Medicinal Chemistry is an art, when you don’t understand the data

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Medicinal Chemists – we (think) we know a lot

✓ Thorough knowledge of organic chemistry

✓ Knowledge of factors that influence ADME characteristics of compounds in vitro and in vivo

✓ Understanding of biology that relates to the disease/target project/toxicology and safety
  • Relevance of *in vitro* and *in vivo* assays adopted by project

✓ Appreciation of patent and literature chemistry/biology information related to competitor compounds

✓ Understanding of clinical and regulatory requirements for disease of interest and related drugs

✓ Familiarity with new biology and chemistry technologies

The synthesizer-designer relationship

- Designers and synthesizers share project team goals
- Designers and synthesizers refine chemical plan: Add/Modify/Deprioritize/Reject targets
- Collocated designers and synthesizers for optimal interactions
## Optimization of design process – keep what works, improve what doesn’t

<table>
<thead>
<tr>
<th>Data storage and visualization</th>
<th>Original circa 2010</th>
<th>Design/Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISIS, Excel spreadsheets, ppt, cdx (C:drives)</td>
<td>Spotfire data packages: editable/customize views, on demand data update</td>
</tr>
<tr>
<td>In silico calculations</td>
<td>Primitive use of chem draw, excel macros, PP tools upon request</td>
<td>Abbvie Designer Workbench: Pipeline pilot - harmonization of calculations</td>
</tr>
<tr>
<td>Justification for ideas/synthesis</td>
<td>Ideas supported by PhD and associate, “Ki is King”</td>
<td>Designer &amp; Chemists ideas supported by prospective calcs/SAR/SPR</td>
</tr>
<tr>
<td>Modeling</td>
<td>Primitive Pymol, RocsDoc, Molecular modelers, ChemDraw 2D overlays</td>
<td>Design support specialist, designers tools MAESTRO, CSD, BROOD, TORCH, Water Map, …</td>
</tr>
</tbody>
</table>

\[ \text{Efficacious dose} \propto \frac{\text{AUC}_{\text{eff}, u} \times \text{CL}_{\text{int}, u} \times \text{target tissue impairment}}{f_a \times f_g} \]
Typical workflow scenario: Chemical matter analysis for a new target

Dr Recon mentions that he’d like to know what chemical matter exists for the Chemokine receptor CCR007. He couldn't find any chemical matter and now needs your expert help. He mutters something about how exciting the target is, and wonders whether we could start a medicinal chemistry program.

You reply that you’d be happy to review the literature and that you’d get back to him in a few hours/days with some information.

You figure that you'll start by reviewing the biology of CCR007 to make sure that your search terms are accurate, and that it should be trivial to find both internal and external data.

Given that you care about Structure Property Relationships both affinity and property data will be ETL into Spotfire and new ideas of compounds will ultimately be discussed with the synthesis community prior to execution (internally and externally).
Design workflow (step 1 of 2)
Aggregate internal and external real and calculated data

Data search from ChEMBL, WOMBAT, PubChem, Abbvie Internal Project, TR Integrity & DrugBank

Assess internal and external Structure Activity & Structure Property Relationships to identify potential lead compounds
Design workflow (step 2 of 2)
Create a potential list of target compounds for synthesis

Type of design → Create Filter → Generate Compounds → Prioritize

- Ligand
- Model
- X Ray

- Pharmacophore Map
- Docking Grid
- Singleton & Library Idea Generation
- Score & Review

- Forge
  - Field based alignment
  - Common substructure
- Maestro 10.4
- BROOD
- LeadIT: Recore
- Schrodinger Core Hopping
- Hyde - SeeSAR
- Schrodinger: Glide
- OpenEye ROCS
Example 1: Kinase project

- Clear trend into more optimal drug like space over time in parallel with achievement of project goals.
Example 2: Protein – Protein interaction
Compounds prepared by 2 groups of medicinal chemists (same project)

“... but we didn't need umpteen years of upheaval to tell us that making compounds that
weight 910 with logP values of 8 are less likely to be successful. Did we?”

Waring, M.J., et al., An analysis of the attrition of drug candidates from four major
Example 2: Protein – Protein interaction
First control physico chemical properties!

What you work on is just as important as what you won’t work on:

“... but we didn't need umpteen years of upheaval to tell us that making compounds that weight 910 with logP values of 8 are less likely to be successful. Did we?”

Chemical Structure Similarity – 800 days of compounds
RocsOverlay comparing 3D shape and color to a reference lead

In vitro binding IC50 / μM

Potent, Lipophilic (~ 7), dissimilar compounds

Potent but similar compounds
RocsOverlay comparing 3D shape and color of compounds prepared in a design/synthesis mode

Program maintains a focus on appropriate physico chemical properties, while maximizing dissimilarity from literature lead.
Similarity allows an assessment of the degree of diversity of compounds synthesized in H2L and LO programs.

Similarity by Color

Small changes influence biological activity
Synthesis is design made real

The quality of synthesis depends upon the wisdom/knowledge of the chemist and their practical skill to complete the synthesis

- Synthetic chemistry knowledge requires familiarity with organic chemistry literature, disconnection skill, and functional group compatibility
- Applicability of flow chemistry, resin supported procedures, parallel synthesis and purification approaches
- Requires experience in triaging multiple potential routes
Cumulative number of reactions performed over a 4 month period by traditional medicinal chemists

1 reaction a day, 5 days a week, over 16 weeks = 80 reactions
Wuxi and Abbvie Chemistry – same scale

Abbvie Chemistry

Wuxi Chemistry

Wuxi chemistry focuses on synthesis
Design/Synthesis allowed chemists to focus more effort in the lab synthesizing compounds of increasing complexity.
Summary

✓ Appropriate application of design tools improves the quality of compounds that are prepared

✓ Expertise in synthesis enables the preparation of preferred compounds

If you think you can walk from the lab and do design in your office for a couple of hours and then go back to synthesis, you don’t understand the complexity of design or synthesis
Abstract

When one considers the considerable expense that is associated with developing a drug, it is clearly the responsibility of the chemist to ensure that they are preparing the most optimal compound. To achieve this we have focused our efforts within Abbvie medicinal chemistry toward excellence in design and excellence in synthesis. Here we will describe the trials and tribulations of this approach.

Talk title: Medicinal Chemistry is an art, when you don’t understand the data. Jeremy J Edmunds, Ph.D., Director, Immunology Medicinal Chemistry, Abbvie