

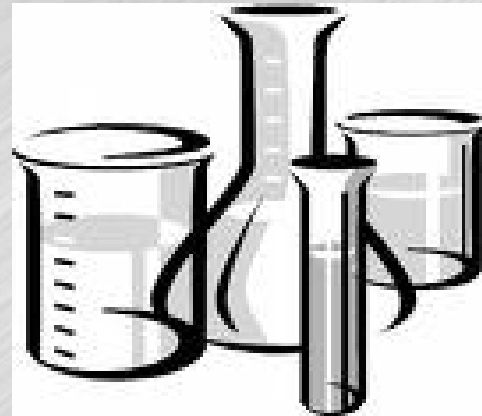
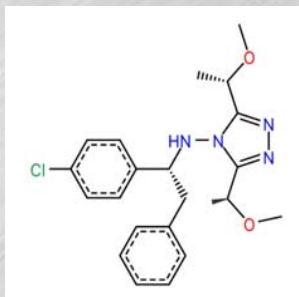
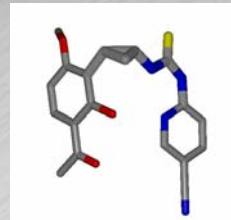
Teaming up Med and Comp Chemists:

Interactive Fragment Growing, Merging, and Linking

Peter Oledzki

The usual way of working together is sequential
... and not interactive

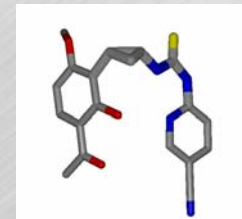
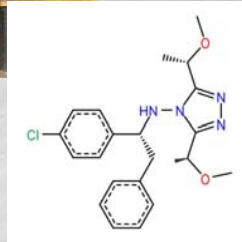
currently what people do



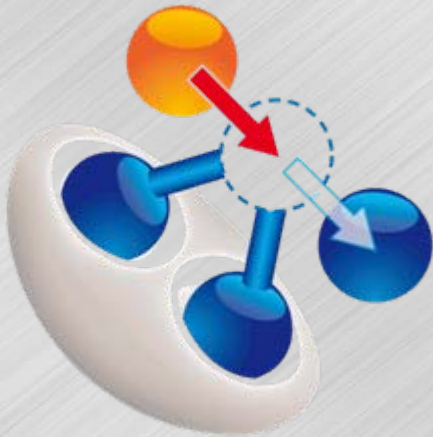
in an ideal world



how can We do it !



2007:



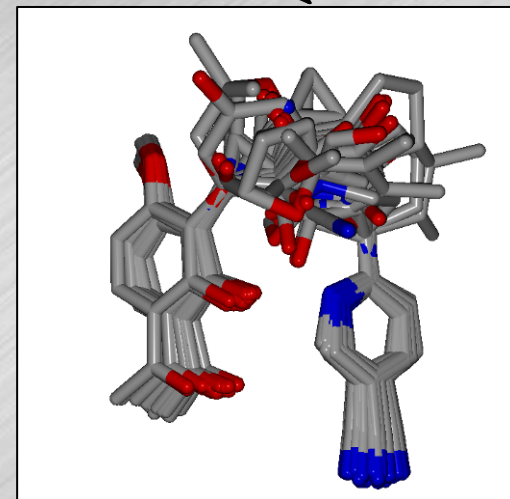
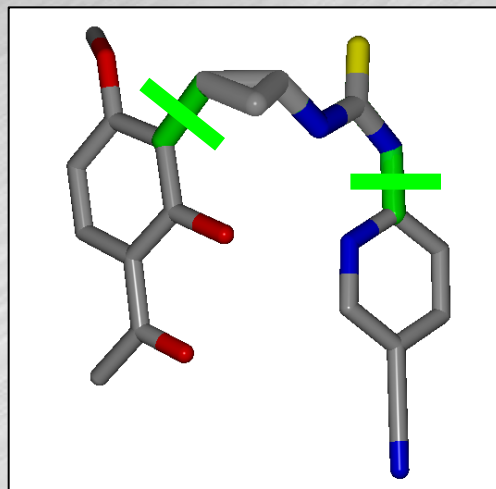
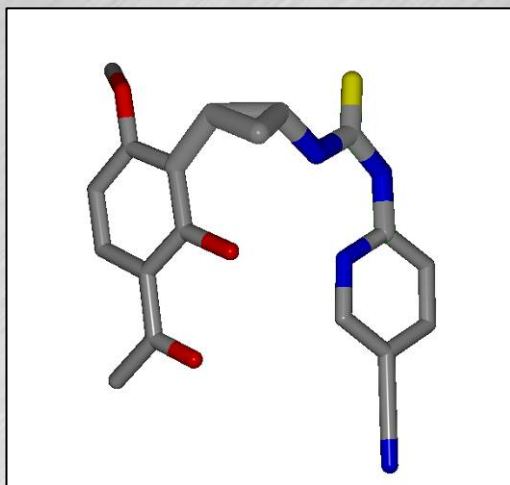
Roche 2007: Re-Scaffolding Using Vectors



define "Exit Vectors"



search 3D fragment library

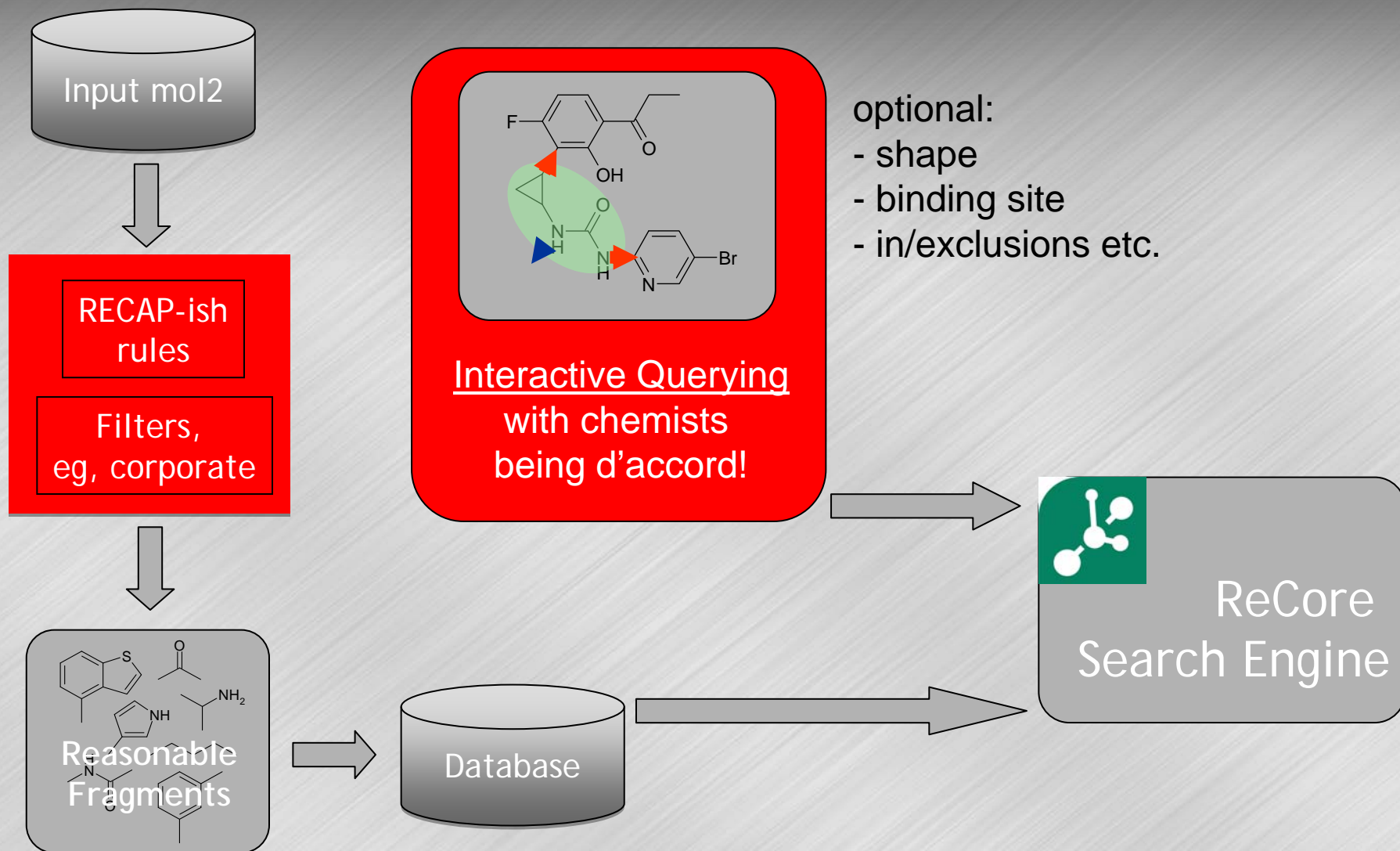


=> **ReCore**. Software development by Maass, Rarey (ZBH, Hamburg) and Roche



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

Synthetic Access Checks & User Chemistry



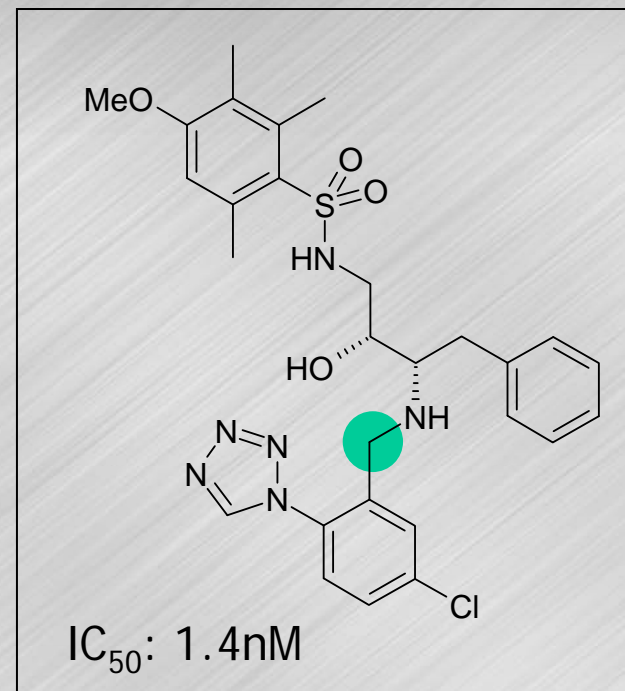
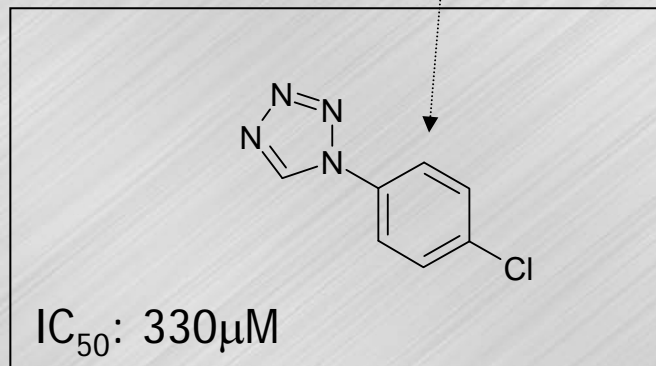
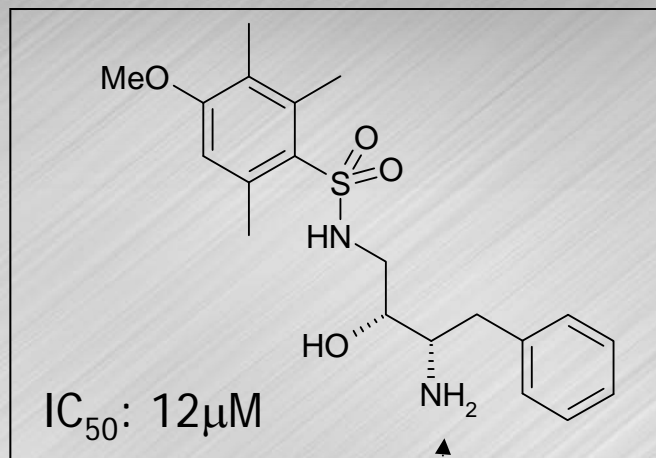
Link, Merge, Grow Fragments

ReCore



Fragment Linking - A First, Simple Example

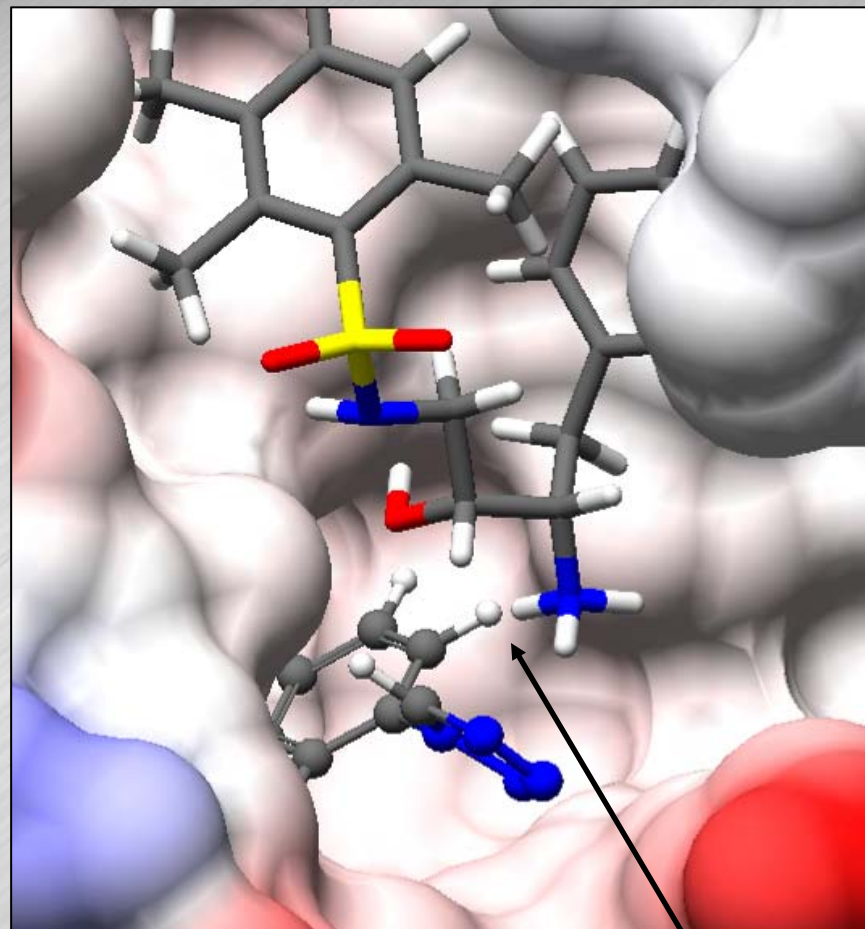
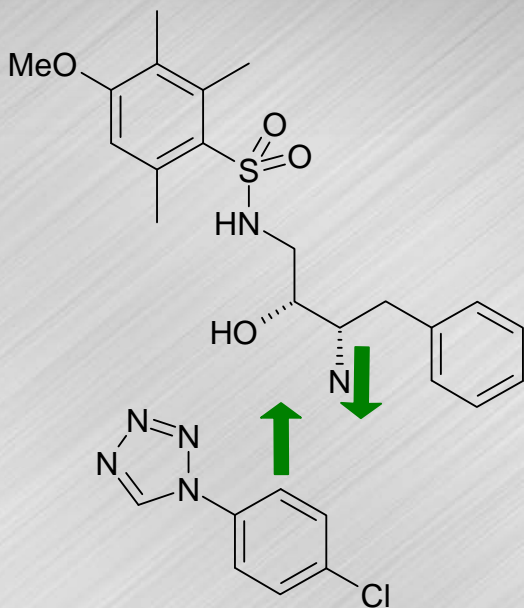
How close do we get to Howard et al.'s JMC success with Thrombin?



Howard et al., JMC 49 1346 (2006)

Fragment Linking - A First, Simple Example

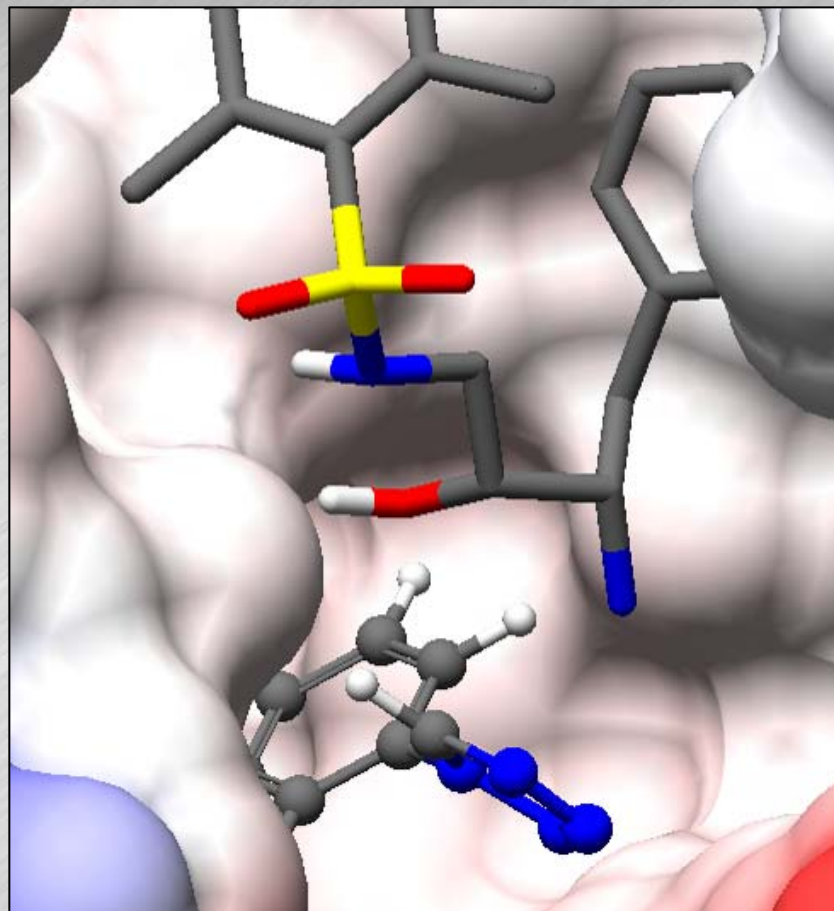
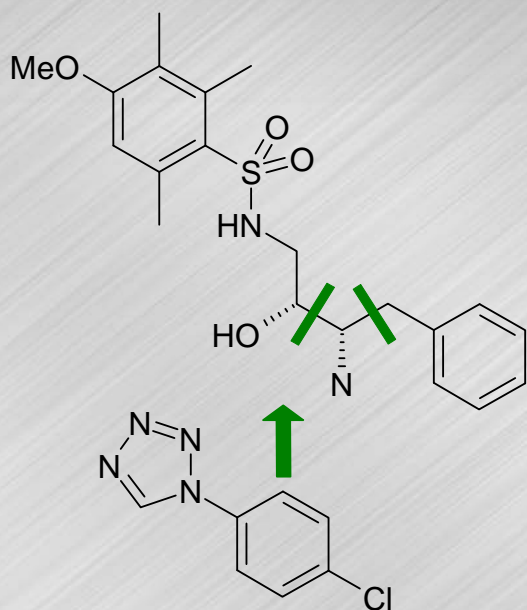
ReCore Queries with alignment of ligand PDBs 2c93 and 2c90:



This is too easy! Roche do not have simple $-C_mH_n-$ as linkers, so we don't either...

Fragment Linking - A First, Simple Example

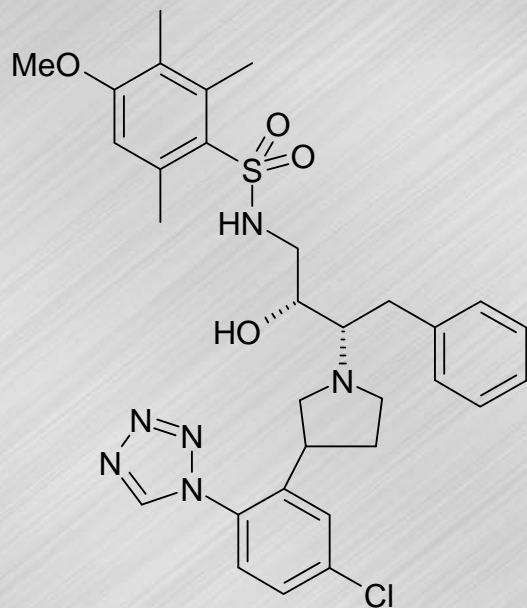
Can we 'carve out' the amine? And still link to the chlorophenyl?



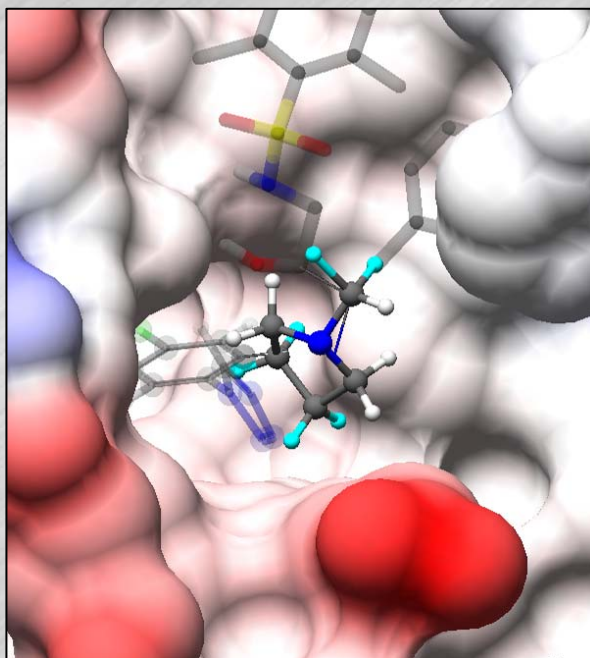
Fragment Linking - A First, Simple Example

Yes, that's possible:

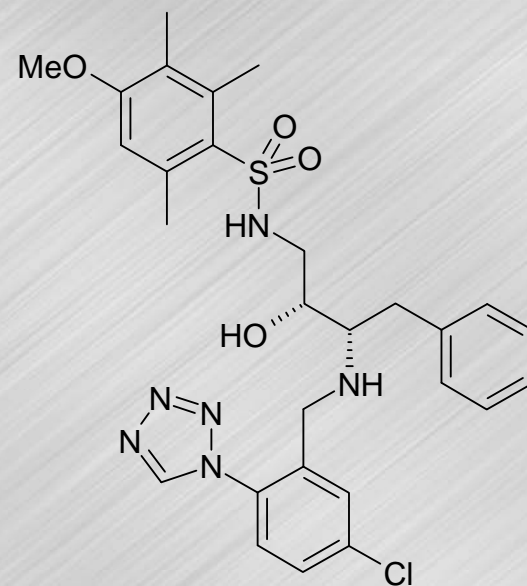
Found first (= Rank 1):



IC₅₀: ??



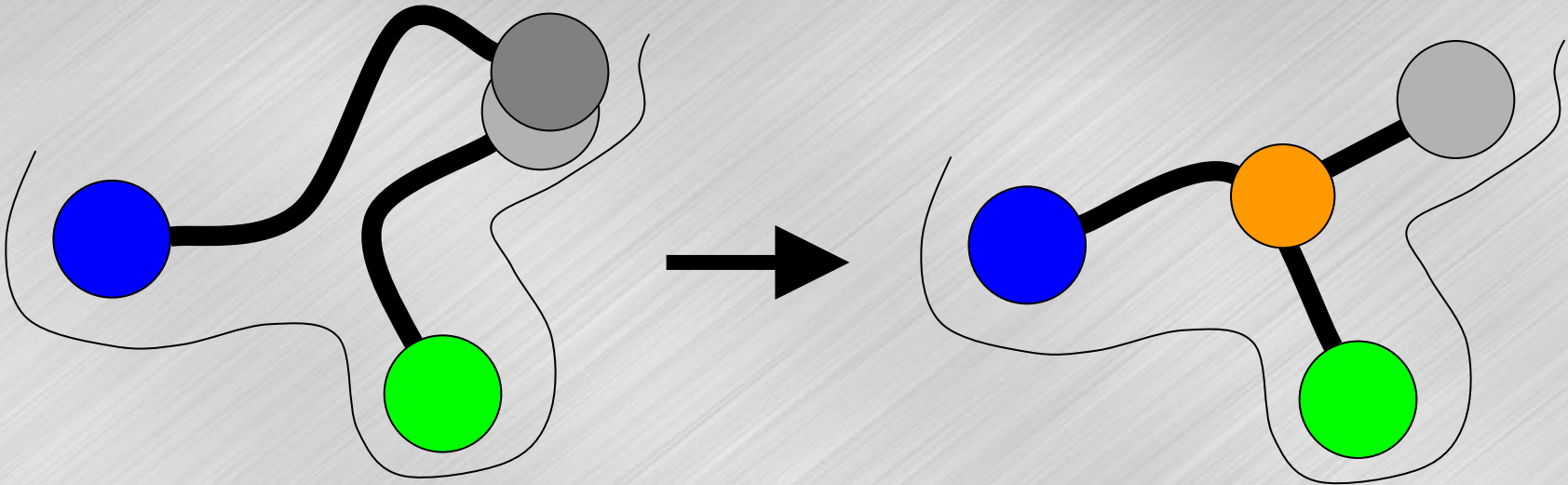
published structure:



IC₅₀: 1.4nM

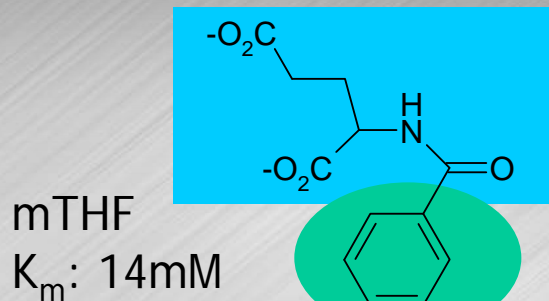
... and: Fragment Merging

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

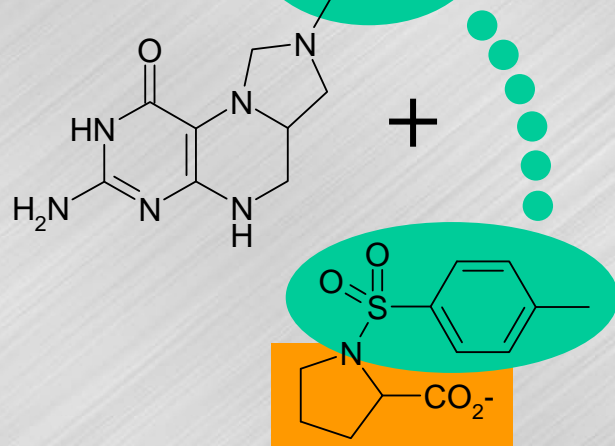


A Tough Merging Example

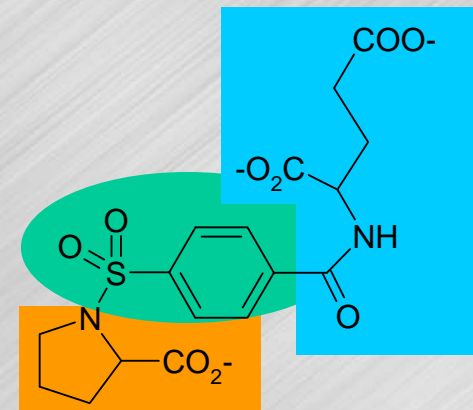
Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)



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



PDB: 1F4E
 K_i : 1.1mM

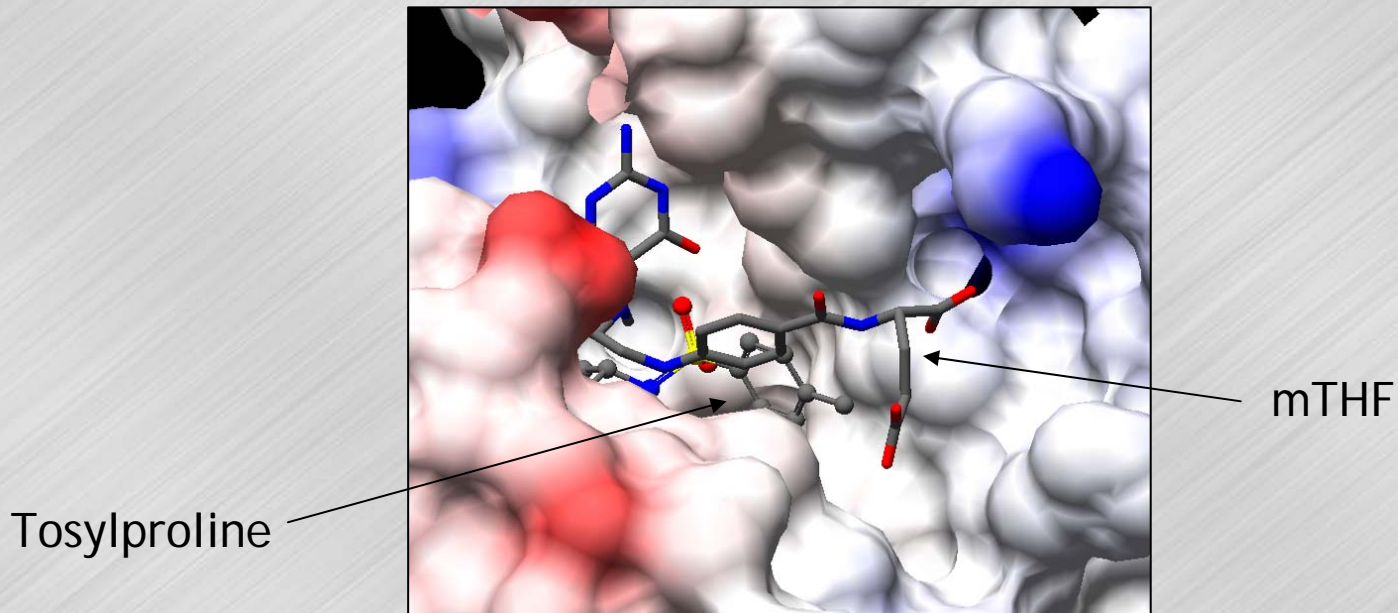


24 μ M,
 further opt'd to 330nM

A Tough Merging Example

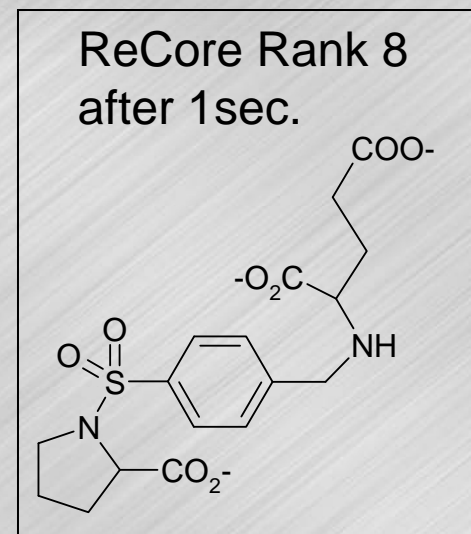
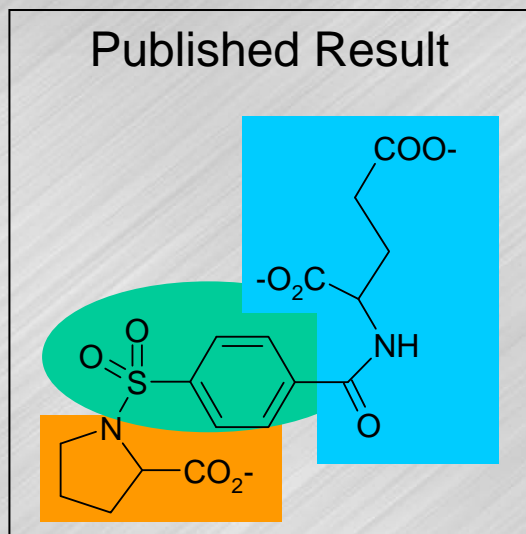
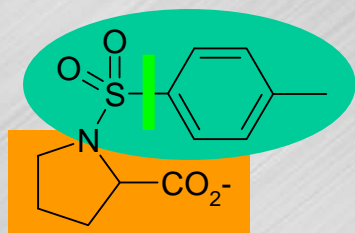
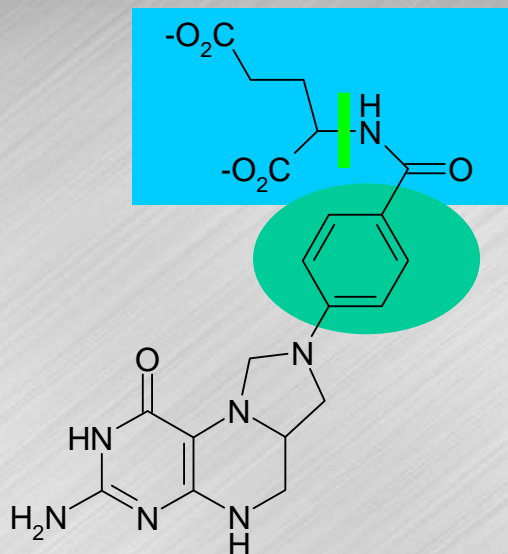
Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)

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



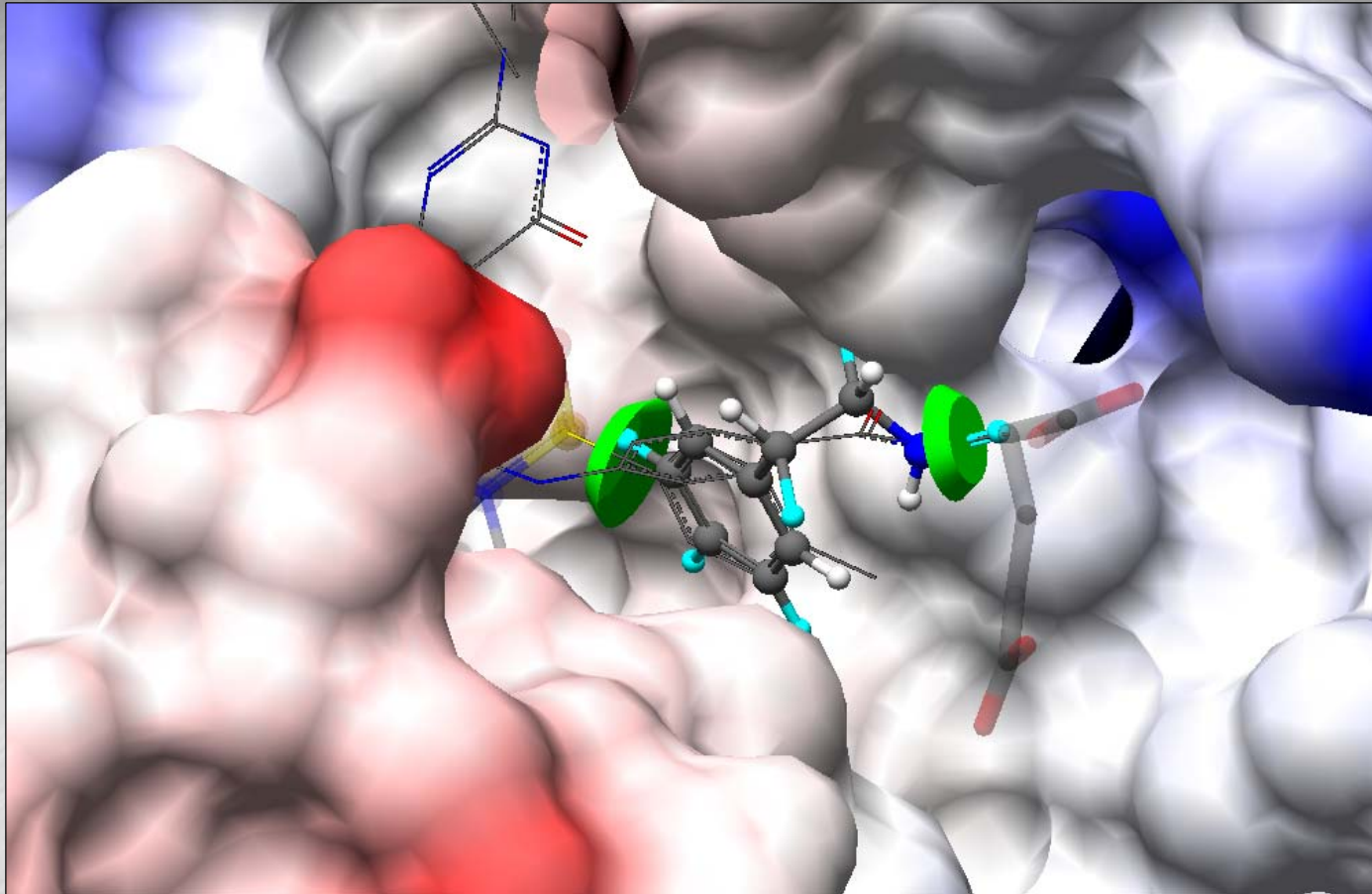
A Tough Merging Example

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 shape was used.

A Tough Merging Example



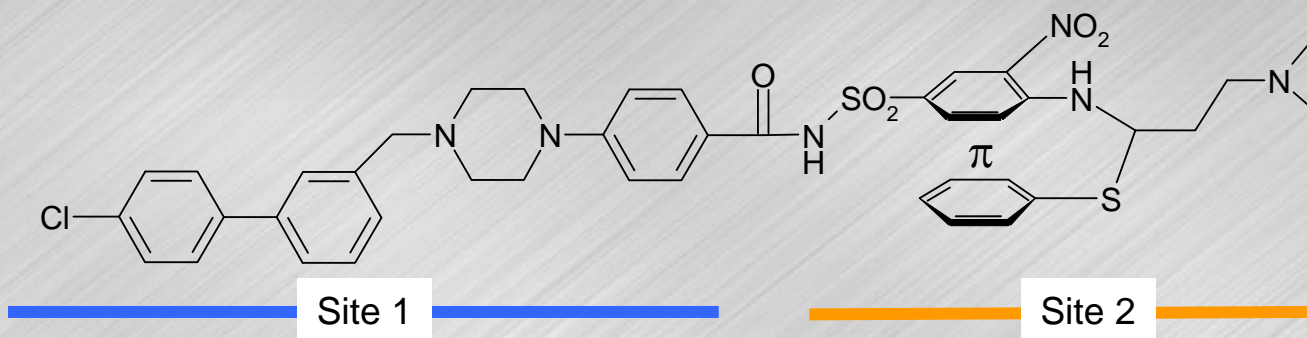
A Growing Example



Growing into a π - π Interaction Pattern

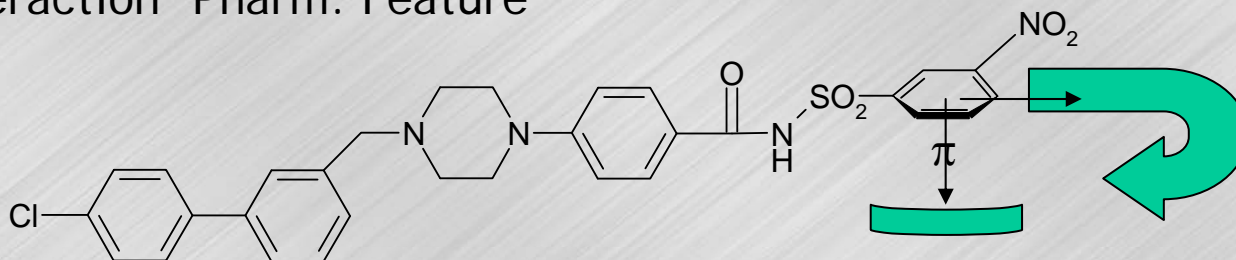
Bcl-2 protein example from Abbott (Oltersdorf et al, Nature 435 (2005) 677).

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



2 vectors are needed for the Query:

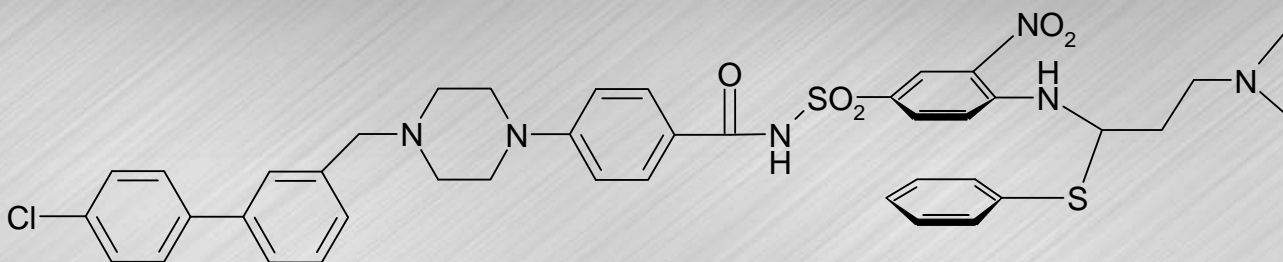
- Exit Vector
- π -interaction 'Pharm. Feature'



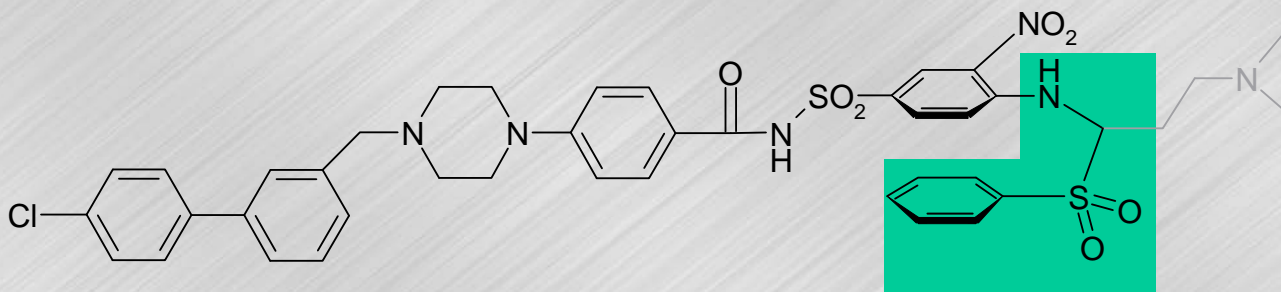
Growing into a $\pi-\pi$ Interaction Pattern

The Result in 2D:

ABT-737

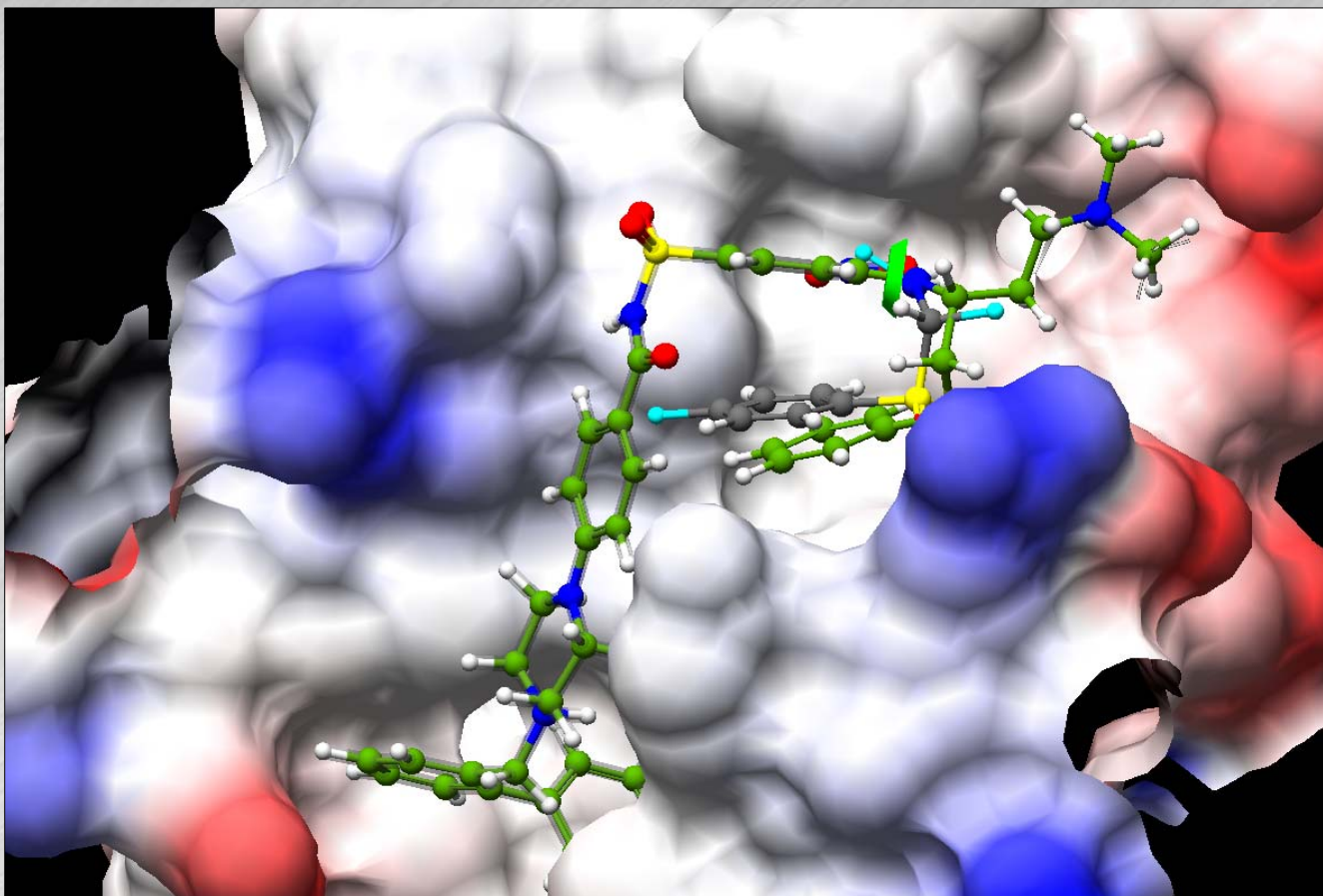


ReCore Solution No.11:



Growing into a π - π Interaction Pattern

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



A Recent JACS Review by John van Drie

restrictions on doing useful work with the demo software. Furthermore, the underlying science has all been disclosed (Maass, P. et al., 2007); this software is not a mysterious “black box”.

In my opinion, software of this sort belongs on the desk of any chemist designing bioactive molecules. It remains to be seen whether ReCore is the optimal answer to this problem, but it is definitely a step in the right direction. Anyone interested in designing bioactive molecules should consider investigating this.

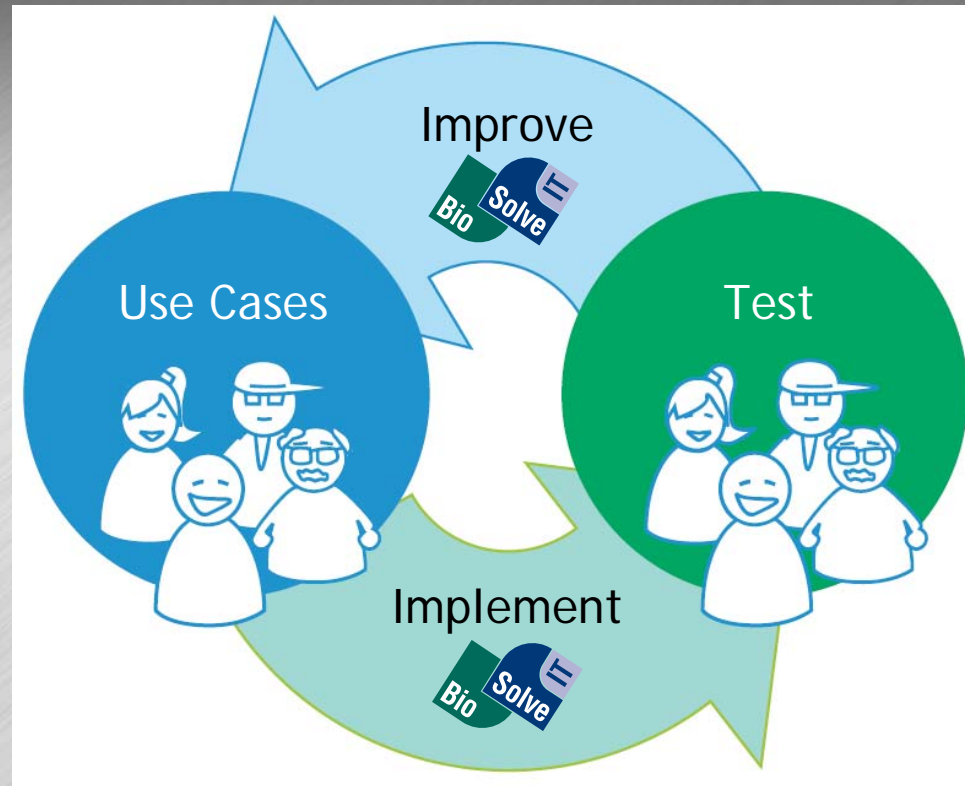
John H. VanDrie,
Van Drie Research LLC

JA900089H

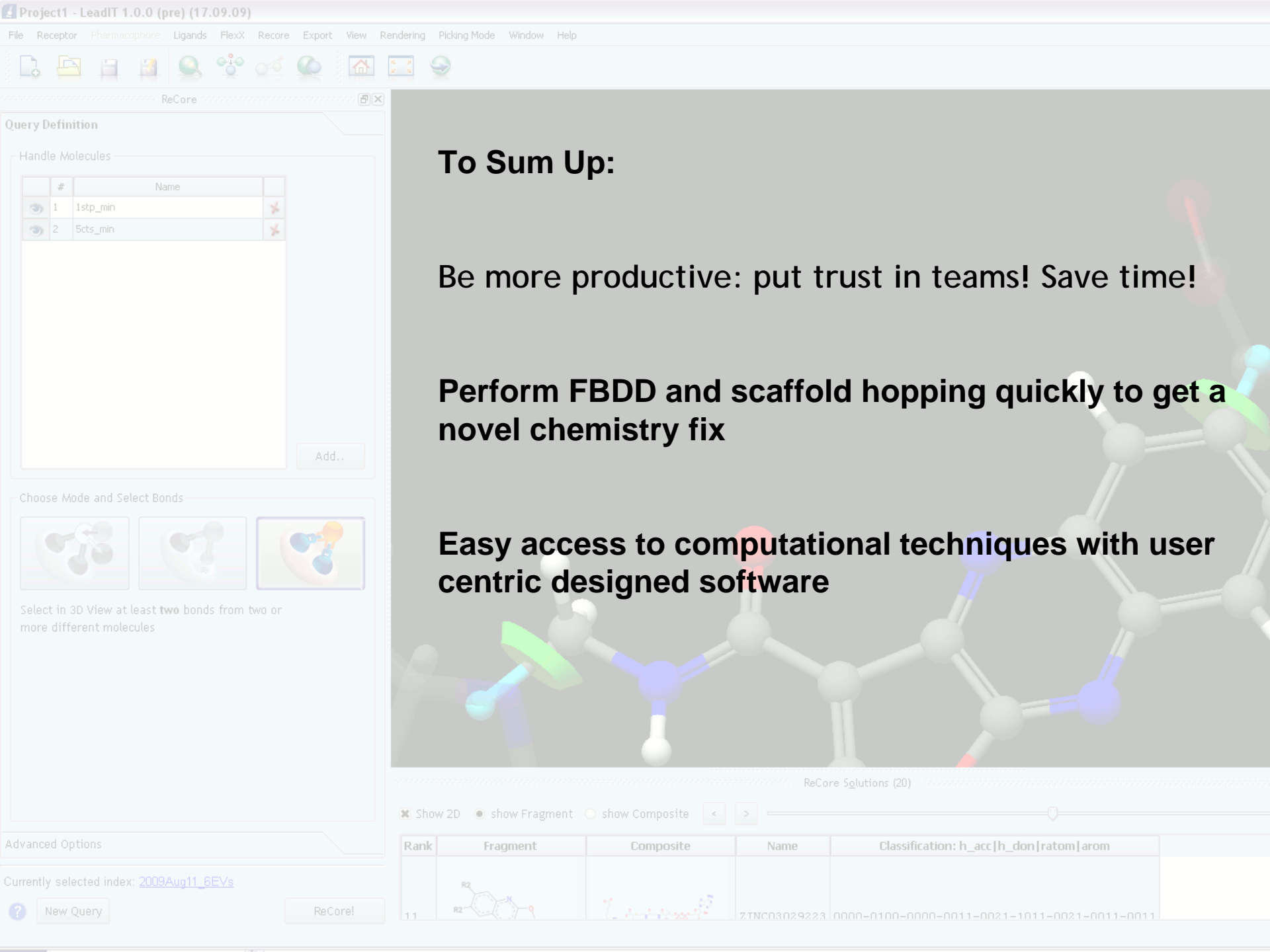
10.1021/ja900089h

J. AM. CHEM. SOC. 2009, 131, 1617 ■ 1617

User Centric GUI Development



- No learning curve -> instant productivity
- Haptics, aesthetics, simplicity -> fun to use
- By design: answers that matter to user



To Sum Up:

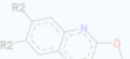

Be more productive: put trust in teams! Save time!

Perform FBDD and scaffold hopping quickly to get a novel chemistry fix

Easy access to computational techniques with user centric designed software

ReCore Solutions (20)

Show 2D show Fragment show Composite

Rank	Fragment	Composite	Name	Classification: h_acc h_don ratom arom
11			ZINC03029223	0000-0100-0000-0011-0021-1011-0021-0011-0011