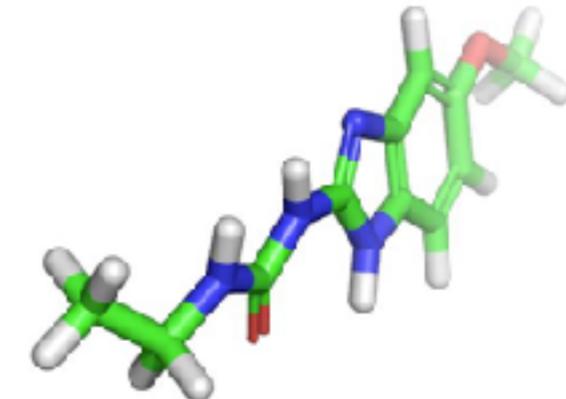
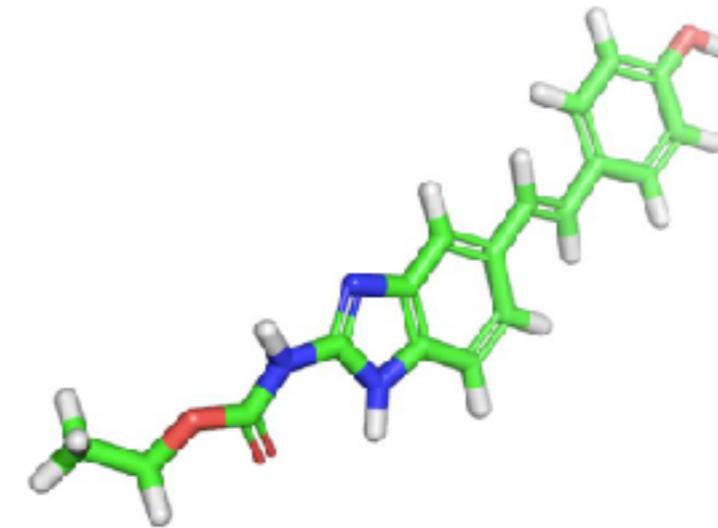
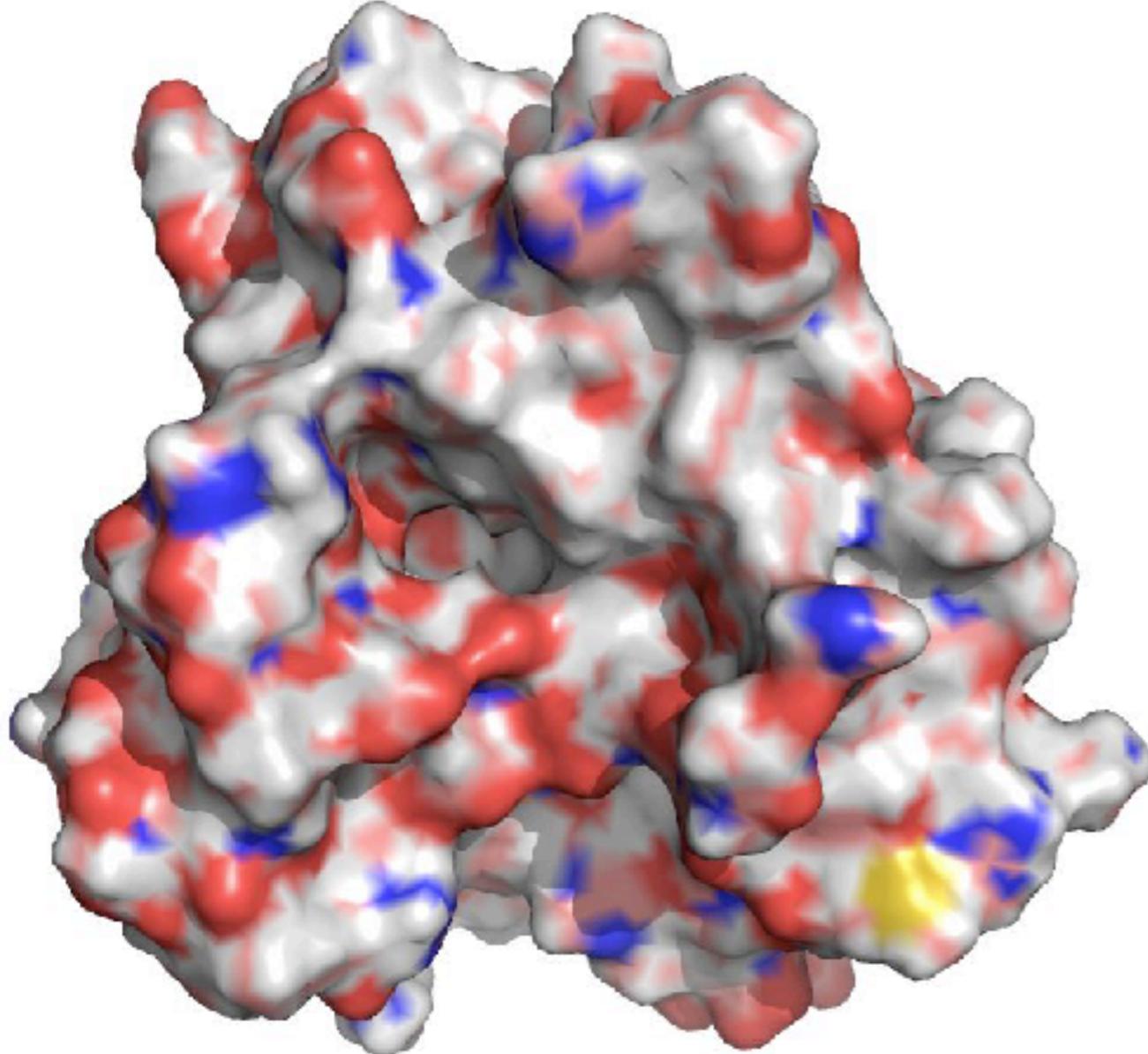
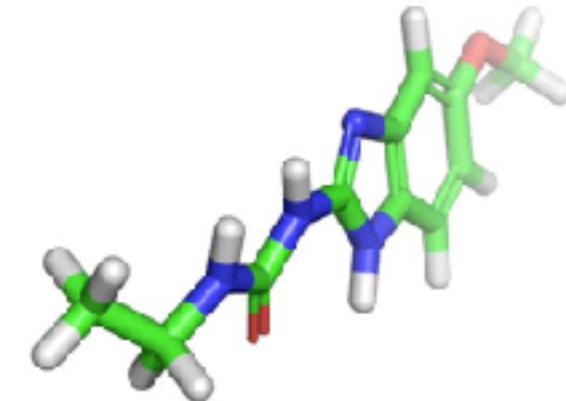
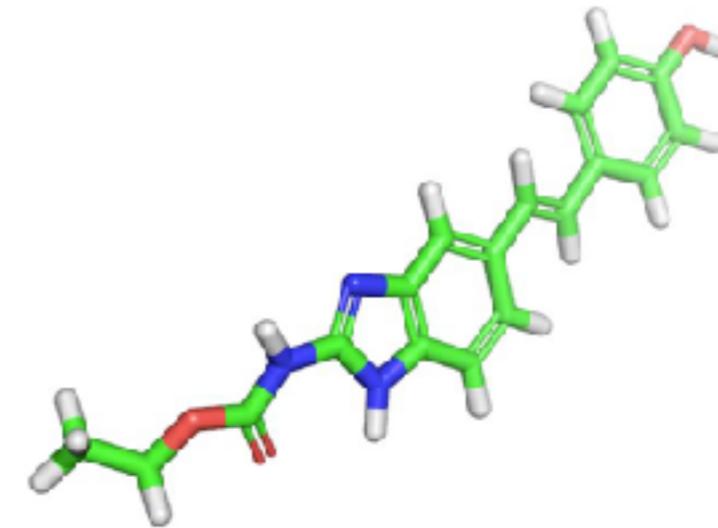
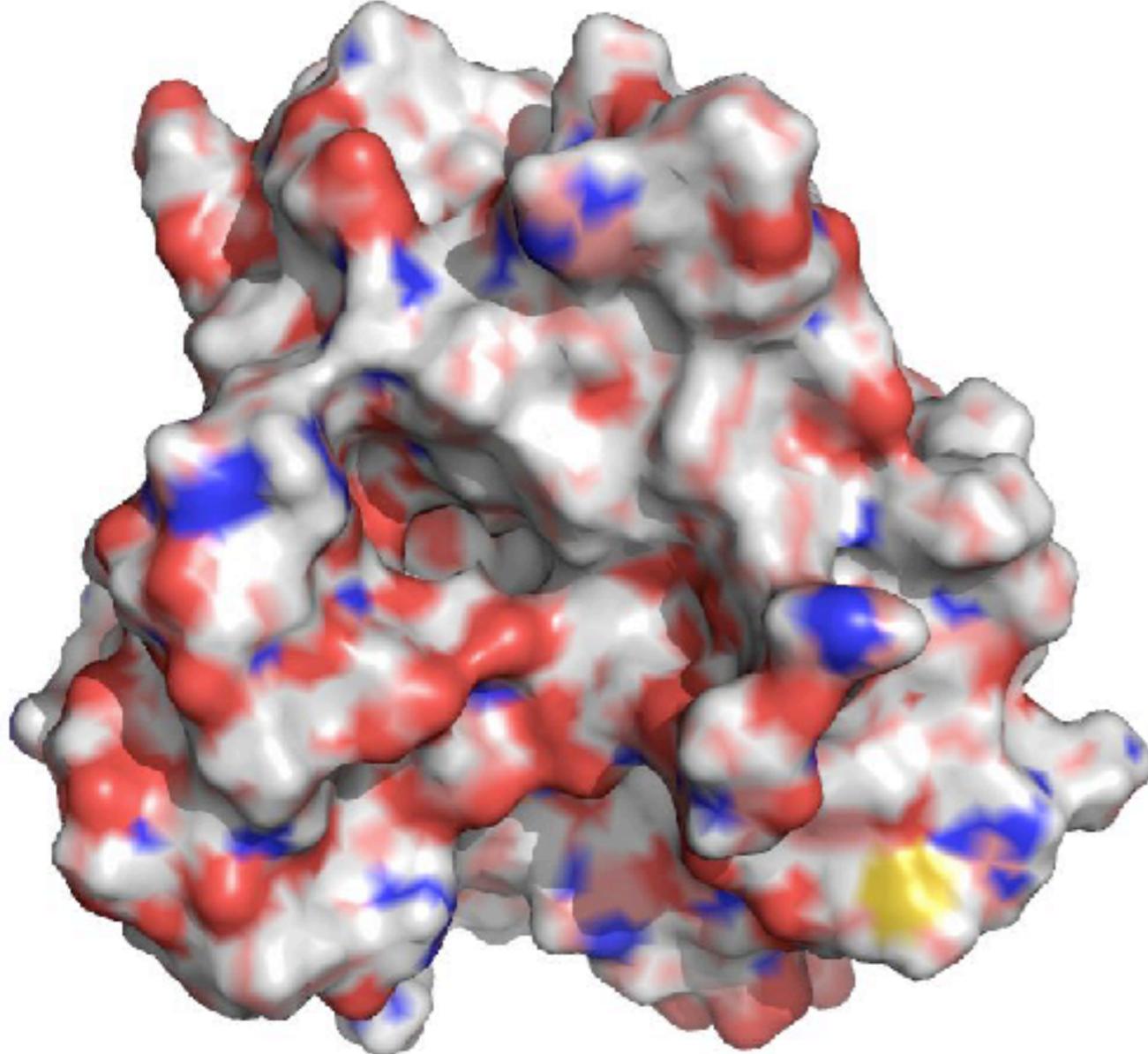


Docking and structure-based design uses structures;
ligand-based design uses ligands



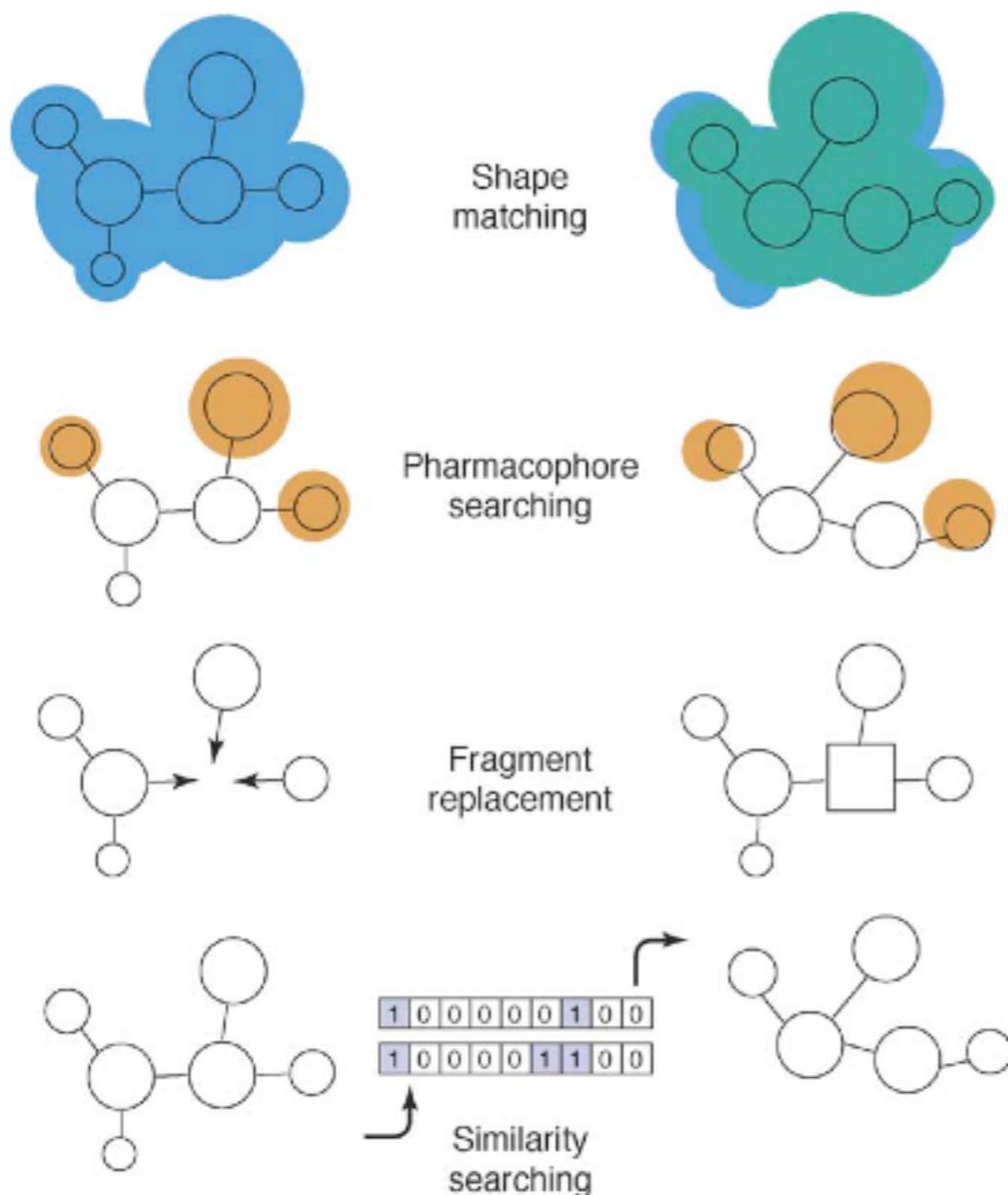
Docking and structure-based design uses structures;
ligand-based design uses ligands



Ligand-based design has several goals

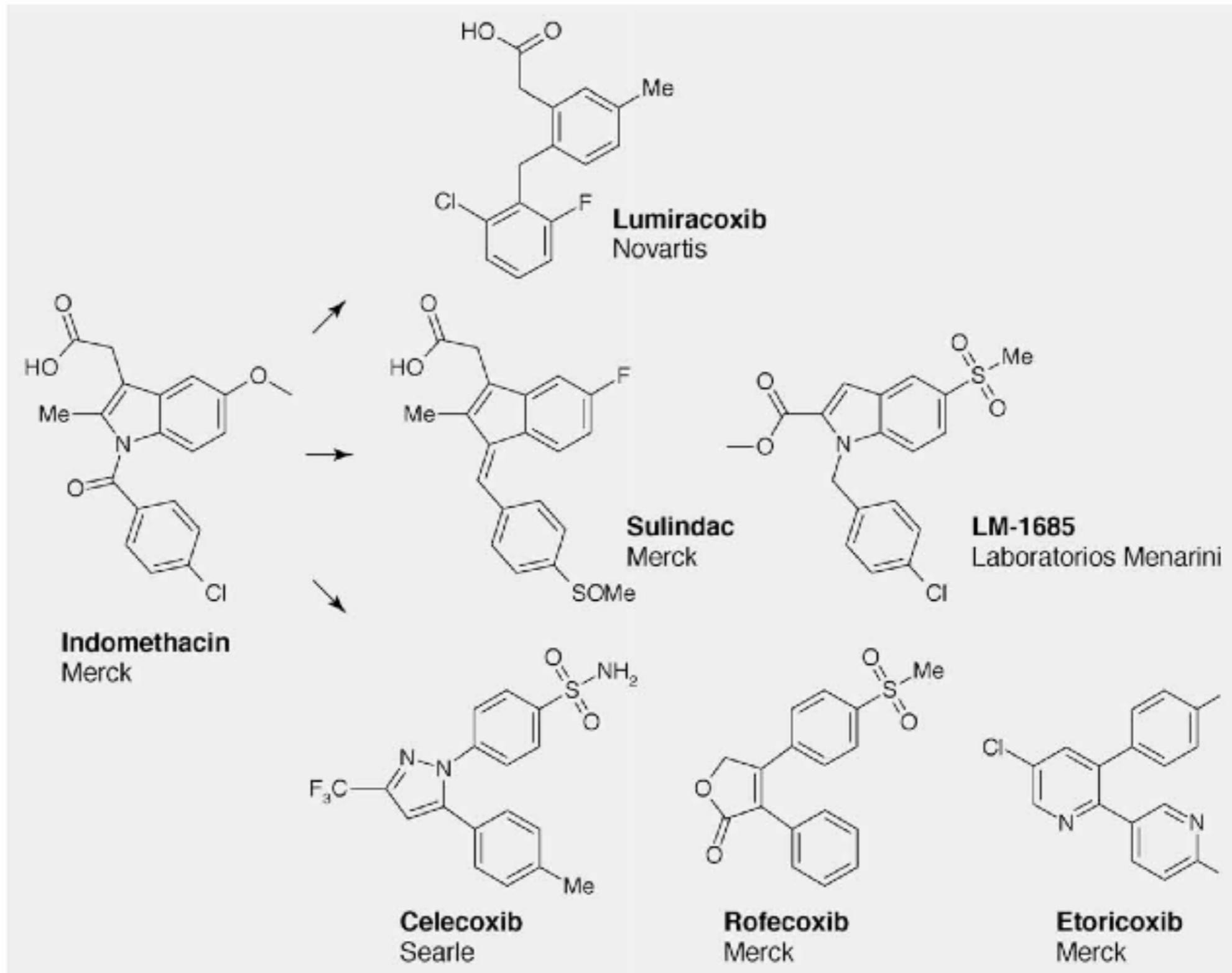
- Patent avoidance
- Scaffold-hopping
 - Patent reasons
 - Discovery reasons -- ADME, synthesis, ...
- New ligands in the absence of structure

Scaffold hopping can be approached by several different strategies



Drug Discovery Today: Technologies

There are many scaffold-hopping examples, including COX-2 inhibitors



Morphine side effects and potency reduced by scaffold-hopping to tramadol

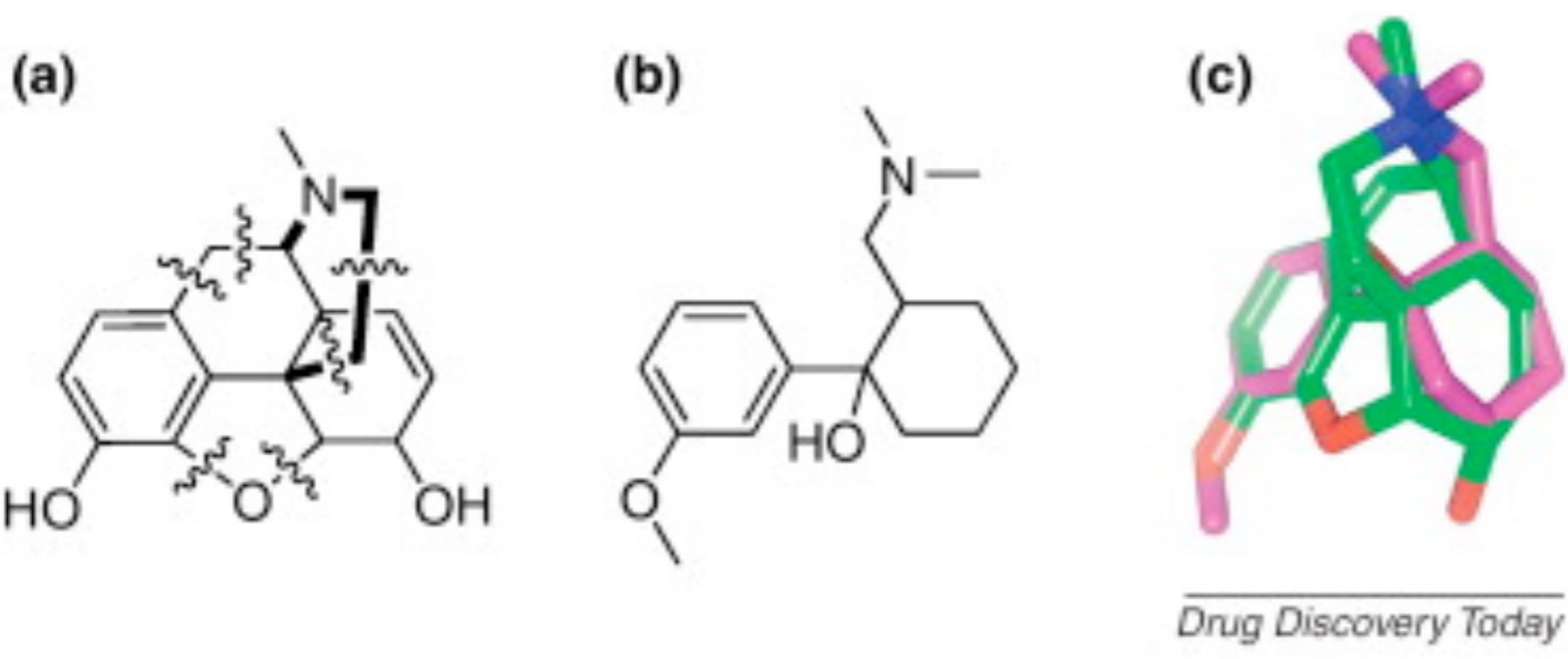


Figure 1.

Structures of pain-killing drugs: (a) morphine, (b) tramadol and (c) 3D superposition of (a) in green and (b) in magenta.

Morphine side effects and potency reduced by scaffold-hopping to tramadol

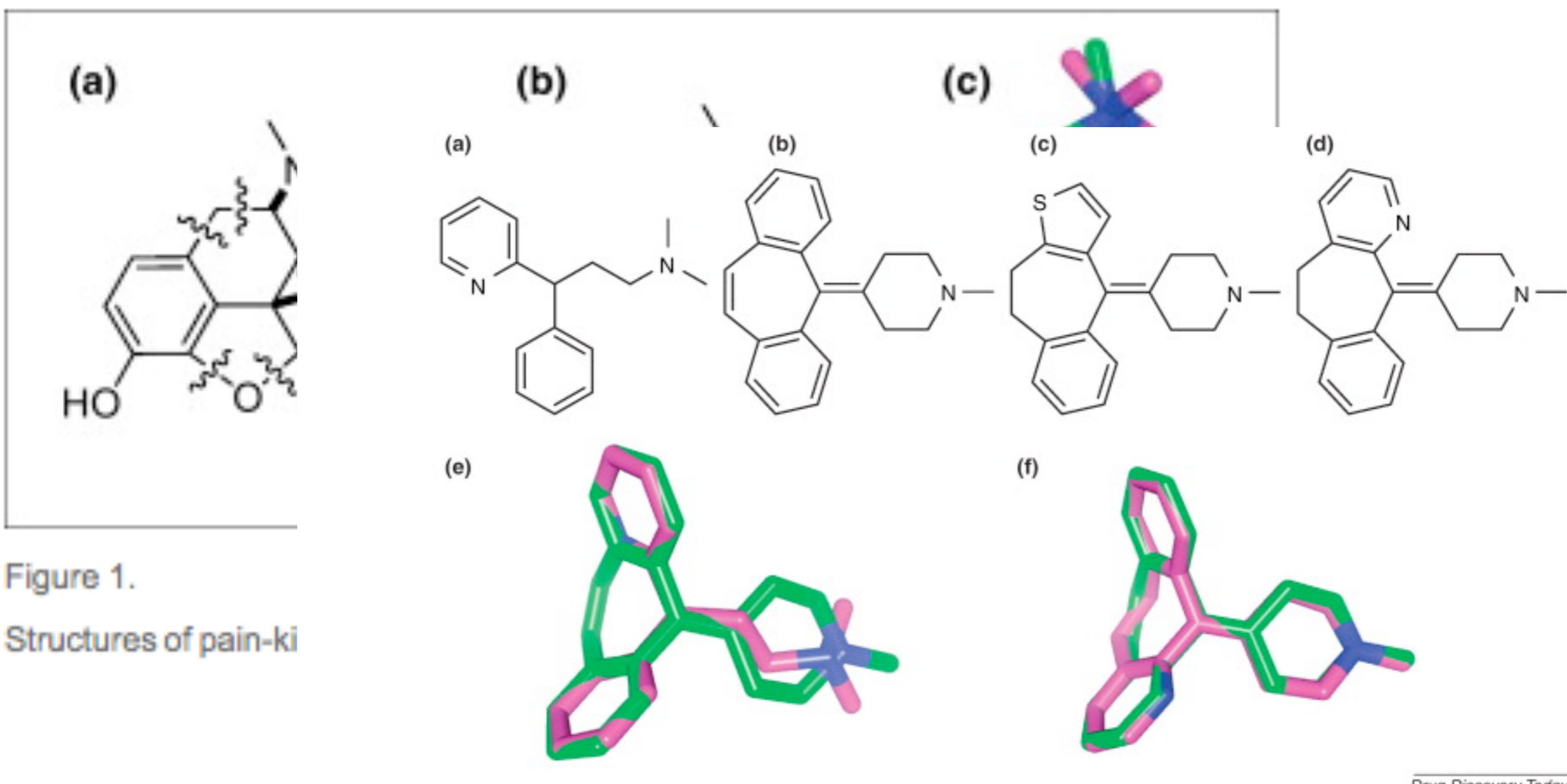


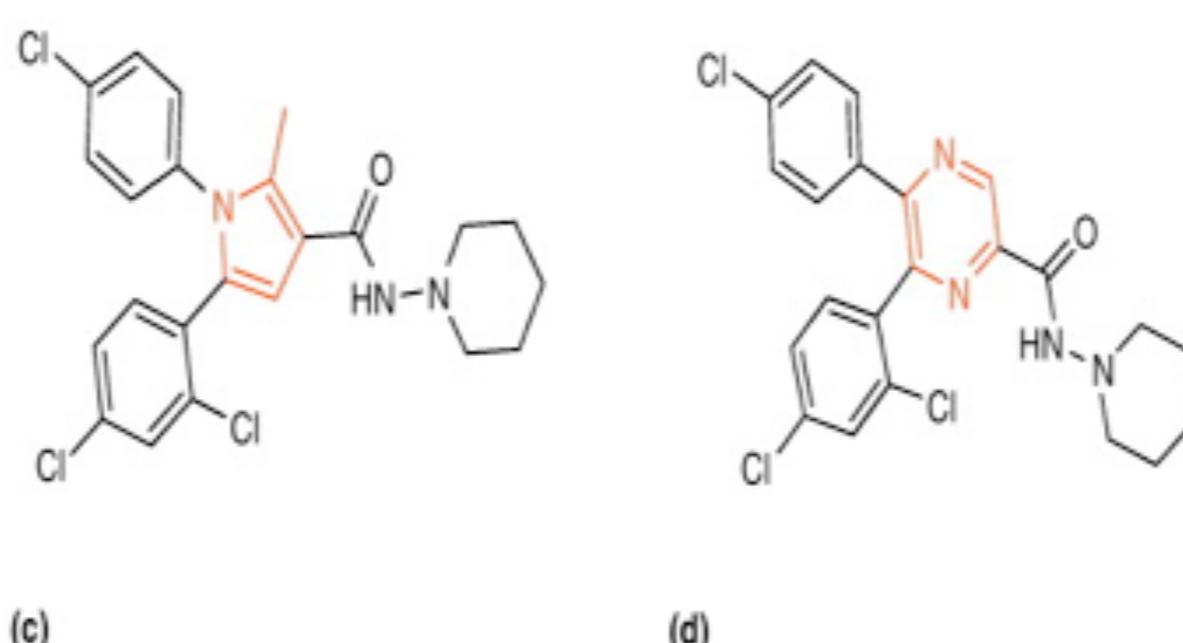
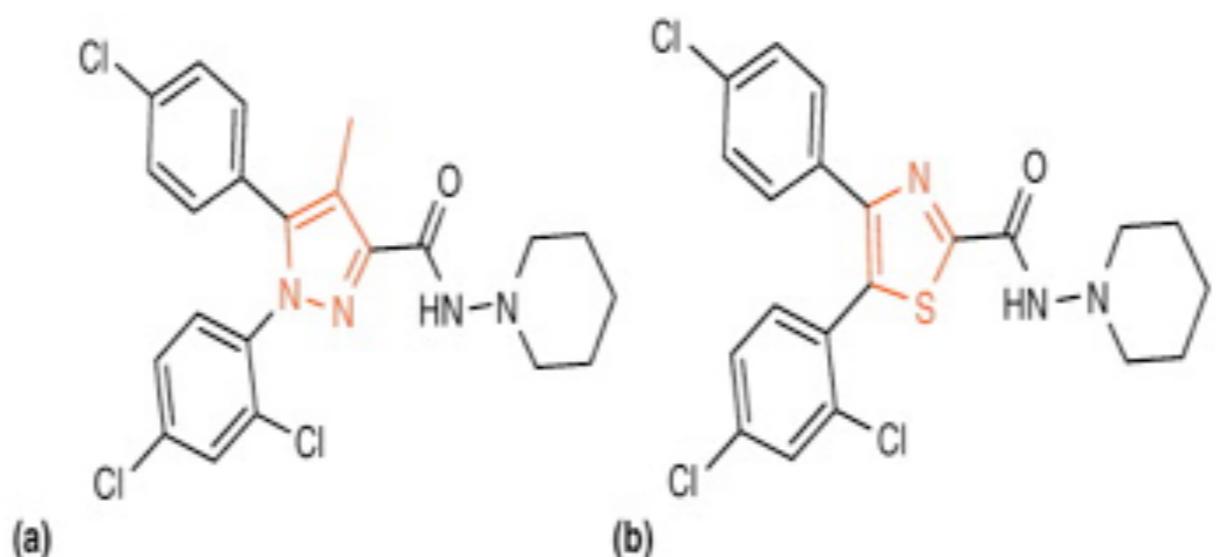
Figure 1.
Structures of pain-ki

Drug Discovery Today

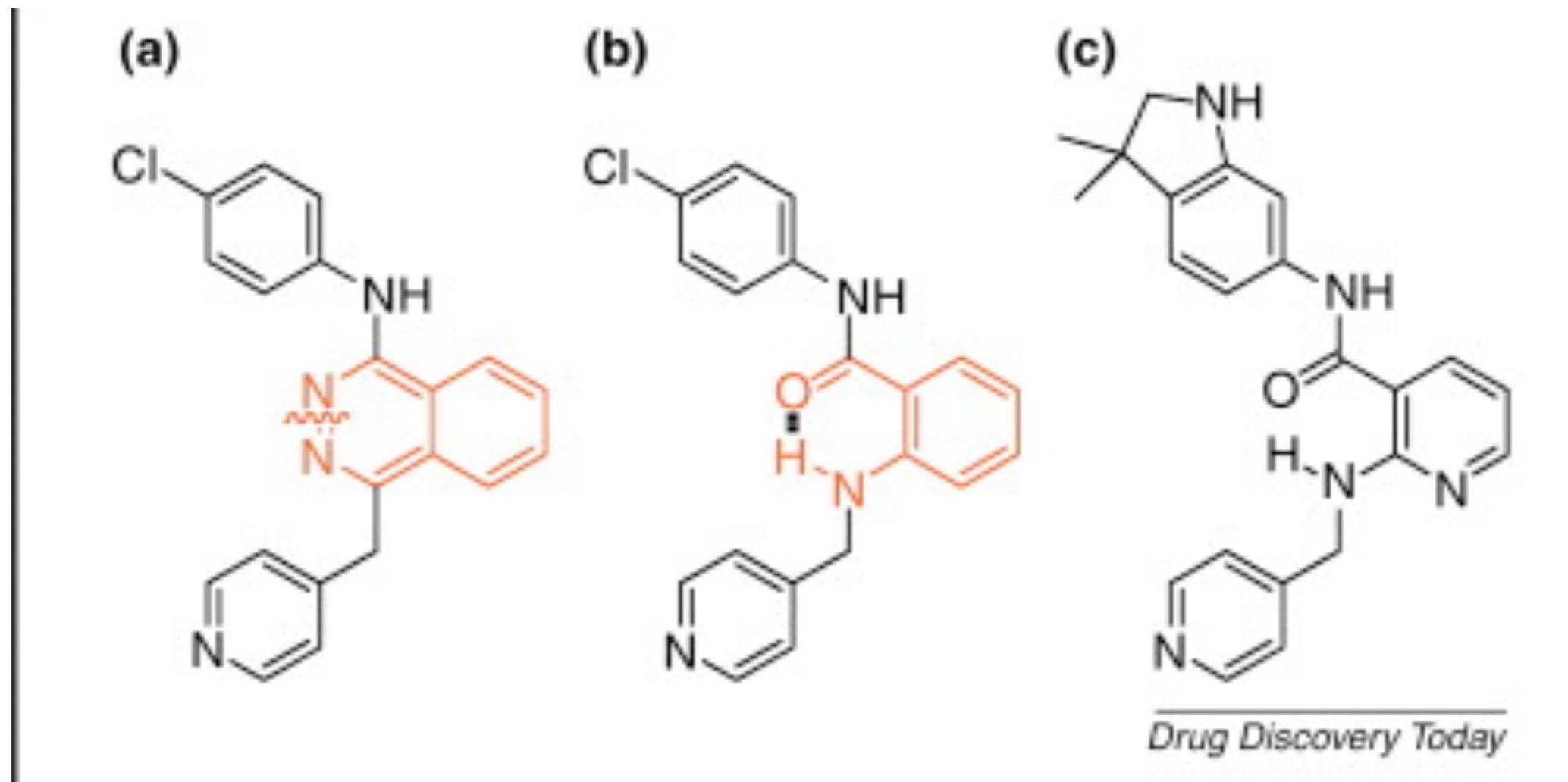
A variety of scaffold-hopping approaches are particularly common

- Heterocycle replacement
- Ring opening and closure
- Pseudopeptides and peptidomimetics
- Topology/shape-based hopping
- Progressively more difficult

Heterocycle replacement is one of the more common and easier approaches

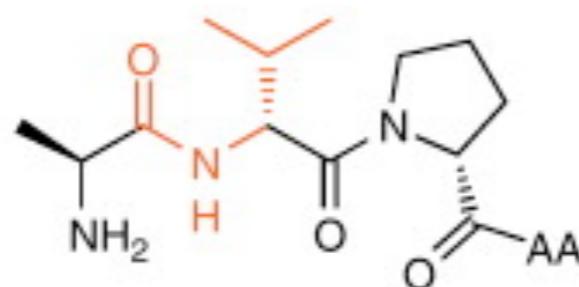


Ring opening and closing also is done quite frequently

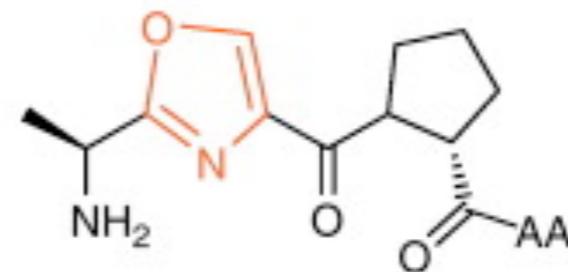


Working to remove peptide character is also particularly common

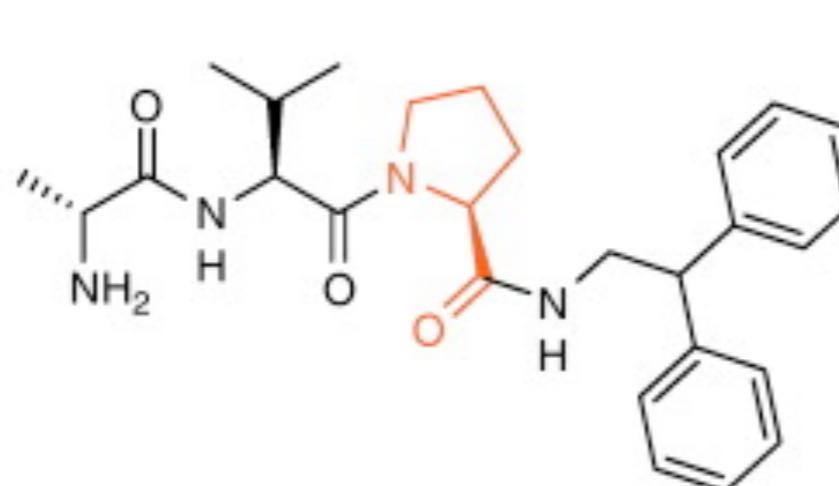
(a)



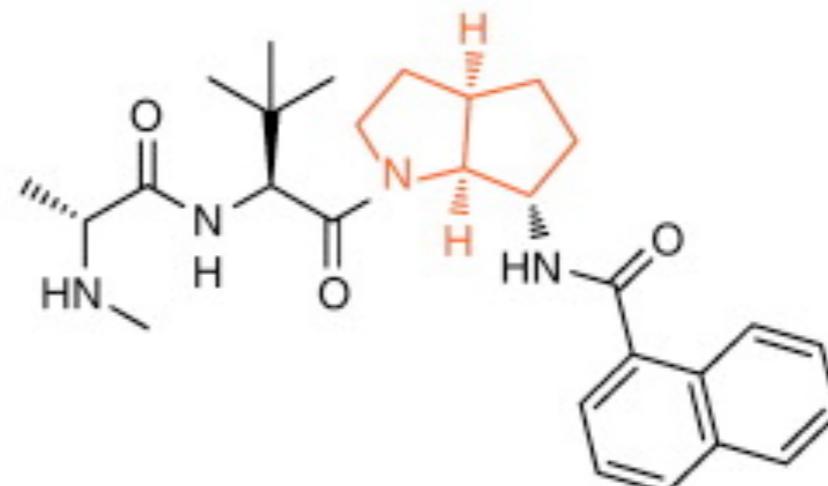
(b)



(c)

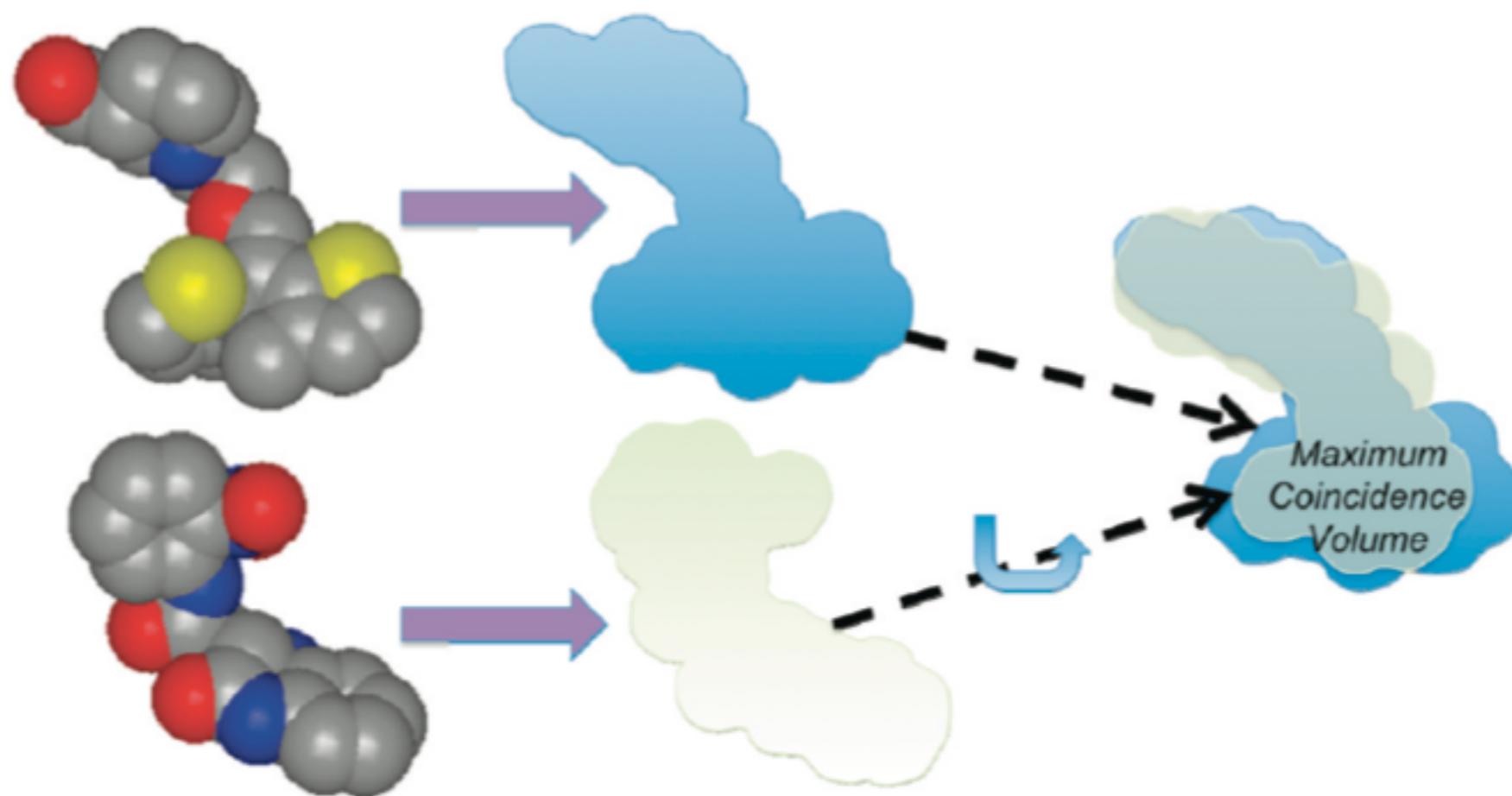


(d)

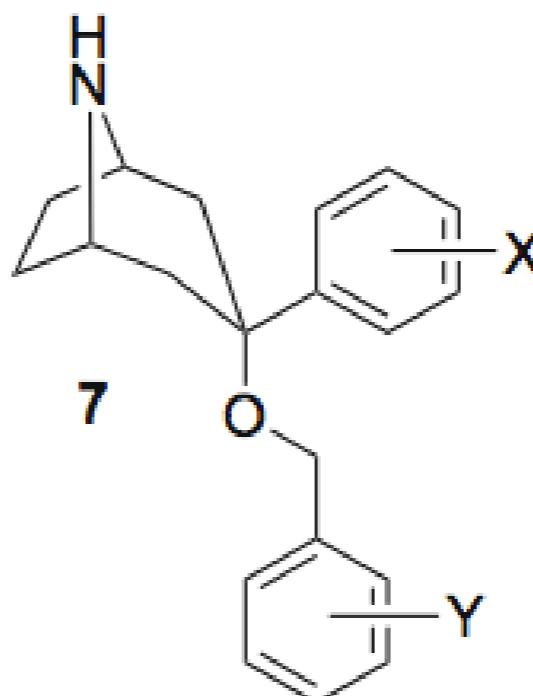
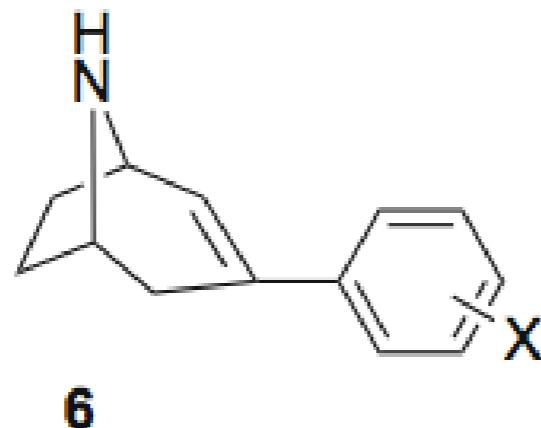


Drug Discovery Today

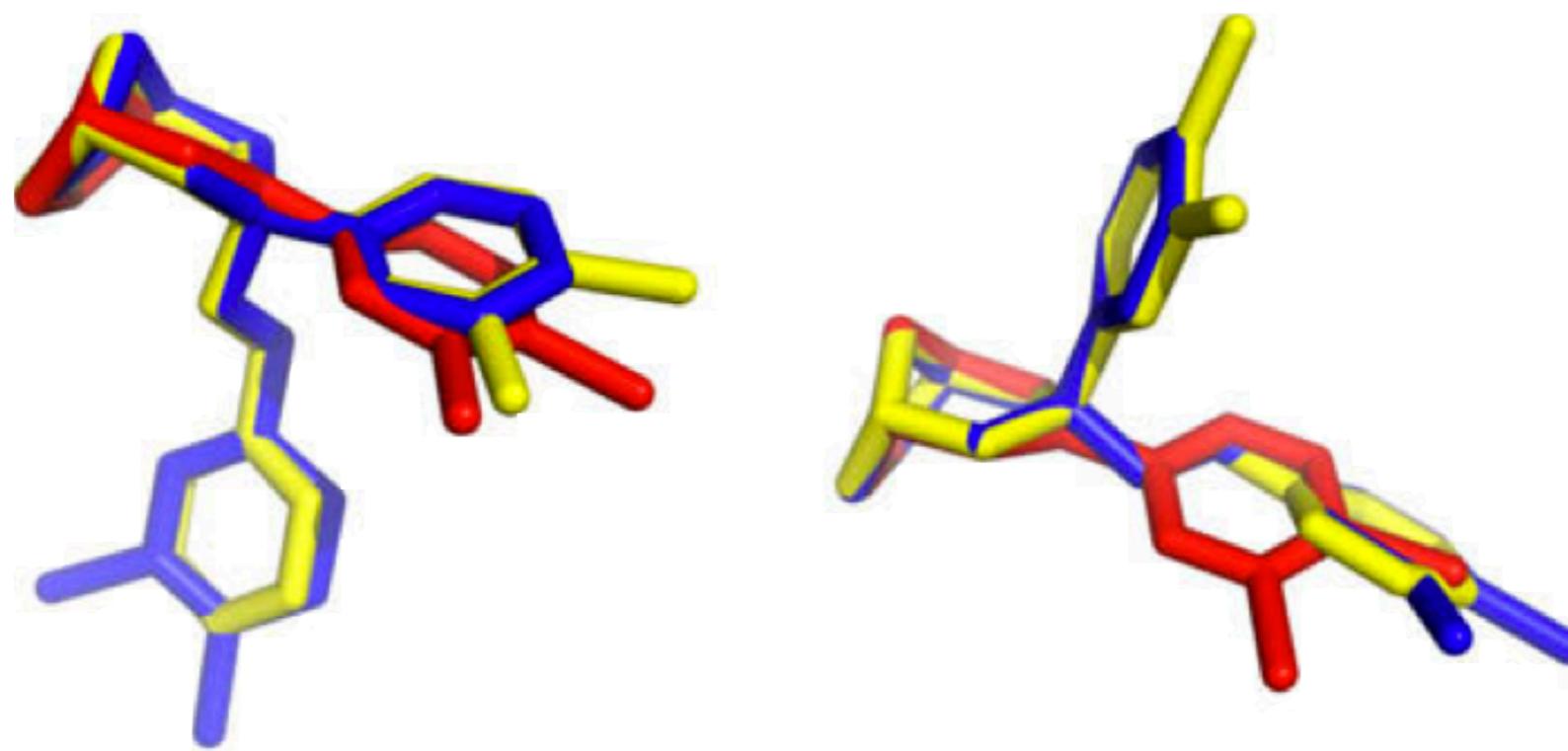
Shape methods are one of the more common ligand-based design methods



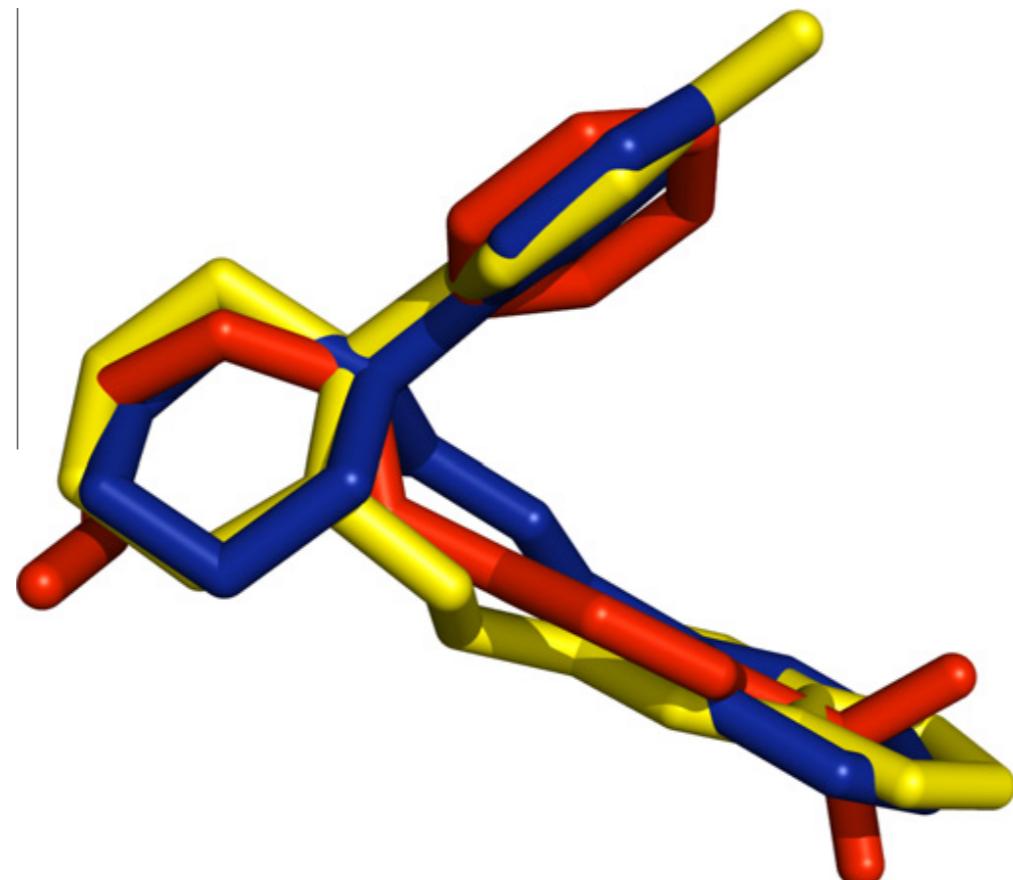
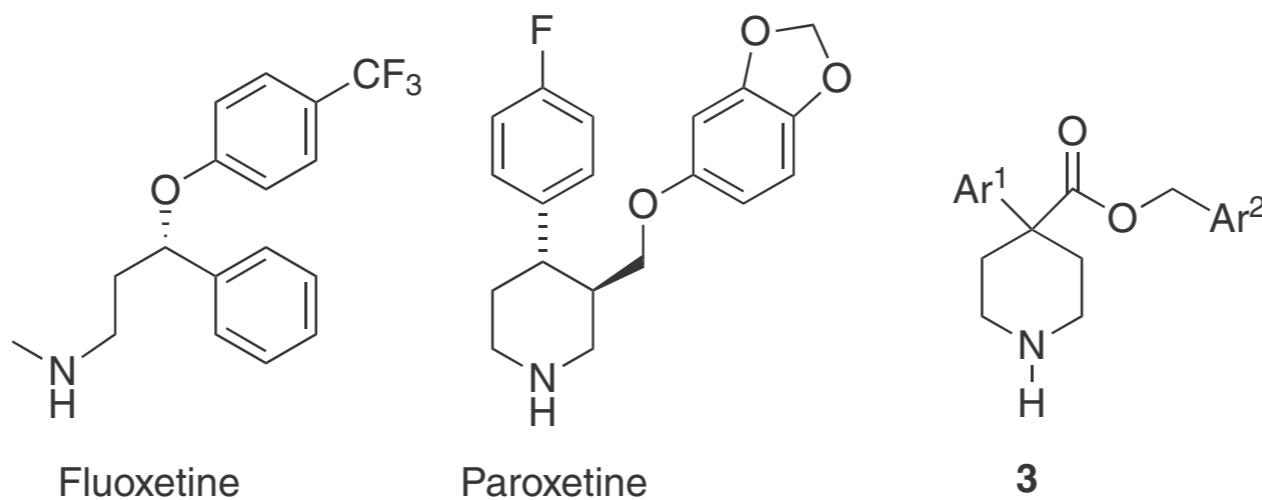
Shape comparisons provide a valuable tool for ligand-based design



6e: $X=3,4-\text{Cl}_2$
7c: $X=\text{H}, Y=3,4-\text{Cl}_2$
7i: $X=3,4-\text{Cl}_2; Y=\text{H}$

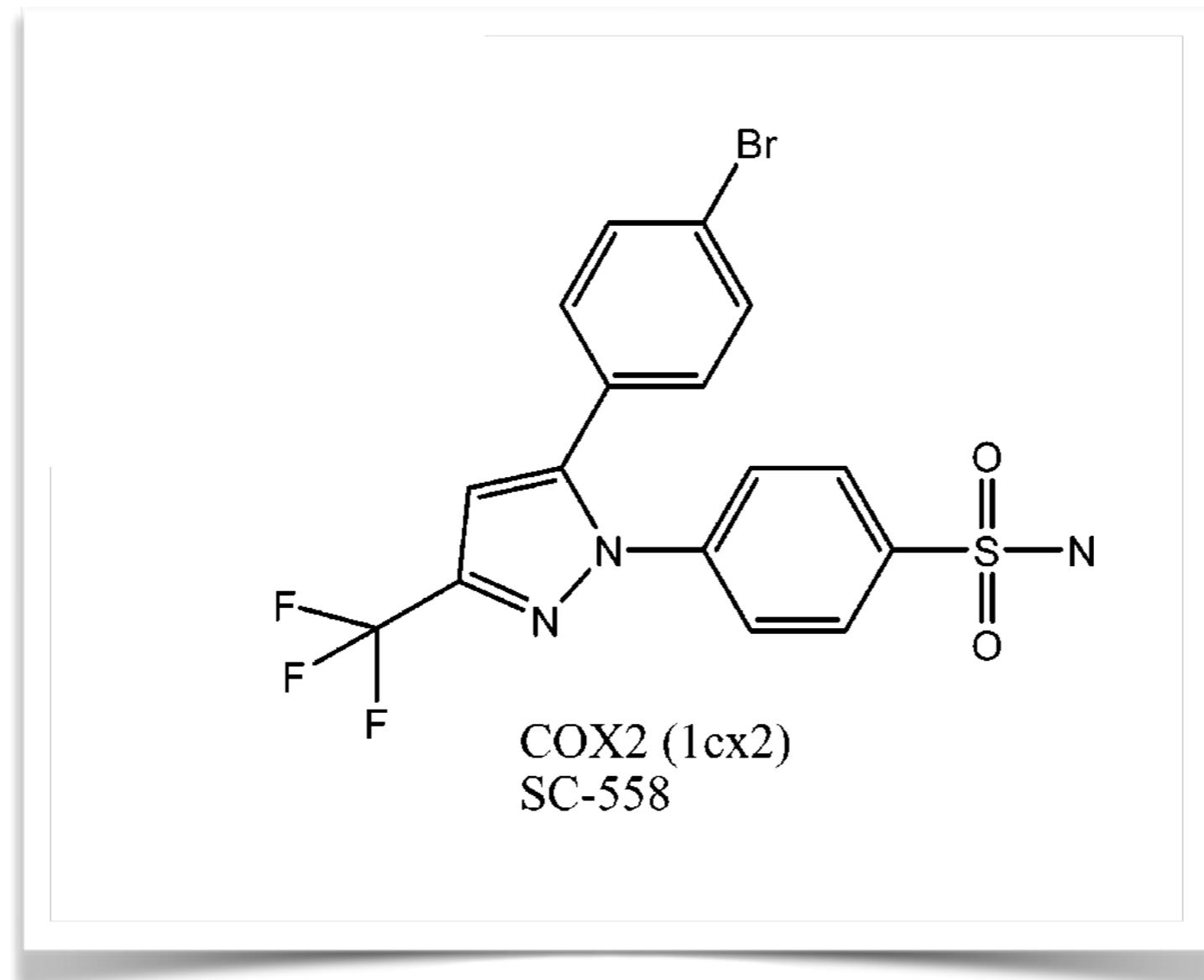


They provide useful information on binding site shape



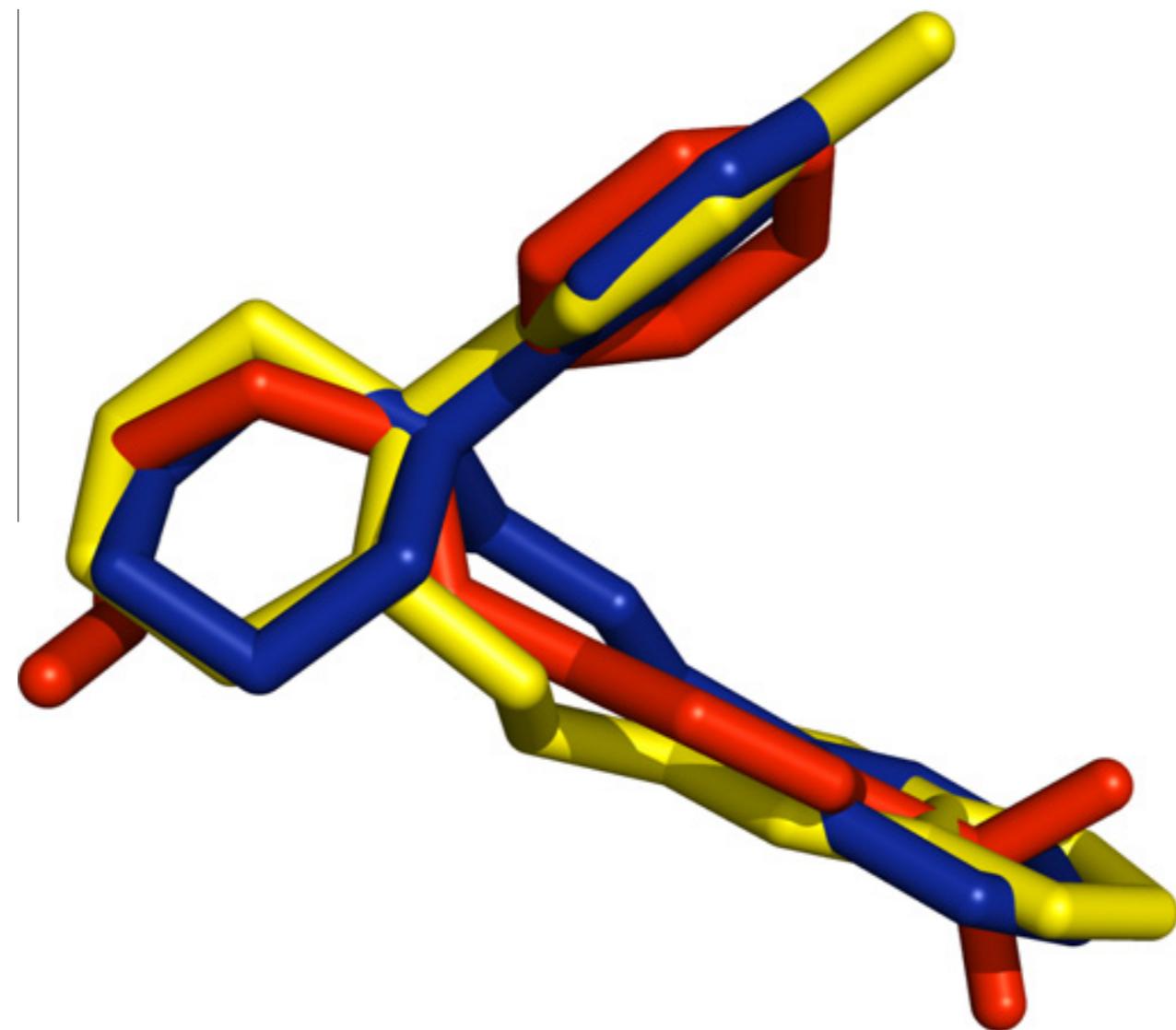
Screening by shape starts with a “query” molecule

Screening by shape starts with a “query” molecule

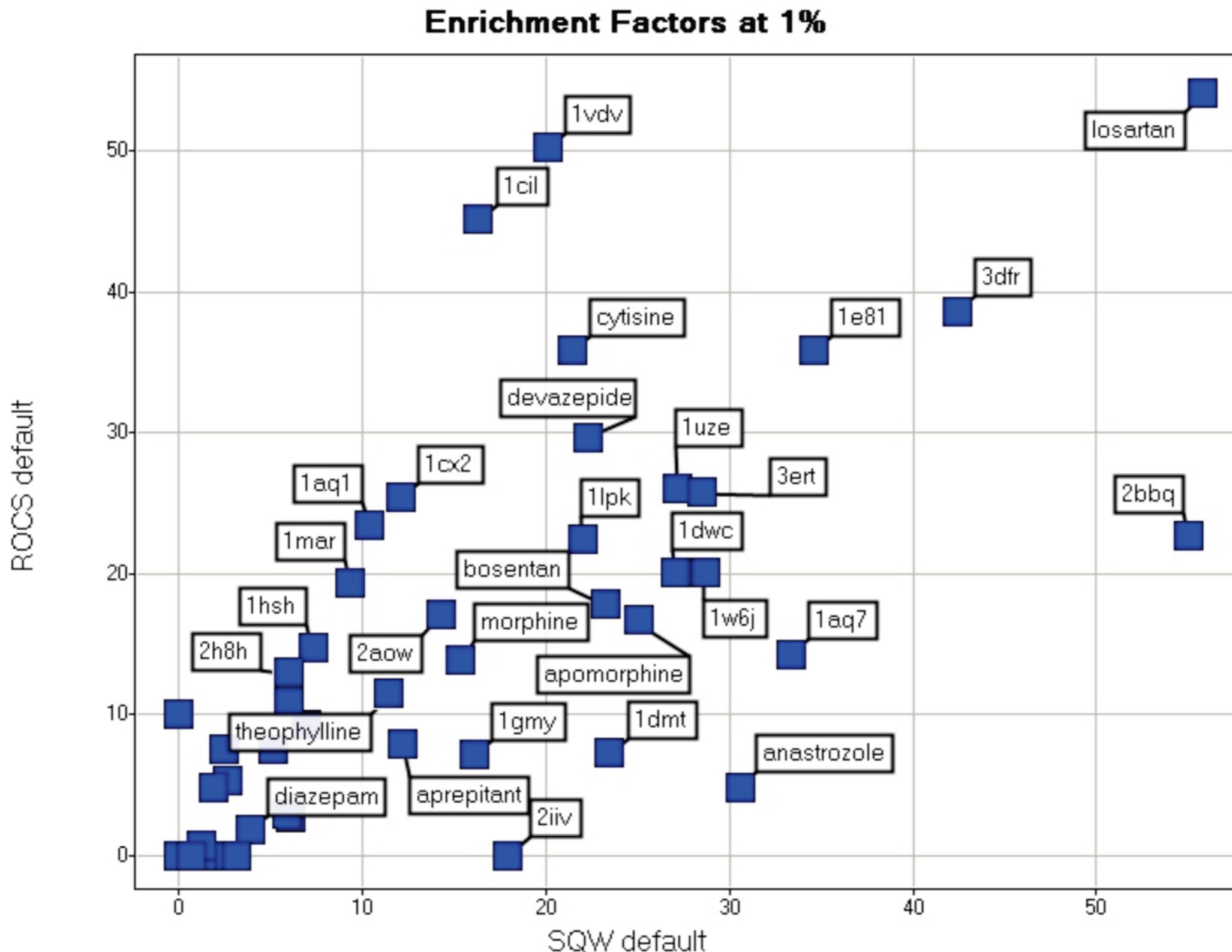


Screening by shape starts with a “query” molecule

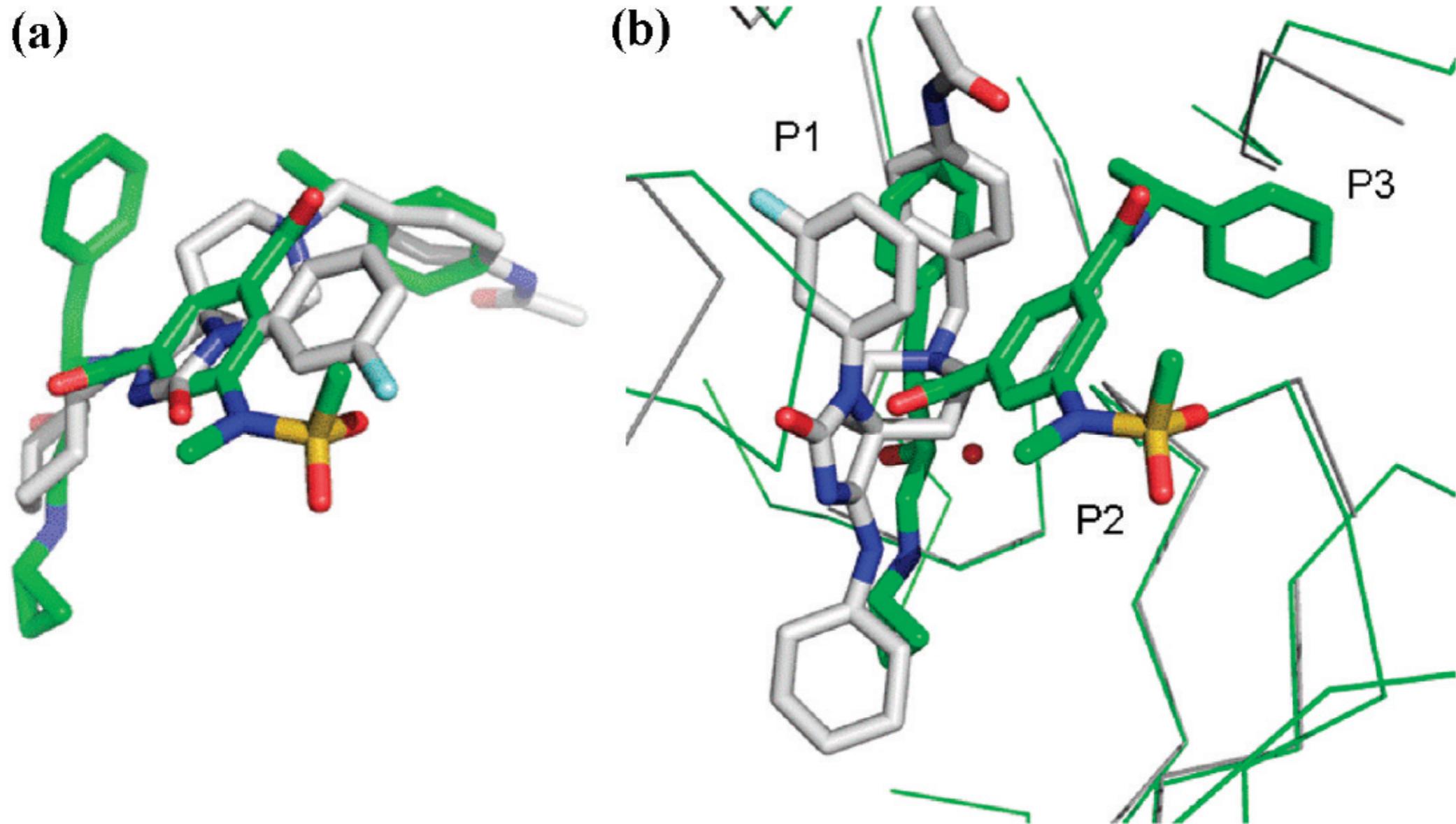
Sort shape matches by Tanimoto score rather than docking score to get “hits”



Shape methods, like docking, do “enrich” actives in tests

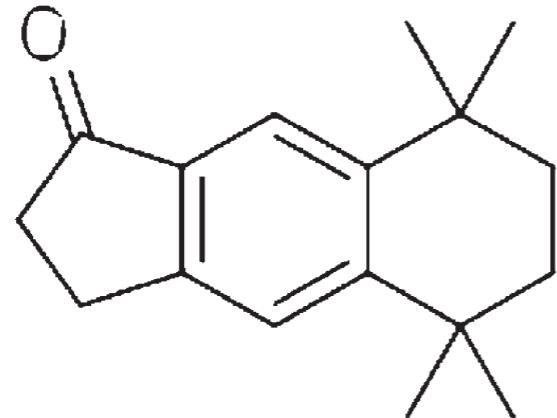
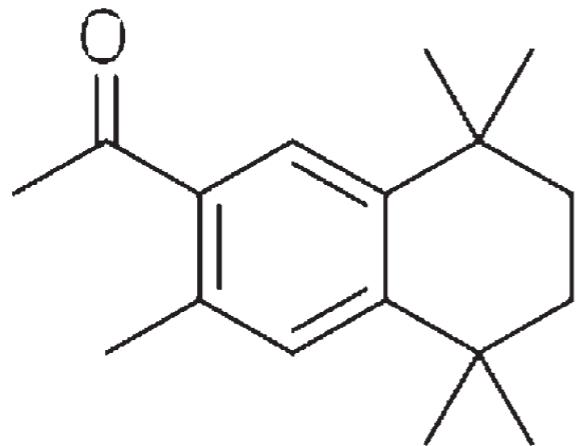


Shape methods have their limits

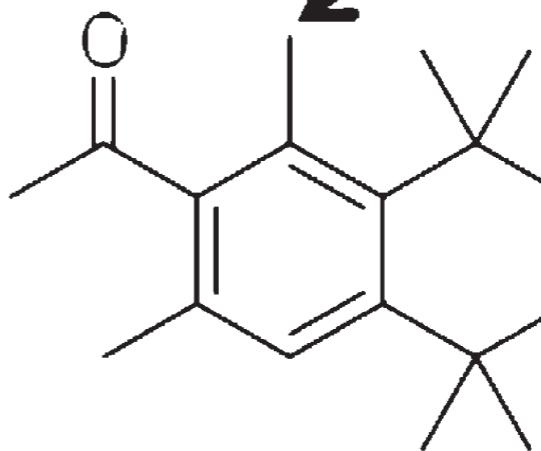
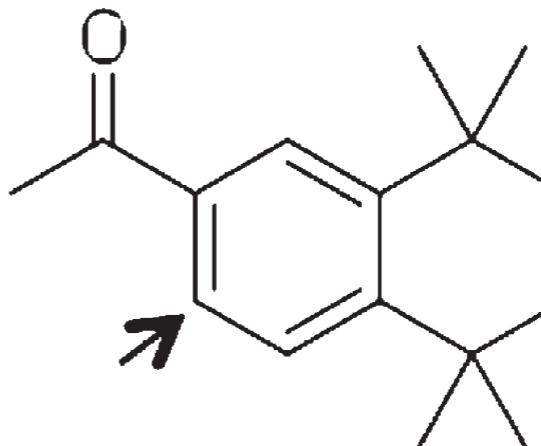


It's hard to know when shape similarity definitely means binding similarity

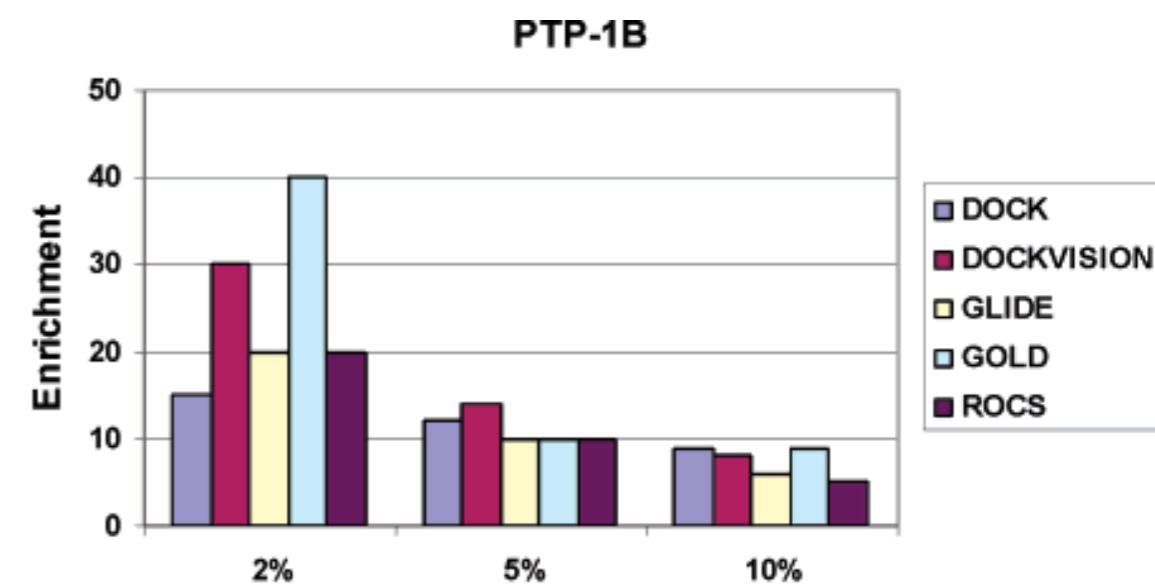
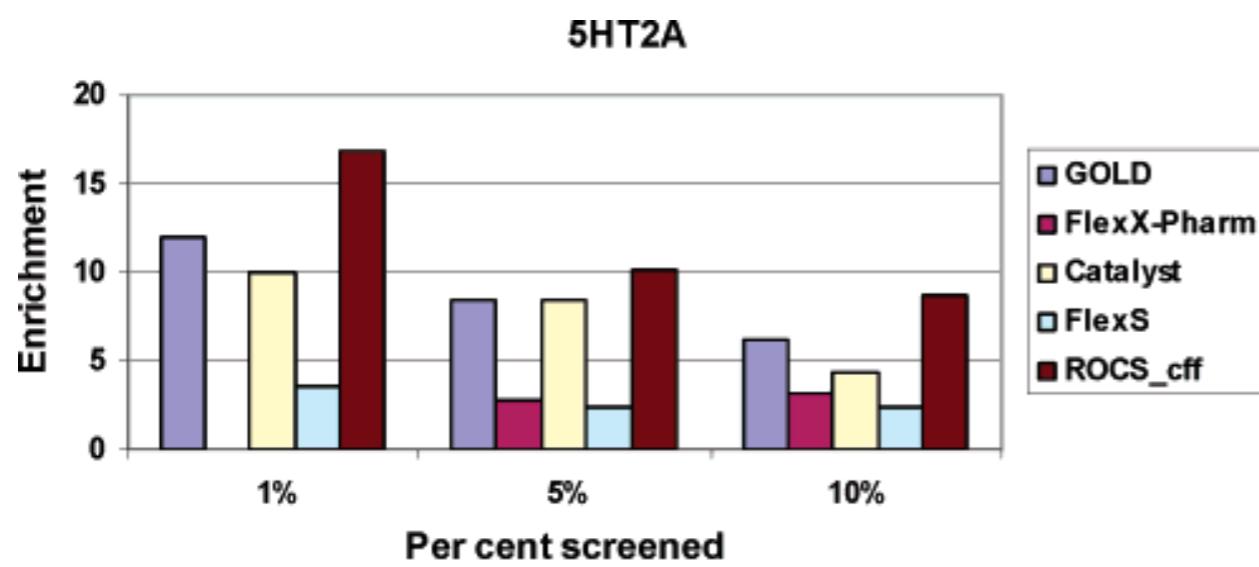
Active



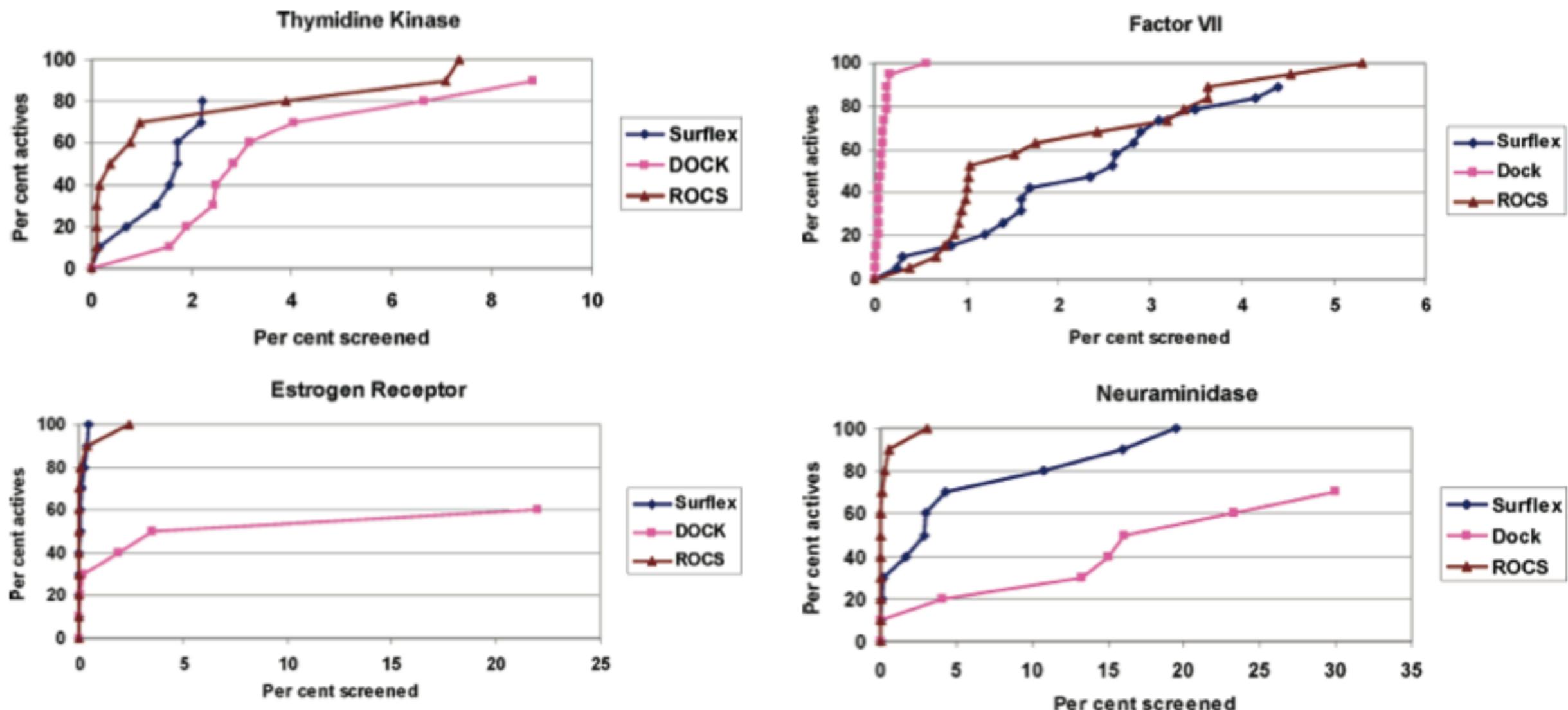
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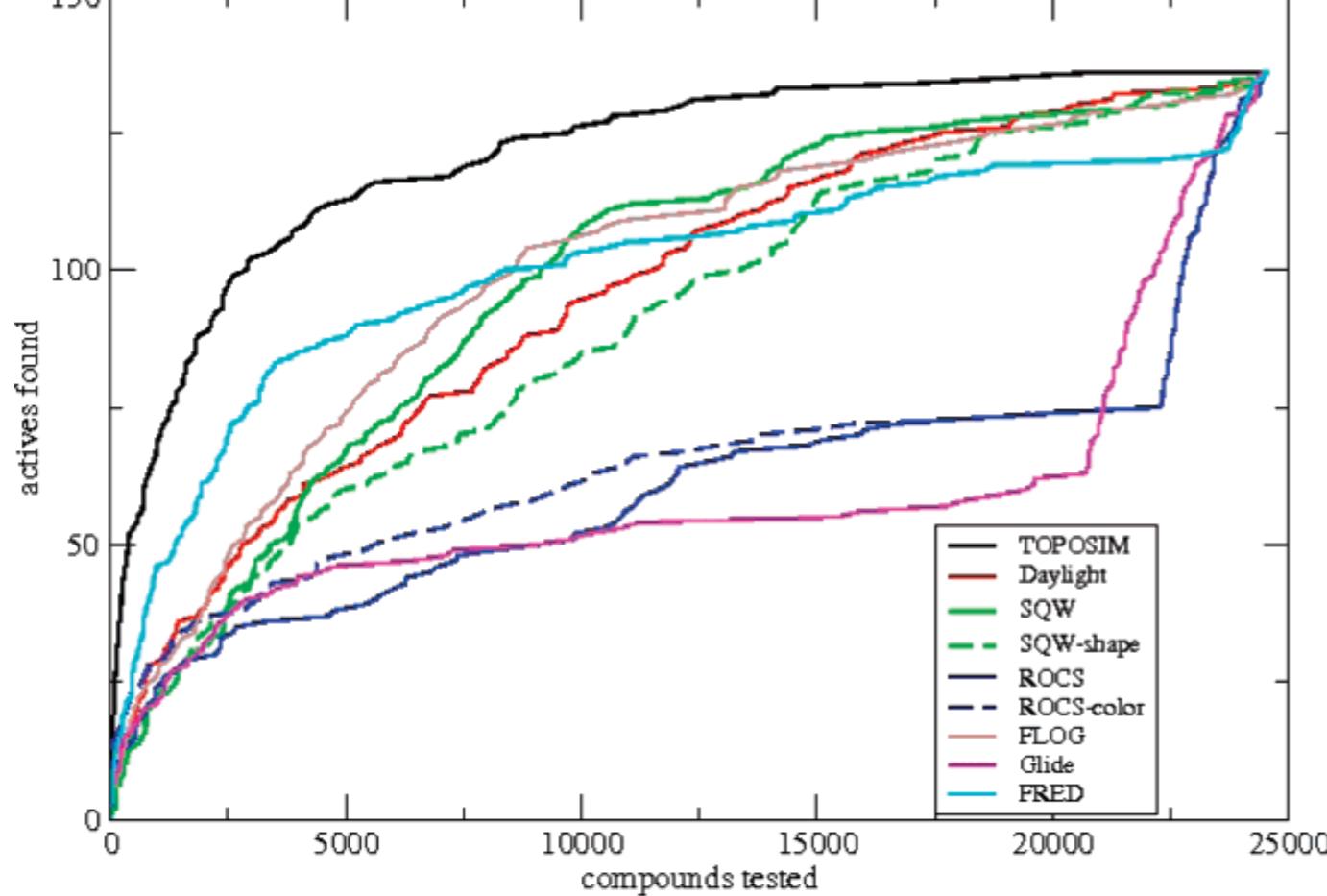


Shape methods work reasonably well in library screening tests

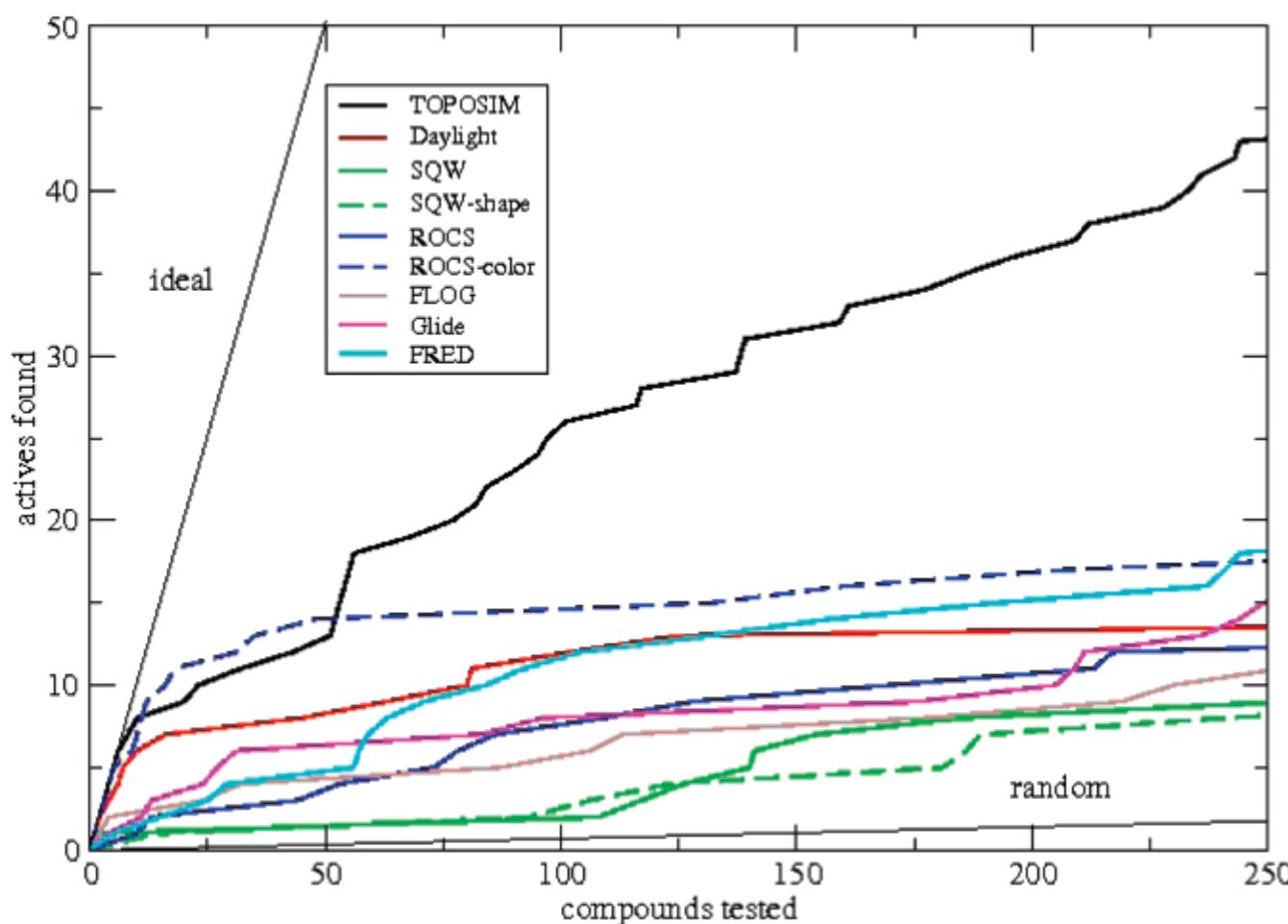


Shape methods work reasonably well in library screening tests





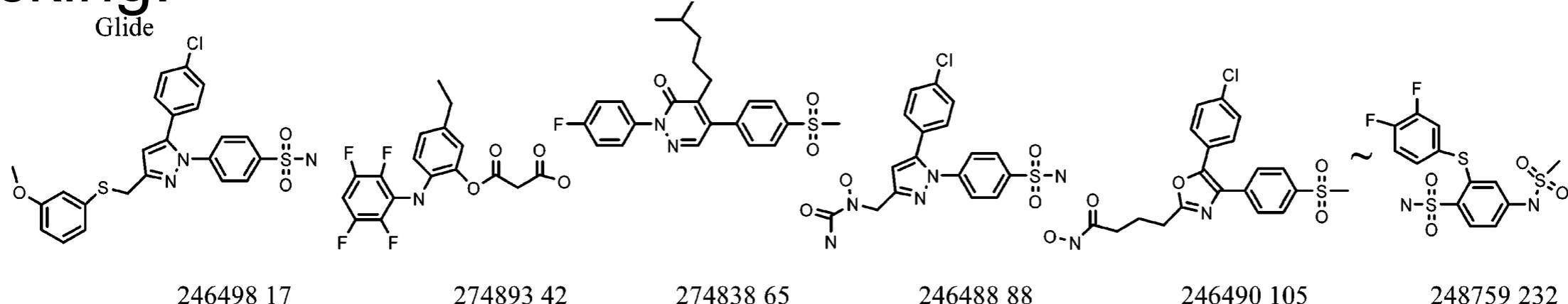
HIV_pr



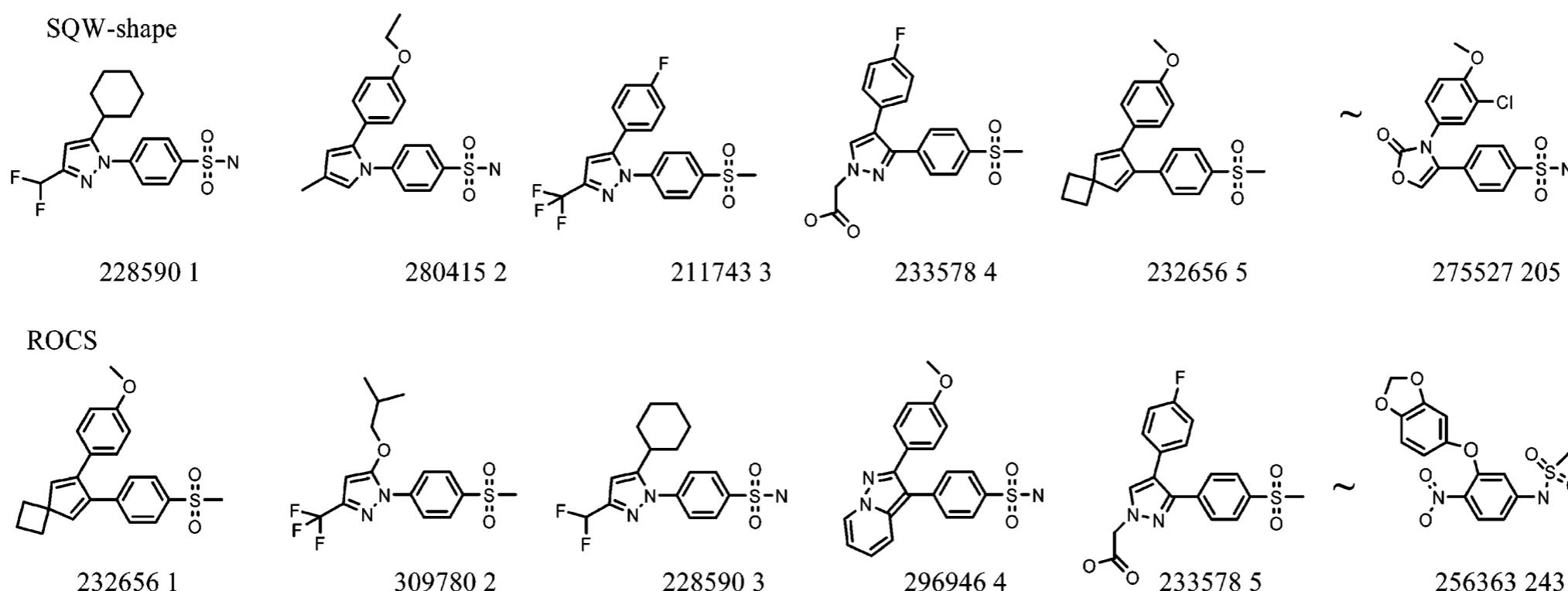
Shape methods work
reasonably well in
library screening tests

Which actives are found depends a lot on the type of method used

Docking:

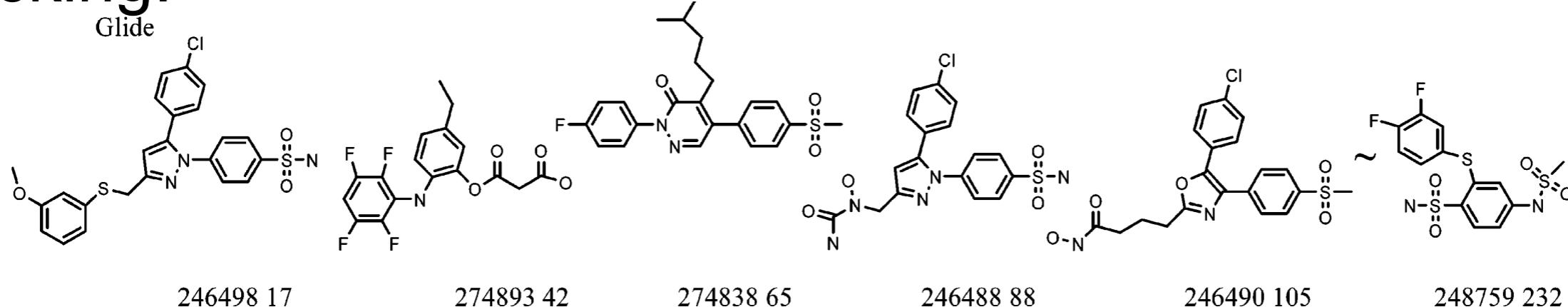


Shape overlay results:

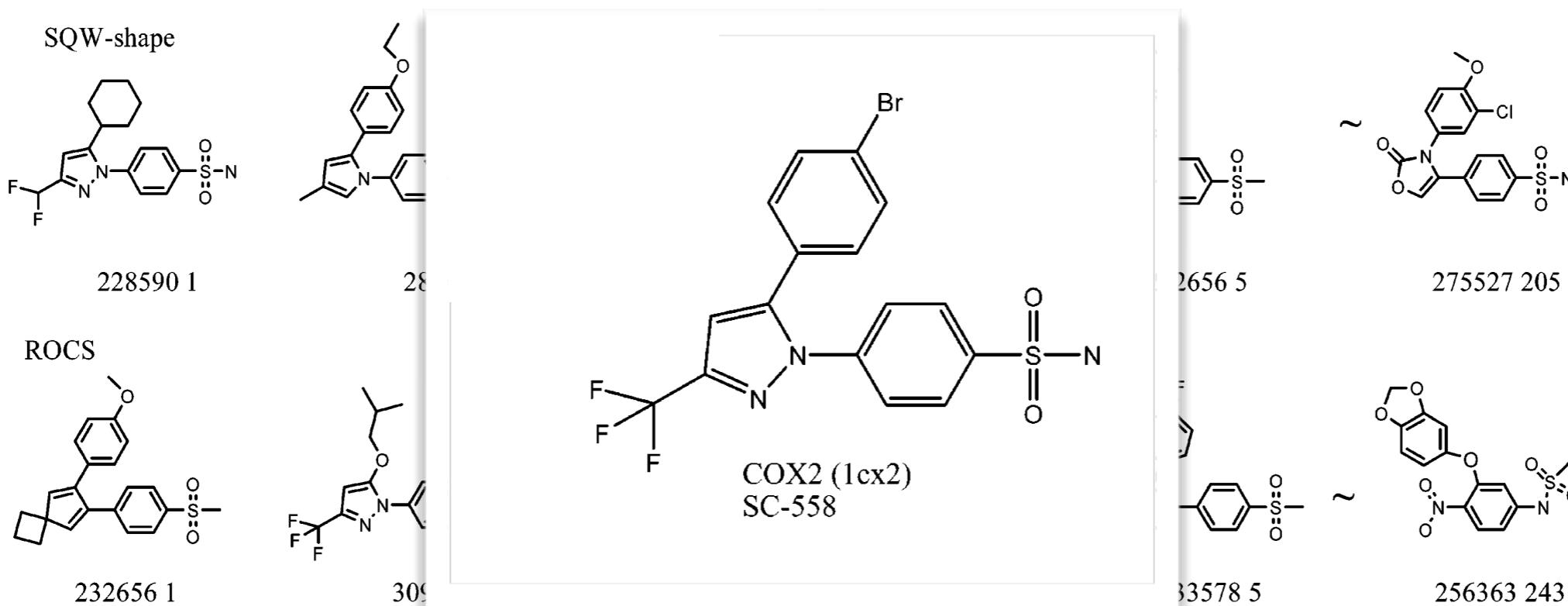


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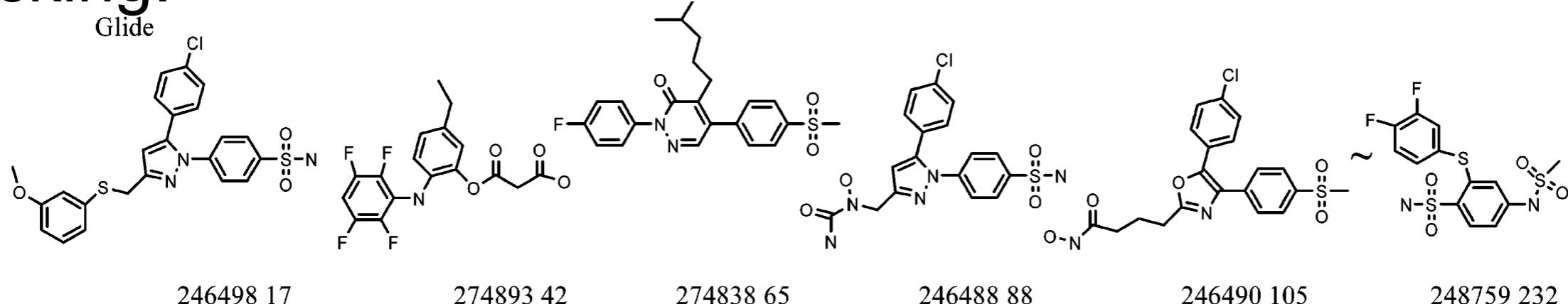


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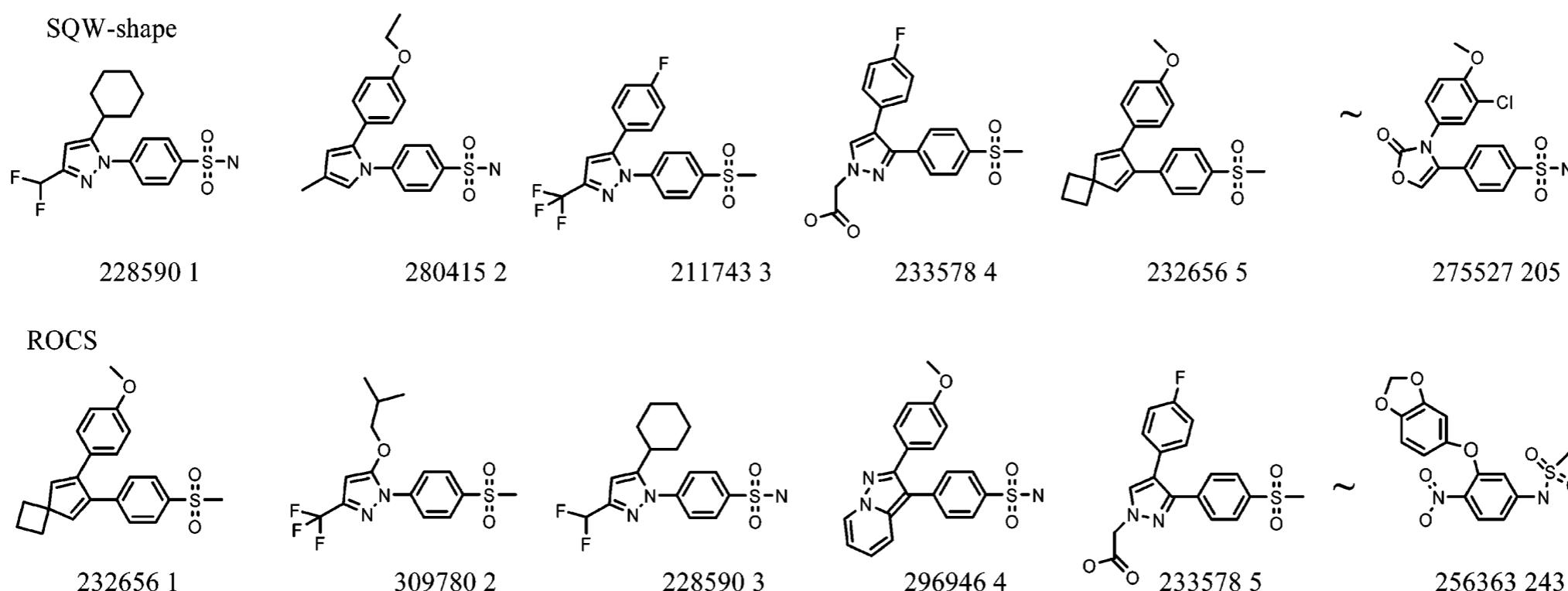


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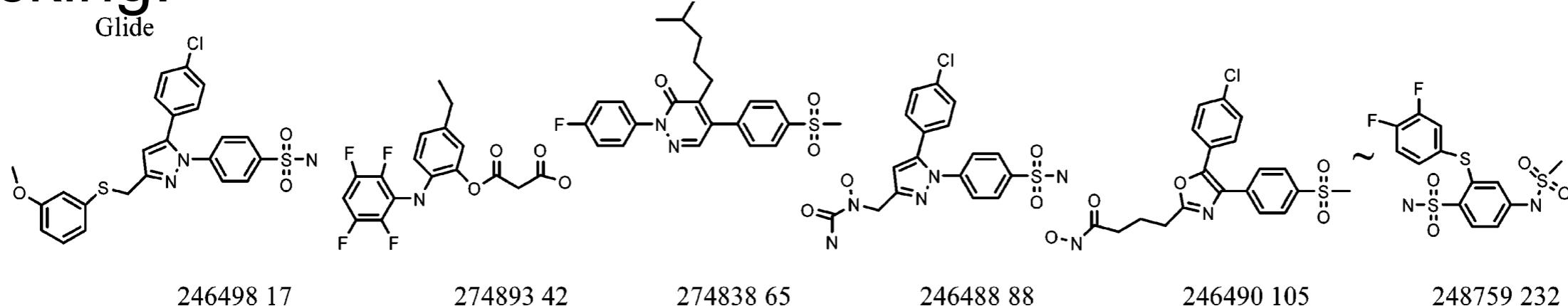


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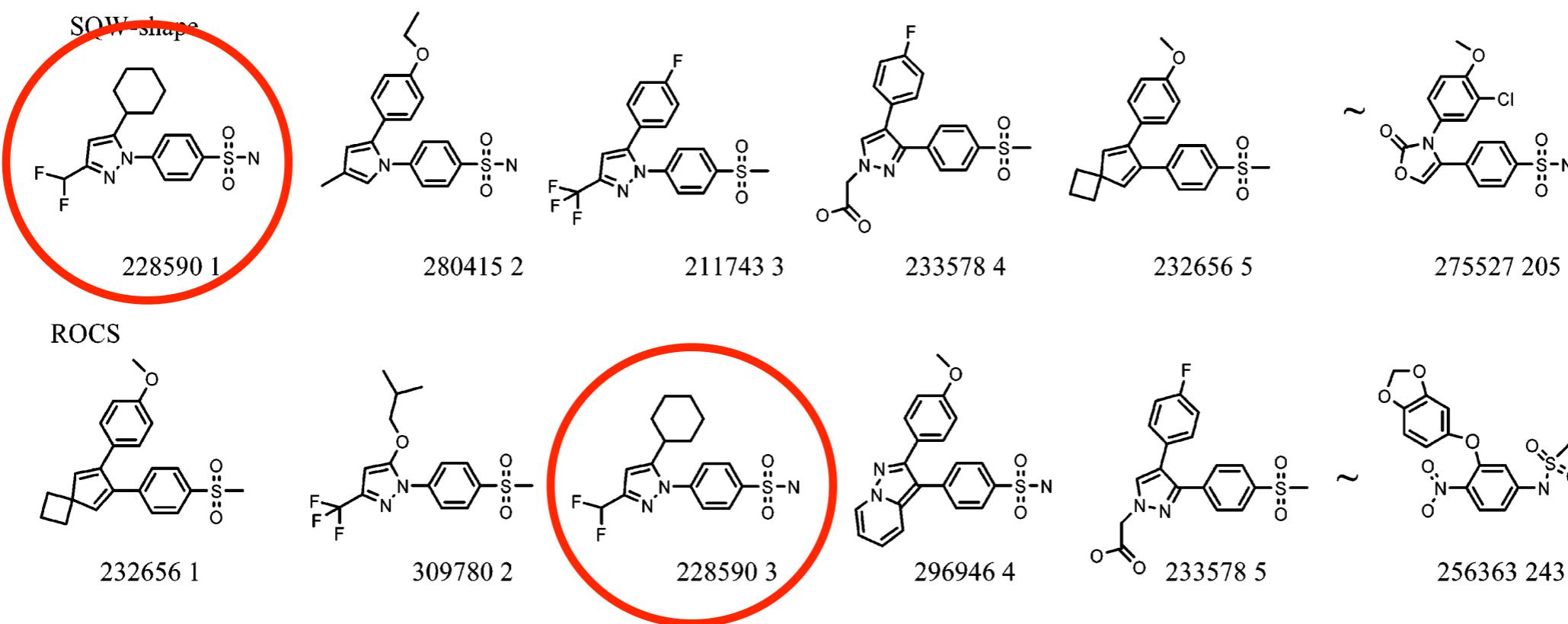


Which actives are found depends a lot on the type of method used

Docking:

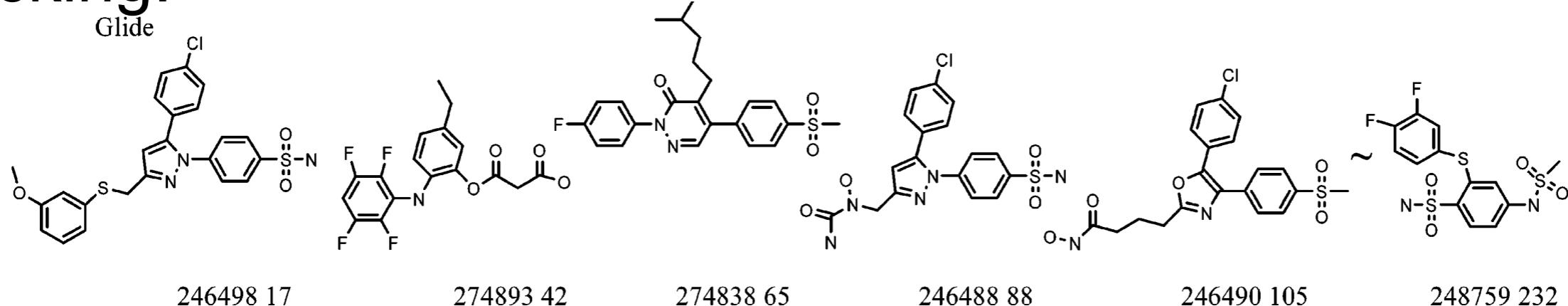


Shape overlay results:

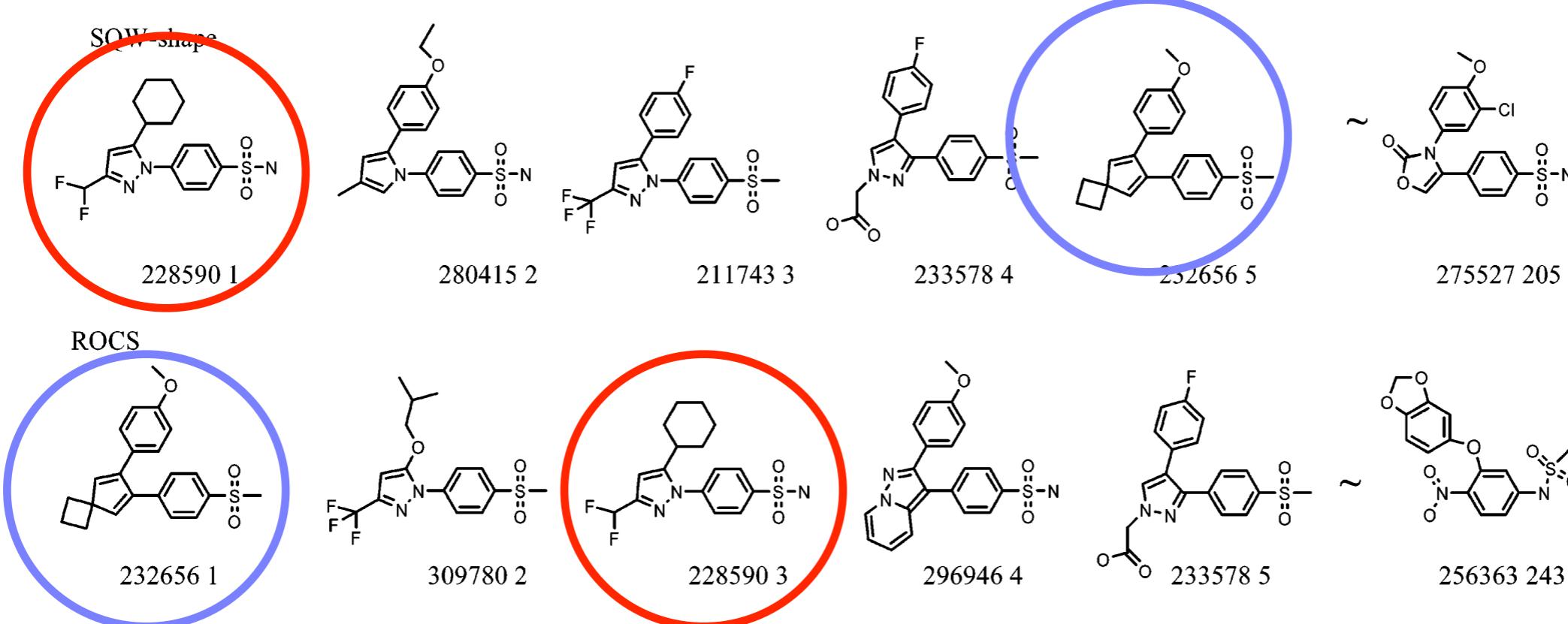


Which actives are found depends a lot on the type of method used

Docking:

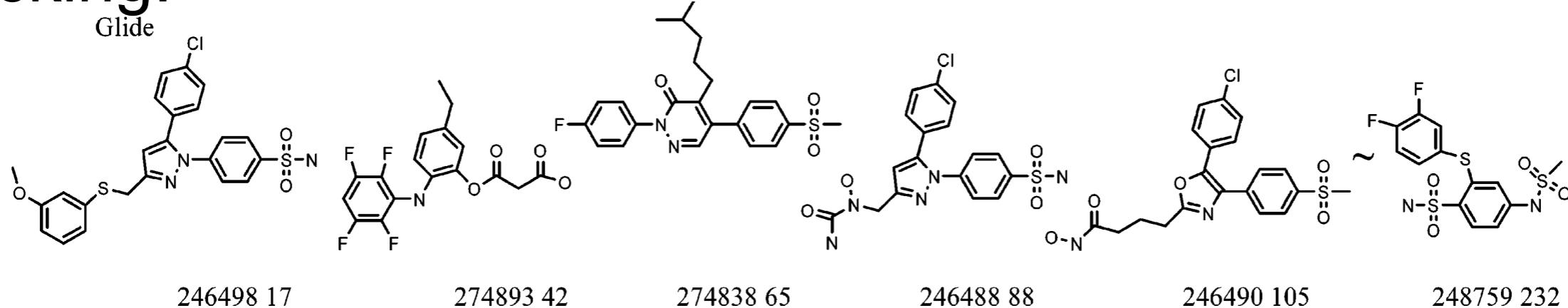


Shape overlay results:

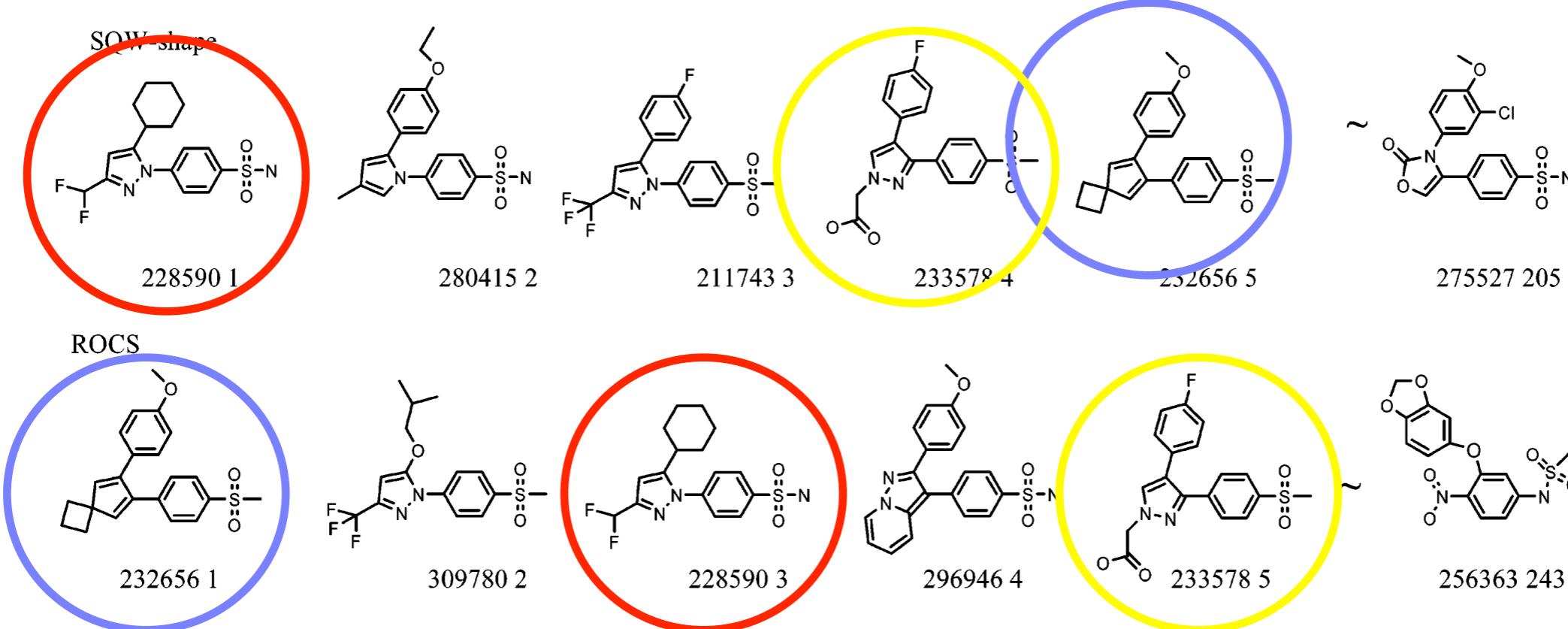


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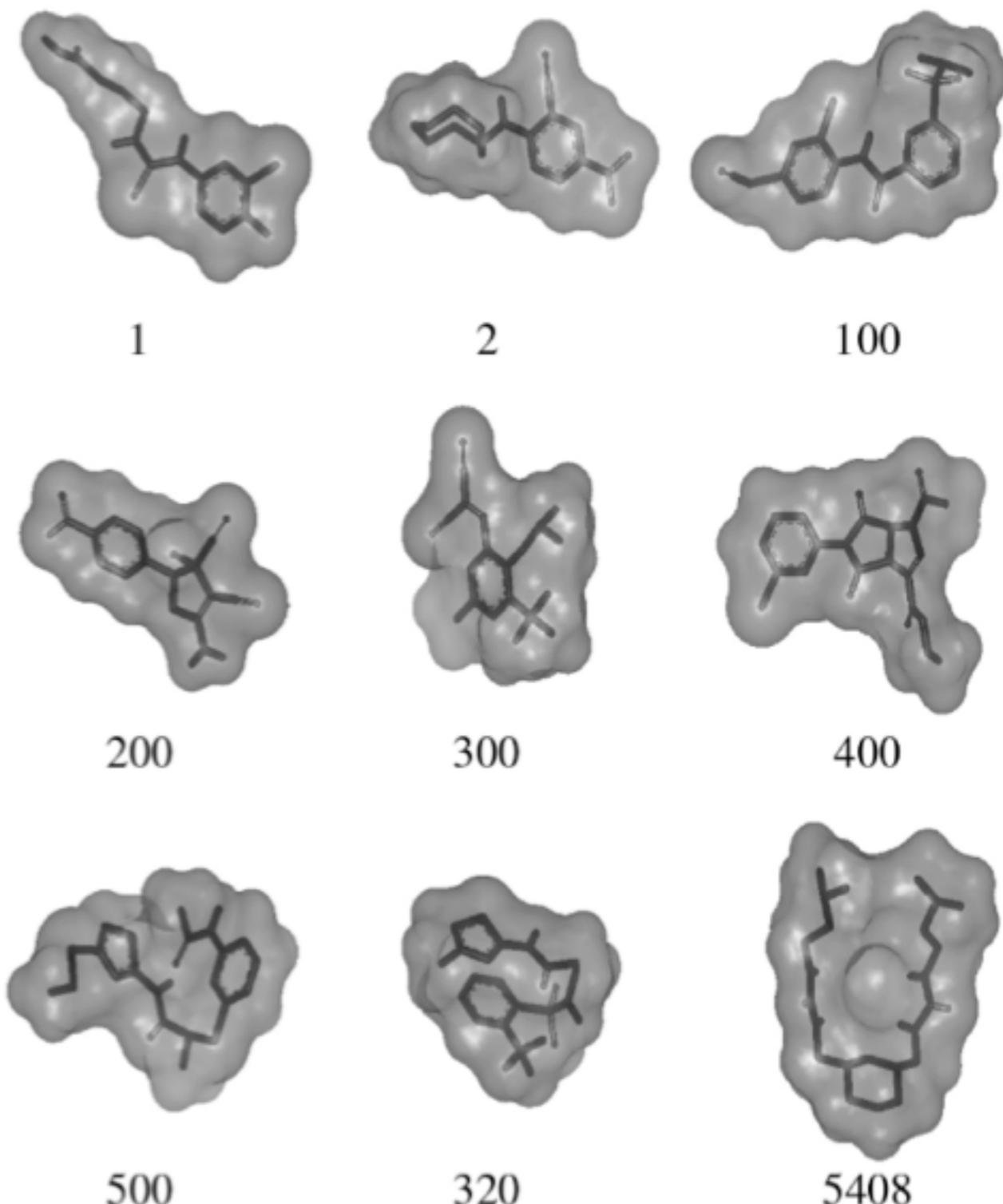
Docking:



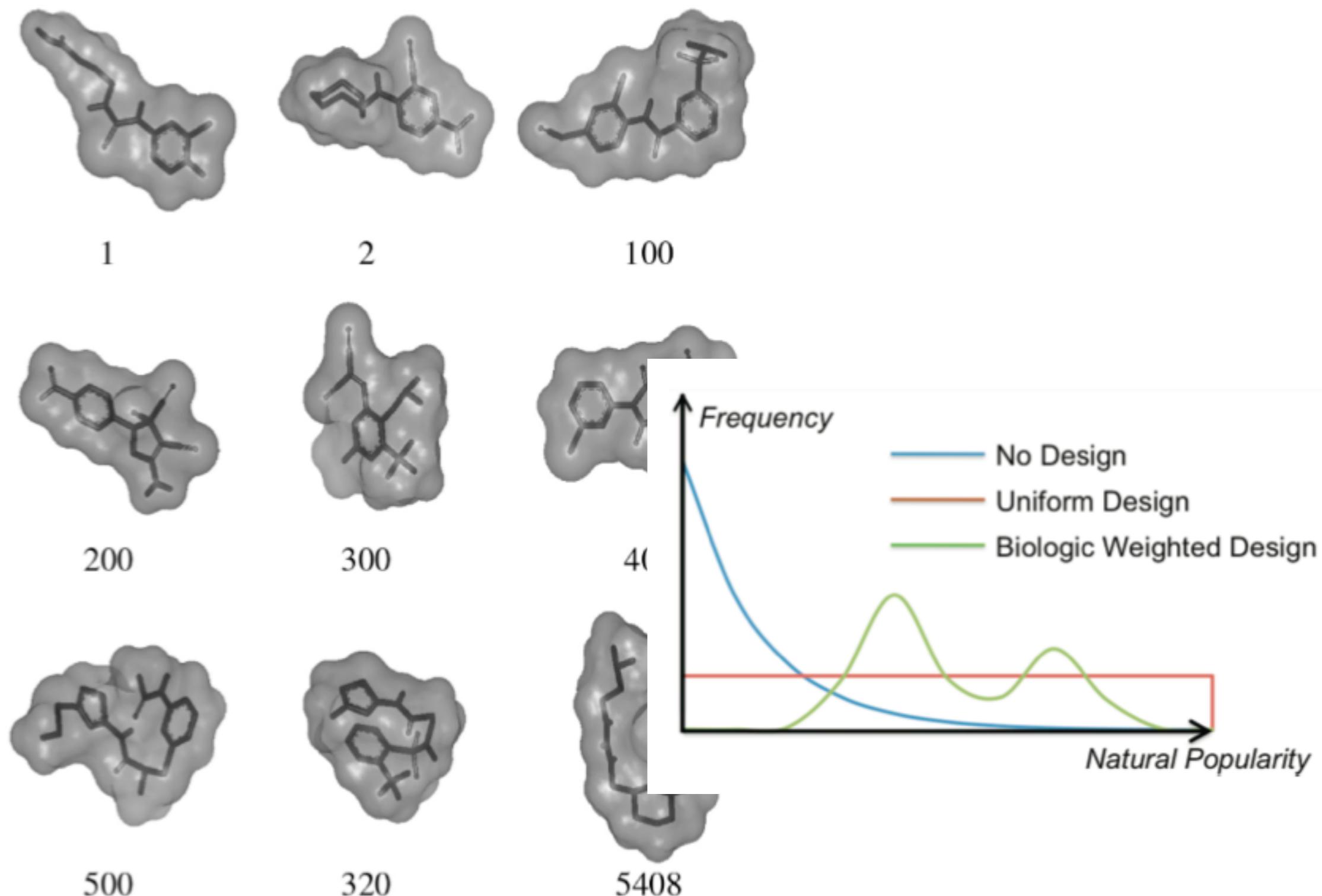
Shape overlay results:



Shape methods can be incorporated into library design

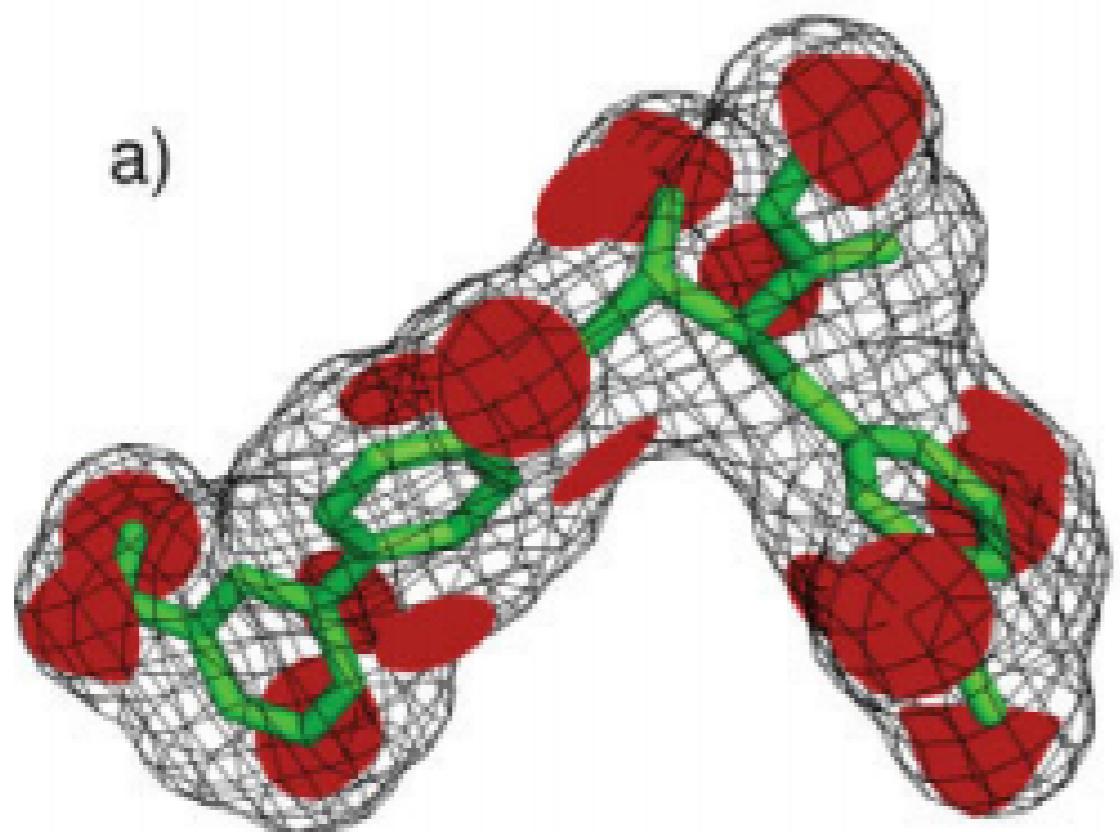


Shape methods can be incorporated into library design

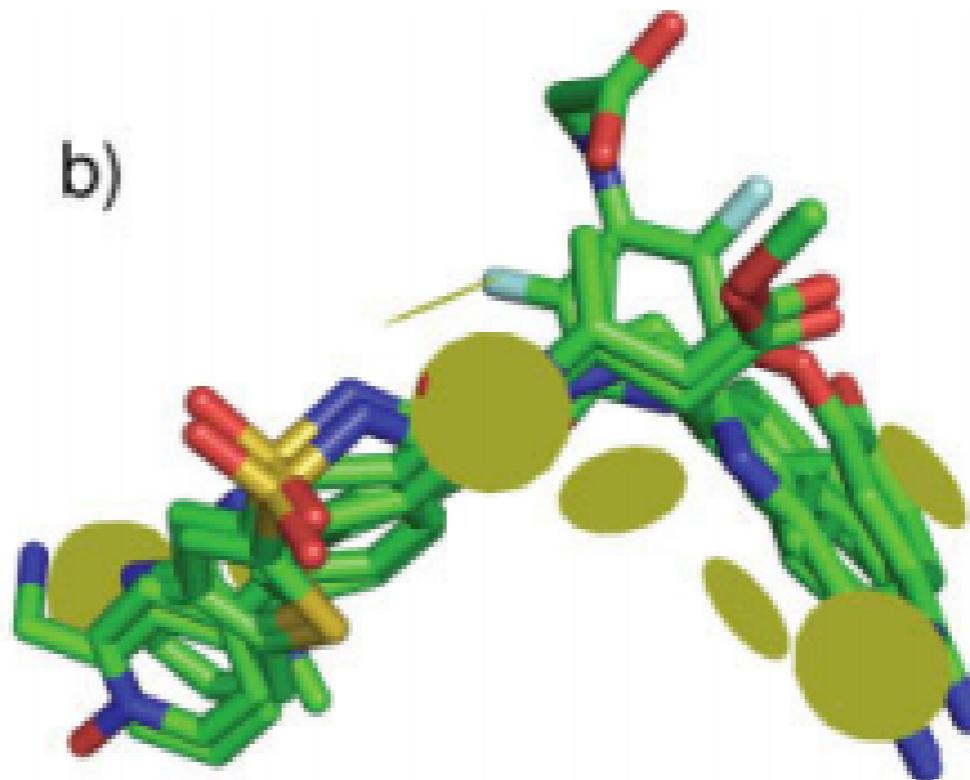


Shape comparisons can also be done using the surface of a molecule

a)



b)



ID and 2D searches are also common in ligand-based design

- ID -- often name-based or with various simple descriptors
 - Sometimes even better than 3D!
 - SMILES strings, pattern matching
- 2D -- based on functional groups
 - Bioisosteres
 - Chemical fingerprints

Ligand-based design also seems to perform fairly well for virtual screening

