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Lead Optimization

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Lead Optimization

Goals

- What needs to be optimized?
  - Potency
  - Physiological properties
  - Novelty/IP position
- Reaching one goal may require revisiting others

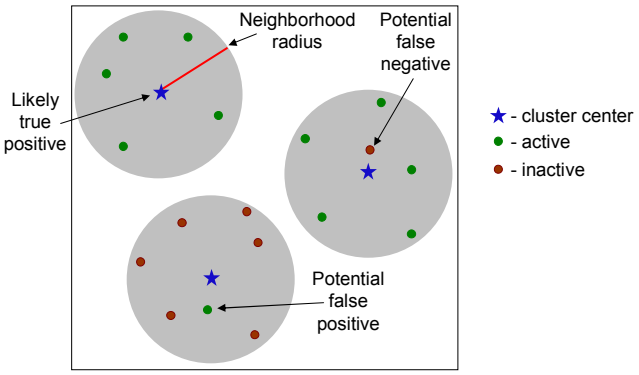
Scope

- How far from existing leads do you want to go?
  - Retain existing scaffold
  - Move to new lead series

Turning Hits into Leads

Initial screening is performed on a large number of compounds at a fixed concentration

The goal of hit to lead analysis is to identify true positives and potential false negatives



By looking at neighborhood behavior, one can discover possible misidentified compounds

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Lead Optimization Process

- Collect knowledge of the target (Knowledge Base)
  - Literature data
  - Customer proprietary/screening data
- Select and implement methodology
  - Physical property profiling/predictions
  - Virtual docking
  - Similarity searching
  - QSAR/CoMFA
- Create and prioritize list of synthetic targets
- Screen compounds and analyze results
  - Iterative process
  - Each set of results provides new knowledge to focus future design

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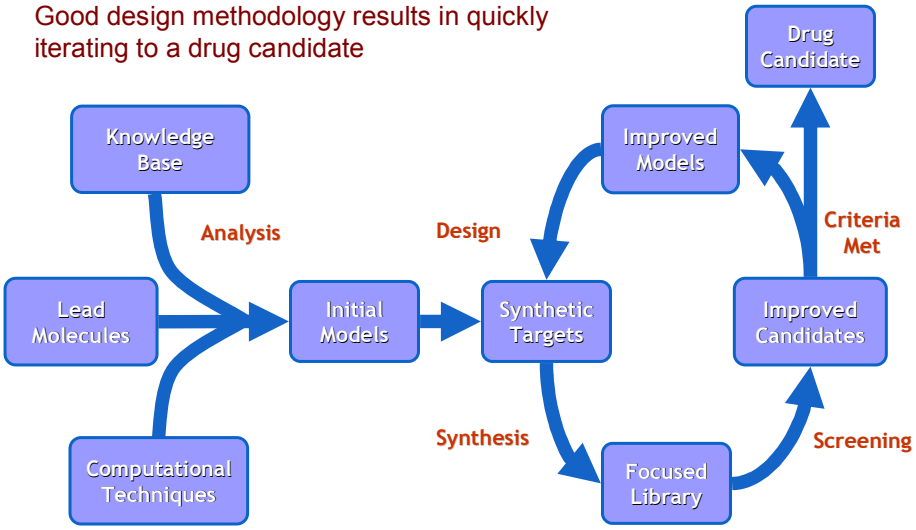
Rapid Optimization of Lead Molecules

Good design methodology results in quickly iterating to a drug candidate



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Physical Property Profiling

Typically libraries are designed to meet Lipinski's "Rule of 5"

Poor absorption or permeation of an orally administered drug is more likely to occur if any two of these criteria are violated:

- Molecular weight is greater than 500
- Lipophilicity is high (ClogP is greater than 5)
- Number of Hydrogen bond donors is greater than 5
- Number of Hydrogen bond acceptors is greater than 10

But in reality properties need to be tailored to target being addressed

Properties of Oral Drugs Categorized by Gene Family

	90% MW	90% ClogP	90% HBD	90% HBA	90% Rbonds
Aminergic GPCRs	460	5.6	2	6	8
Ion Channels	430	4.7	3	6	7
Nuclear Hormone Receptors	495	7.3	2	6	10
Peptide GPCRs	752	6.5	8	10	17
Phospho-diesterases	465	5.2	2	8	9
Protein Kinases	505	5.7	4	7	9
Serine Proteases	572	4.8	4	8	12

Hopkins, et al, Nature Biotechnology **2006,** 7, 805-815

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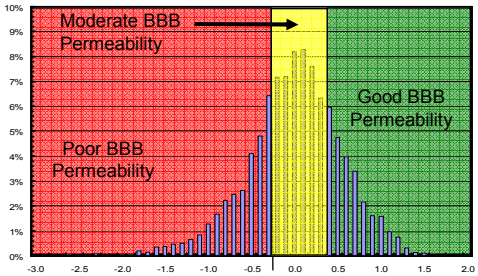
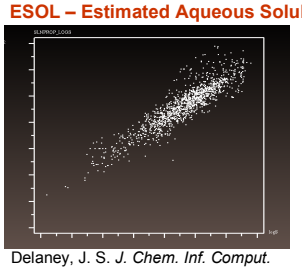
ADMET Predictions

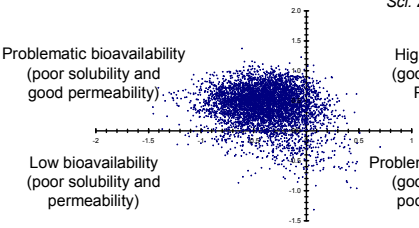
Consider ADMET properties early to minimize problems downstream



ESOL – Estimated Aqueous Solubility



Delaney, J. S. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1000 – 1005.



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Virtual Docking Strategy

Use crystal structure to identify improvements to lead molecules

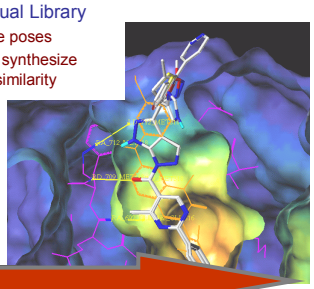
Dock a Diverse Subset of the Virtual Library

- Start with filtered virtual library
- Select by diversity or similarity

	Best	Worst	Avg
P38	-25.6	2.8	-11.6
CDK2	-26.7	2.7	-12.1
Abl	-32.7	-0.8	-17.2
FGFr	-21.9	-5.1	-14.4

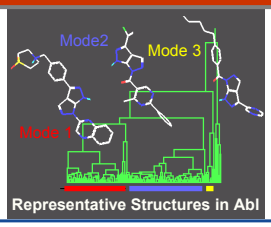
Dock Complete Virtual Library

- Use identified base poses
- Select products to synthesize using scores and similarity



Identify Reasonable Binding Modes

- Cluster on RMS distance between docked structures
- Visually inspect examples from each mode



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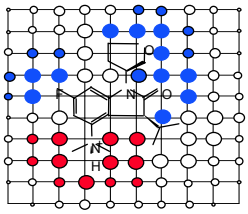
Similarity Searching

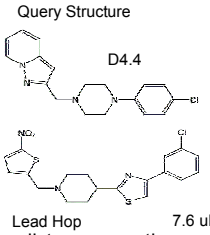
Topomer based searching is effective in searching large virtual libraries

Topomer Fields



Split molecule into 2-3 fragments
Rule-based alignment of fragments onto a grid
Use probe atom to calculate steric potential at grid points

Topomer Distances



Topomer distances are the sum of the pair-wise differences between the fields summed over the fragments plus alignment and steric penalties

An example result from a Tripos validation study is shown above

Topomer fields can also be used for CoMFA predictions in virtual libraries

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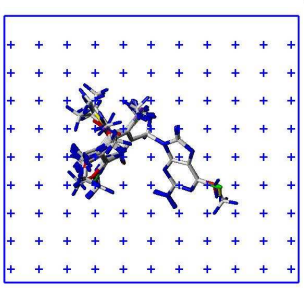
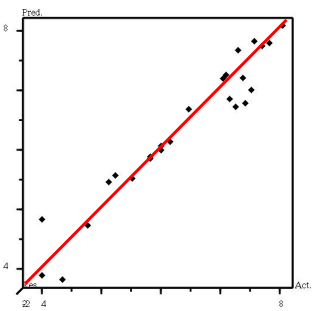
QSAR/CoMFA Model

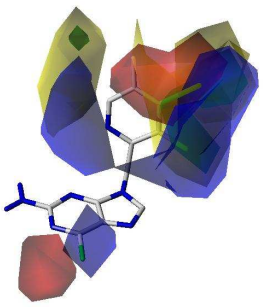
CoMFA models provide more detailed analysis of individual leads and include both positive and negative data in the predictions



Overlay molecules
Compute CoMFA fields



Partial Least Squares Analysis (PLS) to correlate field values with biological activity



Fields indicate areas to increase or decrease steric and electronic properties

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Summary of Lead Optimization

- Methods used will be tailored to customer requirements
  - What is known about the target
  - Quantity and quality of current leads
  - What needs to be optimized
- Large number of computational techniques
  - Multiple methods are likely to be used
  - Alternative methods available for techniques presented earlier
  - Methods validated with customer data to ensure best results
- Coordinate with chemists to ensure best synthetic outcome
- Customer is involved in the entire process
  - Regular meetings to present intermediate results
  - Flexibility to change strategy as information is gained