Computer Simulation of Biosynthetic Modifications to Improve Binding Activity

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Super Bug - *Enterococcus Faecium*

- Potentially lethal, worldwide infection
- Antibiotic-resistant
- Able to survive for long periods on inanimate objects
- Hospital environments

http://efaecium.mlst.net/
Figure 1. Enterococcus Faecium.
Limitations of Existing Drugs

- Vancomycin - resistant
- Penicillin - resistant
- Gentamicin - resistant

- high genome plasticity - Able to acquire numerous other resistances

 lbl.gov
 Figure 2. Enterococcus Faecium
● Experimental drug development:
  o Expensive
  o Time-consuming
  o Sometimes impossible

● Virtual screening of drugs
  o Fast
  o Cheap
  o Effective
  o Flexible - able to make modifications
Project Approach

Virtual screening with drug library

↓

Introduce biosynthetic modifications

↓

Test performance of biosynthetic molecules
Protein Target - Peptide Deformylase

- Production of mature proteins
- Essential for bacterial growth
- Attractive drug target

http://www.rcsb.org/
Figure 3. Crystal structure of Enterococcus Faecium Peptide Deformylase complex with Met-Ala-Ser. PDB ID 3G6N
Virtual Screening

1. Predict binding affinity of drug by docking
   a. estimates the free energy of binding
   b. The more negative the value, the stronger the bond

http://vina.scripps.edu/
Figure 4. AutoDock Vina, used to make binding mode predictions and to find binding affinity
Biosynthetic Database

2. Predict possible molecular modifications by finding similar molecules in KEGG database

3. Test binding affinity for predictions
# Initial Identification

<table>
<thead>
<tr>
<th>Drug ID</th>
<th>Known Activity</th>
<th>Predicted Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZINC53683321</td>
<td>Anti Cancer</td>
<td>-7.8</td>
</tr>
<tr>
<td>ZINC16051958</td>
<td>Anti E. Coli</td>
<td>-7.3</td>
</tr>
<tr>
<td>ZINC96006023</td>
<td>Antibiotic</td>
<td>-7</td>
</tr>
<tr>
<td>ZINC12501002</td>
<td>Coenzyme analog of yeast</td>
<td>-6.5</td>
</tr>
<tr>
<td>ZINC58632138</td>
<td>Related to acetyl-CoA synthetase</td>
<td>-6.3</td>
</tr>
</tbody>
</table>

http://zinc.docking.org/
Figure 6a. Structure of ZINC53683321

http://zinc.docking.org/
Figure 6b. Structure of ZINC16051958
Biosynthesis

- Enzyme-catalyzed
- Convert substrate to more complex molecules
- Generate molecular features for ligand recognition that are more likely to bind to novel targets

biochemj.org
Figure 7. Branched biosynthetic pathway of the modified tetrapyrroles
## Results

<table>
<thead>
<tr>
<th>Original Drug</th>
<th>Original Predicted Affinity</th>
<th>Molecule ID</th>
<th>Predicted Affinity of Modified Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZINC53683321</td>
<td>-7.8</td>
<td>C01849</td>
<td>-10.1</td>
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<tr>
<td>ZINC16051958</td>
<td>-7.3</td>
<td>C05444</td>
<td>-9.1</td>
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<td>~</td>
<td>~</td>
<td>C02807</td>
<td>-8.7</td>
</tr>
<tr>
<td>ZINC58632138</td>
<td>-6.3</td>
<td>C00008</td>
<td>-7.3</td>
</tr>
</tbody>
</table>

Figure 8. (Top) http://zinc.docking.org/
Original Drug molecule of ZINC53683321
Similar molecule with better performance C01849
Discussion

● Improvements for existing drug molecules that target Enterococcus Faecium are found by looking at molecules with similar molecular structures.
● Computer simulations show that drug performance is greatly increased by such modifications.
Future Direction

- Target other organisms in ESKAPE group
- Looking at proteins related to neurological diseases
- Expand drug database and molecule database
- Building new drug molecules using fragment-based design
Intrinsically Disordered Proteins

- Lack a fixed or ordered 3D structure
- Flexible, easy to bind to
- Have close relationships with human diseases such as tumor, Parkinson disease, Alzheimer disease, diabetes, etc.
Acknowledgments

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- Dr. Gil Alterovitz
- University of Science and Technology of China
  - Especially Shilin Zhu and Yicheng Fei
References


Methods - Binding Affinity

- **AutoDock Vina**
- Allows running ligand-receptor docking calculation
Methods - Binding Probability

- Calculate the spectrophore of the drug molecule and the MoRF
- Binding Probability is calculated from the similarity between the drug molecule and the MoRF

openbabel.org
Demonstration of how spectrophores are calculated
Molecular Recognition Features (MoRFs)

- Small, intrinsically disordered region of a protein
- Bind to partners, serves as an initial step in molecular recognition

UC Davis
Examples of molecular recognition features (MoRFs)