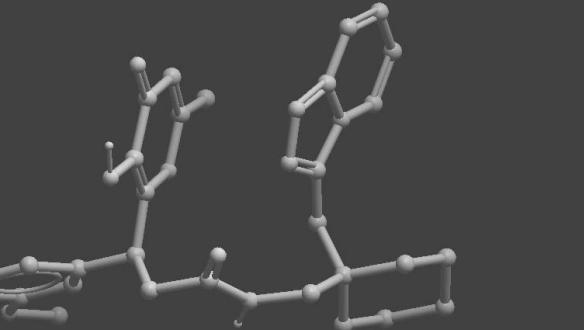




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И ИННОВАЦИИ
РОСАТОМ



AI-based Approaches for *De Novo* Drug Design



Иваненков Ян Андреевич
Руководитель Лаборатории медицинской
химии и хемоинформатики, ВНИИА
yaiivanenkov@gmail.com

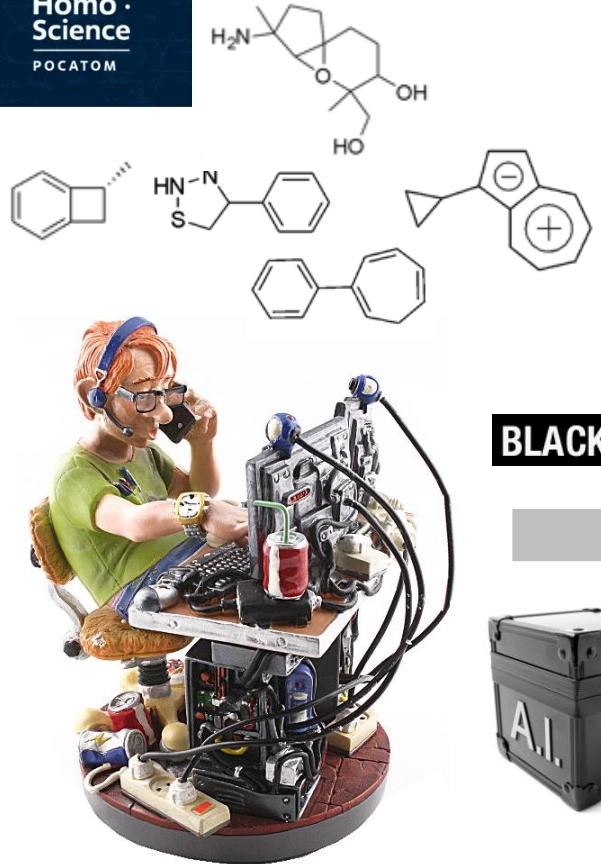
ГОД НАУКИ И ТЕХНОЛОГИЙ В РОССИИ



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РОСАТОМ

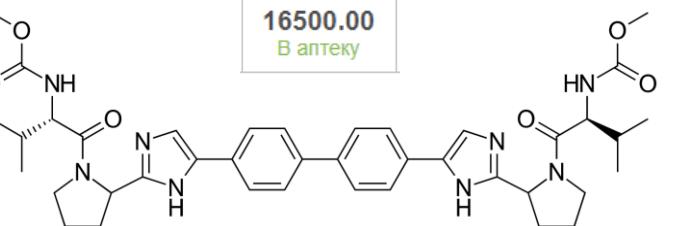


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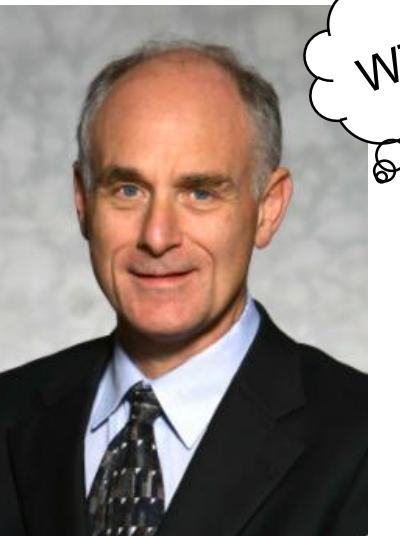


Generative Chemistry
AI-guy who really believes that he is producing the best structures that have ever existed!

How it Works in Real Drug Discovery World



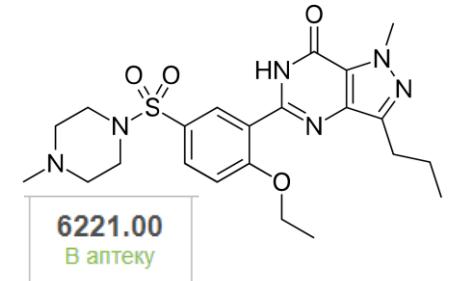
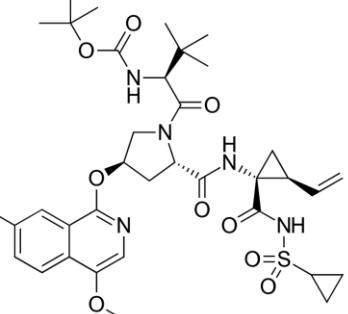
Bristol-Myers Squibb



Dr. Nicholas Meanwell
Medicinal Chemist

Dr. Meanwell has a Ph.D. from the University of Sheffield and completed a Postdoctoral Fellowship at Wayne State University. He joined Bristol-Myers Squibb in 1982 and has led the antiviral chemistry group since 1992. They have pioneered several mechanistically novel antiviral approaches including influenza and respiratory syncytial virus fusion inhibitors, HIV-1 attachment inhibitors and HCV NS5A inhibitors. They have also completed Phase 3 clinical trials of a combination of the HCV NS5A inhibitor daclatasvir and the HCV NS3 inhibitor asunaprevir.

WTF!!!???



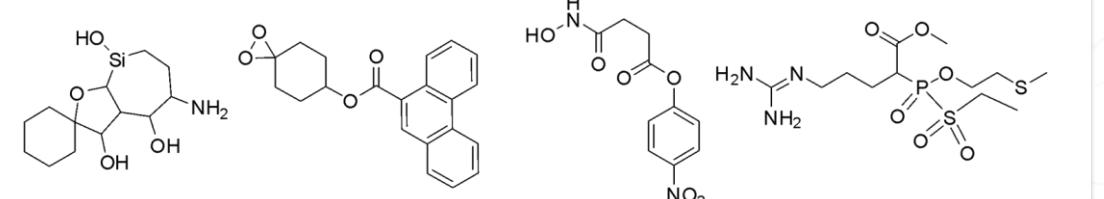
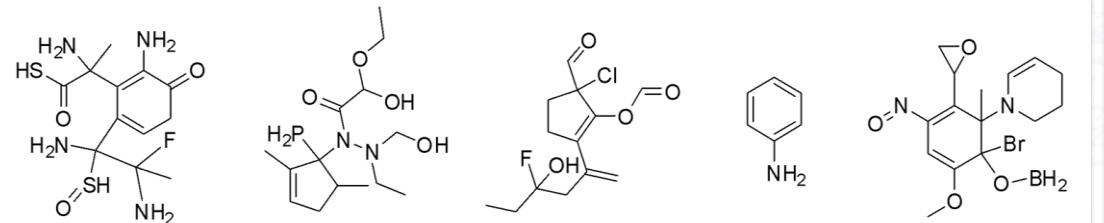
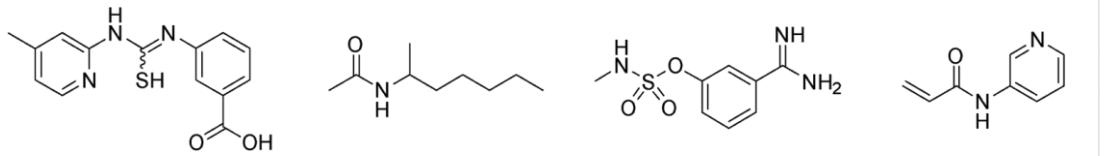
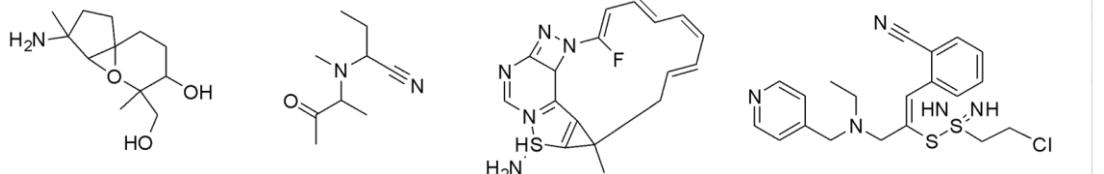
Dr. Declan Doogan
Drug Developer

Dr. Doogan, the Chief Medical Officer of Juvenescence, has more than 30 years experience in the global pharmaceutical industry. He was Head of Worldwide Drug Development at Pfizer, working in the US, UK and Japan. Dr. Doogan was also head of R&D at Amarin where he helped raise \$100m to fund the reorganization and portfolio realignment leading to the NDA approval for Vascepa (icosapent ethyl) for elevated triglycerides. Dr. Doogan delivered many multibillion dollar programs (e.g., Viagra, Lipitor and Zoloft).



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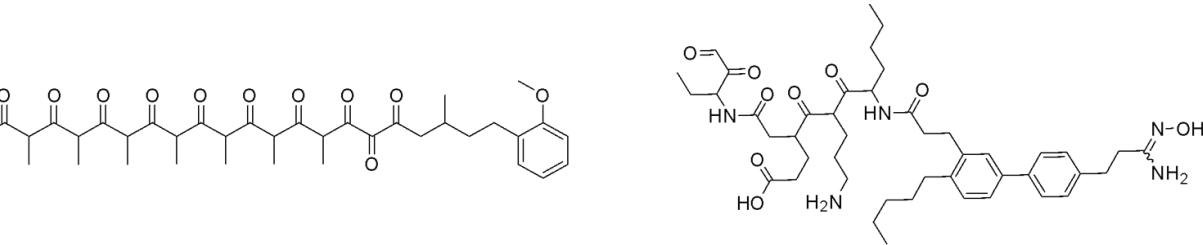
Representative examples of structures generated by different AI players In the field of AI-driven drug design & development



DISTRIBUTION BENCHMKS

<https://www.benevolent.com/guacamol>

benchmark	AAE	Graph MCTS	Random Sampler	SMILES LSTM	VAE	ORGAN
Validity	0.822	1.000	1.000	0.959	0.870	0.379
Uniqueness	1.000	1.000	0.997	1.000	0.999	0.841
Novelty	0.998	0.994	0.000	0.912	0.974	0.686
KL divergence	0.886	0.522	0.998	0.991	0.982	0.267
Frechet ChemNet Distance	0.529	0.015	0.929	0.913	0.863	0.000
	see molecules					



Benevolent has scored these generated structures as very novel, valid and unique!

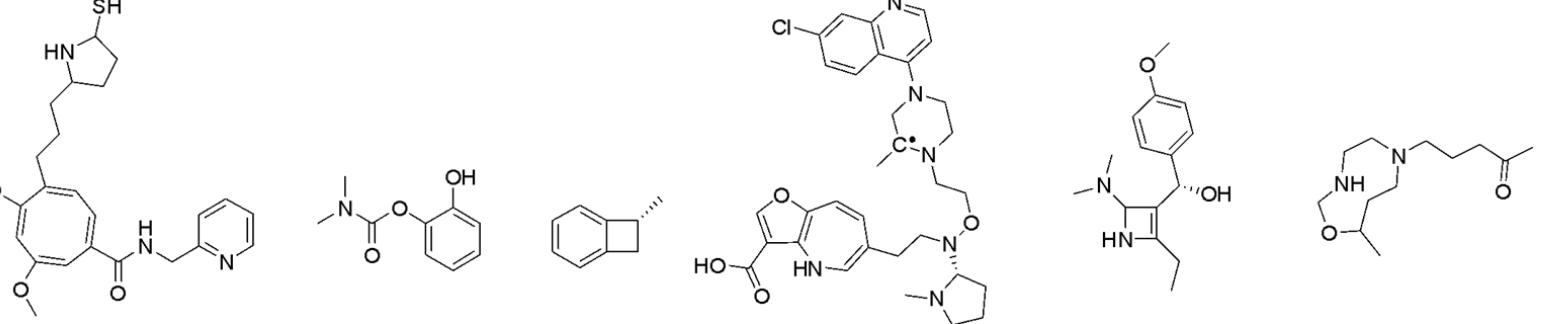


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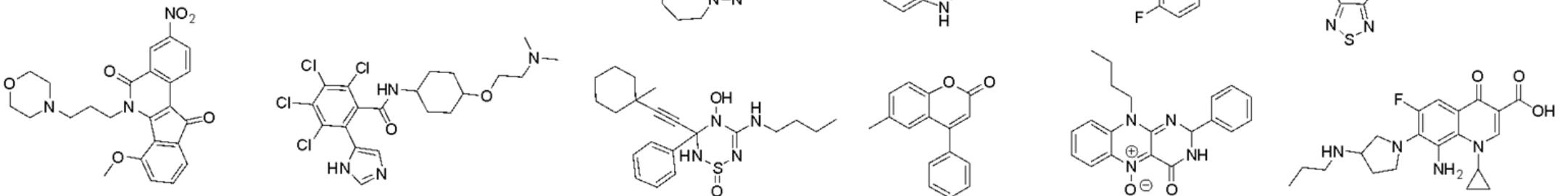
Representative examples of structures generated by different AI players In the field of AI-driven drug design & development



De novo generation of **hit-like molecules**
from gene expression signatures using
artificial intelligence, *Nature Communications*,
2020, 11, 1-10



Generating Focused Molecule Libraries for Drug Discovery with
Recurrent Neural Networks ACS Cent. Sci. **2018, 4** 120–131





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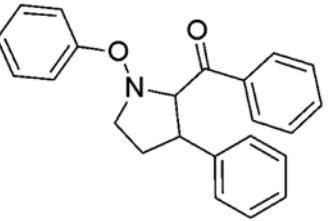
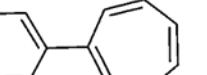
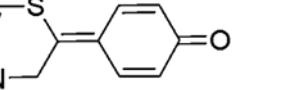
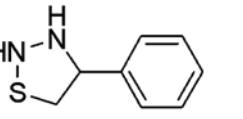
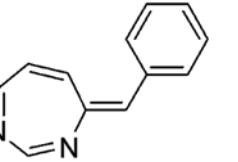
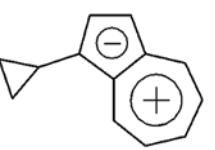


Representative examples of structures generated by different AI players In the field of AI-driven drug design & development

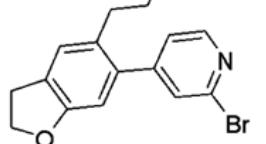
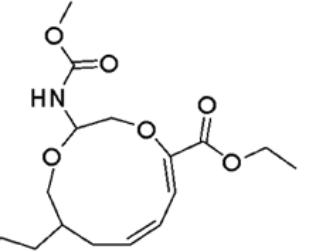
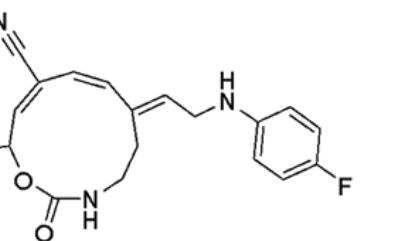
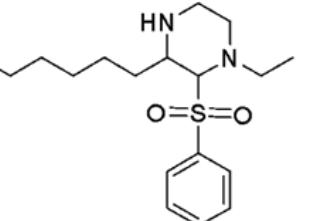
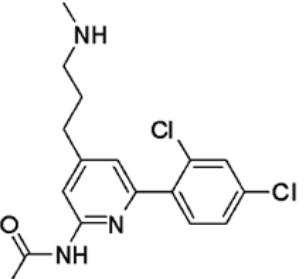
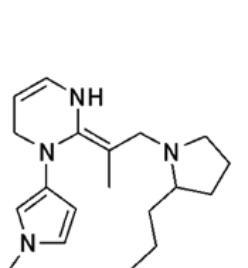


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CogMol: Target-Specific and Selective Drug Design for COVID-19 Using Deep Generative Models (arXiv:2004.01215)



PaccMannRL on SARS-CoV-2: Designing antiviral candidates with conditional generative models (arXiv:2005.13285v2)

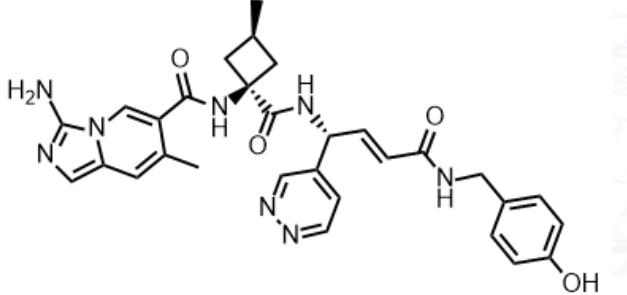




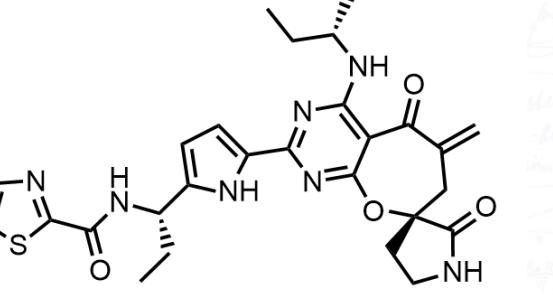
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Representative examples of generated structures by Chemistry42 (v.01)

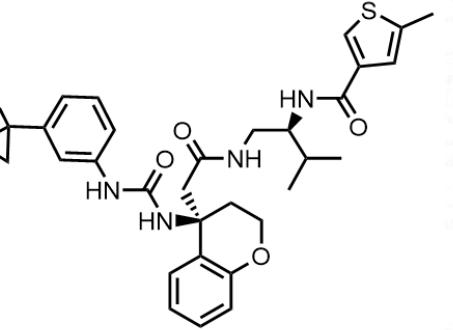
all the generated structures are novel (ChEMBL similarity score < 70.00)



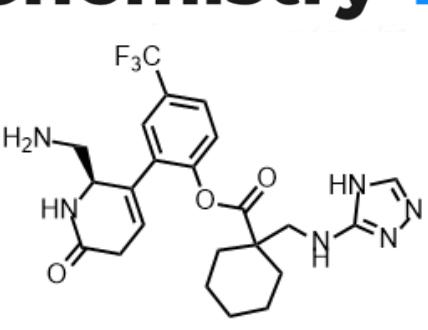
no records with
ChEMBL sim > 40.0



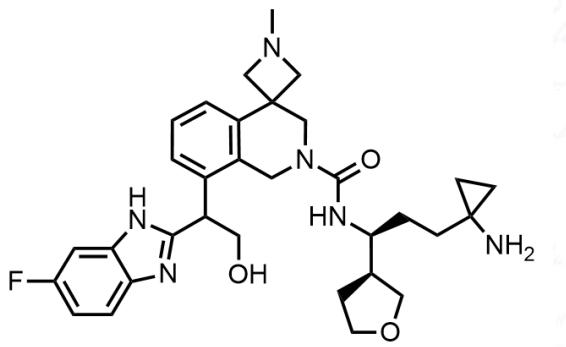
no records with
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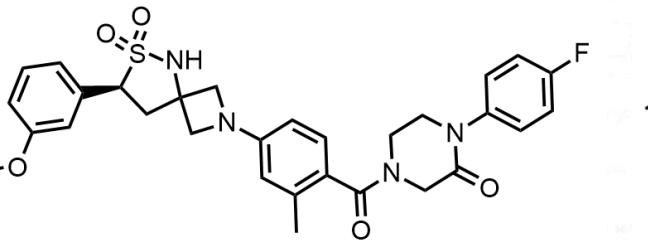
no records with
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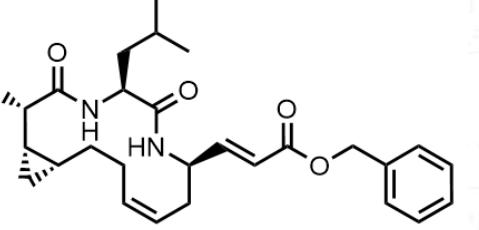
no records with
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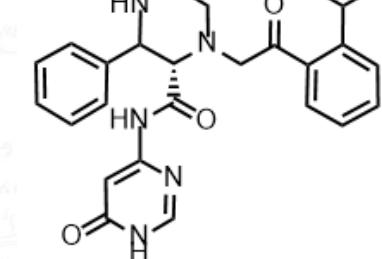
no records with
ChEMBL sim > 40.0



ChEMBL_max_sim = 40.74
[CHEMBL2218536](#)



ChEMBL_max_sim = 41.05
[CHEMBL1921827](#)



no records with
ChEMBL sim > 40.0



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ARTIFICIAL INTELLIGENCE FOR EVERY STEP OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT

ANALYTICS



INTRODUCING FULLY-INTEGRATED DRUG DISCOVERY SOFTWARE SUITE

CHEMISTRY



BIOLOGY



Insilico
Medicine

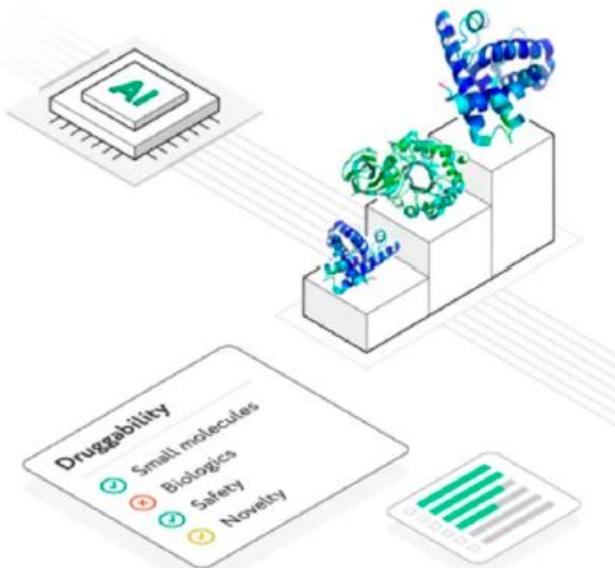
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PandaOmics

Discover and Prioritize

Novel Targets

Enabling multi-omics target discovery and deep biology analysis engine to considerably reduce required time from several months to the span of just a few clicks



Chemistry42

Generate

Novel Molecules

Find novel lead-like molecules in a week through this automated, machine learning de-novo drug design and scalable engineering platform



InClinico

Design and predict

Clinical Trials

Predict clinical trials success rate, recognize the weak points in trial design, while adopting the best practices in the industry





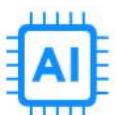
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Chemistry42

Explore uncharted chemical space

Chemistry42 is an automated machine learning platform for drug design capable of finding **novel lead-like molecules in a week**



Automated de-novo drug design

Operate beyond existing screening libraries and skip the effort of scaffold search and structure optimization. Chemistry42 is a **fully-automated machine learning** platform that **delivers new lead-like structures in a week**



Scalable engineering platform

Chemistry42 is a seamlessly **scalable distributed** platform that can be deployed in **cloud and on-premise** environments with predictable hardware-agnostic workload management



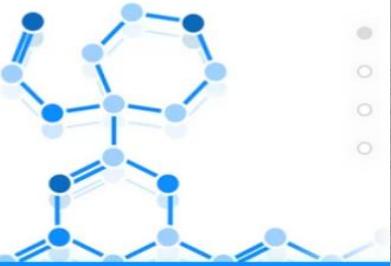
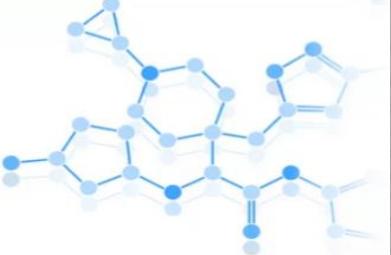
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nature > nature biotechnology > brief communications > article

Brief Communication | Published: 02 September 2019

Deep learning enables rapid identification of potent DDR1 kinase inhibitors

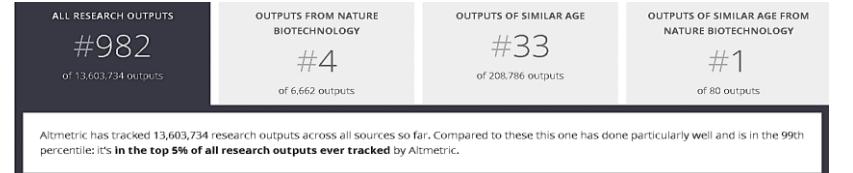
Alex Zhavoronkov✉, Yan A. Ivanenkov, Alex Aliper, Mark S. Veselov, Vladimir A. Aladinskiy, Anastasiya V. Aladinskaya, Victor A. Terentiev, Daniil A. Polykovskiy, Maksim D. Kuznetsov, Arip Asadulaev, Yury Volkov, Artem Zholus, Rim R. Shayakhetmetov, Alexander Zhebrak, Lidiya I. Minaeva, Bogdan A. Zagribelnyy, Lennart H. Lee, Richard Soll, David Madge, Li Xing, Tao Guo & Alán Aspuru-Guzik

Nature Biotechnology 37, 1038–1040(2019) | Cite this article

46k Accesses | 144 Citations | 1590 Altmetric | Metrics

Abstract

We have developed a deep generative model, generative tensorial reinforcement learning (GENTRL), for de novo small-molecule design. GENTRL optimizes synthetic feasibility, novelty, and biological activity. We used GENTRL to discover potent inhibitors of discoidin domain receptor 1 (DDR1), a kinase target implicated in fibrosis and other diseases, in 21 days. Four compounds were active in biochemical assays, and two were validated in cell-based assays. One lead candidate was tested and demonstrated favorable pharmacokinetics in mice.



Chemistry42: An AI-based platform for de novo molecular design

Yan A. Ivanenkov, Alex Zhebrak, Dmitry Bezrukov, Bogdan Zagribelnyy, Vladimir Aladinskiy, Daniil Polykovskiy, Evgeny Putin, Petrina Kamya, Alexander Aliper, Alex Zhavoronkov

Chemistry42 is a software platform for de novo small molecule design that integrates Artificial Intelligence (AI) techniques with computational and medicinal chemistry methods. Chemistry42 is unique in its ability to generate novel molecular structures with predefined properties validated through *in vitro* and *in vivo* studies. Chemistry42 is a core component of Insilico Medicine [this http URL](#) drug discovery suite that also includes target discovery and multi-omics data analysis (PandaOmics) and clinical trial outcomes predictions (InClinico).



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Are We Opening the Door to a New Era of Medicinal Chemistry or Being Collapsed to a Chemical Singularity?

Perspective

Yan A. Ivanenkov*, Bogdan A. Zagribelnyy, and Vladimir A. Aladinskiy

Cite this: *J. Med. Chem.* 2019, 62, 22, 10026–10043

Publication Date: June 12, 2019

<https://doi.org/10.1021/acs.jmedchem.9b00004>

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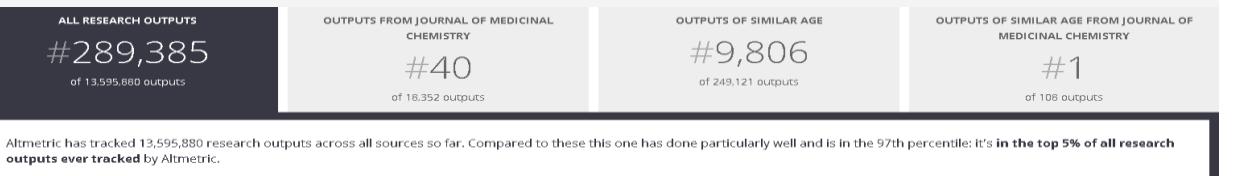
PDF (10 MB)

SI Supporting Info (1) »

SUBJECTS: Chemical structure, Medicinal chemistry, Pharma

Abstract

The paradigm of “drug-like-ness” dramatically altered the behavior of the medicinal chemistry community for a long time. In recent years, scientists have empirically found a significant increase in key properties of drugs that have moved structures closer to the periphery or the outside of the rule-of-five “cage”. Herein, we show that for the past decade, the number of molecules claimed in patent records by major pharmaceutical companies has dramatically decreased, which may lead to a “chemical singularity”. New compounds containing fragments with increased 3D complexity are generally larger, slightly more lipophilic, and more polar. A core difference between this study and recently published papers is that we consider the nature and quality of sp^3 -rich frameworks rather than sp^3 count. We introduce the original descriptor MCE-18, which stands for medicinal chemistry evolution, 2018, and this measure can effectively score molecules by novelty in terms of their cumulative sp^3 complexity.





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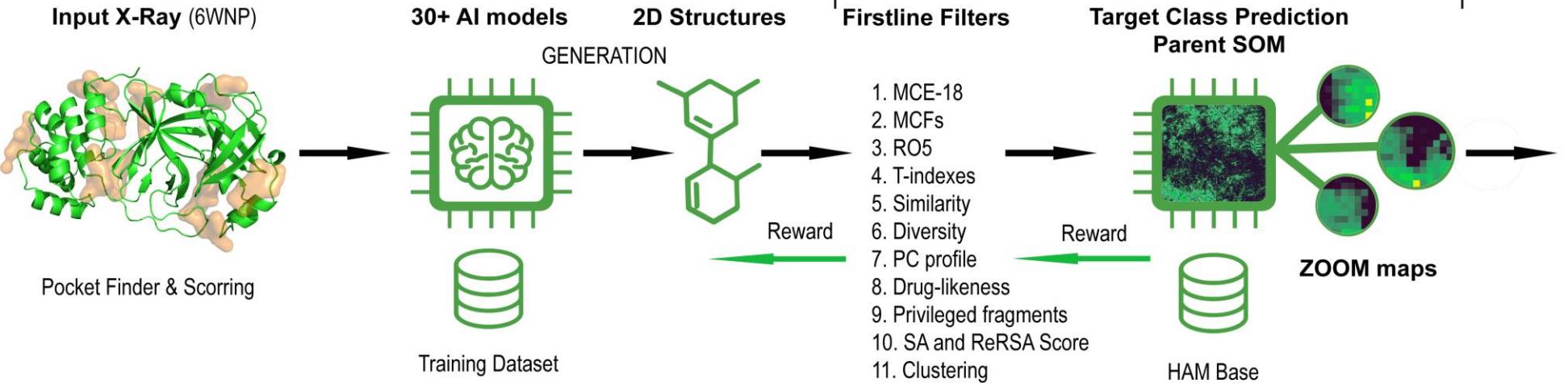
Chemistry42 Generative Pipeline for De Novo Drug Design

Chemistry42

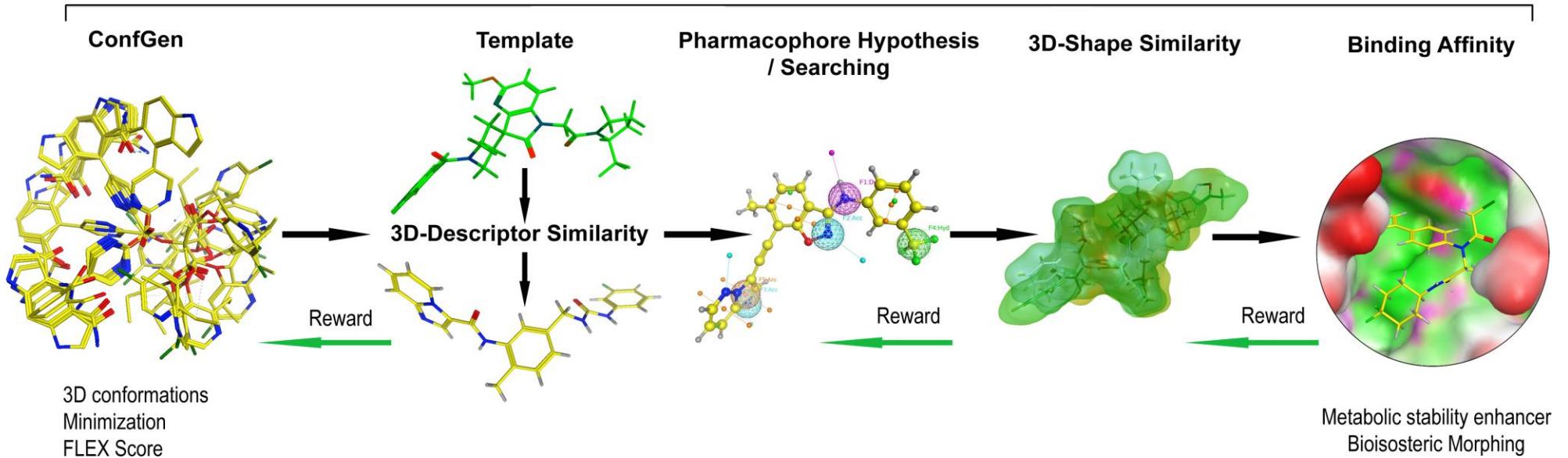
LBDD and SBDD

COVID-19

2D Modules



3D Modules





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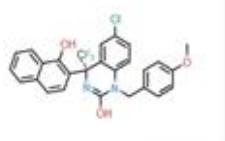


SynFini™ automated synthetic chemistry platform

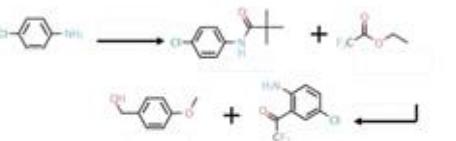


SynRoute™

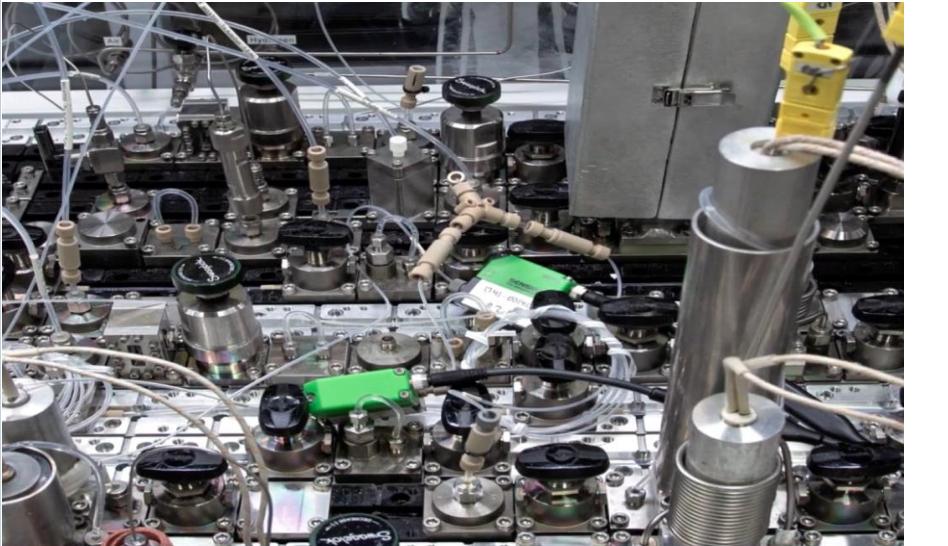
Target Compound



route 1

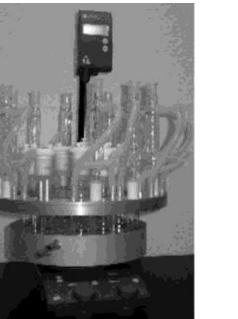


AI & Big Data

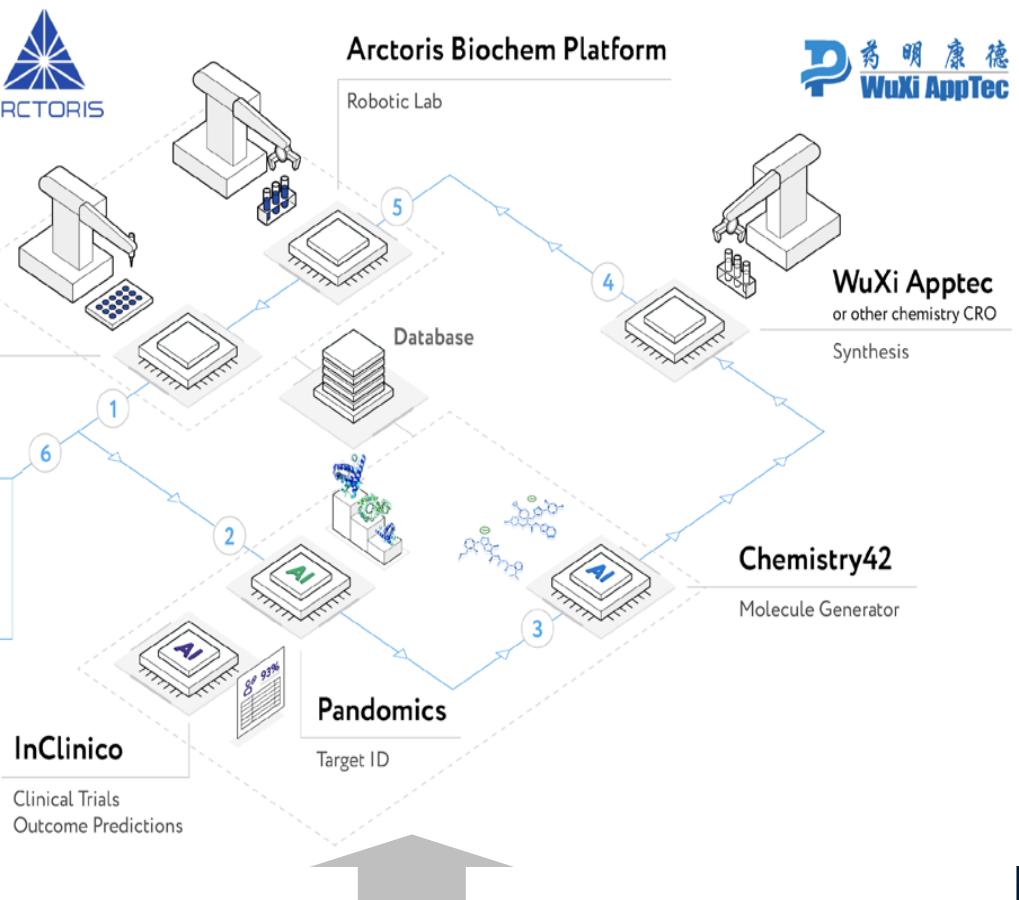


Multistep Synthesis

CombiSyn



years ago



Biological evaluation *in vitro* Organic Synthesis



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SARS-CoV-2 M^{pro} covalent inhibitors

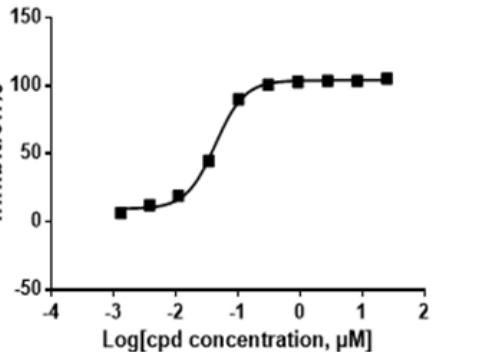
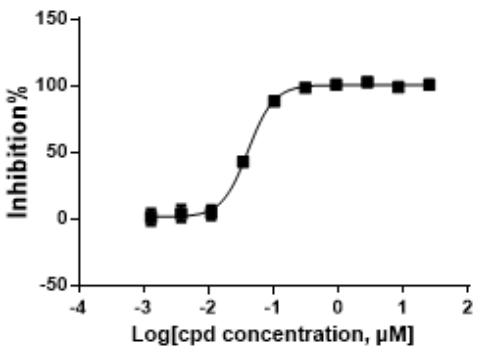
Biological Summary (*In Vitro*)

CASE STUDY

1. SARS-CoV-2 M^{pro} inhibitory assay best compounds

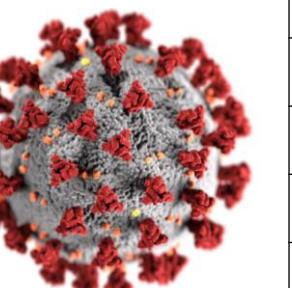
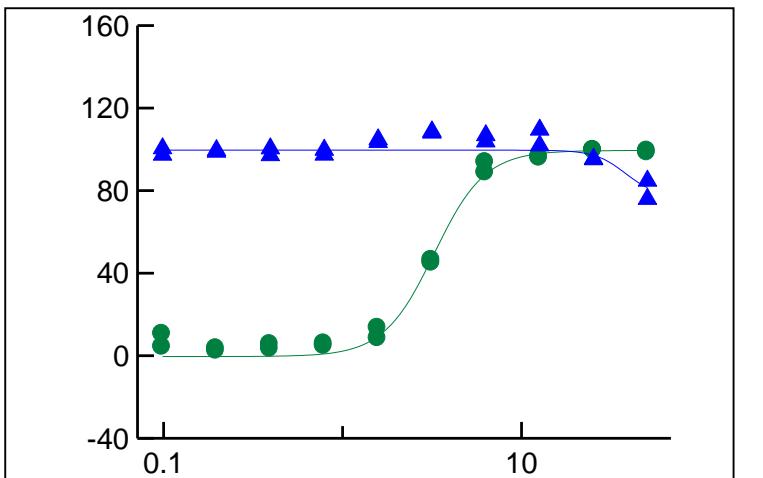
5{60}-R, IC₅₀ = 39 nM

5{43}-R, IC₅₀ = 39 nM



2. SARS-CoV-2 cell-based IFA assay best compound

INSCoV-517, EC₅₀ = 3.22 μM, CC₅₀ > 50 μM



3. Best ADME-panel profile compound

5{43}-±

ID	5{43}-±
SARS-CoV-2 M ^{pro} IC ₅₀ , nM	43
PAMPA, Mean Pe (nm/s)	12.8
CYP 1A2 IC ₅₀ , μM	>50
CYP 2C9 IC ₅₀ , μM	>50
CYP 2C19 IC ₅₀ , μM	>50
CYP 2D6 IC ₅₀ , μM	>50
CYP 3A4 IC ₅₀ , μM	>50
HLM, CLint(mic), (μL/min/mg)	23.6
MLM, CLint(mic), (μL/min/mg)	22.4
Plasma stability, T _{1/2} , min, mice	17.5
Plasma stability, T _{1/2} , min, human	16.2
Kinetic solubility, pH 7.4, μM	5.31



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SARS-CoV-2 M^{pro} covalent inhibitors

CASE STUDY

In Vivo PK Study

PK study results for 5{55}-SR

PK study results for 13a from Rolf Hilgenfeld's team

Study details		Study details	
PK parameters (plasma)		PK parameters (plasma)	
Administration	Subcutaneous	Administration	Subcutaneous
Formulation	5 mg/mL in 0.5% Tween80 in 10 mM PBS PH7.4	Formulation	Olive oil, water, lecithin (40mg/800µL)
Dose	20 mg/kg	Dose	20 mg/kg
Species	Male CD-1(ICR) Mice	Species	Male CD-1 Mice
C _{max} (ng/mL)	777 ± 118	C _{max} (ng/mL)	334.5 ± 109.2
T _{max} (h)	0,5 ± 0,0	T _{max} (h)	0.4 ± 0.1
T _{1/2} (h)	5,09 ± 1,50	T _{1/2} (h)	1.0 ± 0.1
AUC _{0-inf} (ng*h/mL)	2227 ± 927	AUC _{0-inf} (ng*h/mL)	551.2 ± 67.7
MRT _{0-inf} (h)	4,86 ± 1,21	MRT _{0-inf} (h)	1.6 ± 0.2
Lung/plasma ratio at 24h point	2,32 ± 0,88	Lung/plasma ratio at Xh point	NA

- High tendency of the compound to accumulate in lungs is considered as beneficial in COVID-19 conditions

Science

Zhang, L. et al., *Science* Vol. 368, Issue 6489, pp. 409-412
<https://doi.org/10.1126/science.abb3405> (2020).

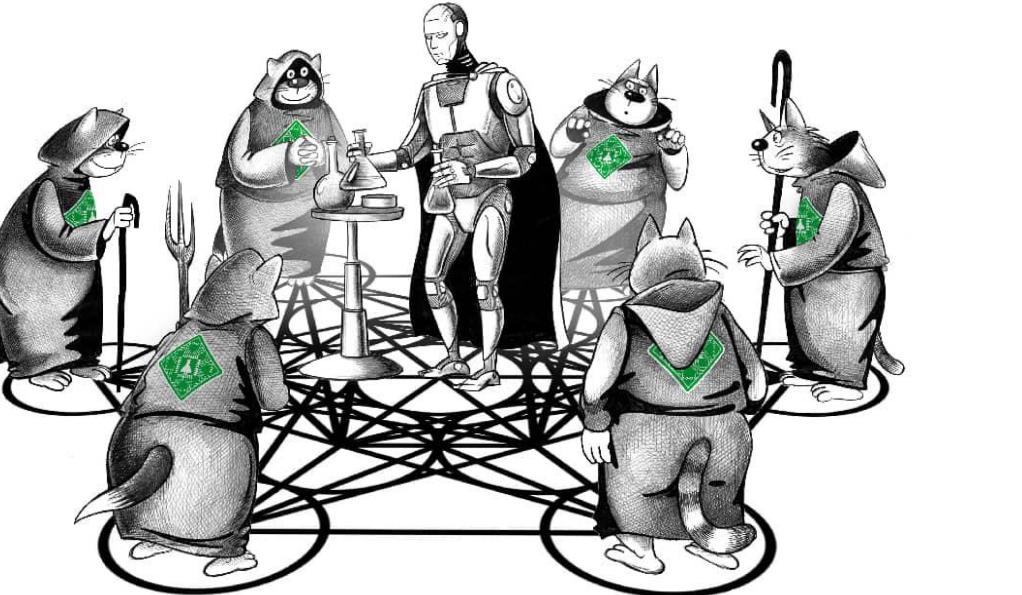
Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors



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Спасибо

DIGITAL ALCHEMY
LET'S DIG DEEPER INTO THE CRAFT



ГОД НАУКИ И ТЕХНОЛОГИЙ В РОССИИ



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