Design of Kinase Target Libraries

Jon Swanson, David Baker, Sun Choi, Richard Foster, and Michael S. Lawless

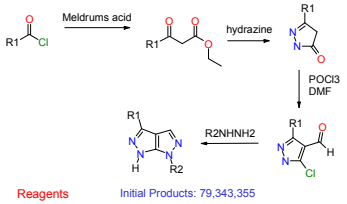
Introduction

Kinases are critically important as pharmacological targets. There are a large number of kinase crystal structures and known kinase inhibitors in the public domain. This data can be transformed into a knowledge base that is used to guide the design of target libraries. One challenge is to identify inhibitory small molecules that discriminate between the specific target of interest and kinases in general. Our approach is to build virtual libraries based on specific scaffolds. Representative subsets of products from the library are docked into the active site of several different targets and the binding modes for the scaffolds identified. The best binding mode(s) are then fixed and the entire virtual library docked, flexing only the sidechains. This technique allows very large libraries to be examined. The best structures are then chosen for synthesis.

Docking Strategy for Kinase Inhibitors

1. Build a ChemSpace® Virtual Library
2. Filter on standard properties, such as molecular weight, ClogP and "drug-like"
3. Generate a hitlist of acceptable compounds
4. Extract a subset either by topomer searching against known candidates or generating a diverse subset with dbdiss or OptiSim™
5. Use FlexX™ to dock the subset
6. Extract representative core placements by creating a dendrogram for the well-docked structures using RMS deviation between the cores
7. Dock the full library specifying the representative core placements as the allowed base placements

Synthetic Route



Reagents

Initial Products: 79,343,355

Reagent	# Available
Acid Chlorides	878
Aromatic Acids	7150
Aliphatic Acids	24963

Reagent	# Available
Hydrazines	2405

Filtered Products

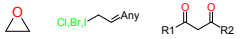
Final Products: 40,507 (33,339 unique)

	Acid Chlorides	Aromatic Acids	Aliphatic Acids	Hydrazines
Lipinski Properties	744	7150	24963	2039
"Drug-like" Filters	639	4881	10771	1900
Reaction Compatible	521	2263	2771	1320
Reagent Availability	244	452	639	240

Filtering Criterion

- **Lipinski Properties**
  - Property filtering was done based on the work of C.A. Lipinski *et.al.* in Advanced Drug Delivery Reviews, 23 (1997) defining criteria applicable to most drugs.
- **Filters Applied**
  - 0 - 5 H bond donors
  - 2 - 10 H bond acceptors
  - MW between 250 and 500
  - ClogP between –2 and 5
  - No nitro groups were allowed
- **Drug-like Filters**
  - Remove compounds with functional groups that are highly reactive or likely to cause other problems.
- **Reaction Compatible Filters**
  - Remove compounds containing functional groups that will result in poor yield or interfere with subsequent reaction steps
- **Reagent Availability**
  - Reagents are scored on cost and availability. Only easily available reagents were considered.

Example: Non-Drug-like Functional Groups



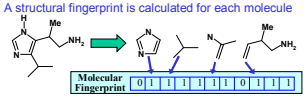
Example: Reaction Incompatible Groups for R1

Diverse Subset Selection

Docking 33,319 products on a single processor SGI requires weeks of CPU time. The process can be greatly accelerated.

- Choose a representative subset of structures from the virtual library
- Dock the representative subset with FlexX
- Identify the unique, relevant docking modes
- Supply these docking modes as base placements to FlexX to dock the full library

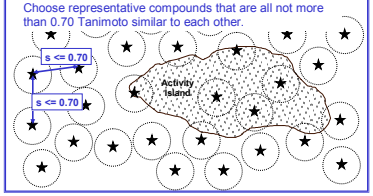
A structural fingerprint is calculated for each molecule



Similarity of fingerprints is determined by the Tanimoto coefficient

Tanimoto coefficient = A ∩ B / A ∪ B

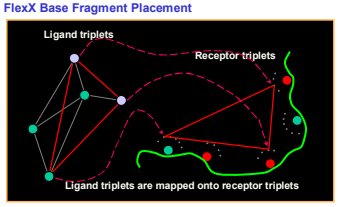
Choose representative compounds that are all not more than 0.70 Tanimoto similar to each other.



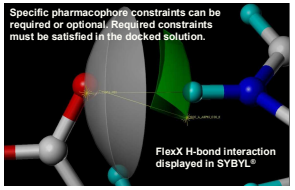
FlexX Methodology

- **Ligand Fragmentation**
  - The ligand is broken into rigid fragments
  - Base fragment(s) are selected
- **Base Fragment Positioning**
  - Interaction surfaces are defined for active site residues
  - Triangles are generated between surfaces in the active site
  - The same done for base fragment(s)
  - Base fragment placed in active site by triangle matching
- **Ligand Build-up**
  - Full ligands are constructed by adding the remaining fragments to the base fragment positions

FlexX Base Fragment Placement



FlexX-Pharm™ Interaction Surfaces



Docking the Diverse Subset

Initial Docking: 544 Compounds

	Best FlexX Score	Worst FlexX Score	Average FlexX Score	Standard Deviation
1a9u (P38)	-25.6	2.8	-11.6	3.8
1ke7 (CDK2)	-26.7	2.7	-12.1	4.6
1m52 (Abl)	-32.7	-0.8	-17.2	5.2
2fgi (FGFr)	-21.9	-5.1	-14.4	4.3

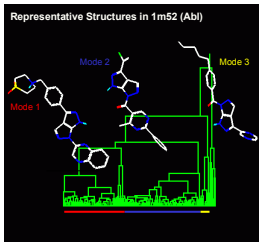
Docking the Full Library

Final Docking: 33,339 Compounds

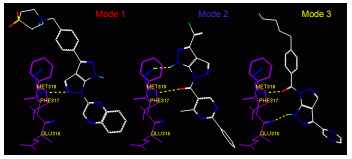
	Best FlexX Score	Worst FlexX Score	Average FlexX Score	Standard Deviation
1a9u (P38)	-24.3	3.0	-9.0	3.1
1ke7 (CDK2)	-33.0	3.5	-12.4	4.8
1m52 (Abl)	-38.3	2.2	-17.7	4.9
2fgi (FGFr)	-35.8	-0.1	-15.2	4.9

Selection of Binding Modes

Binding Modes from the Initial Docking

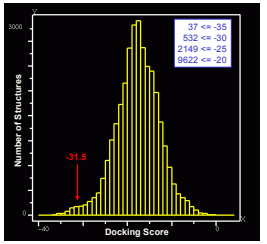


Selected Poses for 1m52 (Abl)

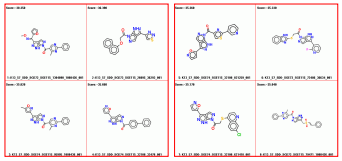


Docking Results

Docking Energy Distribution (Abl)



High Ranking Solutions (Abl)



Best Docked Solutions

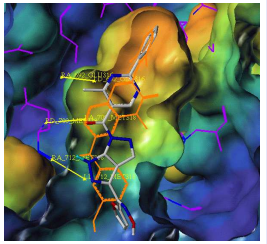
Abl

FlexX Score = -38.35

Best scoring product is colored by atom type.

Original bound ligand is colored orange.

Protein surface is colored by cavity depth.



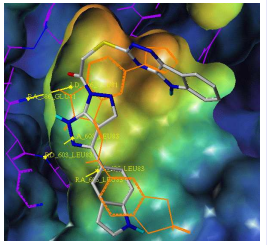
CDK2

FlexX Score = -33.04

Best scoring product is colored by atom type.

Original bound ligand is colored orange.

Protein surface is colored by cavity depth.



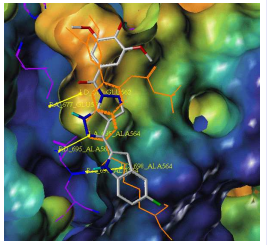
FGFr

FlexX Score = -35.78

Best scoring product is colored by atom type.

Original bound ligand is colored orange.

Protein surface is colored by cavity depth.



P38

FlexX Score = -24.25

Best scoring product is colored by atom type.

Original bound ligand is colored orange.

Protein surface is colored by cavity depth.