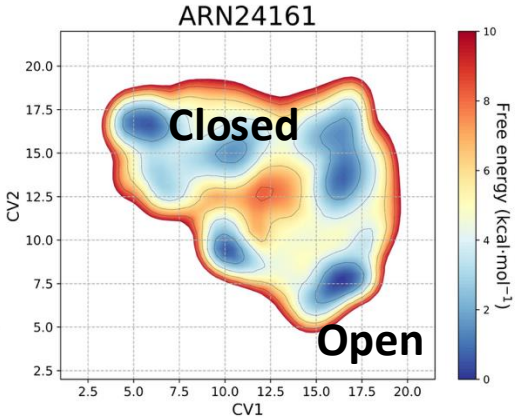






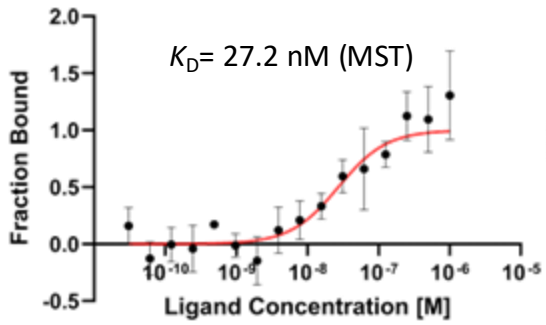


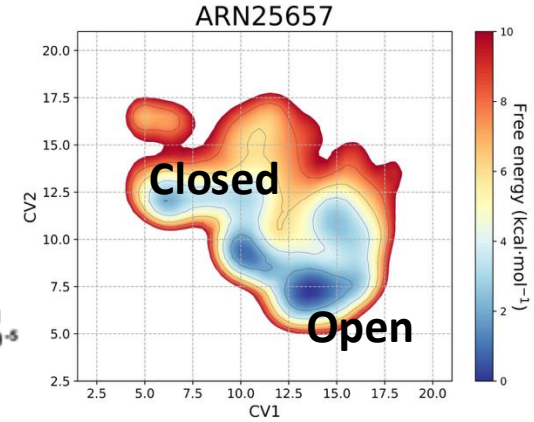




MST binding assays

PCV wt-Metadynamics



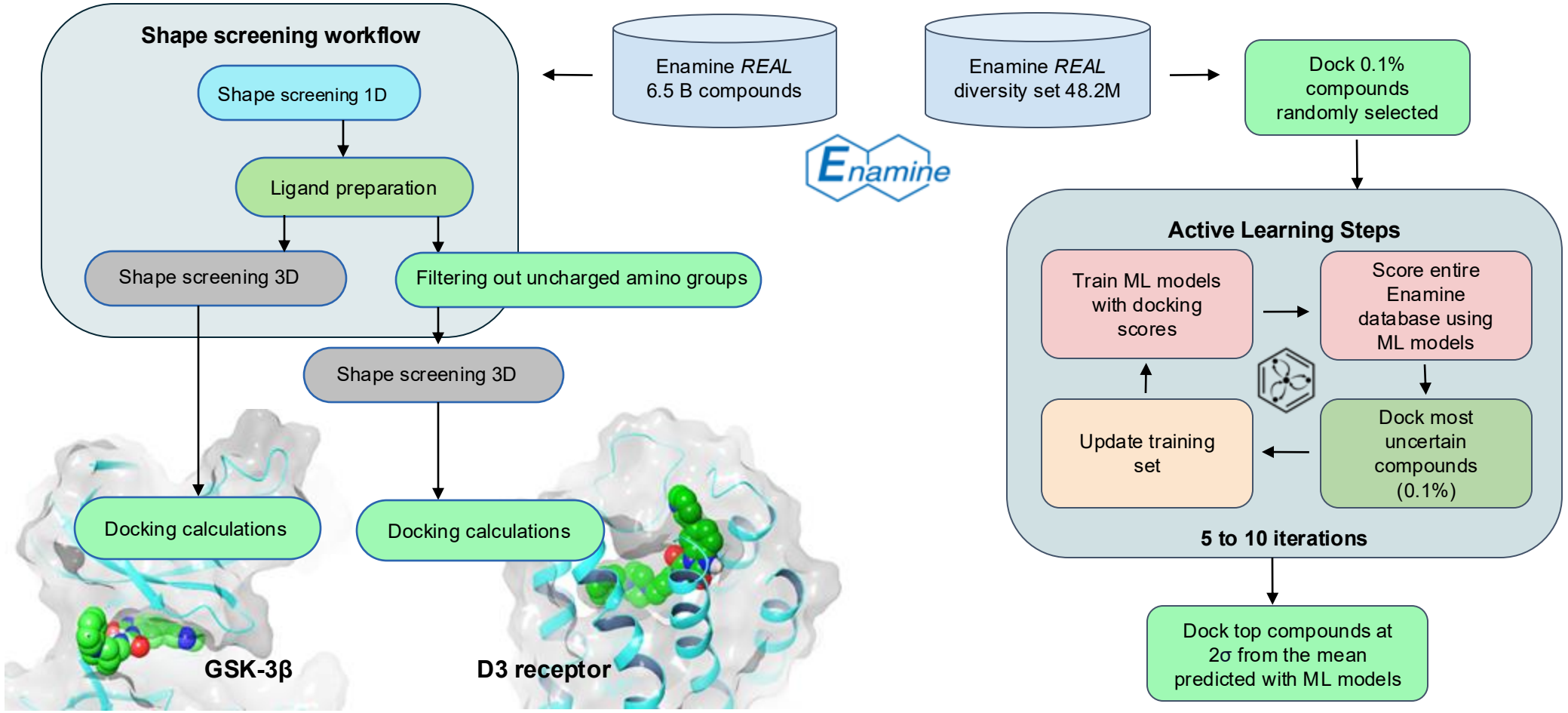


Design and synthesis of macrocyclic derivatives

Interrogation of public databases

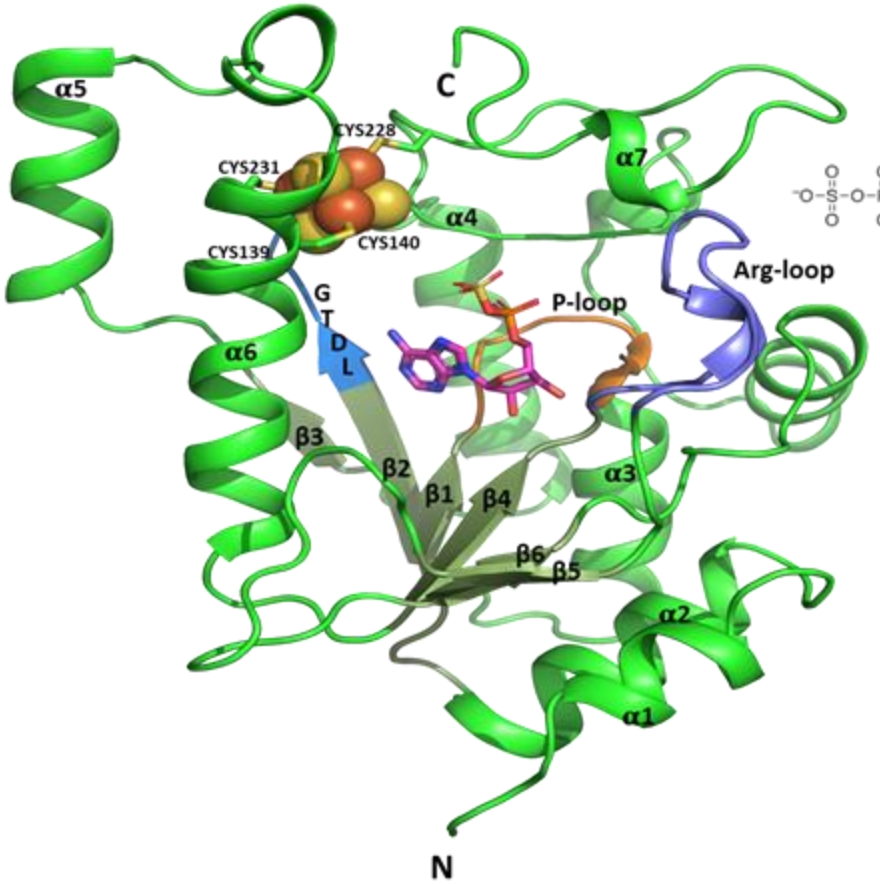
Design and synthesis of spirocyclic derivatives

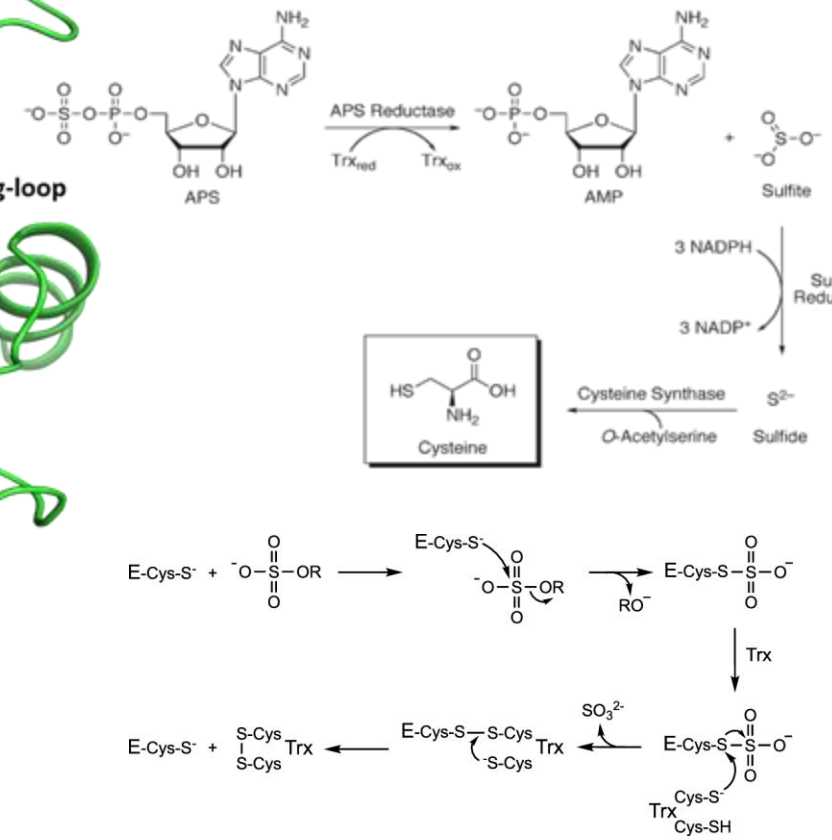
Approaches for virtual screening of commercial compounds



Combating *Pseudomonas aeruginosa* resistant infections

- **Reduction of inorganic sulfate** due ASPR activity is necessary for cysteine biosynthesis.
- Disruption of the *CysH* gene encoding for this enzyme has been correlated to decreased pathogen virulence and **cysteine auxotrophy** in mycobacteria.
- Mechanism is mediated by C256 located in the **non-crystallized *C*-terminal portion**.





Chartron J. et al.,
J. Mol Biol. **2006**, 364, 152-69

Finding APSR enzymatic activity inhibitors through concurrent strategies

prioritizing scaffold diversity

Enamine *REAL* diversity sets

Brute-force docking calculations

Pharmacophore-based screening

Structural interaction fingerprints

Enamine *REAL* 6.5 B compounds

Shape screening workflow

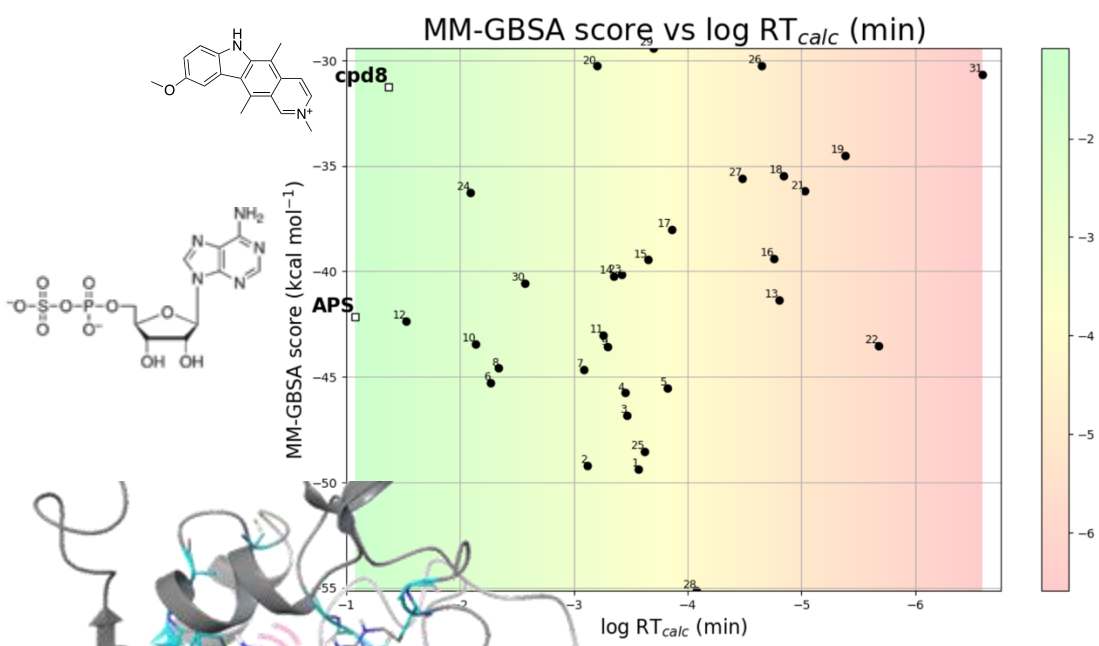
Shape screening 1D

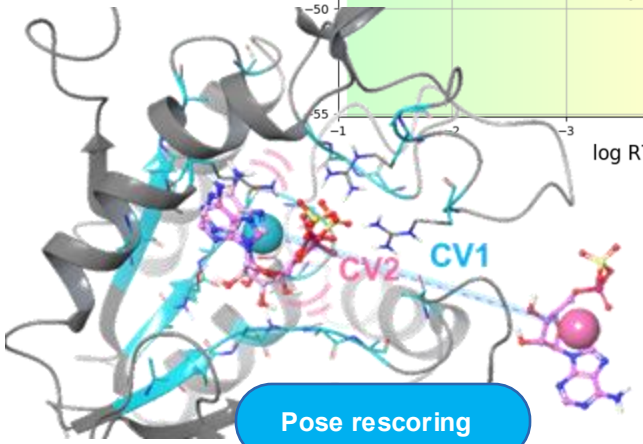
Ligand preparation

Shape screening 3D

Docking calculations

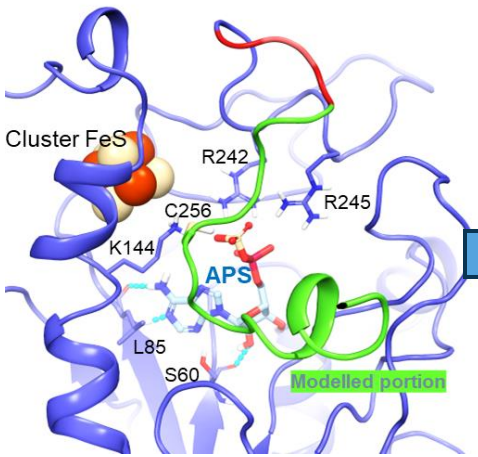
privileging structural analogy with the substrate

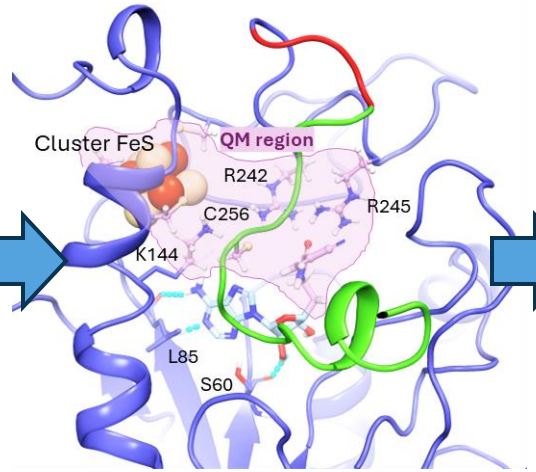


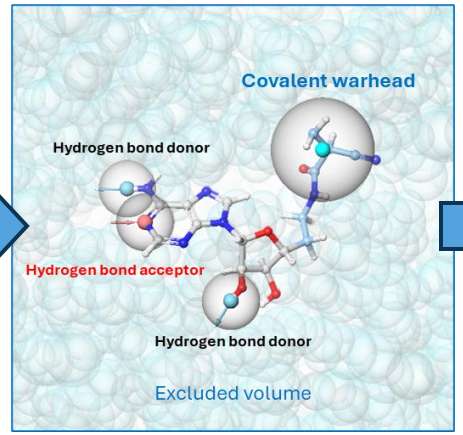


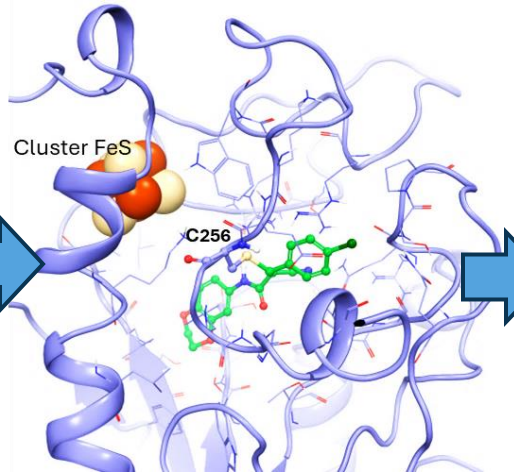
evaluating pose stability and residence time

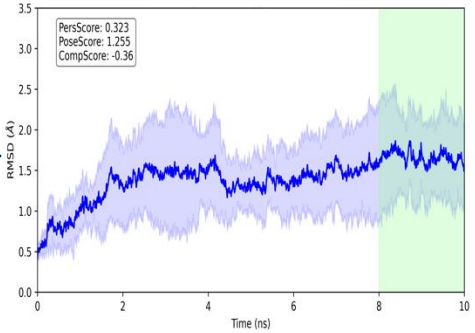
A computational workflow to identify covalent inhibitors of APS reductase enzymatic activity











Modelling of APSR C-terminal loop and positioning of the catalytic cysteine 256.

QM/MM minimizations of Michaelis complex to optimize geometries of potential APS-derived covalent inhibitors.

Pharmacophore modelling to guide docking calculations, by placing the reactive warhead and mimicking substrate polar interactions.

Docking and covalent docking calculations to obtain APSR-ligand adducts and to score compounds.

Binding pose metadynamics to evaluate covalent docking poses stability (binding mode and hydrogen contact stability)

Rational design and synthesis of covalent probes as chemical biology tools to retain APSR in a closed conformation.

Virtual screening of compounds with acrylamide, chloroacetamide, cyanoacrylamide and vinylsulfone warhead

Thanks for the attention