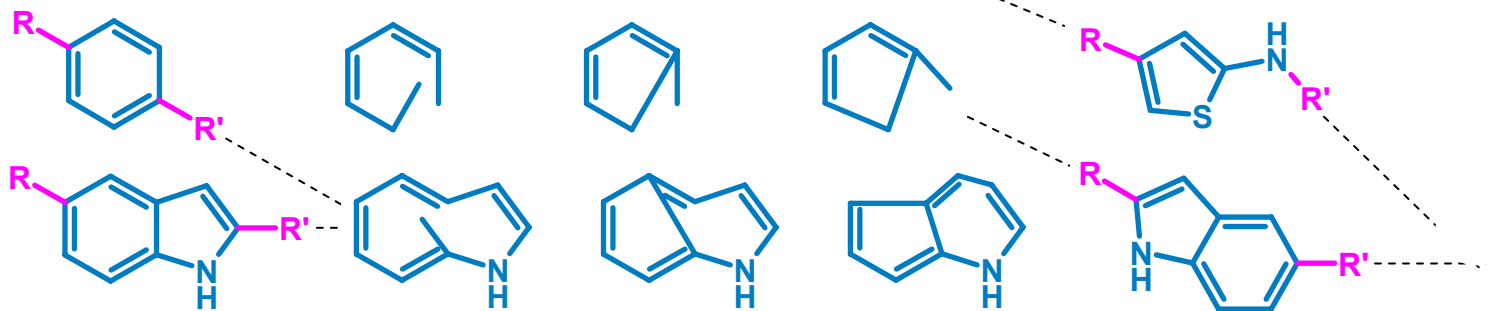


Topological reshuffling: A geometrically rationalized “me too” approach

... or a complex presentation of a simple principle



Eric Gaertner | Montpellier II

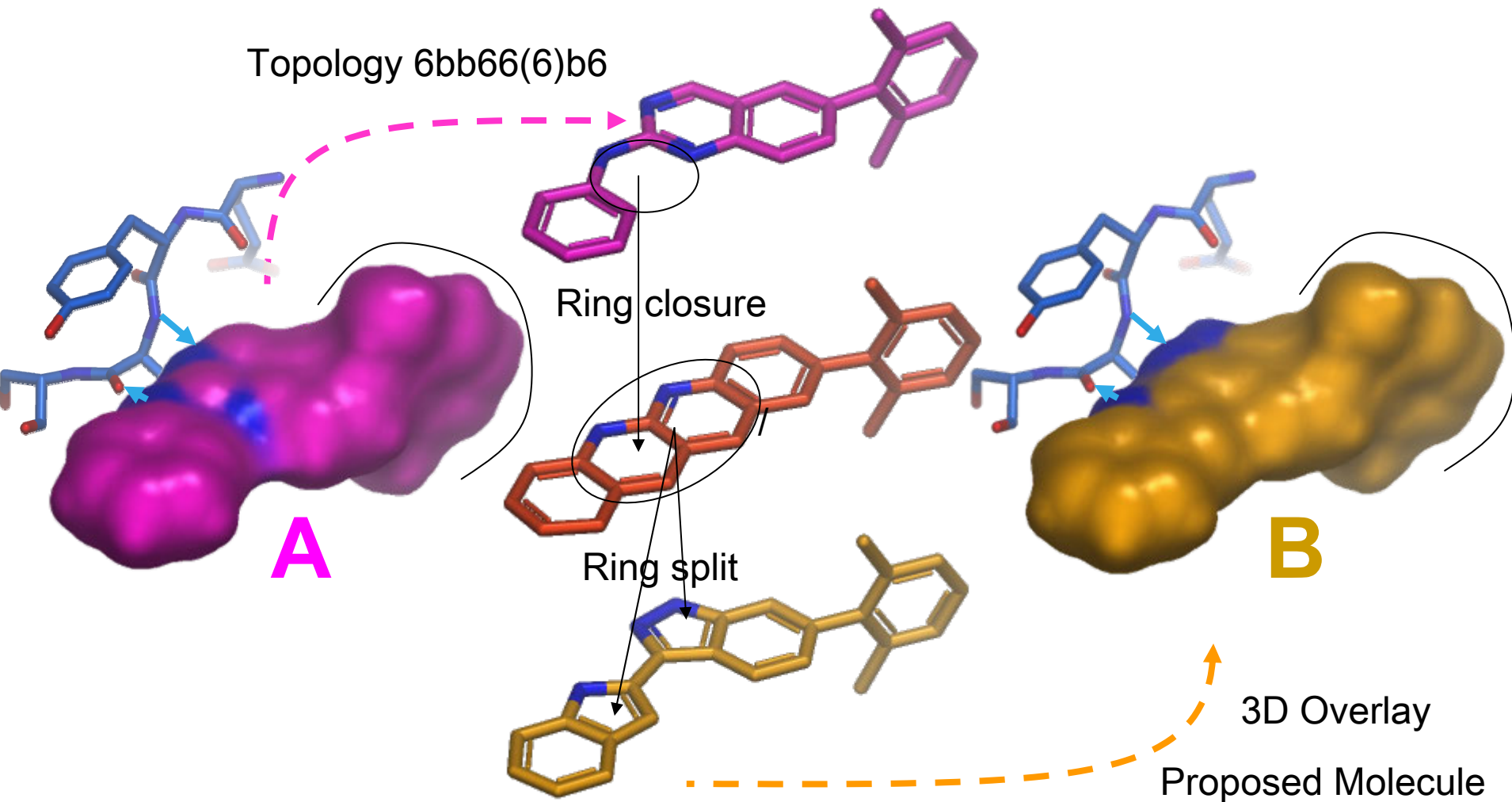
Arnaud Brendel | Paris VII

Frederico Nardi | Drug Design



~~PH4~~ => EP

Topological reshuffling principles



- 1) Identify elementary geometrical transformations that could keep similar overall shape
 - 2) Identify elementary projection rules that could keep identical interaction patterns
- => Maintain binding affinity with the target and modulate PhysChem or IP properties

Source of inspirations

Similar algorithms

- Using empirical Medicinal Chemistry transformations
- Using bioisostere databases

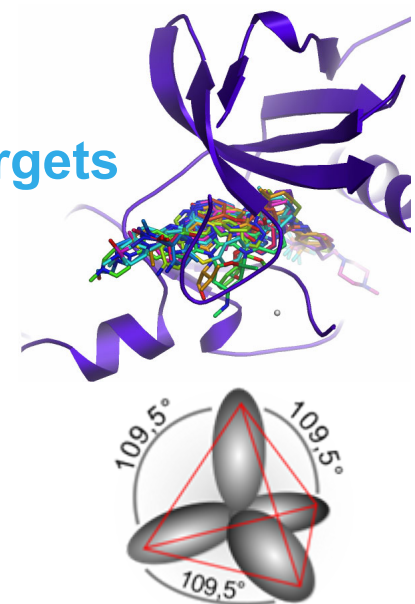
Literature on different chemical series designed for the same target

Comparison of overlaid Xray structures of related targets

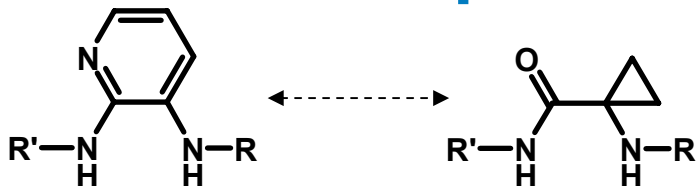
- Target families like PK SP HR ...

Graph / Path and Geometry

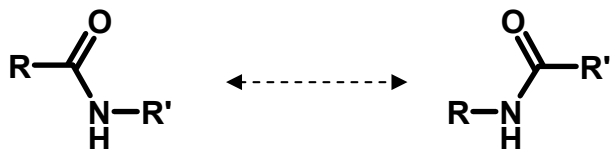
- Euclidian
- Orbital hybridisation / Geometry
 - └ linear planar & tetrahedral sp sp² sp³ relations



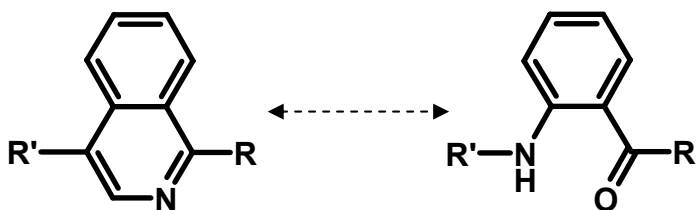
Some examples



BK1 FXa potent bioisosteres
H Zhao DDT 12 3 149 (2007)



Drug Guru / retro amide
K.D. Stewart Bio Med Chem 14 7011 (2007)



Ring opening

...same path same directionality...

AurA 2NP8 2W1C

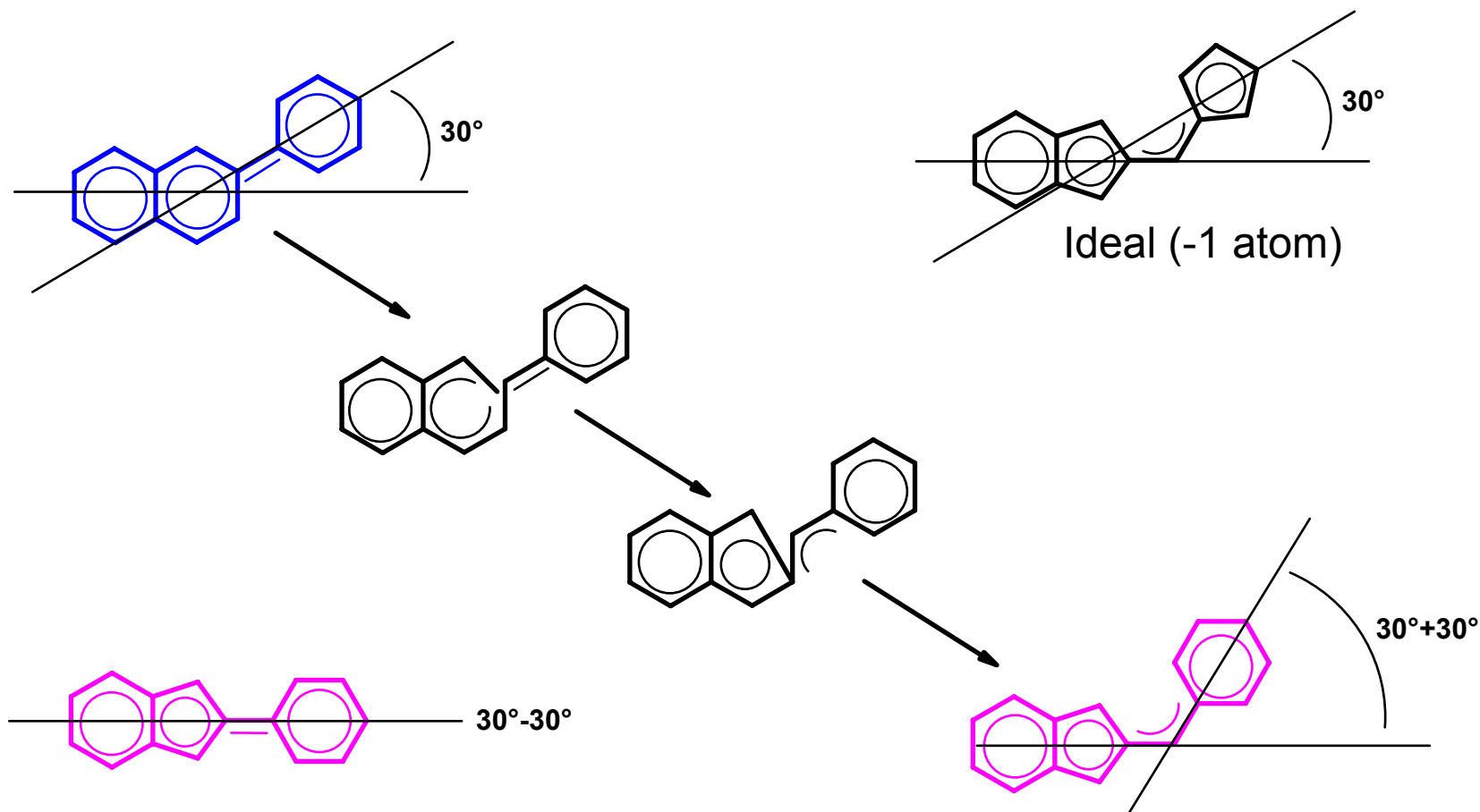
ABL dasatinib 2GQG
pd180970 2HZI

What could be the transformations?

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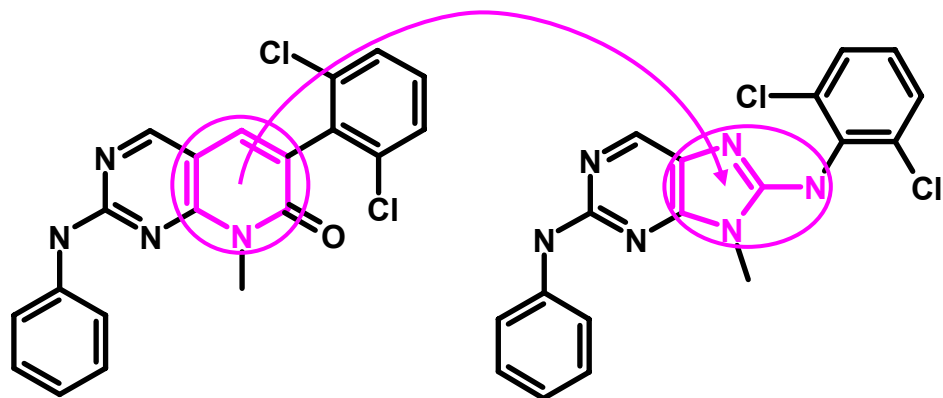
“ring 6” to “ring 5 + bond” transformation and its geometrical rationale



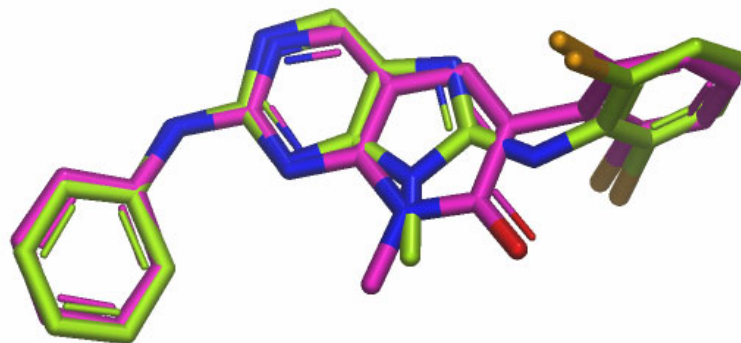
Rigid: R-groups usually not transferable (-1 atom)

Good approximation adding flexibility: R-groups usually transferable (+0 atom)

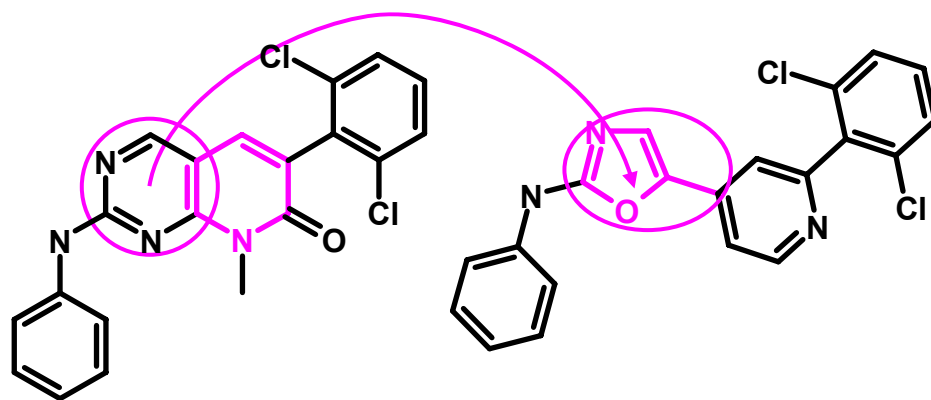
3D details of “6ring” to “5ring+bond” transformation



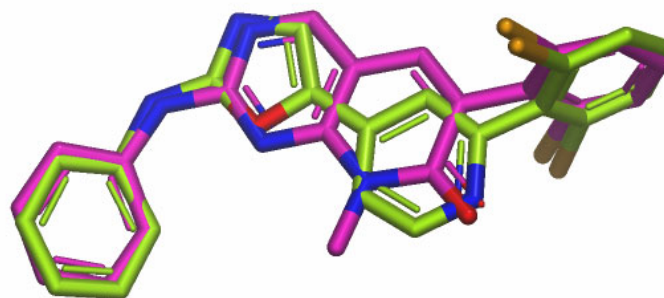
Parke Davis ABL 2G2H based on P38 2GTM



See 3D

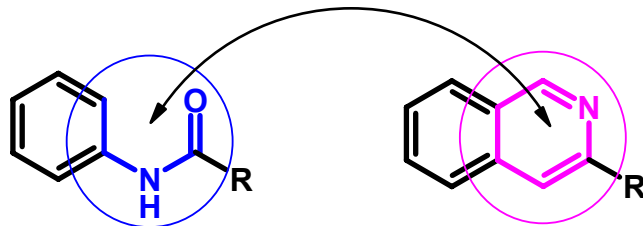


Parke Davis ABL 2G2H based on KDR 1Y6B

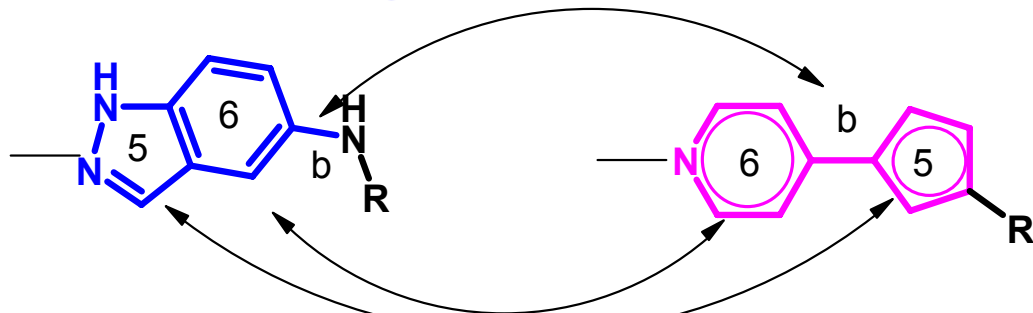


3 basic operations to be implemented

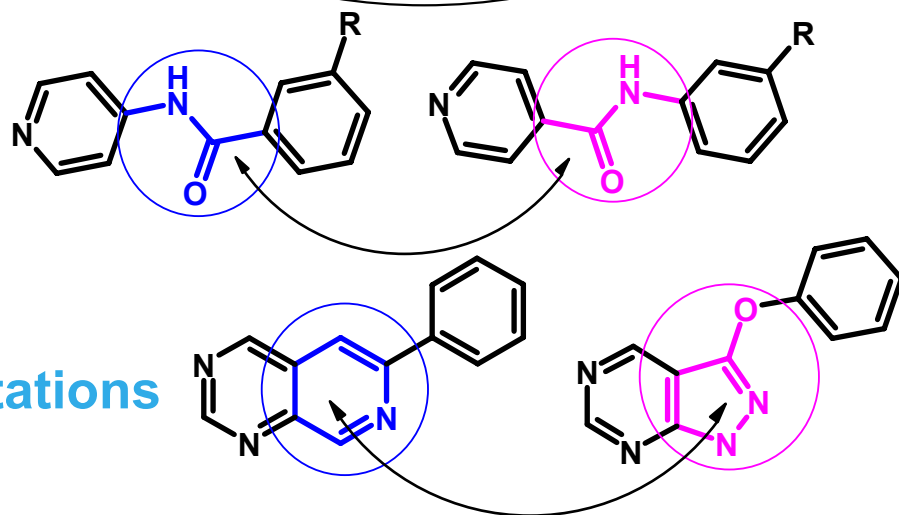
Ring opening / closing



“fragment” swap
or inversion



“ring^N” “ring^{N-1}+bond” mutations

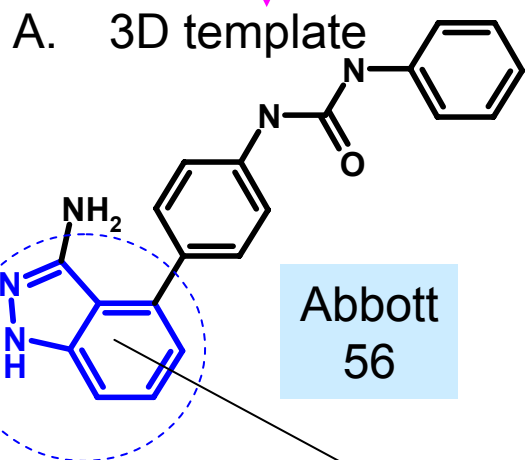


But are they canonical ?

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1st topological reshuffling algorithm



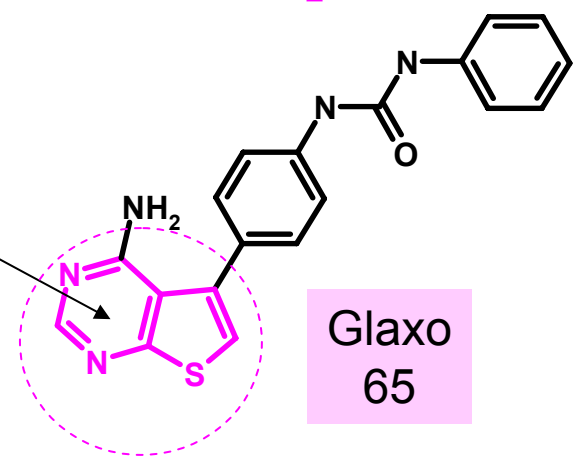
DB difficult to build

DB of explicit elementary 3D transformations

3D
Cut & Paste

Several iterations

B. transform to 3D shape and pharmacophores



1st Results, Problems & Solutions

3D cut & past done

- Fast without or with reduced FF minimization CPU time

3D database of transformation done

- Build manually or semi automatically (not always easy)
 - ┌ Needs 3D in, 3D out + replacement smart
- Potentially huge number of transformation
some db have 1-100 k fragments / entries of equivalent...

Anticipate huge combinatorial cost

- If we take the whole molecule as a template (original plan)

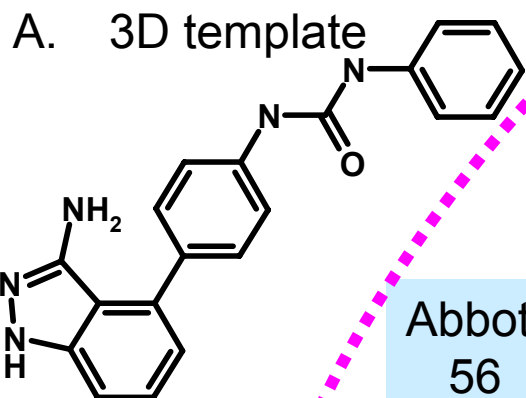
Urgent Need to reduce the number of transformations!

- Or focus into a small portion of the structure template (solution adopted by most de novo scaffold hopping algorithms)

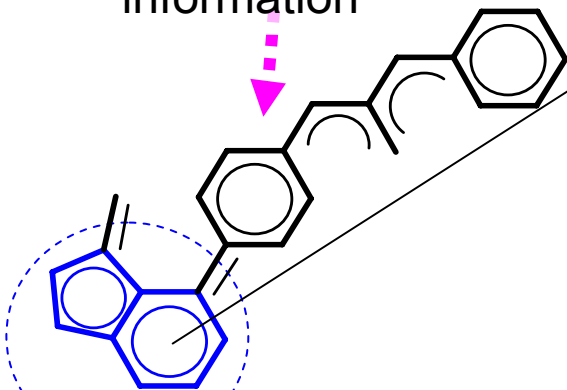
Solution: Increase the level of abstraction

- Divide 3D Chemistry space into 2 non “correlated” space
 - ┌ Geometrical space
 - └ Electrostatic properties space

Current Topological reshuffling algorithm



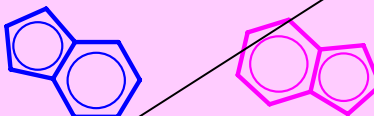
B. transform to 3D graph without hetero atoms but with atomic geometry information



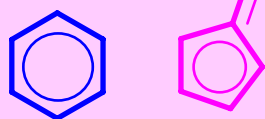
DB of implicit elementary 3D transformations



...

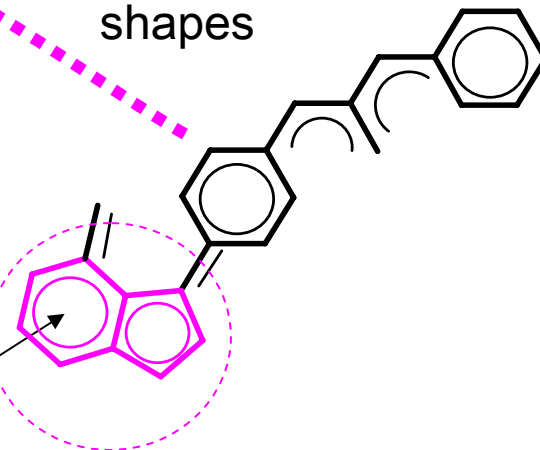


...

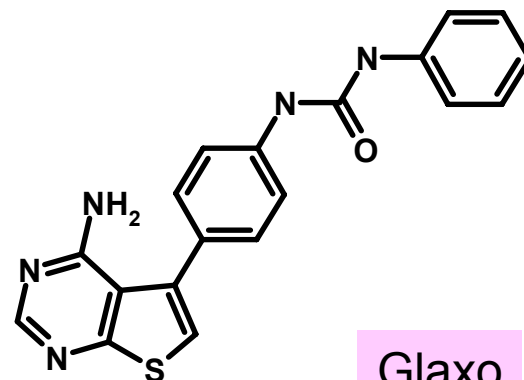


3D
Cut & Paste

C. propose new equivalent shapes



D. project hetero atoms compatible with PH4/ES

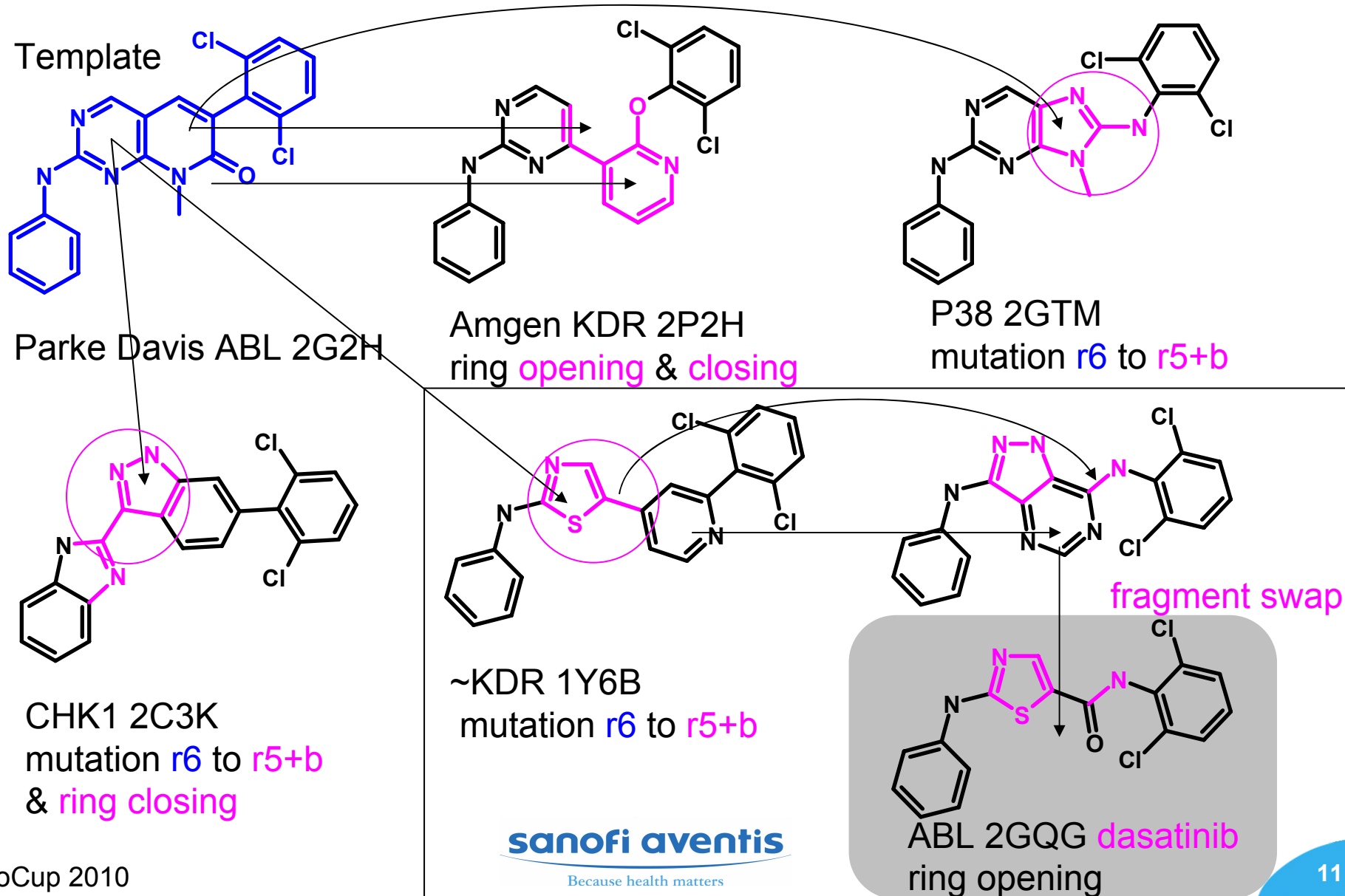


Glaxo
65

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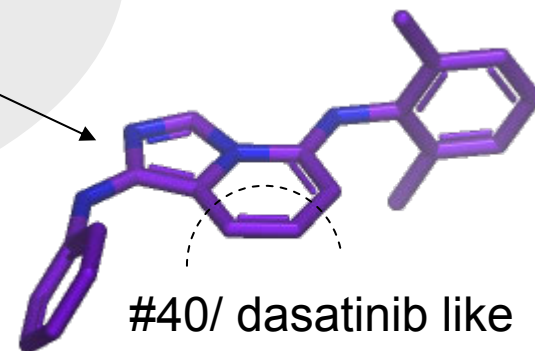
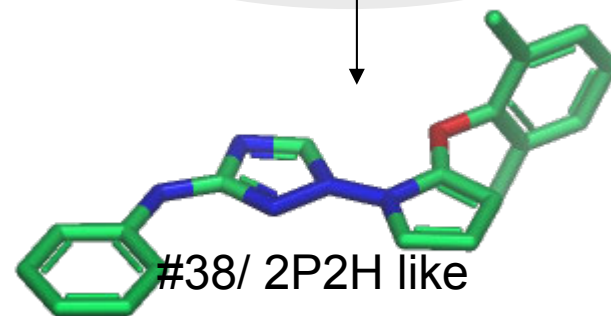
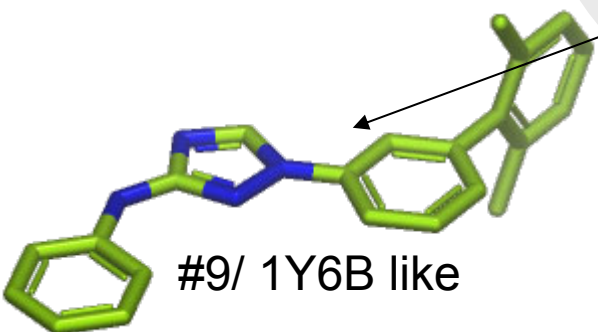
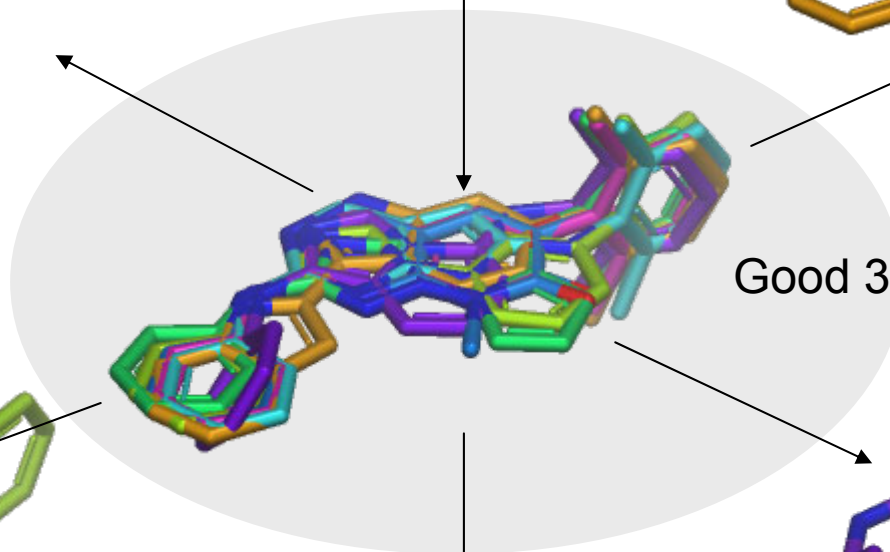
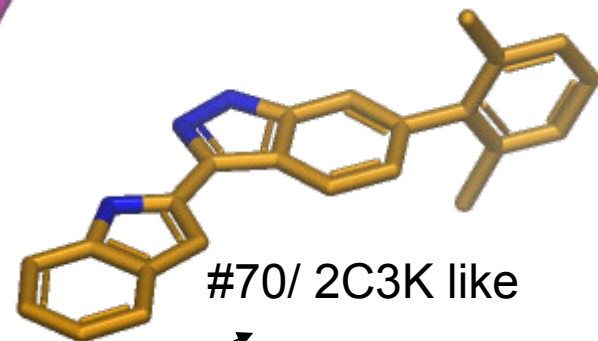
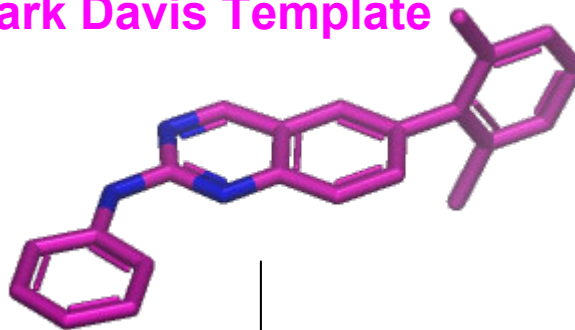
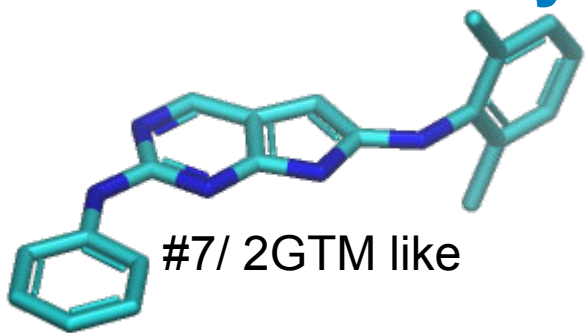
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Some examples of topological reshuffling from public Protein Kinase PDBs



**We are able
to reproduce them
Automatically**

Park Davis Template

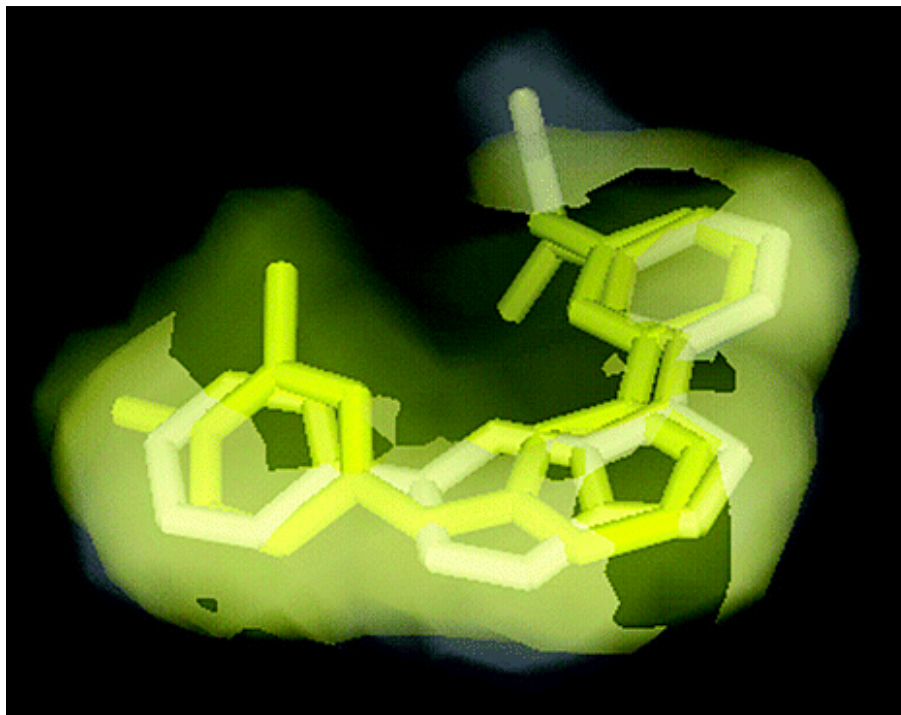


254 automatic proposals

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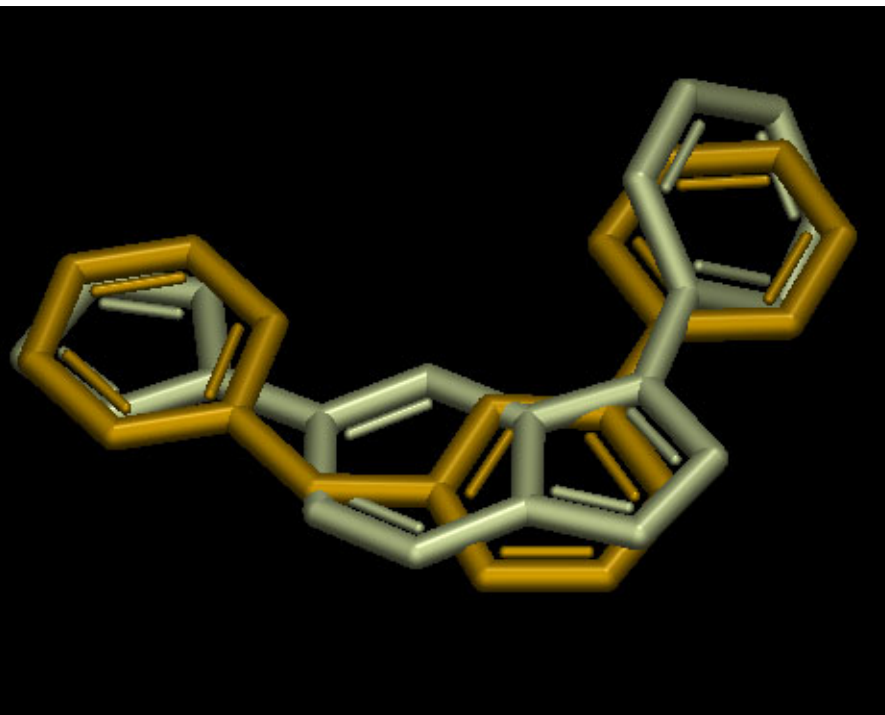
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ROCS as VS



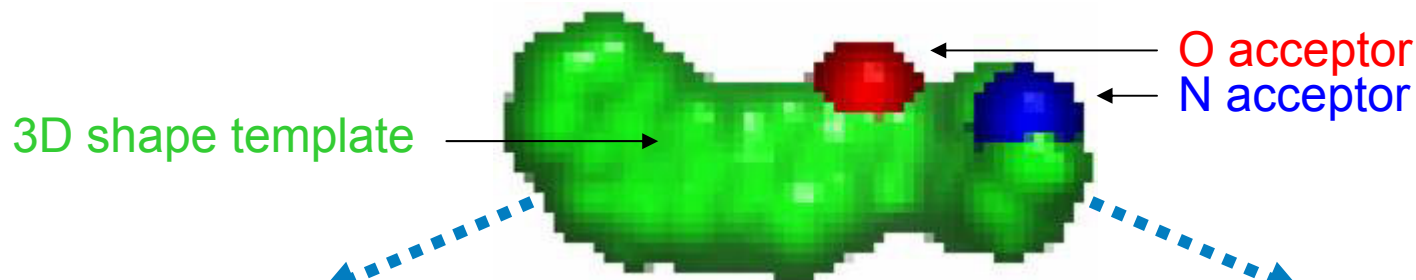
A Shape-Based 3-D Scaffold Hopping Method and Its Application to a Bacterial Protein-Protein Interaction
T.S. Rush III, J.A. Grant, L. Mosyak,
and A. Nicholls
J. Med. Chem. **48** 1489 (2005)

TopResh as de-novo



TopResh is able to reproduce this ROCS finding in seconds time scale
rank 7 out of 57 proposals
rank 3 after visual inspection
(remove trivial and absurd)

TopResh and ROCS used as VS scaffold hopping methods



Topological reshuffling

- 20 SSS templates
- 10000 virtual hits
- 500 active site docking filter
- 40 molecules screened
- 2 extremely potent new series equivalent to advanced series

several months manual process
CPU 2h

ROCS shape + PH4 point filters

- 1.3 G shape comparisons
- 2.6 M shape selected
- 58 k first filter N acceptor
- 5 k second filter O acceptor
- 500 hand selected
- 200 screened
- 4 extremely potent new series equivalent to advanced series

1 day semi automatic process
32 cores

~10nM Bio Chemical
~100nM Phenotypic
MW ~400

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TopResh is accessible at the mouse click on a 3D Drug Design eXchange Platform in D³XP using

1 Draw 2D

2 Load 3D

3 Sample conformations

Select a template

4 Run TopResh

Examine results

More to come

Extremely simple principle (still room for optimization)

- Implemented in SVL so far.

Encouraging results

- as de novo (at the finger tip accessible at D³XP web platform)
- as VS methods

Optimize projection of PH4 (will generate more chemistry friendly molecules)

Optimize process for automatic database nearest neighbors searches using generated molecules or scaffolds

Optimize scoring function (i.e. synthetic feasibility)

Acknowledgments

All chemists and biologists
whom kindly tested the
approach

- Dominique Damour
- Fabrice Vergne
- Pierre Perreaut
- Jean-Robert Labrosse
- Samir Jegham
- Xavier Canat
- Monsif Bouaboula

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suggestions and supports

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- Jean-Marie Bernassau
- Thierry Pages