

# A fragment-based approach to the rational design of protein kinase inhibitors

Peter Kolb and Amedeo Caflisch

Department of Biochemistry, University of Zurich, Switzerland

[pkolb, caflisch]@bioc.unizh.ch

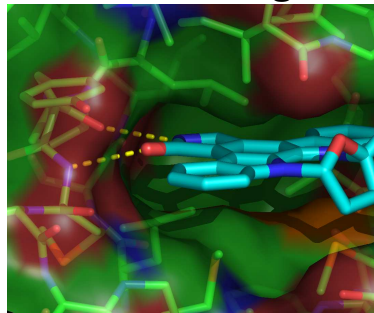


STRUCTURAL BIOLOGY  
National Center of Competence in Research

## Introduction

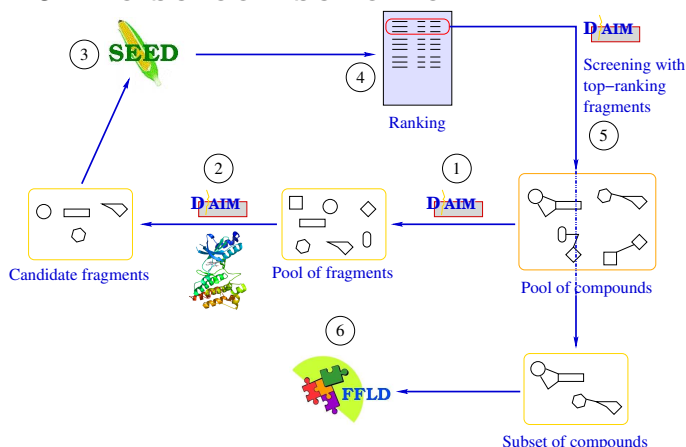
Protein kinases mediate numerous cell signalling pathways. Perturbations of these pathways are linked to diseases such as diabetes, cancer and inflammation. Several known kinase inhibitors target the highly conserved ATP binding pocket, mimicking the binding mode of ATP. We present a fragment-based approach which is used to filter a large database according to the binding mode of ATP (see box on the right).

## Common binding mode



Similar to the interaction of the adenine moiety of ATP, K-252a forms two hydrogen bonds with the hinge region of c-Met.

## Puzzle screen scheme



### Step 1 – Fragment generation

A library of molecules is decomposed into its fragments with DAIM. By using *in silico*-generated fragments, we are independent of existing small compound libraries and can obtain completely novel fragments.

### Step 2 – Fragment selection I

Fragments that could in principle satisfy the common binding mode – the bidental hydrogen bonds to the hinge region – and contain one or two rings are selected.

### Step 3 – Fragment docking

Fragments chosen in Step 2 are docked with the program SEED [1,2] which contains an accurate energy function including solvation. Before processing them further, fragments are ranked according to their score.

### Step 4 – Fragment selection II

Application of the selection criterion. Fragments which do not form the bidental hydrogen bonds in any of their poses are discarded. The top-ranking fragments are then used as queries in the substructure search.

### Step 5 – Substructure search

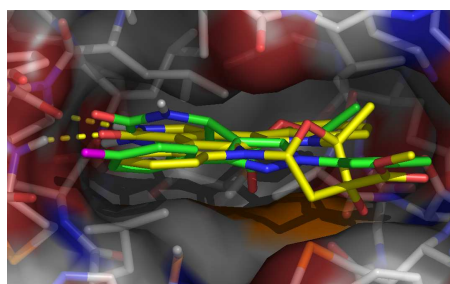
Large molecular libraries are searched for structures that contain the candidate fragments. This step also uses DAIM, which has a graph-subgraph matching algorithm built in.

### Step 6 – Ligand docking

The molecules retrieved in step 5 are docked using our docking package (DAIM/SEED[1,2]/FFLD[3]). Afterwards, poses are minimised with CHARMM and reranked according to a calculation of their interaction energy including solvation effects.

## Application to c-Met

Through selection of 21 appropriate candidates from a pool of 4212 fragments with the above-mentioned criteria, the number of ligands to be docked could be reduced from more than 700k to less than 5k. Eight of the docked molecules have been purchased and will be tested *in vitro* and *in vivo* at ESBATech AG, Switzerland.



c-Met with K-252a (yellow) and one of the suggested molecules (green).

## References

- [1] MAJEUX, N., SCARSI, M., APOSTOLAKIS, J., EHRHARDT, C., AND CAFLISCH, A. Exhaustive docking of molecular fragments with electrostatic solvation. *Proteins* 37 (1999), 88
- [2] MAJEUX, N., SCARSI, M., AND CAFLISCH, A. Efficient electrostatic solvation model for protein-fragment docking. *Proteins* 42 (2001), 256
- [3] BUDIN, N., MAJEUX, N., AND CAFLISCH, A. Fragment-based flexible ligand docking by evolutionary optimization. *Biol. Chem.* 382 (2001), 1365