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

Authors: Yan A. Ivanenkov¹, Alex Zhebrak¹, Dmitry Bezrukov¹, Bogdan Zagribelnyy¹, Vladimir Aladinskiy¹, Daniil Polykovskiy¹, Evgeny Putin¹, Petrina Kamya¹, Alexander Aliper¹, Alex Zhavoronkov¹

Affiliation:

1. Insilico Medicine Hong Kong Ltd. Science Park East Avenue, Hong Kong Science Park, Pak Shek Kok, Hong Kong

Corresponding author: Alex Zhavoronkov, alex@insilico.com

Abstract: 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’s Pharma.ai drug discovery suite that also includes target discovery and multi-omics data analysis (PandaOmics) and clinical trial outcomes predictions (InClinico).

Keywords: generative chemistry, target identification, deep learning, reinforcement learning, drug discovery, *de novo* drug design
Introduction

Deep Learning (DL) has proven to be very effective in speech and image recognition. This is because DL-based architectures are uniquely suited for the automatic identification of patterns within complex, nonlinear data sets without the need for manual feature engineering. DL methods have successfully overcome limitations inherent in the standard techniques used for small molecule design (Chen et al. 2018; Vanhaelen, Lin, and Zhavoronkov 2020; Yang et al. 2019) which offers exciting possibilities for the development of new methods that efficiently explore uncharted chemical space.

Insilico Medicine, a company that develops AI algorithms for target discovery and generative chemistry, was one of the first groups to publish a method that uses a deep adversarial model for new compound generation (Kadurin, Aliper, et al. 2017). Since then, DL-based architectures that combine generative algorithms with reinforcement learning (RL) have been developed and applied in chemistry and pharmacology to generate novel molecular structures with predefined properties. Especially encouraging is the recent progress in the de novo design of active molecules that have been validated in both in vitro and in vivo assays (Zhavoronkov et al. 2019). The field of generative chemistry is now one of the fastest-growing drug discovery areas (Vanhaelen, Lin, and Zhavoronkov 2020; Schneider 2018; Merk et al. 2018). The Chemistry42™ platform has been routinely and successfully used at Insilico Medicine to drive the drug discovery process in several therapeutic areas. In the following sections, we describe the key features of the Chemistry42™ platform.

Overview of the generative capabilities of the Chemistry42™ platform

Chemistry42™ is a platform that connects state-of-the-art generative AI algorithms with medicinal chemistry expertise and best engineering practices. The main objective of this platform is to accelerate the design of novel molecules with user-defined properties. The general workflow for Chemistry42™ is illustrated and described in Figure 1.
Figure 1. Schematic representation of the three-step workflow for a de novo generative experiment using the Chemistry42™ platform. In the first step, the user provides input and configures the generation experiment. Users can upload their data in multiple file formats and provide details on the desired properties of the generated structures. The second step involves deploying up to 30 generative models functioning in parallel to generate the novel structures, where users can specify which models should be enabled at this step. Power users can also choose to install additional custom generative model(s) and run them within the platform. All generated items undergo virtual screening based on a variety of filters for the generation phase. During the virtual
screening/optimization stage, multiple sets of reward and scoring functions, classified as either 2D or 3D modules, are used to dynamically assess the generated structures’ properties according to the predefined criteria. These modules form the backbone of Chemistry42™’s RL-based generation procedure. Data from the virtual screening feeds back into the generative models to benchmark, optimize and provide valuable data to the models, which completes the cycle of reinforcement learning. The final step is analysis. The generated structures are automatically ranked according to customizable metrics based on their predicted properties, including synthetic accessibility, novelty, diversity, etc. The platform also provides users with interactive tools to monitor model performance.

Individual generative experiments are created as projects using the user-friendly web-based interface to Chemistry42™. They can be started using either ligand or structure-based drug design workflows (LBDD or SBDD approaches, respectively). The LBDD approach requires a 2D or 3D ligand structure as input in .sdf or .smi format. A pharmacophore hypothesis can also be added as needed. It can be created either manually using an external widget or automatically created within the platform. In the SBDD approach, the structure of a protein target, either in the apo format or in complex with a ligand, must be uploaded to the platform as a prepared .pdb file. One can pick either the pocket around the ligand (ligand binding site) or select one from the set of alternative pockets indicated by the Pocket Scanner Module. As with the case for LBDD, a pharmacophore hypothesis can also be added as needed (Figure 2). To complete the configuration of a generation experiment, the user defines acceptable ranges for multiple properties (e.g. physicochemical properties and diversity) of the generated structures. In both LBDD and SBDD approaches, advanced options enable the user to specify and fine-tune reward functions and which models should be used in an experiment. Once the configuration of the experiment is completed, the platform begins an interactive generative exploration of the chemical space using multiple generative models in parallel.

The generative procedure in Chemistry42 engages an asynchronous ensemble of proprietary generative models of different nature. These are carefully curated and selected algorithms with diverse architectures implementing distinct strategies. The platform utilizes multiple machine learning models and molecular representations for different scenarios to maximize their contribution and the platform’s efficiency. For example, some of the models focus on the exploration of the chemical space, while others are tailored to improve these explored structures. In the current version of Chemistry42, there are over 30 generative models, including generative
autoencoders (Polykovskiy et al. 2018; Zhavoronkov et al. 2019), generative adversarial networks (Kadurin, Nikolenko, et al. 2017; Kadurin, Aliper, et al. 2017; Putin et al. 2018), evolutionary algorithms, language models and others. Moreover, these models employ different molecular representations — string-based, graph-based, and 3D-based.

It is essential to understand and stimulate the interplay of multiple models. Rather than treating these algorithms as black-box solutions, we provide deep domain-specific analytics to understand the advantages and drawbacks of each approach. Combining various state-of-the-art machine learning methods, Chemistry42 is the most comprehensive generative chemistry effort to date, capable of delivering diverse, high-quality molecular structures in a fully automated fashion with speed. As the structures are generated, they are dynamically assessed using the reward and scoring functions in the platform.

![Chemistry42™ interface for configuring an SBDD generative experiment](image)

The reward and scoring functions used in Chemistry42 for the RL-based generation are classified as either two dimensional (2D) or three dimensional (3D) modules (Figure 1). The 2D modules are composed of multiple scores and in-house medicinal
Chemistry Filters (MCFs) that are used to assess the generated structures. The MCFs include a set of over 460 in-house structure-based rules that exclude “bad” structures that contain structure alerts, PAINS (Baell and Holloway 2010) or functional groups that are reactive, unstable or potentially toxic. The Medicinal Chemistry Evolution (MCE-18) function is a unique molecular descriptor that scores structures by novelty in terms of their cumulative sp³ complexity (Ivanenkov, Zagribelnyy, and Aladinskiy 2019). Other 2D modules include Lipinski's Rule of Five (RO5) (Lipinski et al. 2001), Drug-likeness and T-indexes, a rule-based filter that constitutes a set of rules to eliminate structures with an unbalanced number of carbons and heteroatoms. Similarity scores assess the 2D-similarity (cosine) between the generated structures and the reference dataset corresponding to the predefined and vast chemical space. The physicochemical profile of a compound is assessed using a set of molecular descriptors and predictive models in the PhysChem Profile Predictor module. Drug-likeness is estimated using a set of extended rules. The synthetic accessibility (SA) of the generated structures is assessed using the Retrosynthesis Related Synthetic Accessibility (ReRSA) score. ReRSA is an improved fragment-based SA estimation method that is based on the fragmentation of the generated structure from an organic synthesis perspective, which results in a more accurate estimation of SA. Diversity assessments and clustering metrics are performed for the generated structures using a combination of Finger-Print (FP)-based methods. Tracking the Diversity of the generated structures provides a means of understanding how structurally diverse they are based on the number of generated chemotypes following clustering. Novelty is estimated as (1−similarity), where similarity is calculated to the reported compounds from public sources (e.g. SureChembl). Privileged Fragments (PFs) are automatically defined structural motifs that contribute to the activity against a target or target class (Yet 2018). For each generated structure, this filter assesses the presence of PFs in the generated structures and returns a score. PFs can be specified by the user or generated automatically using the Hierarchical Active Molecules (HAM) dataset which contains biologically active molecules with reported in vitro activities against various targets organized hierarchically. The HAM dataset is also integrated into the platform’s self-organizing maps (SOM) Classifier Module (Kohonen 2001) and ZOOM maps. SOM Classifier Module (general SOM map 100×100) is used to drive the generation towards the chemical space corresponding to a specified target class. Since the general SOM contains neurons with the classification power below the
 predefined threshold for a selected category of molecules, all the reference molecules from such neurons are collected and then subjected to automatically generated ZOOM maps of an adapted size to achieve a reliable classification accuracy. Structure Morphing module contains two components: a rule-based *Metabolic Stability Enhancer* (Kirchmair et al. 2015) to address metabolic instability and *Bioisostere Module* for bioisosteric/isosteric transformation (Brown 2012) to expand the generated chemical classes.

After assessing the generated structures with the 2D modules, the platform utilizes five different 3D modules for further assessment. The first 3D module generates a conformational ensemble for each generated structure (*ConfGen Module*). Conformational ensembles are generated through a combination of a set of rules and pre-defined substructure geometries based on small molecule or co-crystal X-ray data followed by energy minimization. A flexibility assessment (*FLEX score*) component is used to rank molecular structures by intrinsic rigidity. The second module evaluates the 3D similarity between the generated structures and a reference molecule (input ligand) using a set of calculated 3D-descriptors (*3D-Descriptors Module*). The third module is used to generate or construct a pharmacophore hypothesis(es) including all important binding points, distances, angles, and tolerance and automatically score the generated structures against the selected hypotheses (*Pharmacophore Module*). The fourth module (*Shape Similarity Module*) evaluates the 3D-shape similarity to a reference molecule using weighted Gaussian functions (Yan et al. 2013). The fifth module focuses on positioning and scoring the generated structures to assess how well they fit the selected binding site (*Pocket Module*).

All corresponding data including scores, molecular structures and model performance are stored and accessible on the results page of the platform where the generative experiment can be monitored in real-time till completion.

The average duration of a standard experiment that uses all generative models is 72 hours. For each generative model, the performance and convergence rate are monitored. This allows the user to follow the progress of their experiments in real time. The generated structures are automatically evaluated and ranked according to metrics incorporated in the modules that are integrated into the platform. Once a generative experiment is complete, the results can be analyzed through an interactive
interface. The results can also be exported via an application programming interface (API).

**Model benchmarking**

With Chemistry42™, the user can compare the performance of all the generative models used in an experiment. The platform utilises a benchmarking system based on Molecular Sets (MOSES) system for assessing performance, reward components, novelty, diversity, and other metrics during the generation and after the experiment is completed (Polykovskiy et al. 2020). Based on the provided analytics, users can seamlessly compare the models' performance for every experiment. A record of the results and training data is kept during the experiment and stored to ensure that reproducibility and monitoring are both simple and feasible.

**Chemistry42™ interoperability**

Chemistry42™ is accessible through a user-friendly interface built on top of a distributed cloud platform with a scalable cloud architecture. The implementation integrates a variety of features aimed at optimizing its performance. This includes cluster management with Kubernetes, multiple flexible workflows, integrated monitoring and logging. The structure and interoperability of the Chemistry42™ platform allows its deployment on the cloud or on a user’s own premises. For either deployment scenarios, the platform can be integrated into an already established workflow.
Figure 3. PandaOmics and Chemistry42™ platforms integrated into your drug discovery pipeline. The interoperability of these platforms allows an efficient interaction between target identification and de novo small molecule generation.

Chemistry42™ can be connected to Insilico Medicine’s bioinformatics web service PandaOmics (https://pandaoomics.com) (Figure 3). PandaOmics is a comprehensive computational suite for the analysis of -omics data that provides access to information ranging from disease signatures to prospective targets and existing drugs. PandaOmics combines classic bioinformatics methods with signaling pathway analysis using the iPANDA algorithm (Ozerov et al. 2016; Stamatas et al. 2017; Ravi et al. 2018; Salouna et al. 2019; Subbannayya et al. 2019). PandaOmics also provides access to an AI-powered toolkit including deep feature selection for pathway reconstruction, a pathway scoring engine, causal inference, deep-learned transcriptional response scoring engine and an activation-based scoring engine. This multimodal approach combines big data, chemistry, biology, and medicine and allows a complete characterization of the interplay between molecular structures, properties, alteration in biological samples and drug response required for target discovery.

**Conclusion**

The Chemistry42™ platform (https://insilico.com/chemistry42) is a customizable working environment that offers state-of-the-art AI technologies specifically developed for de novo molecular design. The flexible user-friendly interface makes
Chemistry42™ accessible to AI specialists, medicinal chemists, computational chemists, and other scientists working in the field of drug discovery. This unique collaborative feature will enable and foster relationships between different scientific communities and facilitate the decision-making process – a process which is exceptionally demanding in the field of drug design.

Acknowledgements

The authors gratefully acknowledge the valuable comments and suggestions made by Dr. Jiye Shi from UCB Pharma (Slough, UK).

Conflicts of Interest Disclosure

Y.A.I, A.Z., D.B., B.Z., V.A., D.P., E.P., P.K., A.A., A. Zhavoronkov work for Insilico Medicine, a commercial artificial intelligence company that developed the Chemistry42™ platform.

References

Baell, Jonathan B., and Georgina A. Holloway. 2010. “New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays.” Journal of Medicinal Chemistry 53 (7): 2719–40.

Brown, Nathan, ed. 2012. Bioisosteres in Medicinal Chemistry. Vol. 54. Methods and Principles in Medicinal Chemistry. John Wiley & Sons.

Chen, Hongming, Ola Engkvist, Yinhai Wang, Marcus Olivecrona, and Thomas Blaschke. 2018. “The Rise of Deep Learning in Drug Discovery.” Drug Discovery Today 23 (6): 1241–50.

Ivanenkov, Yan A., Bogdan A. Zagribelnyy, and Vladimir A. Aladinskiy. 2019. “Are We Opening the Door to a New Era of Medicinal Chemistry or Being Collapsed to a Chemical Singularity?” Journal of Medicinal Chemistry 62 (22): 10026–43.

Kadurin, Artur, Alexander Aliper, Andrey Kazennov, Polina Mamoshina, Quentin Vanhaelen, Kuzma Khrabrov, and Alex Zhavoronkov. 2017. “The Cornucopia of Meaningful Leads: Applying Deep Adversarial Autoencoders for New Molecule Development in Oncology.” Oncotarget 8 (7): 10883–90.

Kadurin, Artur, Sergey Nikolenko, Kuzma Khrabrov, Alex Aliper, and Alex Zhavoronkov. 2017. "druGAN: An Advanced Generative Adversarial Autoencoder Model for de Novo Generation of New Molecules with Desired Molecular Properties in Silico." Molecular Pharmaceutics 14 (9): 3098–3104.

Kirchmair, Johannes, Andreas H. Göller, Dieter Lang, Jens Kunze, Bernard Testa, Ian D. Wilson, Robert C. Glen, and Gisbert Schneider. 2015. “Predicting Drug Metabolism: Experiment And/or Computation?” Nature Reviews. Drug Discovery 14 (6): 387–404.

Kohonen, T. 2001. Self-Organizing Maps. Third, Extended Edition. Vol. 30. Springer Series in Information Sciences. Berlin, Germany: Springer-Verlag.

Lipinski, C. A., F. Lombardo, B. W. Dominy, and P. J. Feeney. 2001. “Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings.” Advanced Drug Delivery Reviews 46 (1-3): 3–26.

Merk, Daniel, Lukas Friedrich, Francesca Grisoni, and Gisbert Schneider. 2018. “De Novo
Design of Bioactive Small Molecules by Artificial Intelligence.” *Molecular Informatics* 37 (1-2). https://doi.org/10.1002/minf.201700153.

Ozerov, Ivan V., Ksenia V. Lezhnina, Evgeny Izumchenko, Artem V. Artemov, Sergey Medintsev, Quentin Vanhaelen, Alexander Aliper, et al. 2016. “In Silico Pathway Activation Network Decomposition Analysis (iPANDA) as a Method for Biomarker Development.” *Nature Communications* 7 (November): 13427.

Polykovskiy, Daniil, Alexander Zhebrak, Benjamin Sanchez-Lengeling, Sergey Golovanov, Oktai Tatanov, Stanislav Belyaev, Rauf Kurbanov, et al. 2020. “Molecular Sets (MOSES): A Benchmarking Platform for Molecular Generation Models.” *Frontiers in Pharmacology* 11: 1931.

Polykovskiy, Daniil, Alexander Zhebrak, Dmitry Vetrov, Yan Ivanenkov, Vladimir Aladinskiy, Polina Mamoshina, Marine Bozdoganyan, Alexander Aliper, Alex Zhavoronkov, and Artur Kadurin. 2018. “Entangled Conditional Adversarial Autoencoder for de Novo Drug Discovery.” *Molecular Pharmaceutics* 15 (10): 4398–4405.

Putin, Evgeny, Arip Asadulaev, Yan Ivanenkov, Vladimir Aladinskiy, Benjamin Sanchez-Lengeling, Alán Aspuru-Guzik, and Alex Zhavoronkov. 2018. “Reinforced Adversarial Neural Computer for de Novo Molecular Design.” *Journal of Chemical Information and Modeling* 58 (6): 1194–1204.

Ravi, Rajani, Kimberly A. Noonan, Vui Pham, Rishi Bedi, Alex Zhavoronkov, Ivan V. Ozerov, Eugene Makarev, et al. 2018. “Bifunctional Immune Checkpoint-Targeted Antibody-Ligand Traps That Simultaneously Disable TGFβ Enhance the Efficacy of Cancer Immunotherapy.” *Nature Communications* 9 (1): 741.

Saloura, Vassiliki, Evgeny Izumchenko, Zhixiang Zuo, Riyue Bao, Michael Korzinkin, Ivan Ozerov, Alex Zhavoronkov, et al. 2019. “Immune Profiles in Primary Squamous Cell Carcinoma of the Head and Neck.” *Oral Oncology* 96 (September): 77–88.

Schneider, Gisbert. 2018. “Generative Models for Artificially-Intelligent Molecular Design.” *Molecular Informatics* 37 (1-2). https://doi.org/10.1002/minf.201880131.

Stamatas, Georgios N., Jeff Wu, Apostolos Pappas, Paradi Mirmirani, Thomas S. McCormick, Kevin D. Cooper, Mary Consolo, et al. 2017. “An Analysis of Gene Expression Data Involving Examination of Signaling Pathways Activation Reveals New Insights into the Mechanism of Action of Minoxidil Topical Foam in Men with Androgenetic Alopecia.” *Cell Cycle* 16 (17): 1578–84.

Subbannayya, Tejaswini, Pamela Leal-Rojas, Alex Zhavoronkov, Ivan V. Ozerov, Mikhail Korzinkin, Niraj Babu, Aneesha Radhakrishnan, et al. 2019. “PIM1 Kinase Promotes Gallbladder Cancer Cell Proliferation via Inhibition of Proline-Rich Akt Substrate of 40 kDa (PRAS40).” *Journal of Cell Communication and Signaling* 13 (2): 163–77.

Vanhaelen, Quentin, Yen-Chu Lin, and Alex Zhavoronkov. 2020. “The Advent of Generative Chemistry.” *ACS Medicinal Chemistry Letters*, July. https://doi.org/10.1021/acsmedchemlett.0c00088.

Yang, Xin, Yifei Wang, Ryan Byrne, Gisbert Schneider, and Shengyong Yang. 2019. “Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery.” *Chemical Reviews* 119 (18): 10520–94.

Yan, Xin, Jiabo Li, Zihong Liu, Minghao Zheng, Hu Ge, and Jun Xu. 2013. “Enhancing Molecular Shape Comparison by Weighted Gaussian Functions.” *Journal of Chemical Information and Modeling* 53 (8): 1967–78.

Yet, Larry. 2018. *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*. Methods and Principles in Medicinal Chemistry. John Wiley & Sons.

Zhavoronkov, Alex, Yan A. Ivanenkov, Alex Aliper, Mark S. Veselov, Vladimir A. Aladinskiy, Anastasiya V. Aladinskaya, Victor A. Terentiev, et al. 2019. “Deep Learning Enables Rapid Identification of Potent DDR1 Kinase Inhibitors.” *Nature Biotechnology* 37 (9): 1038–40.
