IBMC

Way2Drug PREDICTIVE SERVICES
Understanding Chemical-Biological Interactions
www.way2drug.com

Revealing antiviral hits among billion molecules by combination of ligand- and target-based approaches

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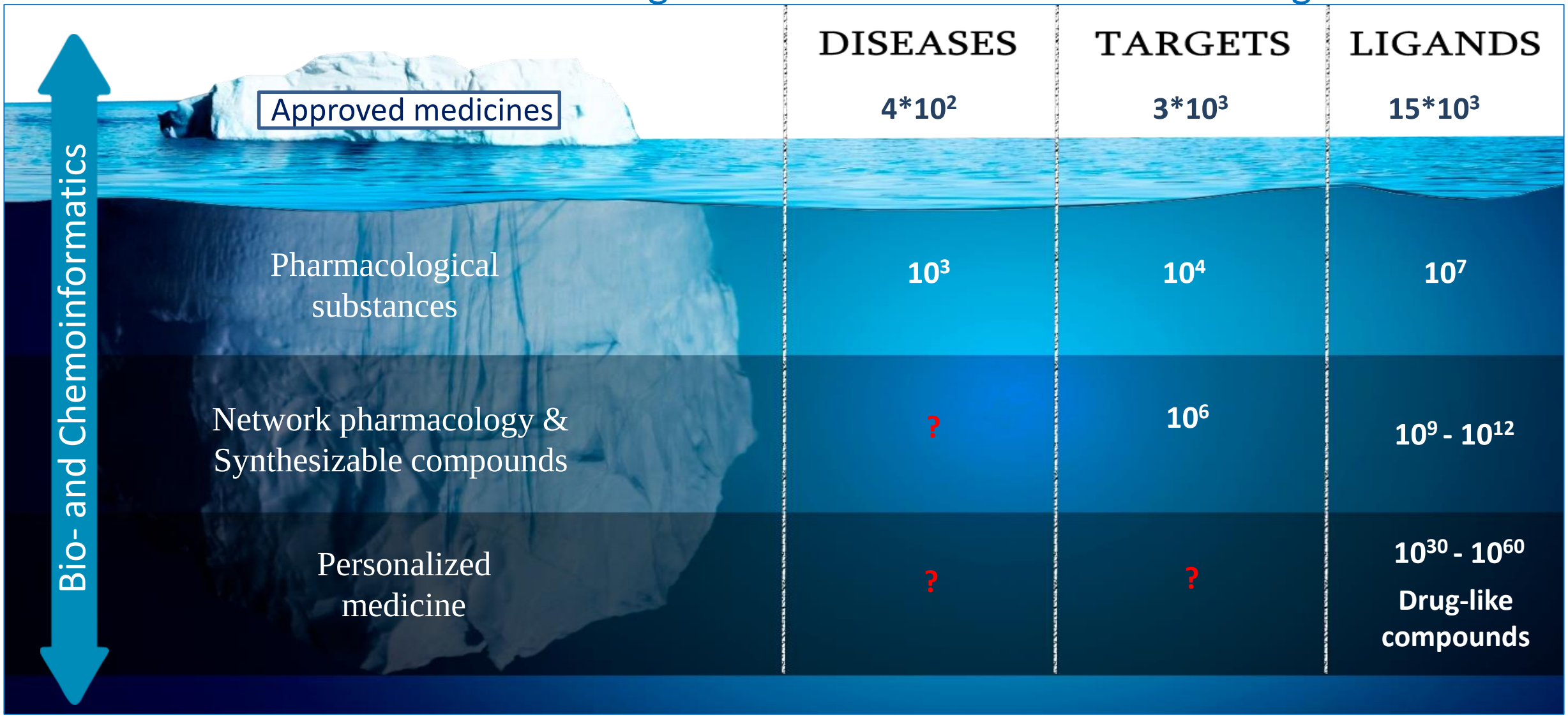
Disclaimer. This document provides an outline of a presentation and is incomplete without the accompanying oral commentary and discussion.

Overview

- Big data in drug discovery.
- Our approach to finding hits in large chemical libraries.
- Finding new anti-HIV hits in SAVI (Synthetically Accessible Virtual Inventory).
- Virtual screening of hits with anti-SARS-CoV-2 action among one billion molecules.
- Summary.

From Molecules to Drugs: Data → Information → Knowledge



Poroikov V.V. Computer-aided drug design: from discovery of novel pharmaceutical agents to systems pharmacology. *Biochemistry (Moscow), Supplement Series B: Biomedical Chemistry*, **2020**, 14 (3): 216–227.

Big Data in virtual chemical space

https://www.biosolveit.de/CoLibri/spaces.html

Exploratory research in Big Chemical databases: “Finding a needle in the haystack”

Local correspondence concept and neighborhoods of atoms descriptors

Dmitry Filimonov

The most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the local correspondence between particular atoms of the ligand and the target.

MOLECULAR BIOLOGY

QUANTUM CHEMISTRY

QUANTUM FIELDS THEORY

$$M = V + VgM = V + VgV + VgVgV + VgVgVg + \ldots$$

$$M_i = V_i + V_i gM = V_i + V_i g(M_1 + M_2 + \ldots + M_m)$$

Descriptors are based on the concept of atoms' of molecule taking into account the influence of the neighborhoods:

MNA - Multilevel Neighborhoods of Atoms
QNA - Quantitative Neighborhoods of Atoms
LMNA - Labeled Multilevel Neighborhoods of Atoms

Filimonov D.A. et al. *J. Chem. Inf. Comput. Sci.*, **1999**, 39 (4): 666-670.
Filimonov D.A. et al. *SAR and QSAR Environ. Res.*, **2009**, 20 (7-8): 679-709.
Rudik A.V. et al. *J. Chem. Inform. Model.*, **2014**, 54 (2): 498–507.

Similarity assessment based on MNA descriptors

For MNA descriptors, the well-known measure of similarity of two discrete sets:

$$T(A,B) = \frac{n(A \cap B)}{n(A \cup B)} \equiv \frac{n(A \cap B)}{n(A) + n(B) - n(A \cap B)} \qquad (1)$$

may be used where $n(A \cap B)$ is the number of MNA descriptors at the intersection of the sets of descriptors of molecules A and B; $n(A \cup B)$ equivalently in their union.

Druzhilovskiy D.S., Stolbov L.A., Savosina P.I., Pogodin P.V., Filimonov D.A., Veselovsky A.V., Stefanisko K., Tarasova N.I., Nicklaus M.C., Poroikov V.V. Computational approaches to identify a hidden pharmacological potential in large chemical libraries. *Supercomputing Frontiers and Innovations*, **2020**, 7(3): 57-76.

Similarity assessment based on QNA descriptors

We propose an estimate *F(A,B)* of the similarity of molecular structures by QNA descriptors, using the Todeschini approach and Tanimoto's similarity measure, defined as:

$$F(A,B) = \frac{n(A \cap B)}{n(A) + n(B) - n(A \cap B)} \qquad (2)$$

where $n(A) = N_A$ and $n(B) = N_B$ is the number of pairs P and Q of the QNA descriptors of molecules A and B, respectively, $n(A \cap B)$ is calculated as:

$$n(A \cap B) = \frac{1}{2}\left(\sum_A \max_{b \in B}[s_{ab}] + \sum_B \max_{a \in A}[s_{ba}]\right) \qquad (3)$$

$$s_{ab} = Exp\left(-12N_B\left((P_a - P_b)^2 + (Q_a - Q_b)^2\right)\right) \qquad (4),$$

$$s_{ba} = Exp\left(-12N_A\left((P_a - P_b)^2 + (Q_a - Q_b)^2\right)\right) \qquad (5),$$

where s_{ab} and s_{ba} are the pairwise similarity of the QNA descriptor of atom *a* of molecule A and the QNA descriptor of atom *b* of molecule B, P_a and Q_a are the QNA descriptor of atom *a* in molecule A, P_b and Q_b are the QNA descriptor of atom *b* in molecule B. The multipliers $12N_B$ and $12N_A$ in the exponent have been chosen empirically. The proposed estimates of the similarity of the structures of drug-like compounds A and B based on our QNA descriptors are entirely new and do not have analogs.

Druzhilovskiy D.S., Stolbov L.A., Savosina P.I., Pogodin P.V., Filimonov D.A., Veselovsky A.V., Stefanisko K., Tarasova N.I., Nicklaus M.C., Poroikov V.V. Computational approaches to identify a hidden pharmacological potential in large chemical libraries. *Supercomputing Frontiers and Innovations*, **2020**, 7(3): 57-76.

Validation of the proposed similarity assessment

Target	Number of structures	Q^2, MNA	Q^2, QNA
HIV-1 integrase	4072	0.7895	0.7946
HIV-1 protease	6390	0.8007	0.8052
HIV-1 reverse transcriptase	6308	0.6933	0.6980

Values of Q^2 based on similarity estimates by MNA and QNA descriptors at 5NN

SUPERCOMPUTING FRONTIERS AND INNOVATIONS
An International Journal

Druzhilovskiy D.S., Stolbov L.A., Savosina P.I., Pogodin P.V., Filimonov D.A., Veselovsky A.V., Stefanisko K., Tarasova N.I., Nicklaus M.C., Poroikov V.V. Computational approaches to identify a hidden pharmacological potential in large chemical libraries. *Supercomputing Frontiers and Innovations*, **2020**, 7(3): 57-76.

PASS 2019 version (launched in July, 2019)

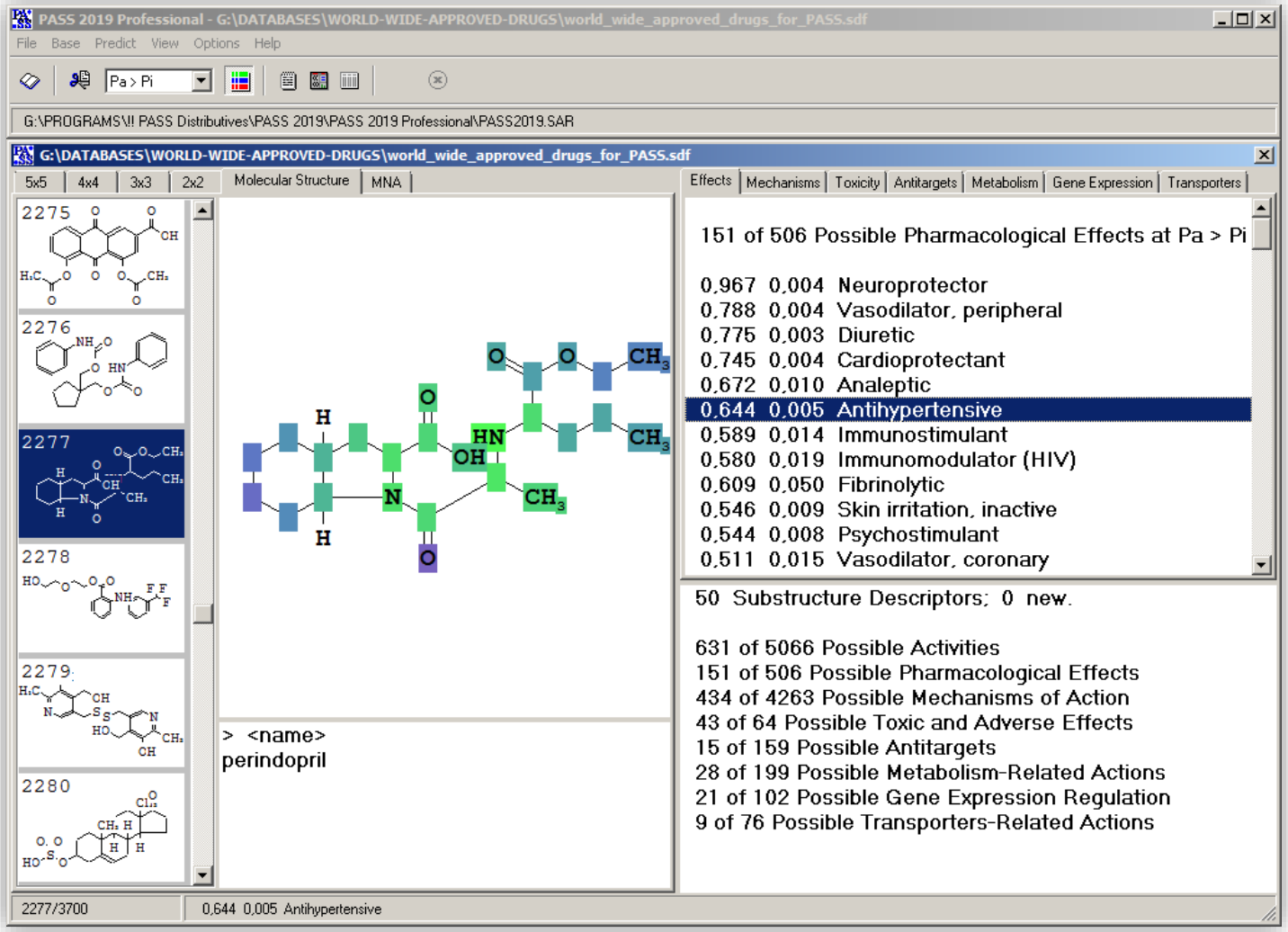
Way2Drug PREDICTIVE SERVICES
Understanding Chemical-Biological Interactions

Prediction of Activity Spectra for Substances

2019

30 Years Anniversary of PASS

SAR Base Information	1989	2019
Substances	9 314	1 025 468
Descriptors		106 816
Activity Types	114	8 054
Selected Activity Types		5 066
Average Prediction Accuracy	0.74	0.96



Burov Yu.V., Poroikov V.V., Korolchenko L.V. National system for registration and biological testing of chemical compounds: facilities for new drugs search. Bulletin of the National Center for Biologically Active Compounds, **1990**, No. 1, p.4-25 (Rus.).

Poroikov V.V., Filimonov D.A., Gloriozova T.A., et al. Computer-aided prediction of biological activity spectra for organic compounds: the possibilities and limitations. *Russ. Chem. Bull.*, **2019**, 68 (12): 2143-2154. DOI: 10.1007/s11172-019-2683-0

PASS Online: First in the world web-service for bioactivity prediction (since 2000)

Dmitry Druzhilovskiy

India Russia Ukraine Mexico China United State Egypt Kazakhstan Brazil . . .

Anastassia Rudik

Authorization/privacy

Free availability 24/7/365

> 1,000 publications with the prediction results

1,075,366 predictions

104 countries

29,268 users

Users relationships

Cross-browser and cross-platform support

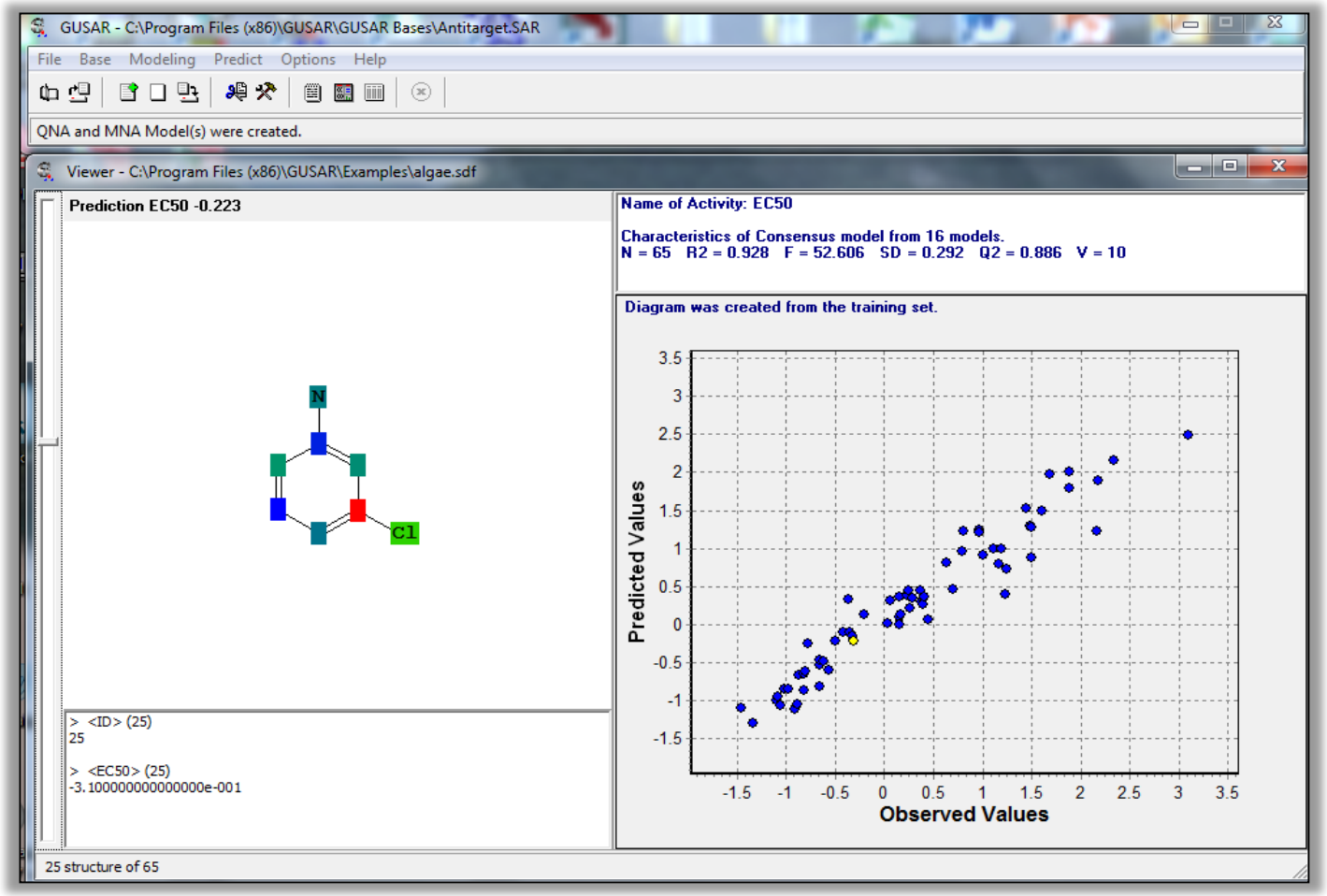
The first publication about PASS Online (PASS Inet).

Lagunin A. et al. *Bioinformatics*, **2000**, 16 (8): 747-748.

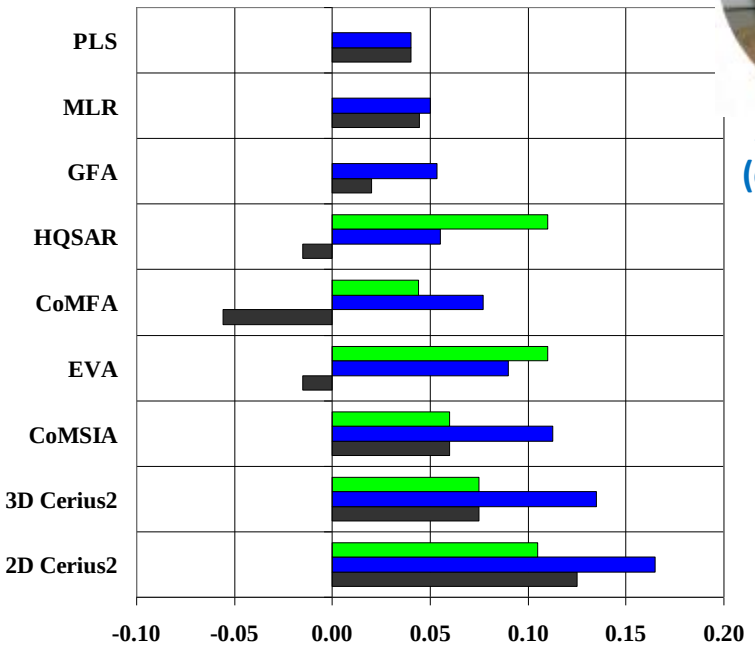
Comparison with the other web services demonstrated the advantages of PASS Online.

Murtazalieva K.A. et al. *SAR and QSAR in Environmental Research*, **2017**, 28 (10): 843-862.

GUSAR: General Unrestricted Structure-Activity Relationships



Alexey Zakharov
(currently, NCATS)



Therapeutic candidates for the Zika virus identified by a high-throughput screen for Zika protease inhibitors

Rachel P. M. Abrams[a,1], Adam Yasgar[b,1], Tadahisa Teramoto[c], Myoung-Hwa Lee[a], Dorjbal Dorjsuren[b], Richard T. Eastman[b], Nasir Malik[a], Alexey V. Zakharov[b], Wenxue Li[a], Muzna Bachani[a], Kyle Brimacombe[b], Joseph P. Steiner[a], Matthew D. Hall[b], Anuradha Balasubramanian[c], Ajit Jadhav[b], Radhakrishnan Padmanabhan[c,2], Anton Simeonov[b,2], and Avindra Nath[a,2]

[a]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892; [b]National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD 20850; and [c]Department of Microbiology and Immunology, Georgetown University, Washington, DC 20057

Filimonov D.A. et al. *SAR and QSAR Environ. Res.*, **2009**, 20: 679-709.
Zakharov A.V. et al. *J. Chem. Inf. Model.*, **2014**, 54: 713-719.
Lagunin A.A. et al. *Frontiers Pharmacol.*, **2018**, 9: 1138.
Stolbov L.A. et al. *Molecules*, **2020**, 25: 87.

www.pnas.org/cgi/doi/10.1073/pnas.2005463117

SAVI: Synthetically Accessible Virtual Inventory

Consortium (2014): Marc Nicklaus & Associates, NCI/NIH; Wolf-Dietrich Ihlenfeldt, Xemistry GmbH; Scott Hutton & Associates, Sigma-Aldrich; Friedrich Rippmann & Associates, Merck KGaA; Peter Ertl, Novartis; Philip Judson & Associates, Lhasa Limited, UK; Alan Long & Associates, Lhasa LLC, U.S.

Marc Nicklaus, NCI/NIH

First (alpha) Release - <u>July 2015</u>

11 transforms were used; 230,000 building blocks; ~610,000 resulting products have been annotated

First (beta) set <u>May 2017:</u>

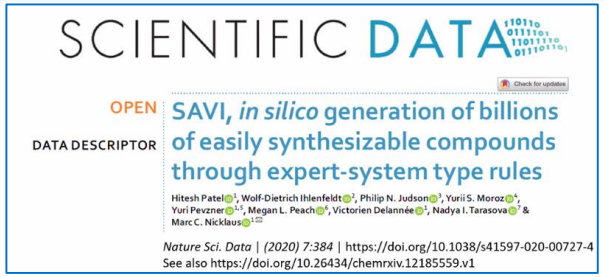
~283 million compounds, generated using 14 "productive" transforms in one-step reactions, was made available for download at **https://cactus.nci.nih.gov/download/savi_download/**

Annotated with 54 properties, such as:

- Data about the building blocks used (Sigma catalog numbers);
- Data about the proposed reaction (reactants, conditions, predicted yield, total cost per gram…);
- "Drug design" properties: RO5/RO3 violations, PAINS filter matches, log P, …

SAVI: Current version

- ~150,000 building blocks (Enamine);
- ~53 transforms;
- 1,75 billion **synthesizable** chemical compounds.



SCIENTIFIC DATA

OPEN

DATA DESCRIPTOR

SAVI, *in silico* generation of billions of easily synthesizable compounds through expert-system type rules

Hitesh Patel[1], Wolf-Dietrich Ihlenfeldt[2], Philip N. Judson[3], Yurii S. Moroz[4], Yuri Pevzner[5,3], Megan L. Peach[6], Victorien Delannée[1], Nadya I. Tarasova[7] & Marc C. Nicklaus[1,8]

Nature Sci. Data | (2020) 7:384 | https://doi.org/10.1038/s41597-020-00727-4

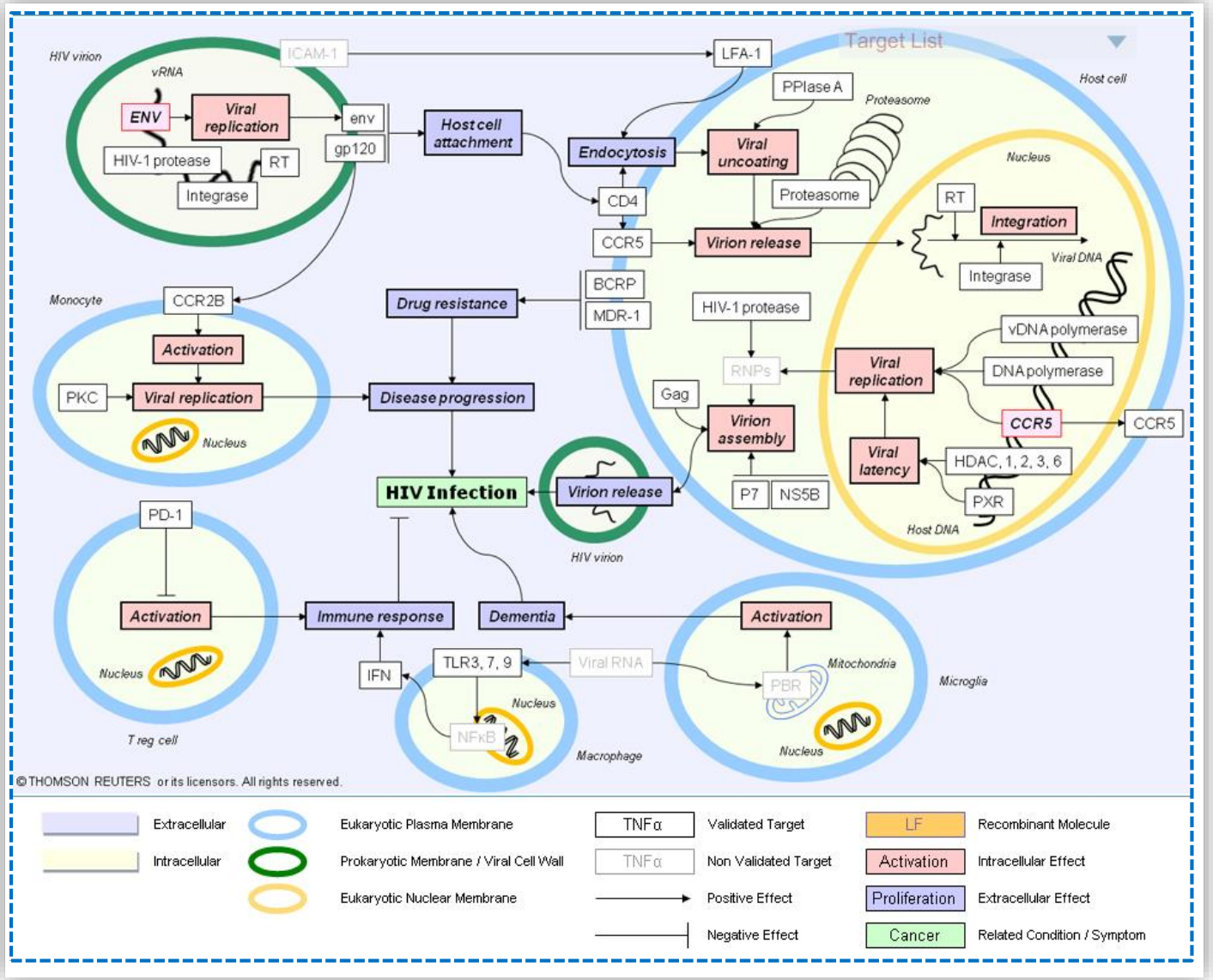
See also https://doi.org/10.26434/chemrxiv.12185559.v1

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

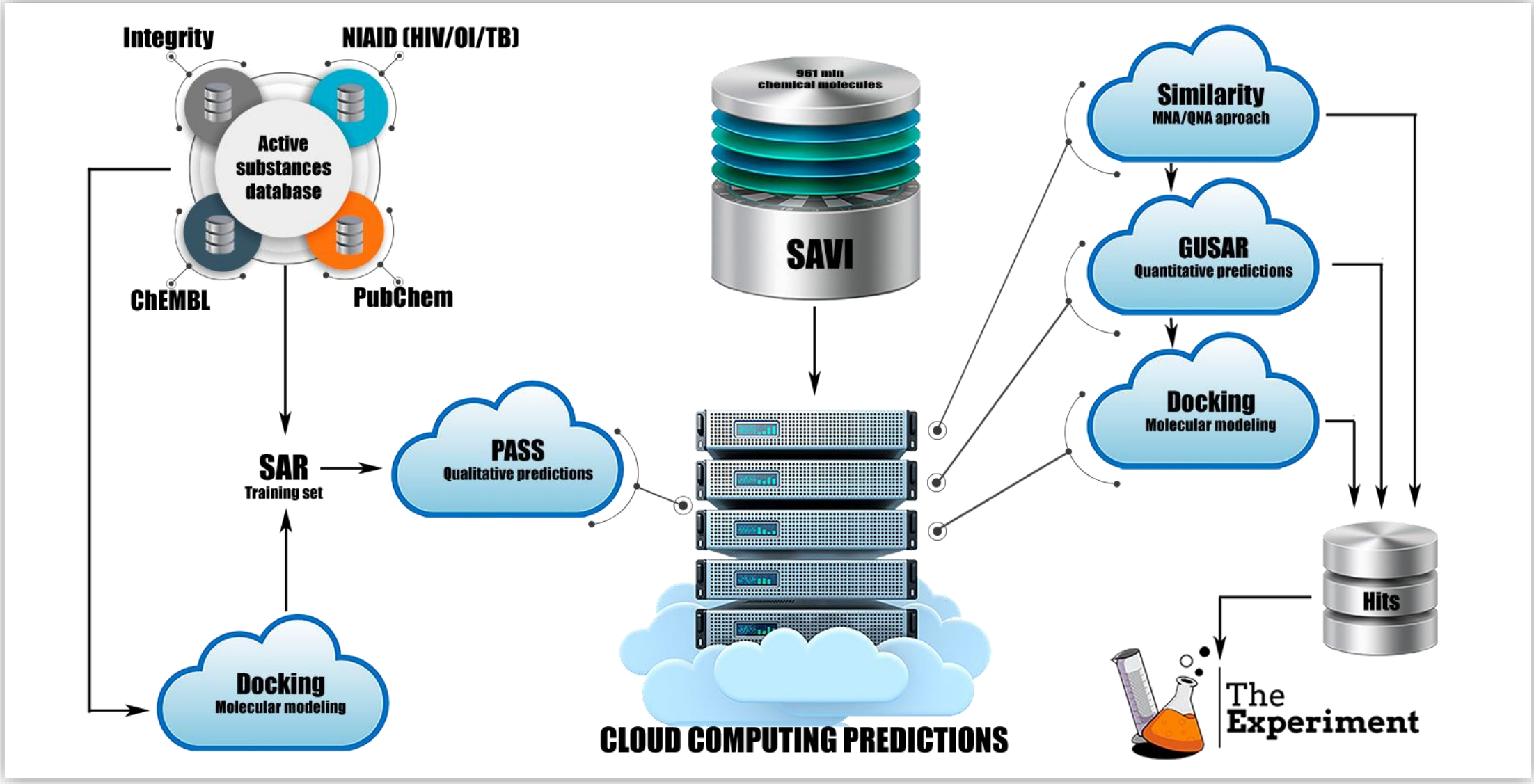
HIV Infection Targetscape



Cortellis Drug Discovery Intelligence

(https://www.cortellis.com/drugdiscovery)

General workflow of the large database analysis for identification of potential pharmacological substances



Creation of the target-specific training sets based on docking

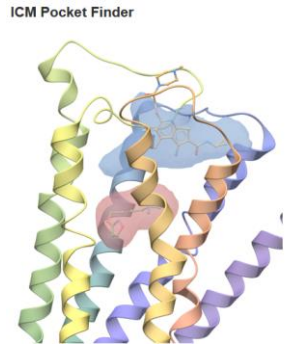
Target	PDB code	Number of compounds before docking	Number of compounds after docking
TLR7	5GMH and 5ZSJ	429	75
STING	4LOH and 5BQX	326	273
Reverse Transcriptase HIV-1	2ZD1	5877	4120
Protease HIV-1	2R5P and 2O4P	2054	1300

Biowulf: NIH's Top-Ranking Supercomputer

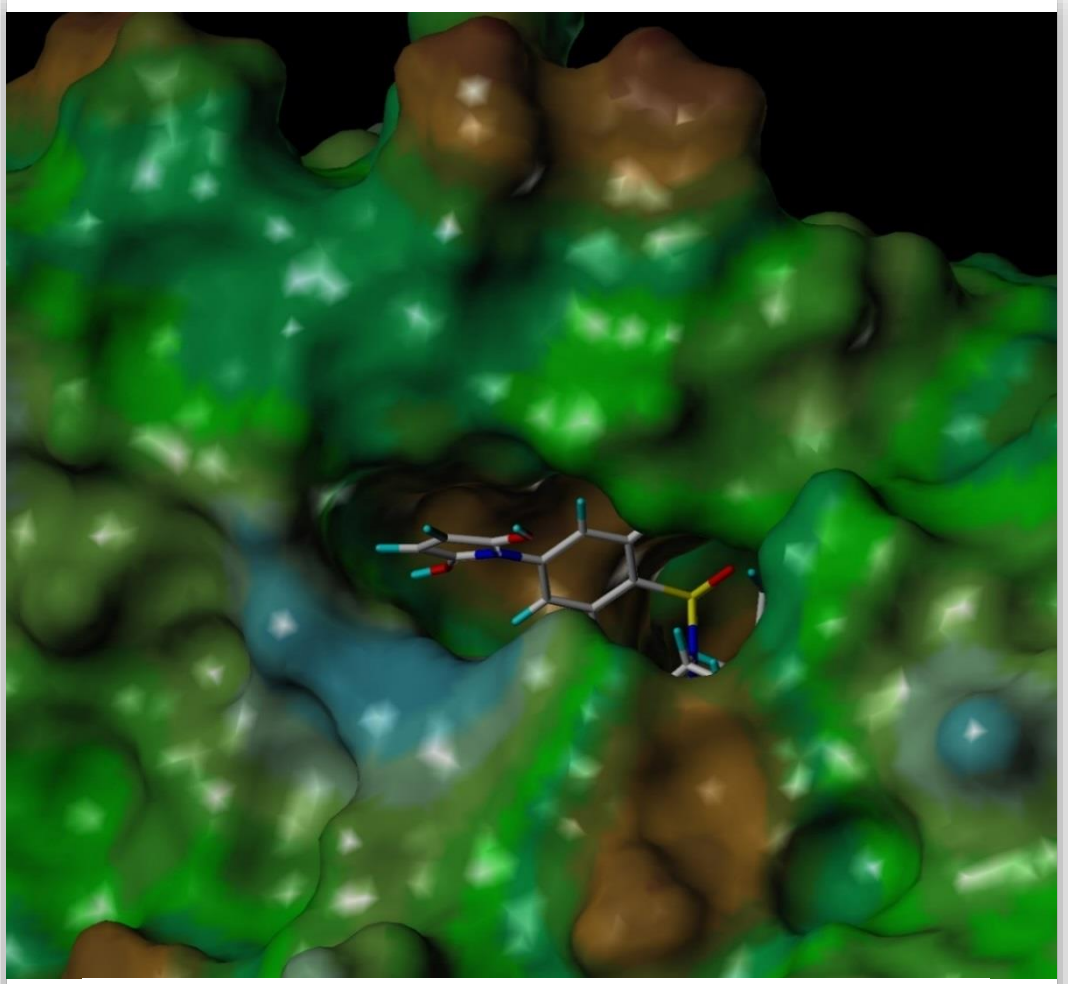
Nadya Tarasova, NCI/NIH

molsoft
molecules in silico

ICM-Pro



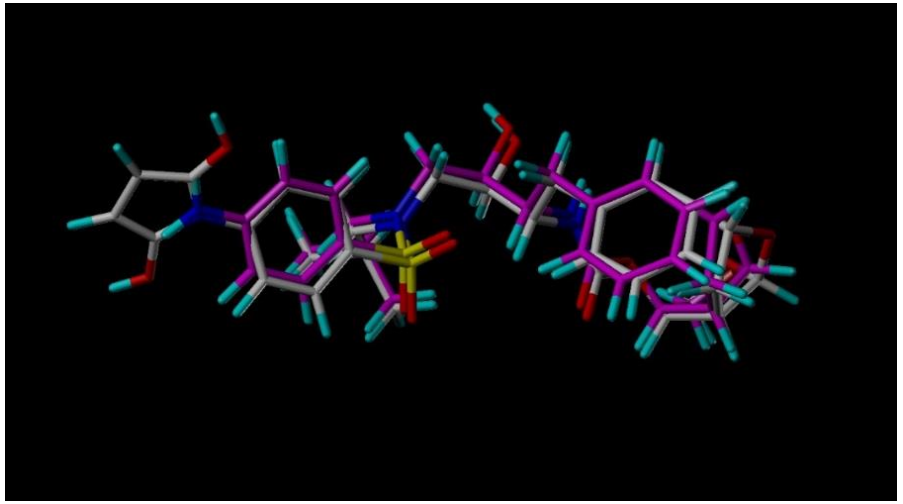
Visual inspection of new hit, found in SAVI in a complex with HIV-1 protease



9A6A69BA66D806BA_98763A2B6A65FDD7_1031(MNA Tanimoto with Darunavir value is 0.78846)

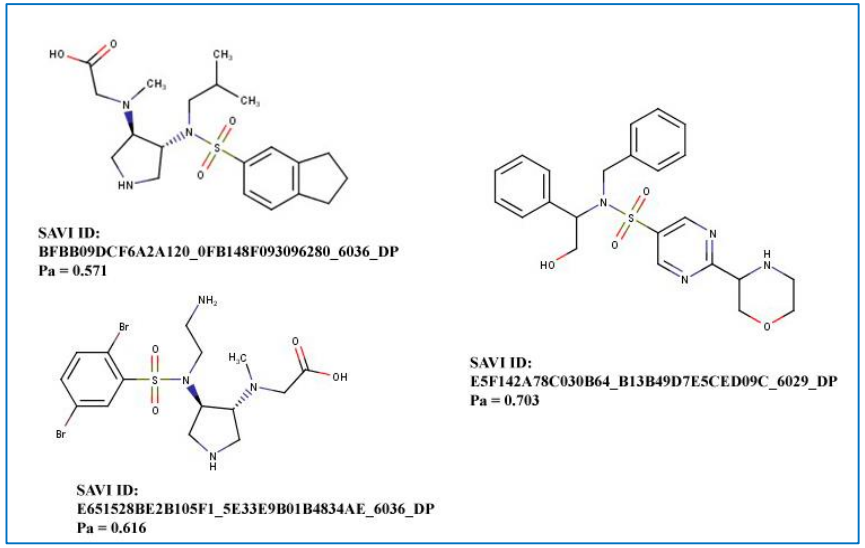
Alexander Veselovsky, IBMC

9A6A69BA66D806BA_98763A2B6A65FDD7_1031
Superposed with Darunavir

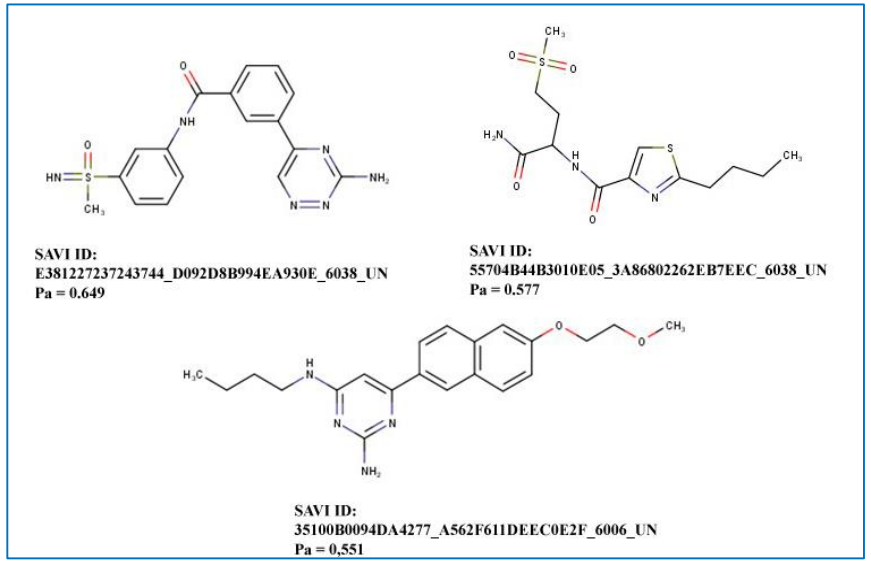


Selection of hits with potential anti-HIV activity

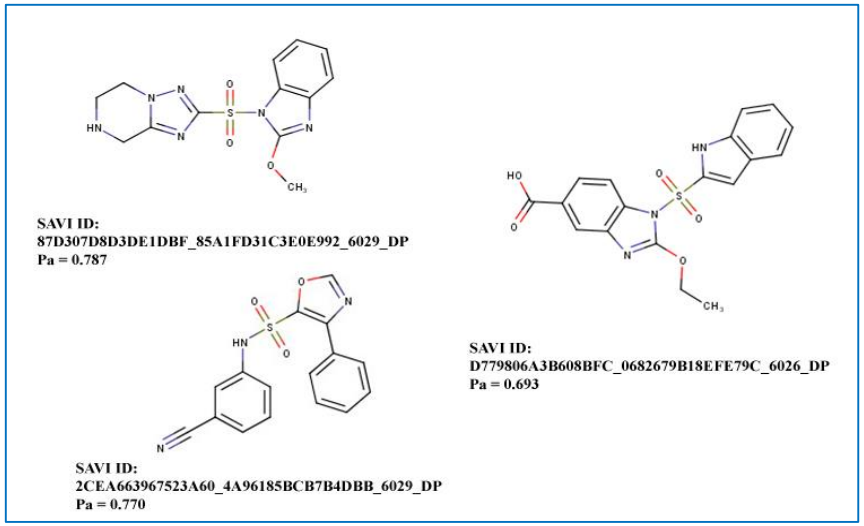
- HIV-1 protease (PR) - **53** comps.
- HIV-1 reverse transcriptase (RT) - **48** comps.
- TLR 7 agonists - **53** comps.
- TLR 8 agonists – **1,378** comps.
- STING agonists - **627** comps.



Examples of potential HIV-1 PR inhibitors

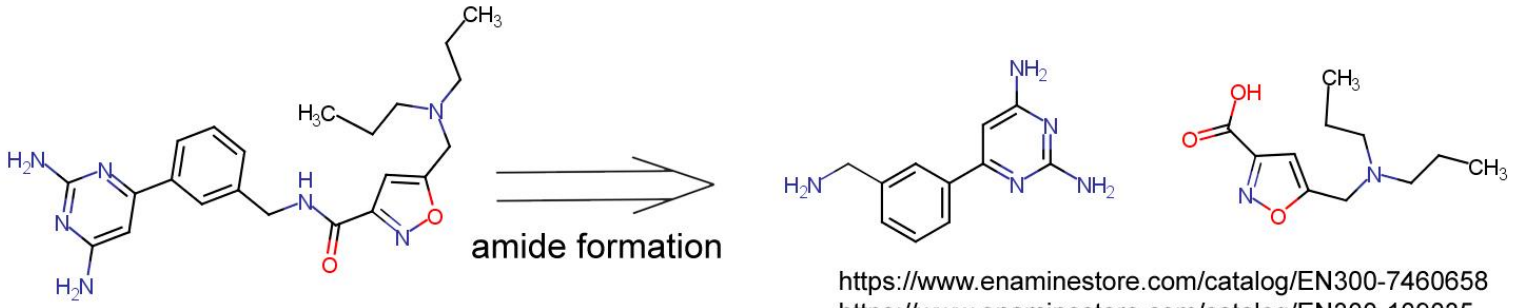


Examples of potential TLR-8 agonists



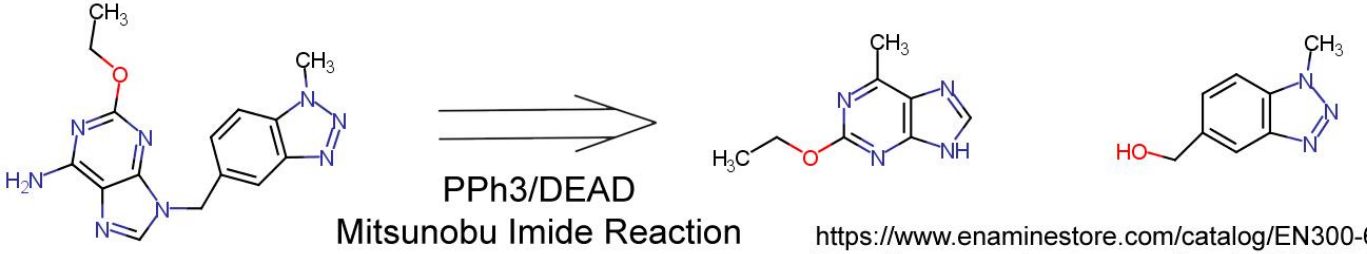
Examples of potential HIV-1 RT inhibitors

Three potential TLR 7/8 agonists selected for experimental testing



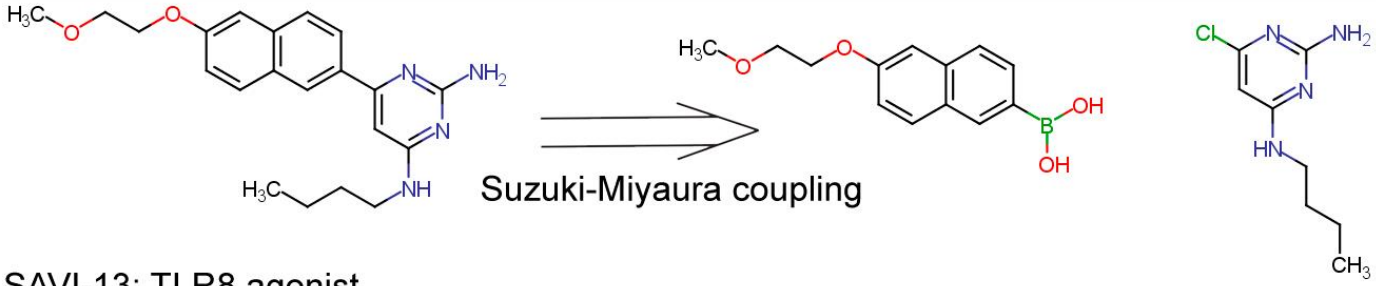
https://www.enaminestore.com/catalog/EN300-7460658
https://www.enaminestore.com/catalog/EN300-109035

SAVI-11: predicted to be TLR8 agonist
BB11807CF29193ED_FFA7714132276655_6038_UN



https://www.enaminestore.com/catalog/EN300-6478794
https://www.enaminestore.com/catalog/EN300-82608

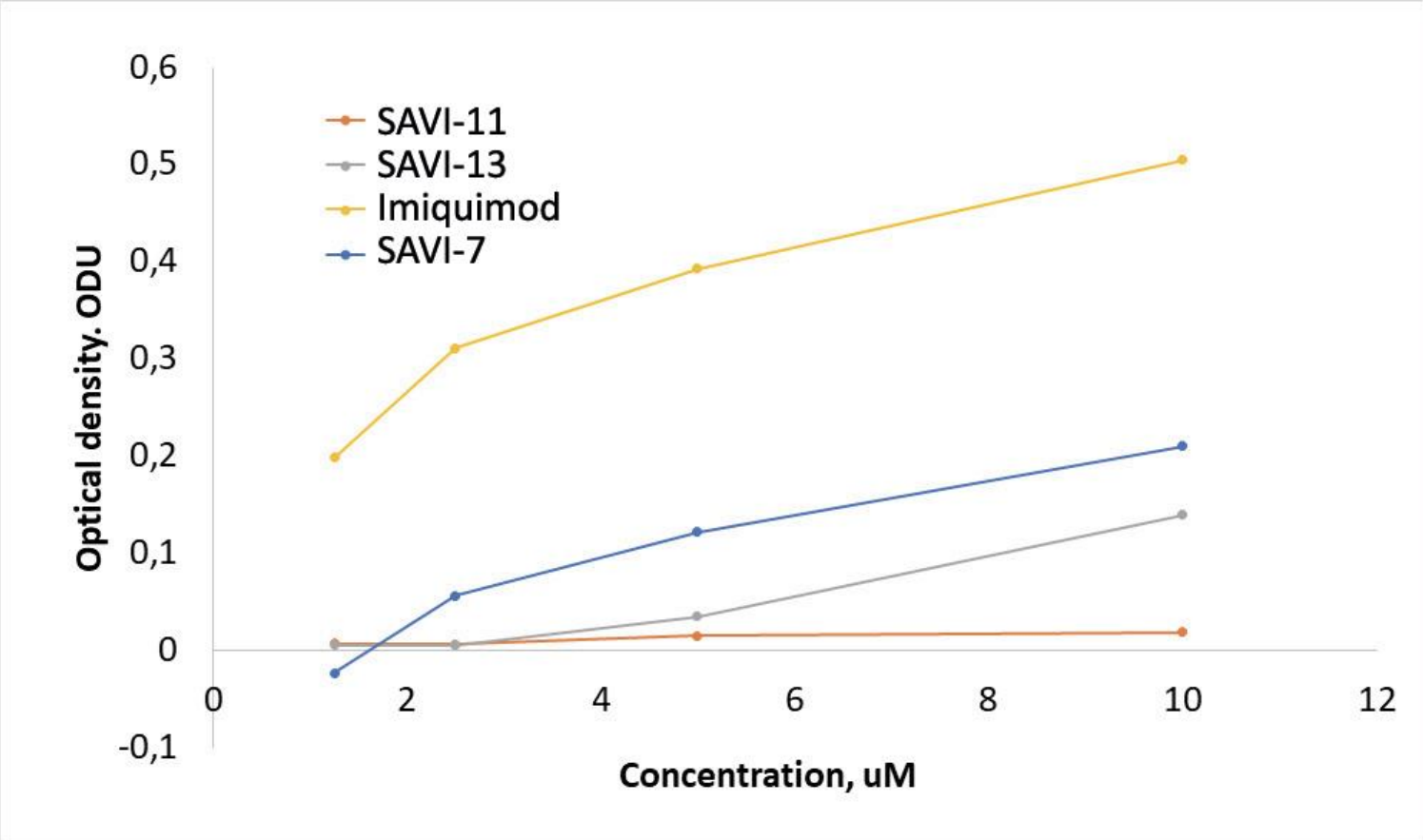
SAVI-7: predicted to be TLR7 agonist
9910454998CB8EDA_8E2F4C4D7EDBE090_6434_UN



SAVI-13: TLR8 agonist
35100B0094DA4277_A562F611DEEC0E2F_6006_UN

https://www.enaminestore.com/catalog/EN300-192468
https://www.enaminestore.com/catalog/EN300-254146

Activation of NF-kB signaling in RAW-Blue reporter cells (reference drug – Imiquimod)



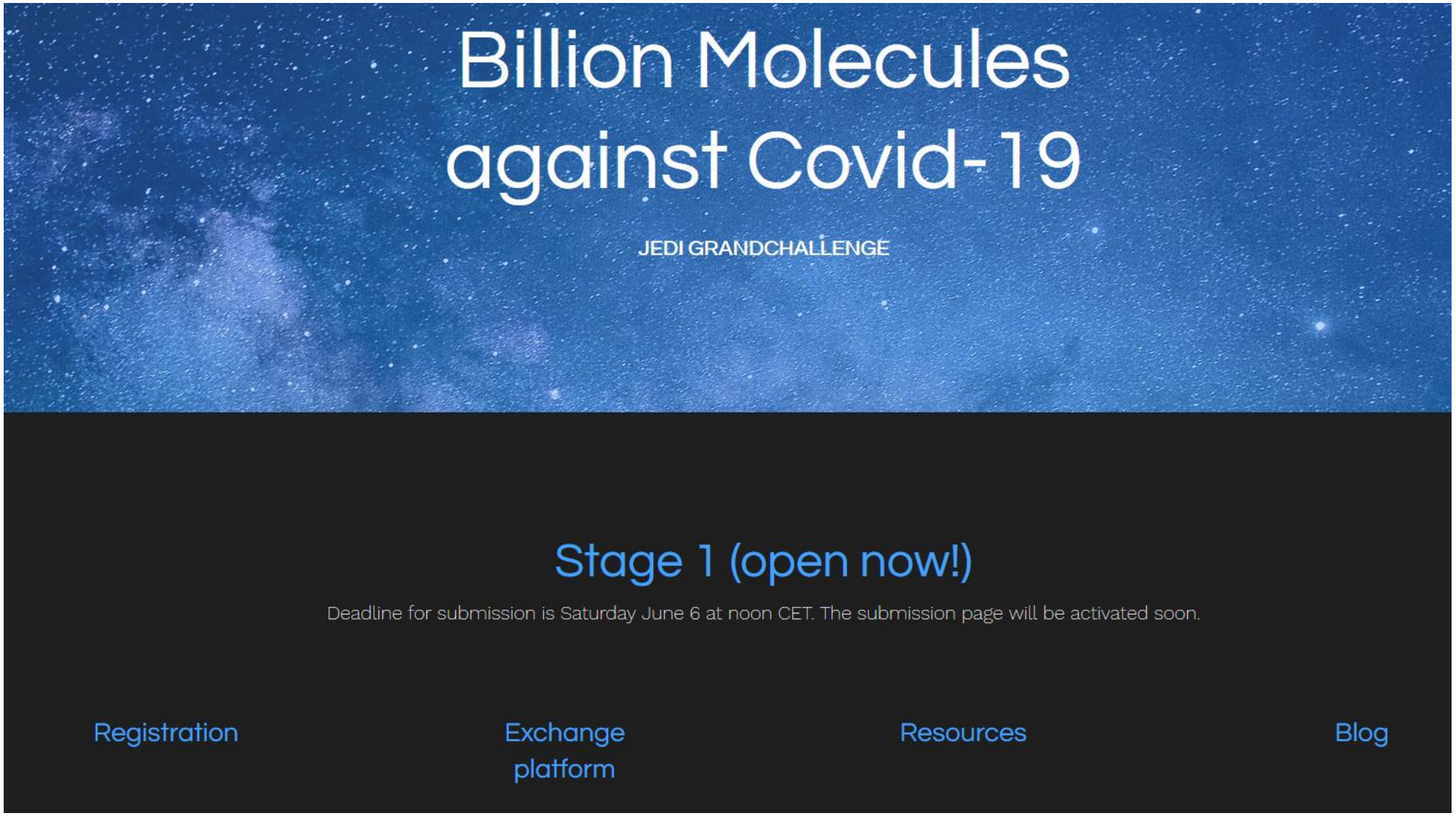
The scaffolds of identified compounds have not been reported to function as TLR7/8 agonists before!

Status of the compounds' synthesis by Enamine on Oct 28, 2020

1	SAVI ID	Transform	transform_name	Synthetic route	Comments on synthetic route used	Status
2	76383DCA52165930_0A1EBE7D8CE1DF4D_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide			in synthesis
3	760B6759B30D708B_4AFB450C65EF3651_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide			in synthesis
4	479FD97E93D659BE_0F1BBEFB74199B13_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide			in synthesis
5	397BA3268CAA0DFD_E64D5A6526E40540_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide			in synthesis
6	E5F142A78C030B64_B13B49D7E5CED09C_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide			in synthesis
7	9B34C569F5F200F3_53B6B9F9BB03A7F1_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide	amide formation with further boc-deprotection	As proposed by SAVI	synthesized
8	B24F972A892DAD34_6A124471A174F3D3_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
9	A9FBA2C5F17C0B1C_6FCB256DE4D59249_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
10	FB5678503D16CC54_16CEB03E24D5AF7A_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide	sulfonamide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
11	A4C9B4FC08AFA4AB_F390F12B02003E95_6029_DP	6029	Sulfonamide Schotten-Baumann from Aryl Bromide	sulfonamide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
12	064FCB529DC3CC6F_F8C54AA5FA432C02_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further ester hydrolysis	As proposed by SAVI	synthesized (delivered)
13	9FBC7C9EA9233C15_540BB47BF9D139CD_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
14	8D63CA8D5D9695F5_B65DB7C74015835E_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
15						
16	3B80ACB623538CC4_8BEB408F00D9AACC_7019_DP	7019	Wittig Reaction	-	-	few attempts of the synthesis were unsuccessful
17	07958A1260D163A0_62C57F29B4E727C6_7019_DP	7019	Wittig Reaction	-	-	few attempts of the synthesis were unsuccessful
18	26D271D38F5A6246_5AA65FA7C532BA31_6026_DP	6026	Sulfonamide Schotten-Baumann			in synthesis
19	834DE8D2B395C846_184627E7A95512F9_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation (starting amine was obtained from 2-hydroxy-5-nitrobenzonitrile)	SAVI-proposed protocol with some variation	synthesized (prepared for the shipment)
20	5CA09E0D72BFA5B8_4B9E8546FF2F055D_6031_DP	6031	Mitsunobu Reaction	ester formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
21	C36F9F523CE14C98_1A9D49C9C9EB1CB5_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
22	0166E196129A7C16_38156465E9886147_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
23	BDF5DFC77B8D437C_9397661FD9F5D439_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (prepared for the shipment)
24	EAD65E816522DB3D_1AA4038D93E13B35_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
25	520DEADEE00F3DFF_4B65219D42849C9A_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
26	3EC8741DBFAA37B1_DB076F5ED4495EED_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
27	9AB19BC4B8E3429D_378739C8EEE6CB1F_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
28	69269DB6886B4F24_A4AE46CD72F4AB53_6026_DP	6026	Sulfonamide Schotten-Baumann	sulfonamide formation	As proposed by SAVI	synthesized (delivered)
29	3388B305D05D627E_D34621B84859C5E7_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
30	EB17217004BE715C_0D71226872E375E9_7013_DP	7013	Benzimidazoles from o-Phenylenediamines and Aldehydes	benzimidazole cyclization from o-phenylenediamines and aldehyde	As proposed by SAVI	synthesized (delivered)
31	BF3C12A5D4161FD7_06A9AD8AC332120F_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
32	7F9EF3D5F49F0007_8245ED377E9EDC0F_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
33	D7A125B567ED5823_F1D30A9A4CFF54FE_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
34	08434304E5F32F22_07242DEC196336B7_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
35	011990799FA2E98C_96ACD102E3601173_6026_DP	6026	Sulfonamide Schotten-Baumann	sulfonamide formation with furthure TBDMS deprotection	SAVI-proposed protocol with some variation	synthesized (delivered)
36	2A4050E12C1C3DB2_C294AA90EF32CDD1_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
37	7F79132B5CE36317_D7B6DC66541D4496_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
38	0713803979A24B4F_A0D0C6157A384D16_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
39	752D9266053162DB_5627E1632FA42F5F_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
40	7A4EBC0F09EC2DD0_C0F14BF547DE6661_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
41	BDACCC673CCB1D12_D249E318C9529344_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
42	67FC723BF2936CED_6CB2FB63C4A56E6E_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further boc-deprotection	As proposed by SAVI	synthesized (delivered)
43	B9574125B7A87CEA_8A04A3D1E28E4705_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
44	3404EB70A0B9F409_6507A80468E2142A_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation	As proposed by SAVI	synthesized (delivered)
45	E40A0214D9E65EE1_A6D50D6EFE96003C_6038_DP	6038	Ester or Amide or Thiolester Formation	amide formation with further ester hydrolysis	As proposed by SAVI	synthesized (delivered)
46	2D52502D599701ED_C5D4777F2B37901B_6029_UN	6029	Sulfonamide Schotten-Baumann from Aryl Bromide	sulfonamide formation (sulfonyl chloride was obtained by another method)	SAVI-proposed protocol with some variation	synthesized (delivered)

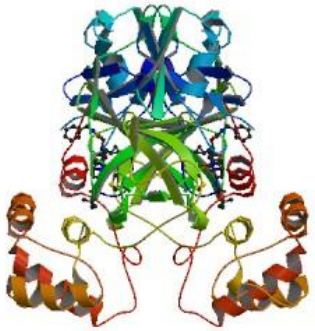
Synthesized (delivered) | Synthesized (prepared for the shipment) | In synthesis | Unsuccessful

Joint European Disruptive Initiative: Grand Challenge Against Covid-19

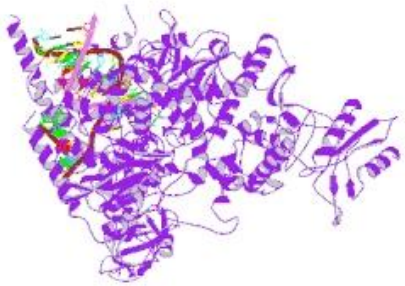


https://www.covid19.jedi.group/

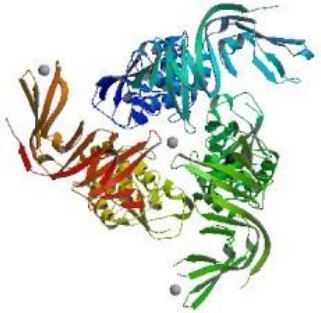
Goal: To find compounds, that inhibit SARS-CoV-2 with IC_{50}<100 nM



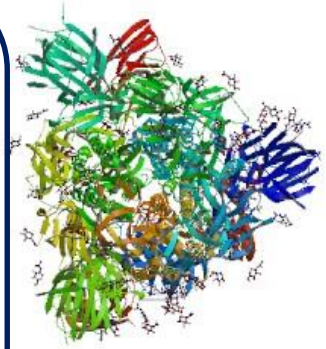
3C-Like Protease (3CLpro/Mpro)



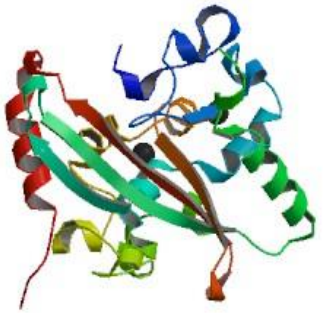
RNA-dependent RNA-polymerase (RdRp)



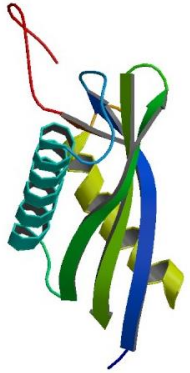
Papain-like protease (PLpro)



Spike protein (Spike/S)

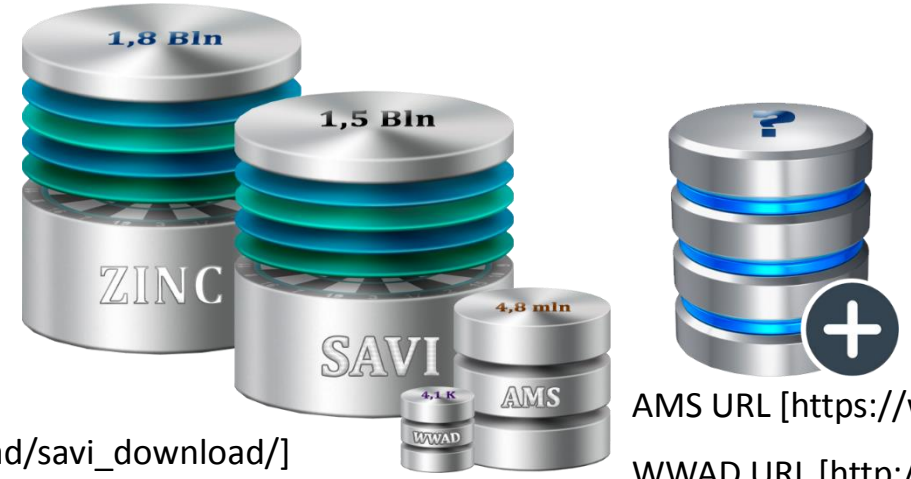


Nucleocapsid (N)



Transmembrane protease, serine 2 (TMPRSS2)

Virtual screening by three independent computational methods among more than one billion available compounds, including the launched drugs.



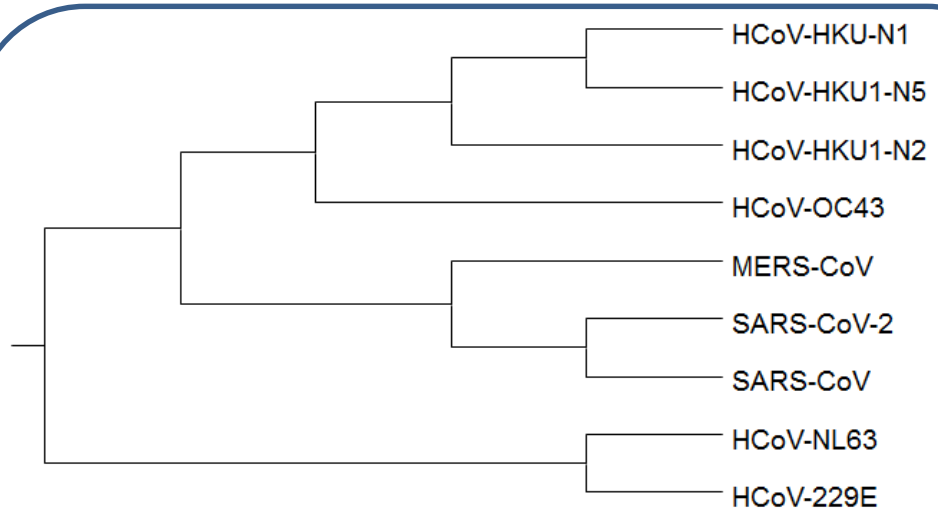
ZINC URL [https://zinc15.docking.org/]

SAVI URL [https://cactus.nci.nih.gov/download/savi_download/]

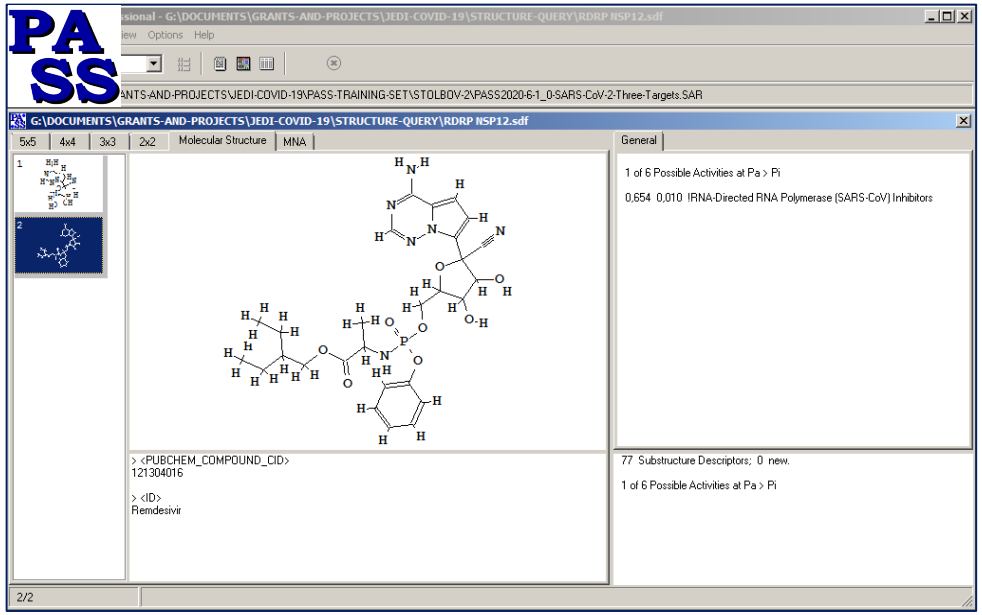
AMS URL [https://www.aldrichmarketselect.com/]

WWAD URL [http://www.way2drug.com/dr/ww_drug_approved.php]

Preparation of the training sets, training of PASS и GUSAR

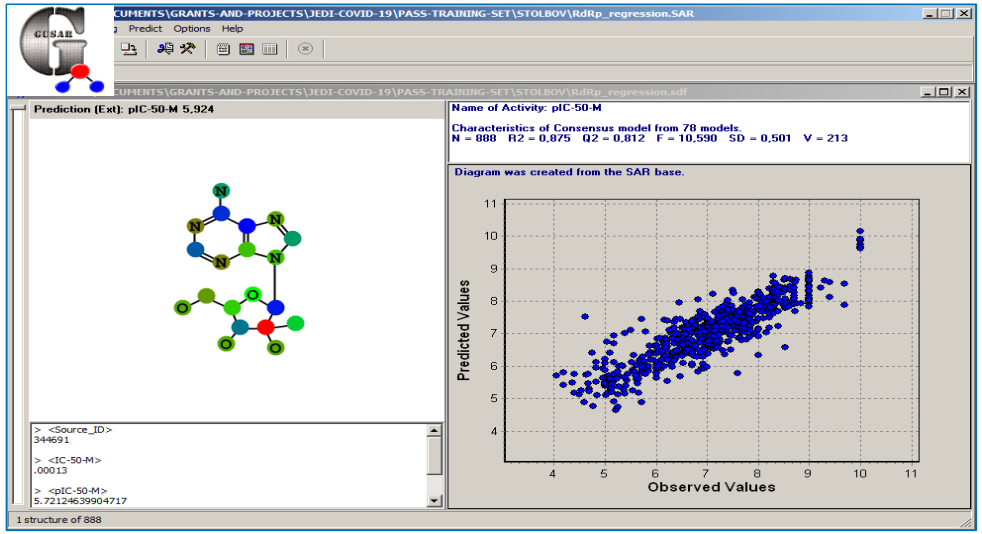


Evolutionary tree of RNA-dependent RNA polymerases of human coronaviruses



Hepatitis C virus
Dengue virus
Coxsackievirus
Zika virus (ZIKV)

Some other viruses with structural-functional similarity of this enzyme with SARS-CoV-2 RNA-dependent RNA polymerases



Current PASS Anti-SARS-CoV-2 knowledgebase

PASS 2019 Professional

File Base Predict View Options Help

Pa > Pi

G:\DOCUMENTS\GRANTS-AND-PROJECTS\JEDI-COVID-19\PASS-TRAINING-SET\FILIMONOV\2020 07 07\PASS_CoV.SAR

SAR Base Information

Substances	1025630
Descriptors	106828
Activity Types	8065
Selected Activity Types	11
Average IAP	0,8759
Prediction	Enabled

Select Activity Types to be Predicted

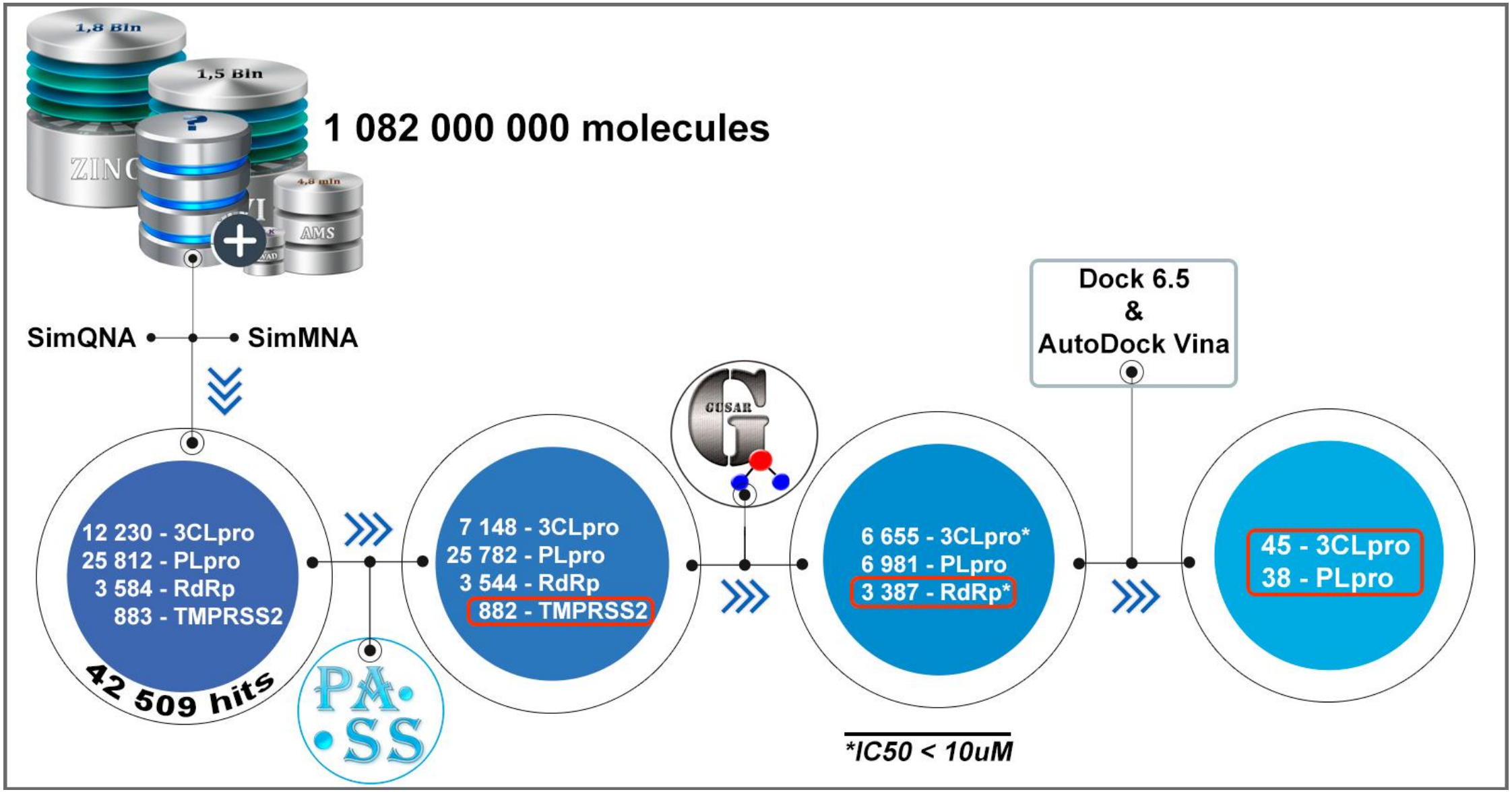
Predictable Activity Type	Group	Number	IAP
SARS-CoV-2 infection reduction in cell-based assay		808	0,7535
Spike Glycoprotein (S) (SARS-CoV-2)/ACE2 Interaction Inhibitors		371	0,8129
3C-Like Protease (SARS-CoV) Inhibitors		62	0,9585
3C-Like Protease (SARS-CoV-2) Inhibitors		18	0,9908
Papain-Like Protease (SARS-CoV-2) Inhibitors		6	0,8296
SARS-CoV-2 viral Entry Inhibitors		5	0,9678
RNA-Directed RNA Polymerase (SARS-CoV-2) Inhibitors		3	0,9970
Transmembrane Protease Serine 2 (TMPRSS2) Inhibitors		3	1,0000

Unused Activity Type	Group	Number	IAP
CoV_sla.SDF		730	0,8002
CoV_ppv.sdf		552	0,7341
SARS-CoV-2 viral replication inhibitors in cell-based assay		372	0,7910

Include ... Load ... Save ... Ok Cancel

Activity Type: 2 of 8 Predictable Activity Types. Selected Activity Types: 8 of 11 Av. IAP: 0,9138

Final results of our virtual screening in the JEDI Grand Challenge



JEDI
JOINT EUROPEAN DISRUPTIVE INITIATIVE

THE EUROPEAN MOONSHOT FACTORY

MAJOR MILESTONE FOR
THE JEDI COVID19 GRANDCHALLENGE
THE FIRST EUROPEAN DARPA-TYPE CHALLENGE

- Stage 1 of the **JEDI Billion Molecules against Covid19 GrandChallenge** is completed. The challenge posed to each participating team was to screen a billion molecules on their interaction with Covid19 ('affinity')
- An estimated **54 Billion molecules were screened**, many of which are novel compounds - a key step forward at a time when repurposing of existing drugs (hydroxychloroquine, remdesivir..) is disappointing
- 10 Million hours of high-performance computing were used
- More than **130 teams from the best institutions and companies** in the world participated, representing 500 scientists
- This GrandChallenge is a radical new approach for pre-clinical **drug discovery** & a major step for **pandemic preparedness**
- The Scientific Committee is assessing results to determine if a team reached the target and wins the **250.000 Euro Prize**

Information from the JEDI organizers of Nov 18, 2020

Dear Vladimir,

We wanted to provide a short update on the progress of the Billion Molecules Against Covid-19 Grand Challenge (https://www.covid19.jedi.group/).

Your team (Way2Drug-IBMC) is in the final teams that have compounds remaining after all selection procedures. Specifically, **48 compounds from your team were marked by our CRO as being feasible for synthesis**. A total of 1200 compounds are on the final list, of which 1000 will be synthesized. As soon as we know the exact compounds that have been synthesized by the CRO we will let you know. We expect the synthesis to be completed in 6 to 8 weeks from now.

We are looking forward to testing your compounds in our binding and activity assays!

All the best,
Thomas Hermans

Prof. Thomas M. Hermans
JEDI Program Manager COVID19
https://covid19.jedi.group
@eurojedi (twitter)

Summary

- To analyze the large chemical databases, we have proposed to apply a complex computational approach, which combines structural similarity assessment, machine learning, and molecular modeling.
- This approach has been applied to the SAVI library, allowing the identification of TLR7/8 agonists with novel scaffolds and new potential anti-HIV agents.
- Synthesability of compounds from the SAVI library has been demonstrated.
- In the JEDI Challenge against COVID-19, we identified potential hits among one+ billion molecules. Our virtual screening results were included in the top 20 out of 130 participating groups for experimental evaluation.
- Large chemical libraries significantly extended the chemical space; however, the ability to identify new pharmacological agents may be limited by the existing knowledge used as the basis for computational estimations.

Acknowledgements

Way2Drug (IBMC) Team

Dmitry Filimonov, Ph.D.
Tatyana Gloriozova,
Alexey Lagunin, Dr.Sci.
Dmitry Druzhilovskiy, Ph.D.
Anastasia Rudik, Ph.D.
Alexander Dmitriev, Ph.D.
Olga Tarasova, Ph.D.
Alexander Veselovsky, Dr.Sci.
Pavel Pogodin, Ph.D.
Boris Sobolev, Ph.D.
Oleg Gomazkov, Dr.Sci.
Sergey Ivanov, Ph.D.
Leonid Stolbov, Ph.D. Student
Dmitry Karasev, Ph.D. Student
Polina Savosina, Ph.D. Student
Nikita Ionov, Ph.D. Student
Nadezhda Biziukova, Student
Vladislav Sukhachev, Student

NCI/NIH Team

Marc Nicklaus
Yuri Pevzner
Hitesh Patel
Nadya Tarasova
Karen Stefanisko

Enamine/Chemspace

Yurii Moroz

SAVI Consortium

RUSSIAN FOUNDATION FOR BASIC RESEARCH

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