Gut Microbial Tryptophanases as a Drug Target

Redinbo Lab

Celebration of Undergraduate Research

Charlie Warren
Gut Microbial Tryptophanases as a Drug Target

Diet with the Essential Amino Acid Tryptophan

Kidney Disease

Uremic Toxin Buildup

Tryptophanase

GI Tract

Indoxyl sulfate

Inhibition

1. Reabsorption
2. Host Liver CYP/SULT

L-Tryptophan

Indole

GI Tract
Tryptophanase Structure

PLP-Charged Holo Enzyme  
PDB: 5W1B

Inhibitor Bound  
PDB: 5W19

Tryptophanase Inhibitors for Drug Development

Cocrystal structure

Ki = 5μM

Induced Fit Docked Structure

PDB: 5W19
Selecting Compound Libraries for High-Throughput \textit{in silico} screening

Database of 156,944 compounds with indole substructure

\textbf{Lipinski's Rules:}
- Molecular Weight < 500 Da
- $c\text{LogP} < 5$ (lipophilicity metric)
- No more than 10 h-bond acceptors
- No more than 5 h-bond donors

139,358 compounds that satisfy “drug likeness”
High-Throughput *in silico* Screening

Precision Cascade

- 139,358 structures that satisfy “drug likeness”

1. HTVS (low precision Glide algorithm)
   - 12,264

2. SP (medium precision Glide algorithm)
   - 1,226

3. XP (high precision Glide algorithm)
   - 122

Validate “hits” (top 10) Experimentally

Repeat this process with Pyrroles, Pyridines, and Pyrimidines

Medicinal Chemistry to Improve Inhibitor Potency
Promising Poses from Indole Screen

Large heterocycle with building room

Fluorine hydrogen bond acceptors
## Unbiased Nitrogen Heterocycle Libraries

<table>
<thead>
<tr>
<th></th>
<th>Indole</th>
<th>Pyrrole</th>
<th>Imidazole</th>
<th>Pyridine</th>
<th>Total Structures</th>
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</thead>
<tbody>
<tr>
<td>Structures</td>
<td>156,239</td>
<td>139,358</td>
<td>746,767</td>
<td>1,767,526</td>
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<tr>
<td>Drug-like</td>
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<td>131,759</td>
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<tr>
<td>SP</td>
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<td>9,945</td>
<td>11,996</td>
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<tr>
<td>XP</td>
<td>122</td>
<td>99</td>
<td>484</td>
<td>40</td>
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</tr>
</tbody>
</table>
Commercially Available Hits and Validation

*No Activity

*No Activity

*No Activity

*No Activity

*No Activity

*No Activity

Structurally Unique

*Low Potency: ~ 500 μM

Structurally Unique

Indole Screen
Notable Structure
Future Directions for Inhibitor Design

• Validate more hits from screens

• Medicinal chemistry studies using analogs of existing inhibitors
  o Schrödinger Ligand Designer

![Chemical structures and Ki values](image)
Creativity in Inhibitor Design!

Leverage Mechanism

Structural Changes

X = PLP warhead
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The Next Step…