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Design, Dock, Simulate: An Open-Source Stack for Drug Discovery

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The current state

WHAT A MODERN CAMPAIGN MUST DO

Search chemical space at scale
Docking of millions to billions of structures

Refine docking with physics-based methods
Simulations of hundreds of protein-ligand complexes, to resolve what a rigid score cannot

Automation and reproducibility
Restartable, auditable, HPC-friendly runs

WHAT TODAY'S TOOLING DELIVERS

Licensing barriers
Per-seat and per-node fees

Fragmented workflows
Every stage is a separate tool and data format; ad-hoc glue scripts become the pipeline

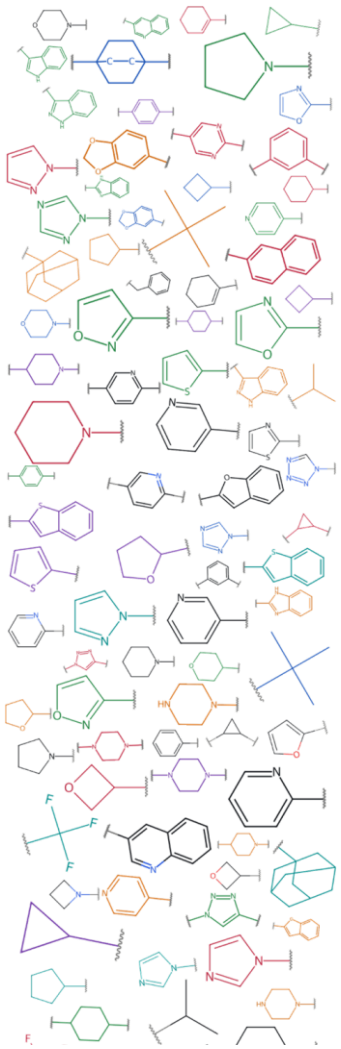
Rebuilt, never reused
Each group re-implements similar infrastructure and pipelines for every new project

Lack of validation of components
Applicability and limitations of the incorporated modules and tools are not always established

Missing: **one open stack - design, dock, simulate - at scale, on different hardware, with no licence in the way.**

The virtual screening and de novo design pipelines

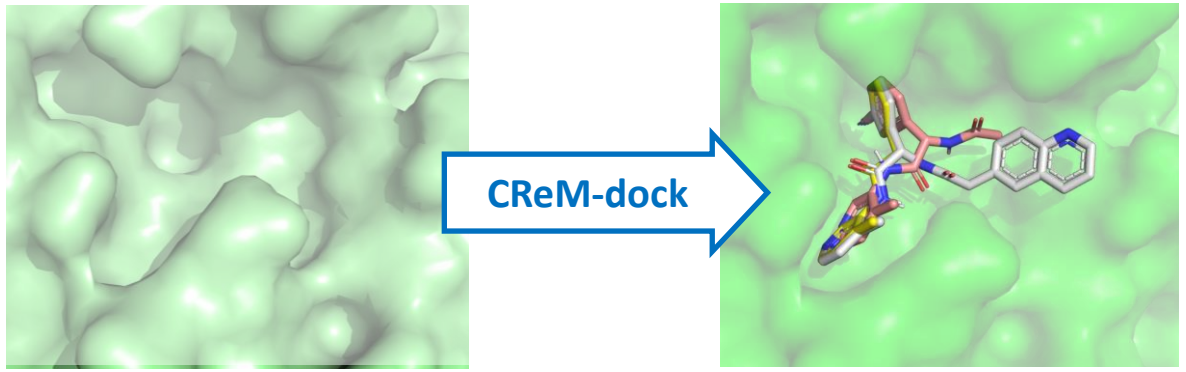
CReM fragment database (ChEMBL, Enamine, in-house)



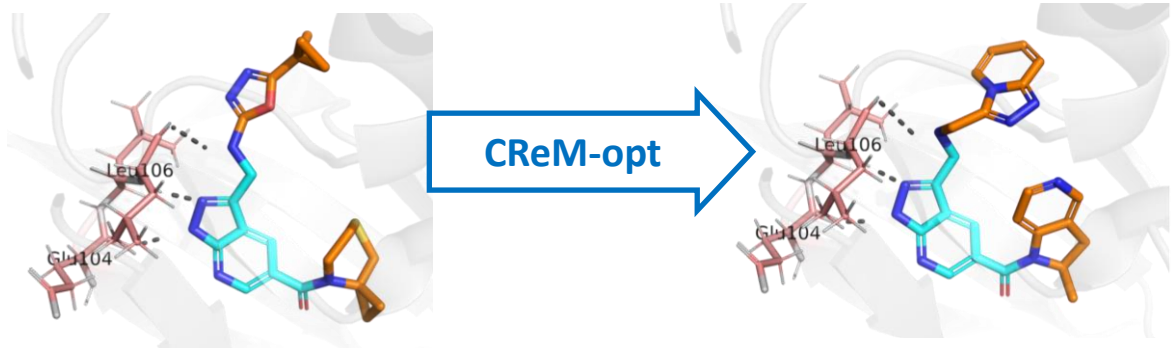
De novo design / optimization

3D pharmacophore

binding site



structure for optimization



Virtual screening

Compound library 10^2-10^7 structures

Docking (**EasyDock**)

10^2-10^3 structures

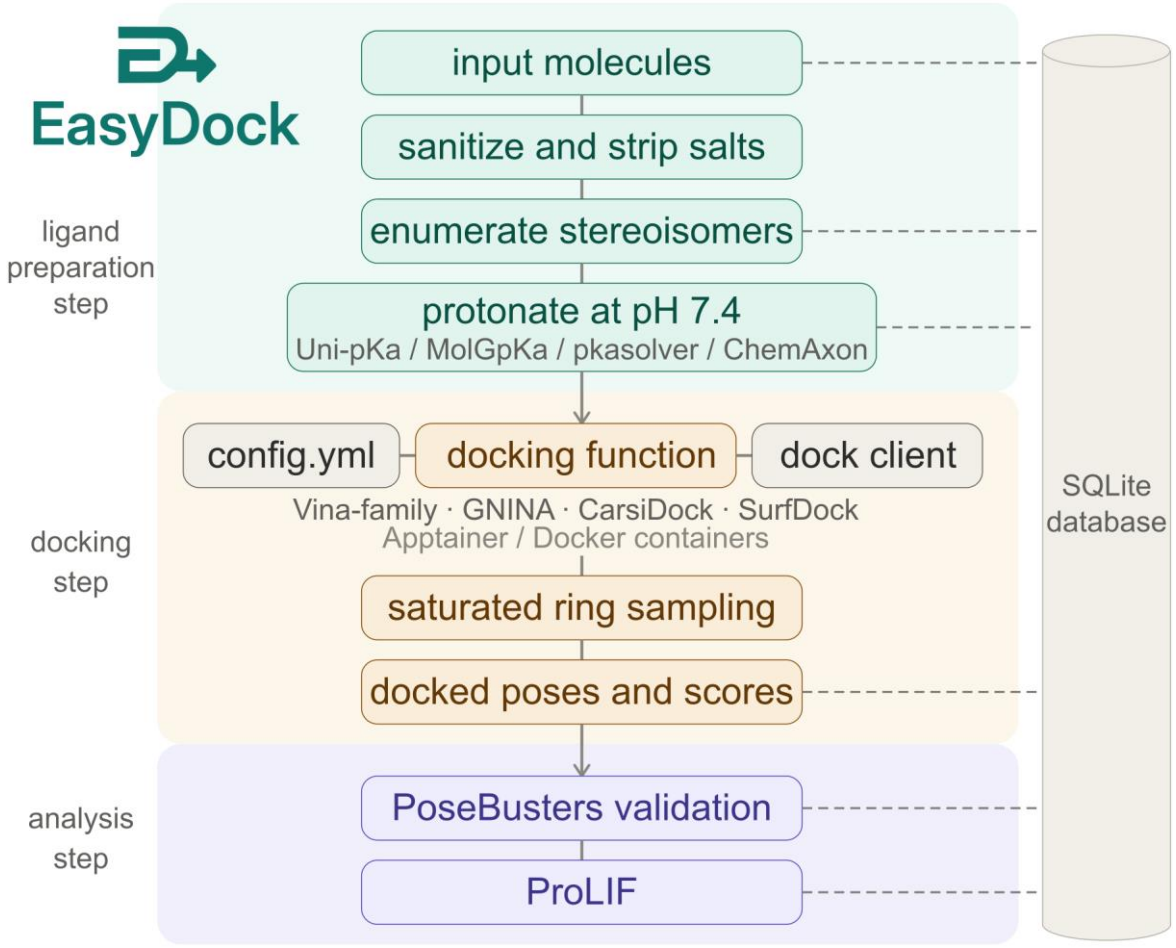
Rescoring: MM-GBSA (**StreaMD**)

10-500 structures

Rescoring: Absolute binding free energy (A3FE)

5-20 structures

EasyDock: scalable and customizable molecular docking



https://github.com/ci-lab-cz/easydock

Modular client-server architecture

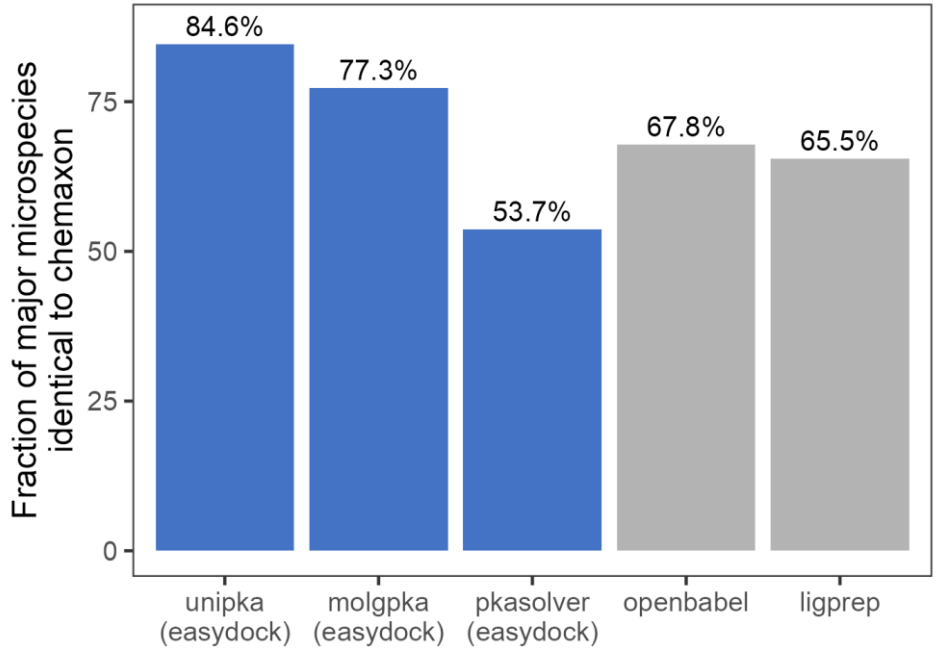
simplify integration of new tools

One interface, many engines

AutoDock Vina, Smina, QVina2, GNINA, plus GPU Vina-family and deep-learning CarsiDock & SurfDock — orthogonal scoring for consensus ranking.

Built for scale

Prepare ligands once and reuse across targets/engines; distributed task handling; CLI and Python API for embedding in larger workflows.



G. Minibaeva, A. Ivanova and P. Polishchuk, *J. Cheminf.,* **2023**, 15, 102.
G. Minibaeva, V. Yap and P. Polishchuk, *J. Chem. Inf. Model.,* **2026**, 66, 8691-8687.

EasyDock: scalable and customizable molecular docking

Command-line

```
easydock
  -i ligands.smi
  -o dock.db
  --protonation ~/imgs/unipka.sif
  --program vina
  --config config_vina.yml
  -c 4
  -v
```

config_vina.yml

```
protein: protein/5ufx_protein.pdbqt
protein_setup: protein/grid.txt
exhaustiveness: 16
seed: 0
n_poses: 5
ncpu: 4
```

Python API

```python
from easydock.run_dock import docking
from easydock.dock.vina_dock import mol_dock
from easydock.protonation import protonate_molgpka
from rdkit import Chem

# protonation
data = [('NCC(=O)O', 'glycine'), ('C1CNCCN1',  'piperazine'])

for smi, name in protonate_molgpka(data):
    mol = Chem.MolFromSmiles(smi)
    if mol:
        mol.SetProp('_Name', name)
        mols.append(mol)

# docking
for mol_name, res in docking(mols, dock_func=mol_dock,
    dock_config='config.yml', ncpu=4):
    print(f'Molecule: 'mol_name')
    print(f'Results: 'res')
```

Guzel Minibaeva

Veincent Yap

Dr. Aleksandra Ivanova

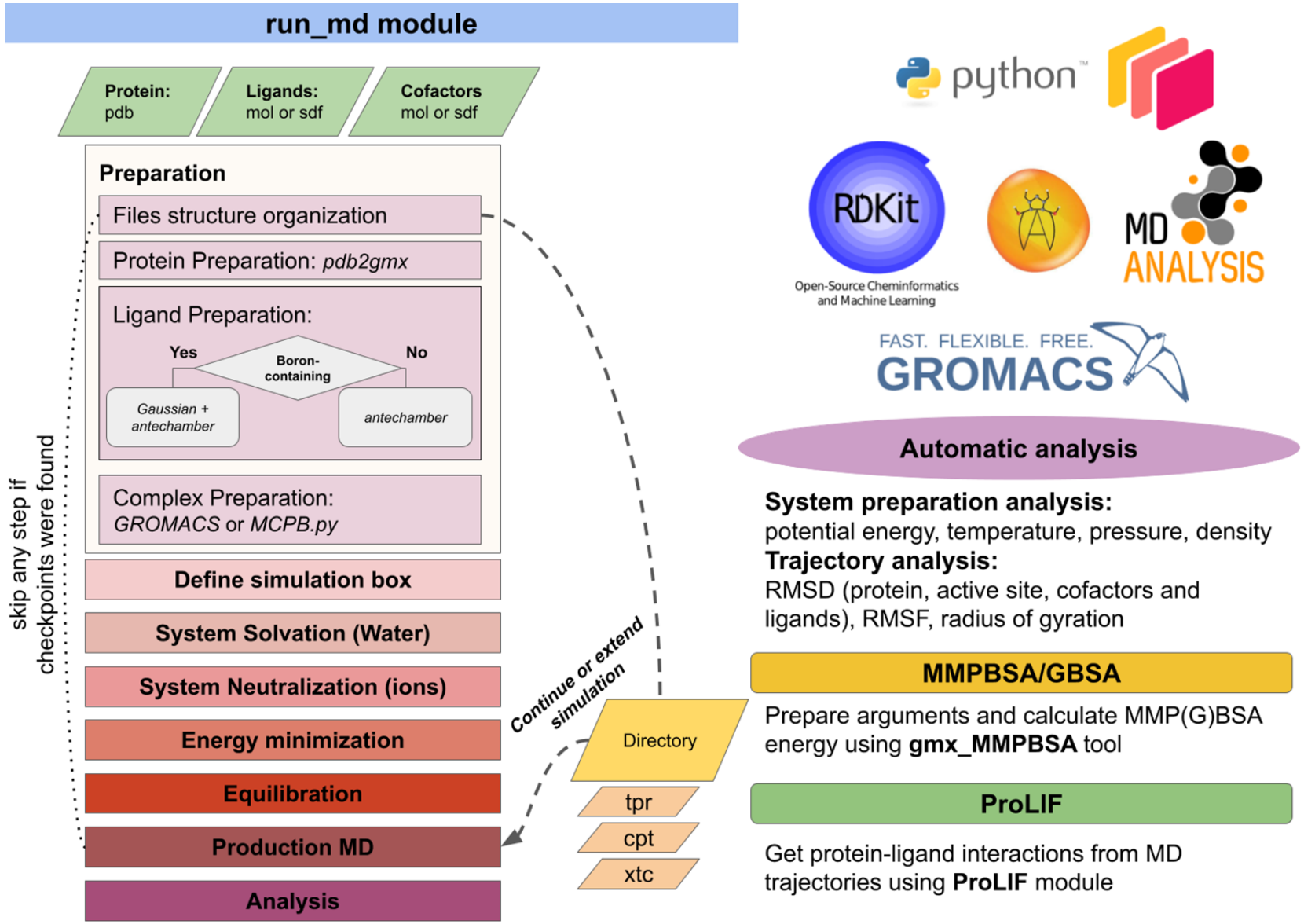
G. Minibaeva, A. Ivanova and P. Polishchuk, *J. Cheminf.*, **2023**, 15, 102.
G. Minibaeva, V. Yap and P. Polishchuk, *J. Chem. Inf. Model.*, **2026**, 66, 8691-8687.

StreaMD: classical MD simulations at scale

Default force field (AMBER99SB-ILDN) can be changed by the user.

Position restraints are automatically applied to the heavy atoms of all protein, ligand and cofactors.

By default**, system Minimization** proceeds until the maximum force value reaches **1000.0 kJ/mol/nm** or less, but not exceeding 50000 steps. Following this, consecutive **1000 ps NVT** and **NPT equilibrations** are executed (the time duration can be customized by a user).



https://github.com/ci-lab-cz/streamd

A. Ivanova, O. Mokshyna and P. Polishchuk, *J. Cheminf.*, **2024**, 16, 123.

StreaMD: classical MD simulations at scale

Dr. Aleksandra Ivanova

To install:

pip install streamd

To run simulation:

run_md -p protein.pdb -l ligands.sdf --md_time 10

To extend simulation:

run_md --wdir_to_continue md_files/md_run/protein_ligand_*/ --md_time 20

G(P)BSA calculations:

run_gbsa --wdir_to_run md_files/md_run/protein_ligand_*

ProLIF calculations:

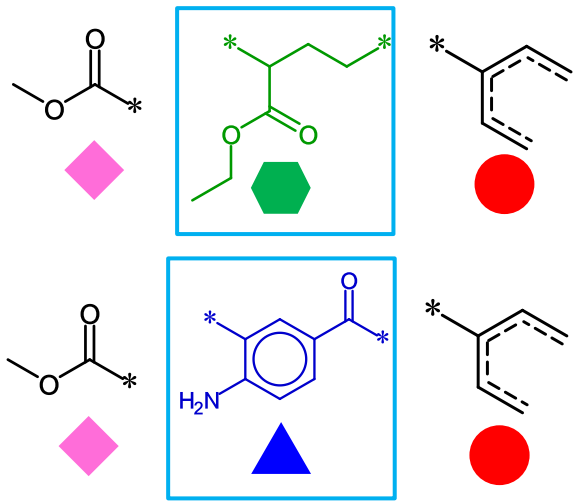
run_prolif --wdir_to_run md_files/md_run/protein_ligand_*

```
md_files/
├─ md_preparation/
│   ├─ protein/
│   ├─ ligands/
│   └─ cofactors/
└─ md_run/
    ├─ protein-id_ligand-id
    ├─ …
    …
```

```
run_md -h
usage: run_md [-h] [-p FILENAME] [-d WDIR] [-l FILENAME] [--cofactor FILENAME] [--clean_previous_md] [--hostfile FILENAME]
              [-c INTEGER] [--mdrun_per_node INTEGER] [--device cpu] [--gpu_ids GPU ID [GPU ID ...]] [--ntmpi_per_gpu int]
              [--topol topol.top] [--topol_itp topol_chainA.itp topol_chainB.itp [topol_chainA.itp topol_chainB.itp ...]]
              [--posre posre.itp [posre.itp ...]] [--protein_forcefield amber99sb-ildn] [--noignh] [--md_time ns]
              [--npt_time ps] [--nvt_time ps] [--seed int] [--no_dr] [--not_clean_backup_files] [--steps [STEPS ...]]
              [--mdp_dir Path to a directory with specific mdp files] [--wdir_to_continue DIRNAME [DIRNAME ...]]
              [-o OUT_SUFFIX] [--deffnm preffix for md files] [--tpr FILENAME] [--cpt FILENAME] [--xtc FILENAME]
              [--ligand_list_file all_ligand_resid.txt] [--ligand_id UNL] [--activate_gaussian module load Gaussian/09-d01]
              [--gaussian_exe g09 or /apps/all/Gaussian/09-d01/g09/g09] [--gaussian_basis B3LYP/6-31G*]
              [--gaussian_memory 120GB] [--metal_resnames [MN ...]] [--metal_cutoff 2.8] [--metal_charges {MN:2, ZN:2, CA:2}]
```

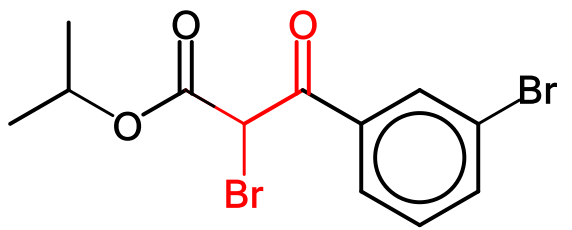

A. Ivanova, O. Mokshyna and P. Polishchuk, *J. Cheminf.*, **2024**, 16, 123.

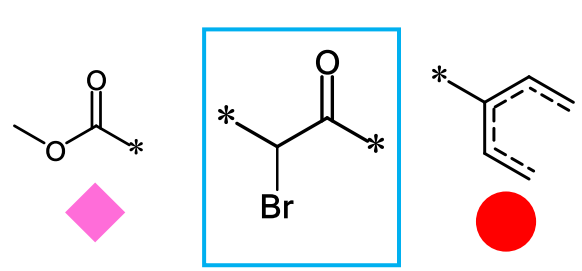
CReM: chemically reasonable mutations



CReM DB
(interchangeable fragments)

environment (radius = 3)	fragments
◆ ●	⬢ ▲ ...
...	...





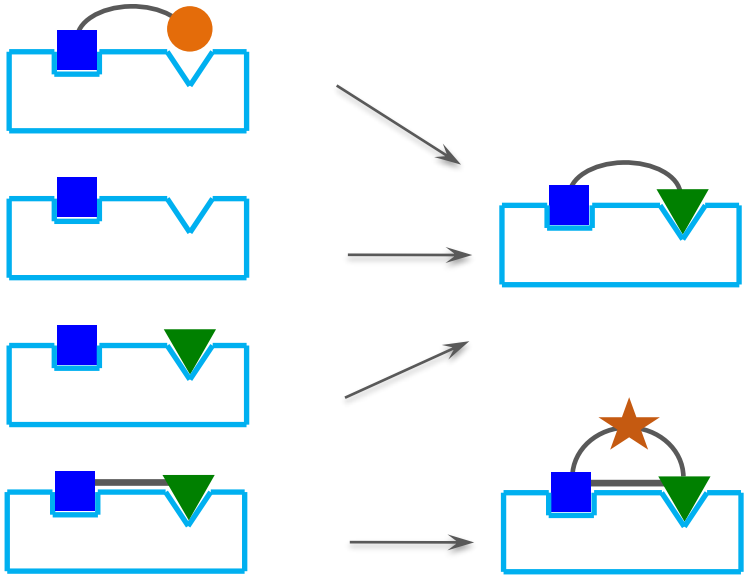
Modes

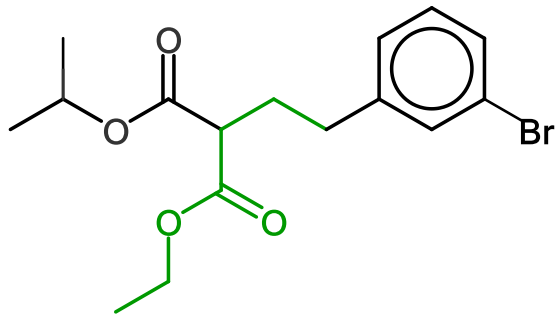
MUTATE

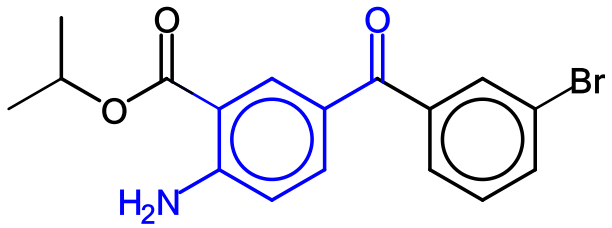
GROW

LINK

CYCLE



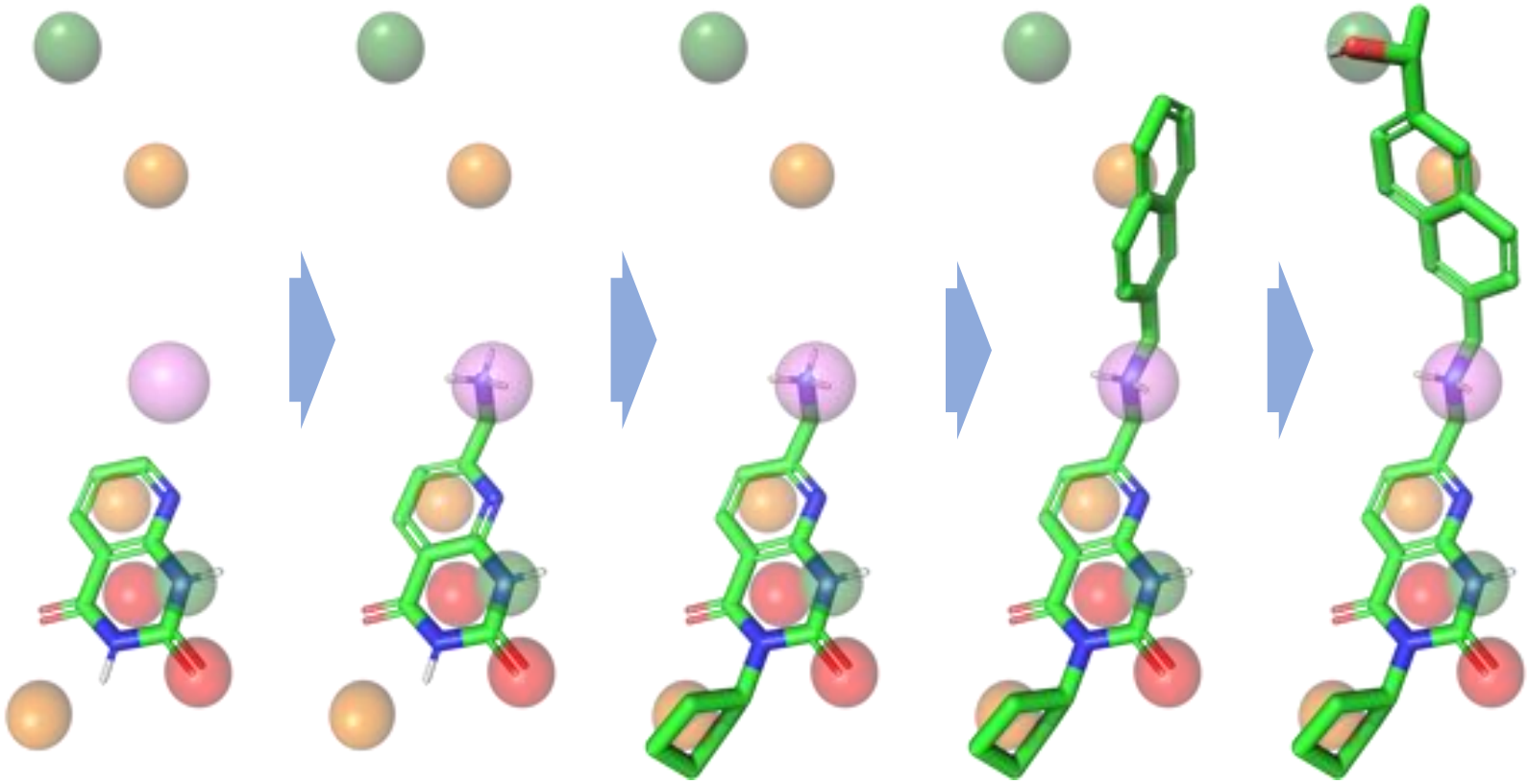




https://github.com/DrrDom/crem

P. Polishchuk, *J. Cheminf.*, **2020**, 12, 28.

CReM-pharm: de novo growing guided by 3D pharmacophore models



Alina Denzler

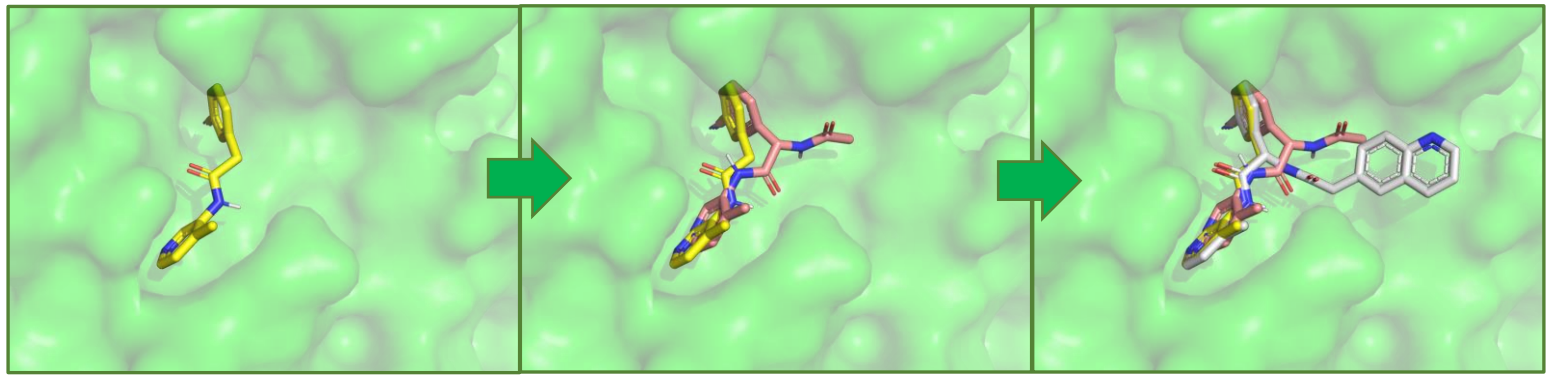
Dr. Dinesh Kumar

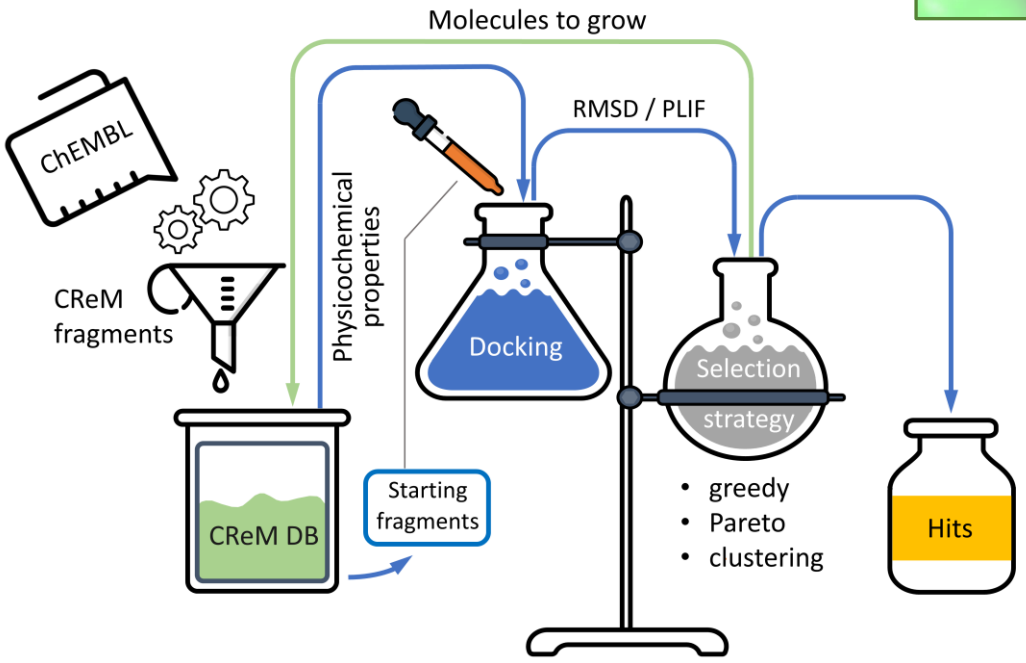
https://github.com/ci-lab-cz/crem-pharm

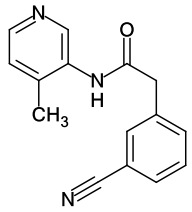
A. Denzler, D. K. Sriramulu, J. Pecha and P. Polishchuk, *J. Cheminf.,* **2026**, 18, 70.

CReM-dock: de novo growing guided by molecular docking

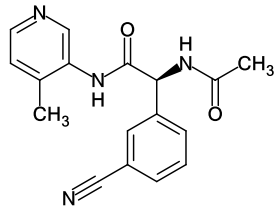
Guzel Minibaeva



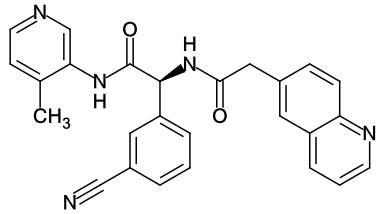




-6.2



-7.0



-9.4

https://github.com/ci-lab-cz/crem-dock

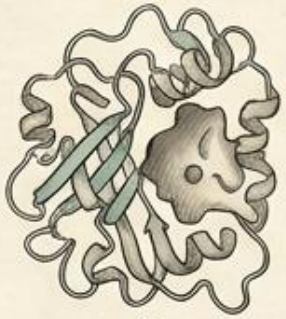
G. Minibaeva, H. Du, F. Clark, J. Michel and P. Polishchuk, *Digital Discovery,* **2026**, 5, 2271-2291.

Case study 1:
searching for CDK16 inhibitors in ultra-large databases

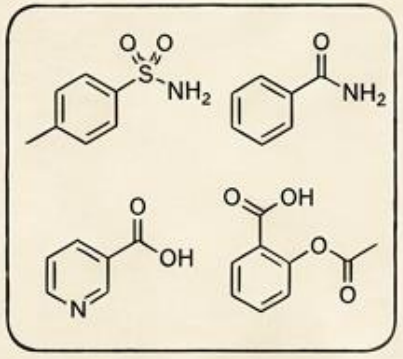
Design the Bait. Fish the Ocean.

1. De novo generation

Create seed molecules



Target protein



Seeds (bait)

2. Similarity search in ultra-large libraries

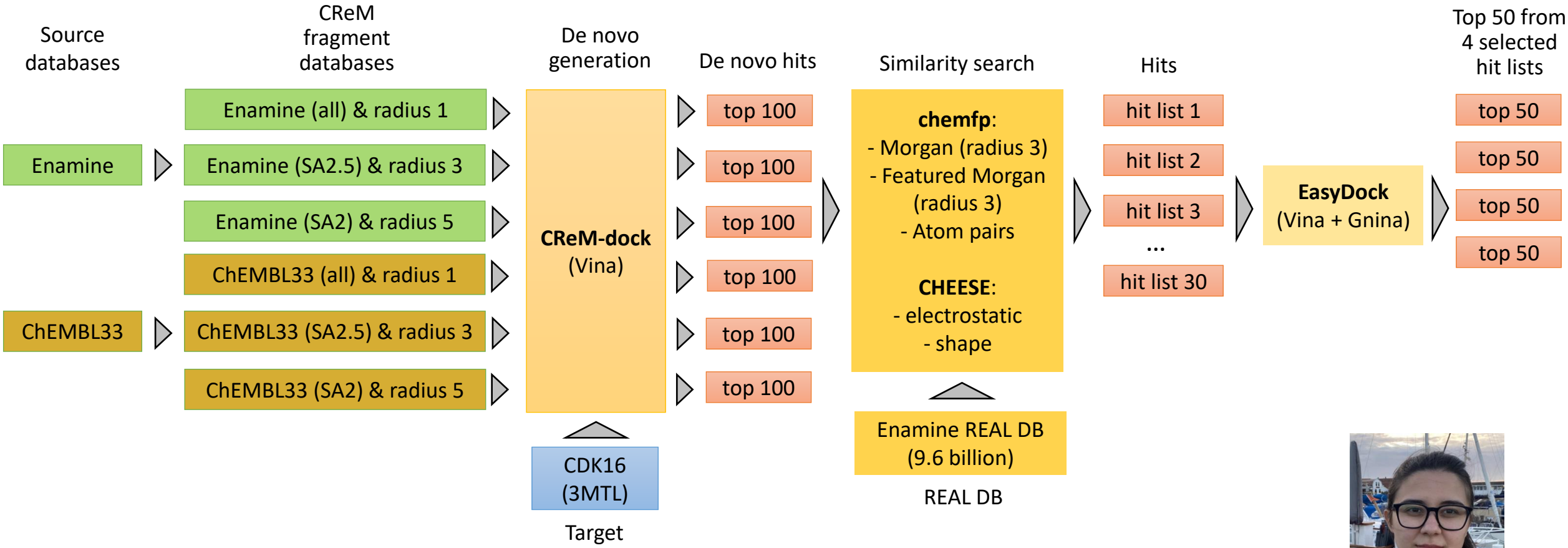
Find similar molecules (the catch)

3. Prioritize & test

Select best hits for experiments

CReM-VS: searching in ultra-large databases guided by de novo designed hits

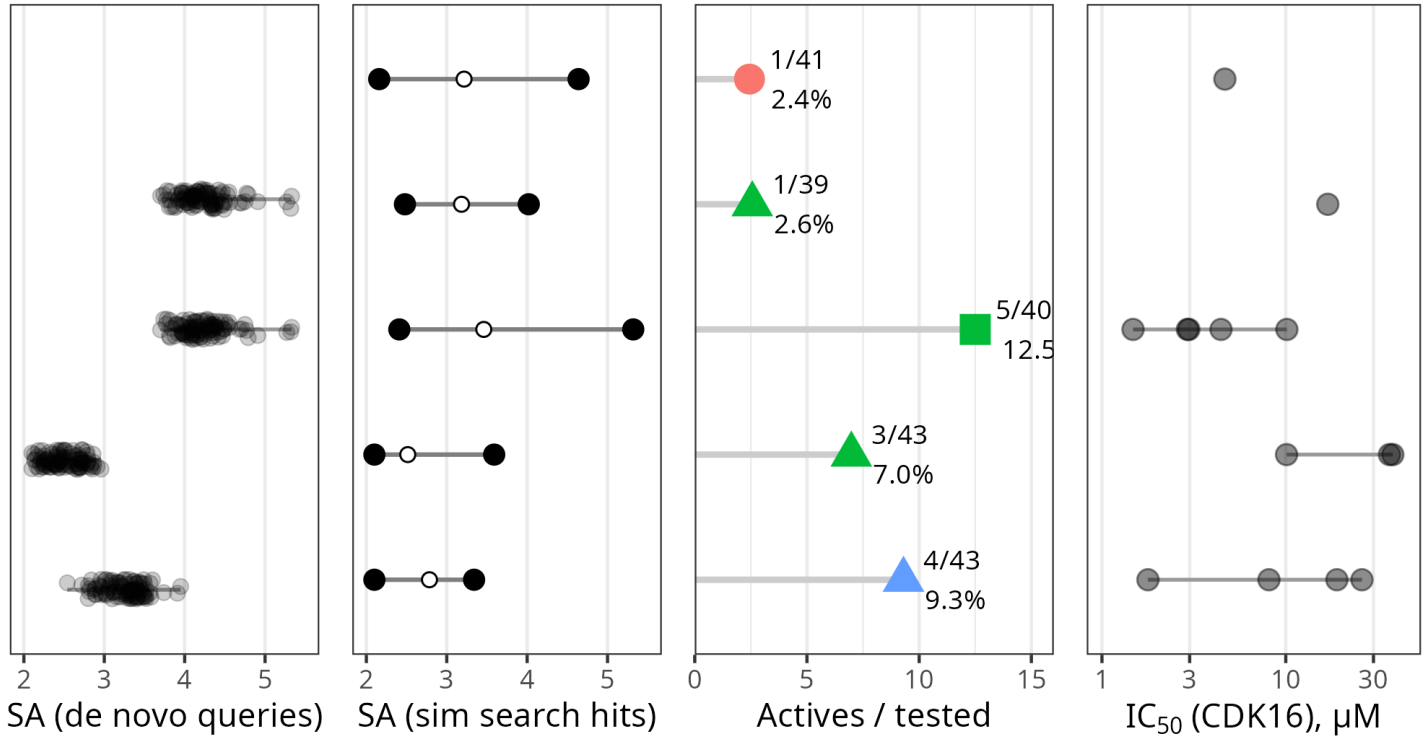
CDK16 study



Guzel Minibaeva

CReM-VS: searching in ultra-large databases guided by de novo designed hits

	Fragments	SA filter	Radius	Fingerprint
Virtual screening	—	—	—	—
CReM-VS	ChEMBL33	all	1	2D Atom pairs
CReM-VS	ChEMBL33	all	1	3D Electrostatic
CReM-VS	ChEMBL33	SA ≤ 2	5	2D Atom pairs
CReM-VS	Enamine	SA ≤ 2.5	3	2D Atom pairs



1. Poor synthetic accessibility of de novo queries does not affect downstream similarity search
2. 3D electrostatic fingerprints were better than 2D structural fingerprints
3. Source of fragment may have importance on activity of found hits

Case study 2:
discover novel DYRK1b inhibitors

De novo design of DYRK1b inhibitors

Stanislav Tricolici

CReM fragment DB
(Enamine, radius 5)

Pharmacophore pre selection & HAC ≤ 12·& predicted docking ≤ −5 & Chiral centers ≤ 1

29 250 starting fragments

CReM-pharm
Pharmacophore-seeded growing

EasyDock

top 1000

CReM-dock
Docking-guided growing

CReM-opt
Genetic-algorithm optimization

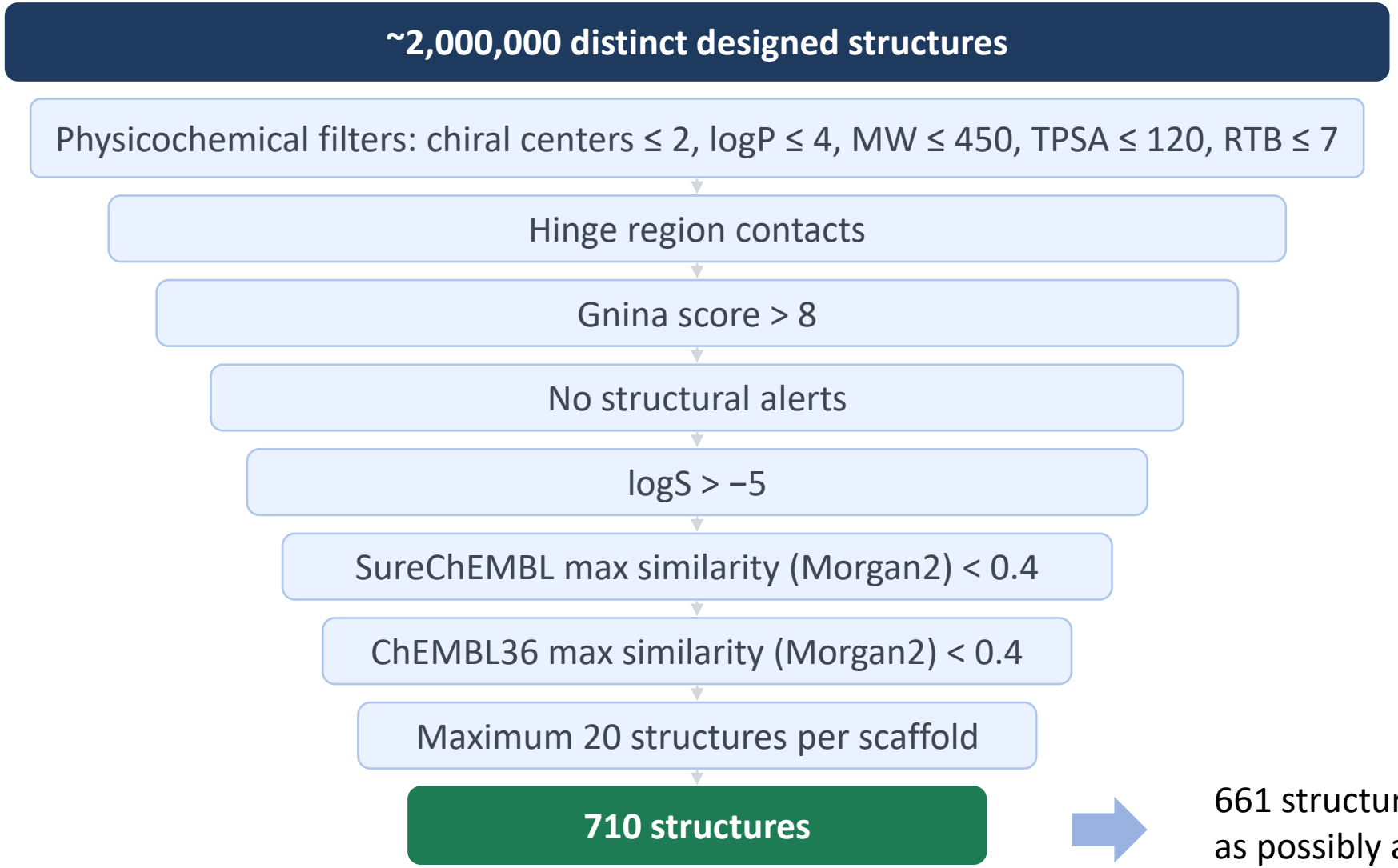
Generated Molecules

Physicochemical & structural filters + docking score

A3FE
(Absolute binding free energy)

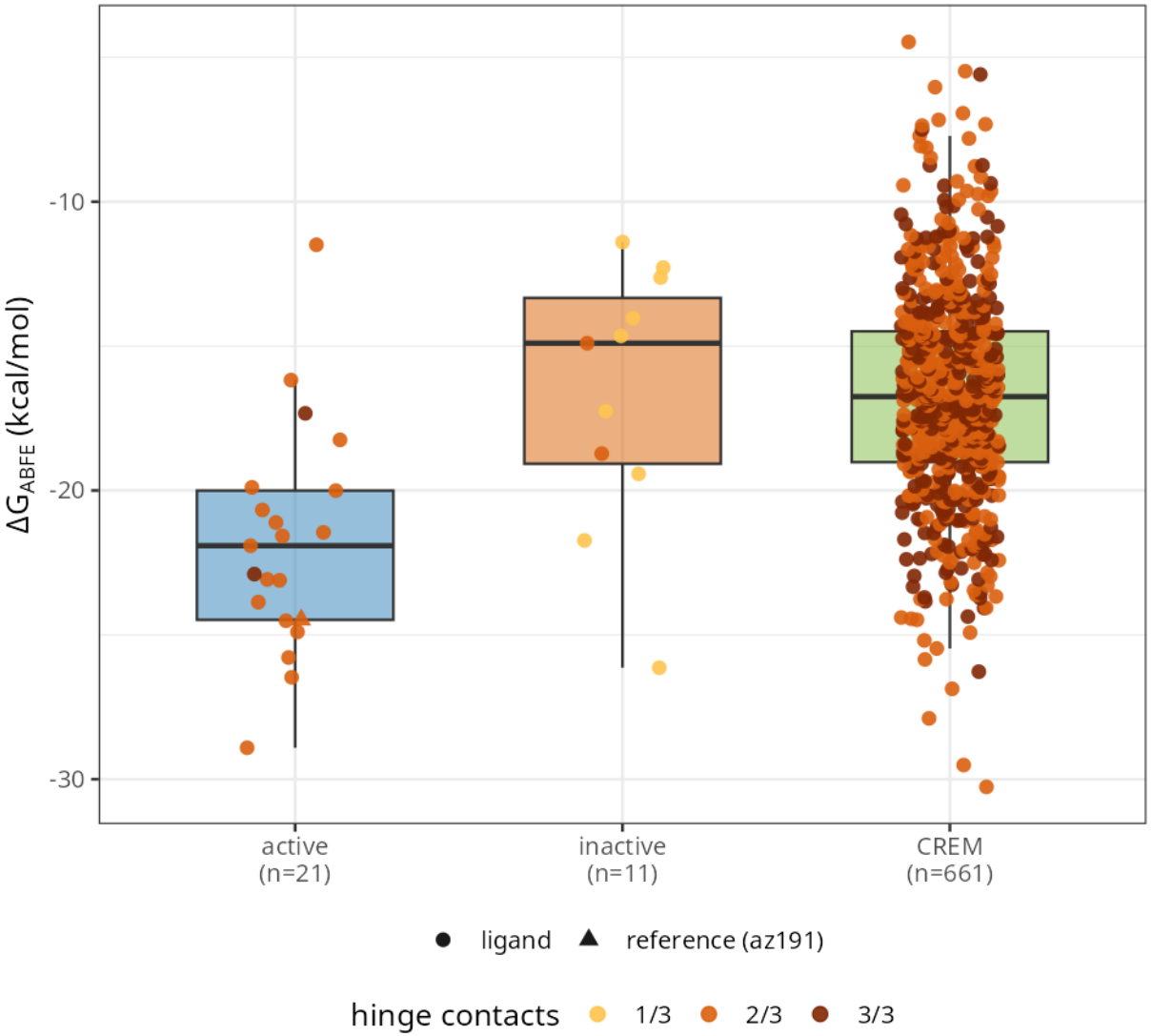
Synthesis of promising candidates

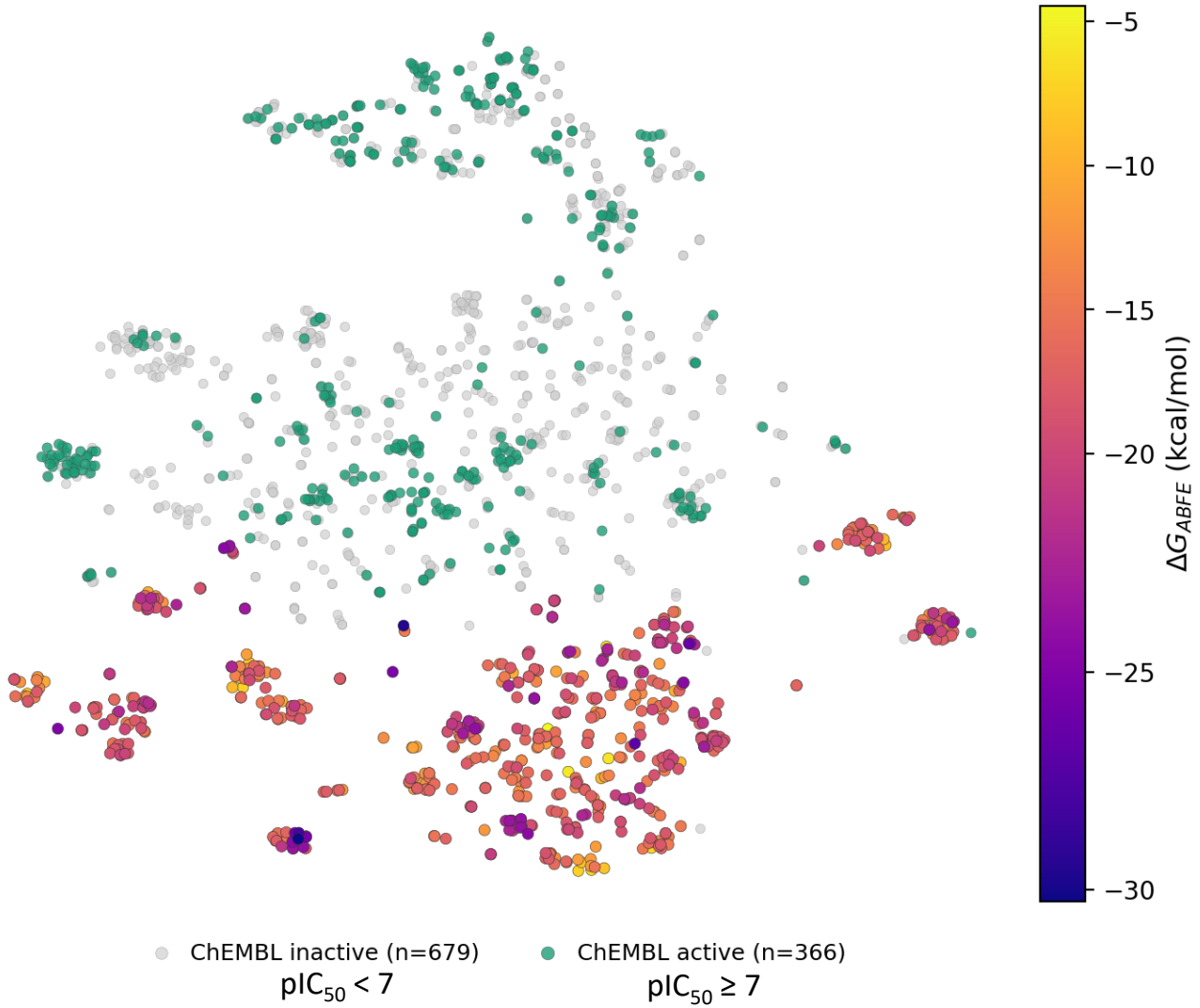
De novo design of DYRK1b inhibitors



661 structures were assessed as possibly accessible (93%)

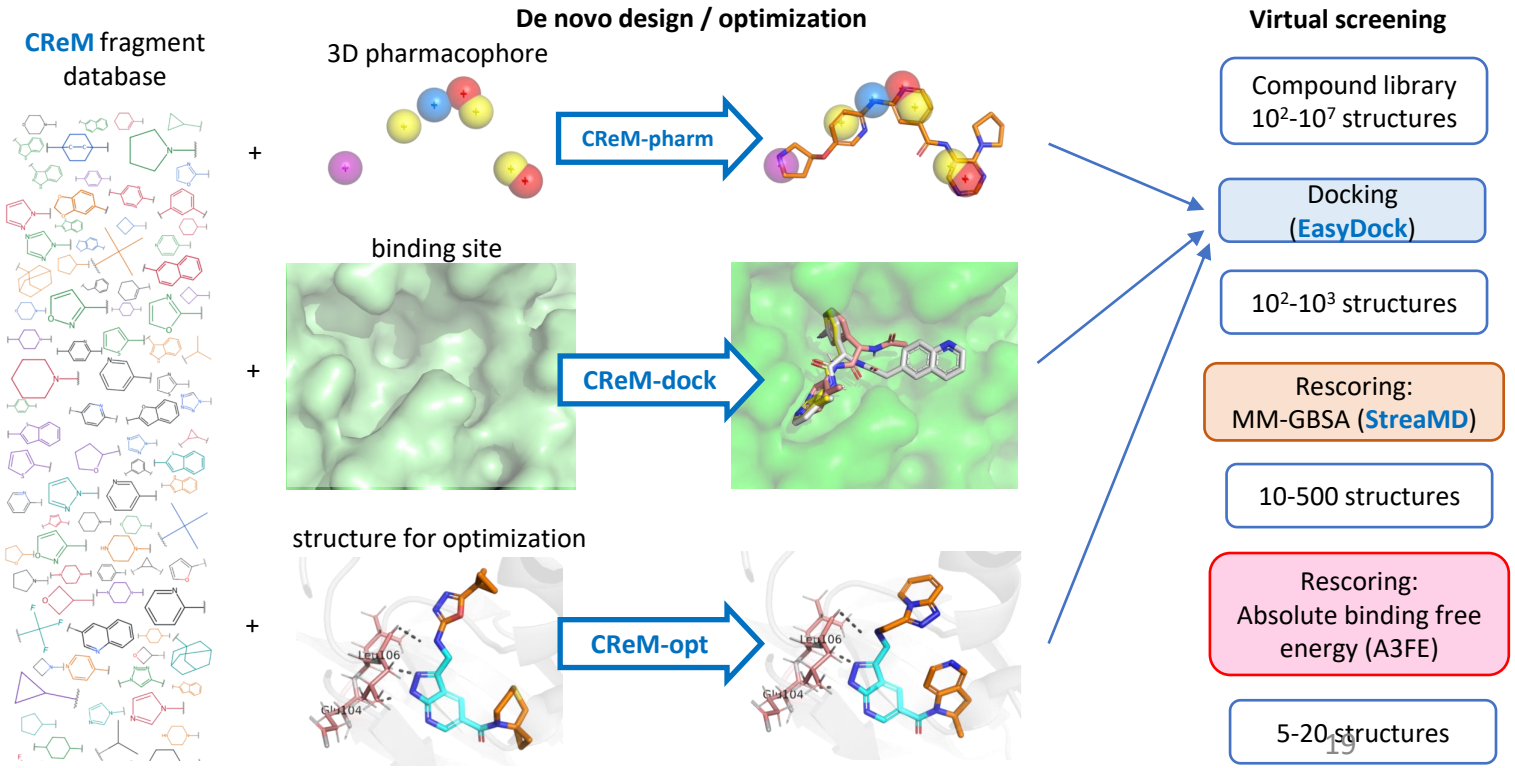
De novo design of DYRK1b inhibitors





Conclusions

- The tools were developed to be modular, extensible, computationally efficient, and easy to use through both CLI and API interfaces.
- All tools are comprehensively documented and designed to be accessible to students and researchers with limited prior experience.
- Regular use by the developers supports continuous maintenance and further development.
- The tools are interoperable, can be combined into higher-level workflows, and they use compatible database schemas to simplify downstream analysis.
- In both prospective case studies, compound selection was fully automated and based exclusively on predefined computational criteria, allowing evaluation of the pipelines independently of medicinal-chemistry intuition or manual intervention.



IMTM

Virtual screening

EasyDock – automated scalable molecular docking

Features:

- automated ligand preparation & docking
- different docking engines
- extensible client-server architecture
- post-docking analysis

Molecular dynamics

StreaMD – automated scalable classical molecular dynamics simulations

Features:

- GROMACS engine
- fully automated workflow
- post-MD analysis
- MM-PBSA/GBSA calculation

De novo design / optimization

- **CReM** – fragment based structure generation
- **CReM-pharm** – de novo design guided by 3D pharmacophore models
- **CReM-dock** – de novo design and scaffold decoration guided by molecular docking
- **CReM-opt** – de novo design and optimization guided by molecular docking

Features:

- exploration of ultra-large chemical libraries and beyond
- high structural novelty
- tunable synthetic accessibility

IMTM

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Dr. Petr Dzubak
Dr. Martina Kintlova
Dr. Sona Gurska
Doc. Marian Hajduch

External

Veincent Yap
Haolin Du
Dr. Finlay Clark
Dr. Julien Michel

Dr. Andrew Dalke

DeepMedChem
Inte:ligand

https://github.com/DrrDom/crem
https://github.com/ci-lab-cz/easydock
https://github.com/ci-lab-cz/streamd
https://github.com/ci-lab-cz/crem-pharm
https://github.com/ci-lab-cz/crem-dock
https://github.com/ci-lab-cz/crem-opt

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