Pharmacophore Guided Fragment-Based Drug Design

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Discovery Studio 2.1: New Science and Customized Workflows for Drug Discovery Research
10th July 2008
• Combination of small fragments results in high diversity
• Addressing sub-site specificity and ligand efficiency
• Low molecular weight compounds represent suitable basis for optimisation of ADME properties

Why Pharmacophores?

- Smaller fragments may bind in various parts of the binding cavity
- From the way a fragment docks, it may be difficult to discover how the ligand containing that fragment may dock
- The pose of the fragment in a ligand may not be a top hit when the fragment is docked
- When two or more fragments are joined properly, the chances of finding the ligand pose seems greater
- Pharmacophores can direct the fragment to the location occupied when the fragments form a ligand

Fragment-Based Workflow

Protein Target File

Reference Query

Fragment Queries

Hit Refinement

Fragment Database

Screen / Focus Database

Scoring & Prioritisation

Hit Lists

Library Enumeration

De-novo Library

Focused Hit List

Synthetic Feasibility Filtering

Refined Hit List

Reference Query

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Example: Thymidine Kinase

- Fragment based approach applied to thymidine kinase

1. Protein preparation
2. Pharmacophore construction and link definitions
3. Enumeration and hit refinement
4. Selection of candidate molecules
The Target

- Example: HSV Thymidine Kinase (1kim.pdb)
Protein Preparation

- Fully automated protocol dealing with protein preparation:

1. Cleans the protein/ligand complex
   - All Hydrogen are added
   - Alternate residue conformation are removed
   - Names are standardized
   - Missing residues completed

2. CHARMM pKa calculation to protonate the protein

http://forums.accelrys.org/eve/forums/a/tpc/f/2011007181/m/3601080603
Describing the Interactions

- 3HBD, 1HBA, 1Hydrophobe
• **Two options explored**
  - Difference in the resulting molecules expected
  - The link atom queries need to be formulated differently
• Link atom does not have to be of the same type
  - Sometimes a different atom type in each fragment is required for enumeration
Fragment Queries

- Link1 and Link2

Strategy 1 and Strategy 2

Shape parameters can be tuned
• Commercial, corporate
• Customised

- 120000 compounds
- 20000 fragments
- Conversion into a multi-conf database
• Molecular Networks (www.molecular-networks.com)

• ISV partner (Pipeline Pilot Components)

• Fast estimation of synthetic accessibility of organic compounds
  - Scoring of compounds on a scale from 1 and 10
    - 1 - Easy to synthesise
    - 10 - Difficult to synthesise

• Prioritisation of chemical compounds
  - Generated by de novo design experiments
  - Generated by inverse QSAR/QSPR experiments
  - Large virtual compound libraries

SYLVIA - Components of Accessibility Scoring

• **Structure-based**
  - Molecular graph complexity \(^1\)
  - Ring complexity \(^2\)
  - Stereochemical complexity

• **Starting material-based**
  - Similarity to starting materials

• **Product bond-based**
  - Reaction fitness: based on presence of product reaction center substructures (RCSS) extracted from reaction databases

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**Fragment Screening**

- **Customised Database**
  - 20000 compounds
  - Synthetic feasibility filtering (threshold: 4)
  - Multiple searches done simultaneously

<table>
<thead>
<tr>
<th>Hit List From Fragment-library</th>
<th>Query1</th>
<th>Query2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy1</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Strategy2</td>
<td>116</td>
<td>61</td>
</tr>
</tbody>
</table>
Energy or structural filters are applied → Number of successful molecules is not the simple product of number of fragments

<table>
<thead>
<tr>
<th></th>
<th>Enumerated Library</th>
<th>Focused Library</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy1</strong></td>
<td>159 (899)</td>
<td>146</td>
</tr>
<tr>
<td><strong>Strategy2</strong></td>
<td>704 (7076)</td>
<td>388</td>
</tr>
</tbody>
</table>
Hit Refinement

- Focused lists are just a starting point for additional refinement
- Refinement is a Multiple Step procedure
- Is project dependent

In this example, focused hit lists are:
- Docked into the active site of thymidine kinase (CDOCKER)
  - 2-deoxythymidine is used for comparison
- Filter the poses with the pharmacophore
- Evaluated against a library of pharmacophores built from kinase targets - pharmacological profiling
• DeoxyThymidine CDOCKER energy: 25.05 - 21.96
• For 57 compounds, best pose CDOCKER energy > best pose CDOCKER energy of DeoxyThymidine
Hit Refinement - Results: Strategy 1 continued

- Filtering CDOCKER poses with the pharmacophore
- 24 compounds
<table>
<thead>
<tr>
<th>Compound</th>
<th>Kinase Target</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>TK (HSV1)</td>
<td><img src="profile1.png" alt="Profile 1" /></td>
</tr>
<tr>
<td>163584</td>
<td>CDK2, CDK5, Hck</td>
<td>Kinase target</td>
</tr>
<tr>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>TK (HSV1)</td>
<td><img src="profile2.png" alt="Profile 2" /></td>
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<tr>
<td>164538</td>
<td>CDK2, CDK5, Pim1</td>
<td>Kinase target</td>
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<tr>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>TK (HSV1)</td>
<td><img src="profile3.png" alt="Profile 3" /></td>
</tr>
<tr>
<td>224933</td>
<td>CDK2, CDK5</td>
<td>Kinase target</td>
</tr>
<tr>
<td><img src="image4.png" alt="Compound 4" /></td>
<td>TK (HSV1)</td>
<td><img src="profile4.png" alt="Profile 4" /></td>
</tr>
<tr>
<td>233894</td>
<td>CDK2, CDK5</td>
<td>Kinase target</td>
</tr>
</tbody>
</table>
• DeoxyThymidine CDOCKER energy: 25.05 - 21.96
• For 180 compounds, best pose CDOCKER energy > best pose CDOCKER energy of DeoxyThymidine
Filtering CDOCKER poses with the pharmacophore

131 compounds
Hit Refinement - Results: Strategy 2 continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kinase Target</th>
<th>Profile Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td>TK (HSV1) CDK2</td>
<td>109397-17414</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image 2" /></td>
<td>TK (HSV1) CLK1</td>
<td>109397-75886</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image 3" /></td>
<td>TK (HSV1) CDK2 c-Met</td>
<td>109397-148362</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image 4" /></td>
<td>TK (HSV1) CLK1</td>
<td>109397-254659</td>
</tr>
</tbody>
</table>
Conclusion

- Easy to set and fast procedure
- Used here for lead hopping, but can also be used for Lead optimization (scaffold + pharmacophore)
- Focused hit list is only the starting point for refinement
- Synthetic feasibility score used to filter the compounds during enumeration phase
• Remy Hoffmann

• Konstantin Poptodorov

• Catalyst Development Team
  - Jon Sutter
  - Al Maynard
  - Jiabo Li
  - Roman Kuchkuda
  - Christoph Koelmel
Thank You

• Thank You for attending today’s webinar. If you have any further questions please e-mail me at tluu@accelrys.com

• You can also contact us using the form on our website: http://accelrys.com/company/contact/

• We will be exhibiting at the following upcoming events:
  - CHI Protein Kinase Targets (June 23 - 25, Boston, Booth #4)
  - CHI Structure Based Design (June 25 - 27, Boston, Booth #7)
  - Drug Discovery Technology and Development (August 4 - 7, Boston, Booth #512)
  - ACS Fall 2008 (August 17 - 21, Philadelphia, Booth #211)

• Reminder: The next webinar in this series will be:
  - Advances in Pharmacophore Modeling and Parallel Screening (Ragi Raghavan)
  - July 17, 2008 - 3pm GMT (7am PST) and 10am PST
Discovery Studio 2.1: New Science and Customized Workflows for Drug Discovery Research

• Advances in Protein Modeling and Protein-Protein Interactions in Discovery Studio
  - Francisco Hernandez-Guzman - June 12, 2008

• Physics Based Protein Ionization and pK Estimation
  - Francisco Hernandez-Guzman - June 19, 2008

• Towards Increased Accuracy in Computational Drug Discovery with QM/MM
  - Dipesh Risal - June 26, 2008

• Pharmacophore Guided Fragment-Based Drug Design
  - Tien Luu - July 10, 2008

• Advances in Pharmacophore Modeling and Parallel Screening
  - Ragi Raghavan - July 17, 2008

• Workflow Customization with DS Developer Client

• Tips and Tricks in using Discovery Studio
  - Al Maynard - July 31, 2008