



Fragment based drug discovery in teams of medicinal and computational chemists

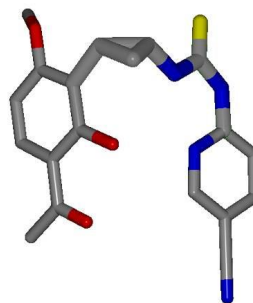
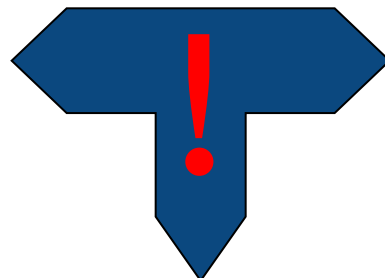
Carsten Detering

BioSolveIT - Quick Facts

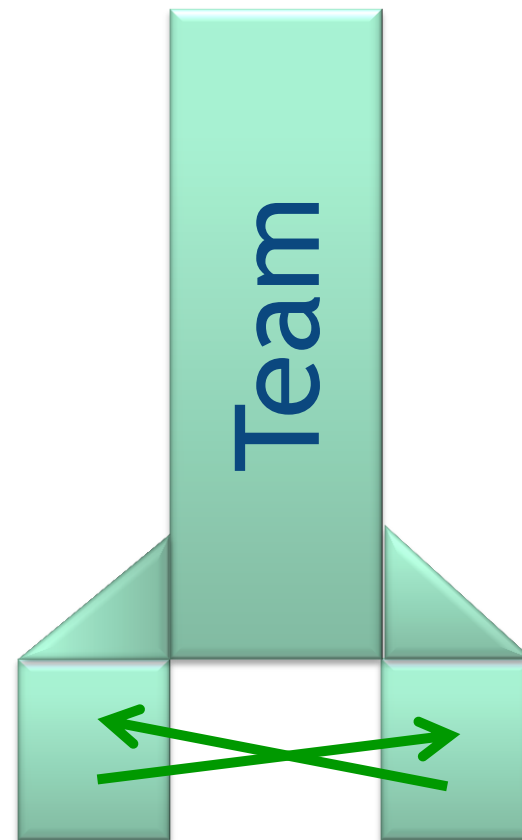
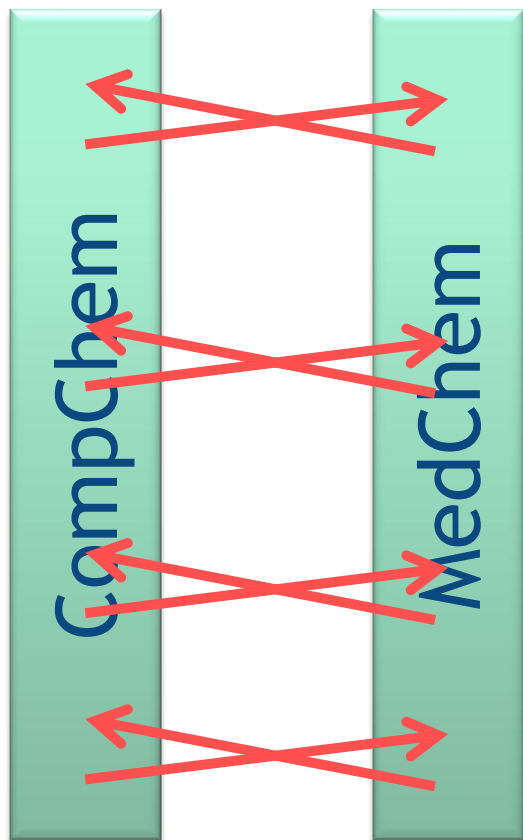
- Founded in 2001 by the developers of FlexX
- ~20 people
- Core expertise: docking, screening, FBLD, GUIs
- Offers
 - collaborative custom development
 - licenses and contract maintenance
 - training and consulting services
- Strong scientific backbone:
 - Thomas Lengauer
 - Matthias Rarey
 - Gerhard Klebe
 - Hugo Kubinyi
 - Chris Lipinski



The LeadIT/ReCore idea

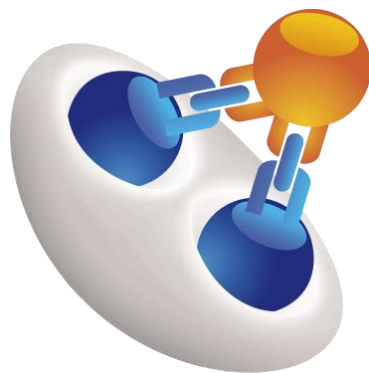
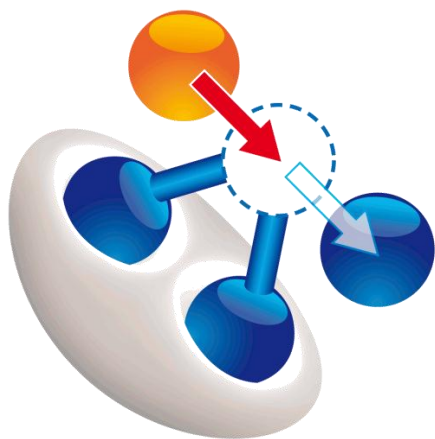


Early Stage Teamformation



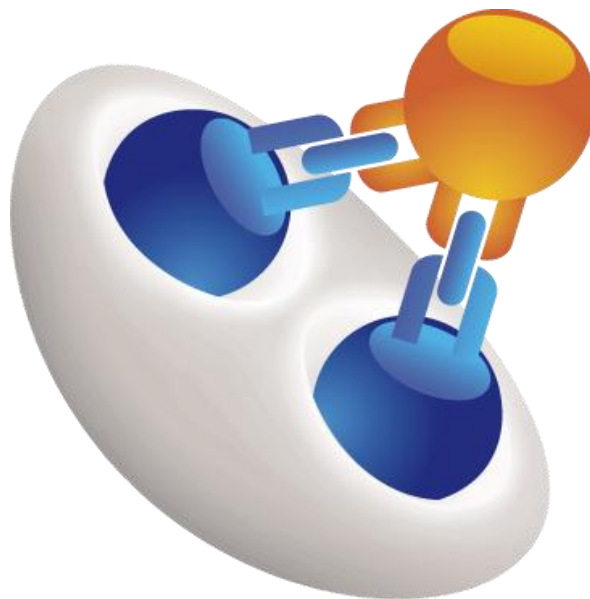
Link, Merge, Grow Fragments

ReCore in LeadIT



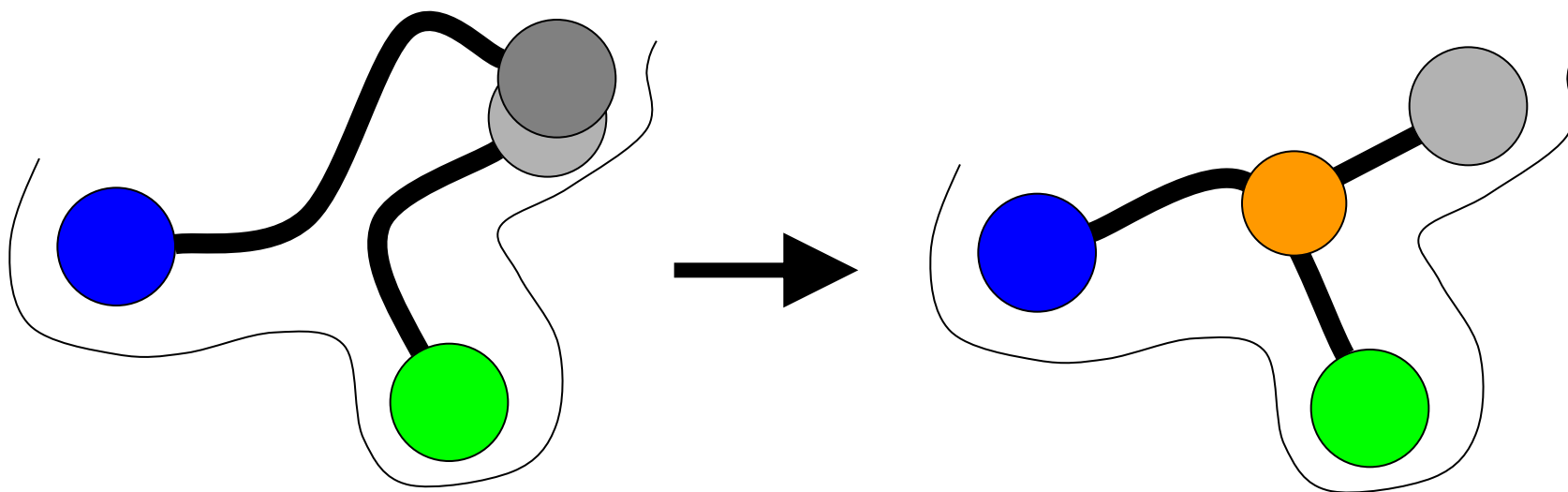


Case Study: Merging Fragments



Fragment Merging

The idea: Connect multiple known fragment binders where they overlap.

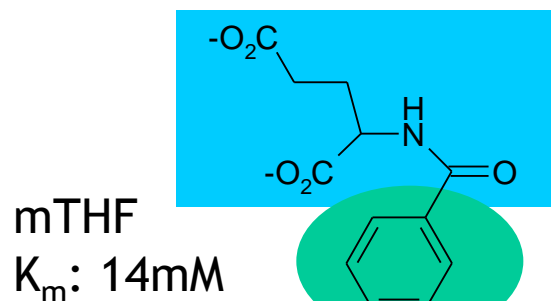


P. Hajduk: “Fragment-Based Drug Design at Abbott“
(Talk at the FBLD'2008, San Diego)

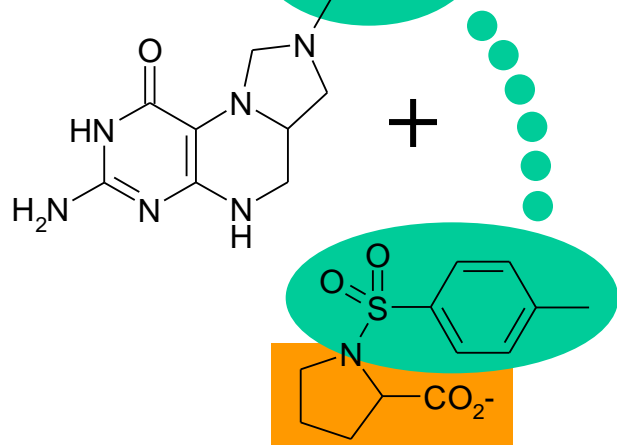
and many, many others nowadays.

A Tough Merging Example

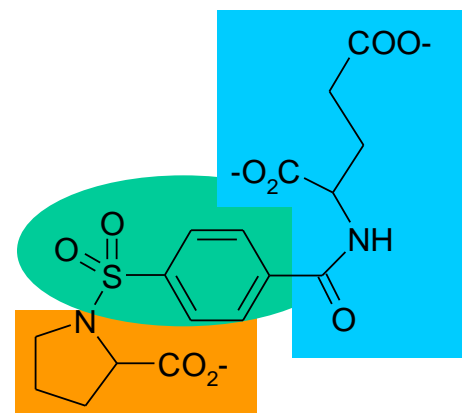
Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 **97** 9367)



“...tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate...”



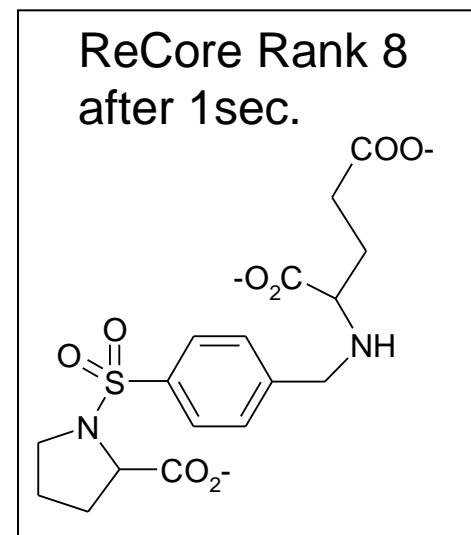
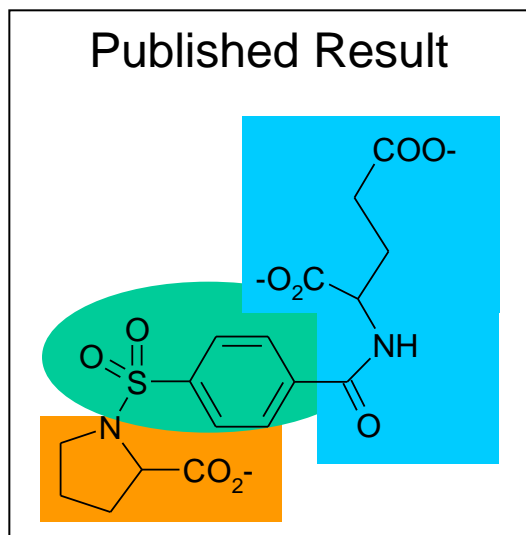
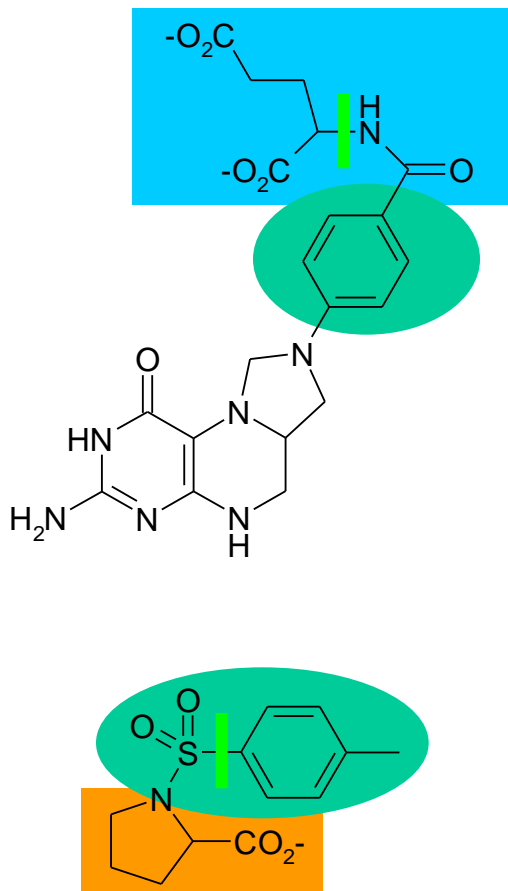
PDB: 1F4E
K_i: 1.1mM



24μM,
further opt'd to 330nM

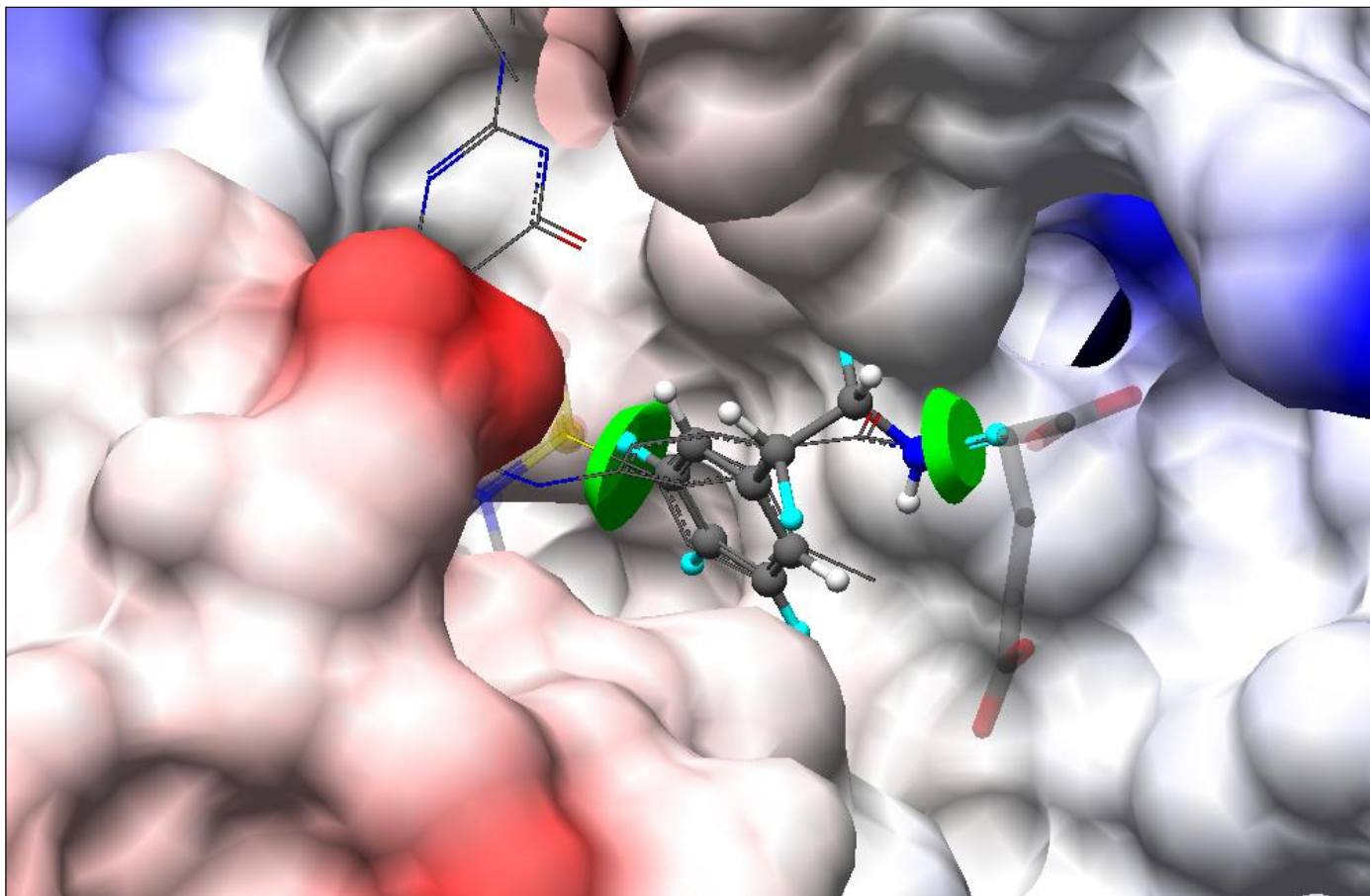
A Tough Merging Example

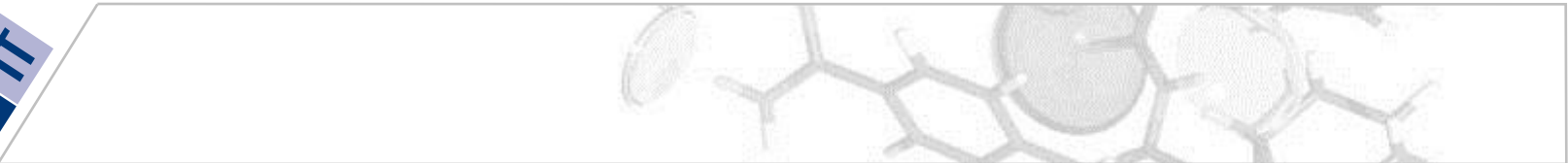
Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)



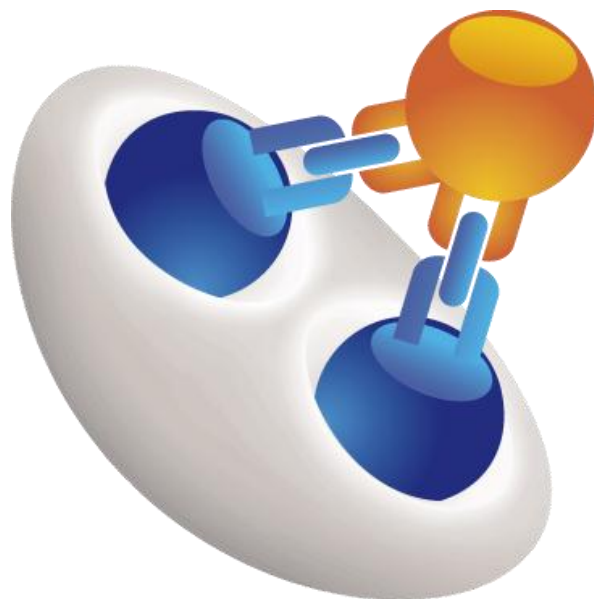
To ensure the result accommodates in the pocket the input ligand envelope shapes were used.

A Tough Merging Example



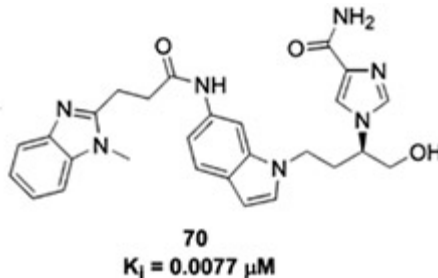
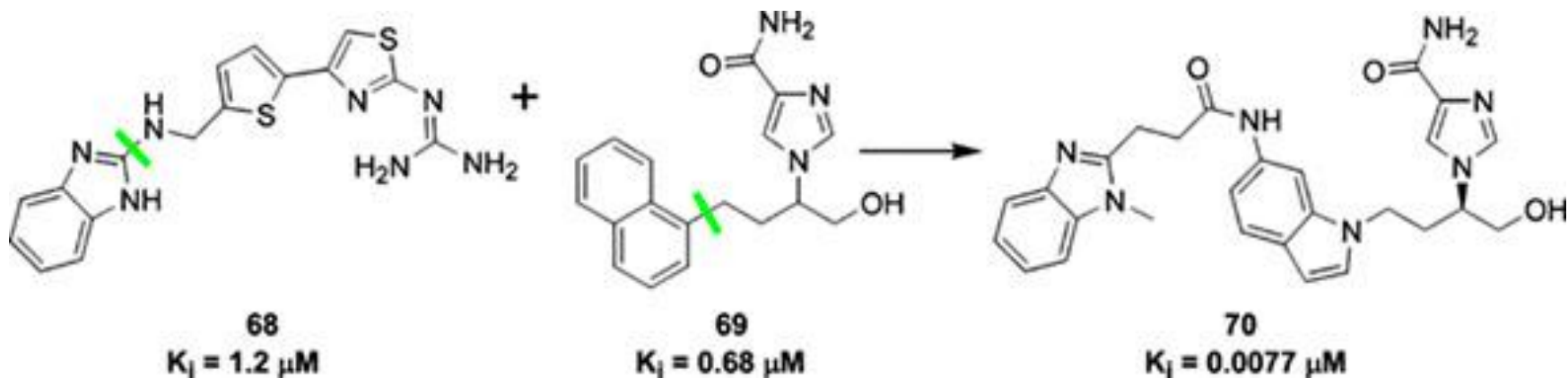


Case Study : Merging Fragments



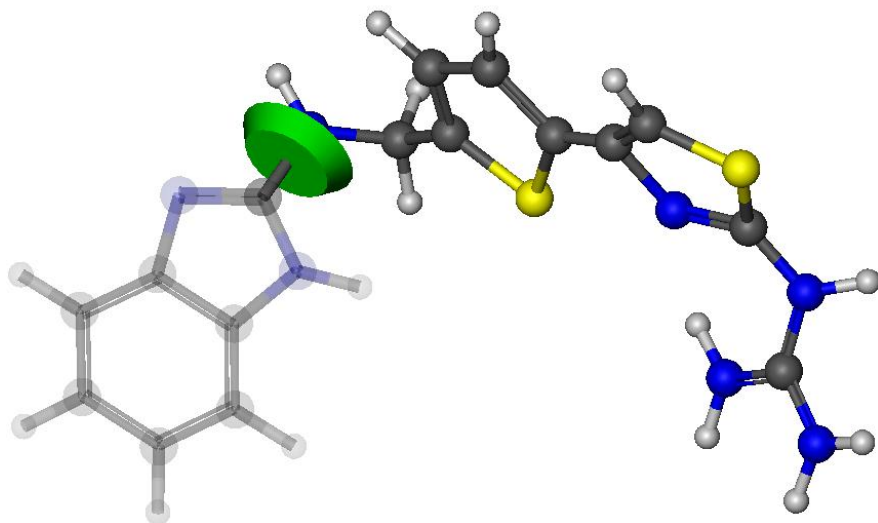
A Fragment Merging Exercise

Adenosine Deaminase: Erlanson, D.A. et al., . J. Med. Chem. 2004, 47, 3463 ff.

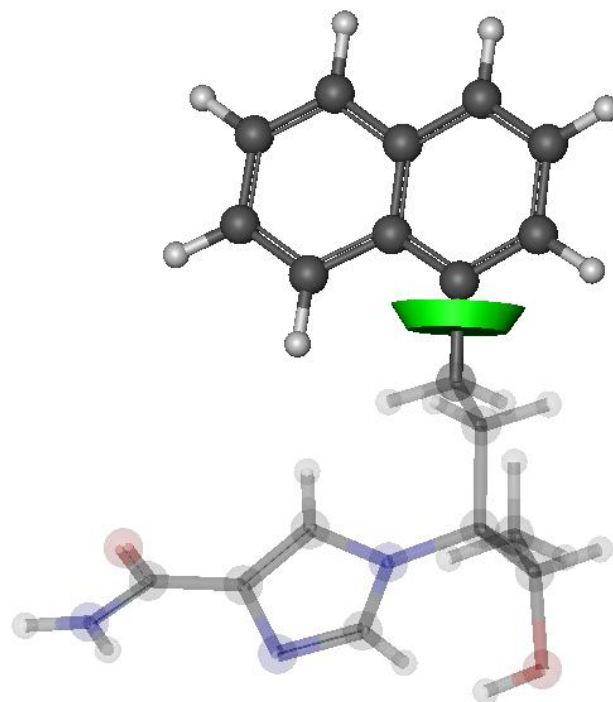


A Fragment Merging Exercise

Adenosine Deaminase: Erlanson, D.A. et al., . J. Med. Chem. 2004, 47, 3463 ff.

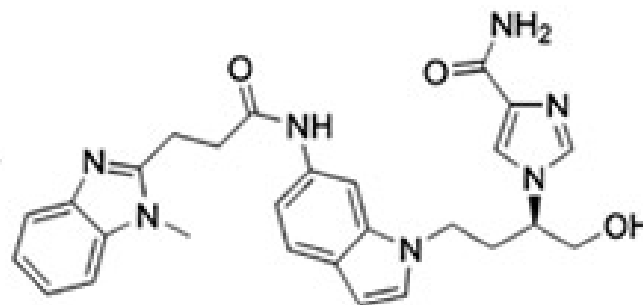
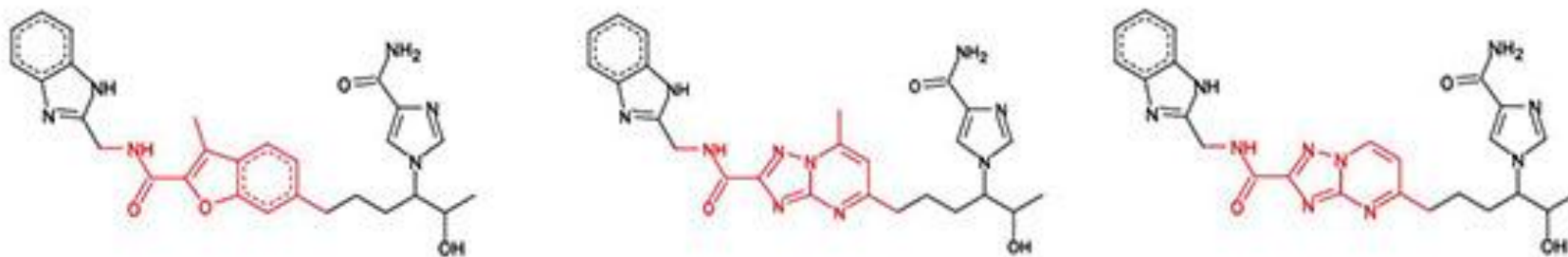


1ndv

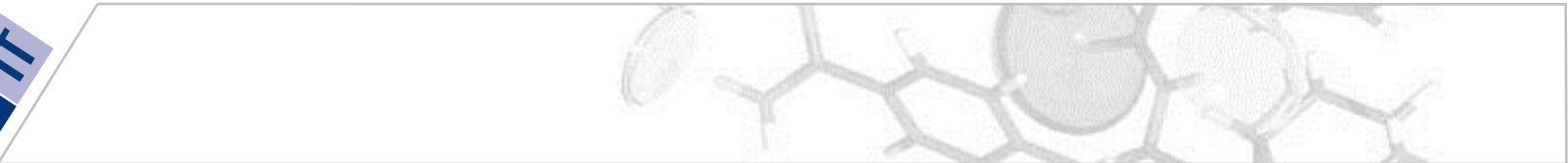


2e1w

A Fragment Merging Exercise



70
 $K_i = 0.0077 \mu\text{M}$



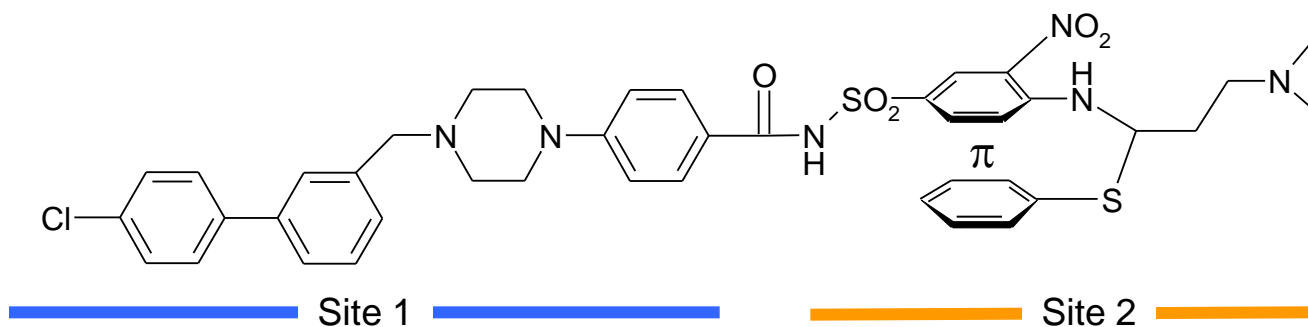
Case study: Growing a Fragment



Growing into a π - π Interaction Pattern

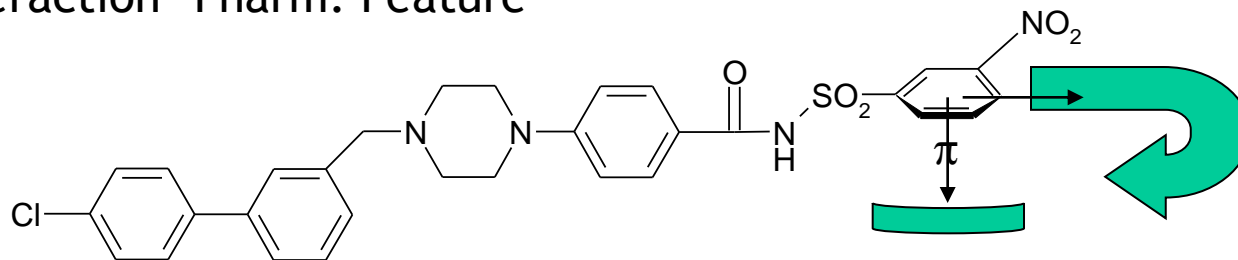
Bcl-2 protein example from Abbott (Oltersdorf et al, Nature 435 (2005) 677).

Let us try to get the π -stacking right as in the original finding in ABT-737



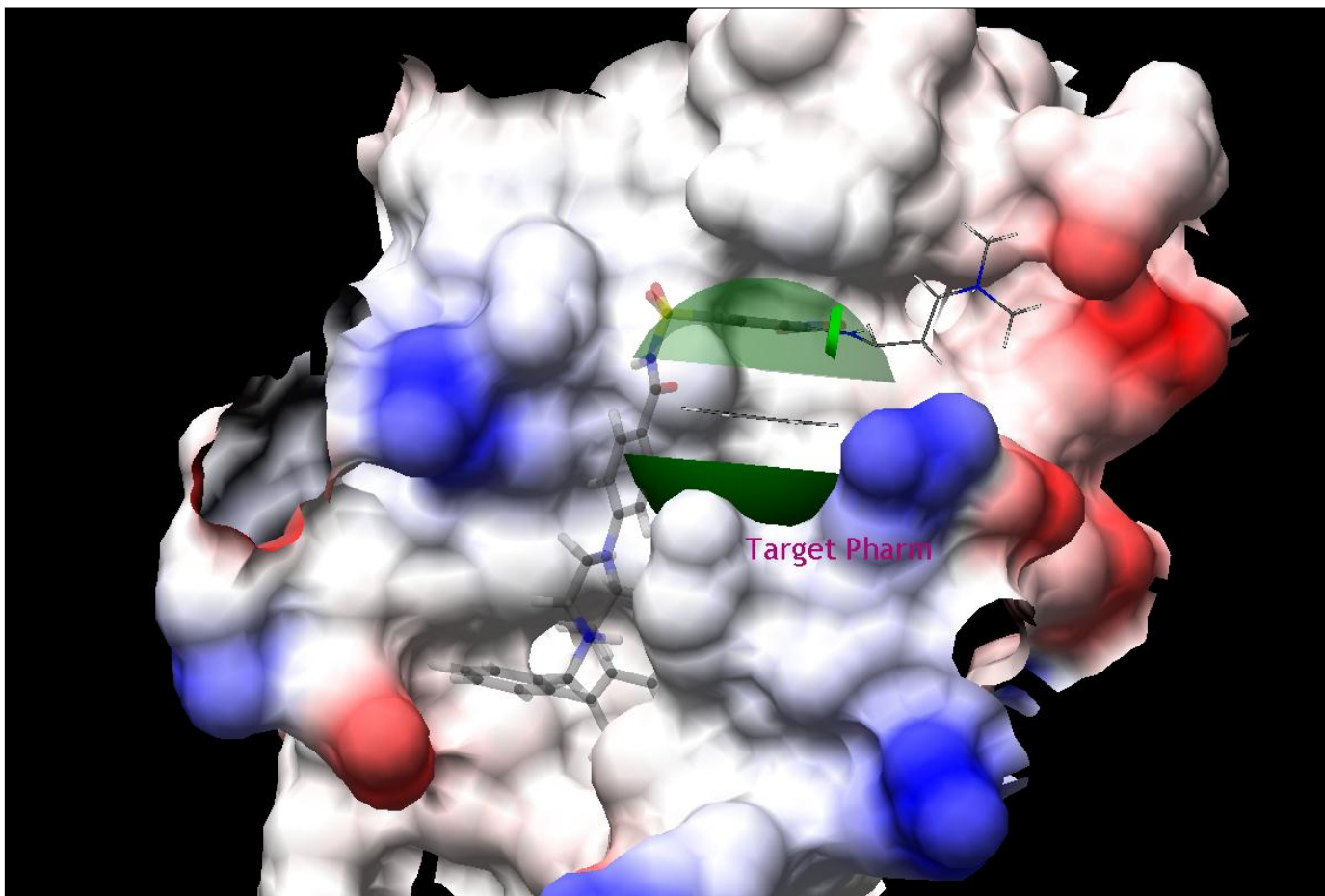
2 vectors are needed for the Query:

- Exit Vector
- π -interaction 'Pharm. Feature'



Growing into a π - π Interaction Pattern

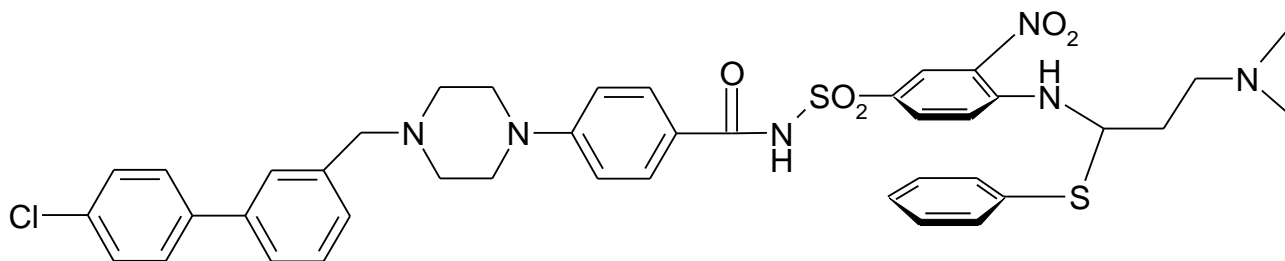
Here it is in 3D:



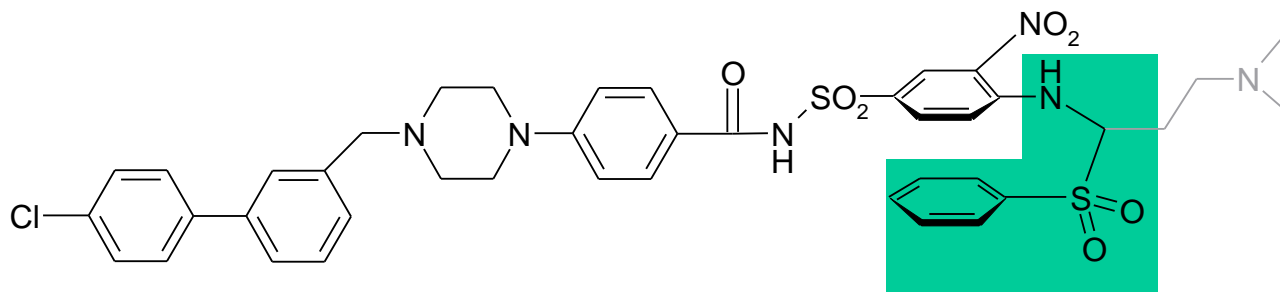
Growing into a $\pi-\pi$ Interaction Pattern

The Result in 2D:

ABT-737

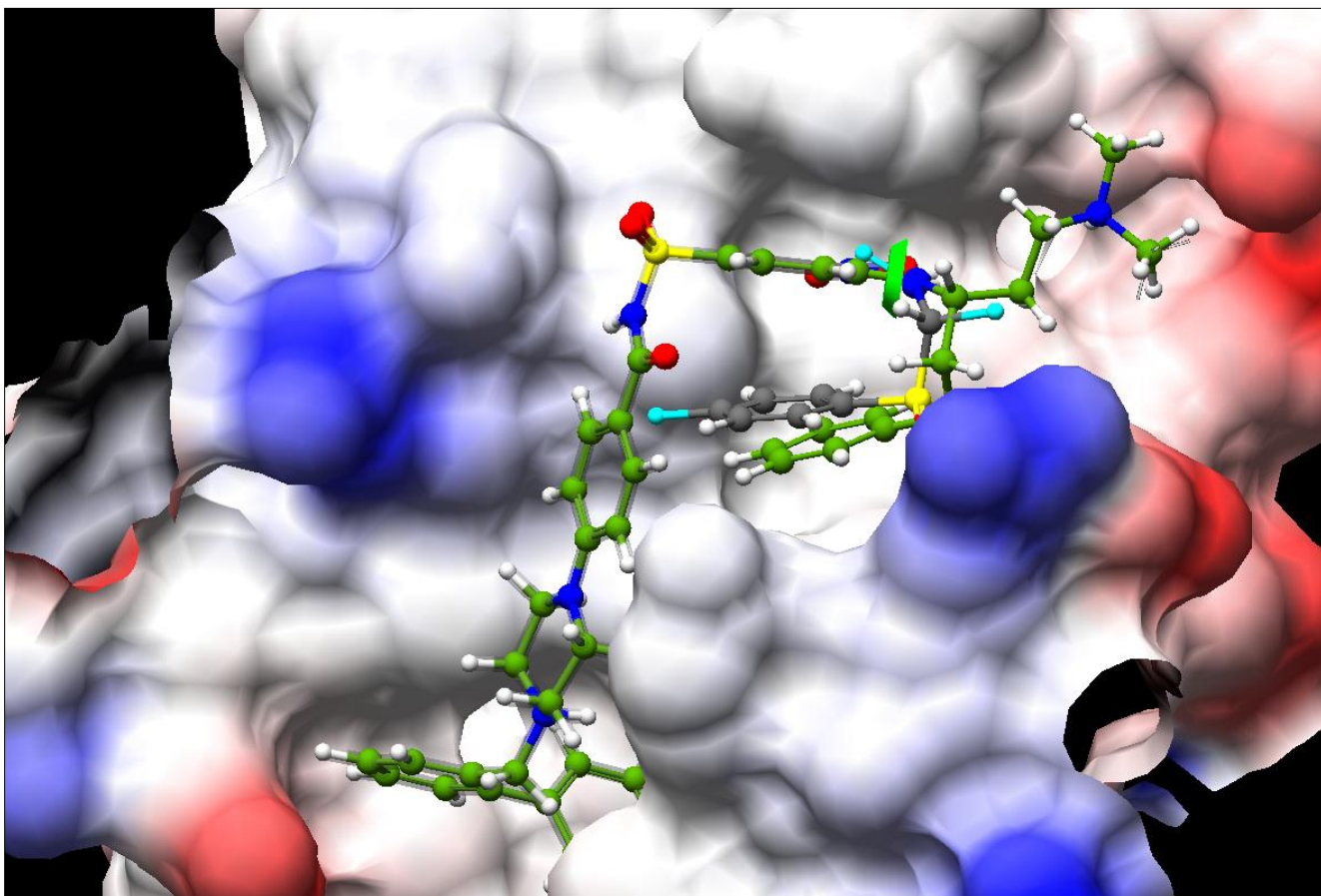


ReCore Solution No.11:



Growing into a π - π Interaction Pattern

Solution No. 11 in comparison to ABT-737 (green):
Almost identical positions obtained!

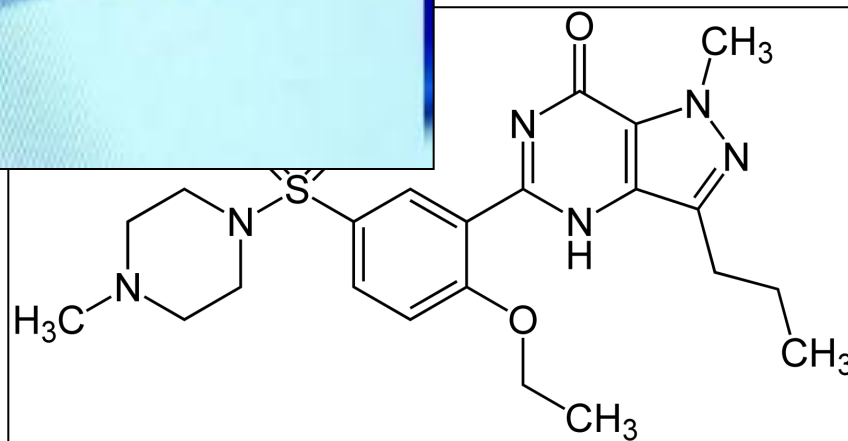


Software for Medicinal Chemists



Target Pharm

Match	Lipo	Ambig	Clash	Rot	RMSD	Siml	AMatch
-31.8024	-9.8689	+6.8415	1.3123	7.0000	0.8880	0.8727	8
-33.8918	-8.2690	+6.7122	1.8764	7.0000	0.4294	0.4294	8



1

Handle Chemistry

2

Grow With Requirements

3

Make MedChem happy!

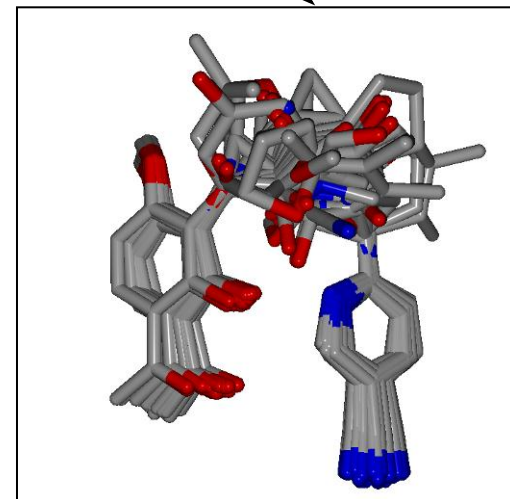
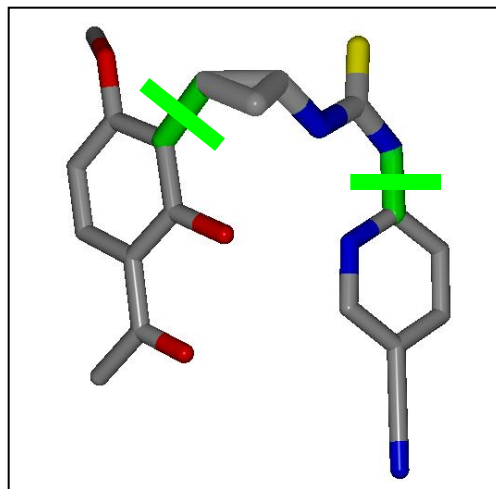
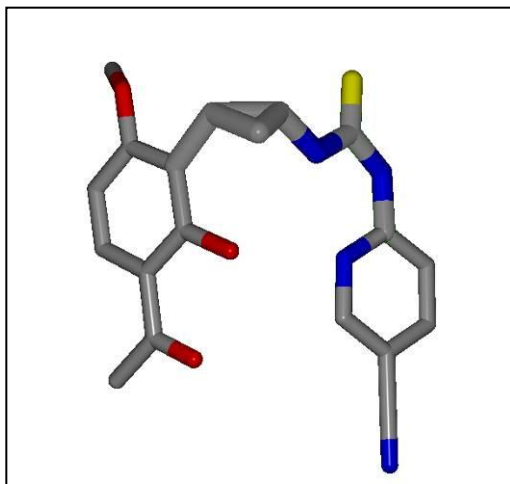
Roche 2007: Scaffold Hopping Using Vectors



define "Exit Vectors"



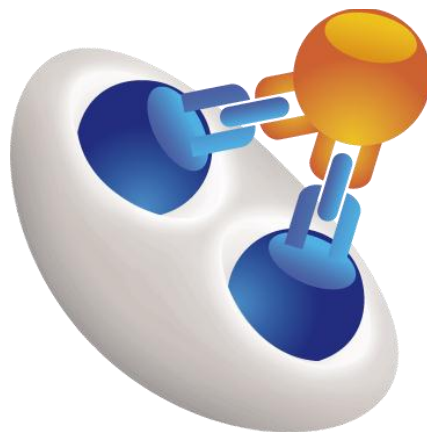
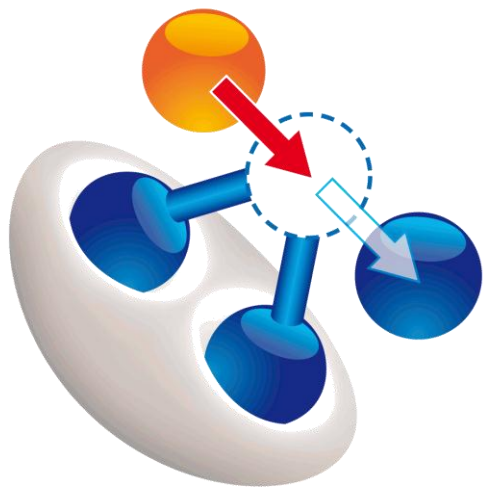
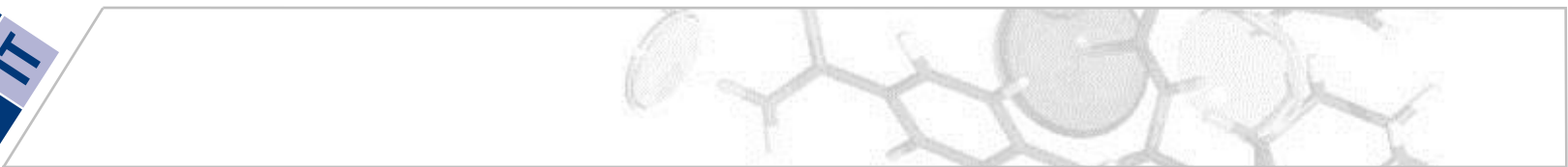
search 3D fragment library



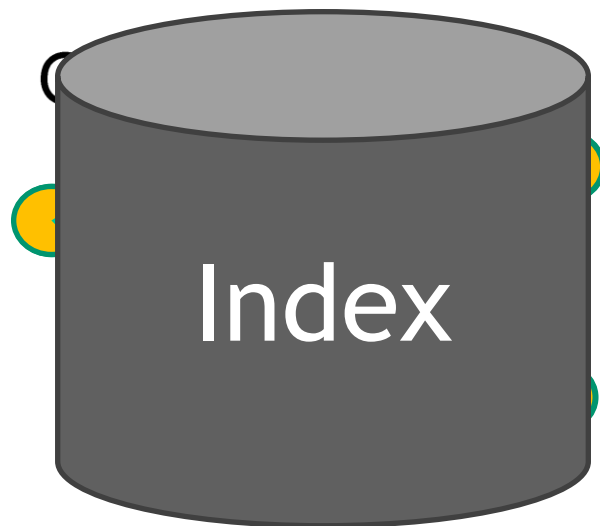
=> **ReCore**. Software development by Maass, Rarey (ZBH, Hamburg) and Roche

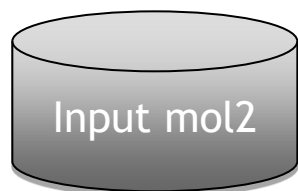


Maaß, Schulz-Gasch, Stahl Rarey, *J. Chem. Inf. Mod.*, **47**, 390-399 (2007)

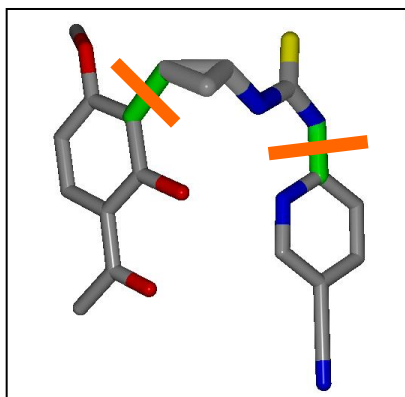
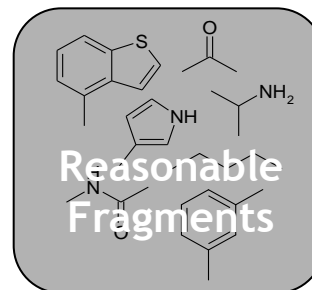
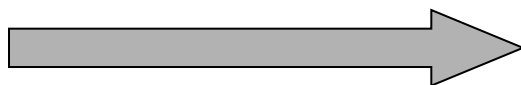


Index Generation

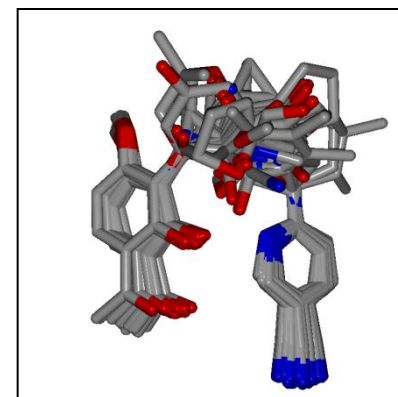
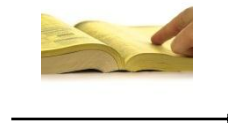
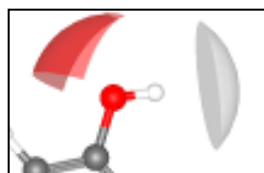


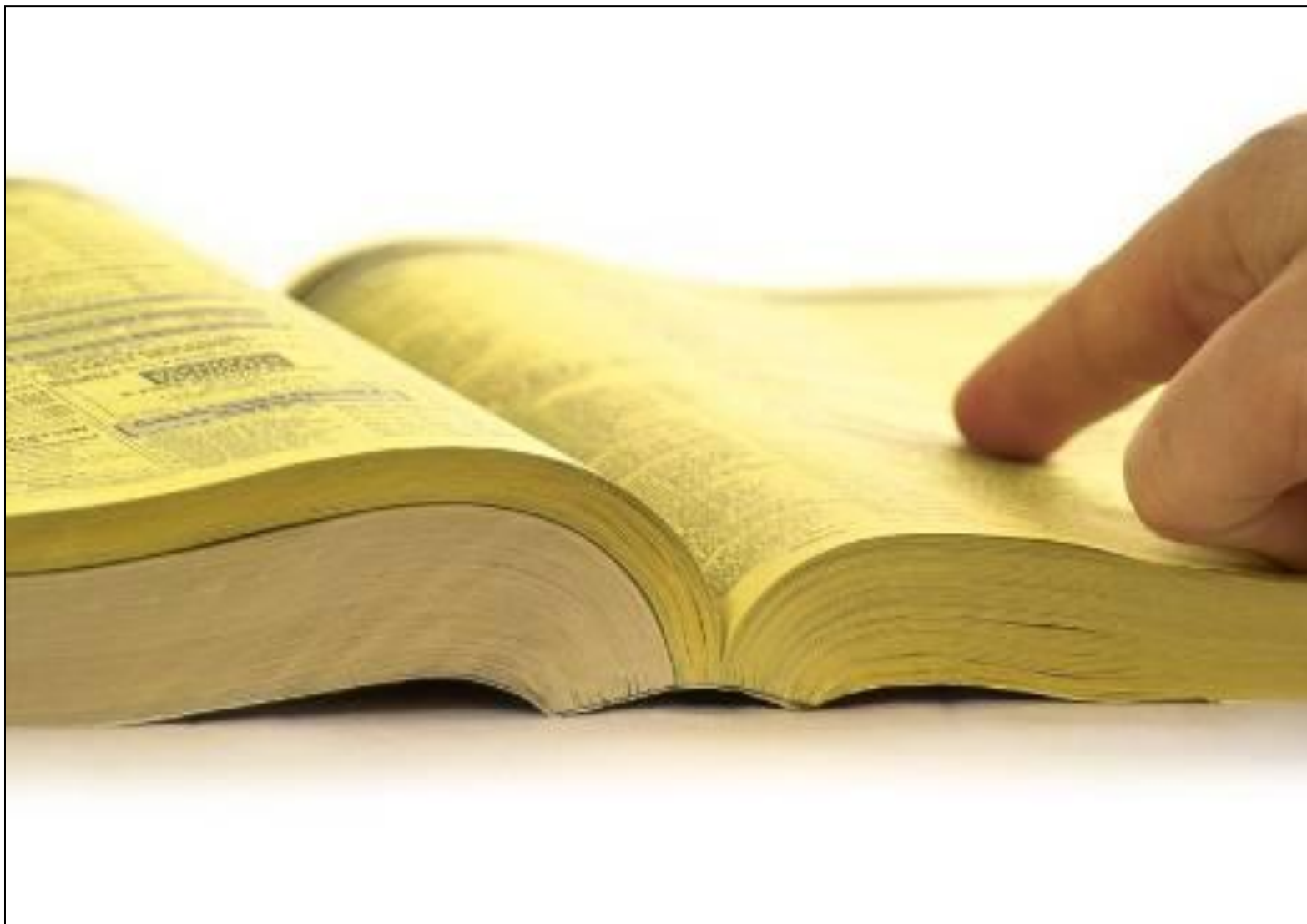


Rules



+





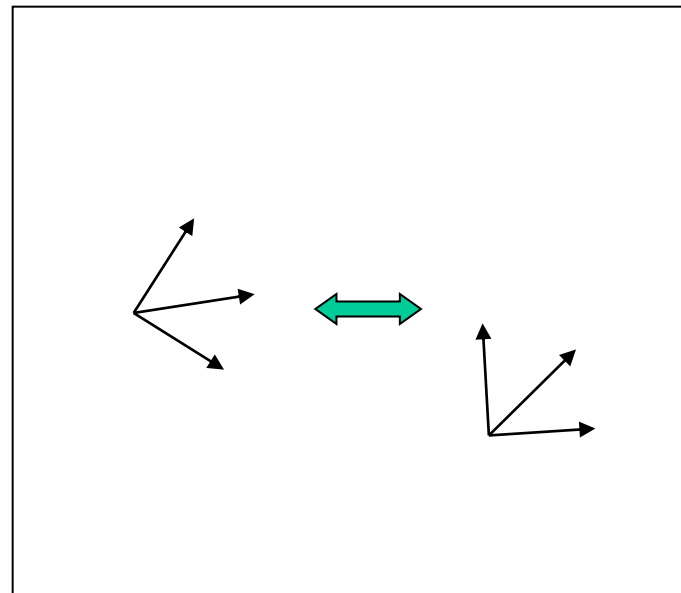
ReCore: Indexed Searching

The Index needs a pre-generated “descriptor”:

Telephone book: alphabet



ReCore: Vector relationships



Google-like Searching



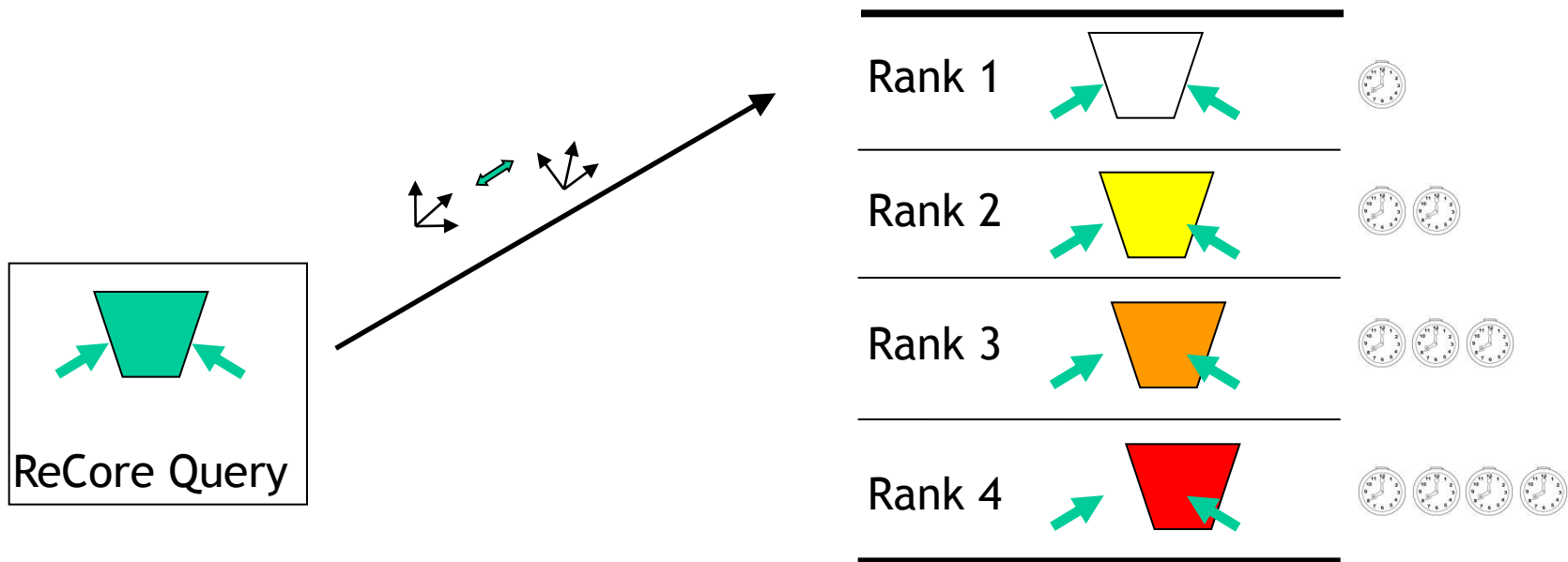
I feel lucky

LeeeeeeeaaaaaaadIT

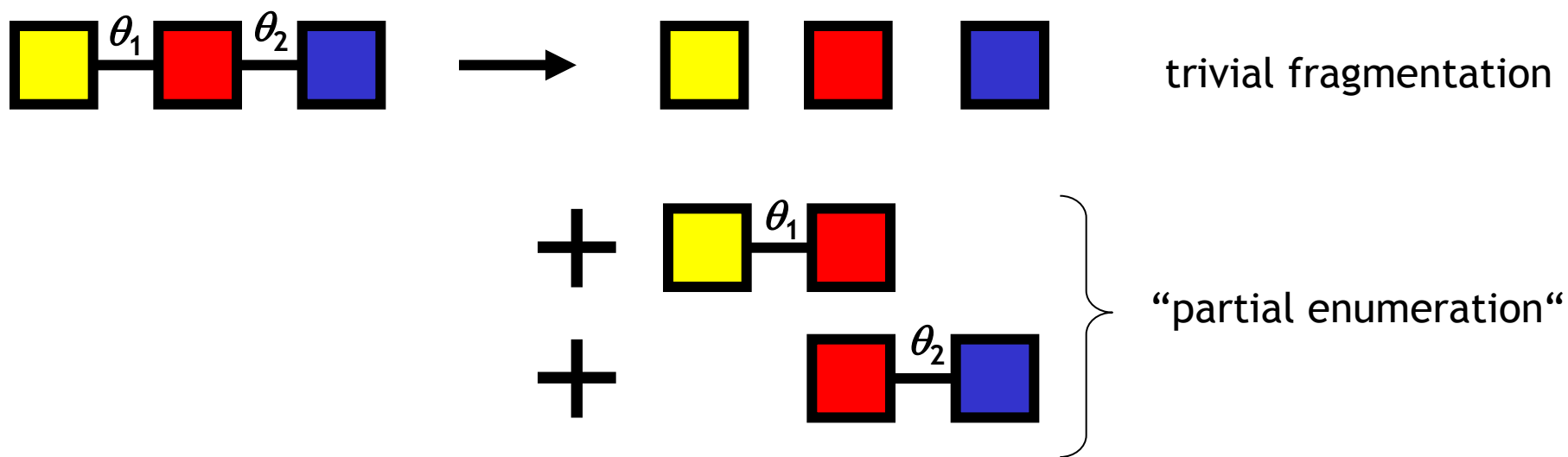
The better the geometric fit, the better the rank

ReCore: Results Delivery

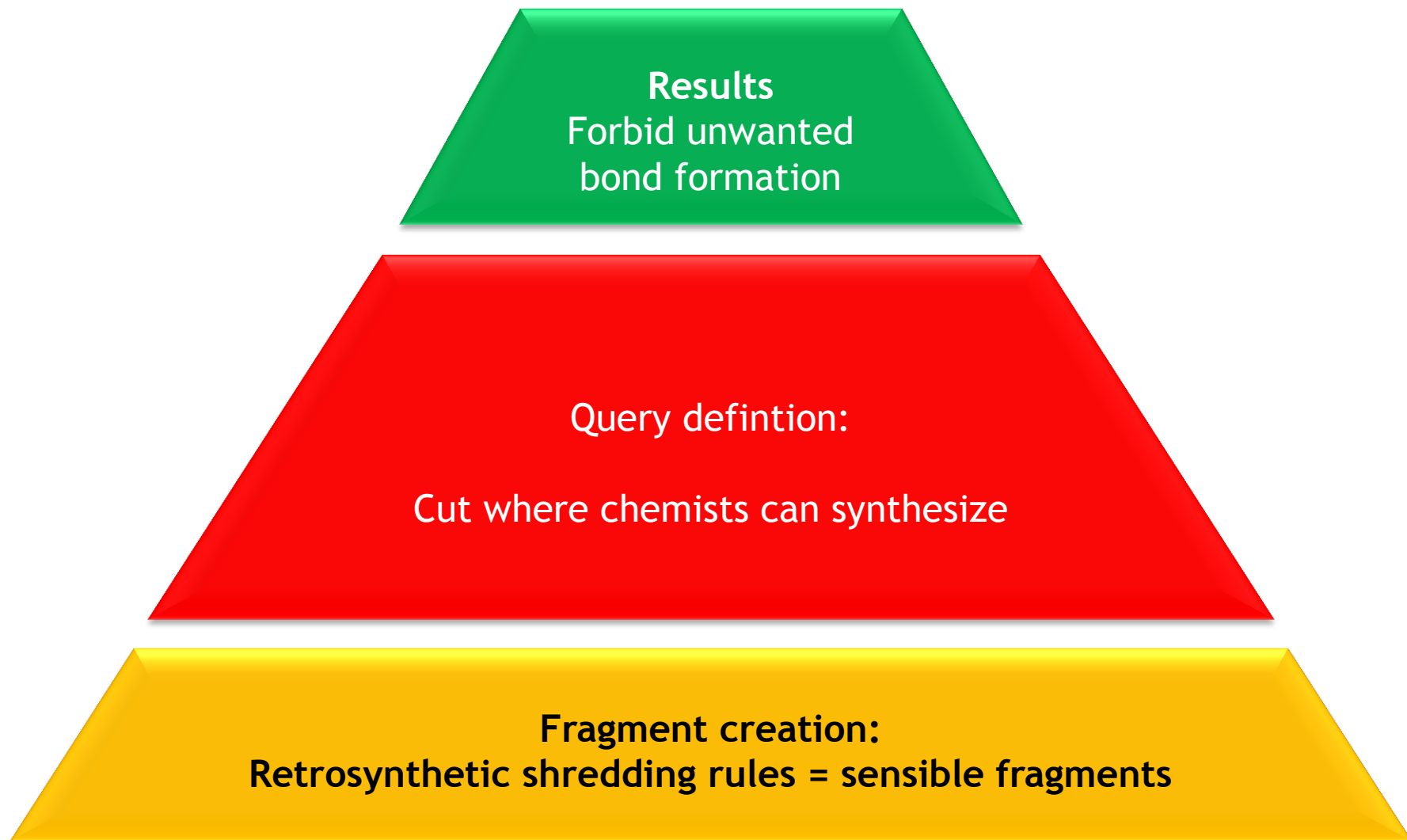
- By design the best fitting replacements are found first
- The ranking is according to deviation from perfect vector overlap



A ReCore Specialty: “3D Shredding”

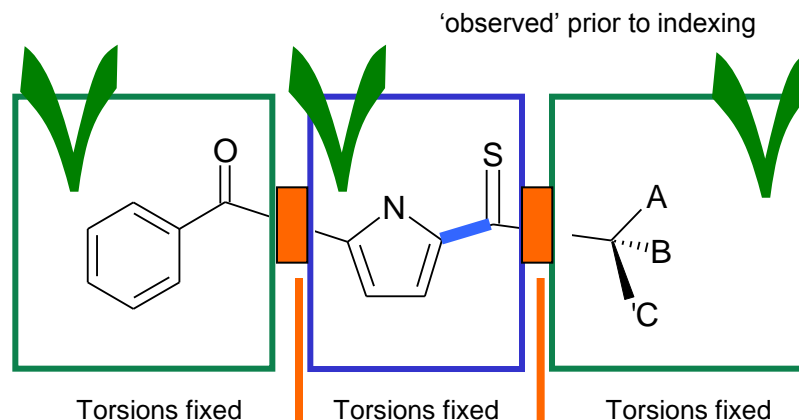


Bring in chemists in every step

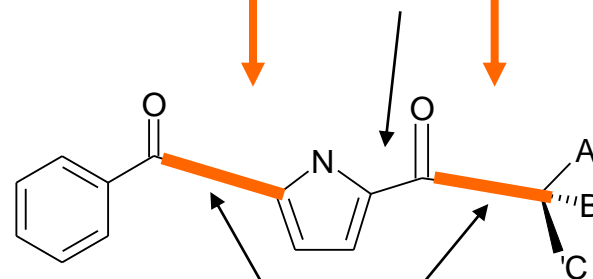


Bring in low energy conformations

1. Torsions within the fragment (typically from experiment)



2. Torsions upon new single bonds formation: Link Constraints



torsions controllable by user,
connections can even be forbidden

Growling_Example* - LeadIT 1.2.0 (02.07.10)

LeadIT Receptor Docking ReCore Display Window Help

ReCore

Query Definition

Handle Molecules

#	Name
1	BTN-300_

Add...

Choose Mode and Select Bonds

Select in 3D View one bond and one Pharm Feature from one or more molecules

Show Pharm Feature in 3D View: h_don

Mol. No.	Infile #	Interaction	Atom	Surface
	Rec	h_don	_N	

Advanced Options

Currently selected index: [DUD_MurckoUnique](#)

New Query ReCore!

Project Tree ReCore

FlexX Solutions (324)

Show 2D Show displaced water

# /	Ligand	Structure	Rank	Score	Match	Lipo	Ambig	Clash	Rot	RMSD	Simil	#Match
1	(1) 1stp_min		1	-34.5204	-31.8024	-9.8689	-6.5615	1.3123	7.0000	0.5830	0.5727	8
2	(1) 1stp_min		2	-33.5856	-33.8918	-8.2580	-5.7122	1.8764	7.0000	0.6294	0.6294	8

Project Notes Information Stream FlexX Solutions (324)

- Technology
- Key applications
 - Core replacement
 - Fragment linking & merging
 - Fragment growing
 - Docking (pose checking)
 - Binding affinity assessment
- Key advantages
 - 1 ■ Low energy conformations (-> bioactivity)
 - 2 ■ Pharmacophores (-> target specificity)
 - 3 ■ Grows with requirements (-> IP)
 - Interactive search (-> TEAM building)
 - Use fragments (-> chemical universe)
 - Index created by user



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contact@biosolveit.de

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