infiniSee

BioSolveIT
expect actives!

Christian Lemmen

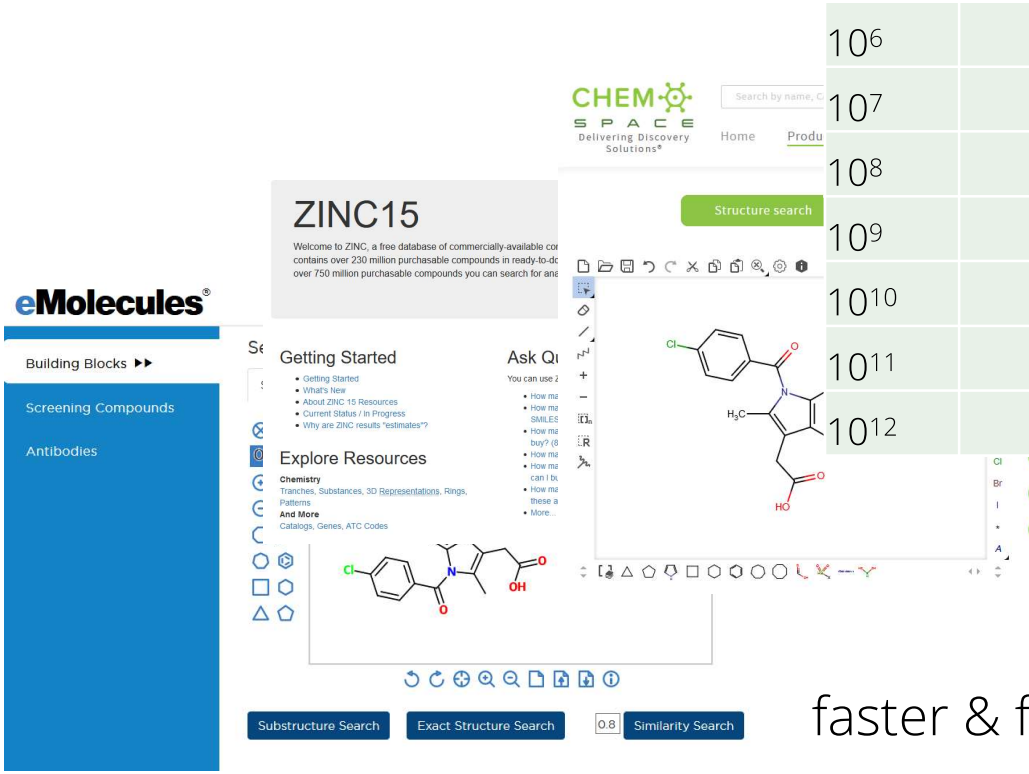
Efficient 3D exploration of multi-billion compound spaces

Stop searching – start discovering

Libraries The Classical Way

- Enumeration of XXL-libraries requires
  - loads of memory – particularly for 3D conformers
  - special hardware and/or significant processing time

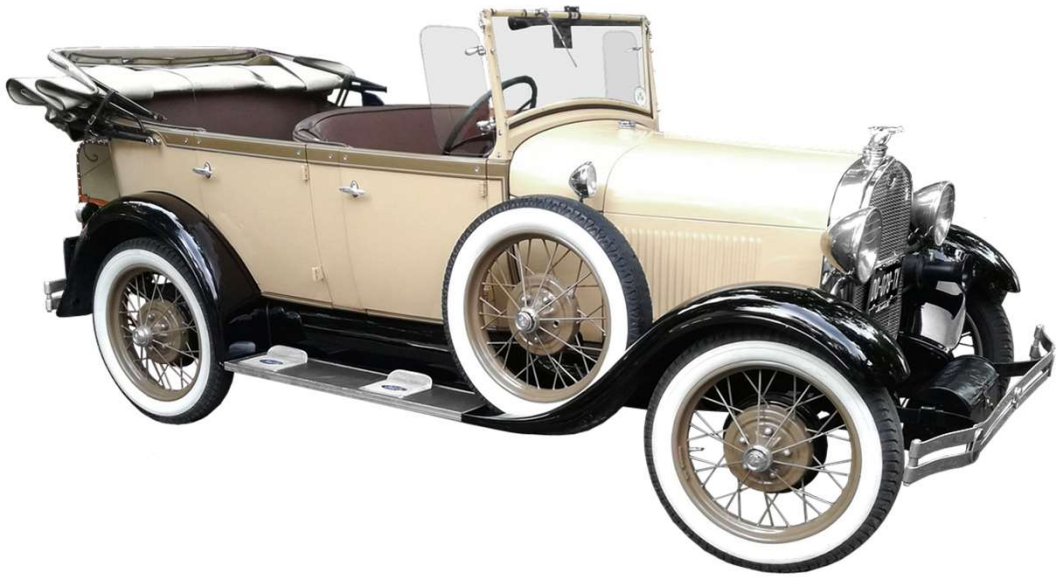
10^6	1.000.000	3,8 MB	1 sec
10^7	10.000.000	38 MB	10 sec
10^8	100.000.000	380 MB	1,7 min
10^9	1.000.000.000	3,8 GB	17 min
10^{10}	10.000.000.000	38 GB	2,8 hrs
10^{11}	100.000.000.000	380 GB	28 hrs
10^{12}	1.000.000.000.000	3,8 TB	12 days



faster & faster & faster…

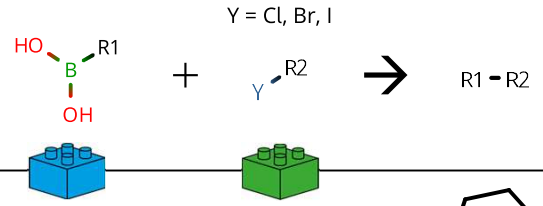
*"If I had asked my customers what they wanted, they would have said **faster horses**"*

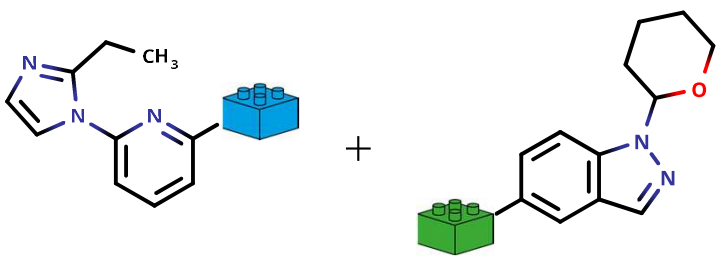
- Henry Ford

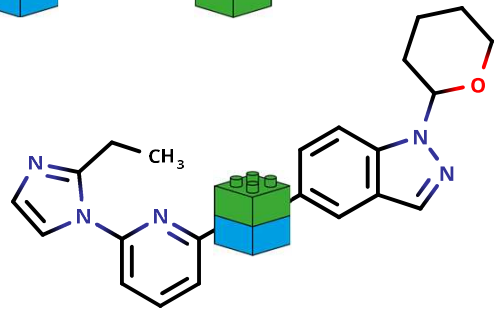


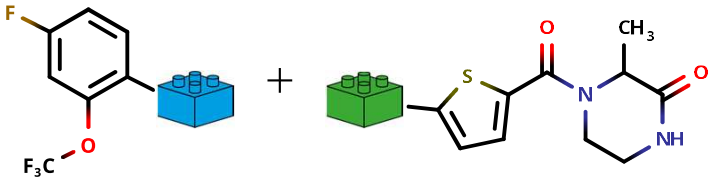
Our “Idea” of a Car

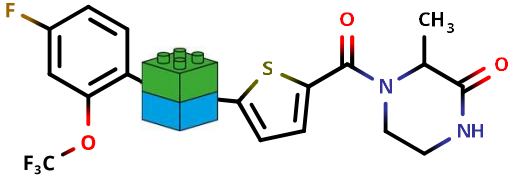
Reactions, e.g. Suzuki coupling:

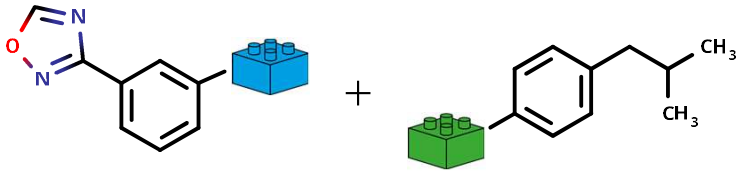


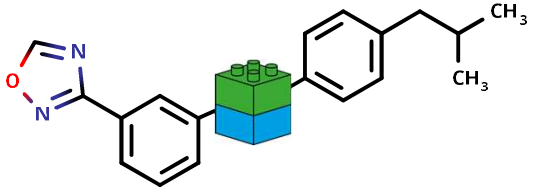






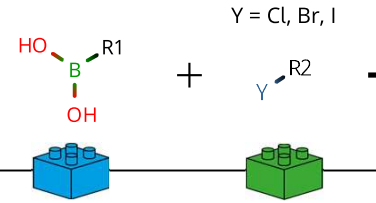


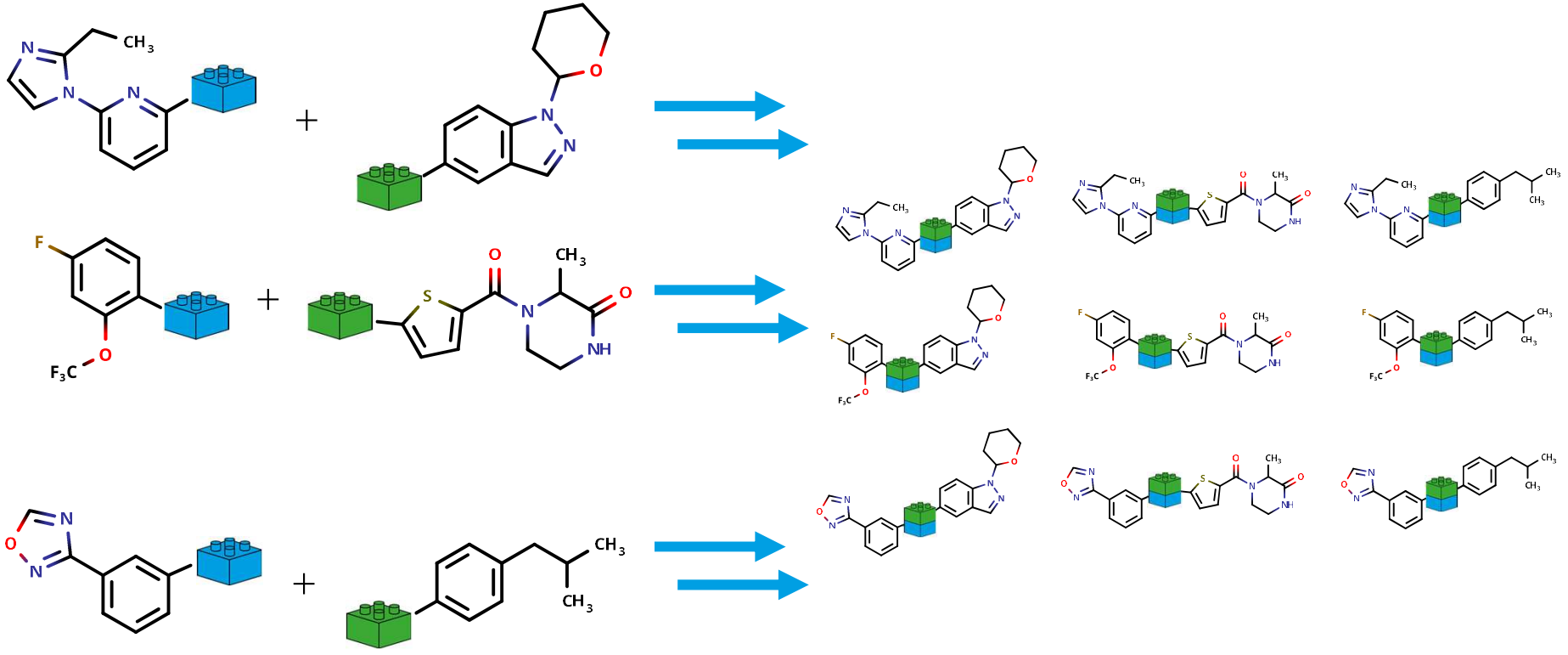




Our “Idea” of a Car

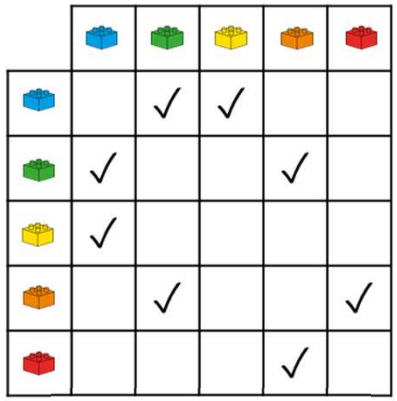
Reactions, e.g. Suzuki coupling:



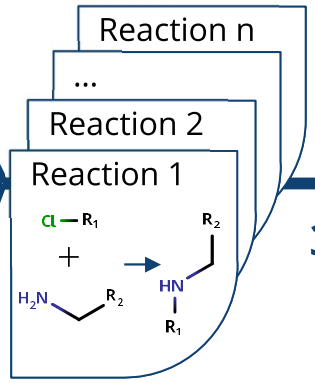


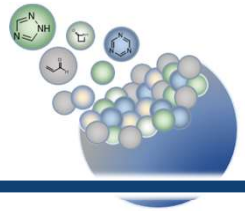
Multiple Reactions → Chemical Space

1. chemistry know-how

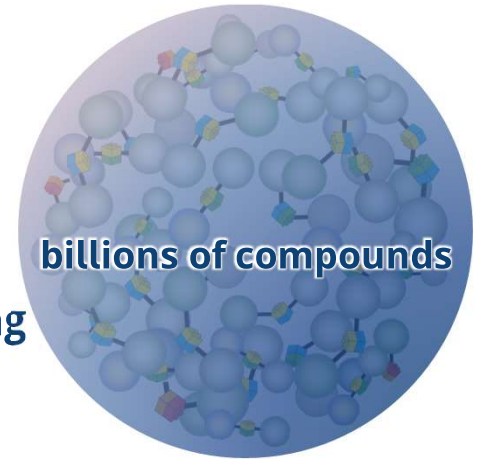


compatibility

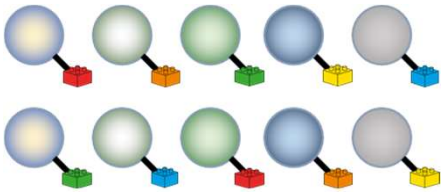




3. preprocessing



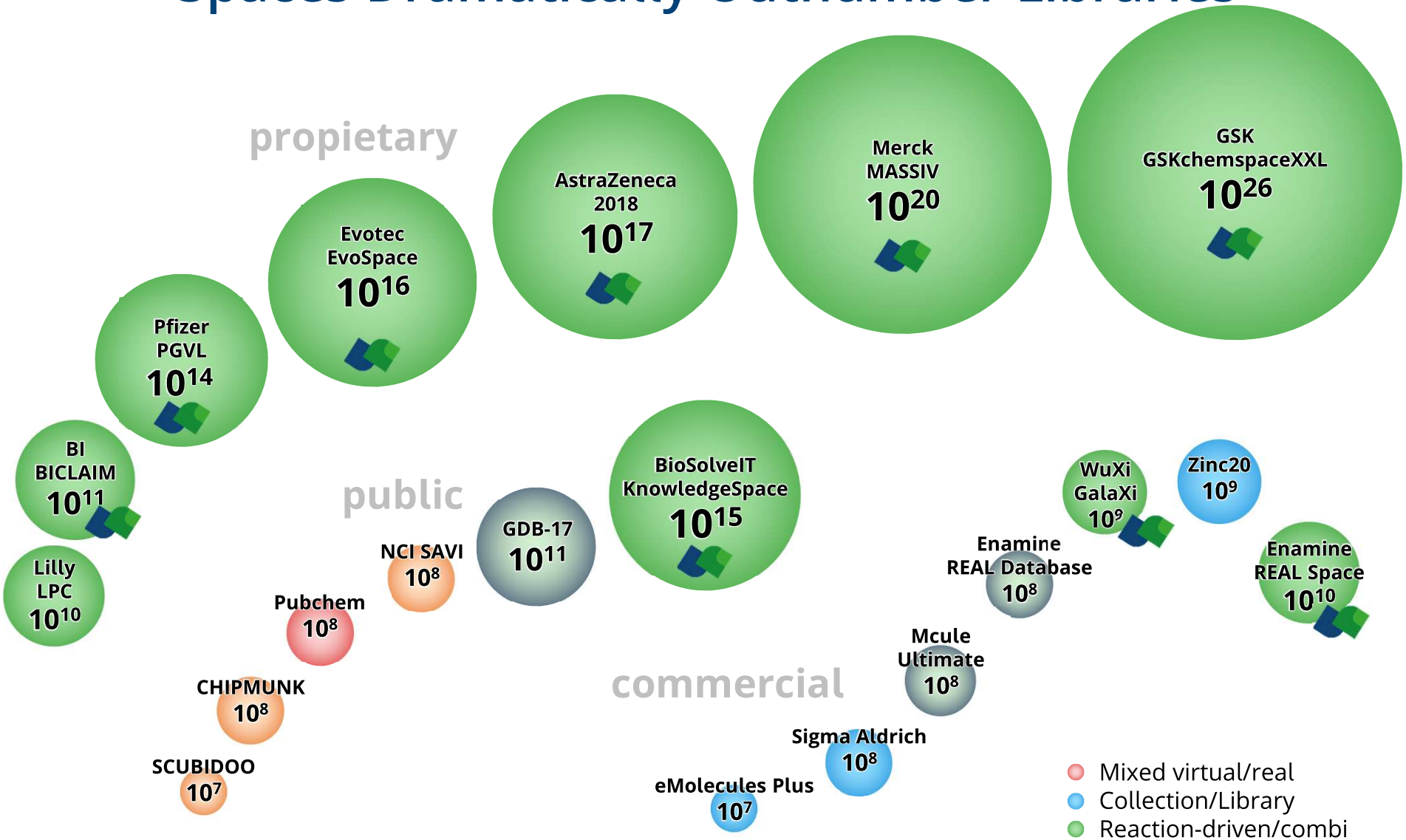
chemical space



...

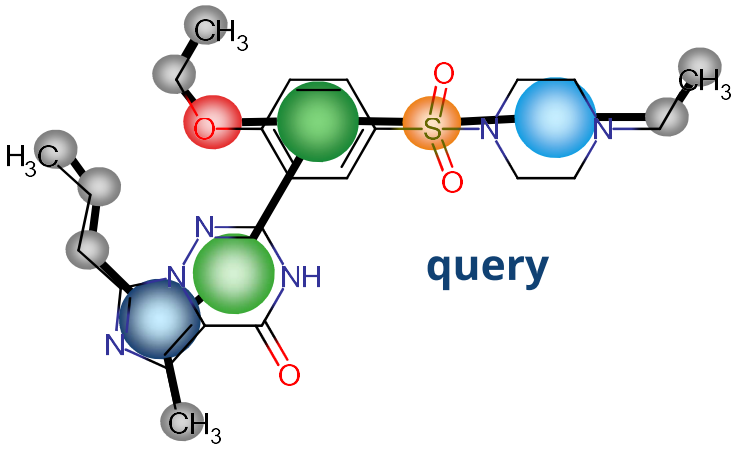
2. building blocks

Spaces Dramatically Outnumber Libraries

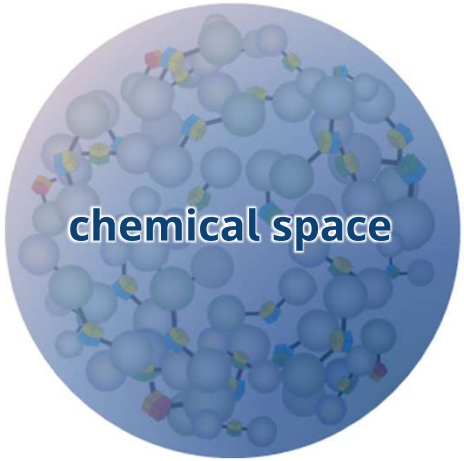


*Hoffmann, Gastreich, DDT, 2019, 24(5), 1148-1156

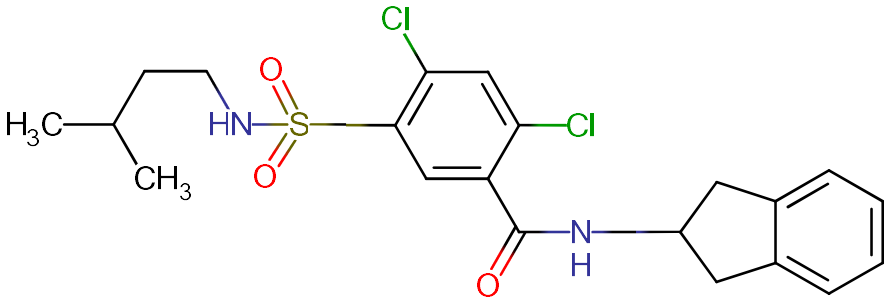
Similarity Searching without Enumeration



query



Dynamic Programming Algorithm

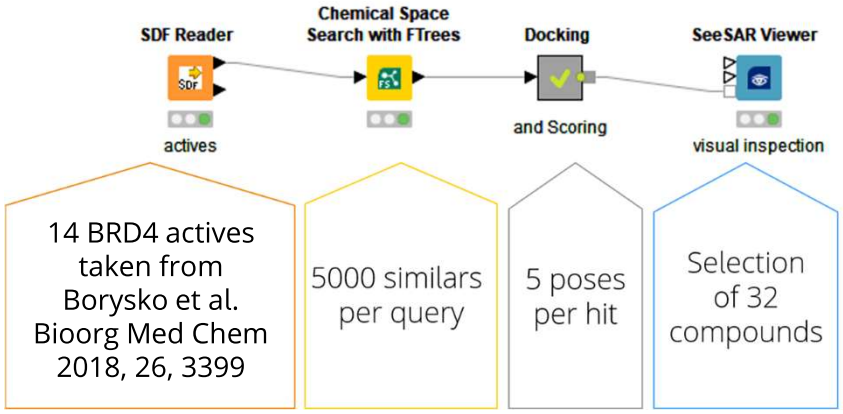


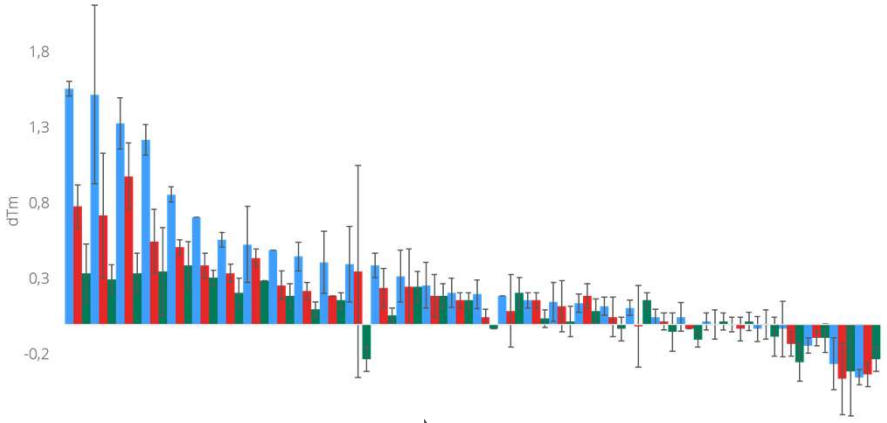
Rarey et al, JCAMD 2001, 15, 497

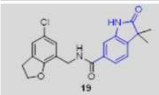
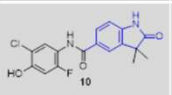
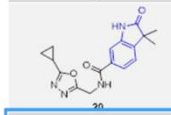
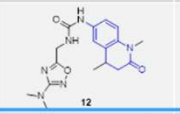
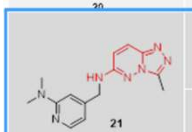
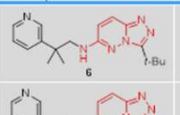
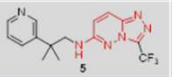
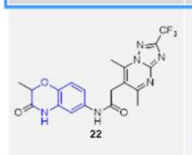
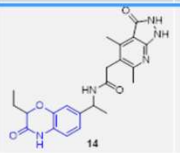
From Krier & Klingler, curious2018 Darmstadt, Germany

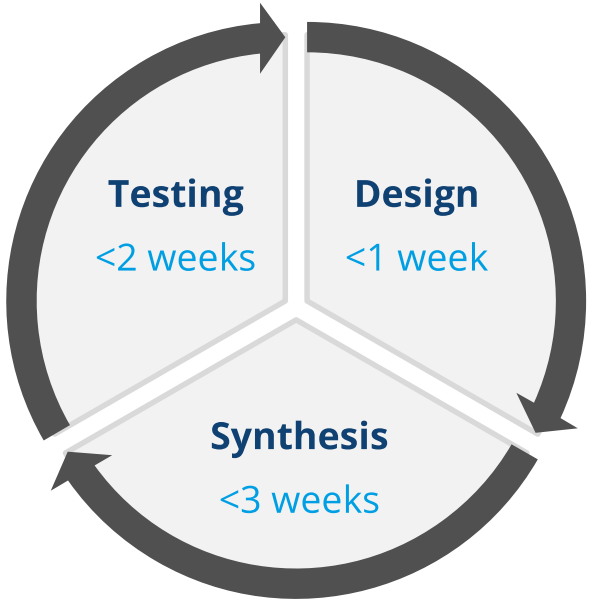
Similarity Searching + 3D Works

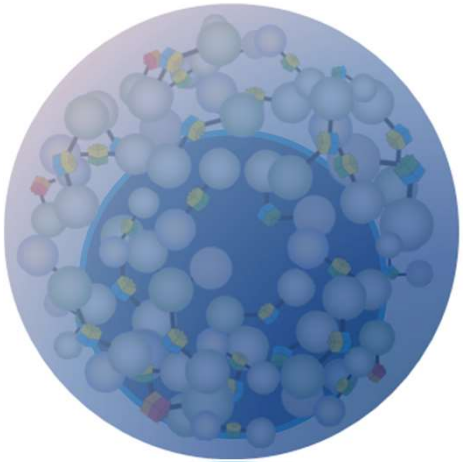
Klingler et al, *Molecules* **2019**, 24(17), 3096





Query	Hit	Tanimoto sim	FTrees sim	ΔT_m (@40µM)	IC_{50} (µM)
		0.456	0.956	0.7	10
		0.277	0.920	1.5	26
		0.323	0.933	1.3	44
		0.333	0.953	1.5	68
		0.356	0.932	0.5	141

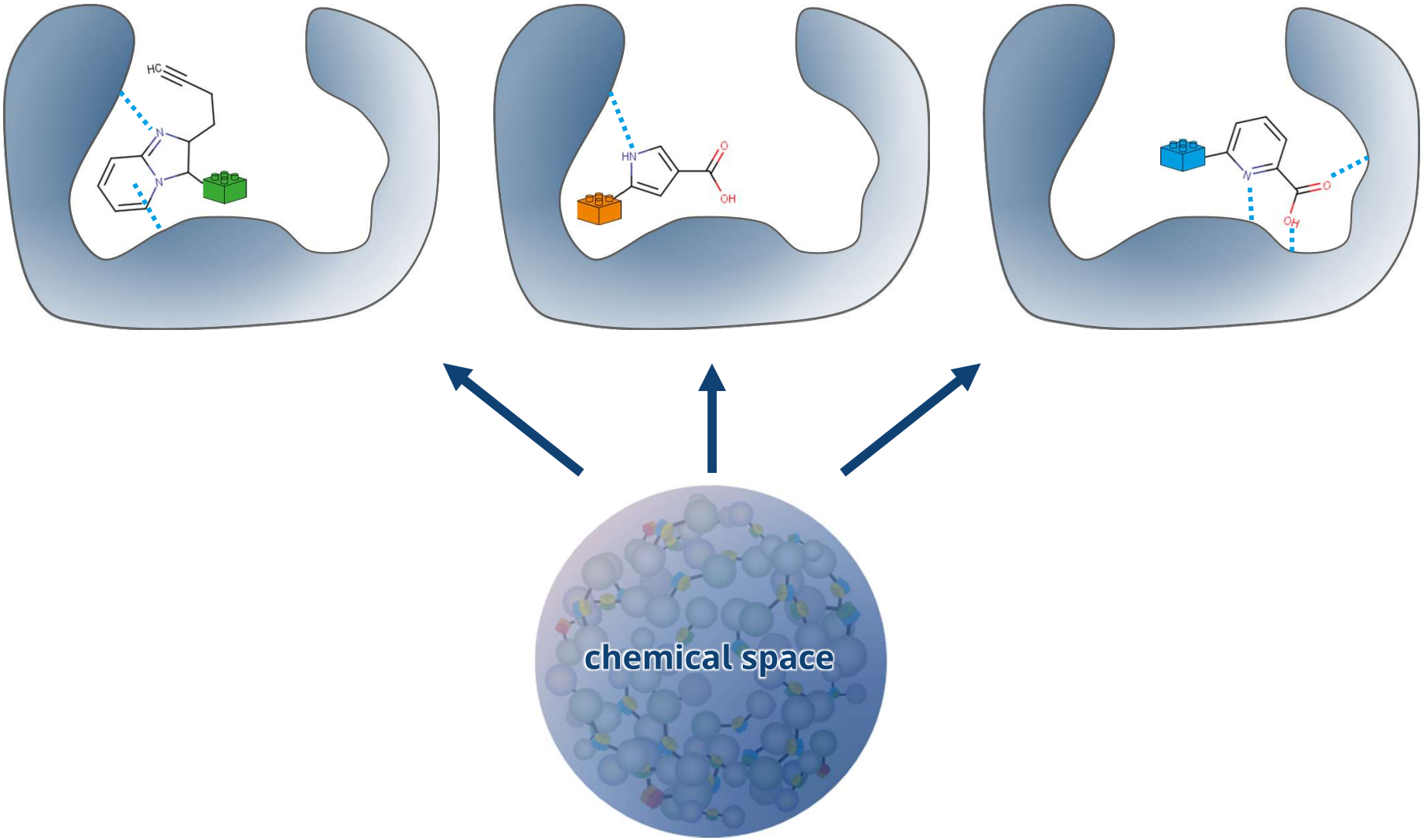




Can we use these vast resources also directly in 3D-structure-based design?

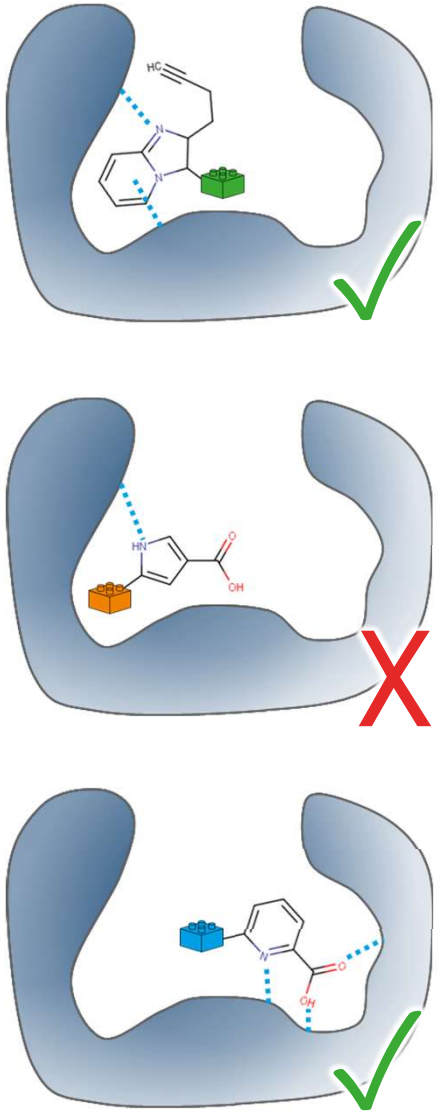
→ Chemical Space Docking

Building Block Placement

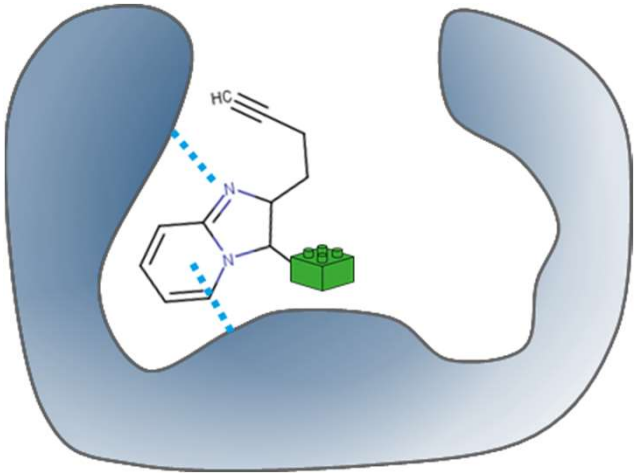


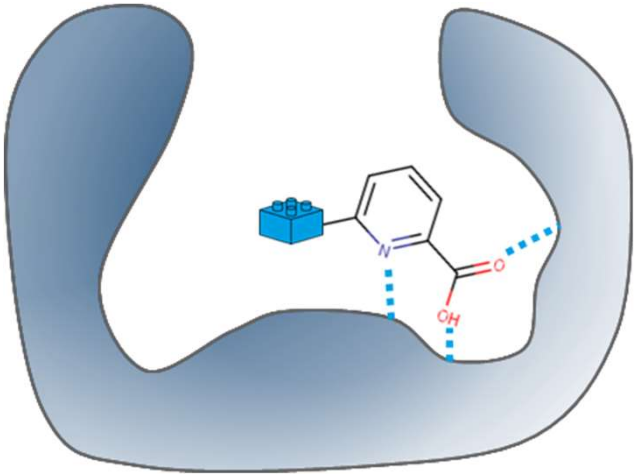
Building Block Filtering

- Automated
  - unwanted linker positions
  - low scores
  - few interactions
- Manually
  - pharmacophores
  - unspecific binding



Combinatorial Expansion



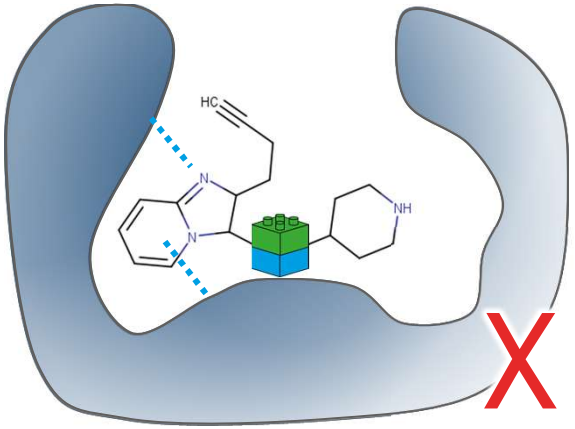


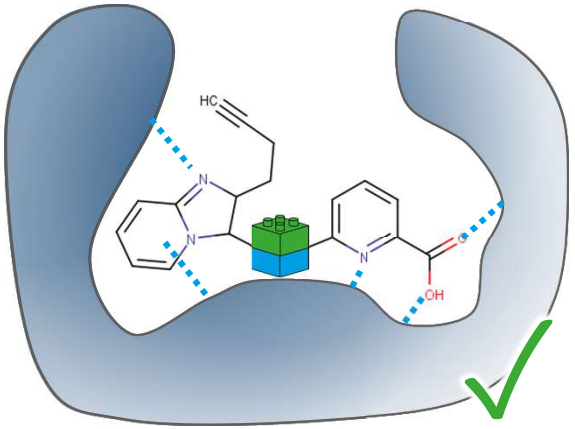
		✓	✓		
	✓			✓	
	✓				
		✓			✓
				✓	

compatibility

- Enumerate libraries with compatible reagents for chosen fragments

Placement and More Filtering





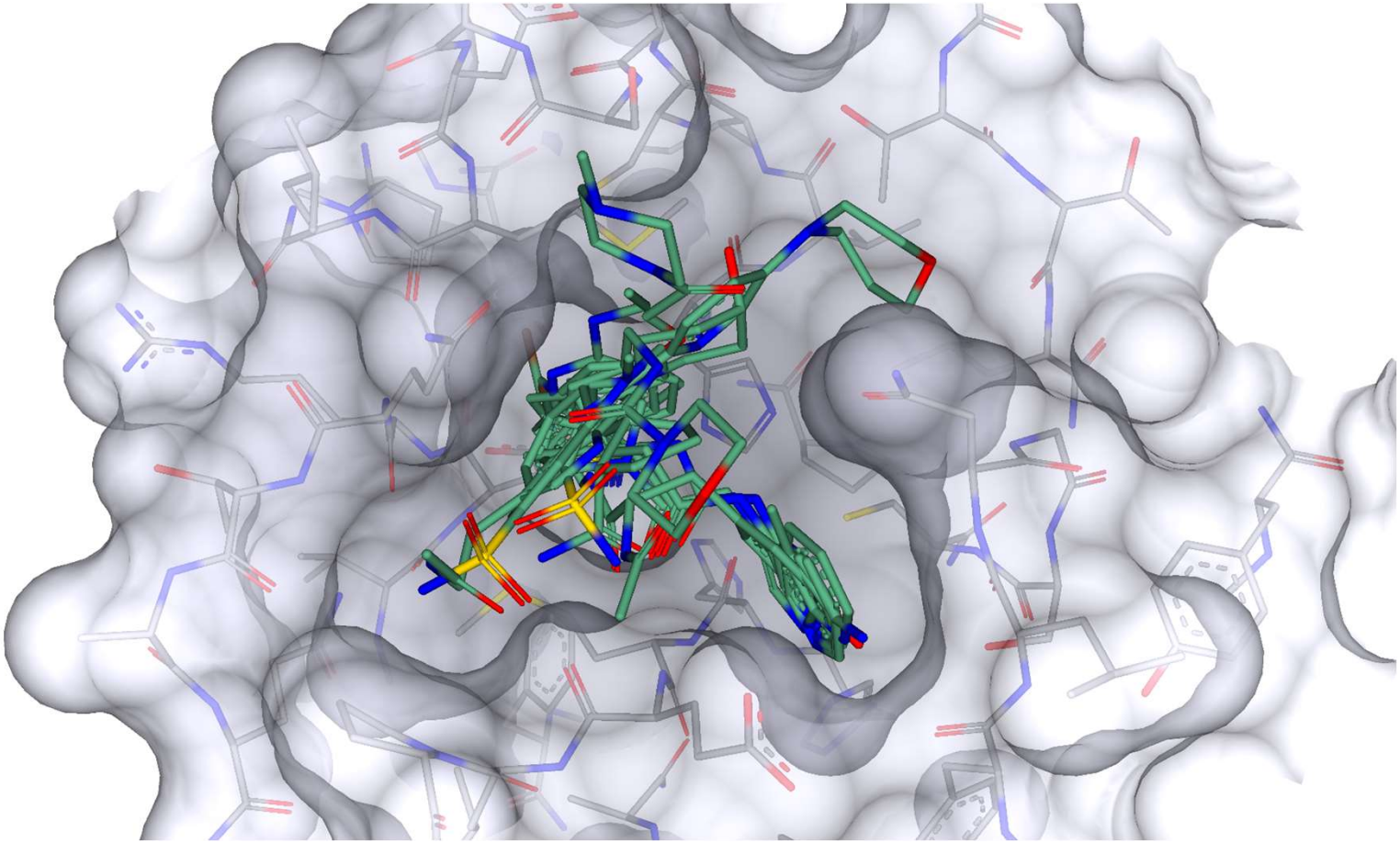
Template-based Docking:

- Fragment from step 1 stays in place
- Added reagent is flexibly attached

- 2nd round of filtering and eyeballing to extract the top of the list

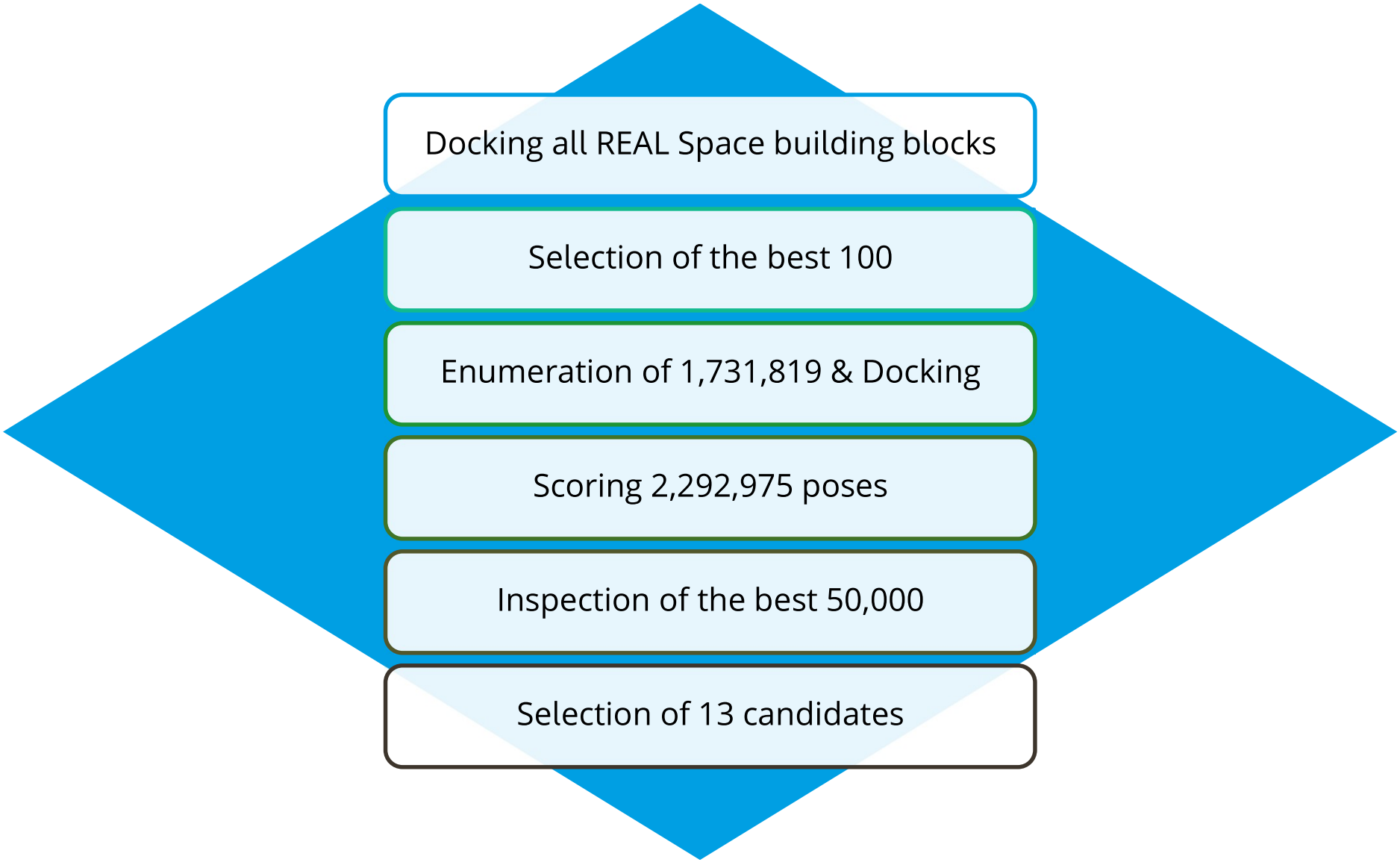
SARS-CoV-2 main protease (M^{pro})

- Starting point: 17 non-covalent crystal structures by X-Chem

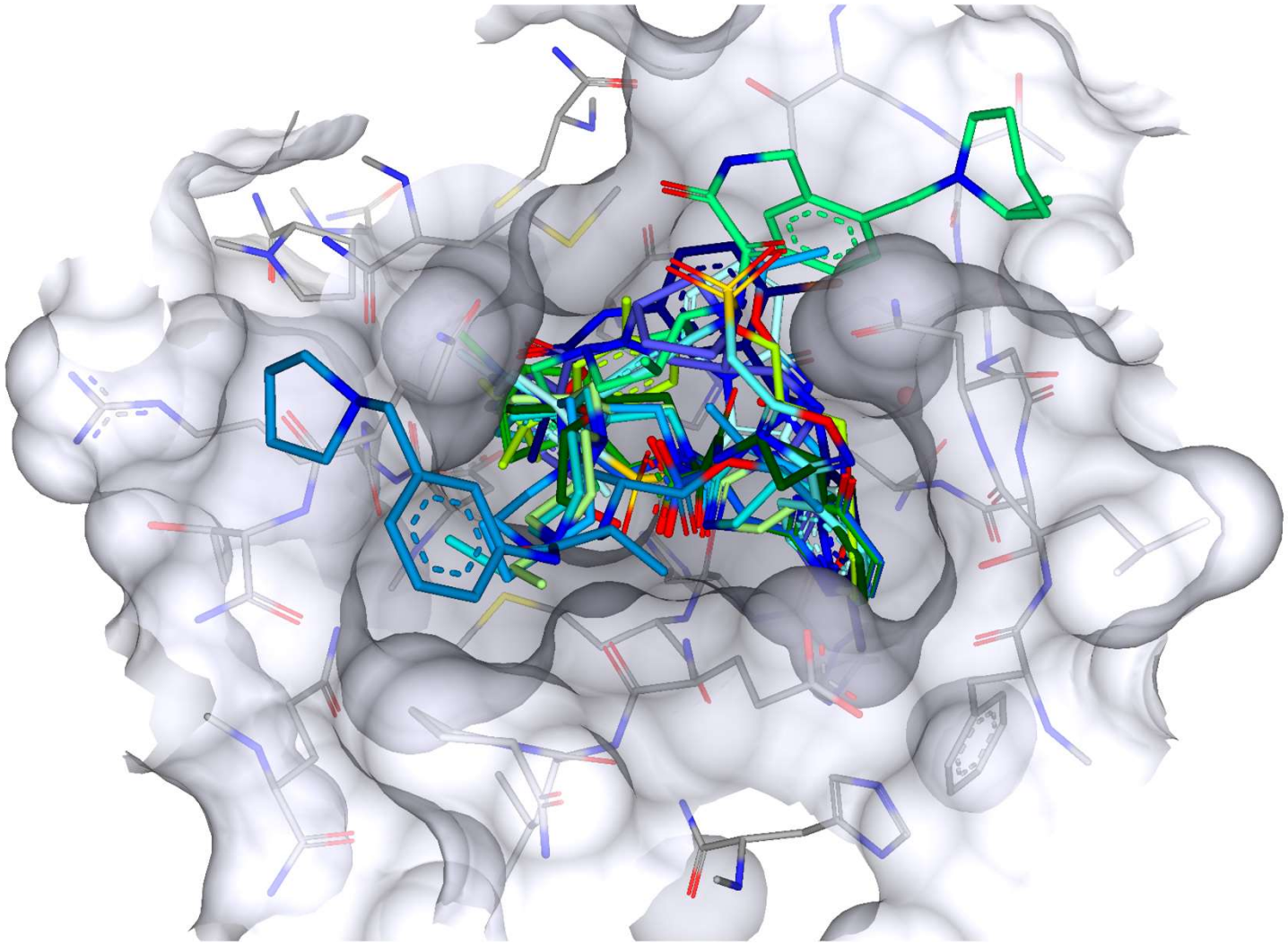


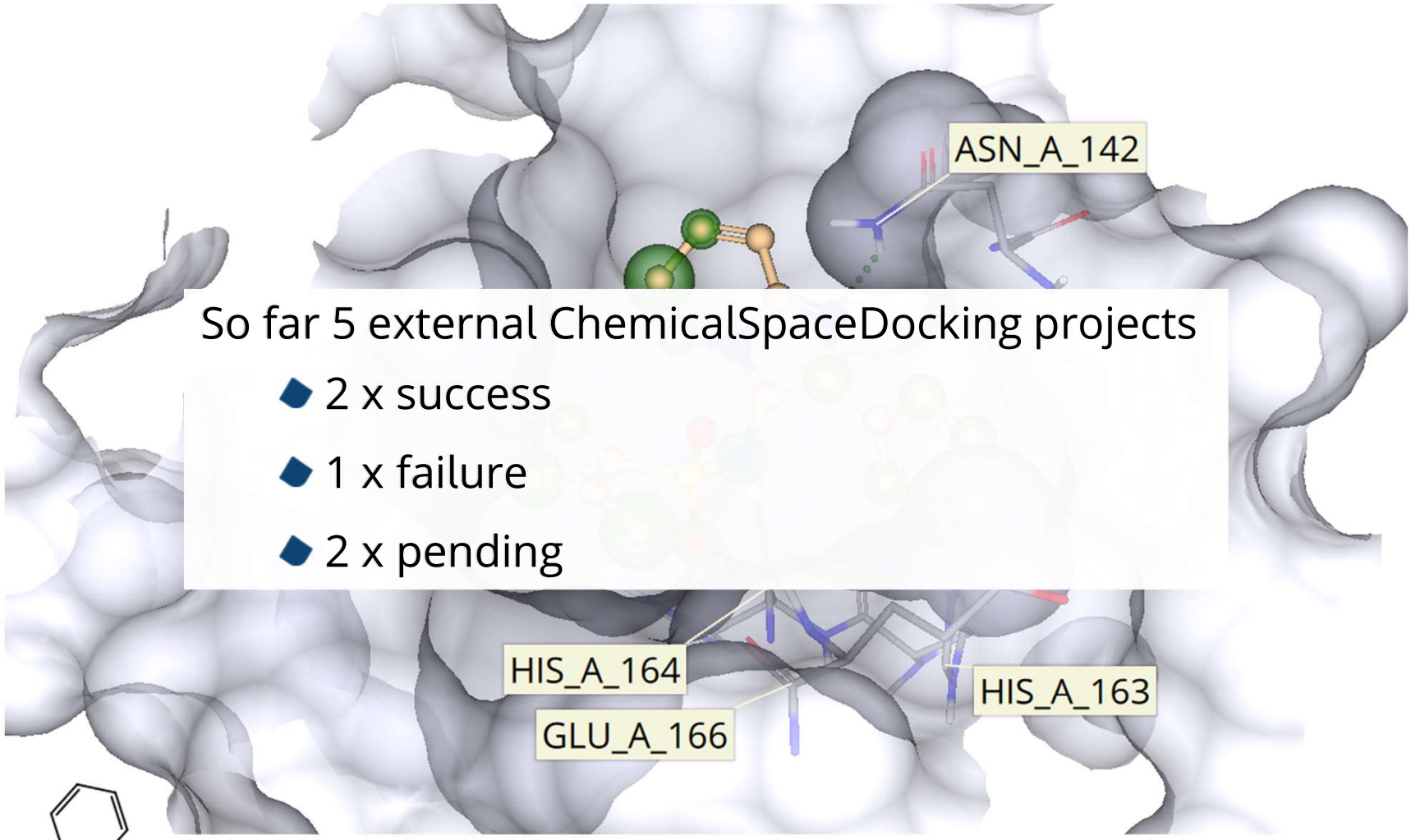
https://covid.postera.ai/covid

Chemical Space Docking Workflow



Candidates





So far 5 external ChemicalSpaceDocking projects

- 2 x success
- 1 x failure
- 2 x pending

s232682__6950814__3005078

Unique Advantages of this Approach

- Explores billions of compounds via docking
- Virtual hits become real: e.g. through Enamine or WuXi
- Saves a lot of time and money

The Future – What's in it for me?

More & bigger Spaces
Chemical Similarity, Substructure & 3D Searching

Interested? – Join the Chemical Space Club!

- Keep in touch with the key players
- Discussions & presentations
- Early announcements
- linkedin.com/groups/9004052/