ChemModeling

Lead Generation

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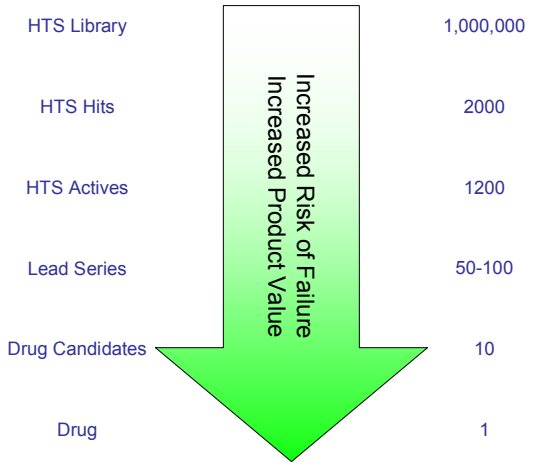
Drug Discovery is a Difficult Process



Oprea, Ed. ChemoInformatics in Drug Discovery, Wiley, 2005, p. 28

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Knowledge-Driven Design Finds Optimal Candidates

- Where do we look?
  - Libraries of existing compounds
    - In-house collections
    - Vendor collections
  - Virtual Libraries
    - Suggestions from chemists
    - Constructed from “Ideas” databases
    - De Novo scaffold generation
- How do we look?
  - Properties specific to the target
  - Similarity to known active compounds
  - Match of pharmacophore model built from known actives
  - Relevant docking pose and reasonable score in crystal structure
- What do we look for?
  - Medicinal chemistry relevance
  - Optimal diversity/representativeness of compound set
  - Embedded SAR potential for quick optimization
  - Reasonable chemistry allowing rapid follow-up
  - High quality compounds (pure, well characterized, reliable vendor)

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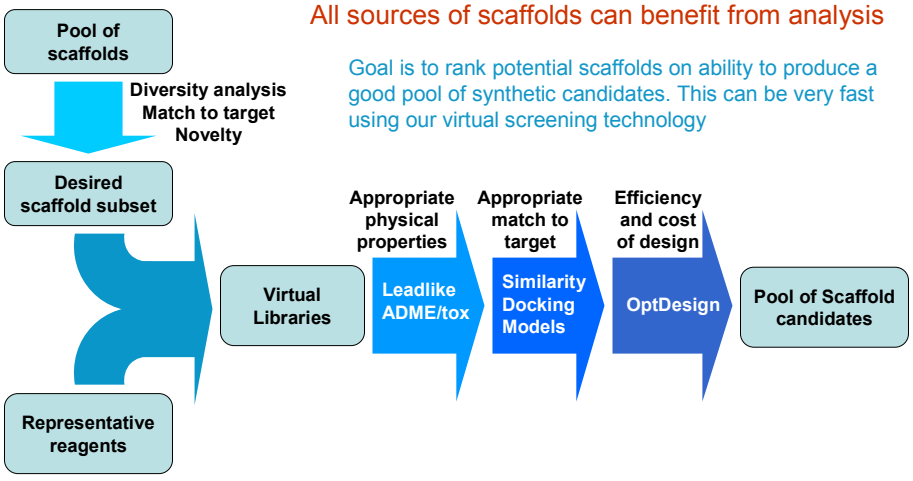
3

For Virtual Libraries: First Select the Best Scaffolds



All sources of scaffolds can benefit from analysis

Goal is to rank potential scaffolds on ability to produce a good pool of synthetic candidates. This can be very fast using our virtual screening technology

Process most important for scaffolds with the least prior medicinal chemistry input

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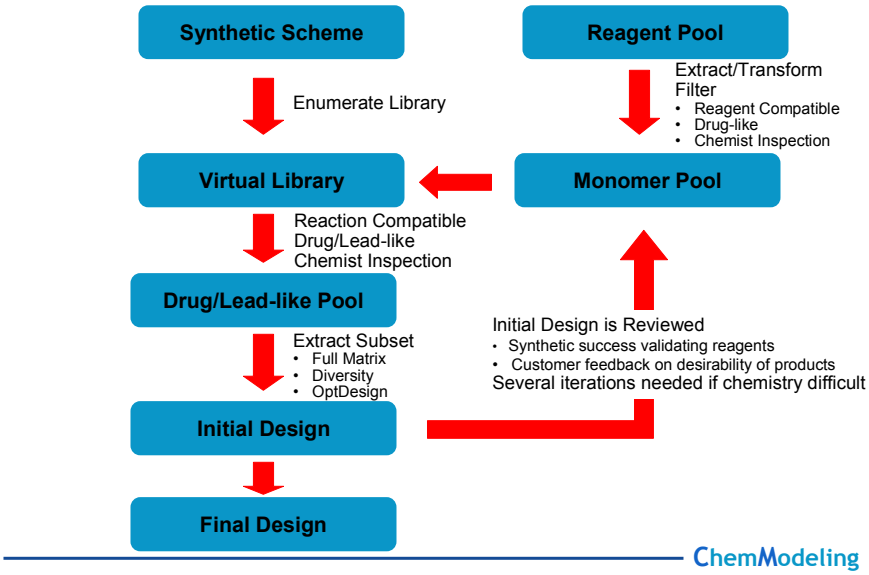
4

Best Scaffolds are Used in a Full Library Design



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Considerations for Virtual Docking

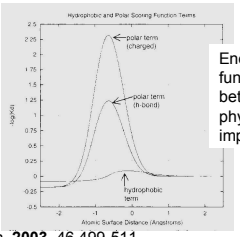
- You need to find the right conformation
  - Generate conformations up front
  - Incremental build-up
- You need a way to score these conformations
  - Molecular mechanics type functions
  - "Potential of Mean Force" methods
- You need to rank the results
  - Functions used during docking are necessarily fast and simple
  - Post docking, better methods can be used
- Ideally, protein flexibility can also be considered

FlexX Scoring Function

$$\Delta G = \Delta G_0 + \Delta G_{rot} N_{rot} + \Delta G_{hb} \sum_{h-bonds} f(\Delta R, \Delta\alpha) + \Delta G_{ion} \sum_{ionic} f(\Delta R, \Delta\alpha) + \Delta G_{aro} \sum_{aromatic} f(\Delta R, \Delta\alpha) + \Delta G_{lipo} \sum_{lipo} f(\Delta R)$$

Strength of interactions function of the deviation from ideal

SurFlex Potentials



Energy of interaction function distance between atoms, physical effects are implicit.

Rarey, et al J Mol Bio **1996**, 251, 470-480; Jain, J Med Chem, **2003**, 46,499-511

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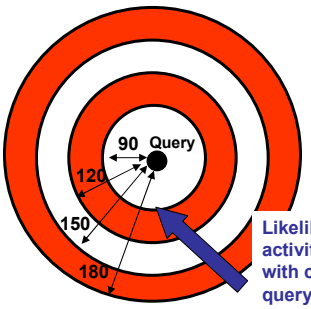
Considerations for Similarity Searching

- You need a suitable function to assess similarity
  - Field based approach
  - Distance to critical features
  - Overlap of atoms/critical features
  - CoMFA model predictions
- You need get the right conformations
  - Rule-based construction
  - Incremental alignment of fragments
  - Generate a fixed set of conformations
- You need an efficient way to search large numbers of structures
  - Generate distances for components of a virtual library
  - Vector-based assessment of similarity from representative population

Distribution of topomer hits from BMS/Tripos validation



region	# tested	% active
< 90	4	0.50
90 - 120	61	0.08
120 - 150	176	0.00
150 - 180	156	0.00
>189	28	0.00

Cramer, R.D., Poss, M.A., Hermsmeier, M.A, Caulfield,T.J, Kowala,M.C., Valentine, M.T J Med Chem **1999**, 42, 3919-3933

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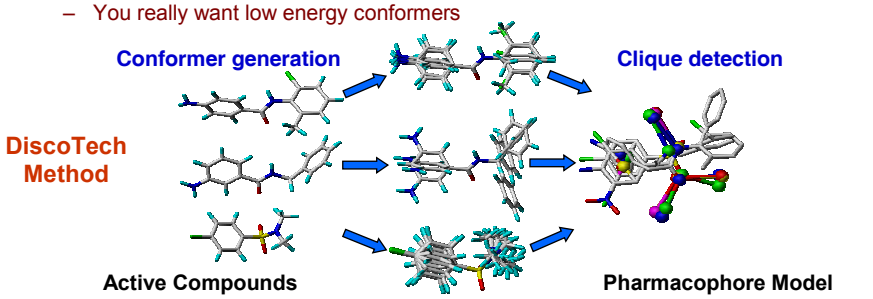
Considerations for Pharmacophore Modeling

- You need to find the right conformations
  - Generate a fixed set of conformations
  - Modify conformations on the fly (typically using a genetic algorithm)
- You need to find the right model
  - Programs typically generate tens to hundred of alternates
  - Pick models that distinguish actives from in-actives
- Once you have the pharmacophore, you need to find matches
  - Typically done with 3D flexible searching
  - You really want low energy conformers



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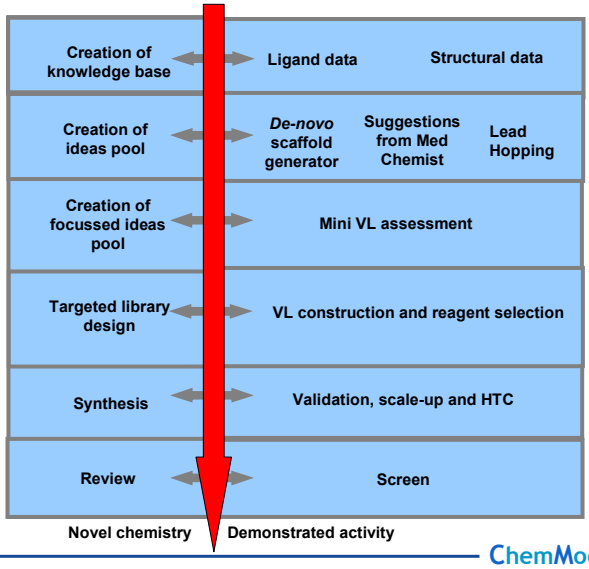
Example: Kinase Targeted Libraries

The complete process from collecting data to obtaining active compounds



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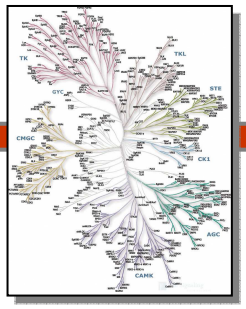
Creation of the Knowledge Base



Copyright Cell signalling

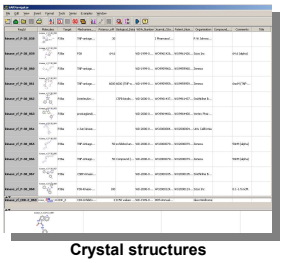
Which kinases do we target?

CDK2, P38a, FGFR, GSK3b, JnK3….

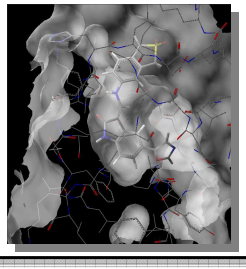
Selection criteria

- Occurrence
- Therapeutic relevance
- Availability of ligand /structural information
- Commercial screen
- Diversity

Ligand database



Crystal structures



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Creation of the Ideas Pool

100's of scaffolds

Creation of VLs: from drug-like reagent pool

4 boronic acids ⇨ **Kinase 104 scaffold** ⇦ **17 amines**

Ranked
- Docking score
- Visualisation
- Similarity
- Properties
- Synthetic feasibility

name	synthesis notes	size	property violations	topomer similar	(raw) flexs rank	(nor) flexs rank	(vl) flexx f rank	(ex) flexx rank
kinase_59	5	60	2	1	2	5	1	1
kinase_104	5	68	1	4	1.5	3	1.5	1
kinase_110*	4	561	3	0	1.5	10	1.5	5.5

Library	1a9u	1ke7	1m52	2fgi	Average Rank	Overall Rank
kinase104	4	2	1.5	1	2.12	1.5

Scaffolds selected for full design

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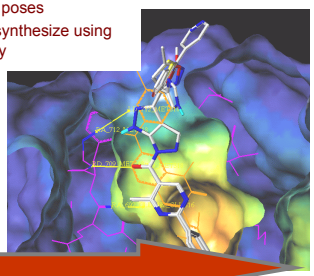
Fast Docking Strategy

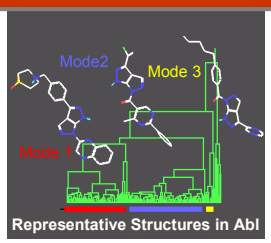
Dock a Diverse Subset of the Virtual Library
- Start with filtered virtual library
- Select by diversity or similarity

	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



Representative Structures in Abl

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Results: Enhancement Rates – p38 MAP Kinase

Baseline - 10 Actives From 97 Screened for p38 = 10.3%

Subset	Subset size	No Actives	% Actives
All	97	10	10.3
Dock (< -20)	58	9	15.5
Topomer (< 120)	26	6	23.1
Intersection	14	5	35.7

Combination of docking & topomer searches = *~36% hit rate*

Good basis for creating designs from large virtual libraries

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Results for All Libraries

Library	# actives	# cmpds
1	6	15
2	3	22
3	3	11
4	1	22
5	1	28
6	2	19
7	0	28
8	3	10
9	7	12
10	12	20
11	3	16
12	0	27
13	4	10
14	1	4
15	10	16
16	0	7
17	9	11
18	6	6
Total	71	284
Hit Rate	25%	

- ~225 library ideas evaluated computationally
- ~48 library evaluated synthetically
- ~3800 compounds from 19 different scaffolds produced
- Assay performed by Upstate in the UK
  - Panel of 9 kinases
  - Measure % control at 10 uM ligand concentration
  - Results are the average of two assays
  - 10 uM ATP concentration
  - Active is defined as 50% of control or less
- 13 batches tested
- 284 compounds tested

- # of actives = # of compounds which show >50% inhibition @ 10uM in at least one assay.
- A compound displaying multiple kinase activity counts as one active.

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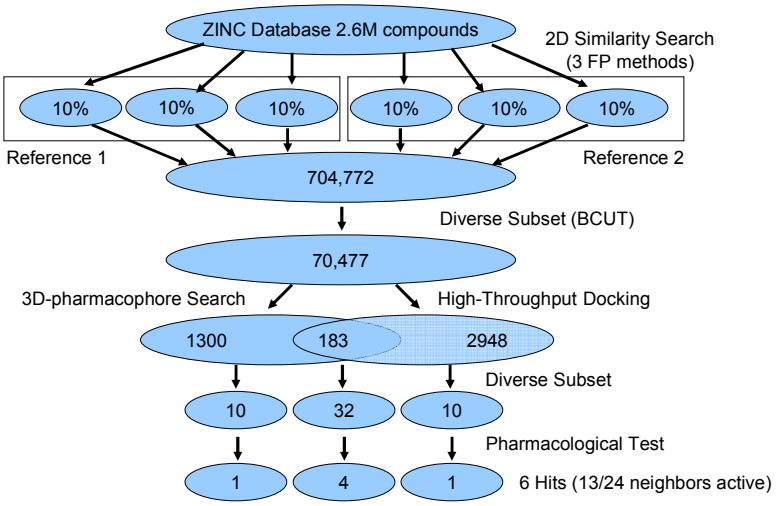
An Example of Computer-Aided Drug Discovery



Tikhonova, I.G;Sum, C.S; Neumann, S.; Engel, S.; Raaka, B.M.; Costanzi, S.; Gershengorn, M.C.. J. Med. Chem. 2008, 51, 625-633.

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15

Summary of the Complete Process

- Most compounds that enter the drug discovery process fail
  - Use target knowledge early to eliminate poor candidates
- Reduce the attrition rate through intelligent (informatics-based) application of appropriate tools
  - Efficient library design process
  - Property filters and predictions
  - Activity prediction tools (receptor and ligand based)
  - Chemistry expertise and knowledge
- Goal is to obtain lead compounds with
  - Appropriate biological activity
  - Appropriate target selectivity
  - Acceptable ADME-Tox profile
  - Patentable position
- All accomplished in as short a time as possible

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16