Handling large chemical spaces in Structure-Based Drug Design

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Ninth Joint Sheffield Conference on Chemoinformatics

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References to "FY" in this presentation for periods prior to 1 January 2018 are to the 12-month periods commencing in each case on April 1 of the year indicated and ending on March 31 of the following year, and the 9 month period from April 1 2017 to December 31 2017. From January 1 2018 the Company changed its fiscal year to the 12-month period commencing in each case on January 1. References to "FY" in this presentation should be construed accordingly.

Outline

1. Introduction
2. Generative Design of A2A ligands
3. Mol2Synthon: Make synthons from Enamine REAL
4. Gabby: Genetic Algorithm of building blocks
5. SynthonConnect: Join synthon poses
6. Generative Design of Enamine REAL molecules

1

Introduction

Sosei Heptares GPCR Structure-Based Drug Discovery Company

Delivered 25+ pre-clinical candidates, produced 10+ clinical candidates

>6 new pre-clinical candidates expected in the next 2 years for internal and collaboration programs

R&D CENTRE
CAMBRIDGE, UK (Heptares)

~170 EMPLOYEES

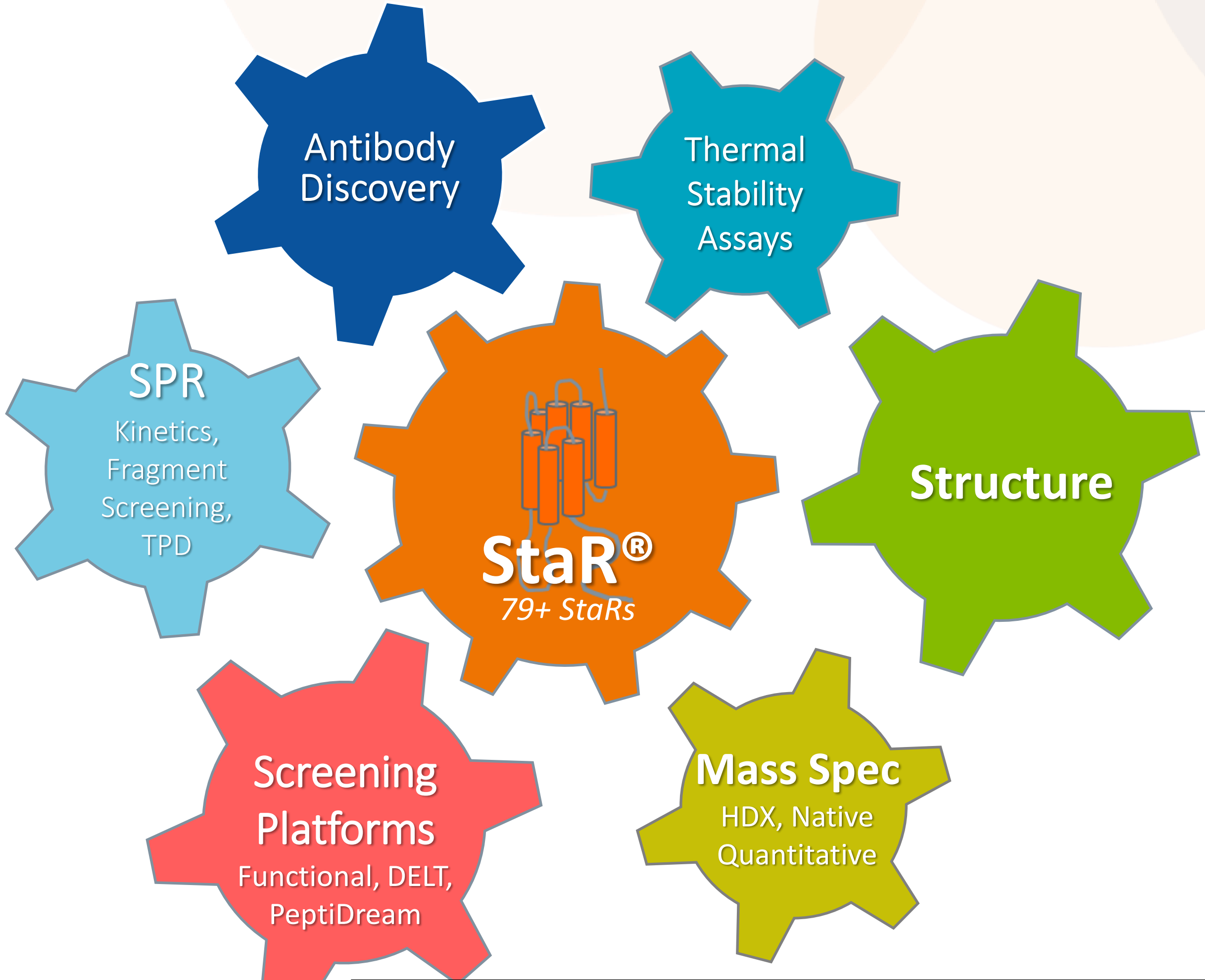
HEADQUARTERS
TOKYO, JAPAN (Sosei K.K.)

~25 EMPLOYEES

DRUG DISCOVERY/EARLY DEVELOPMENT DRIVEN BY STAR® / SBDD ENGINE					LATE STAGE DEVELOPMENT	
PRE-DISCOVERY	DISCOVERY	PRECLINICAL	PH 1a	PH 1b	PH 2/3	APPROVAL
StaR® Technology Structure Hit ID Target Validation ✓	**Structure Based Drug Design** Chemistry Pharmacology ✓	DMPK Toxicology Translation ✓	SAD MAD Experimental Medicine ✓	Dosing assessment Proof of Mechanism ✓	Tactical development team sources global tx for Japanese patients	
					PMDA Clinical Efficacy ✓	PMDA Pharmacovigilance ✓

Programs advanced to PoM or PoC before partnering / seeded into co-owned investment vehicles

StaR® Technology enabling GPCR Structure-Based Drug Discovery



Antibody Discovery

Thermal Stability Assays

SPR
Kinetics, Fragment Screening, TPD

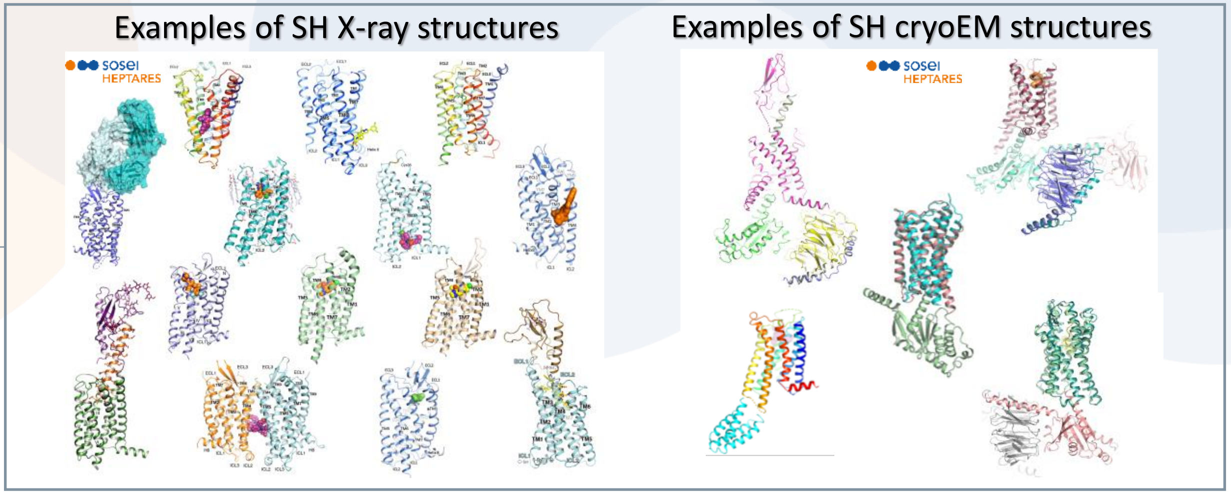
StaR®
79+ StaRs

Structure

Screening Platforms
Functional, DELT, PeptiDream

Mass Spec
HDX, Native Quantitative

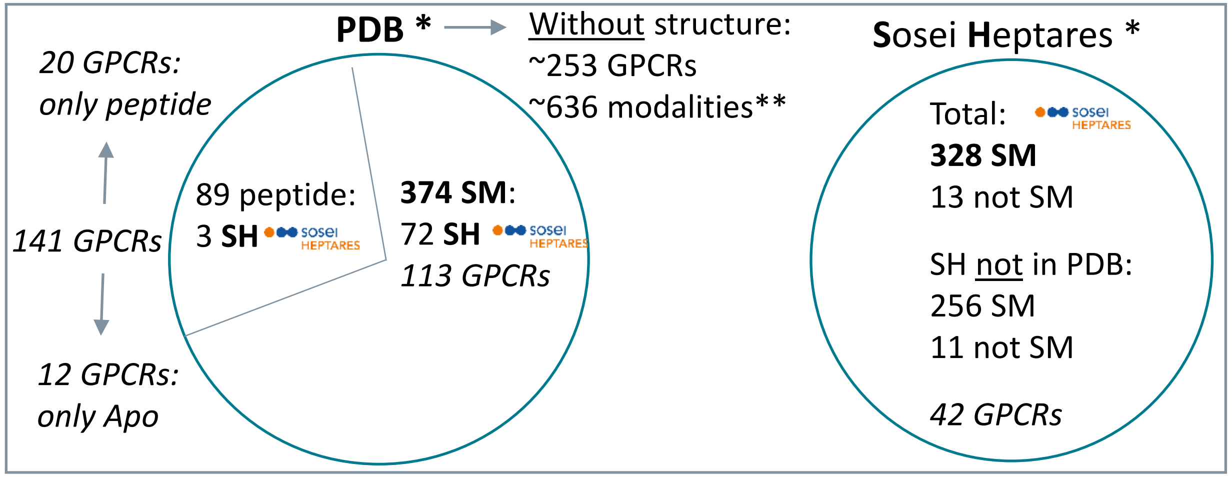
X-ray crystallography platform complemented by Cryo-EM structural enablement to expand scope of GPCR SBDD



Examples of SH X-ray structures

Examples of SH cryoEM structures

StaRs double small molecule ligand bound GPCR structures for SH SBDD



PDB *

<u>Without</u> structure:
~253 GPCRs
~636 modalities**

20 GPCRs:
only peptide

141 GPCRs

12 GPCRs:
only Apo

89 peptide:
3 **SH**

374 SM:
72 **SH**
113 GPCRs

Sosei **H**eptares *

Total:
328 SM
13 not SM

SH <u>not</u> in PDB:
256 SM
11 not SM

42 GPCRs

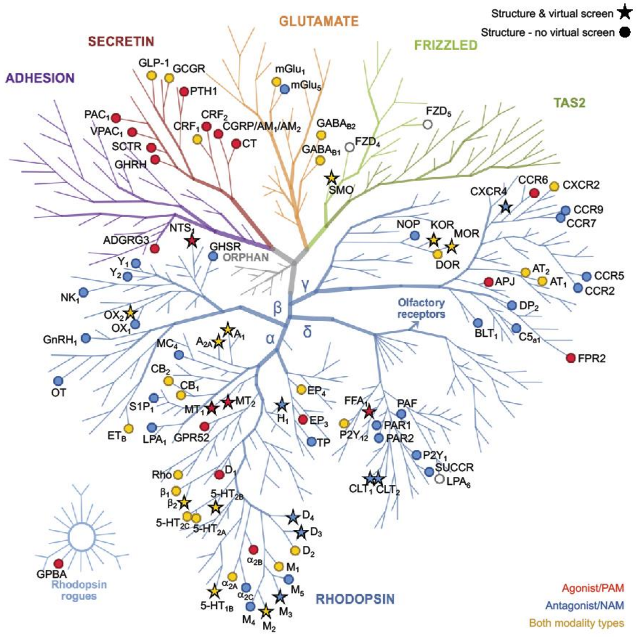
See **Poster 35**: Sonja Peter, Anna Pallo. Navigating the Orthosteric and Allosteric Structural GPCR Pocketome for Structure-Based Drug Discovery

* September 2022, unique GPCR-ligand complexes
** Assuming 403 non-olfactory GPCRs x 2 modalities (agonist/PAM, antagonist/NAM)

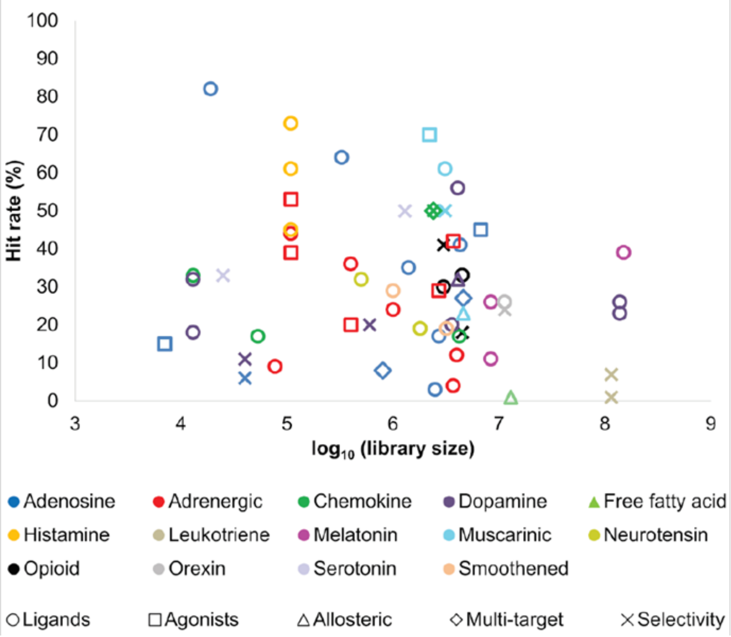
GPCR Structure-Based Virtual Screening – What can Docking do for you?

- 2021: 55 X-ray structure docking-based virtual screening studies for 22 GPCRs[1] – Increasing opportunities for X-ray/cryo-EM GPCR SBVS
- Hit rates of experimentally validated ligands >20% for e.g. aminergic, adenosine receptors – peptide GPCRs can be more challenging[1]
- Recently, increasing vendor/virtual library sizes[2] are leading to challenges in throughput
- New/orthogonal approaches required to efficiently sample chemical space compatible with diverse GPCR binding sites

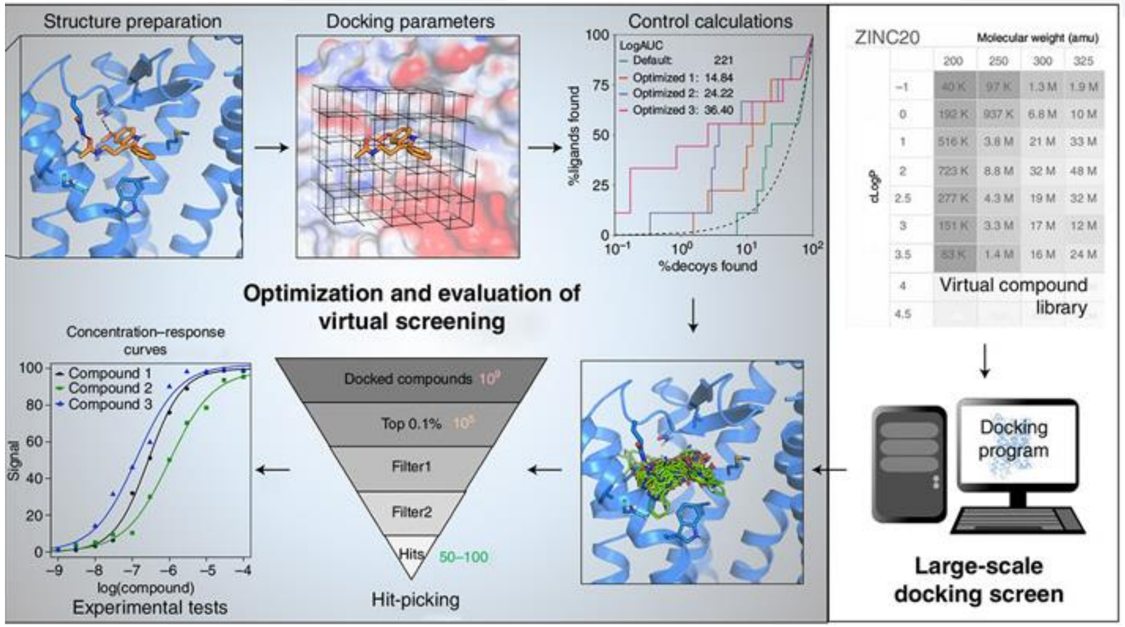
GPCR crystal structure docking-based VS studies[1]



% Experimentally validated docking VS hits[1]



Docking workflow – ultra-large libraries[2]



[1] Ballante, Kooistra, Kampen, de Graaf, Carlsson (2021) 73, 527

[2] B Bender et al. A practical guide to large-scale docking. *Nat. Protocols.* **2021**, *16*, 4799

2

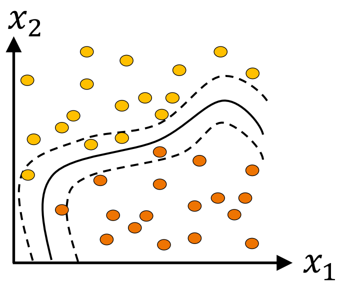
Generative Design of A2A ligands

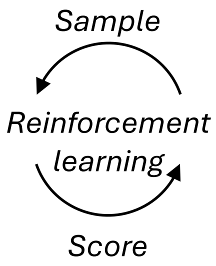
Structure-based optimization improves de novo molecule generation

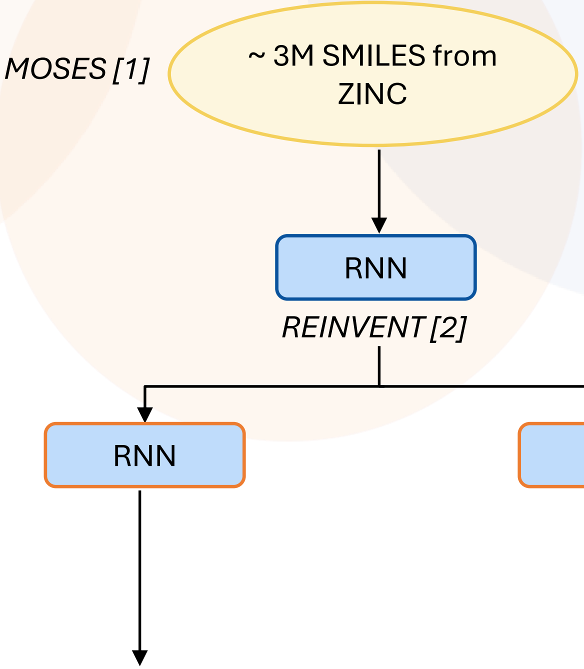
- Thomas, Smith, O'Boyle, de Graaf, Bender (2021) *J Cheminform* 13, 39
- Thomas, Bender, de Graaf (2023) *Curr Opin Struc Biol* 79, 102559

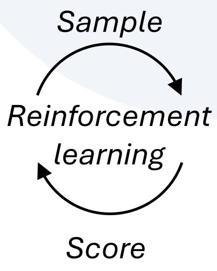
Ligand-based approach (SVM-Agent)

Machine learning model trained on D_2 ligands



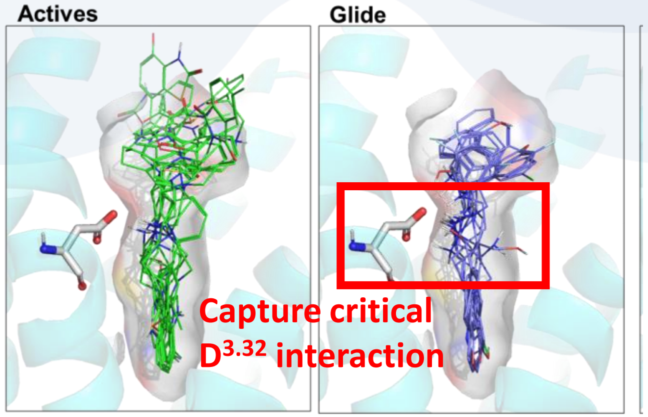






Structure-based approach (Glide-Agent)

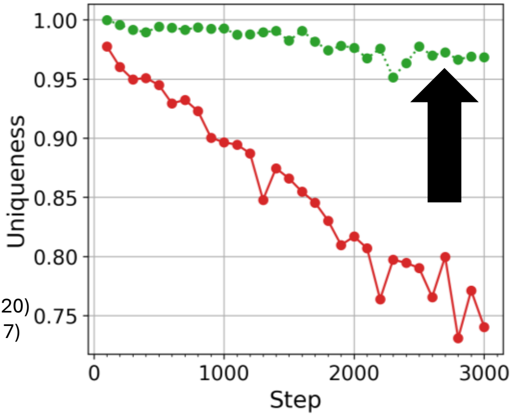
Docking into D_2 crystal structure



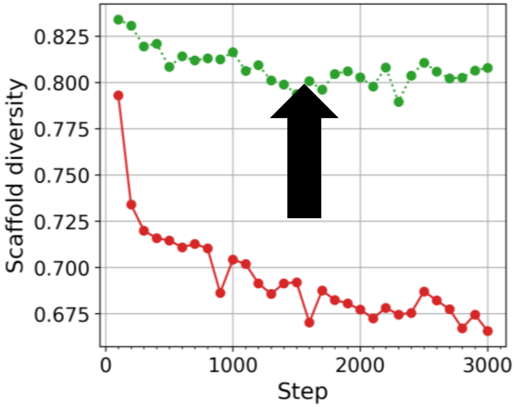
Capture critical $D^{3.32}$ interaction

Glide-Agent has ...

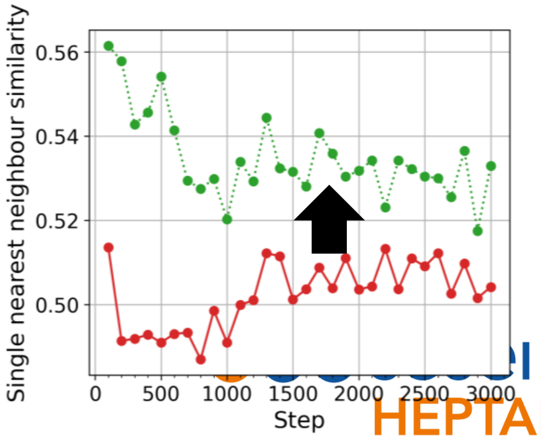
... more **unique** molecules



... higher scaffold **diversity**



... higher **similarity** to the **training set**



[1] PolyKovskiy, D., et al. Front Pharmacol 11 (2020)
[2] Olivecrona, M., *et al.* J Cheminform 9, 48 (2017)

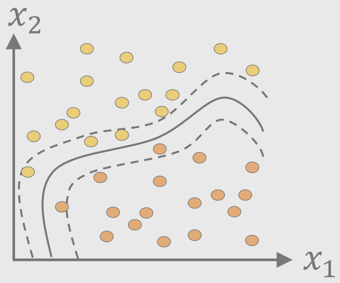
Structure-based optimization improves de novo molecule generation

- Thomas, Smith, O'Boyle, de Graaf, Bender (2021) *J Cheminform* 13, 39
- Thomas, Bender, de Graaf (2023) *Curr Opin Struc Biol* 79, 102559

MOSES [1]   ~ 3M SMILES from ZINC

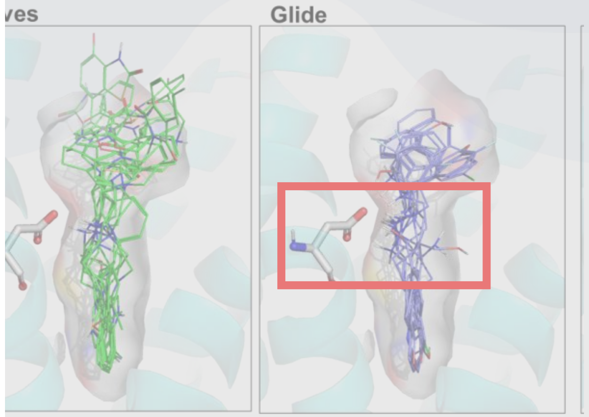
Ligand-based approach (SVN

Machine learning model trained on l

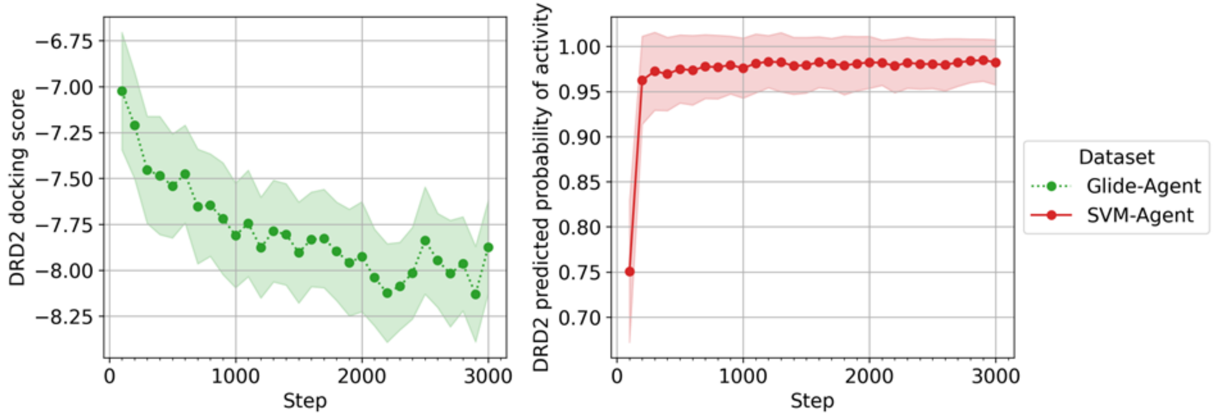


ture-based approach (Glide-Agent)

Docking into D_2 crystal structure



However, structure-based reinforcement learning suffers from sampling efficiency



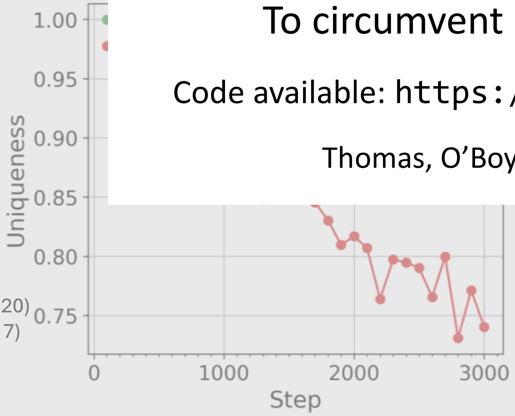
To circumvent speed losses, use an **Augmented Hill Climb**

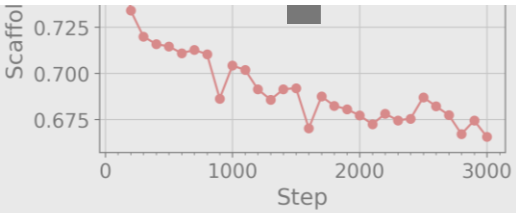
Code available: `https://github.com/MorganCThomas/SMILES-RNN`

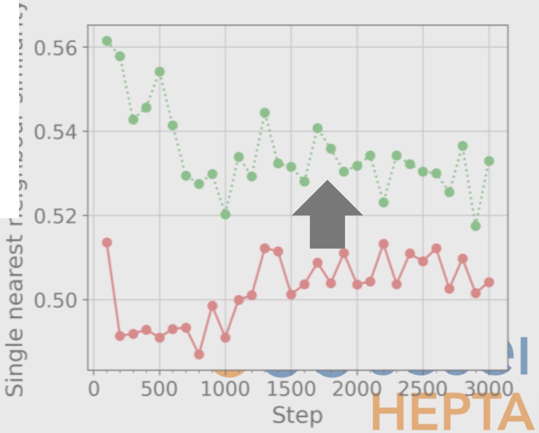
Thomas, O'Boyle, Bender, de Graaf (2022) *J Cheminformatics* 14: 68

Glide-Agent has ...   ... mo

similarity to the training set



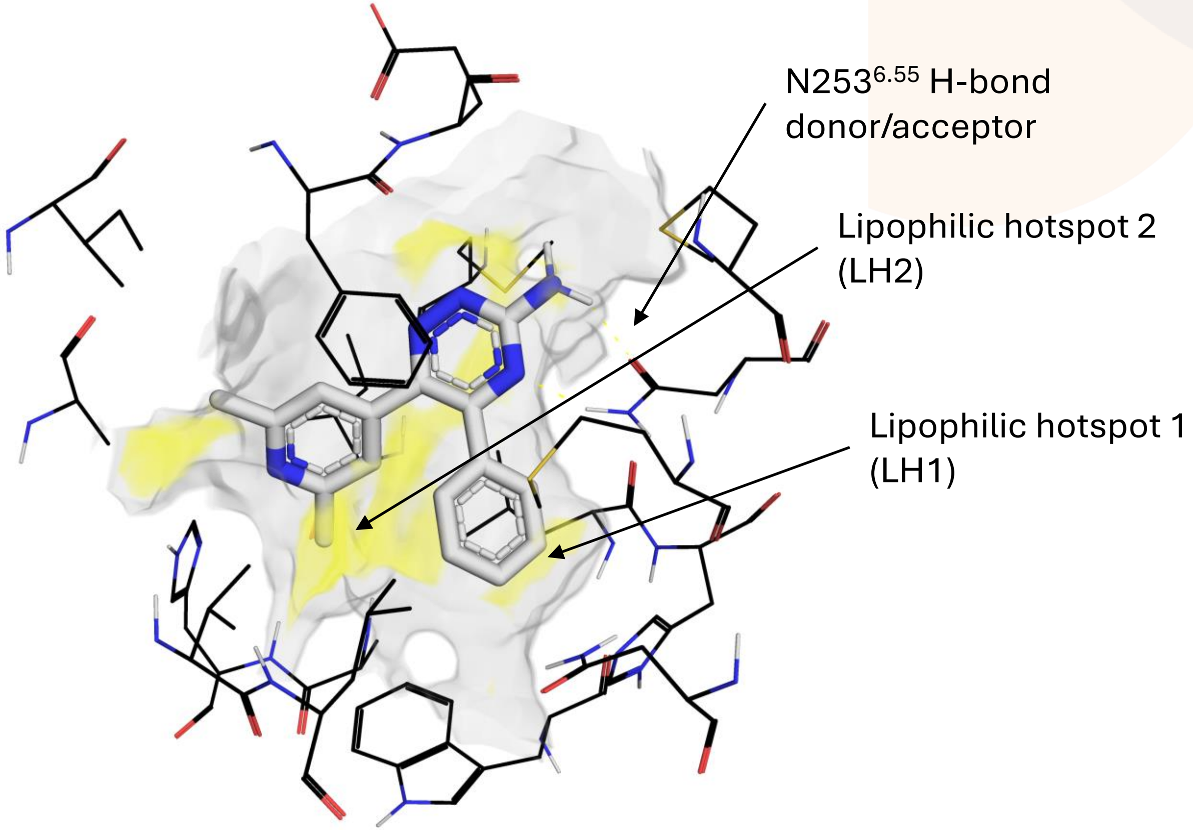




[1] PolyKovskiy, D., et al. Front Pharmacol 11 (2020)
[2] Olivecrona, M., *et al.* J Cheminform 9, 48 (2017)

Generative Structure-Based A_{2A} Adenosine Receptor Antagonist Design*

A_{2a} StaR® receptor in complex with antagonist [1]



N253$^{6.55}$ H-bond donor/acceptor
Lipophilic hotspot 2 (LH2)
Lipophilic hotspot 1 (LH1)

A_{2a} is a well-liganded G protein-coupled receptor with many known chemotypes and crystal structures

Curated set of 79 known A_{2a} chemotypes [2]

Multi objective optimization

Structure-based:

Glide-SP docking

N253$^{6.55}$ H-bond acceptor/donor [optional]

Lipophilic hotspots LH1 & LH2 [optional]

Property-based:

1 <= CLogP <= 3

1 <= CRotBonds <= 3

HBond donors <= 3

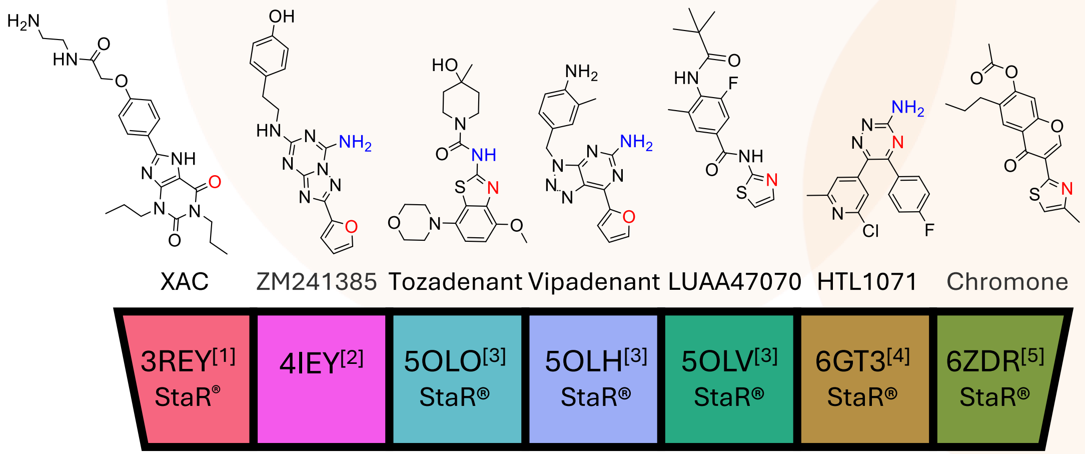
Synthesizability-based:

RAScore [3]

[1] Congreve, M., *et al.* J Med Chem 55, 1898-1903 (2012)
[2] Weiss, D.R., *et al.* J Chem Inf Model 54, 642-651 (2016)
[3] Thakkar, A., *et al.* Chem Sci 12, 3339-3349 (2021)

* Unpublished case study - Sosei Heptares, Univ Cambridge

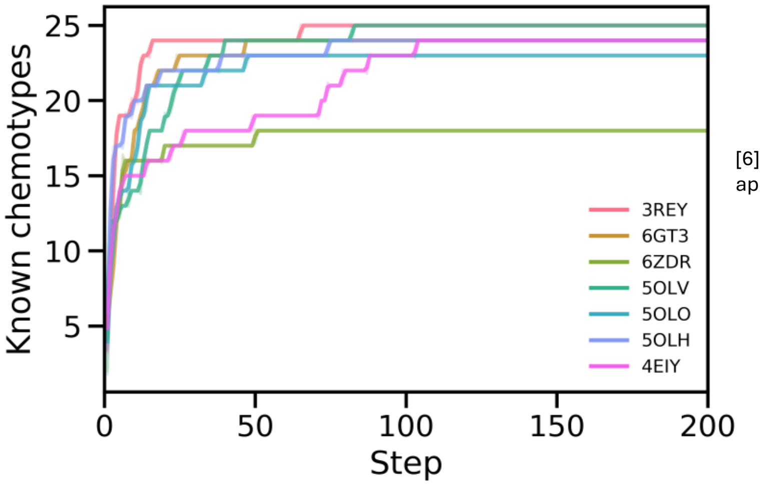
A_{2A} antagonist co-crystal structure influences chemotypes generated*



XAC	ZM241385	Tozadenant	Vipadenant	LUAA47070	HTL1071	Chromone
3REY[1] StaR®	4IEY[2]	5OLO[3] StaR®	5OLH[3] StaR®	5OLV[3] StaR®	6GT3[4] StaR®	6ZDR[5] StaR®

Conduct de novo molecule generation optimizing the docking score with different xstal structures[1-5]

[1] Dore, *et al.* Structure 19, 1283 (2011)
[2] Liu *et al.* Science 337, 232 (2012)
[3] Rucktooa *et al.* Sci Rep 8, 41 (2018)
[4] Borodovsky *et al.* J Immunother Cancer 8, e000417 (2020)
[5] Jespers *et al.* Angew Chem Int Ed Engl 59, 16536 (2020)



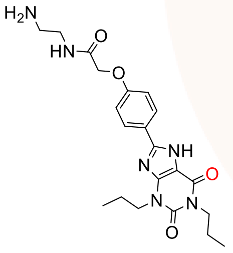
Some A_{2A} xtal structures recover more chemotypes than others

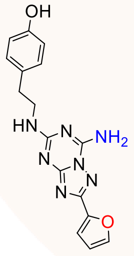
30 known chemotypes[6] recovered in total – some more than others

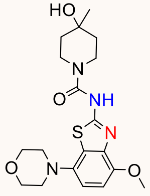
[6] Weiss, *et al.* J Chem Inf Model 54, 642 (2016) appended with A_{2A} chemotypes since 2016

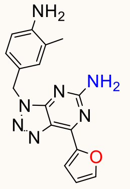
* Unpublished case study - Sosei Heptares, Univ Cambridge

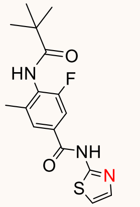
Prospective Generative Structure-Based A_{2A} Antagonist Screening*

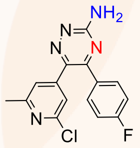

XAC

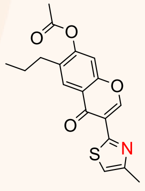

ZM241385

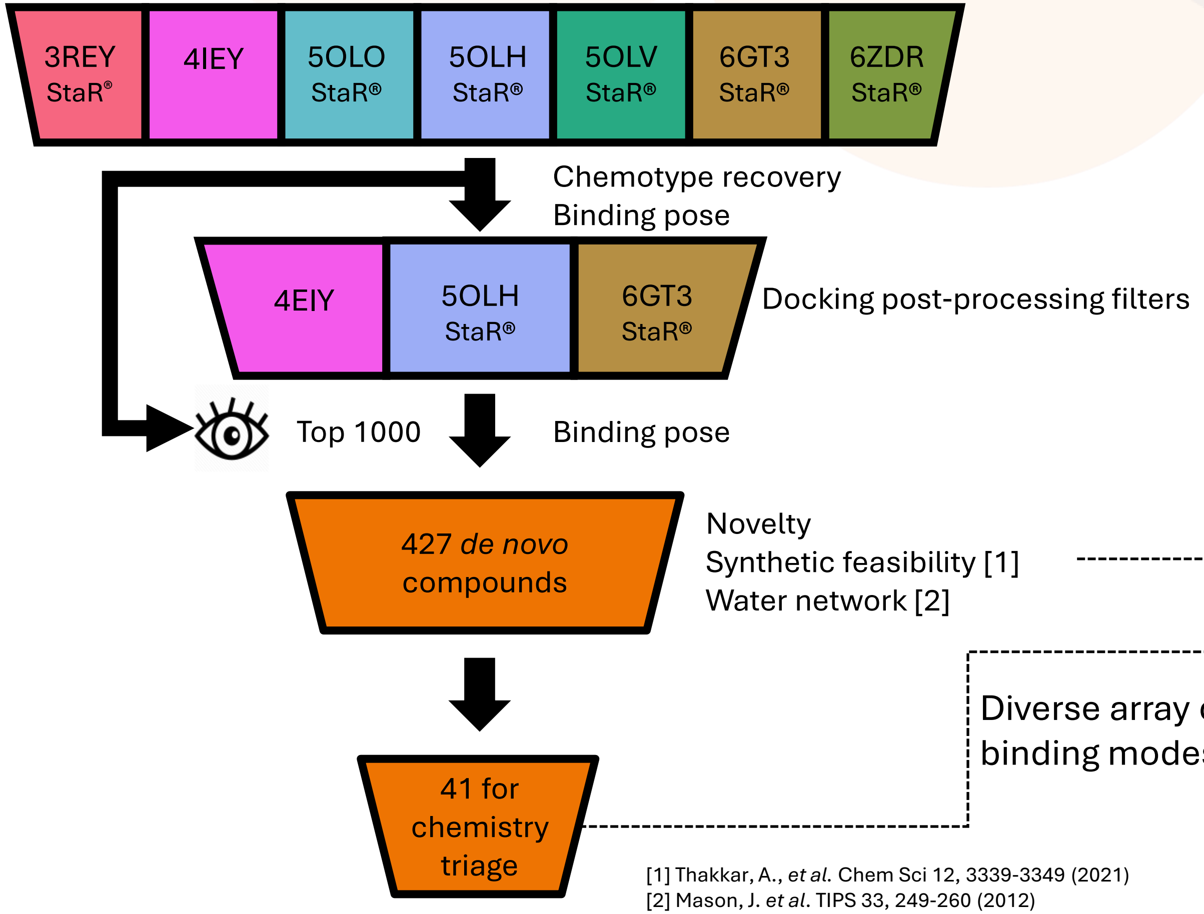

Tozadenant


Vipadenant


LUAA47070


HTL1071


Chromone


3REY StaR®

4IEY

5OLO StaR®

5OLH StaR®

5OLV StaR®

6GT3 StaR®

6ZDR StaR®

Chemotype recovery
Binding pose

4EIY

5OLH StaR®

6GT3 StaR®

Docking post-processing filters

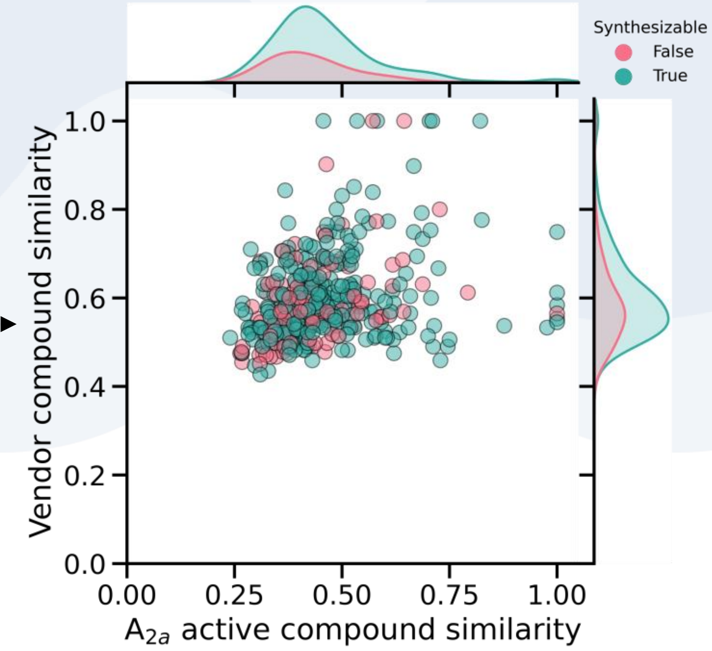
Top 1000

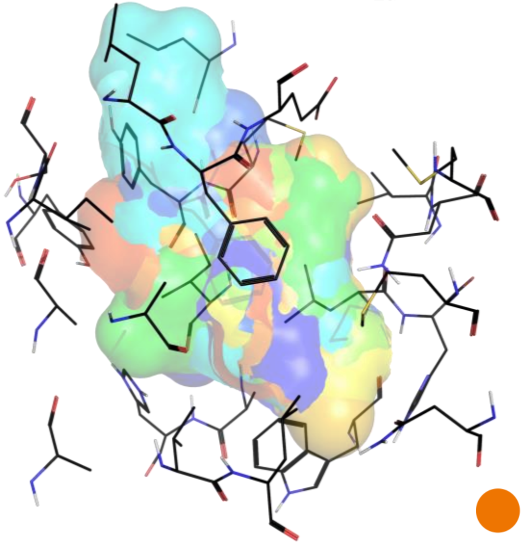
Binding pose

427 *de novo* compounds

Novelty
Synthetic feasibility [1]
Water network [2]

41 for chemistry triage





Diverse array of predicted binding modes

[1] Thakkar, A., *et al.* Chem Sci 12, 3339-3349 (2021)
[2] Mason, J. *et al.* TIPS 33, 249-260 (2012)

* Unpublished case study - Sosei Heptares, Univ Cambridge

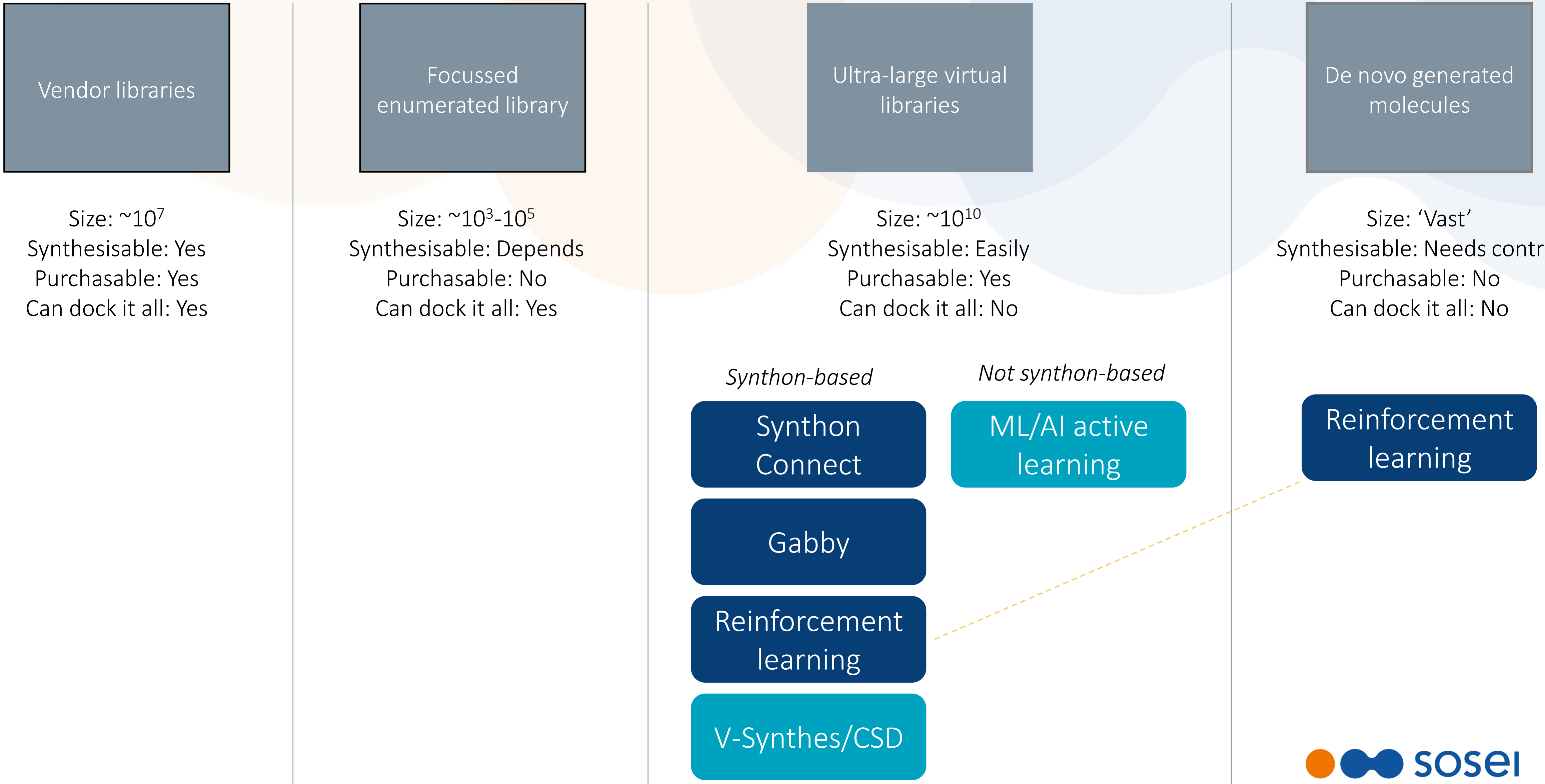
Conclusions from A_{2A} generative modelling

- Generative modelling can successfully be applied to SBDD of GPCR structures
- In comparison to a ligand-based approach, structure-guided models allow capturing of key interactions in the binding pocket
  - However, a multi-parameter optimisation is needed to prevent the model exploiting inaccuracies in the scoring function
- Using multiple crystal structures identifies a broader range of known chemotypes

- The adenosine A_{2A} system is a good test bed for new structure-based virtual screening (SBVS) techniques:
  - A_{2A} antagonist SBVS hit was identified and optimised using A_{2A} StaR® X-ray SBDD, leading to a Ph2 clinical candidate, HTL1071/AZD4635
    - Langmead *et al. J. Med. Chem.* **2012**, 1904; Congreve *et al. J. Med. Chem.* **2012**, 1898, Borodovsky et al. *J Immunther Cancer* **2020**, 8: e000417

- Another recent example of successful application of SBVS to a GPCR is identification of an M_1 partial agonist:
  - M_1 SBVS fragment hit was identified and optimised using M_1 StaR® X-ray SBDD, leading to a PoM, as part of extensive SBDD program incl. multiple M_1/M_4 structures enabling design of further generations of selective agonists
    - Brown et al. *Cell.* **2021**, *184*, 5886

Structure-based drug discovery in large chemical spaces



Vendor libraries

Size: ~10^7
Synthesisable: Yes
Purchasable: Yes
Can dock it all: Yes

Focussed enumerated library

Size: ~10^3-10^5
Synthesisable: Depends
Purchasable: No
Can dock it all: Yes

Ultra-large virtual libraries

Size: ~10^{10}
Synthesisable: Easily
Purchasable: Yes
Can dock it all: No

Synthon-based

- Synthon Connect
- Gabby
- Reinforcement learning
- V-Synthes/CSD

Not synthon-based

- ML/AI active learning

De novo generated molecules

Size: 'Vast'
Synthesisable: Needs control
Purchasable: No
Can dock it all: No

- Reinforcement learning

Searching REAL: A **Re**adily **A**ccessib**L**e ultra-large virtual space

- Enamine REAL
  - Publicly available – 5.5B (2022q1-2), 6.0B (2022q3-4)
  - 1.1B two-component reactions in 2022q1-2 Enamine REAL
    - Remainder are almost exclusively three-component reactions
- Enamine REAL Space
  - Available under NDA – 31.5B (2022q1-2), 36B (2022q3-4)
- 167 synthesis protocols, 137K BBs, 14M Bemis-Murcko scaffolds

- How can we efficiently screen/explore these ultra-large synthetically accessible virtual spaces in the context of SBDD?
- Let's look at three approaches
  - Each will have a budget of 1M protein-ligand dockings using Glide
  - Here, for simplicity we focus on finding good docking scores
  - In production we adopt a more sophisticated approach including post-processing, additional constraints, MPO

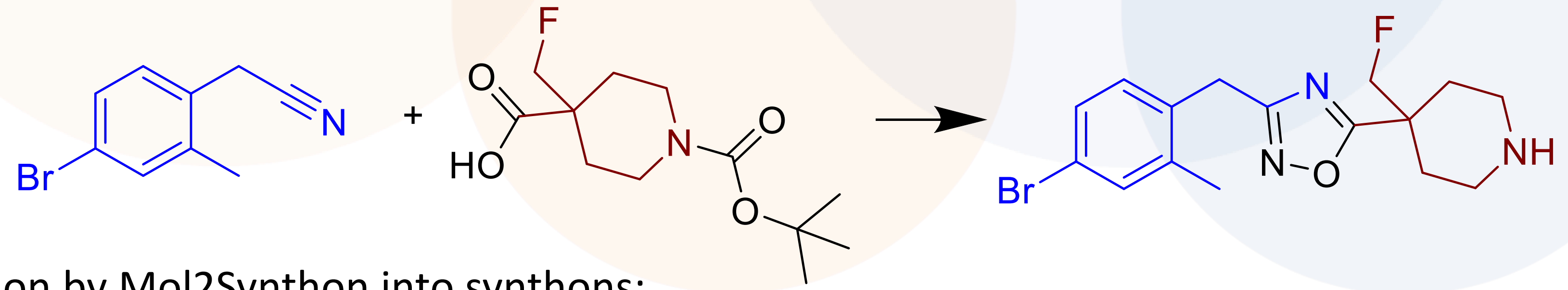
3

Mol2Synthon

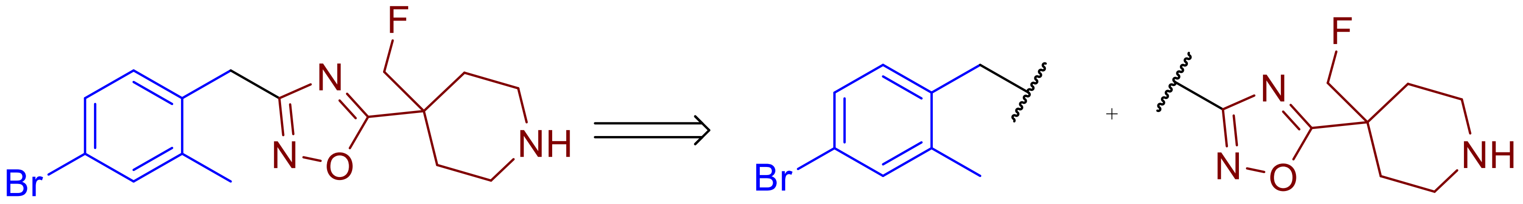
Make synthons from Enamine REAL

Mol2Synthon: example

- A 2-component reaction from Enamine REAL: note leaving groups, loss of atoms, gain of atoms

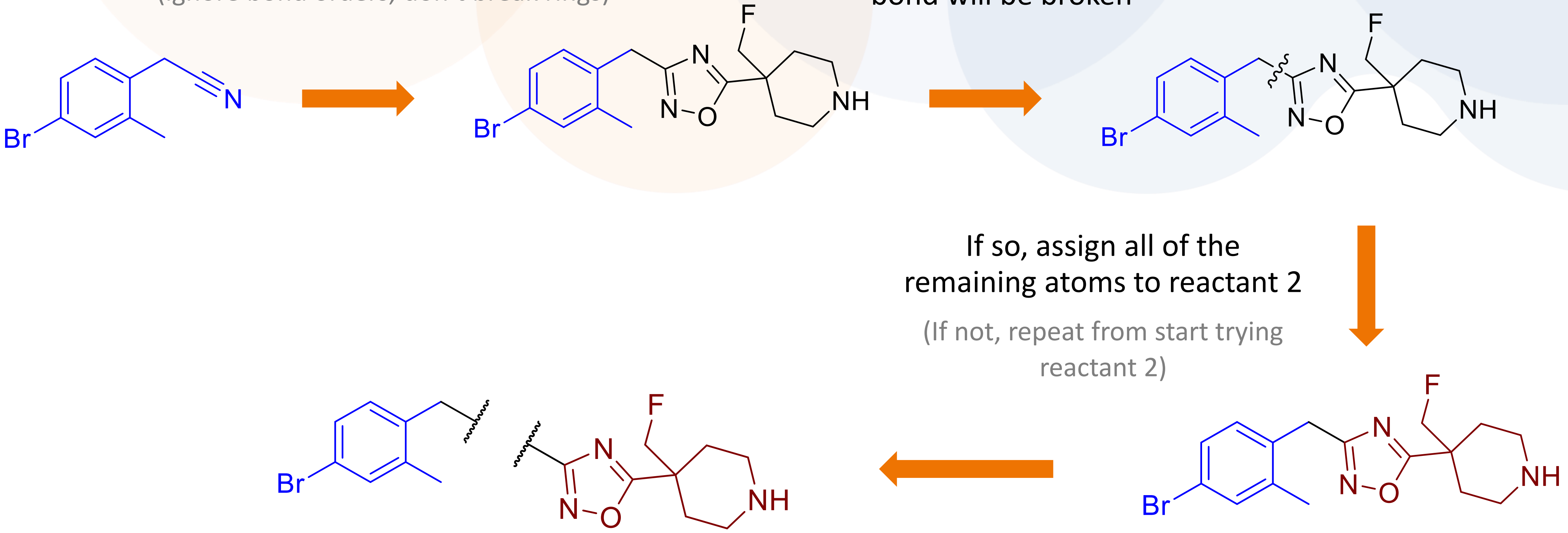


- Decomposition by Mol2Synthon into synthons:



- Compared to using the original reactants:
  - Synthons incorporate the structural features of the final structure (e.g. in this case, the ring)
  - Synthons do not incorporate extraneous features (e.g. the protecting group, carboxylic acid, nitrile)
- => Synthons are better suited for fragment docking and other applications than the original reactants

Mol2Synthon: basic algorithm



Map reactant 1 onto the product using MCS

(ignore bond orders, don’t break rings)

Check whether only a single bond will be broken

If so, assign all of the remaining atoms to reactant 2

(If not, repeat from start trying reactant 2)

Break the connecting bond

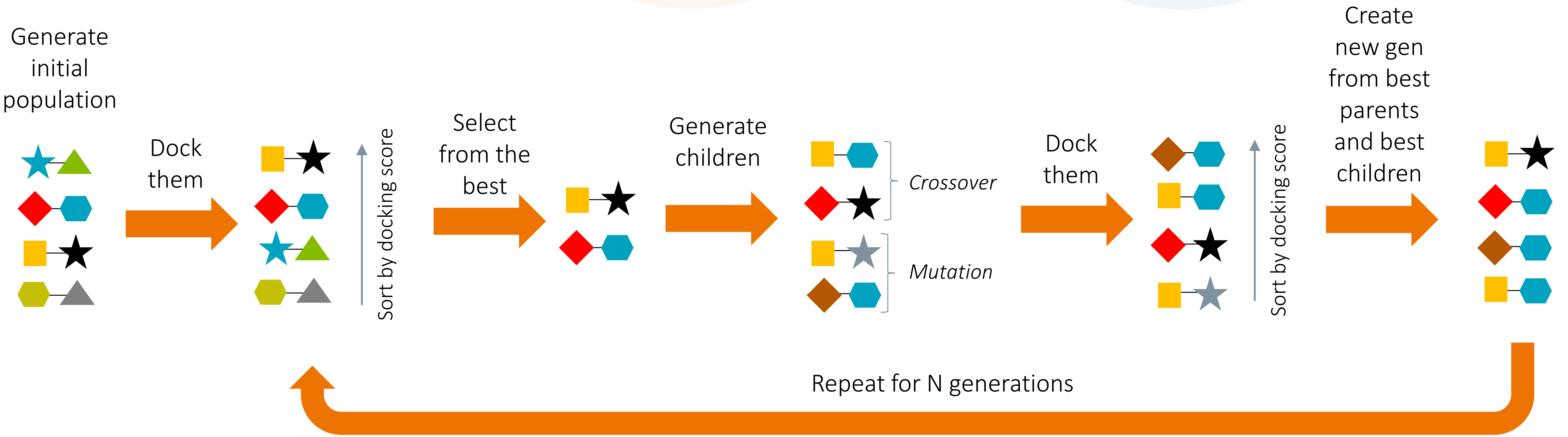
4

Gabby

Genetic Algorithm of building blocks

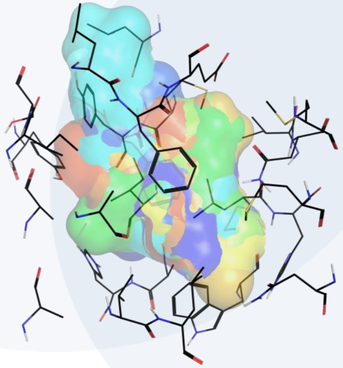
Gabby: a genetic algorithm to search across synthon-space

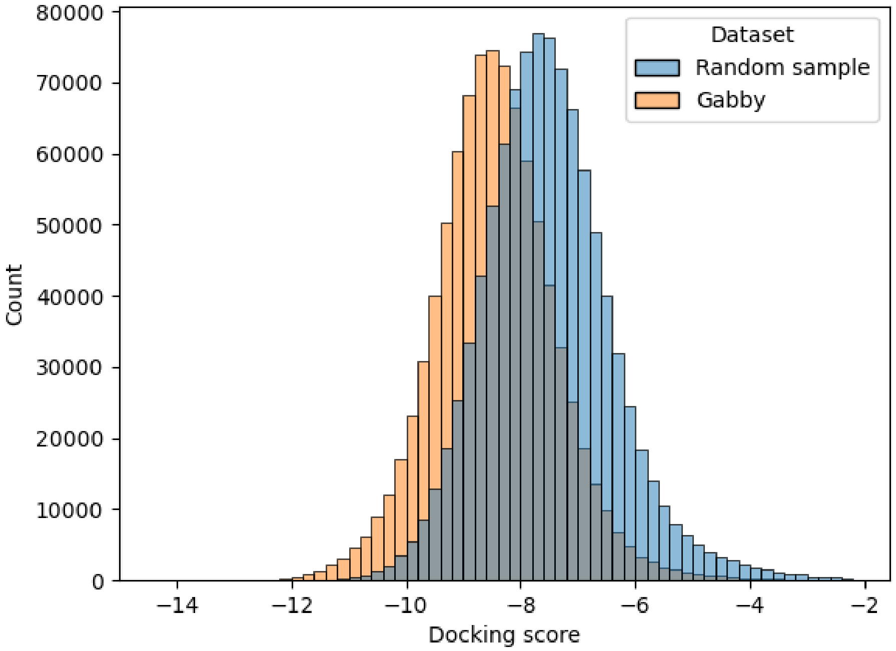
- **Preparation:**
  - Distinguish the synthons from Mol2Synthon based on their SMILES, attachment point, and reactant position
    - This gave 313K synthons
  - Measure the pairwise similarity of the synthons, after replacing the attachment point with Xe
  - Describe each molecule in terms of the two synthons that compose it

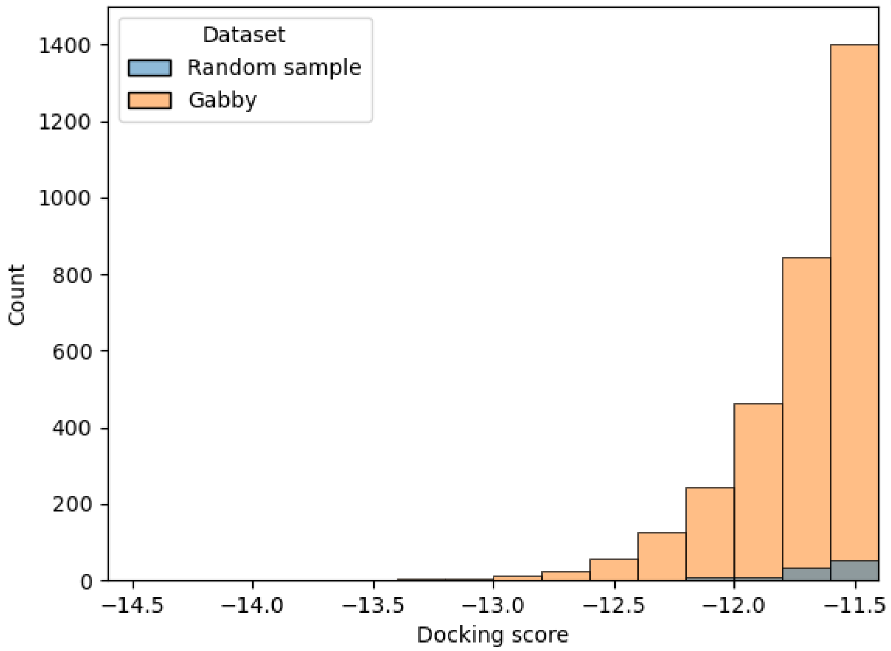


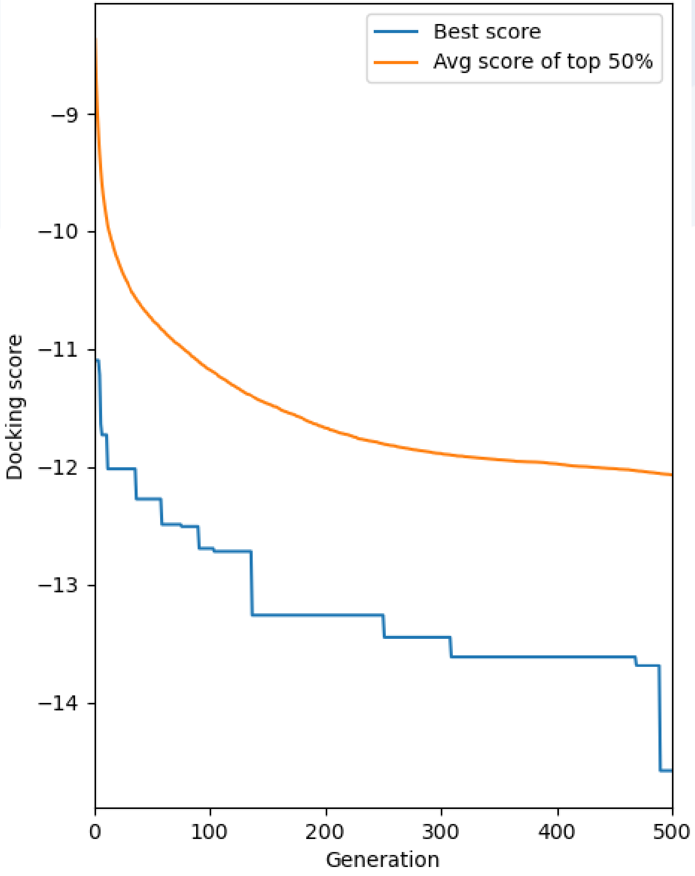
Gabby results

- 902K dockings from 500 generations x 2000 molecules
- Best/1000th best score: -14.6/-11.8 (vs -13.2/-10.8 for random)
- Number of molecules with scores ≤ -12: 477 (vs 12 for random)









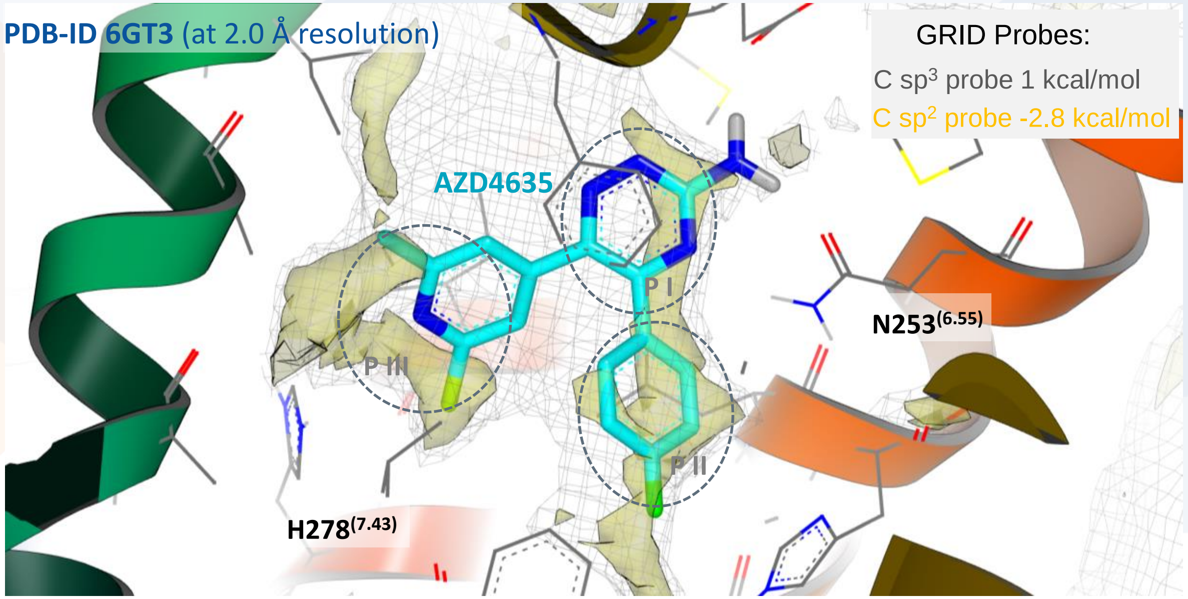
5

SynthonConnect

Join high-scoring synthon poses

SynthonConnect algorithm

- Synthon attachment points are replaced with H
  - Reduces the number to dock to 265K
- Synthons are docked with Glide
  - Expanded sampling, max number poses of 100
- Iterate over the docked poses to find compatible synthon pairs, combinations where:
  - Attachment points (for pairs involved in the same reaction) are within range for a plausible bond to be made
  - Local orientation around the connection point is complementary
- Select from those with best sum of synthon scores



SynthonConnect algorithm

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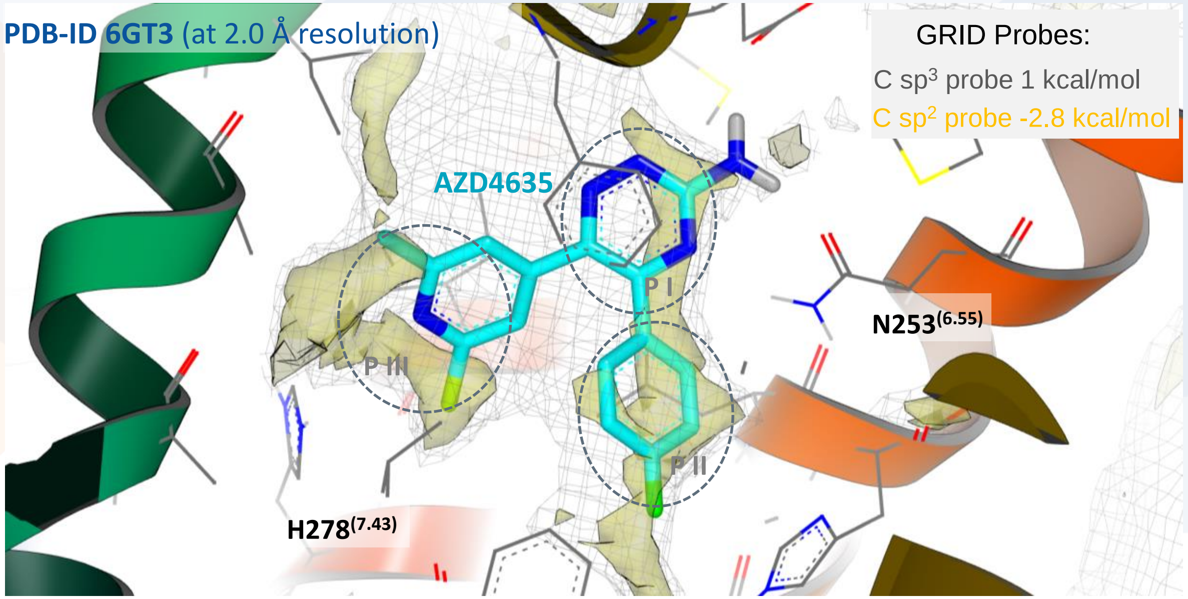
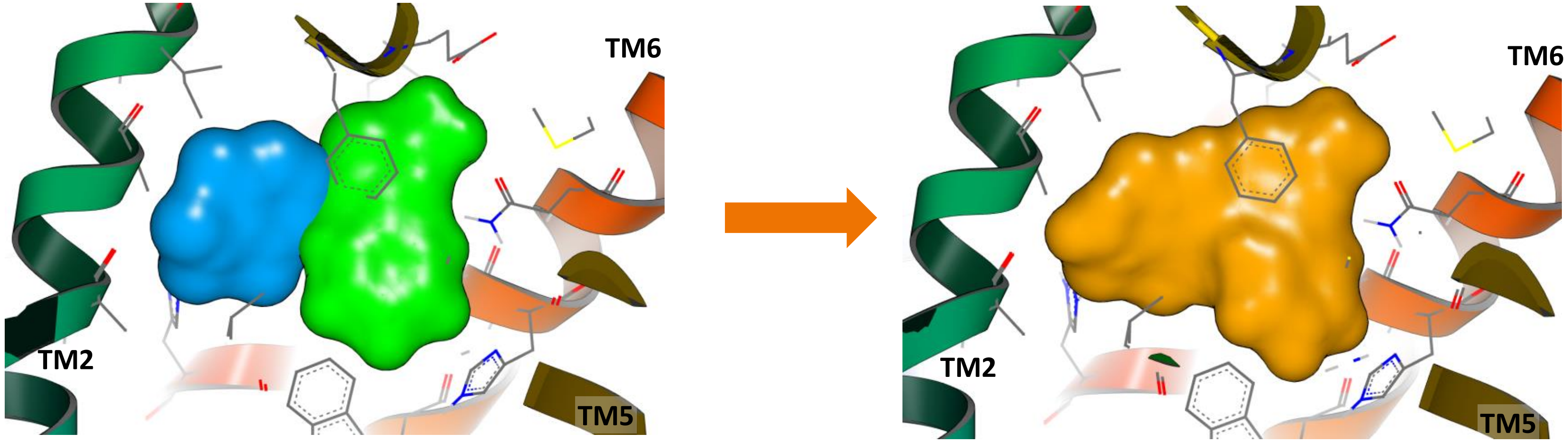
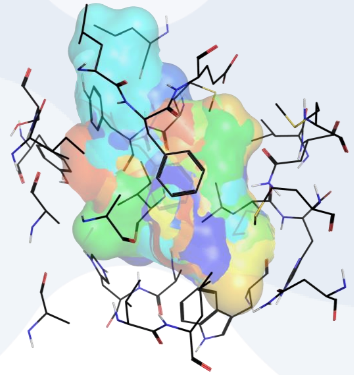
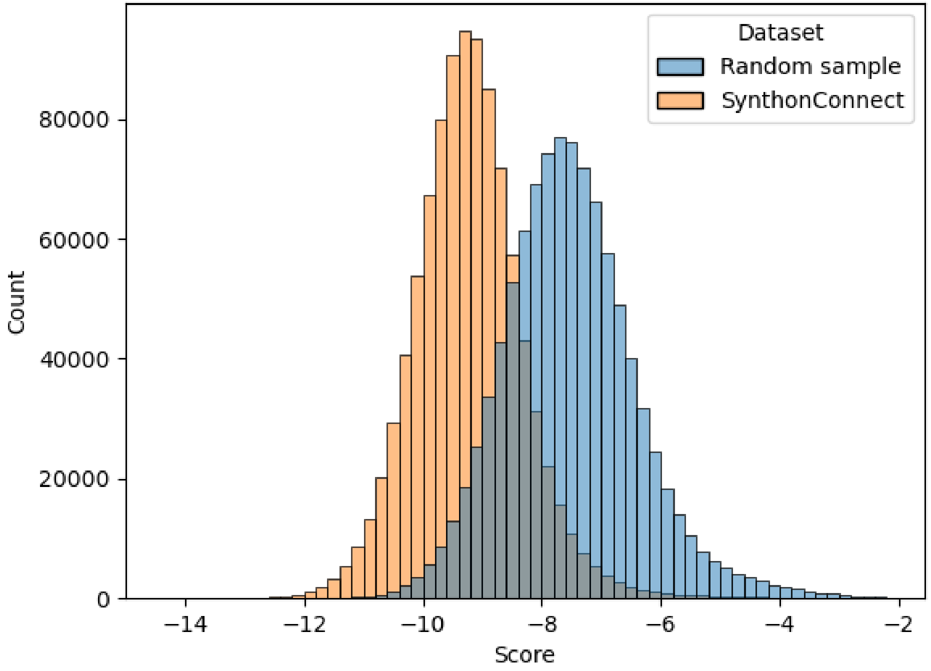

PDB-ID 6GT3 (at 2.0 Å resolution)
GRID Probes:
C sp^3 probe 1 kcal/mol
C sp^2 probe -2.8 kcal/mol
AZD4635
P I
P II
P III
N253$^{(6.55)}$
H278$^{(7.43)}$

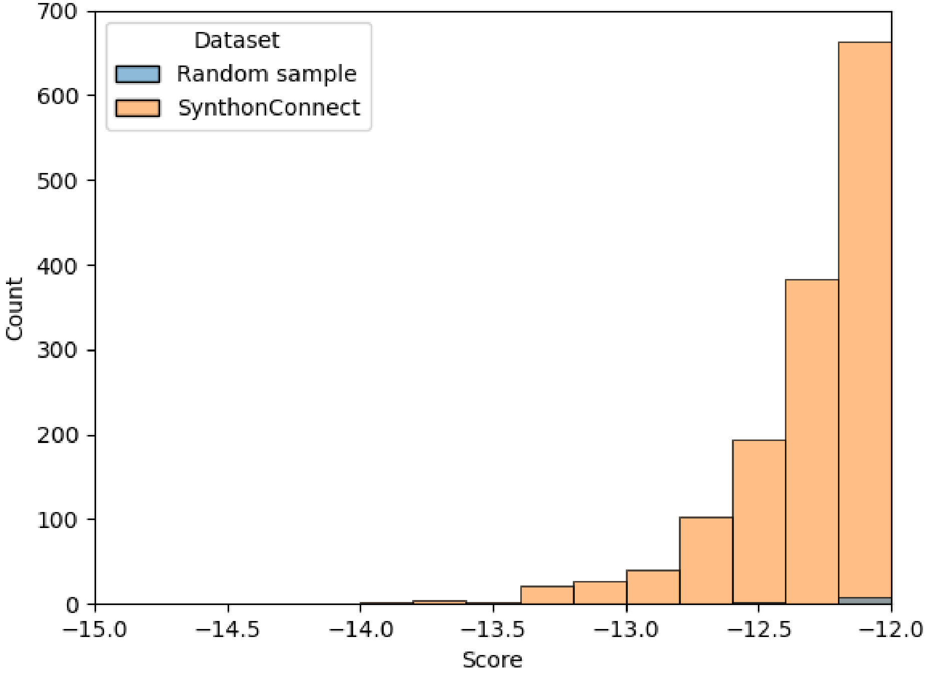


SynthonConnect results

- 1M dockings of Enamine REAL molecules
  - Plus additional dockings of synthons
- Best/1000th best score: -14.5/-12.1 (vs -13.2/-10.8 for random)
- Number of molecules with scores ≤ -12: 1448 (vs 12 for random, 477 for Gabby)



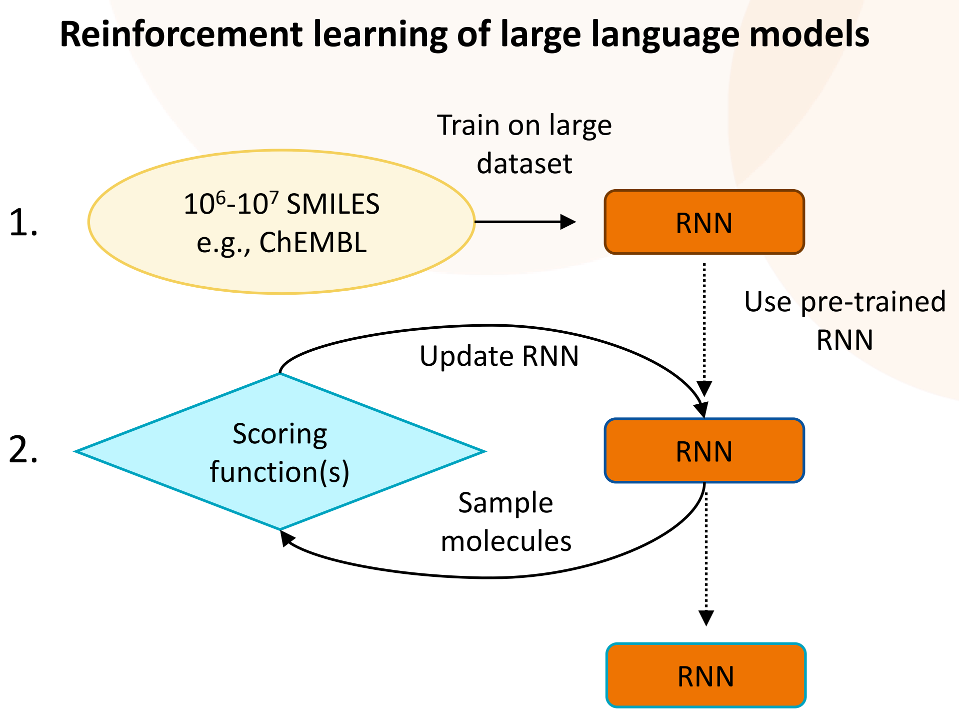




6

Generative design of Enamine REAL molecules

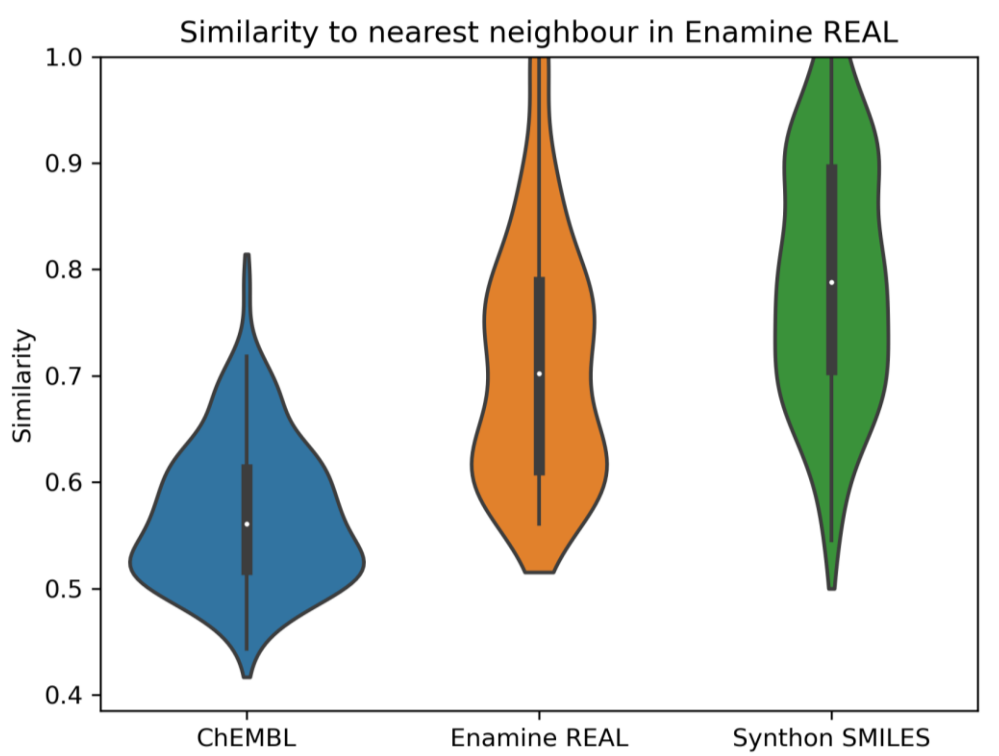
Generating molecules that look like Enamine REAL molecules



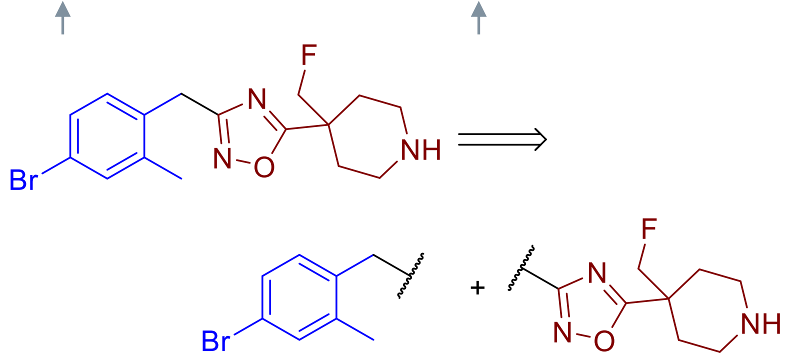
- During the reinforcement learning (RL) iterations, deviations from the original learned dataset probabilities are penalised
  - That is, if you train on ChEMBL, the generated molecules will resemble ChEMBL entries
- What if we instead train on Enamine REAL entries?
  - We can then use reinforcement learning over a virtual space that remains close to entries in Enamine REAL
  - Generated molecules or a close neighbour may be purchasable from Enamine REAL, rather than requiring synthesis

- M Olivecrona, T Blaschke, O Engkvist, H Chen. Molecular de-novo design through deep reinforcement learning. *J. Cheminform.* **2017**, *9*, 48
- M Thomas, RT Smith, NM O'Boyle, C de Graaf, A Bender. Comparison of structure- and ligand-based scoring functions for deep generative models: a GPCR case study. *J. Cheminform.* **2021**, *13*, 39.
- M Thomas, NM O'Boyle, A Bender, C de Graaf. Augmented Hill-Climb increases reinforcement learning efficiency for language-based de novo molecule generation. *J. Cheminform.* **2022**, *14*, 68.
- https://github.com/MorganCThomas/SMILES-RNN
- https://github.com/MorganCThomas/MolScore

Generating molecules that look like Enamine REAL molecules



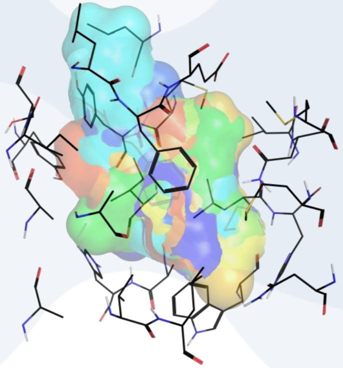
- During the reinforcement learning (RL) iterations, deviations from the original learned dataset probabilities are penalised
  - That is, if you train on ChEMBL, the generated molecules will resemble ChEMBL entries
- What if we instead train on Enamine REAL entries?
  - We can then use reinforcement learning over a virtual space that remains close to entries in Enamine REAL
  - Generated molecules or a close neighbour may be purchasable from Enamine REAL, rather than requiring synthesis
- Can we do better? Introducing ‘Synthon SMILES’
  - Write each entry in terms of its synthons, both written with the attachment point first and separated by a dot disconnection
    - `C9c1ccc(Br)cc1C.c91nc(C2(CF)CCNCC2)on1`

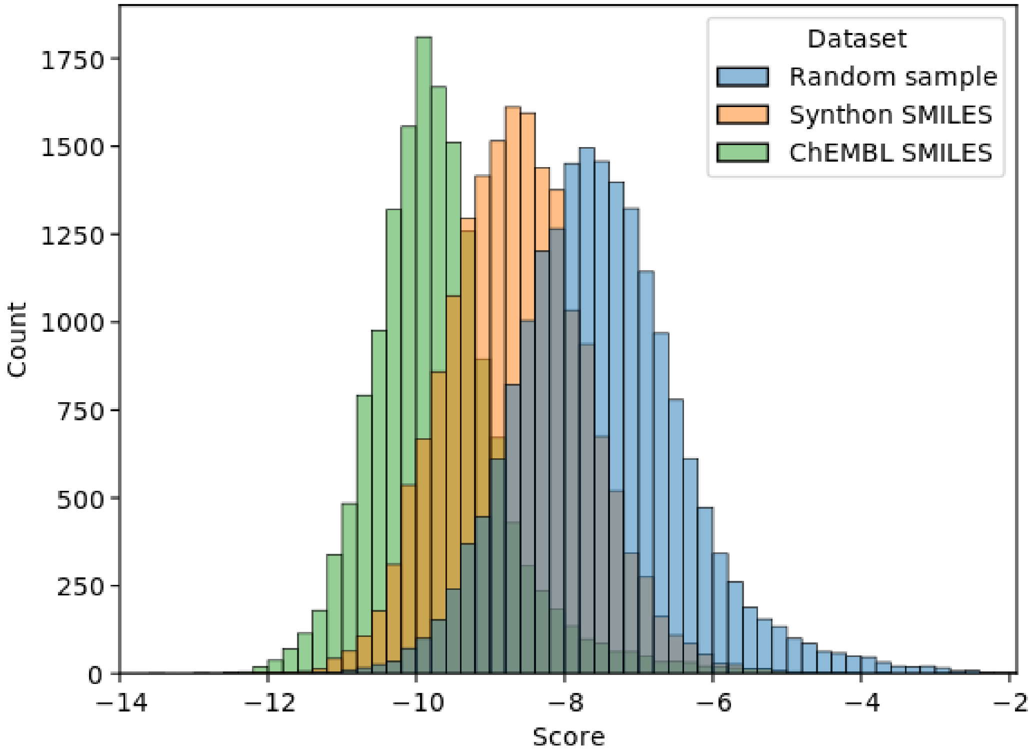


- M Olivecrona, T Blaschke, O Engkvist, H Chen. Molecular de-novo design through deep reinforcement learning. *J. Cheminform.* **2017**, *9*, 48
- M Thomas, RT Smith, NM O’Boyle, C de Graaf, A Bender. Comparison of structure- and ligand-based scoring functions for deep generative models: a GPCR case study. *J. Cheminform.* **2021**, *13*, 39.
- M Thomas, NM O’Boyle, A Bender, C de Graaf. Augmented Hill-Climb increases reinforcement learning efficiency for language-based de novo molecule generation. *J. Cheminform.* **2022**, *14*, 68.
- https://github.com/MorganCThomas/SMILES-RNN
- https://github.com/MorganCThomas/MolScore

Generative model results

- 19K dockings from 300 generations x 64 molecules
- MPO involving docking score, RAScore, CLogP, consecutive rotatable bonds, HBD
- Best/1000th best score: -12.1/-10.1 (vs -11.6/-9.2 for 19K random, -14.6/-10.9 for ChEMBL SMILES)
- Number of molecules with scores ≤ -11.5: 13 (vs 2 for 19K random, 197 for ChEMBL SMILES)





- M Thomas, NM O'Boyle, A Bender, C de Graaf. Augmented Hill-Climb increases reinforcement learning efficiency for language-based de novo molecule generation. *J. Cheminform.* 2022, *14*, 68.

7

Conclusion

Conclusions

	Requires synthons	Involves docking synthons	Can be restricted to REAL	Not just docking	Converges over iterations	Molecules with scores ≤ -12	Progress
SynthonConnect	🟩	🟩	🟩			1448/1M	🟨
Gabby	🟩		🟩	🟩	🟩	477/1M	🟨
Generative model	🟩			🟩	🟩	4/19K	🟨
Active Learning			🟩	🟩	🟩		🟨
V-Synthes/CSD	🟩	🟩	🟩				🟨

- Mol2Synthon generates synthons that can be used as the basis for several approaches
- Both SynthonConnect and Gabby can identify molecules that dock with high scores
  - Caveat for Gabby is that the large number of iterations used here is inefficient
  - An advantage of SynthonConnect is that it only involves a single docking of synthons and then one of full molecules
- *De novo* design based around Enamine REAL is promising
- Work is continuing on all fronts to improve performance further, also finishing active learning and CSD
- Next step is to go beyond optimising docking score, include interactions and physicochemical properties.
  - For example, incorporating QSAR models (see Poster 15).

Acknowledgements

- Sosei Heptares Computational Chemistry
  - Chris de Graaf – Head of Group
  - Jon Tyzack – Mol2Synthon, SynthonConnect
  - Daniel Santos-Stone – Active Learning
  - Pierre Matricon, Francesca Deflorian, Jon Mason – A2A SBDD
- Sosei Heptares Medicinal Chemistry
  - Charlotte Fieldhouse – A_{2A} AI/SBDD MedChem
  - Robert Gillespie – A_{2A} AI/SBDD MedChem
- University of Cambridge
  - Andreas Bender – A2A generative modelling
  - Morgan Thomas – A2A generative modelling, MolScore, SMILES-RNN, AHC

Posters

- Poster 15: Jon Tyzack
  - Development of QSAR Models for SBDD of GPCRs
- Poster 28: Morgan Thomas
  - MolScore: A Semi-automated Platform for Generative Model Molecule Scoring and Evaluation in Drug Design
- Poster 35: Sonja Peter, Anna Pallo
  - Navigating the Orthosteric and Allosteric Structural GPCR Pocketome for Structure-Based Drug Discovery

Current Job Openings!!

sosei HEPTARES