Predictive Application of Bioisostere Transformations to Identify Novel High Quality Compound Ideas

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Overview

• Concepts
  – Bioisostere and bioanlogue transformations
  – Automatic compound idea generation
  – Multi-parameter optimization (MPO) in drug discovery

• Retrospective example: Alogliptin

• Conclusions
Bioisostere and Bioanalogue Transformations
Bioisosteres, Bioanalogues and Biosterism

• Bioisosteres – “compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties such as hydrophobicity. Bioisosteric compounds affect the same biochemically associated systems as agonists or antagonists and thereby produce biological properties that are related to each other” *

• Bioanalogues – “molecules or group that, in the context of a given biological parameter, elicit analogous responses” **

• Biosterism – “encompasses classical bioisosteric pharmacophore functional groups, linker replacements, homologization, the introduction of conformation constraints..., reversible derivatizations..., and the incorporation of reactive functional groups” ***

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** Floersheim, P et al. (1992) Isosterism and bioisosterism case studies with muscarinic agonists. Chimia, 46, 323-334
*** Ujváry and Hayward, in Methods and Principles in Med. Chem. (Vol. 54), N. Brown (ed)
BIOSTER

• Database of >27,000 pairs of bioisosteres, bioanalogues, etc.*
  – Manually curated from the literature by Dr István Ujváry

• Addresses various questions, e.g.
  – What modifications have been successfully applied to similar compounds?
  – Identify potential lead-hopping strategies
  – Search for patent protection/busting strategies

• Library of transformations defined from pairs of molecules

* Ujváry and Hayward, in Methods and Principles in Med. Chem. (Vol. 54), N. Brown (ed)
Generating Transformations

- Bioisosteric substructure manually defined
- Handle different substitutions
  - Matched using heuristics
- Avoid promiscuity
  - Constraints on application
- 22,574 transformations generated (82% success)
Transformation Library

Benzamide to aminoquinazoline

SMIRKS: \([\text{Smiles String}]\)

Bioster No.: 282
ID code: AMID55

Names & Key Phrases:
- Antiarrhythmic

References:
- Stout D M et al., J Med Chem, 28(5) p. 295, 1985
Comparison of Electrostatic Fields

N.B. Field calculations performed with Cresset torch3D module for StarDrop
Automatic Compound Idea Generation
Compounds generated must ‘make sense’ from a medicinal chemistry perspective

Apply ‘transformation rules’, derived from medicinal chemistry experience, to initial compound(s)*

- A ‘drug-like’ molecule might be transformed into 200 - 300 new compounds
- >94% of structures generated acceptable to med. chemists
- Not only functional group replacement but also framework transformations

Generating Compound Ideas
Applying Med. Chem. ‘Transformation Rules’

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Linker modification: e.g. ester to amide
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Ring addition:
e.g. benzene to indole
Exponential Growth!
Controlling the Process

- Specify initial structure
- A region can be selected to be fixed (no changes allowed)
Controlling the Process

- Select transformations to apply
- Transformations can be managed for specific objectives
Controlling the Process

- Apply multiple generations of transformations
- Bias selection in favour of property, score or diversity
Multi-parameter Optimization
The Objectives of Drug Discovery
Multi-parameter optimisation*

• Identify chemistries with an optimal **balance** of properties

• Quickly identify situations when such a balance is not possible
  – Fail fast, fail cheap
  – Only when **confident**

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Approaches for MPO
Probabilistic Scoring* – Scoring Profile

<table>
<thead>
<tr>
<th>Property</th>
<th>Desired Value</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>pIC50</td>
<td>&gt; 8</td>
<td></td>
</tr>
<tr>
<td>logS</td>
<td>&gt; 1</td>
<td></td>
</tr>
<tr>
<td>BBB log([brain]:[blood])</td>
<td>-0.2 -&gt; 1</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic. (pLD50)</td>
<td>≤ 5</td>
<td></td>
</tr>
<tr>
<td>logP</td>
<td>0 -&gt; 3.5</td>
<td></td>
</tr>
<tr>
<td>P-gp category</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Ames</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>hERG pIC50</td>
<td>≤ 5</td>
<td></td>
</tr>
<tr>
<td>2C9 pKi</td>
<td>≤ 6</td>
<td></td>
</tr>
<tr>
<td>2D6 affinity category</td>
<td>low medium</td>
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</tr>
</tbody>
</table>

StarDrop Prioritisation
Probabilistic Scoring

- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

**Score (Likelihood of Success)**
- Confidence in score

Data do not separate these as error bars overlap

Error bars show confidence in overall score

Bottom 50% may be rejected with confidence

Retrospective Example: Alogliptin
Alogliptin Project Lead Compound*
Objective: Anti-diabetic, DPP IV inhibitor

• Scoring profile:
  – Orally dosed
  – Non-CNS target

• Lead compound:

Results of Application to Lead Compound

Alogliptin

Rank...

0.47 2...

23...

0.34

0.33 38...

229
Conclusion

• Illustrated integration of three concepts to prioritise new compound ideas
  – Med. Chem. transformations
  – Compound idea generation
  – Multi-parameter optimisation

• Applications include:
  – Rigorous exploration of chemistry around hits
  – Investigation of optimisation strategies to overcome liabilities
  – Identification of potential lead-hopping opportunities
  – Searching for patent protection/busting strategies

• For more information:
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