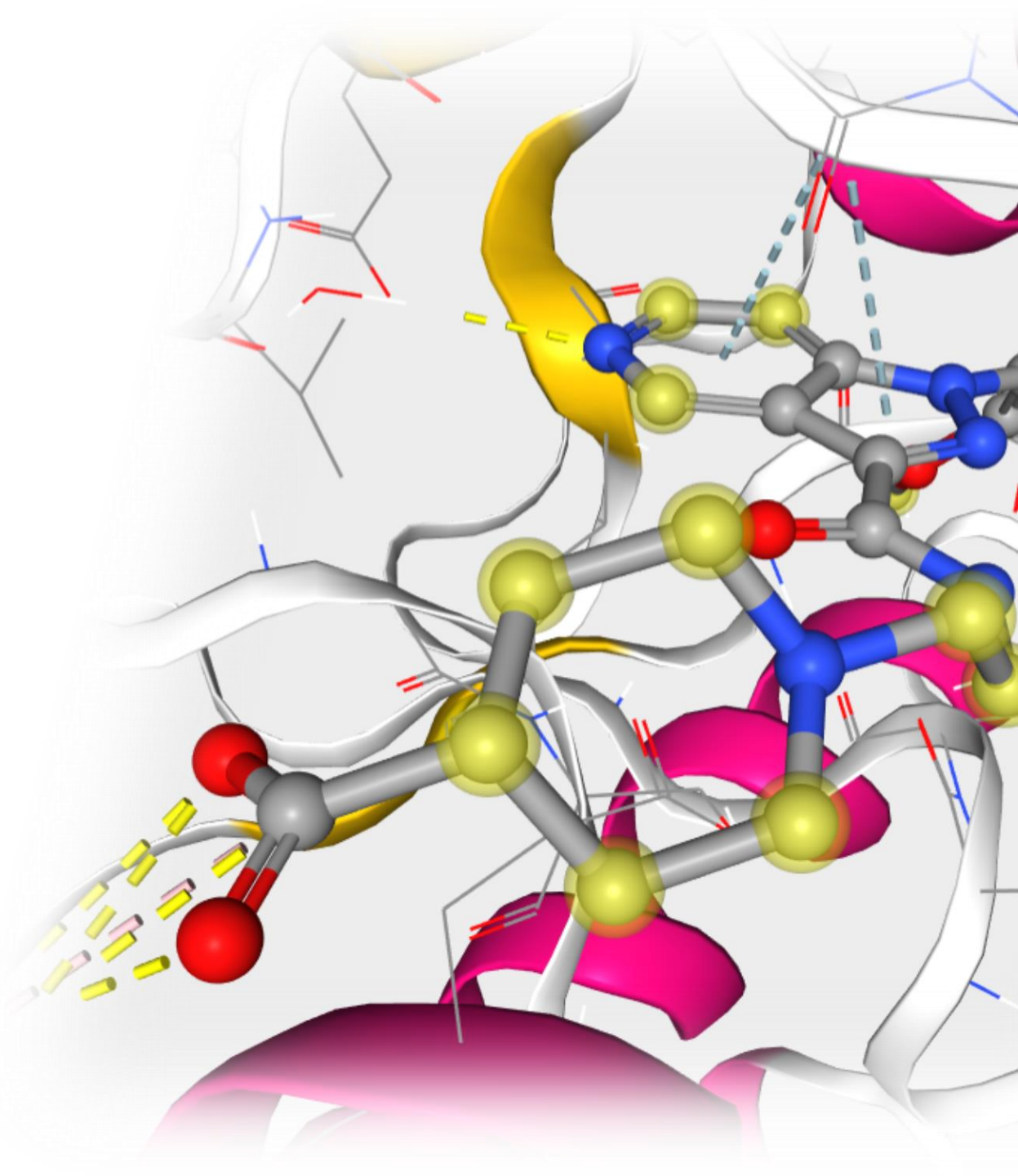
Structure-based Drug Design

Sergei Evteev
Lead Scientist
FSUE VNIIA

Fall into ML 2024

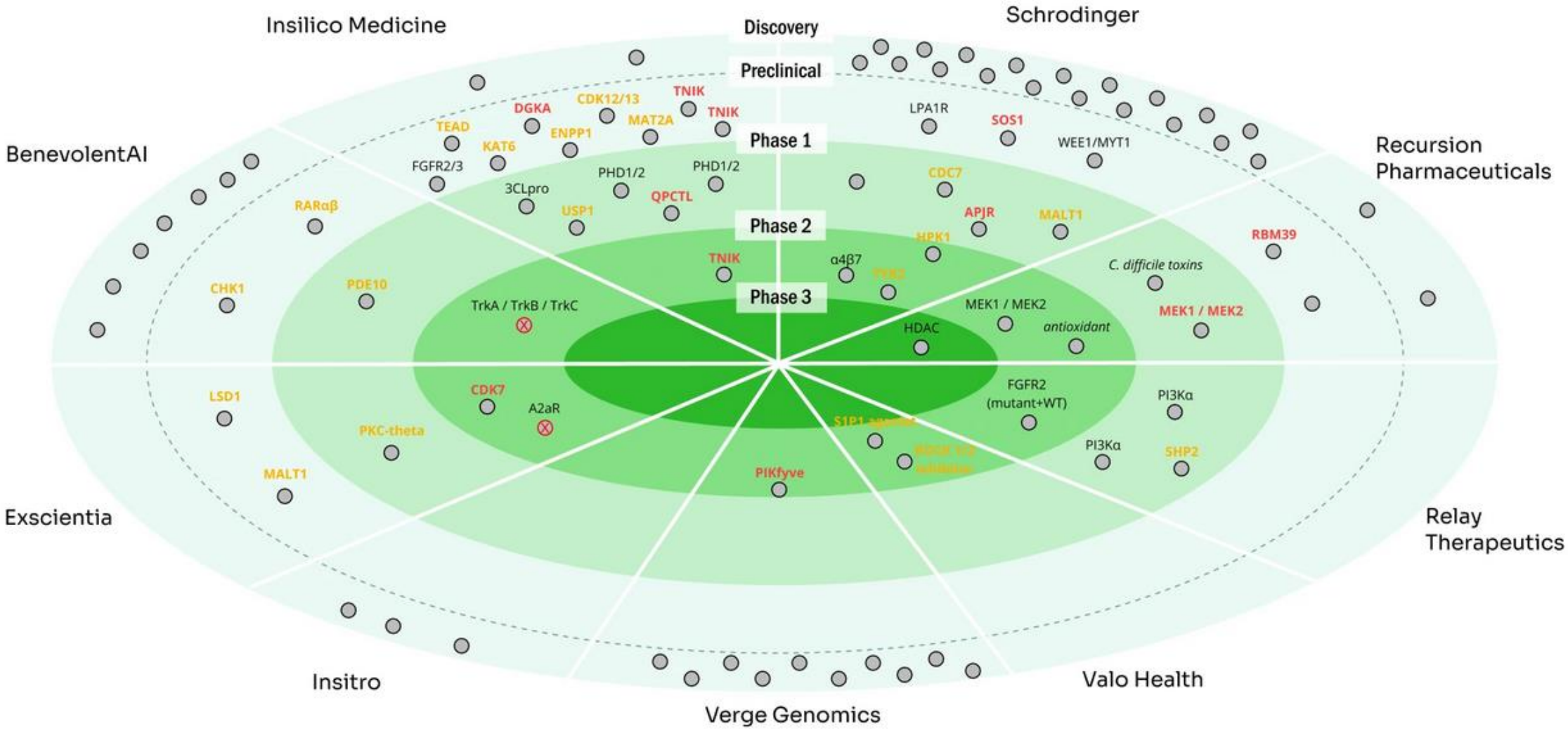


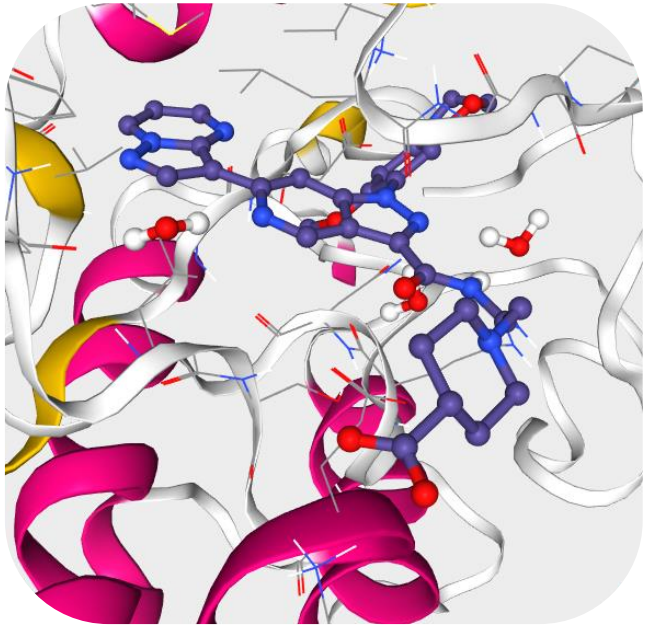
The Landscape of AI-discovered Drug Candidates and Targets

The indicated data are for 2023

Legend

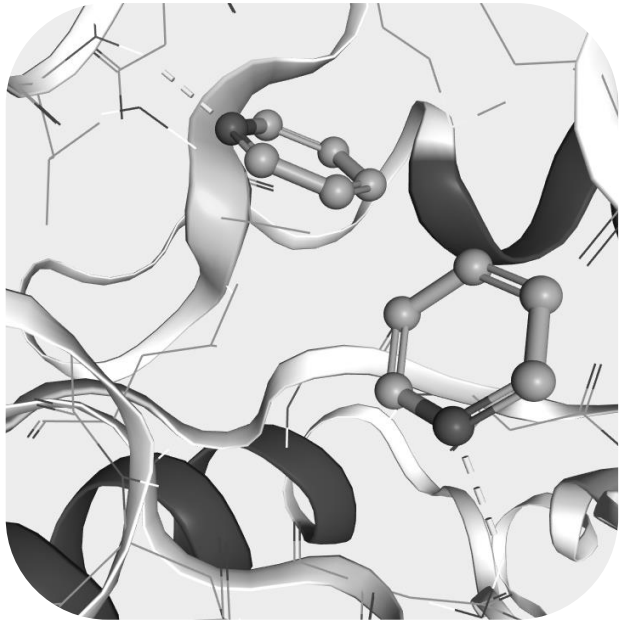
Target Novelty	Low	Moderate	High
Pipeline	Active	molecule failed or discontinued	



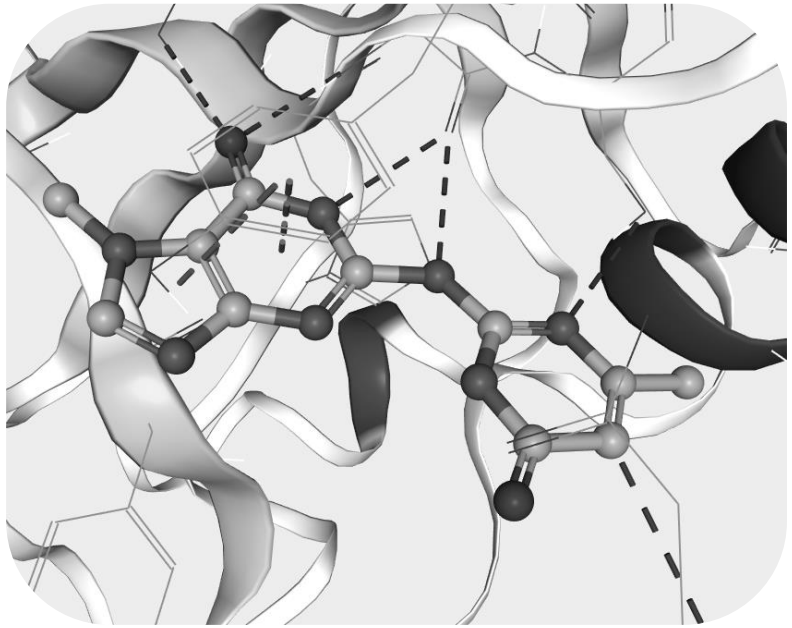


Model preparation

Binding site identification



Hot spots identification



de novo generation

Russian Chemical Reviews, 2024, Volume 93, Issue 3, RCR5107
DOI: https://doi.org/10.59761/RCR5107

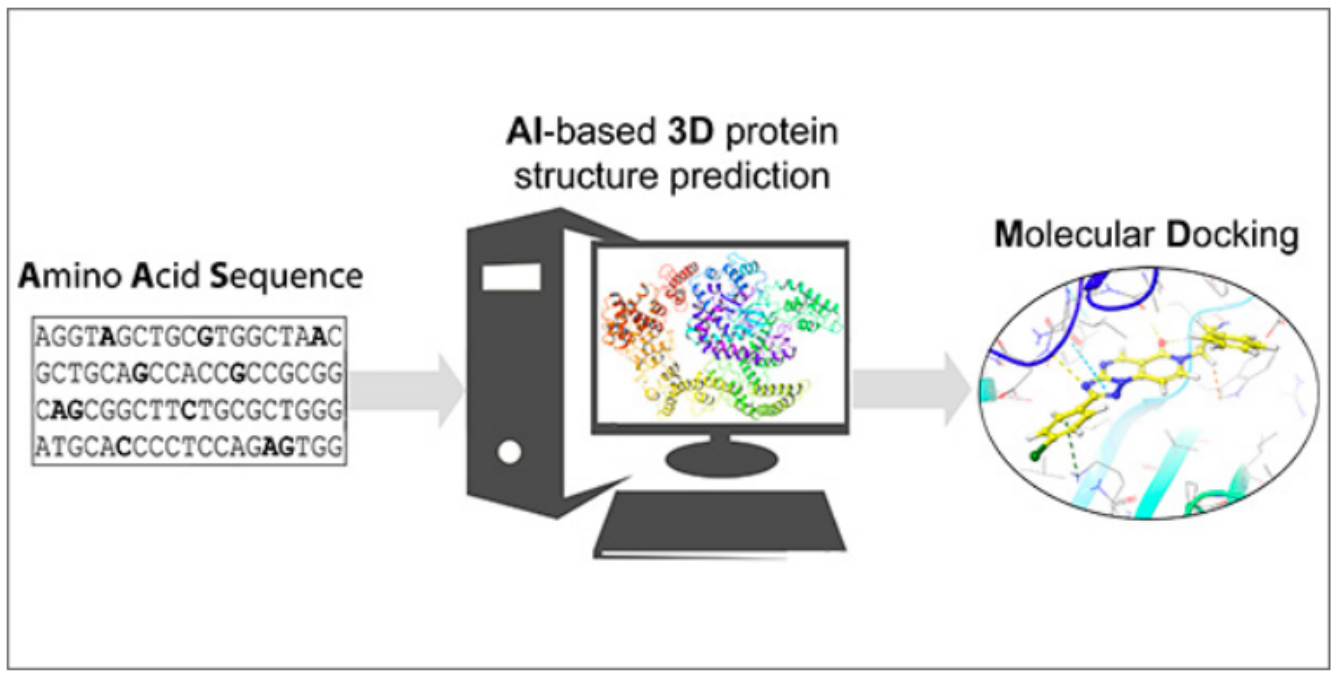
AlphaFold for a medicinal chemist: tool or toy?

Ya. A. Ivanenkov[ab], S. A. Evteev[ab], A. S. Malyshev[ab], V. A. Terentiev[ab], D. S. Bezrukov[c], A. V. Ereshchenko[ab], A. A. Korzhenevskaya[a], B. A. Zagribelnyy[c], P. V. Shegai[a], A. D. Kaprin[da]

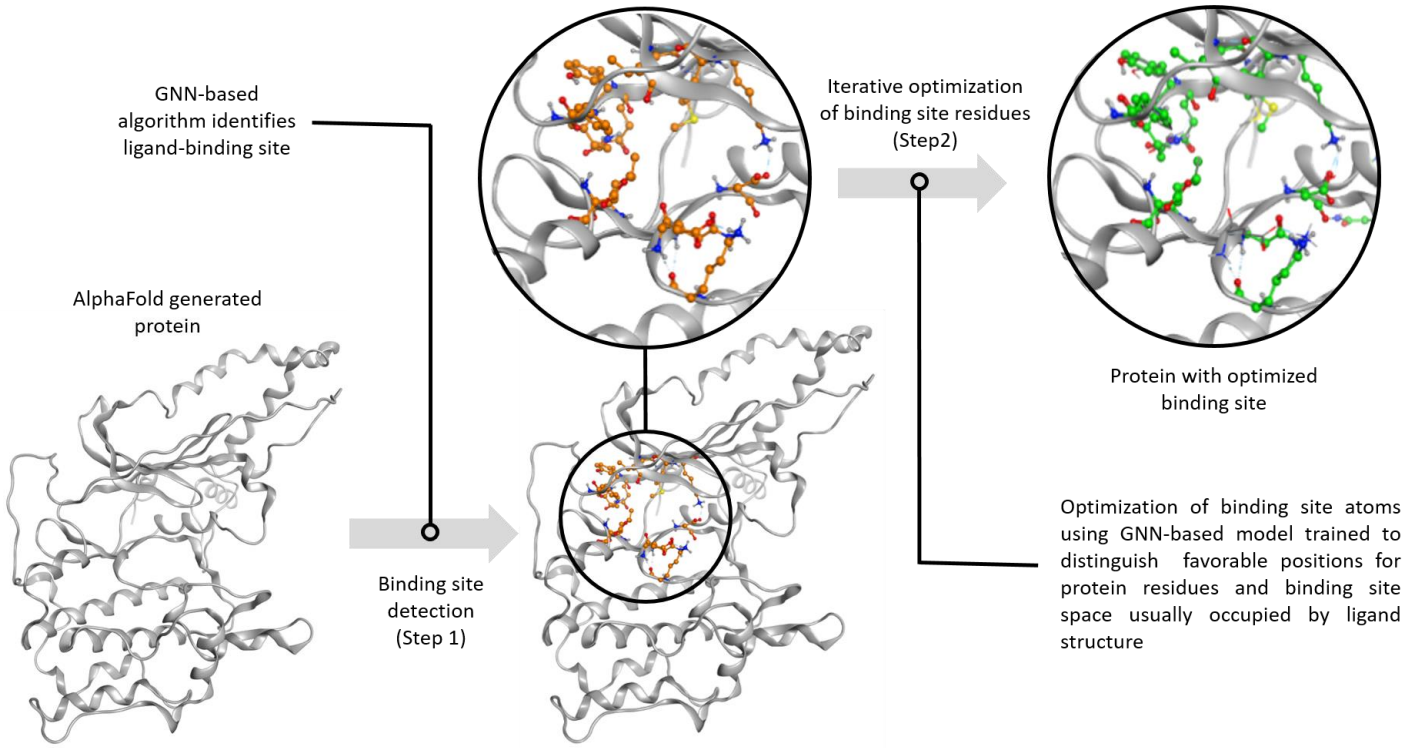
[a] *P.Hertsen Moscow Oncology Research Institute, Moscow, Russian Federation*
[b] *Dukhov Automatics Research Institute (VNIIA), Moscow, Russian Federation*
[c] *Department of Chemistry, Lomonosov Moscow State University, Moscow, Russian Federation*
[d] *Peoples' Friendship University of Russia (RUDN), Moscow, Russian Federation*

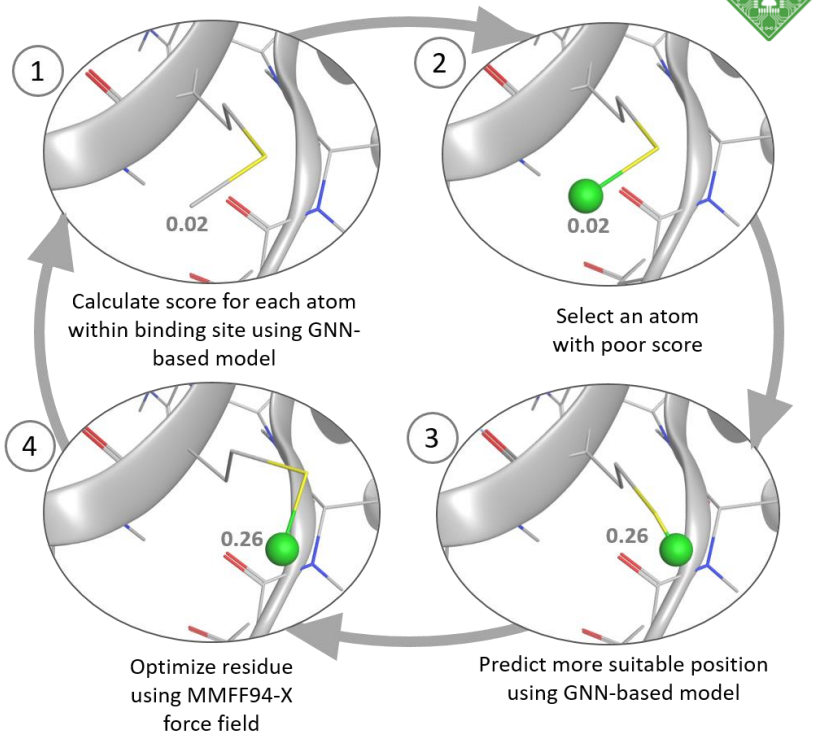
English full-text

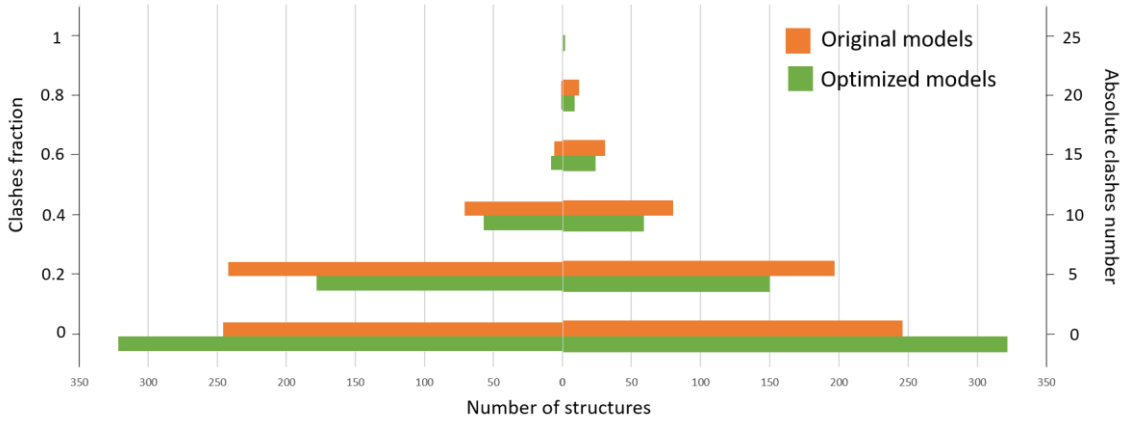
DOI: https://doi.org/10.59761/RCR5107

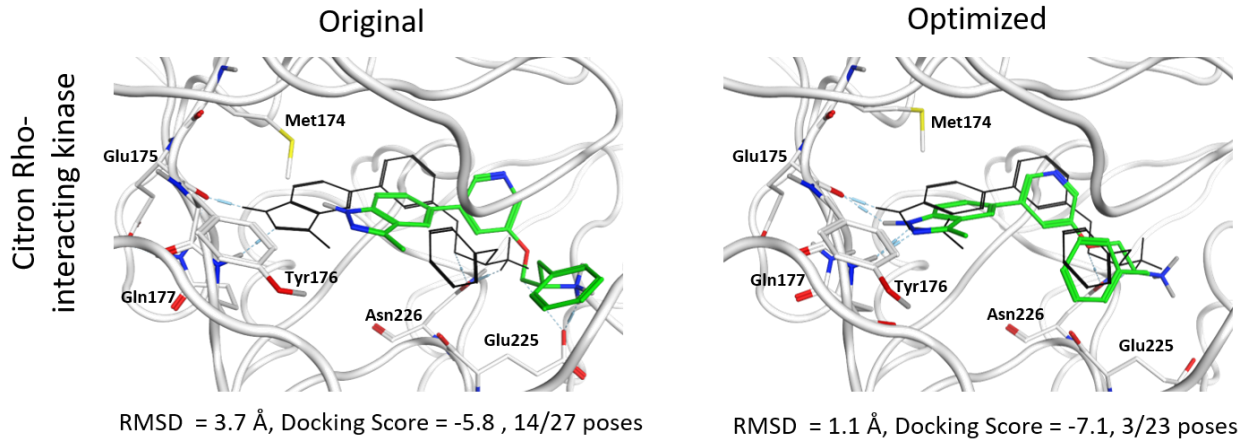


AlphaFold Optimizer

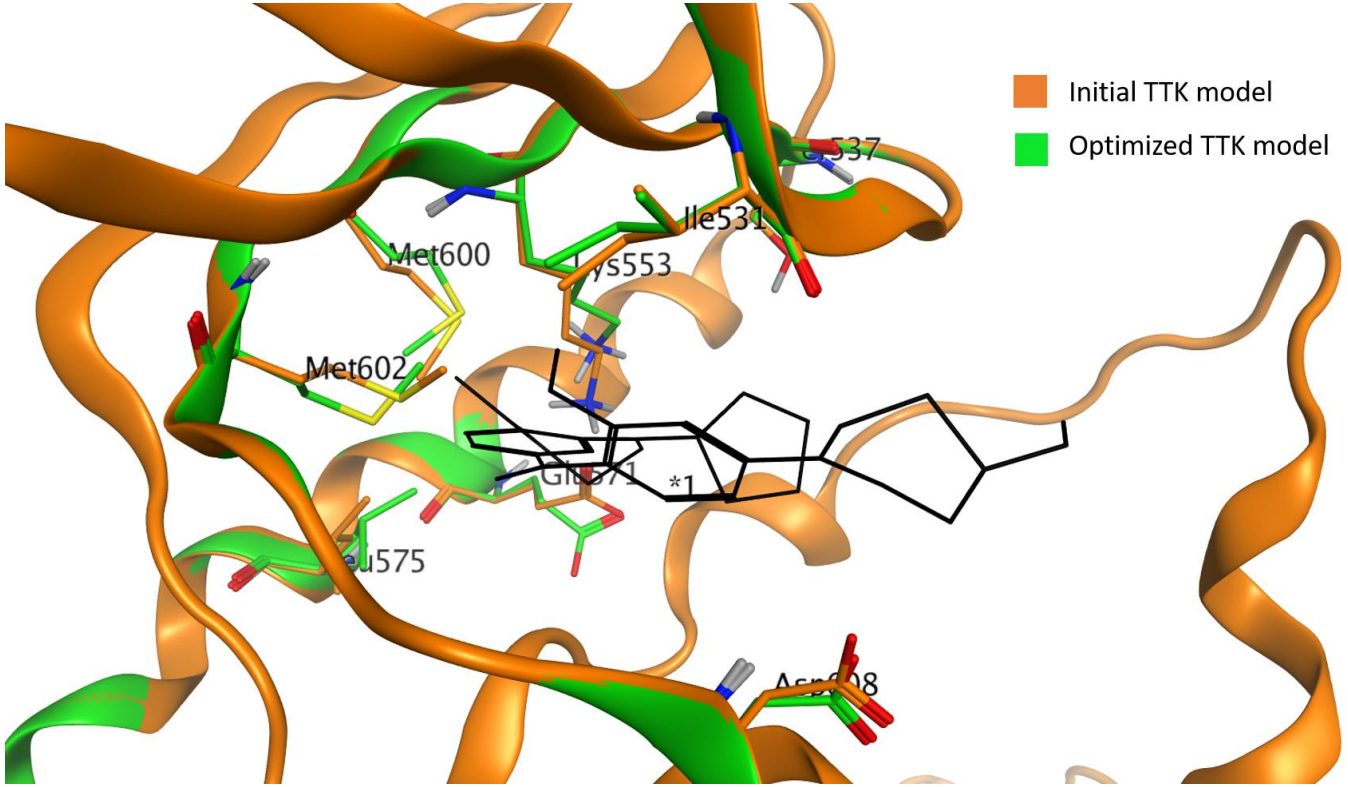




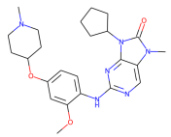
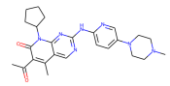
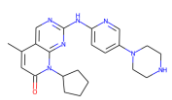
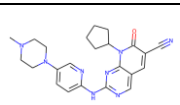
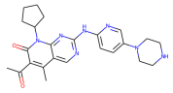
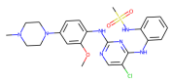
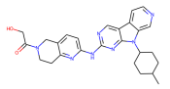
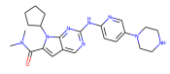
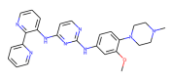
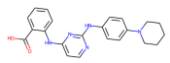


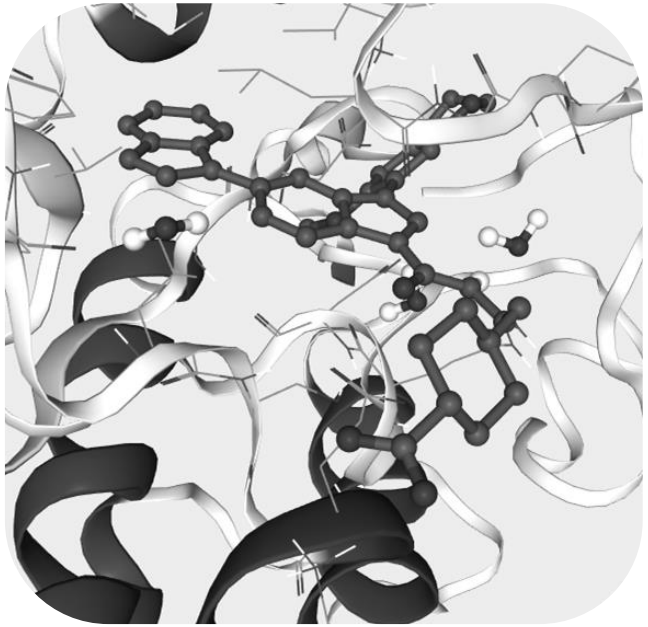


AlphaFold Optimizer

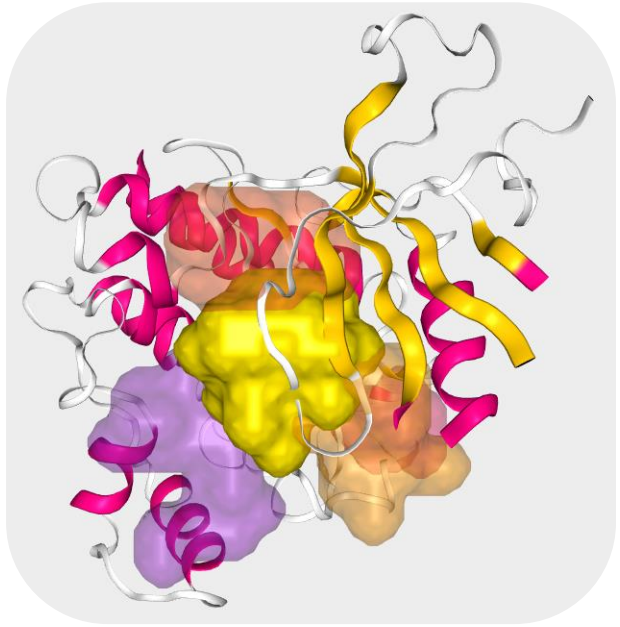


- Virtual screening was performed using both original and optimized Alphafold models
- Among 39 compounds tested, 10 hits were found
- All 10 hits were detected using optimized model while only 7 of them were detected using original AlphaFold structure

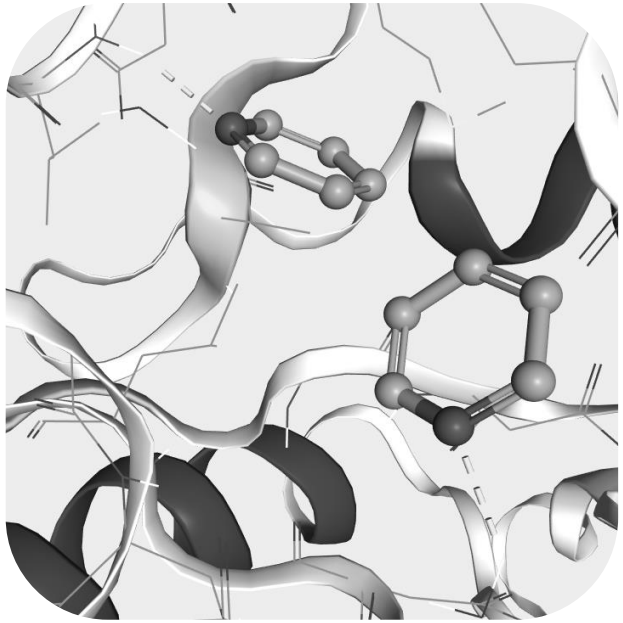
Compound ID	Structure	Inhibition, %	Predicted by initial model	Predicted refined model
1		94	+	+
2		84	-	+
3		93	+	+
4		92	-	+
5		86	+	+
6		84	+	+
7		100	+	+
8		51	-	+
9		54	+	+
10		70	+	+



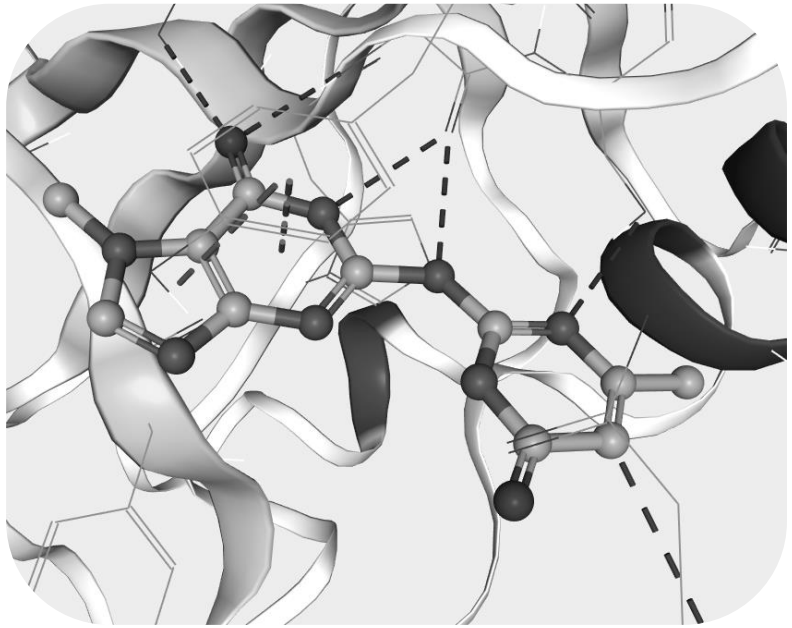
Model preparation



Binding site identification



Hot spots identification



de novo generation

Journal of Chemical Information and Modeling > Vol 63/Issue 4 > Article

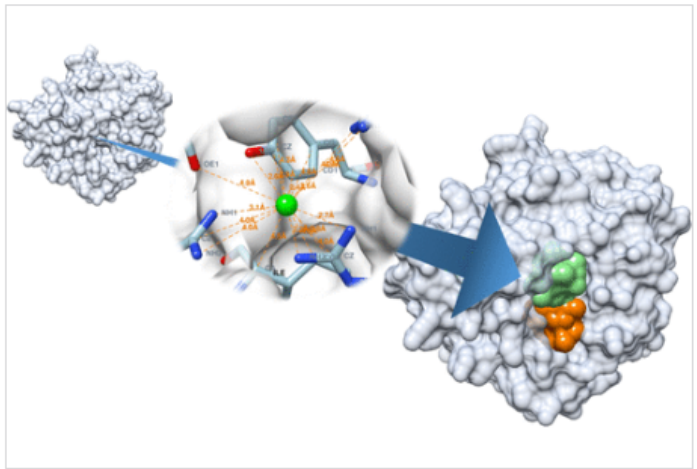
MACHINE LEARNING AND DEEP LEARNING | February 6, 2023

SiteRadar: Utilizing Graph Machine Learning for Precise Mapping of Protein–Ligand-Binding Sites

Sergei A. Evteev*, Alexey V. Ereshchenko, and Yan A. Ivanenkov

Abstract

Identifying ligand-binding sites on the protein surface is a crucial step in the structure-based drug design. Although multiple techniques have been proposed, including those using machine learning algorithms, the existing solutions do not provide significant advantages over nonmachine learning approaches and there is still a big room for improvement. The low ability to identify protein–ligand-binding sites makes available approaches inapplicable to automated drug design. Here, we present SiteRadar, a new algorithm for mapping cavities that are likely to bind a small-molecule ligand. SiteRadar shows higher accuracy in binding site identification compared with FPocket and PUResNet. SiteRadar demonstrates an ability to detect up to 74% of true ligand-binding sites according to the top N + 2 metric and usually covers approximately 80% of ligand atoms. Therefore, SiteRadar can be regarded as a promising solution for implementation into algorithms for automated drug design.



Journal of Chemical Information and Modeling
Cite this: *J. Chem. Inf. Model.* 2023, 63, 4, 1124–1132

https://doi.org/10.1021/acs.jcim.2c01413
Published February 6, 2023

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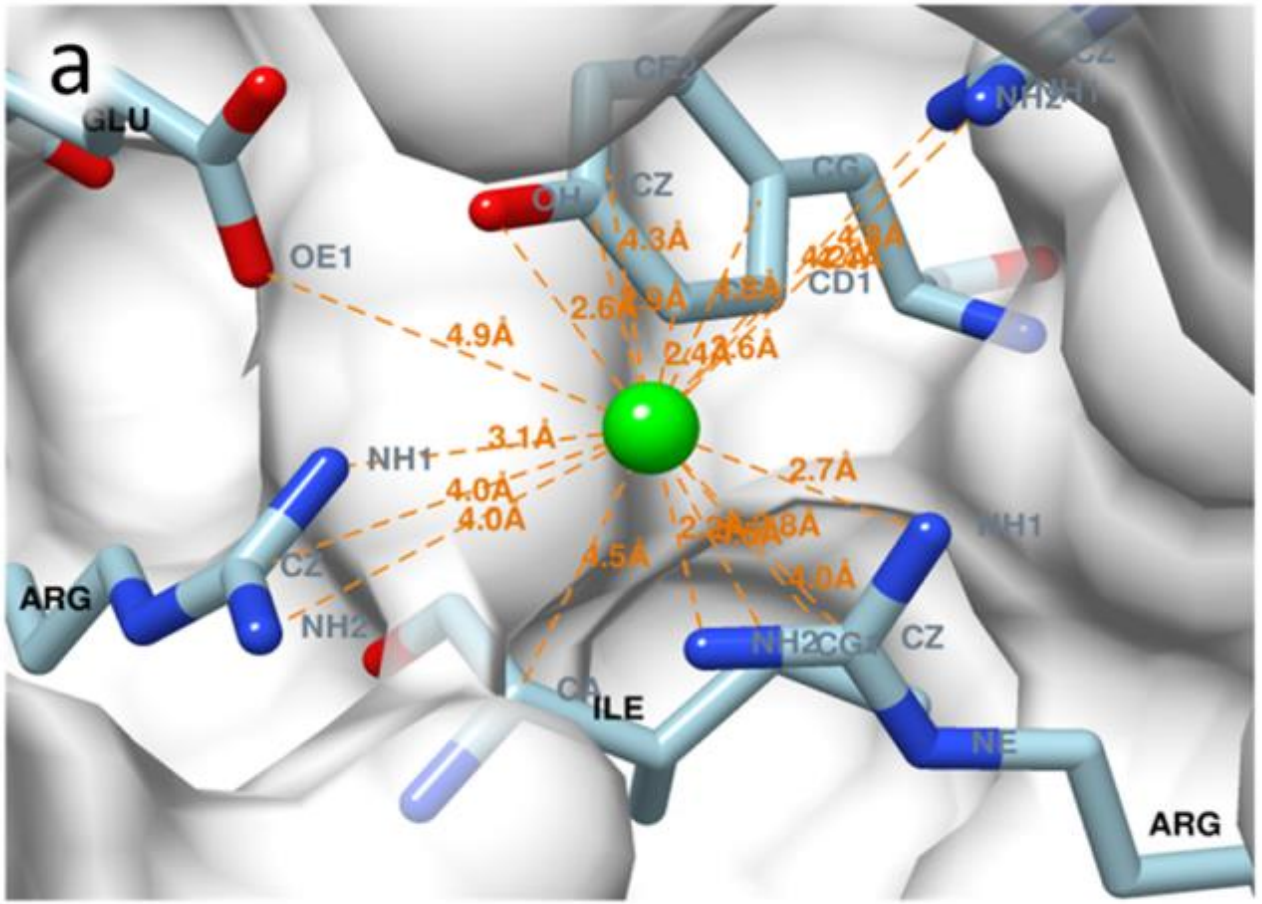
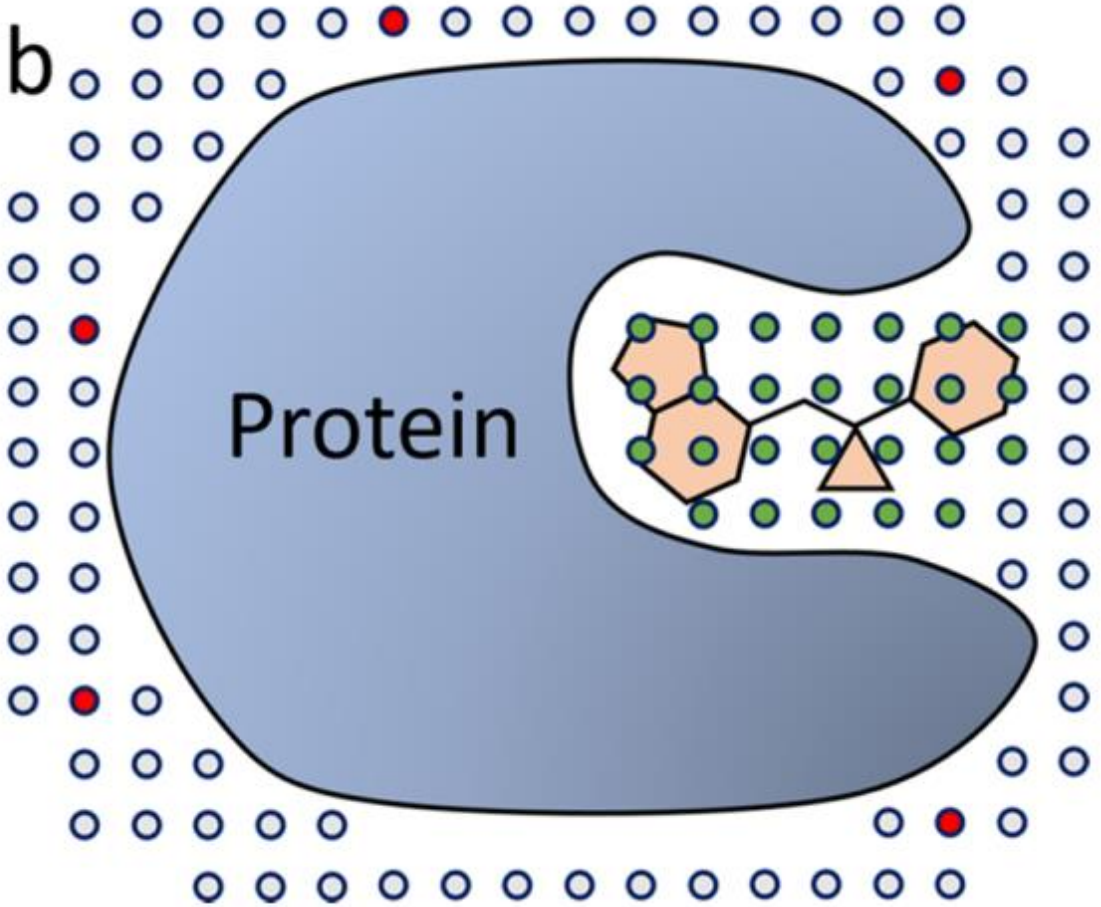
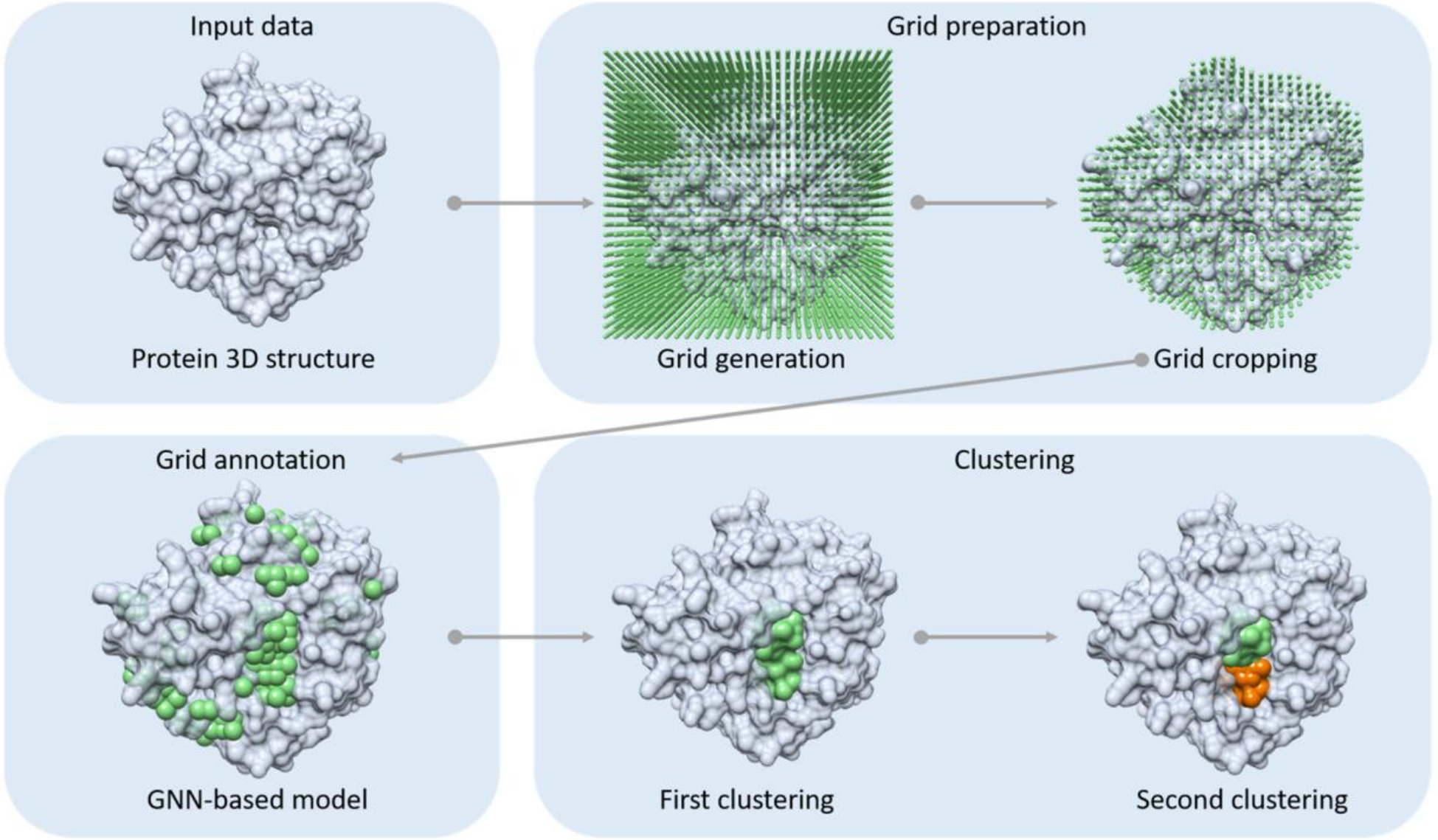
PLANET: A Multi-objective Graph Neural Network Model for Protein–Ligand Binding Affinity Prediction
June 15, 2023 | *Journal of Chemical Information and Modeling*
Xiangying Zhang, Haotian Gao, Haojie Wang, Zhihang Chen, Zhe Zhang, ...

Graph-based approach





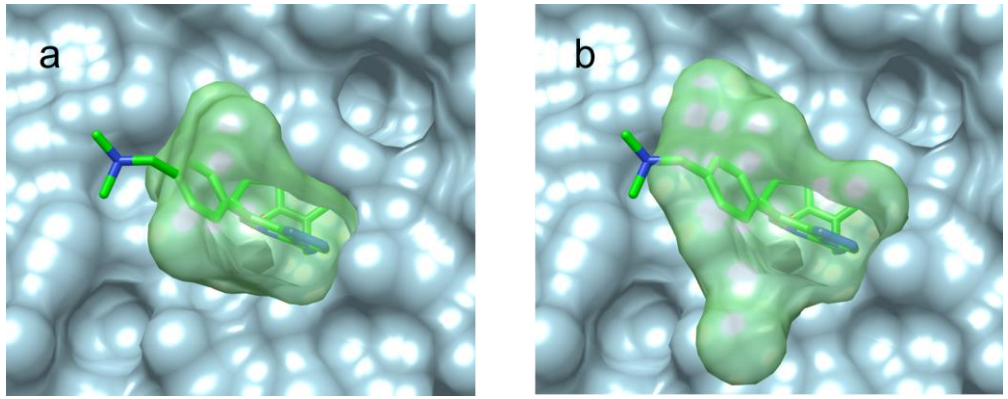
SiteRadar Pipeline



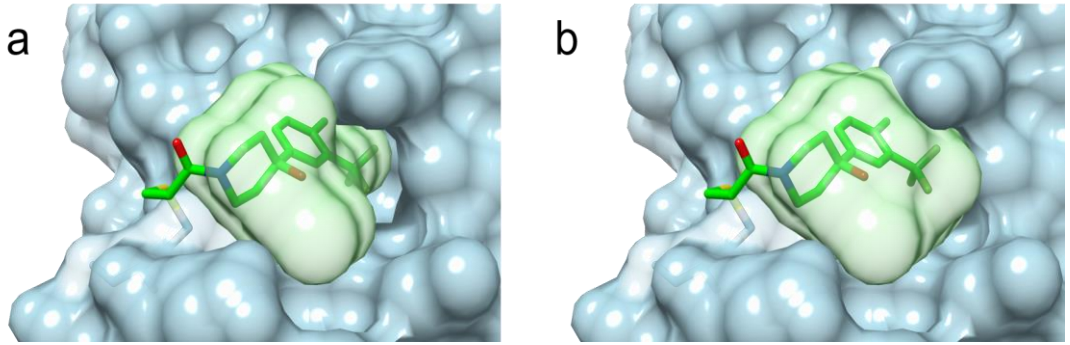
Evteev S.A. et al. SiteRadar: Utilizing Graph Machine Learning for Precise Mapping of Protein-Ligand-Binding Sites. J. Chem. Inf. Model. 2023

Case studies

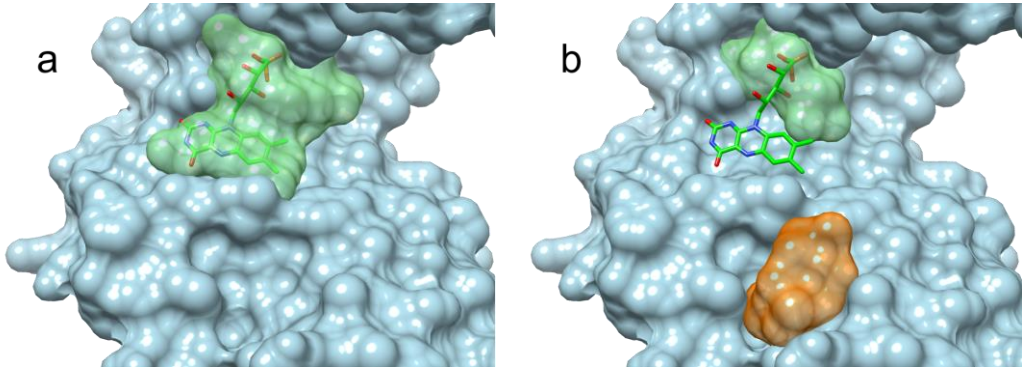
Allosteric binding site



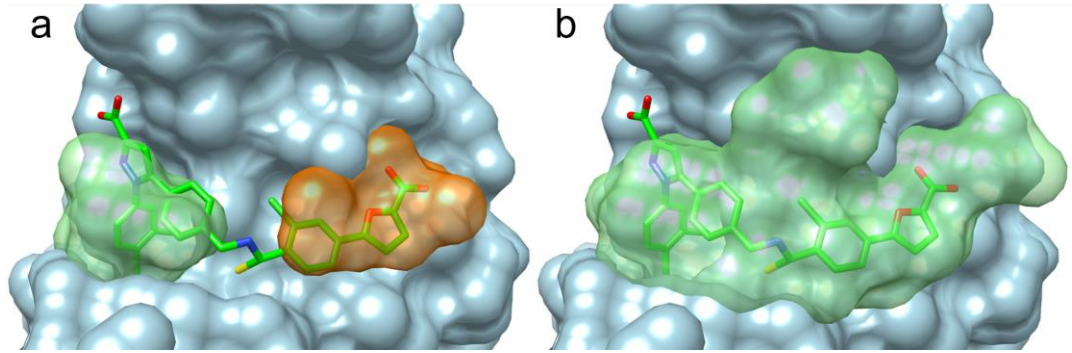
Site for covalent ligand binding



Solvent-exposed binding site



Protein-protein interaction

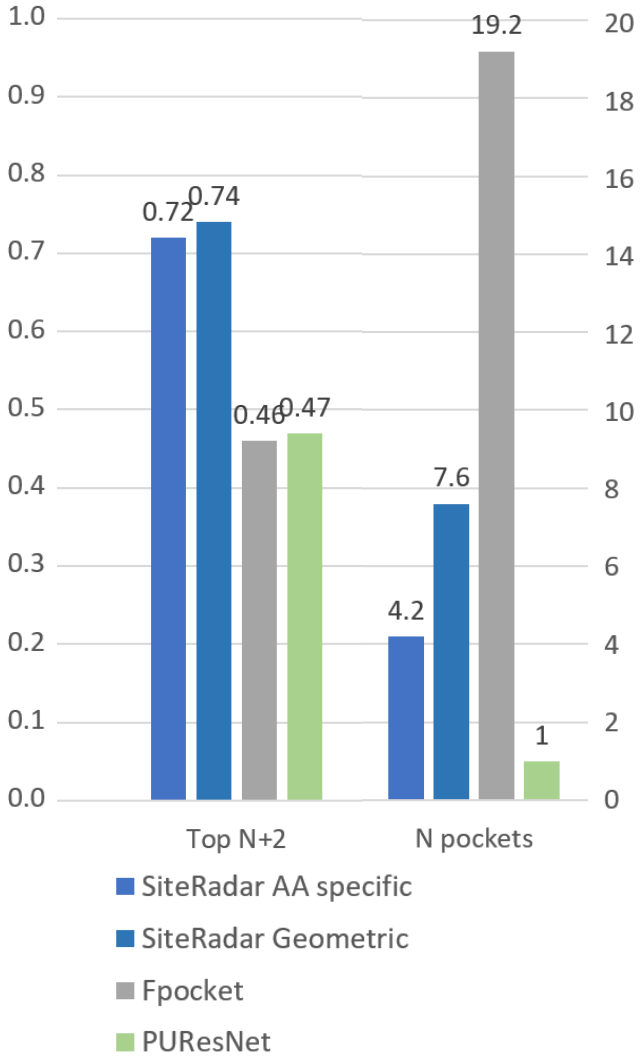


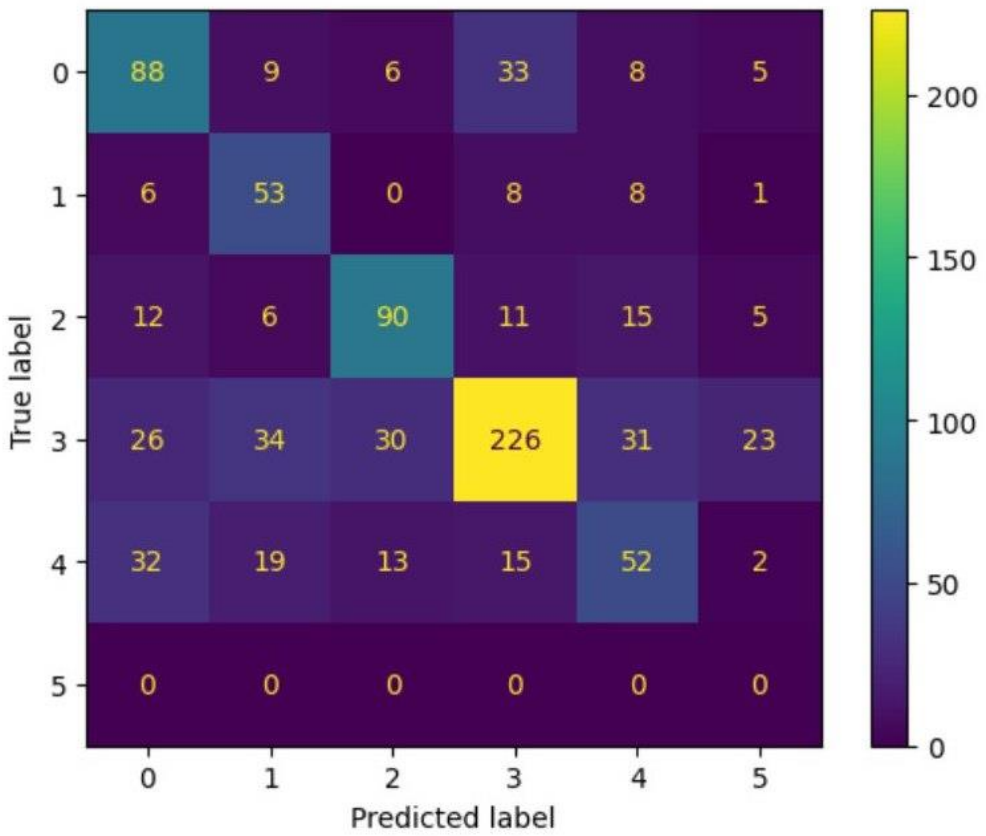
a - AA specific

b - Geometric


Elements
Cartoon
Input parameters
View
Pockets
Merge mode
Extend size, Å
0 2 4 6
Pocket characteristic
Druggability 0.89
0.01 Nucleic Acid
Allosteric 0.04
0.12 Peptide
Covalent 0.57
0.88 Nucleotide/ATP
Carbohydrate 0.28
Heme 0

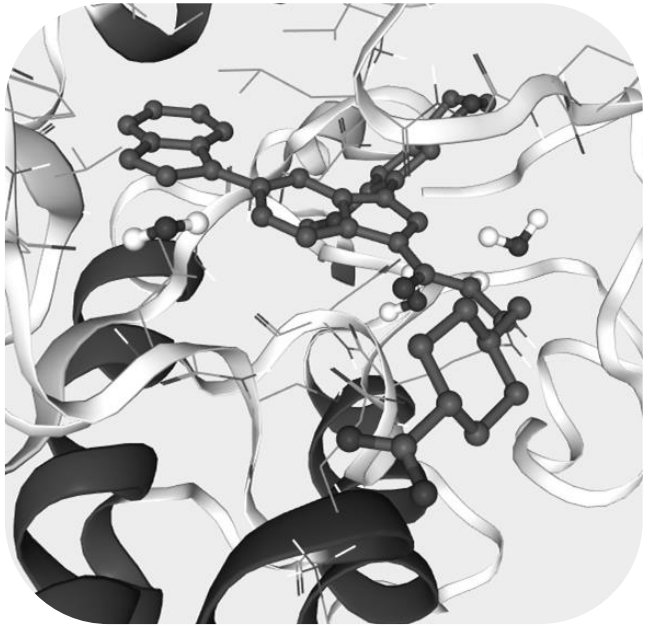
in silico validation





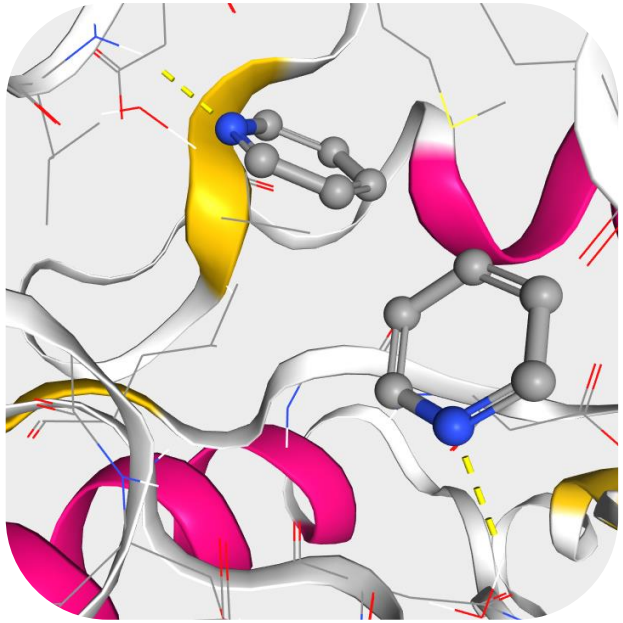
0 – Nucleic acids
1 – Carbohydrates
2 – Heme
3 – Nucleotides / ATP
4 – Peptides
5 – Undefined

Evteev S.A. et al. SiteRadar: Utilizing Graph Machine Learning for Precise Mapping of Protein-Ligand-Binding Sites. J. Chem. Inf. Model. 2023

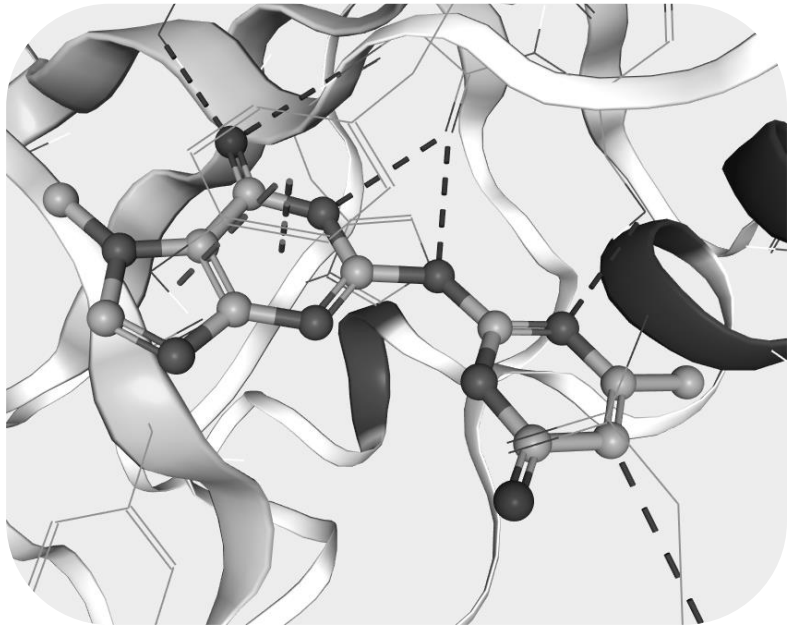


Model preparation

Binding site identification



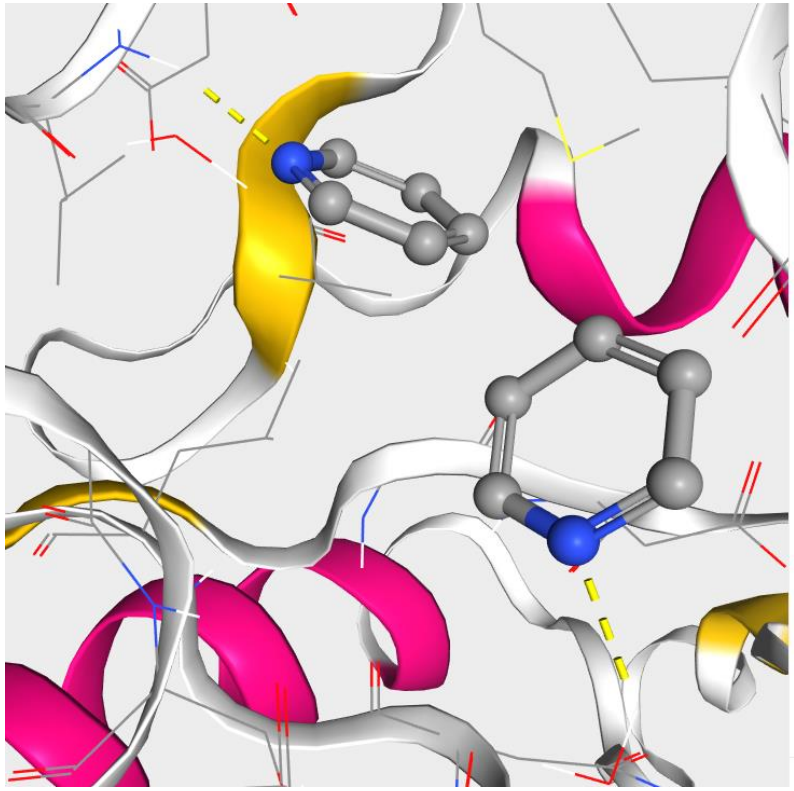
Hot spots identification



de novo generation

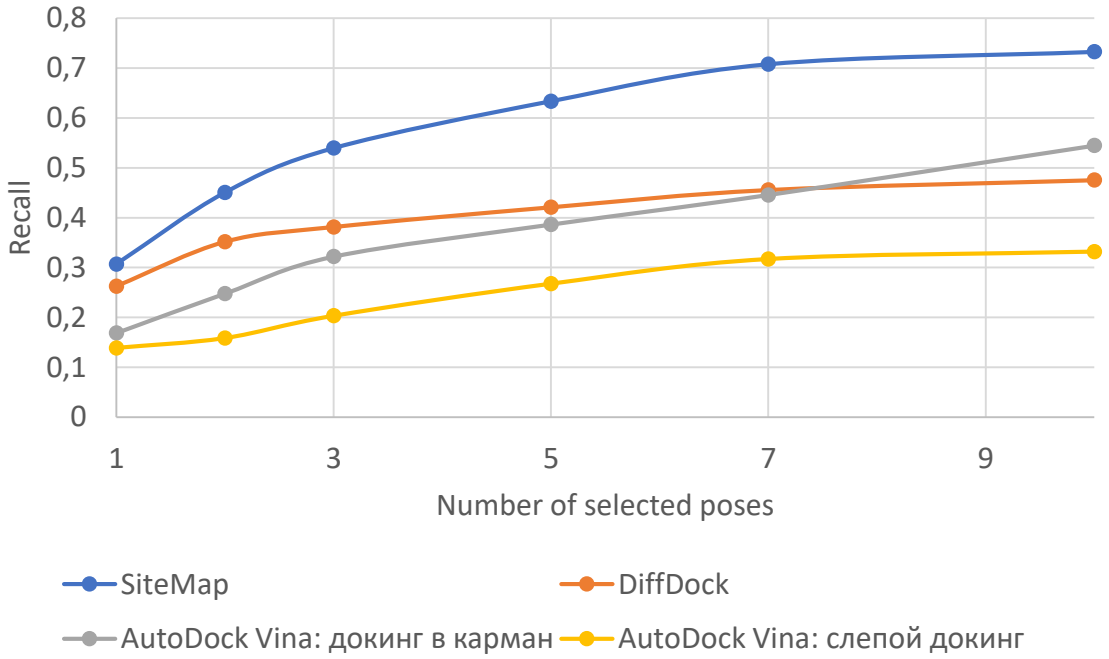
SiteMap

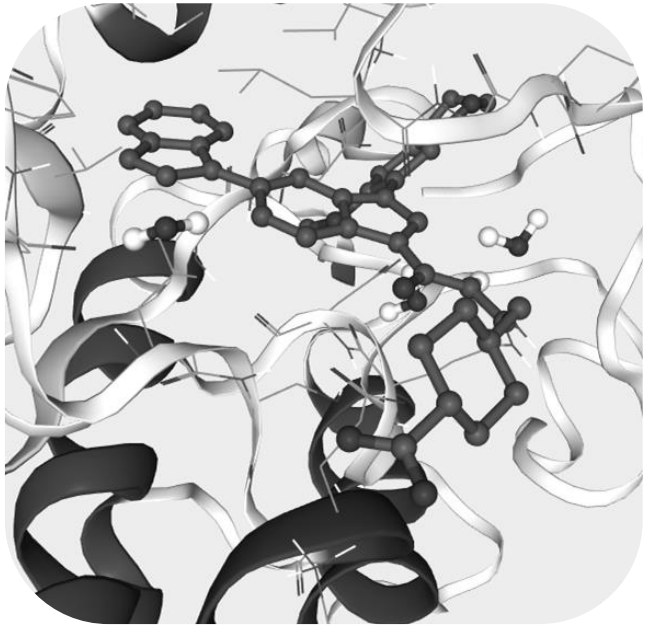
Utilizes traditional docking, diffusion and positional filters



Scaffolds Selected 0 / 3

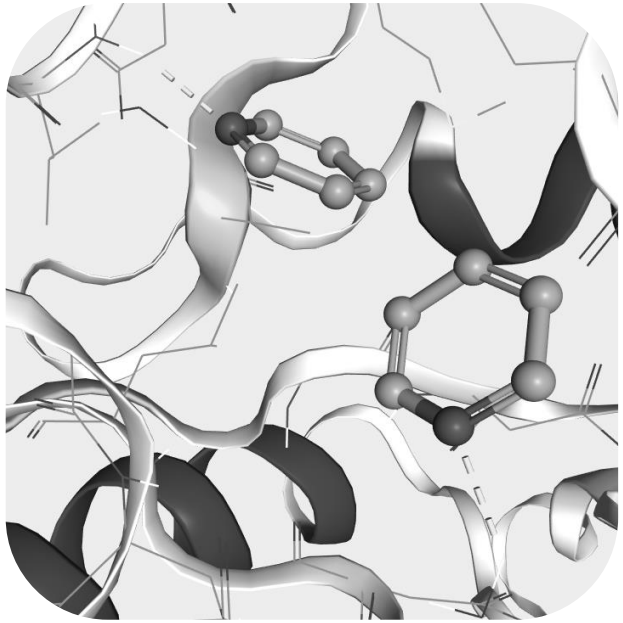
ID	SMILES	Docking score
Mol-0.1	c1ccncc1	-3.95
Mol-0.2	c1ccncc1	-3.70
Mol-0.3	c1ccncc1	-3.69





Model preparation

Binding site identification



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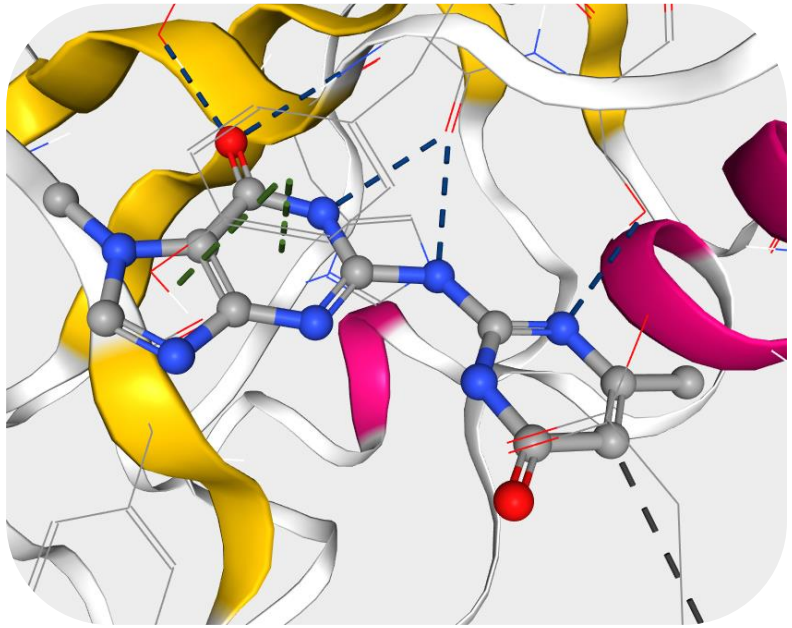

de novo generation

ACS Medicinal Chemistry Letters > Vol 14/Issue 7 > Article

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MICROPERSPECTIVES | June 29, 2023

The Hitchhiker's Guide to Deep Learning Driven Generative Chemistry

Yan Ivanenkov, Bogdan Zagribelnyy, Alex Malyshev, Sergei Evteev, Victor Terentiev, Petrina Kamya, Dmitry Bezrukov, Alex Aliper, Feng Ren, and Alex Zhavoronkov*

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Abstract

This microperspective covers the most recent research outcomes of artificial intelligence (AI) generated molecular structures from the point of view of the medicinal chemist. The main focus is on studies that include synthesis and experimental *in vitro* validation in biochemical assays of the generated molecular structures, where we analyze the reported structures' relevance in modern medicinal chemistry and their novelty. The authors believe that this review would be appreciated by medicinal chemistry and AI-driven drug design (AIDD) communities and can be adopted as a comprehensive approach for qualifying different research outcomes in AIDD.

ACS Medicinal Chemistry Letters
Cite this: *ACS Med. Chem. Lett.* 2023, 14, 7, 901–915
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Generative Models as an Emerging Paradigm in the Chemical Sciences
April 13, 2023 | *Journal of the American Chemical Society*

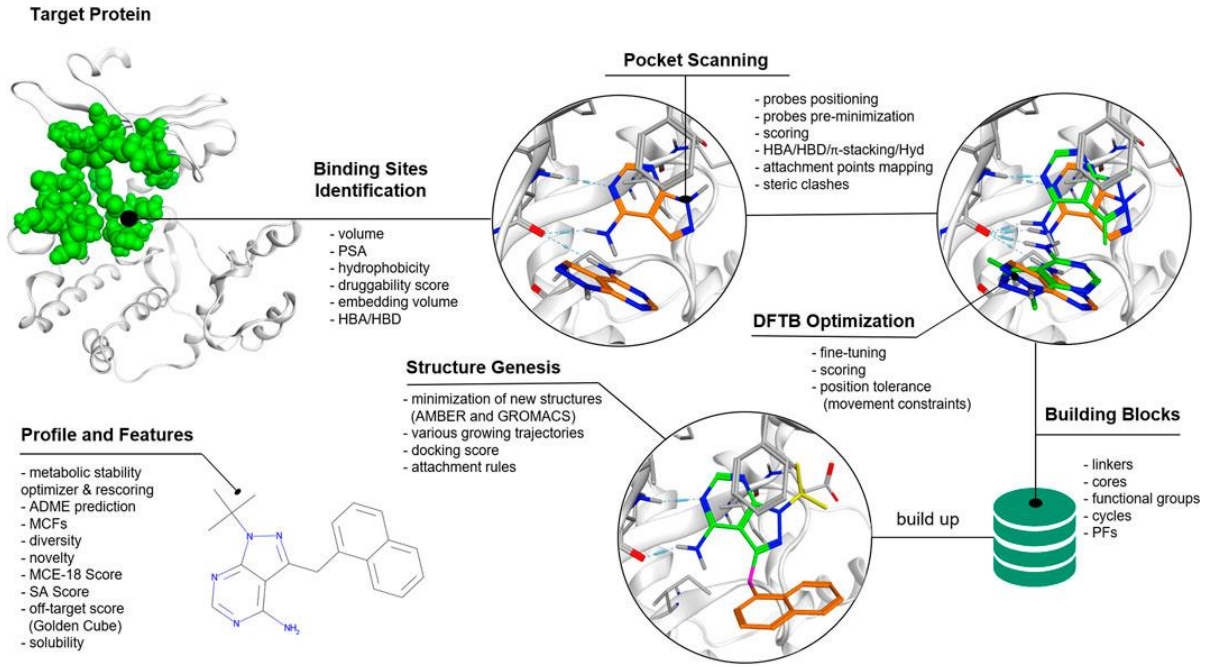
Quantum-assisted fragment-based automated structure generator (QFASG) for small molecule design: an *in vitro* study

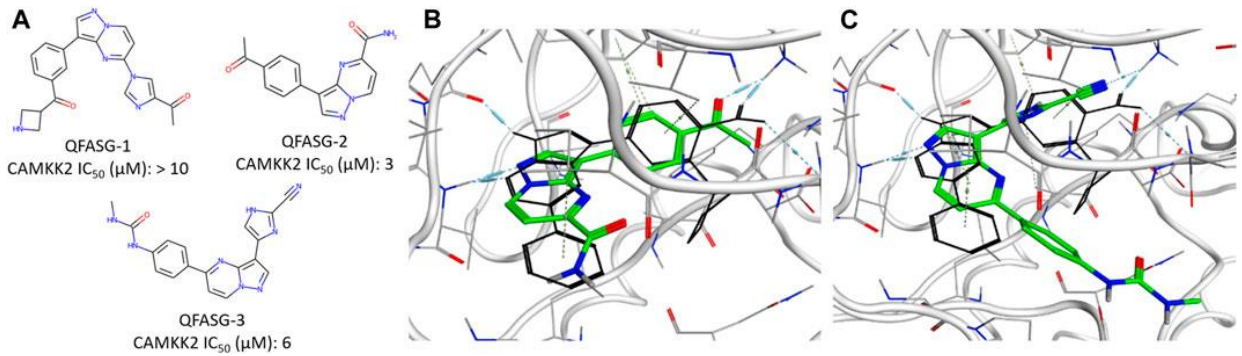
Sergei Evteev[1*] Yan Ivanenkov[1] Ivan Semenov[1] Maxim Malkov[2] Olga Mazaleva[1]

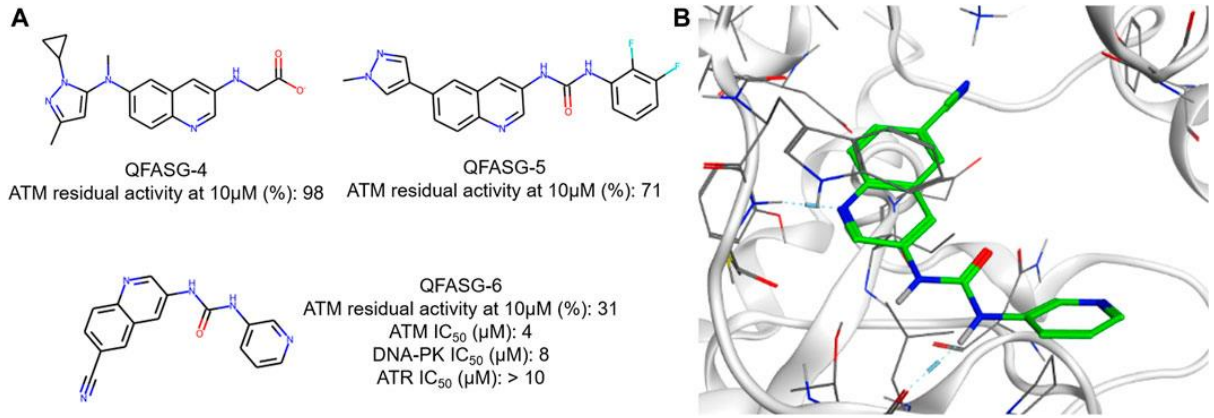
Artem Bodunov[1] Dmitry Bezrukov[2] Denis Sidorenko[1] Victor Terentiev[1] Alex Malyshev[1]

Bogdan Zagribelnyy[2] Anastasia Korzhenevskaya[1] Alex Aliper[2] Alex Zhavoronkov[2]

[1] Insilico Medicine Hong Kong Ltd., Hong Kong, Hong Kong SAR, China
[2] Insilico Medicine AI Limited, Abu Dhabi, United Arab Emirates

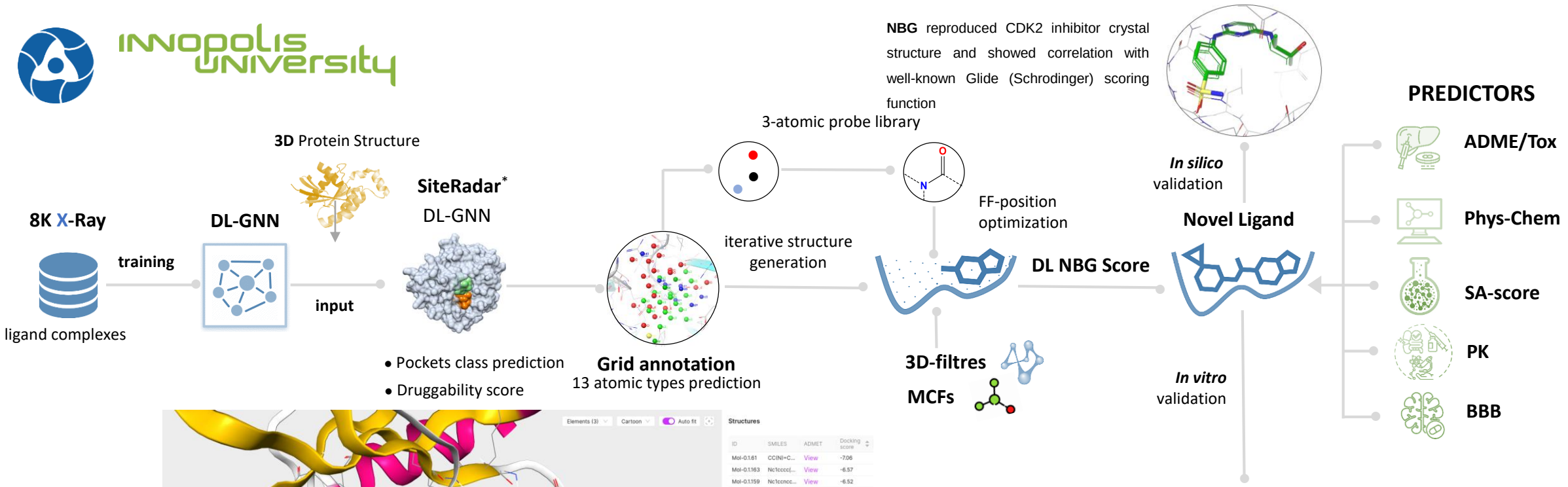






NATURE-BASED GENERATOR (NBG)

Atom-wise Generation of Ligand Structures Complementary to Macromolecular Environment



Target X inhibitors (Presude Lifesciences)

- Synthesis is ongoing

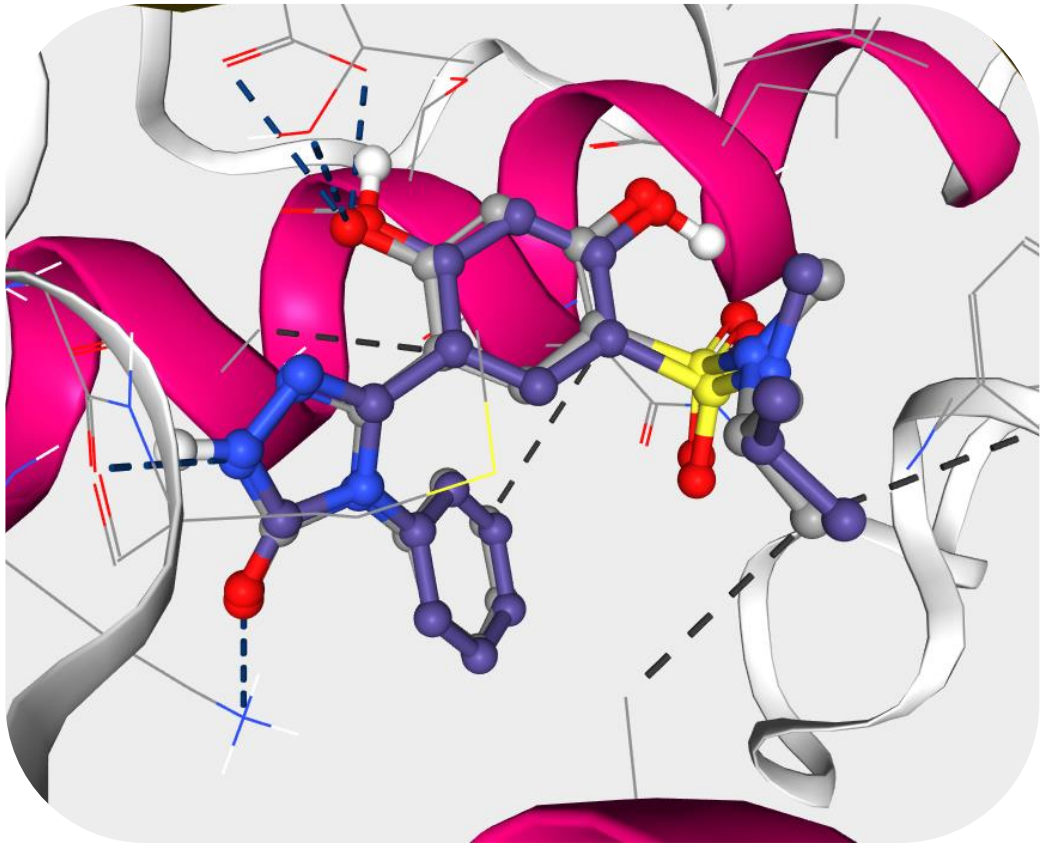
Kinase inhibitors (*in*-house program)

- Novel kinase with no ligand reported
- Hit-compound was developed with good selectivity

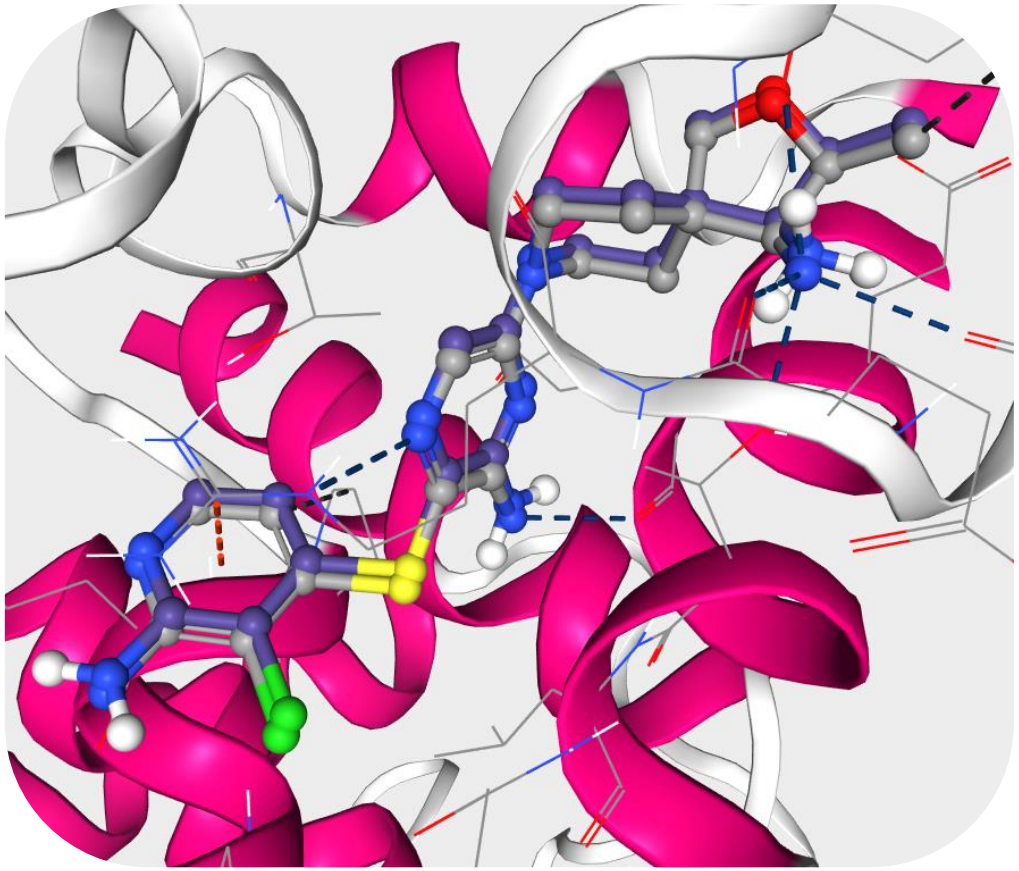
*Evteev SA, Ereshchenko AV, Ivanenkov YA. SiteRadar: *Utilizing Graph Machine Learning for Precise Mapping of Protein–Ligand-Binding Sites*. J. Chem. Inf. Model. **2023**, 63, 4, 1124–1132

Structure generation

Known crystals reproduction



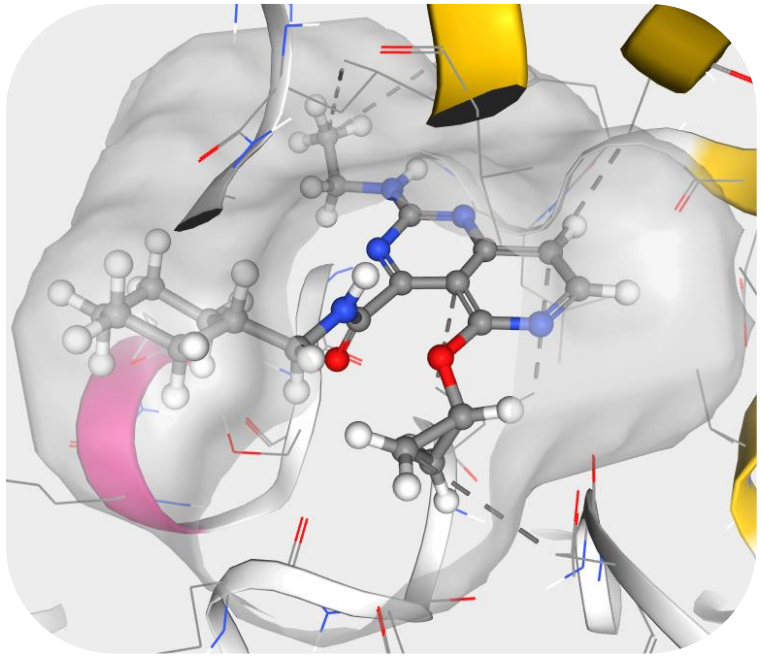
Heat shock protein 90-α
PDB ID 5J82



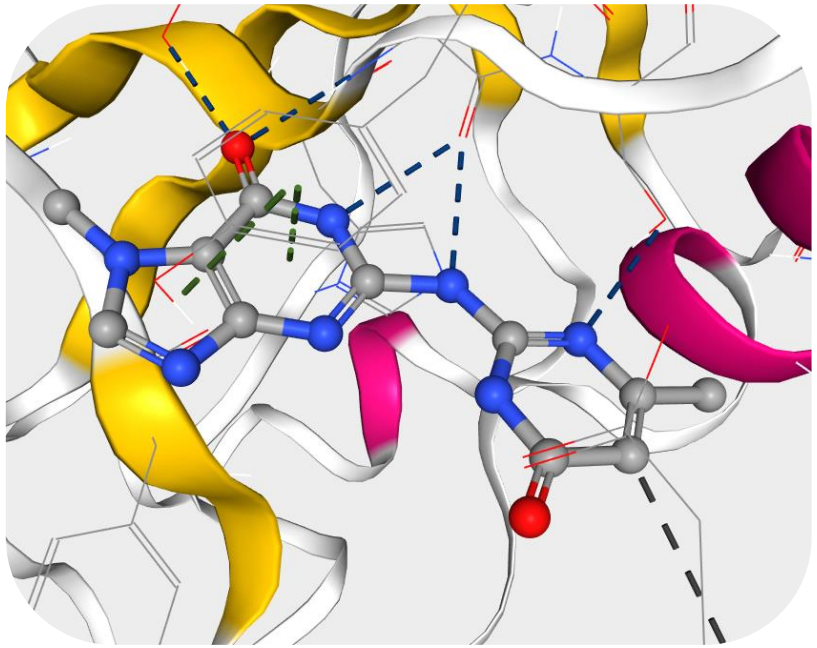
Phosphatase SHP2
PDB ID 7JVM

Structure generation

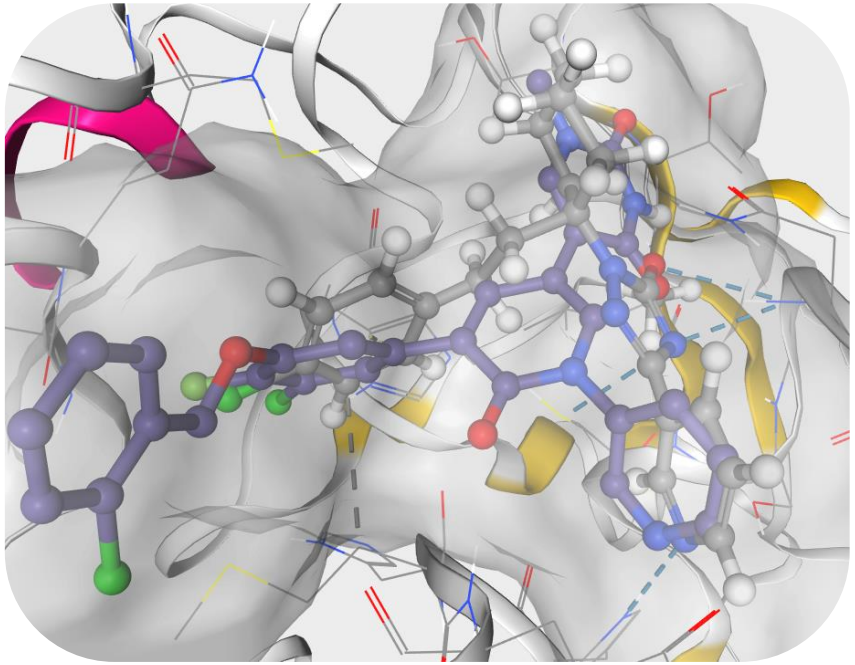
Design of new compounds



JAK1
PDB ID 6ELR



PARP1
PDB ID 4ZZZ



SARS Cov2 main protease
PDB ID 8UR9

Target X (Presude Lifesciences)

- Hit compound with IC_{50} = 3µM was obtained

Thank you

Sergei Evteev

saevteev@vniia.ru

@SERGEI_EVTEEV