



Artificial Intelligence in Drug Discovery: Computational Chemistry, Natural Products, and Clinical Translation

Elham Rezaee ^{1, *}

¹ Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

* **Corresponding Author:** Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: elham_rezaee63@yahoo.com

Received: 9 September, 2026; **Revised:** 13 September, 2026; **Accepted:** 13 September, 2026

Keywords: Artificial Intelligence, Drug Discovery, Medicinal Chemistry, Machine Learning, Natural Products, Clinical Translation

Dear Editor,

The rapid development of artificial intelligence (AI) in pharmaceutical sciences has created new opportunities in medicinal chemistry and drug discovery. Machine learning (ML) and deep learning can integrate chemical, biological, and pharmacological information to support target identification, virtual screening, molecular property prediction, quantitative structure-activity relationship (QSAR) modeling, ADMET prediction, and molecular design (1, 2). However, the value of AI in drug discovery should not be assessed solely based on computational performance. Its ultimate value depends on whether computational predictions improve experimental decision-making and, ultimately, clinical translation. Therefore, AI should be viewed not as a replacement for medicinal chemists or experimental pharmacologists but as part of an integrated computational-experimental workflow.

1. AI and Computational Molecular Design

Computer-aided drug discovery has traditionally relied on molecular docking, pharmacophore modeling, molecular dynamics simulations, and ligand-based approaches. AI is expanding these methods by enabling analyses of larger and more heterogeneous datasets and facilitating the exploration of chemical space (1, 3). A notable example is the use of deep learning for the rapid identification of potent DDR1 kinase inhibitors, in which computationally prioritized compounds were experimentally evaluated and shown to have biological activity (4). Such studies illustrate an important principle:

computational models are most useful when they generate experimentally testable hypotheses rather than being treated as independent evidence of therapeutic efficacy.

Recent studies have also shown how computational approaches can complement medicinal chemistry. Pharmacophore modeling and molecular dynamics-based in silico repositioning have been applied to identify potential dual c-MET/EGFR inhibitors, and molecular docking has been incorporated into the design and evaluation of novel GABAA receptor agonists (5, 6). These applications underscore the continuing role of computational modeling in prioritizing compounds and formulating mechanistic hypotheses for experimental investigation.

2. From Computational Discovery to Human Studies

The transition of AI-assisted drug discovery from computational research to clinical development is an important, albeit still incomplete, process. DSP-1181, an AI-created 5-HT1A receptor agonist developed for obsessive-compulsive disorder, entered Phase I clinical development in Japan in 2020 (7). Although subsequent development did not demonstrate clinical efficacy, its progression into human testing represented an early example of an AI-assisted drug discovery program advancing to clinical development.

A more recent example is rentosertib (formerly ISM001-055/INS018_055), a small-molecule TNIK inhibitor discovered and designed using generative AI approaches for idiopathic pulmonary fibrosis. The compound was

evaluated in a randomized Phase IIa clinical trial, providing a concrete example of an AI-discovered candidate reaching human clinical evaluation (8). Importantly, progression to clinical development should not, in itself, be interpreted as evidence that AI has solved the problem of drug discovery. Rather, these examples indicate that AI can contribute to candidate generation and prioritization, while fundamental challenges related to clinical efficacy, safety, pharmacokinetics, and patient selection remain.

3. Experimental Validation Remains Essential

The increasing sophistication of AI models makes experimental validation more, not less, important. Computational predictions can be influenced by the quality and representativeness of the training data, dataset bias, data leakage, inappropriate validation strategies, and differences between the chemical or biological space represented in training datasets and that encountered in prospective applications (2, 9). External validation, prospective testing, reproducibility, uncertainty estimation, and experimental confirmation are therefore essential components of responsible AI-assisted drug discovery.

Explainable AI (XAI) may further enhance the practical utility of computational models for medicinal chemists. Rather than simply reporting a predicted activity, interpretable models may help identify molecular features, fragments, substructures, or chemical descriptors that contribute to the prediction (10). Such information may guide rational structural modification and help researchers determine whether a prediction is chemically plausible.

Generative AI offers additional opportunities but also important limitations. Generated molecules may be synthetically inaccessible, chemically unstable, biologically implausible, or optimized for computational objectives that do not translate into potency, selectivity, pharmacokinetic properties, or safety (11). The output of generative models is also strongly influenced by the quality and chemical-space coverage of their training data (11). Therefore, generative AI should currently be regarded primarily as a tool for exploring chemical space and generating hypotheses, with medicinal chemists retaining responsibility for assessing synthetic feasibility and biological relevance (11).

4. Opportunities for Natural-Product Drug Discovery

AI may be particularly valuable in natural-product research, which is highly relevant to the pharmaceutical

sciences. Natural products provide chemically diverse scaffolds but also present substantial analytical and pharmacological complexity. Complex extracts can contain numerous constituents, making compound identification, metabolite characterization, and prioritization of biologically relevant candidates challenging. For example, the isolation and structural characterization of acetylenic metabolites from *Artemisia biennis* required extensive chromatographic and spectroscopic analyses (12). AI-assisted dereplication can integrate metabolomics and spectral data to prioritize known compounds and reduce redundant isolation of previously characterized metabolites. In parallel, ML models can support the prediction of compound-target interactions from chemical and biological data, potentially aiding interpretation of the polypharmacology of multicomponent herbal preparations, in which multiple targets and pathways contribute to the observed biological effects (13). By combining these computational approaches with experimental validation, AI could facilitate the prioritization of promising natural products and guide subsequent isolation, characterization, and pharmacological studies. Metabolomics-based approaches may help characterize complex biological responses to natural-product extracts and identify perturbed metabolic pathways, thereby providing mechanistic insights into their pharmacological effects (14, 15). Nevertheless, such predictions should remain hypothesis-generating and require chemical characterization and experimental pharmacological validation (9, 16).

Illustrating this broader experimental context, computational characterization has been combined with experimental evaluation, as reported for *Lactobacillus acidophilus* bacteriocins investigated as potential ROR γ -targeted therapeutics (17). Other studies of quercetin and curcumin have demonstrated the complexity of multitarget pharmacology and the involvement of interconnected biological pathways rather than isolated molecular targets (18). These examples reinforce the potential value of computational approaches for generating mechanistic hypotheses while emphasizing the need for experimental confirmation. AI-based prediction can also support pharmacokinetic optimization. For example, ML has been applied to predict drug permeability across the blood-brain barrier, illustrating how data-driven approaches can assist in evaluating an important drug-disposition property (19).

5. The Translational Gap

Despite rapid methodological advances, the clinically relevant impact of AI in drug discovery remains difficult to establish (2, 9). AI models may perform well on

retrospective benchmarks yet provide limited improvement in real-world drug-development decision-making. This issue arises partly because drug discovery relies on complex, conditional biological data and because many computational endpoints are only indirect proxies for clinically meaningful outcomes (2).

Accordingly, future evaluation of AI should move beyond model accuracy to include prospective validation and evidence that computational tools improve decision-making in active discovery programs. Key questions include whether AI improves the selection of clinically relevant targets, reduces late-stage attrition, identifies molecules with superior pharmacological profiles, or increases the probability of successful clinical translation.

From a practical perspective, the adoption of AI does not necessarily require extensive computational infrastructure. Resource-limited medicinal chemistry laboratories can begin with publicly available chemical and biological databases and accessible open-source cheminformatics and ML tools. Initial applications may include molecular property prediction, virtual screening, compound prioritization, and data visualization. The objective should be to integrate computational analyses into existing experimental workflows rather than replace established laboratory approaches.

6. Conclusion

AI-driven drug discovery should be regarded as an evolving component of modern pharmaceutical research rather than an autonomous replacement for experimental science. Its greatest potential is likely to arise from the iterative integration of computational prediction, medicinal chemistry expertise, experimental validation, and translational decision-making. Future progress will depend on higher-quality and more representative datasets, prospective and externally validated models, uncertainty-aware prediction, interpretable computational outputs, and stronger links between computational endpoints and clinically meaningful outcomes.

In natural-product research in particular, AI-assisted dereplication, target prediction, polypharmacology analysis, and molecular prioritization may provide valuable tools for navigating complex chemical space. Ultimately, the success of AI in pharmaceutical research should be measured not by algorithmic sophistication or retrospective benchmark performance alone but by whether these approaches generate reproducible, experimentally validated, and clinically meaningful advances in drug discovery.

Footnotes

AI Use Disclosure: The author declares that no generative AI tools were used in the creation of this article.

Authors' Contribution: The author was responsible for the conception and design of the work, literature review, drafting and revising the manuscript, and approval of the final version.

Conflict of Interests Statement: The author declares no conflict of interest related to this manuscript.

Ethical Approval: Ethical approval was not required for this work, as it did not involve laboratory experiments, human participants, animal subjects, or the collection of personal data.

Funding/Support: No funding or financial support was received for this work.

References

1. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov*. 2019;18(6):463-477. [PubMed ID: 30976107]. [PubMed Central ID: PMC6552674]. <https://doi.org/10.1038/s41573-019-0024-5>.
2. Bender A, Thomas MC, Scannell JW, Shaywitz DA, Ghiandoni GM, Greener JG, et al. Artificial intelligence in drug discovery-what it is, where we stand and the path forward. *Nat Rev Drug Discov*. 2026;7:1-22. [PubMed ID: 42567977]. <https://doi.org/10.1038/s41573-026-01496-2>.
3. Schneider G. Automating drug discovery. *Nat Rev Drug Discov*. 2018;17(2):97-113. [PubMed ID: 29242609]. <https://doi.org/10.1038/nrd.2017.232>.
4. Zhavoronkov A, Ivanenkov YA, Aliper A, Veselov MS, Aladinskiy VA, Aladinskaya AV, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat Biotechnol*. 2019;37(9):1038-1040. [PubMed ID: 31477924]. <https://doi.org/10.1038/s41587-019-0224-x>.
5. Abkhiz S, Tarighi P, Azizian H. Dual inhibitors of c-MET and EGFR in triple-negative breast cancer: pharmacophore modeling and molecular dynamics-based in silico drug repositioning. *Iran J Pharm Res*. 2025;24(1). e164183. [PubMed ID: 41234389]. [PubMed Central ID: PMC12606863]. <https://doi.org/10.5812/ijpr-164183>.
6. Nassiri Koopaei M, Moghimirad P, Saeedian Moghadam E, Nassiri Koopaei N, Amanlou M, Akbarzadeh T, et al. Design, synthesis, anticonvulsant evaluation, and molecular docking studies of new GABAA agonist derivatives. *Iran J Pharm Res*. 2025;24(1). e157392. [PubMed ID: 40718438]. [PubMed Central ID: PMC12296643]. <https://doi.org/10.5812/ijpr-157392>.
7. Sumitomo Dainippon Pharma Co Ltd, Exscientia Ltd. Sumitomo Dainippon Pharma Co Ltd, Exscientia Ltd. Sumitomo Pharma; 2020, [cited 2026 Sep 21]. Sumitomo Dainippon Pharma and Exscientia joint development: new drug candidate created using artificial intelligence (AI) begins clinical study. Available from: <https://www.sumitomo-pharma.com/news/20200130.html>.
8. Xu Z, Ren F, Wang P, Cao J, Tan C, Ma D, et al. A generative AI-discovered TNIK inhibitor for idiopathic pulmonary fibrosis: a randomized phase 2a trial. *Nat Med*. 2025;31(8):2602-2610. [PubMed

- ID: 40461817]. [PubMed Central ID: PMC12353801]. <https://doi.org/10.1038/s41591-025-03743-2>.
9. Walters WP, Barzilay R. Critical assessment of AI in drug discovery. *Expert Opin Drug Discov*. 2021;**16**(9):937-947. [PubMed ID: 33870801]. <https://doi.org/10.1080/17460441.2021.1915982>.
 10. Jiménez-Luna J, Grisoni F, Schneider G. Drug discovery with explainable artificial intelligence. *Nat Mach Intell*. 2020;**2**(10):573-584. <https://doi.org/10.1038/s42256-020-00236-4>.
 11. Liu X, Liu H. Evaluating AI-generated molecules for drug discovery: from generic metrics to translational readiness. *Int J Mol Sci*. 2026;**27**(13):5916. [PubMed ID: 42450185]. [PubMed Central ID: PMC13362286]. <https://doi.org/10.3390/ijms27135916>.
 12. Najafi M, Shokoohinia Y, Mojarab M. Acetylenic metabolites and a 2-phenoxychromone derivative from the aerial parts of *Artemisia biennis*. *Iran J Pharm Res*. 2025;**24**(1). e160050. [PubMed ID: 40708931]. [PubMed Central ID: PMC12285677]. <https://doi.org/10.5812/ijpr-160050>.
 13. Mullowney MW, Duncan KR, Elsayed SS, Garg N, van der Hooft JJJ, Martin NI, et al. Artificial intelligence for natural product drug discovery. *Nat Rev Drug Discov*. 2023;**22**(11):895-916. [PubMed ID: 37697042]. [PubMed Central ID: PMC13118512]. <https://doi.org/10.1038/s41573-023-00774-7>.
 14. Malekzadeh R, Arjmand M, Akbari Z, Sadeghi S, Haji Hosseini R. The effect of *Xanthium strumarium* root extracts on growth inhibition of epithelial ovarian cancer SK-OV-3 cell line: a metabolomics-based study. *Jundishapur J Nat Pharm Prod*. 2023;**18**(2). e135038. <https://doi.org/10.5812/ijnp-135038>.
 15. Ahmadi M, Akbari Z, Zamani Z, Haji Hosseini R, Arjmand M. Study the mechanism of antileishmanial action of *Xanthium strumarium* against amastigotes stages in *Leishmania major*: a metabolomics approach. *Jundishapur J Nat Pharm Prod*. 2021;**16**(3). e106431. <https://doi.org/10.5812/ijnp-106431>.
 16. Wang L, Han Y, Lei Y, Liu J, Yu J, Li G. Quercetin induces macrophage polarization through PI3K-AKT pathway in atherosclerosis: network pharmacology, molecule docking and in vitro analysis. *Iran J Pharm Res*. 2026;**25**(1). e168202. [PubMed ID: 42170638]. [PubMed Central ID: PMC13187692]. <https://doi.org/10.5812/ijpr-168202>.
 17. Soheili S, Rezaghi Barez S, Siadat SD, Hejazi SH, Abtahi H. In silico and in vitro characterization of *Lactobacillus acidophilus* bacteriocins as ROR-1-targeted therapeutics in breast cancer. *Iran J Pharm Res*. 2025;**24**(1). e163509. [PubMed ID: 41477115]. [PubMed Central ID: PMC12749213]. <https://doi.org/10.5812/ijpr-163509>.
 18. Shamsi M, Mohammadzadeh G, Hatami M, Roshanazadeh M, Noor-Behbahani M, Rashidi M. Dual modulation of canonical and non-canonical TGF- β /ROS/Erk1/2 pathways: synergistic activation of Nrf2 and antioxidant enzymes (SOD1, GPx, HO-1) by quercetin loaded in solid lipid nanoparticles and curcumin in atherosclerosis therapy. *Iran J Pharm Res*. 2024;**23**(1). e151428. [PubMed ID: 40066126]. [PubMed Central ID: PMC11892753]. <https://doi.org/10.5812/ijpr-151428>.
 19. Jafarpour S, Asefzadeh M, Aboutaleb E. The application of machine learning in predicting the permeability of drugs across the blood-brain barrier. *Iran J Pharm Res*. 2024;**23**(1). e149367. [PubMed ID: 40066117]. [PubMed Central ID: PMC11892787]. <https://doi.org/10.5812/ijpr-149367>.