

SARS-CoV-2 Nsp13 Fragments and the Open Chemistry Network

Prof Matthew H. Todd

Chair of Drug Discovery, University College London

@mattoddchem

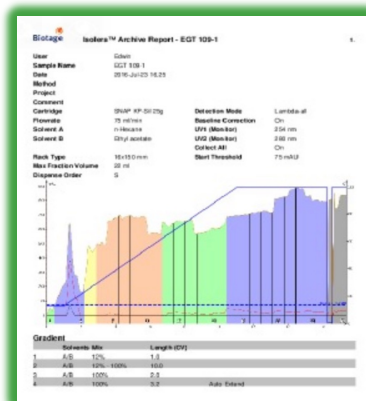


The Basic Approach

- 1st Law: All data are open and all ideas are shared
- 2nd Law: Anyone can take part at any level
- 3rd Law: There will be no patents
- 4th Law: Suggestions are the best form of criticism
- 5th Law: Public discussion is much more valuable than private email
- 6th Law: An open project is bigger than, and is not owned by, any given lab

NTDs: *Nature Chem* **2011**, 3, 745; *PLoS NTD* **2011**, 5(9):e1260. **Malaria:** *ACS Cent. Sci.* **2016**, 2, 687; *J. Med. Chem.* **2020**, 63, 11585; *J. Org. Chem.* **2020**, 85, 13438; *J. Med. Chem.* **2021**, 64, 16450. **TB:** *J. Med. Chem.* **2018**, 61, 11327. **Antifungals:** *PLoS NTD* **2018**, 12(4): e0006437; *PLoS NTD* **2022**, 16, e0010159. **Platform:** *Chem. Sci.* **2015**, 6, 1614; *Parasitology* **2014**, 141, 148. **Laws:** *ChemMedChem*, **2019**, 14, 1804. **Translation/Policy:** *PLoS Med.* **2017**, 14(4): e1002276; *Wellcome Open Res.* **2021**, 6:146.

Components



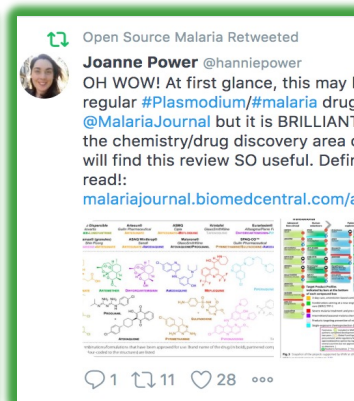
Laboratory
Notebooks

July 2019 Compounds for Metabolic/Physchem Evaluation	Biological Data	FYI
Next batch of compounds sent for biological testing Jul 2019	Biological Data	FYI
Write-up of the Predictive Modelling Competition Results		
KinomeScan of Series 4 and telesubstitution compounds	FYI	Waiting on results
Remaining Data Needed for OHOH Compound(s)	Biological Data	Question
November 2018 Potency results	Biological Data	
Compounds for hERG Evaluation Round 2	FYI	
Exploration of 6-substituted compounds	Being Synthesized Now	
Potency results on the repeated biotransformation	Biological Data	Question
April 2018 Dundee Potency Results	Biological Data	

Public To Do
Lists/Discussion

A	B	C	SMILES
Internal ID	PubChem CID		
OSM-E-1	PT-1-10	57519183	FC1=CC=C(N2C
OSM-E-10	PT-1-6; PT-1-7; PT-1-8; PT-1-9		FC1=CC=C(N2C
OSM-E-11	PT-1-11		FC1=CC=C(N2C
OSM-E-12	PT-1-4		FC1=CC=C(N2C
OSM-E-13	PT-1-3		FC1=CC=C(N2C
OSM-E-14	PT-1-13	10877131	O=C(O)C(=O)C
OSM-E-15	JS 21-1		FC(O)C(=O)C
OSM-E-16	JS 19-1		CC(C)=C(C)C
OSM-E-17	JS 20-1		N(C)C(=O)C
OSM-E-18	JS 10-1		CC1=CC=CC=N
OSM-E-19	JS 11-1		CC1=CC=CC=N
OSM-E-2	PT-1-12		FC1=CC=C(N2C
OSM-E-20	JS 12-1		CC1=CC=CC=C
OSM-E-21	JS 15-1		O=C(NC1=CC=CC
OSM-E-22	JS 16-1		O=C(NC1=CC=CC
OSM-E-23	TF 8-1		OCC(O)C(=O)C
OSM-E-24	TF 16-1		NC1=C2C(C)C=C
OSM-E-25	TF 3-1		NC1=C2C(C)C=C
OSM-E-26	TF 4-1		NC1=C2C(C)C=C
OSM-E-27	TF 7-1		OCCNC1=C2C(C
OSM-E-28	TF 1-1		CC1=C2C(C)C=C
OSM-E-29	TF 2-1		NC1=C2C(C)C=C
OSM-E-3	PT-1-6		FC1=CC=C(N2C

Open Data



Community

Contributions



Students → Pharma

“Open” Needs Clarity re Freedoms

Open Access – to read

Open Data – to re-use

Open Innovation – to ... what?

Open Science – something more, like samples, liberal licence

Open Source – all that, and **full details** and can **participate**

Licences (yawn) define the essential freedoms

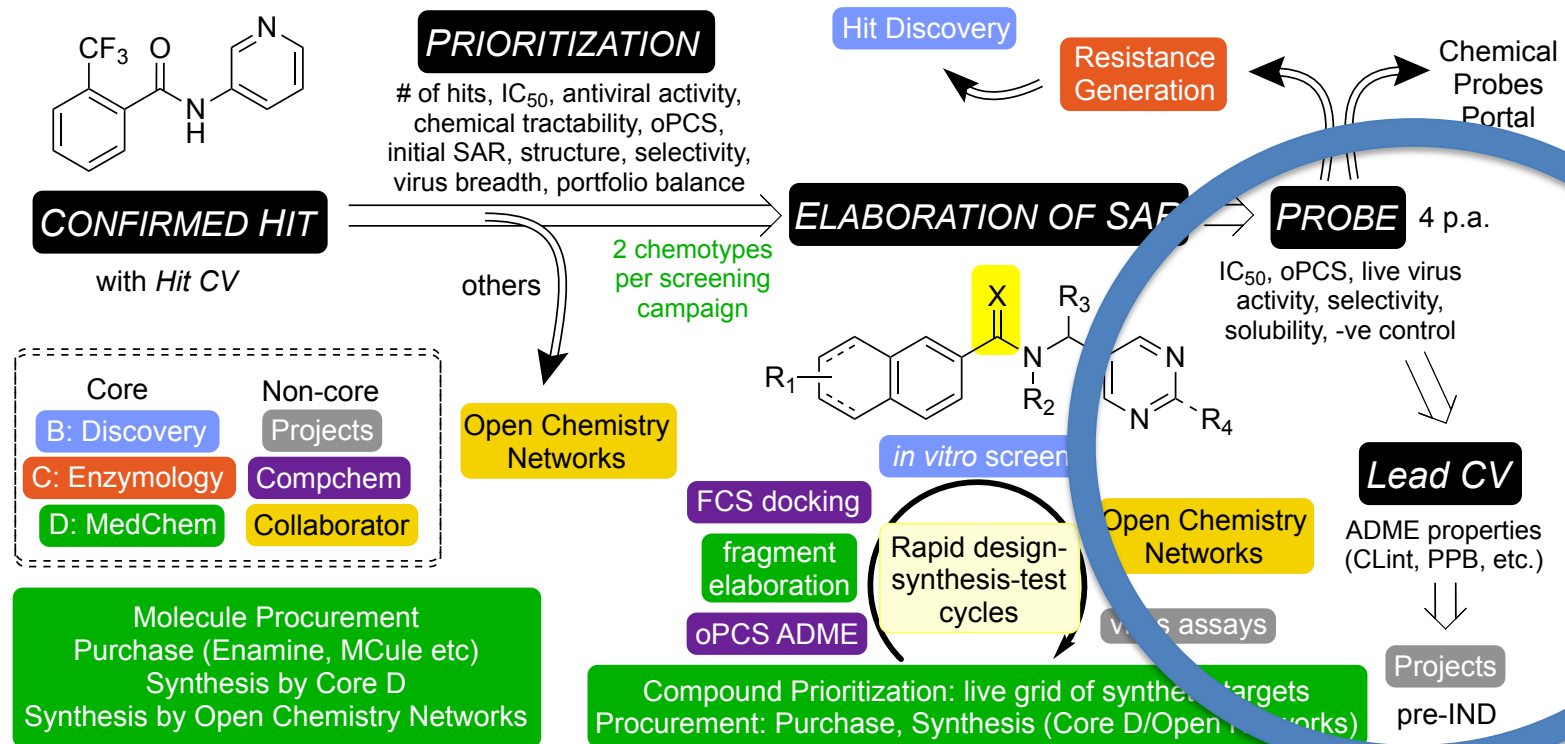
e.g. Wikipedia’s licence:

This page was last edited on 21 September 2022, at 05:49 (UTC).

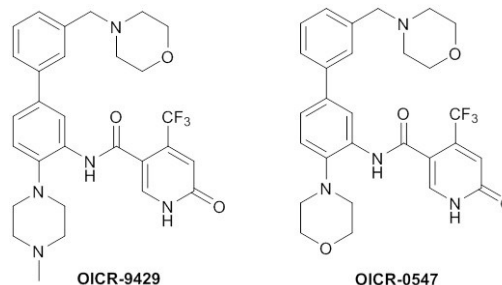
Text is available under the [Creative Commons Attribution-ShareAlike License 3.0](#); additional terms may apply. [Edit this page](#).
Wikimedia Foundation, Inc., a non-profit organization.

READDI-AViDD: All Hit to Probe 100% Open, Providing Translational Options

A biological tool molecule ("probe") can be converted into a drug (which is different)



e.g.: Public domain tool for protein WDR5



→ \$1Bn investment from Celgene to progress it towards a drug

Structure of SGC Open Chemistry Networks Projects

SGC Open Chemistry Networks

Parent SGC website

Not community curated
Lists targets, status, rationale
RULES and LICENCE
Links out to project hubs

Raw Data

Managed by individuals
Electronic Lab Notebooks
Essential criteria:
1) Openness/licence; 2) Completeness
3) Permanence; 4) Machine readability

Probe Hubs

Managed by 1) science leads; 2) community; 3) industry mentor;
4) *Student Champion*
Includes: project status suitable for outsiders, To Do Lists, discussion forum, file store etc

Living Paper

Hosted by a journal
New version released upon milestones
Cleanest version of Project Status
Maintains authorship list
Incentivizes
(We've a journal interested)

Monthly Science Meetings

Each project.
Open to all.
Zoom, recorded.
Placed on Youtube
Linked to Action Items on Hub

SGC Chemistry Networks Social Media

Used by SGC admin, probe leads, contributors
Disseminates new results
Sends out community requests
Advertises through fun posts of contributors

Publicity/Outreach

Promoting project
Route to donations
Logo:
"Proudly Partnering with the SGC"
(click here to find out what this means)
→ Page of terms

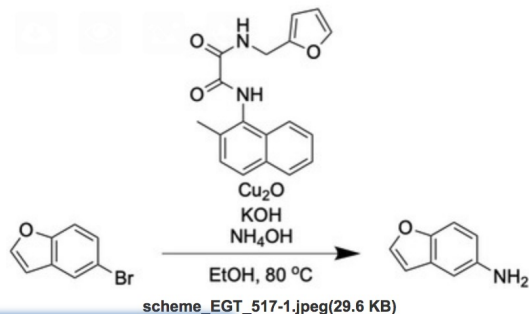


Open Tech: Simple Technologies Help Dramatically with *Discoverability*

Public Lab Notebooks and Other Data Tools are Available, but Under-used. They'll grow.

Synthesis of benzofuran-5-amine (EGT 517-1)

Edwin Tse - Nov 09, 2020, 9:47 PM



scheme_EGT_517-1.jpeg(29.6 KB)

Strings

BrC1=CC2=C(OC=C2)C=C1

to

NC1=CC2=C(OC=C2)C=C1

InChI=1S/C8H5BrO/c9-7-1-2-8-6(5-7)3-4-10-8/h1-5H

to

InChI=1S/C8H7NO/c9-7-1-2-8-6(5-7)3-4-10-8/h1-5H,9H2

AYOVPQORFBWFNO-UHFFFAOYSA-N

to

GMOLCSICTCPZCU-UHFFFAOYSA-N

Discoverable

Machine-Readable

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5

All Maps Shopping Images News More Settings To

3 results (0.67 seconds)

pubchem.ncbi.nlm.nih.gov › compound

2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole | C11H11N3

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5,7H2.

Computed by InChI 1.0.5 (PubChem release 2019.06.18). PubChem ...

au-mynotebook.labarchives.com › share

Edwin Tse/OSA Series 2/EGT 467-3 - LabArchives, Your Electronic

...

Edwin Tse/OSA Series 2/EGT 467-3 - created by Edwin Tse on 2020-09-07 17:22:06 UTC. ...

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5,7H2. to.

InChI=1S/C11H10BrN3/c12-11-10(8-4-1-2-6-13-8)14-9-5-3-7-15(9)11/h1-2,4,6H,3,5,7H2 ...

au-mynotebook.labarchives.com › share

Edwin Tse/OSA Series 2/EGT 466-3 - LabArchives, Your Electronic

...

Architecture – Some READDI-AViDD Components

Discussion/To Dos

<https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B>

Nsp13 Pharma Champion: James Day, Astex

Nsp13 Student Champion: Tom Knight (UCL)

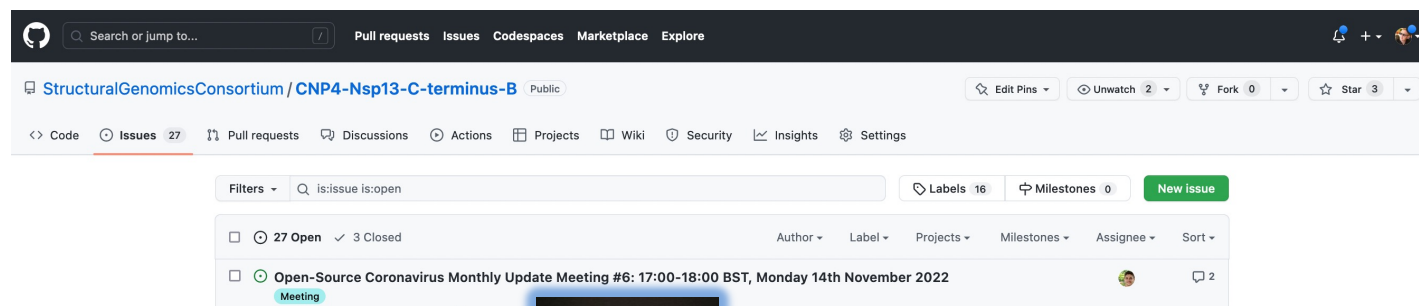
Open lab notebooks, simple compound registration → public data

Socmed for community building: @thesgconline, #sgcoen

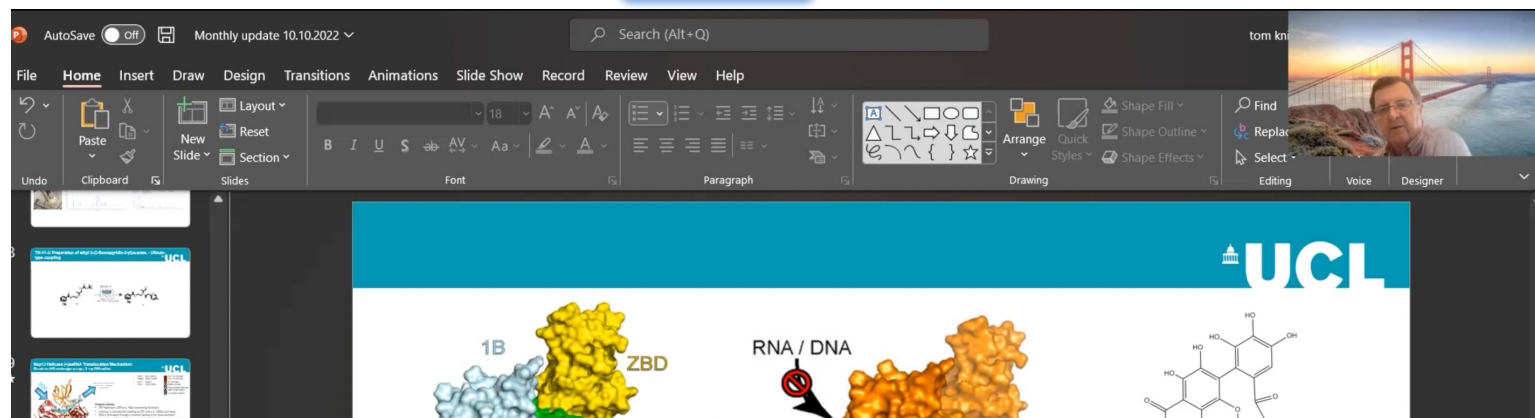
Recorded Zooms → Youtube

Collaborators incoming, e.g.

<https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues/27>



labarchives
Better Science



Fragment Starting Points

https://fragalysis.diamond.ac.uk/viewer/react/preview/target/nsp13

MENU FRAGALYSIS: NSP13 SAVE SHARE DOWNLOAD STRUCTURES

TIMELINE diamond SGC janssen COVID Moonshot CONTRIBUTORS

Tag Details

Tag name	Category	Creator	Date
✓ A - Nucleotide Site	Sites		10/27/2021
B - RNA-3' Site	Sites		10/27/2021
B2 - RNA-3' Site 2	Sites		10/27/2021
C1 - RNA-5' Site	Sites		10/27/2021
C2 - RNA-5' Proximal	Sites		10/27/2021
D1 - RNA-central	Sites		10/27/2021

Hit List Filter: Union

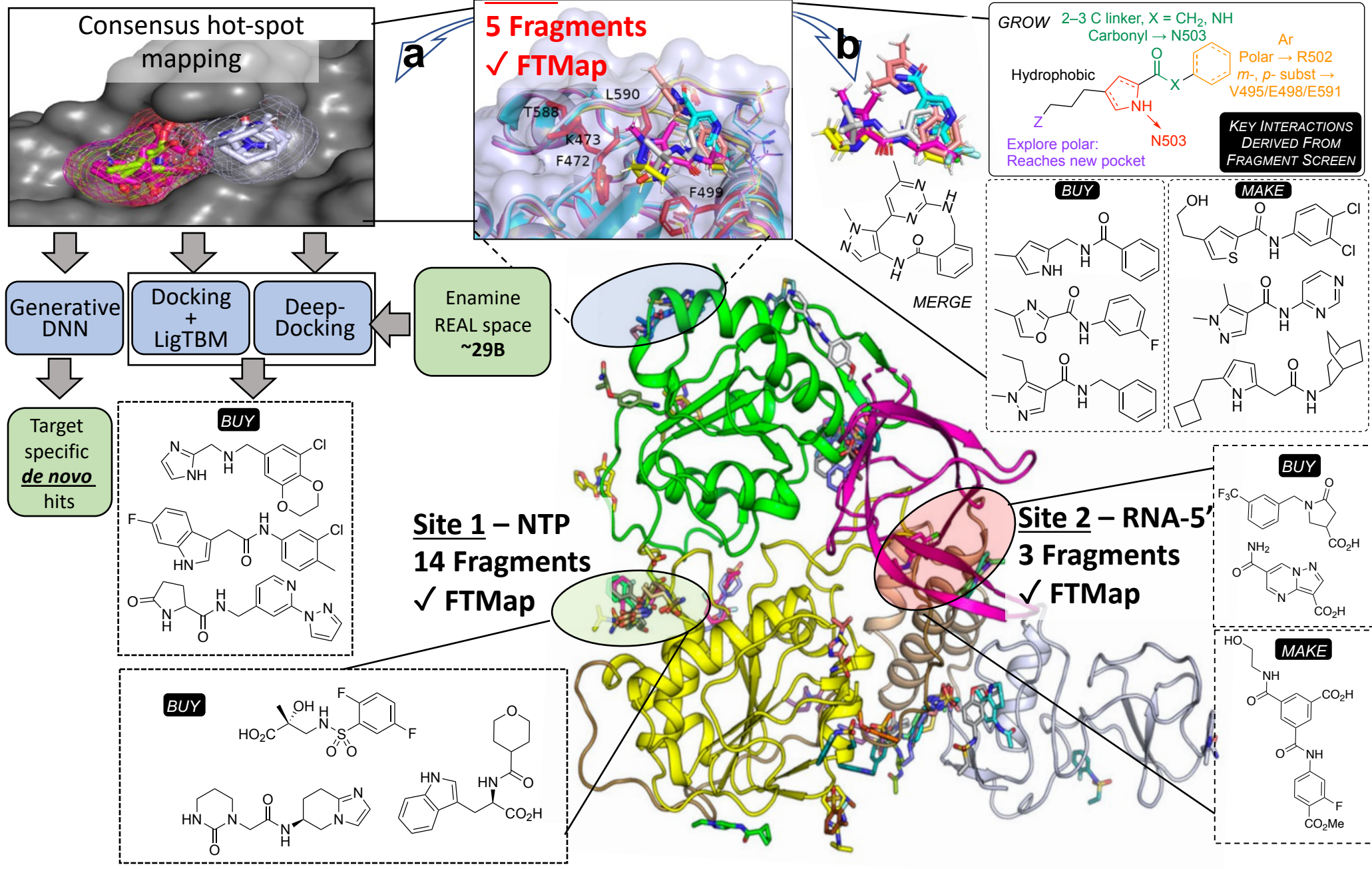
Sites	Series	Discussion	Other
A - Nucleotide Site			
B - RNA-3' Site			
B2 - RNA-3' Site 2			
C1 - RNA-5' Site			
C2 - RNA-5' Proximal			
D1 - RNA-central			
E - Stalk			

Hit navigator

MW	logP	TPSA	HA	Hacc	Hdon	Rots	Rings	Velec	SELECT ALL HITS	Selected: 0
<input type="checkbox"/> X0029_0A	197	1	66	14	2	2	2	1	74	<chem>CC(=O)Nc1ccc(O)c(O)c1</chem>
<input type="checkbox"/> X0034_0B	203	1	60	13	2	1	2	1	72	<chem>Nc1ccc(S(=O)(=O)c2ccccc2)cc1</chem>
<input type="checkbox"/> X0176_0B	199	1	46	13	2	1	4	1	72	<chem>Nc1ccc(S(=O)(=O)CCc2ccccc2)cc1</chem>
<input type="checkbox"/> X0183_0B	199	1	60	13	2	1	3	1	72	<chem>Nc1ccc(S(=O)(=O)C(C)Cc2ccccc2)cc1</chem>

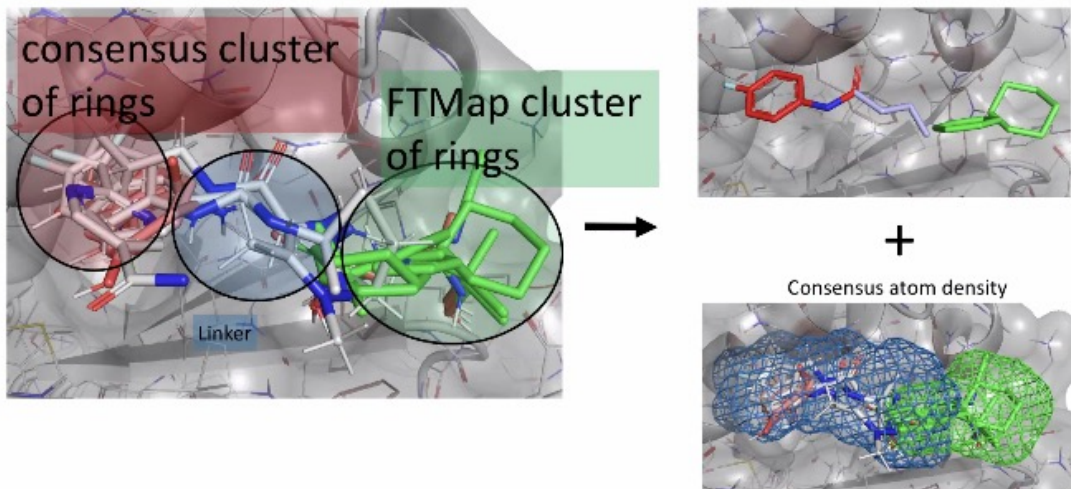
TOTAL 13 LOAD NEXT 30 LOAD NEXT 100 LOAD FULL LIST

LHS [Navigation icons] RHS



Fragment Hits → Pharmacophore Identification/Frag merging

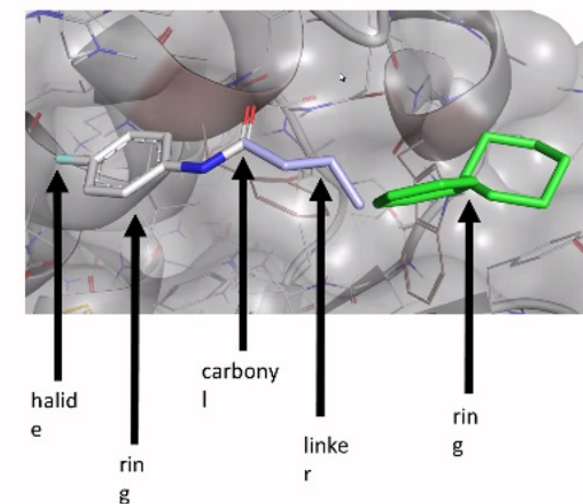
Pharmacophore identification



Pharmacophore identification

Score points:

- 1 point: Has only a halide
- 1 point: Has only a ring
- 1 point: Has only a carbonyl
- 2 points: Has a halide and a ring, unconnected
- 2 points: Has a carbonyl and a ring, unconnected
- 2 points: Has a halide and a carbonyl, unconnected
- 3 points: Has a halide, a carbonyl, and a ring, unconnected
- 3 points: Has a halide and ring connected correctly
- 3 points: Has a carbonyl and a ring connected correctly
- 4 points: Has a halide and a ring connected correctly, and a carbonyl
- 4 points: Has a carbonyl and a ring connected correctly, and a halide
- 5 points: Has full pharmacophore match



Oxford Soaking Results Jan 2022 #14

[Open](#) edwintse opened this issue on Jan 24 · 2 comments

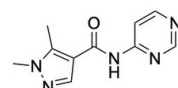
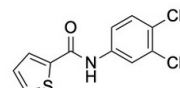


edwintse commented on Jan 24

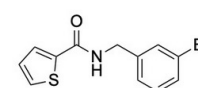
Member

Following from issue #9, the results from the soaking experiments are summarised below:

NO DIFFRACTION

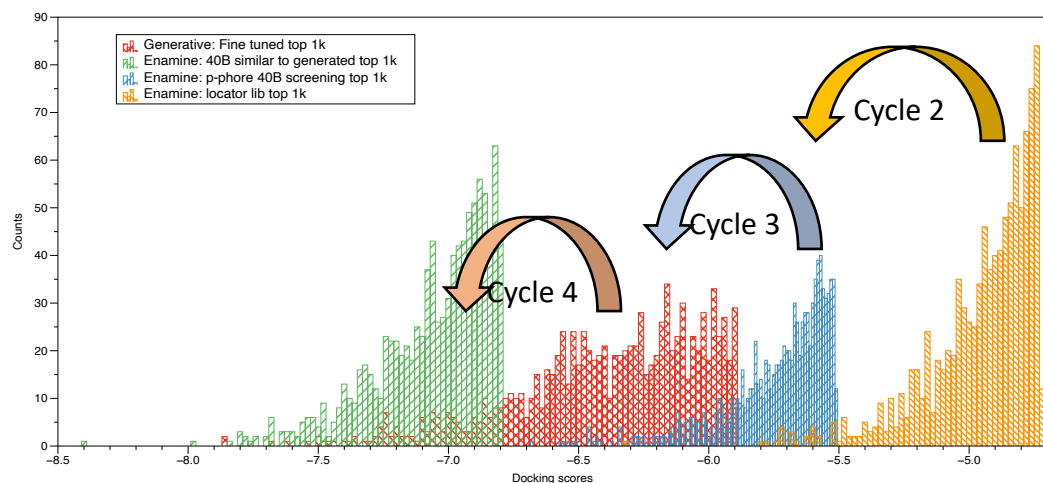
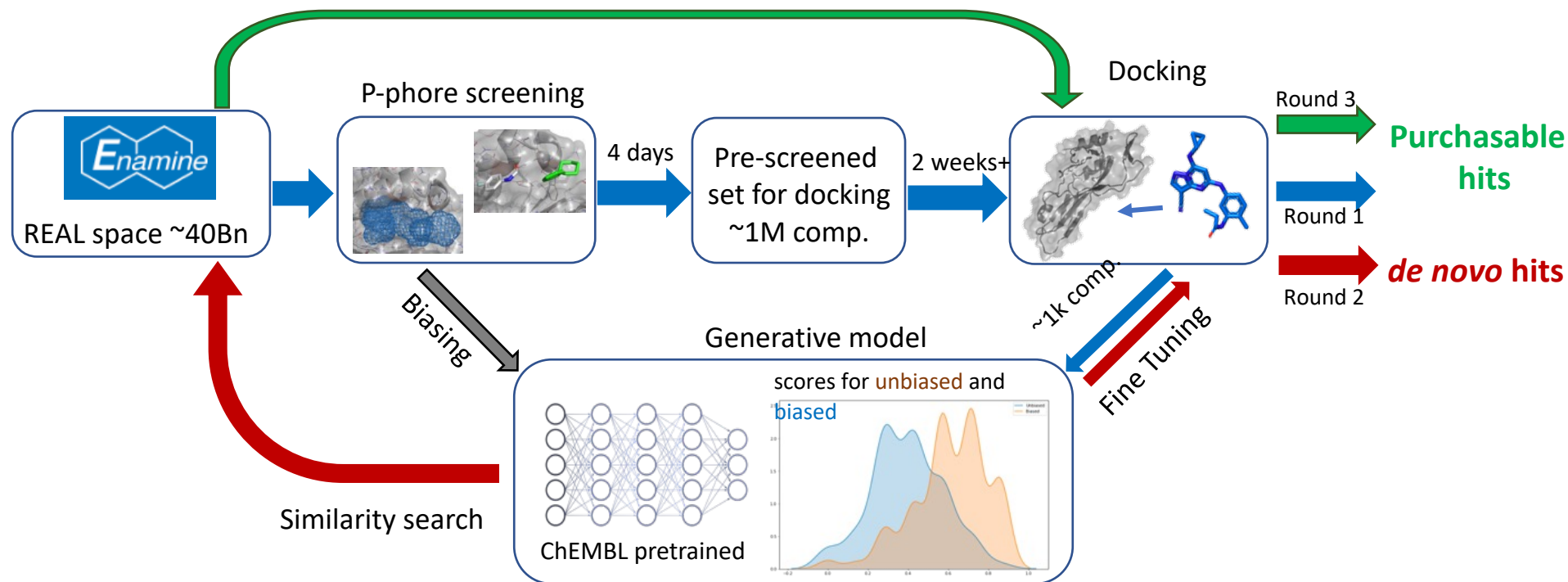


MISSED DIFFRACTION



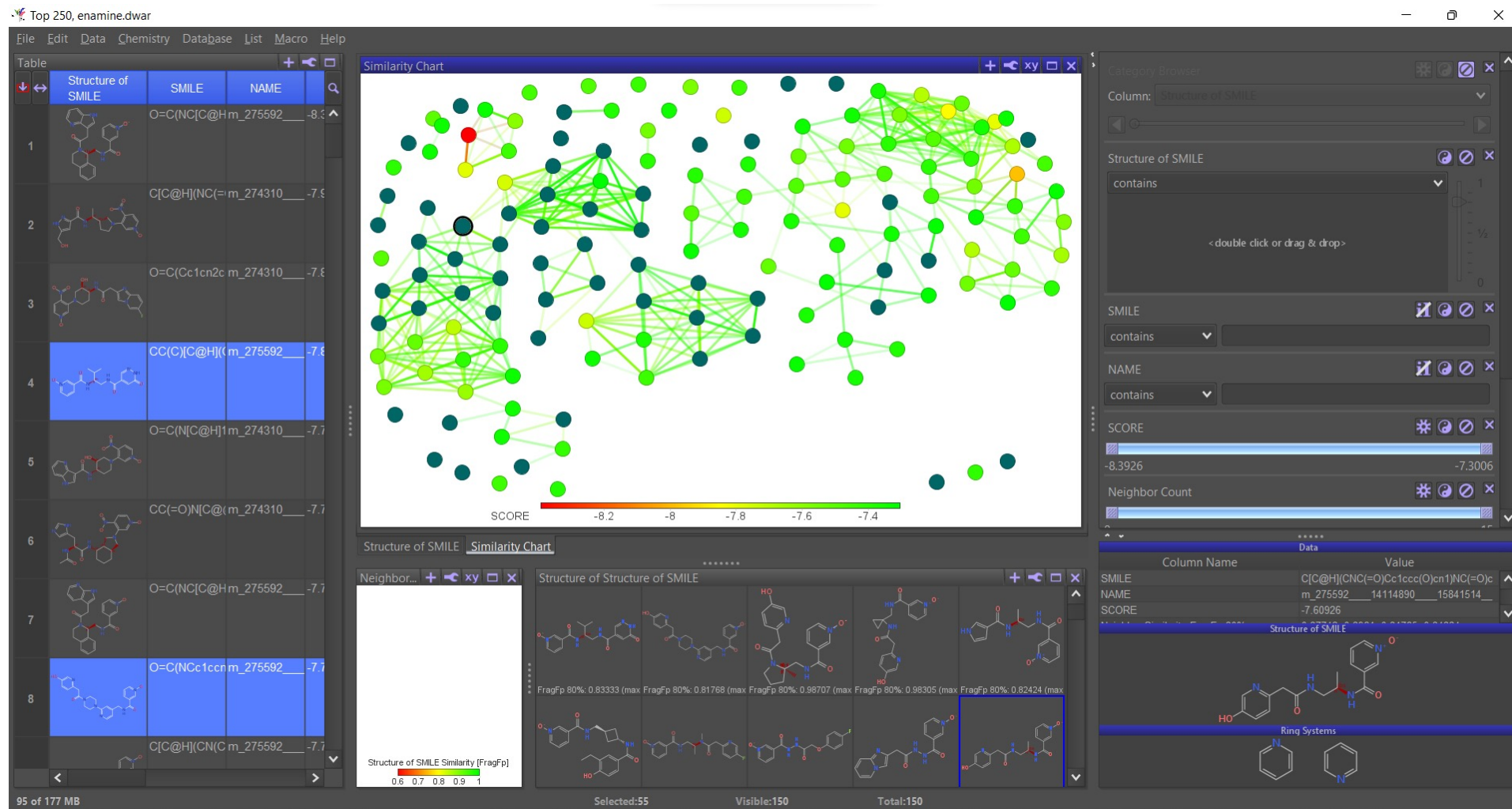
Kostya Popov, Alex Tropsha, Heba Agha, Joe Newman, Ed Tse

Forget the Frags: Structure-based virtual screening workflow





- Pharmacophore screening of 40 Billion analogs.
- Each cycle seeds the next generative model.
- Iterative improvement in docking scores.

Enamine REAL Space, Glide Top Ranked 150 Molecules: DataWarrior Analysis to Visualise the Covered Chemical Space

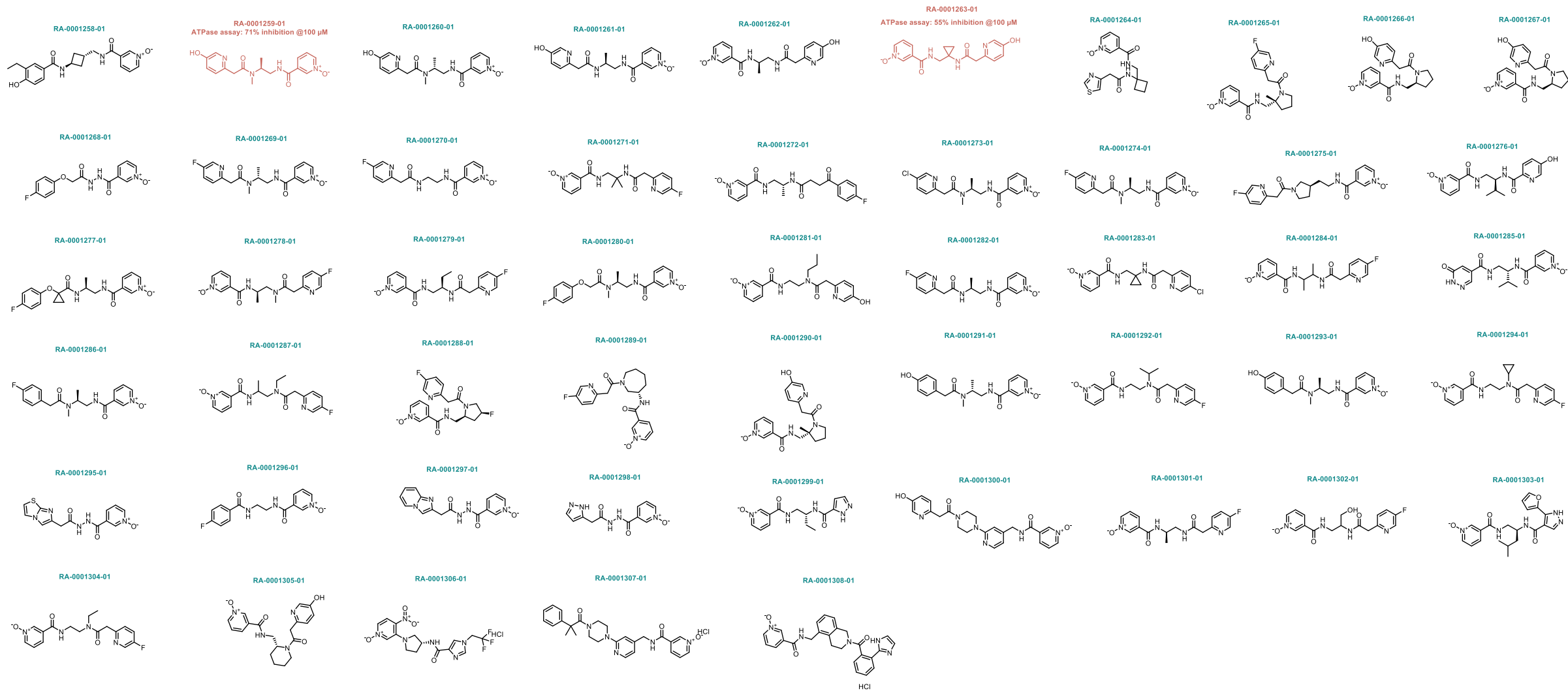


- Similarity chart clusters molecules based on scaffold similarity.

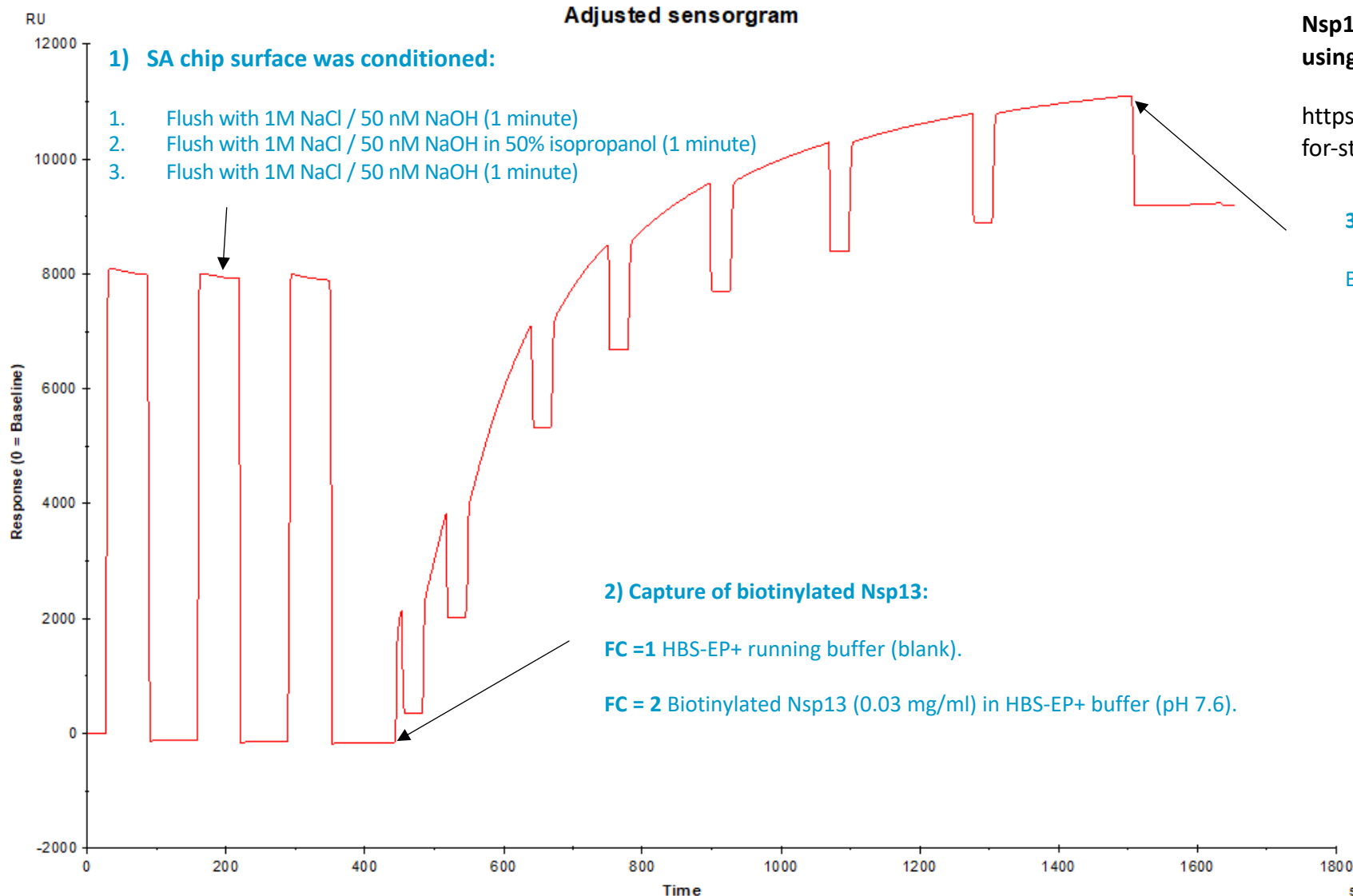
 Enamine make-on-demand (Buy = 55 molecules).
 Glide score -8.1 to -7.2 (Make = 95 molecules).

Enamine REAL Space, Glide Top Ranked 150 Molecules: DataWarrior Analysis to Visualise the Covered Chemical Space

- Enamine make-on-demand; 51/55 compounds purchased.
- 51 compounds in DMSO (50 μ L, 20 mM) for SPR screen (ongoing).



Developing an SPR Assay: High-affinity capture of biotinylated Nsp13 onto streptavidin (SA) chip surface.

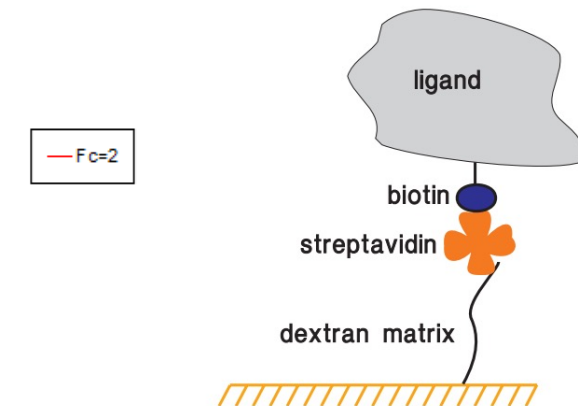


Nsp13 protein was coupled to a Cytiva Series streptavidin (SA) chip using the Biocore T100 standard SA-Biotin capture protocol:

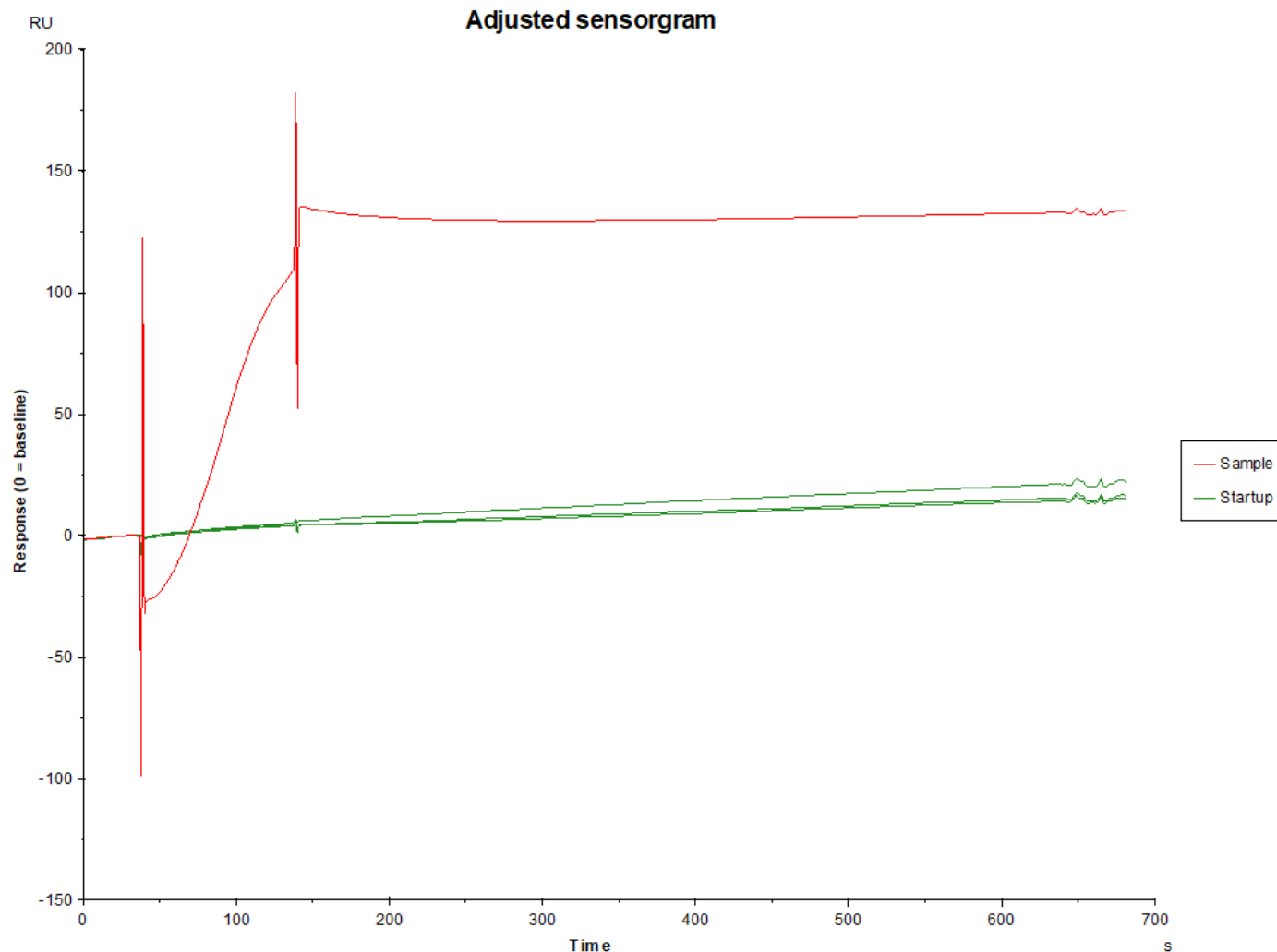
https://info.cytivalifesciences.com/Biacore-help-files_Biotinylation-for-streptavidin-biotin-capture.html

3) Capture of biotinylated Nsp13 reaches near saturation:

Biotin capture was successful, just under 10'000 RU was reached.

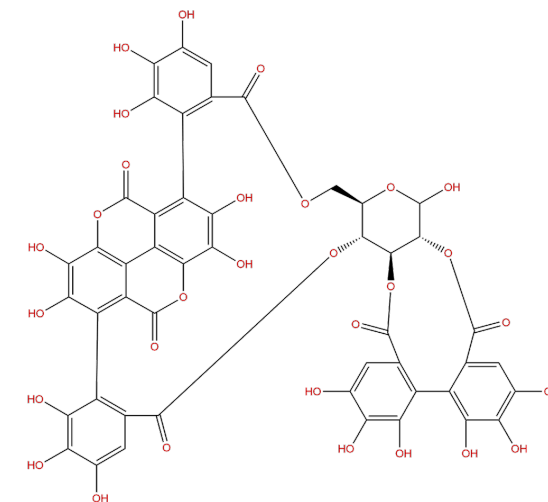


SPR: Screening of control compound #1 (Punicalagin)



A positive control binder (Punicalagin, a.k.a. PUG, $K_D = 21.6$ nm) was flowed over the capture protein to confirm it as a nanomolar binder to Nsp13; <https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues/22#issuecomment-1270191492>

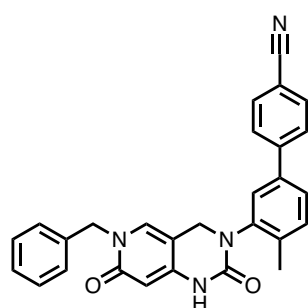
1. PUG, [CAS-No: 65995-63-3] (1.5 mg) was diluted into DMSO (1 mL) to give a 1.3828 mM stock solution.
2. This stock was then diluted to 216 nM (10X K_D) by dissolving 1.5 μ L of the stock solution up to 10 mL with phosphate-buffered saline (PBS, https://info.cytivalifesciences.com/Biacore-help-files_Buffers-for-small-molecule-screening.html) with 2% DMSO.



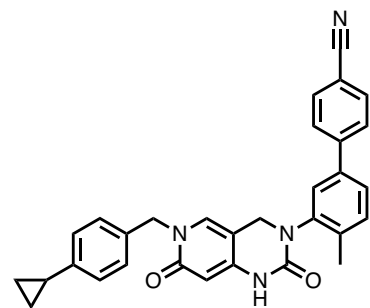
- PUG showed irreversible binding to Nsp13.
- Spikes likely due to mismatched composition of buffers (HBS-EP+ vs PBS).

SARS-CoV-2 Nsp13 First Hits! Targeted Library and Docking of Enamine Real

Targeted Library Designed
for Nsp13
(but different site)*

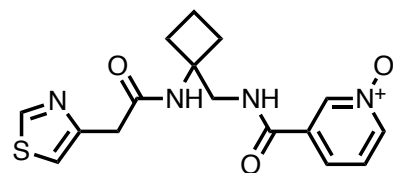


RA-0001313-01

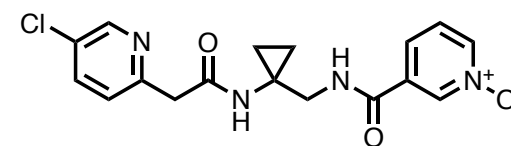


RA-0001335-01

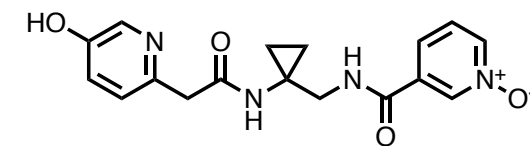
From the docking of 40B compounds
(designed for "site 3")



RA-0001264-01



RA-0001283-01



RA-0001263-01

SARS-CoV-2
SPR KD (μM)

3

3

6

8

11

MERS
SPR KD (μM)

4

3

5

7

11

SARS-CoV-2
ATPase IC₅₀ (μM)

83

NT

48

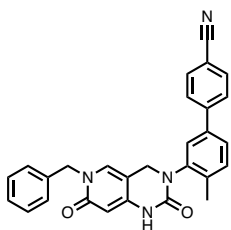
NA

12

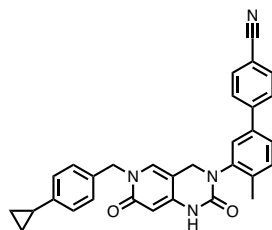
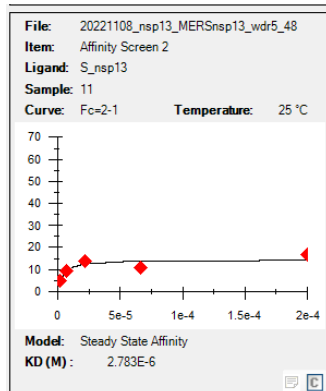
Sumera Perveen, Anwar Hossain, Konstantin Popov.

*Based on allosteric Inhibitors targeting the spliceosomal RNA helicase Brr2, 10.1021/acs.jmedchem.7b00461.

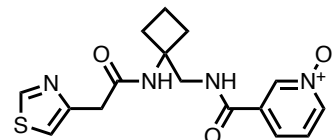
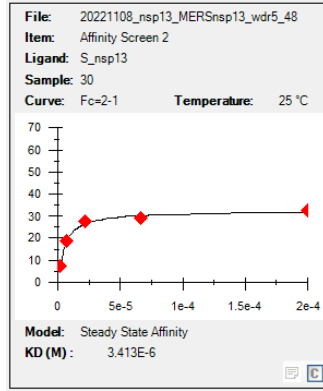
SARS-CoV-2 Nsp13 SPR Sensograms



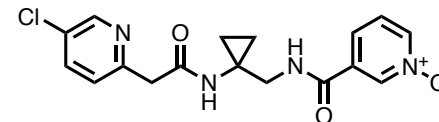
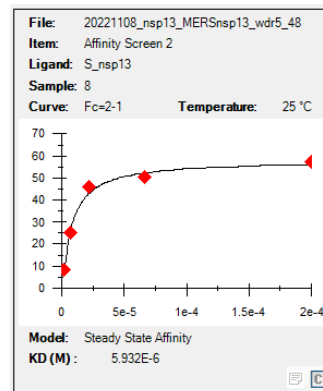
RA-0001313-01



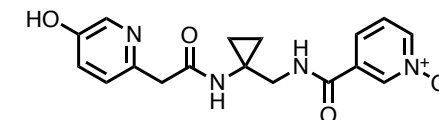
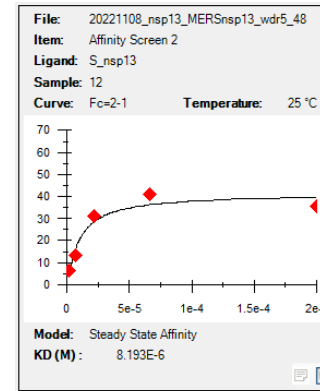
RA-0001335-01



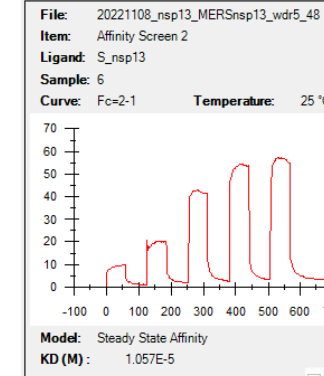
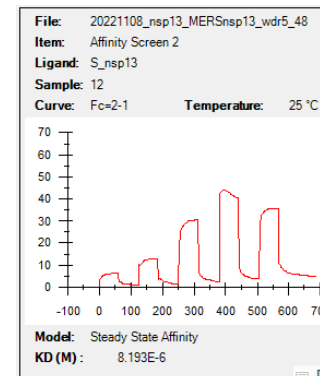
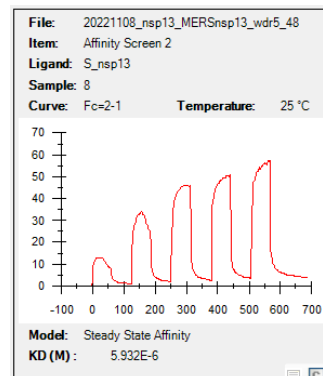
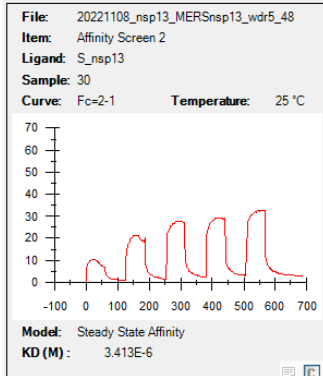
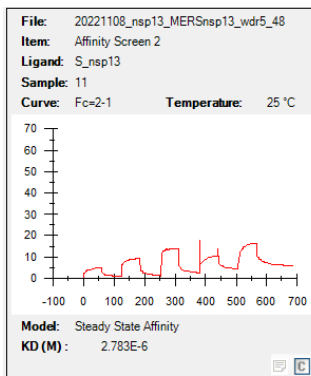
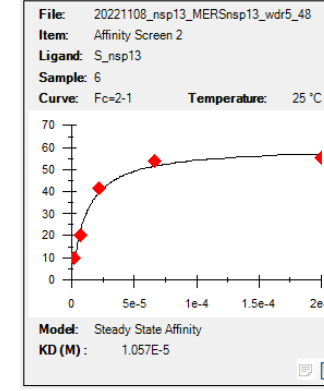
RA-0001264-01



RA-0001283-01



RA-0001263-01



You're Invited

CC-BY-4.0 applies to all hit discovery and hit to lead – i.e. essential freedoms baked in

Join in!

**STRUCTURAL GENOMICS
CONSORTIUM'S OPEN
CHEMISTRY NETWORKS**



tinyurl.com/OCNFAQ

Join in!  **OCN**
Open Chemistry Networks



**STRUCTURAL GENOMICS
CONSORTIUM'S OPEN
CHEMISTRY NETWORKS**



https://github.com/StructuralGenomicsConsortium/Chemistry_TechOps_HowTo/issues/2

Hiring Soon at UCL

Postdoc Chemistry Champions
PDRA Screening/Assays
Lab manager
Ex-Pharma Project Coordinator
Website/Data developer

Volunteer Pharma Champions for all series (time commitment: 3 hrs per month)

See how it works:

Next open, online meeting: December 12th at <https://ucl.zoom.us/j/97172937586>
(<https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues>)

Some Nsp13 People and Funders



UCL: Tom Knight, Ed Tse, Kangping Liu, Jemima Haque, Linda Patio, Robin Ketteler, David Selwood, Clara Gathmann

Chapel Hill: Tim Willson, Nat Moorman, Alex Tropsha, Konstantin Popov, Heba Agha, Peter Brown, Anwar Hossain

Toronto: Cheryl Arrowsmith, Sumera Perveen and team **Diamond/Oxford:** Joseph Newman, Daren Fearon **Astex:** James

Day

And others and the rest of the READD-LAVIDD team



SGC

