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Unleashing the power of generative AI in drug discovery

Amit Gangwal [1], **Antonio Lavecchia** [2,*]

[1] Department of Natural Product Chemistry, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule 424001, Maharashtra, India
[2] "Drug Discovery" Laboratory, Department of Pharmacy, University of Naples Federico II, I-80131 Naples, Italy

Artificial intelligence (AI) is revolutionizing drug discovery by enhancing precision, reducing timelines and costs, and enabling AI-driven computer-aided drug design. This review focuses on recent advancements in deep generative models (DGMs) for *de novo* drug design, exploring diverse algorithms and their profound impact. It critically analyses the challenges that are intricately interwoven into these technologies, proposing strategies to unlock their full potential. It features case studies of both successes and failures in advancing drugs to clinical trials with AI assistance. Last, it outlines a forward-looking plan for optimizing DGMs in *de novo* drug design, thereby fostering faster and more cost-effective drug development.

Keywords: drug discovery; artificial intelligence; machine learning; deep learning; generative models; de novo drug design

Introduction

Drug discovery is a costly and time-consuming process, with expenses exceeding US$2.8 billion and a duration of over 12 years for the development of a novel drug.(p1),(p2) To expedite this process and to address the rising costs, it is crucial that efficient strategies are explored. High-throughput screening (HTS)

AmitGangwal served as a professor and as principal at Shri Vithal Education & Research Institute's College of Pharmacy, Pandharpur Maharashtra. At present, he is an associate professor at the prestigious Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule. He is an academic-researcher with >18 years of teaching and research experience. Dr Gangwal has published more than 20 peer-reviewed publications in various journals. He has authored two books on AI and has developed an online course on AI and pharmaceutical science. His research interests encompass natural product chemistry, the bioactivity-guided isolation of phytoconstituents, the development and standardization of nutraceuticals or fast-moving consumer goods (FMCGs) of herbal origin, and applications of AI in pharmaceutical science.

AntonioLavecchia Professor of Medicinal Chemistry and Head of the Drug Discovery Laboratory at the Department of Pharmacy, University of Napoli Federico II, also serves as a Responsible Scientist at the Excellence Laboratory of Molecular Modeling. He earned his PhD in pharmaceutical sciences from the University of Catania in 1999, conducting research at the University of Minnesota (USA). Prof. Lavecchia's research integrates computational chemistry with biological experiments, focusing on the development and application of AI algorithms and protocols to accelerate drug discovery across therapeutic areas including cancer, diabetes, dyslipidemia, and inflammation. With over 170 publications, six books, and six PCT patents, he is a distinguished speaker and serves on the editorial boards of international journals. Recognized with awards such as the Farmindustria Prize for Pharmaceutical Research (2006) and the "Start Cup Campania Award" (2009, 2010), his expertise in peroxisome proliferator-activated receptors (PPARs) saw him recognized as a 'World Expert' by 'Expertscape' in 2021.

* *Corresponding author. Lavecchia, A. (antonio.lavecchia@unina.it)*

accelerates drug identification by evaluating large volumes of candidate compounds.[p3] Virtual screening (VS) complements this by identifying potential active molecules and filtering out undesired structures. The field of VS has experienced rapid progress, propelled by advancements in computational power. Two primary strategies are commonly employed: structure-based screening, which utilizes the known protein structure of the target, and ligand-based screening, which relies on confirmed active compounds or probes.[p4] In the structure-based approach, techniques such as molecular docking,[p5] molecular dynamic simulations,[p6],[p7] and fragment-based approaches[p8] are utilized. These methods virtually assess receptor–ligand interactions across a large compound set, facilitating the identification of potential hits. On the other hand, the ligand-based strategy incorporates methods such as pharmacophore modeling,[p9] scaffold hopping,[p10] and structural similarity searches.[p11] This approach aims to optimize known hits in the drug discovery process, providing valuable insights for further development.

The rapid progress in both artificial intelligence (AI) and computational power first introduced machine learning (ML)-based decision-making models[p12] and subsequently incorporated

Box 1 Glossary.

- **Active learning:** a method in which the AI model solicits assistance during the learning process. It identifies data points that it finds perplexing and requests additional information or labels for these specific data points, facilitating faster improvement.
- **Adversarial autoencoder:** similar to a variational autoencoder but uses a system (like that in a generative adversarial network) where one network competes against another. This setup enhances the learning process.
- **Artificial intelligence:** AI entails developing intelligent computer systems capable of thinking, learning, and decision-making akin to humans.
- **Autoencoders:** neural networks that learn to copy their input to their output. They are used for reducing dataset size (dimensionality reduction), eliminating data noise, or acquiring efficient data representations.
- **Black box:** in AI, a black box model allows users to observe the input and output but not the internal processes through which the model operates to generate the output.
- **Convolutional neural network:** a neural network type particularly effective for analyzing data with grid-like structures, such as images.
- **Decoder:** the part of the autoencoder that reconstructs the input data from the dense representation.
- **Deep learning:** the part of an AI model that uses algorithms known as neural networks to learn from data; it's akin to instructing a computer to recognize patterns.
- **Dimensionality:** the number of features or variables within a dataset; high dimensionality can be challenging for AI models.
- **Encoder:** part of the autoencoder that compresses the input into a smaller, dense representation.
- **Explainable AI (XAI):** AI decisions that are understandable to humans; in drug discovery, XAI would aid scientists in comprehending why an AI model suggests a specific compound as a potential drug, enhancing the model's trustworthiness and utility..
- **Federated learning:** a collaborative way of training AI models. Different organizations can train the same model using their own data without actually sharing the data itself.. This is important for drug discovery, especially when dealing with sensitive or proprietary data.
- **Generative adversarial network:** a pair of neural networks that operate in opposition to each other to generate new data. One network generates new molecular structures, while the other evaluates them. This process aids in the discovery of potential new drugs.
- **Graph:** a map-like grid composed of points (called nodes) interconnected by lines (called edges). It iserves to illustrate intricate relationships, such as the interactions between different proteins in the body.
- **Ground truth:** the actual, real-world information used to train AI models, akin to the 'correct answers' from which the model learns..
- **Labeled data:** data that have been tagged with labels to inform the AI about their identity; for example, if images of cats are labeled as 'cat', the AI will learn to recognize cats..
- **Latent space:** a condensed, simplified representation of data utilized internally by a neural network; it encapsulates the essence of the data.
- **Molecular graph:** a special type of graph used to represent the structure of a molecule, where atoms serve as nodes and the bonds between them as edges. It helps in understanding how different parts of a molecule affect its properties and interactions.
- **Neural network:** a foundational framework in AI, inspired by the workings of the human brain, , which enables computers to learn from data.
- **Objective function:** the 'goal' for an AI model. In drug discovery, the objective function could be to maximize the accuracy of predicting effective drugs or to minimize the occurrence of side effects.
- **Recurrent neural network:** a neural network specialized in processing sequential data, such as time series or sentences.
- **Reinforcement learning:** an AI approach where an agent learns decision-making through actions and feedback, often in the form of rewards or penalties.
- **Transfer learning:** instructing an AI model in a new domain using knowledge gained from a different domain; for instance, adapting a model trained to recognize chemical structures to predict the efficacy of novel drugs.
- **Unlabeled data:** data lacking tags or descriptions; in drug discovery, these could include raw experimental data. The model must learn from such data without predefined labels.
- **Variational autoencoder:** a type of autoencoder that not only learns to compress and decompress data but also generates new data resembling what it has been trained on.
- **Vector:** in AI, a vector is a list of numbers representing data, with each number in the vector corresponding to a feature of the data.

deep learning (DL) techniques[p13] as alternatives to the VS campaigns carried out in recent and past decades (See Box 1). The data-enriched field of drug discovery favors ML and DL methods because of their proficiency in handling large datasets, uncovering hidden patterns, and efficiently predicting future data. These capabilities position ML and DL as the preferred methods for constructing HTS and VS pipelines for cheminformatics and drug discovery, thereby reshaping pharmaceutical research and development. Since 2017, numerous pharmaceutical companies have partnered with AI startups and academics or have initiated internal AI Research and Development (R&D) programs. Applications of AI techniques, from training deep neural networks on transcriptional data to predict bioactive compounds[p14] to generating novel small molecule drug leads, have rapidly expanded across various areas of biomedical and drug discovery research.[p15]

In recent years, DL generative modeling has flourished, yielding potential novel solutions to the field and bringing fresh opportunities and insights.[p16],[p17] The creative process of deep generative models (DGMs) extends our comprehension of machine intelligence to a higher plane, spanning from creating human faces that are indistinguishable from those of real individuals[p18] to crafting text generation tools that replicate the tone and vocabulary of specific authors.[p19] It is worth mentioning that a generative pre-trained transformer (GPT) designed for chemistry belongs to the category of generative chemistry that employs DL models to create new molecules possessing specific properties.[p20] Lately, the convergence of drug discovery and generative modeling has delved into the realm of automated *de novo* molecule generation. This innovative approach is entirely data-driven and operates independently of predefined rules. By assimilating a vast repository of molecular structure data, it effectively 'learns' the underlying probability distribution of structure description, thereby grasping the intricate rules that govern medicinal chemistry in compound design. Consequently, DGMs possess the theoretical capability to explore the entire drug-like space, generating novel structures with desired physical, chemical, and/or bioactivity properties that extend beyond the explicit boundaries defined by the original virtual library. A notable success story involving DGMs includes the discovery of inhibitors for a kinase target that is associated with fibrosis. This achievement was realized within a computer-based process that concluded in a mere 21 days.[p21]

DGMs facilitate the design of novel molecular structures for potential drugs and accelerate early-stage drug discovery by sifting through vast biological datasets to identify disease-associated targets. Variational autoencoders (VAEs) and generative adversarial networks (GANs) are examples of DGMs that can produce molecular structures with desired properties. AI-driven optimization techniques iteratively refine these structures to enhance drug efficacy, minimize toxicity, and improve pharmacokinetics. DL uncovers intricate relationships between genes, proteins, and diseases, streamlining drug development and boosting success rates while reducing time and costs. Generative AI aids in personalized medicine by analyzing genetic and clinical data to predict optimal treatment, improving outcomes and reducing adverse effects. Despite considerable discussion within the ML community,[p22] the application of DGMs in medicinal chemistry remains nascent.[p13],[p16] There is a notable gap in computational exploration concerning DGMs for *de novo* molecule generation, underscoring the need for dedicated research in this domain. Although DGMs hold tremendous potential to revolutionize drug discovery, their practical implementation requires a balanced assessment of their achievements and limitations. This evaluation entails understanding the efficacy of DGMs in generating novel molecular structures that have desired properties such as good bioactivity, stability, and pharmacokinetic profiles, as well as scalability and generalizability across diverse chemical spaces and target classes. In addition, for regulatory compliance and clinical translation, it is crucial that DGM-generated results are interpreted correctly and that their reliability is ensured. Understanding the robustness of these models, their susceptibility to biases or artifacts, and the potential impact of data limitations on their predictive accuracy is paramount for informed decision-making in drug discovery pipelines. Furthermore, a holistic assessment should include evaluation of the computational resources and expertise required to implement and validate DGMs effectively. From data preprocessing and model training to validation protocols and result interpretation, each stage presents challenges that must be navigated with diligence and transparency. In essence, although DGMs hold immense promise for accelerating and innovating drug discovery, their practical utility hinges on a nuanced understanding of their capabilities, limitations, and the broader ecosystem in which they operate. A balanced and critical evaluation will pave the way for harnessing the full potential of DGMs while mitigating risks and optimizing outcomes in pharmaceutical R&D.

This article focuses on recent advancements in DGMs for *de novo* drug design, unraveling the intricate nuances of these groundbreaking approaches. The exploration traverses a diverse spectrum of algorithms, spotlighting their profound impact on the field. Furthermore, the review critically dissects the challenges and limitations that are intricately associated with these innovative technologies, offering strategic insights that suggest how hurdles can be overcome and their full potential unlocked. In addition, it discusses collaborations between AI and pharmaceutical companies, highlighting successful partnerships that have accelerated drug discovery efforts. Case studies highlighting both the successes and failures of AI-powered drug discovery in the pharmaceutical industry are discussed, showcasing the transformative impact of AI in bringing novel therapies to market. Finally, this review outlines a forward-looking plan for optimizing DGMs in *de novo* drug design, envisioning an expedited, cost-effective future for the development of effective treatments across various diseases.

Deep generative architectures for *de novo* molecular design

At present, DGMs are primarily categorized into two types based on whether the structure is described using the Simplified Molecular Input Line Entry System (SMILES) language[p23] or relies on a molecular graph. Initially, SMILES played a significant role in molecule generation, with the modeling process involving its conversion into a continuous vector for optimization and subse-

quent decoding back into a SMILES string. This method assumed that optimization in the latent molecular space is smoother than that in discrete molecular space, simplifying the optimization process. However, limitations in the smoothness of the generated latent space prompted researchers to transcend SMILES, developing encoding and decoding algorithms for efficient handling of molecular graphs. These novel approaches, which incorporate the multiresolution capture of molecules and integrate 3D information, produce outputs that are more robust and diverse, even within non-smooth hidden spaces. Nevertheless, molecular-graph-based algorithms are still in a relatively early stage of development.

When compared to SMILES-based DGMs, graph models imitate the human method of drawing structures, atom by atom and bond by bond. This approach results in a significantly larger search space at each step. In addition, in graph models, each molecular structure must be broken down into a series of substructures during training, leading to a substantial increase in the amount of data in the training set. These two factors contribute to a slower training speed for graph models. Recently, the novel open-source framework REINVENT 4, which utilizes recurrent neural networks (RNNs) and Transformer architectures for molecule generation, has excelled in SMILES-based encoding and decoding tasks.[p24] Nevertheless, SMILES and similar molecular line notations may produce invalid sequences, requiring adherence to specific syntax and chemical rules. To rectify this, O'Boyle *et al.*[p25] introduced DeepSMILES, which resolves unbalanced parentheses by exclusively using close parentheses. Krenn *et al.*[p26] introduced Self-Referencing Embedded Strings (SELFIES), a resilient sequence-based representation of constrained graphs with self-referencing recursive functions.[p26] Although SELFIES ensures 100% validity, it is subject to the limitation known as collapse. Translator models, akin to those in grammatical error correction (GEC), theoretically rectify invalid SMILES sequences.[p27] Zheng *et al.*[p28] demonstrated the applicability of these models in correcting syntax errors in short SMILES sequences, with successful application in other SMILES-based tasks. Figure 1 provides a summary of several major DGM architectures.

RNNs constitute essential components within the generative neural networks used for comprehending human language. They are invaluable in representing systems that have a sequential or temporal aspect, demonstrating effectiveness in tasks such as automated computer code generation,[p29] sentences framing, and musical composition.[p30] Molecular representation, exemplified by SMILES, operates on the same underlying principles as human language. Consequently, leveraging RNNs to generate molecules via a sequential representation appears logical. In this process, sequential data are progressively fed into the RNN, where each input influences the subsequent output. Figure 1a illustrates how the RNN utilizes logic to generate molecular structures in a DL-driven *de novo* design. Long Short-Term Memory (LSTM)[p31] and Gated Recurrent Unit (GRU),[p32] unlike standard RNNs, incorporate a gate mechanism that enables them to retain crucial input information across an extensive sequence of steps. The choice between LSTM and GRU may depend on the given application. When compared to GRU, the LSTM cell exhibits a greater capacity to preserve a longer sequence of past information. Nevertheless, the incorporation of additional parameters into LSTM models might increase the risk of overfitting. RNNs that employ LSTM or GRU architectures exhibit significant potential in generating *de novo* small compounds using the SMILES format.[p33]

Another prevalent technique for learning data representations in *de novo* drug design involves the use of autoencoders (AEs). An AE comprises two networks: an encoder network trained to transform the input into a lower-dimensional latent vector; and a decoder network that maps the latent vector back to the original input data. The basic AE constructs a latent space by reproducing the input. To address issues such as overfitting and discontinuities in the original AE, the Variational Autoencoder (VAE) employs a regularization technique in the latent space. This technique replaces individual latent space points with probability distributions. VAE has been applied in molecule generation, introducing a novel approach to *de novo* drug design.[p34] Figure 1b depicts the application of a VAE structure to molecules. The process begins with a molecular input (e.g., acetic acid), with the encoder network generating mean and standard deviation vectors. These vectors serve as parameters for a normal distribution, enabling the sampling of a vector in the latent space (z). This latent vector becomes the input for a decoder network, which generates a molecular representation (in this case, glycolic acid). The VAE training loss comprises two parts: the first ensures that the original input resembles the generated output (reconstruction loss), and the second encourages structurally similar molecules to cluster together in the latent space. In Figure 1b, glycolic acid and oxalic acid, which are structurally similar, are close in the latent space, whereas gamma-butyrolactone, which is less similar, is farther away. After training, the encoder component can be omitted, allowing the generation of new molecules by sampling diverse z vectors from a standard normal distribution.

In recent times, there has been a growing interest in obtaining disentangled representations for VAE. The primary goal is to ensure that each latent variable in the latent vector encodes a distinct and independent characteristic or aspect of the data.[p35] The effective implementation of a disentangled VAE for molecular generation could enable the modification of a specific molecular property without altering any other characteristics. This can be achieved by adjusting the latent variables that are linked to that particular property. The versatility of this framework is demonstrated in its application for sampling and optimizing molecules across various contexts, such as ChemVAE,[p34] GrammarVAE,[p36] and SD-VAE.[p37] In the latter two, additional processing is incorporated into both the input and output stages to pre-process and correct the syntax of the SMILES, both before training and during the sampling process.

Conditional VAE (CVAE) is an extension of classical VAE, incorporating molecular properties as information during encoding that can be manipulated during decoding.[p38] This approach enables the generation of drug-like molecules that have specific properties, such as the desired hydrogen bond donors and acceptors, molecular weight, logP, and topological polar surface area (TPSA). An additional advantage of this method is the ability to control individual properties without altering the overall molecular properties. Numerous studies have explored the application

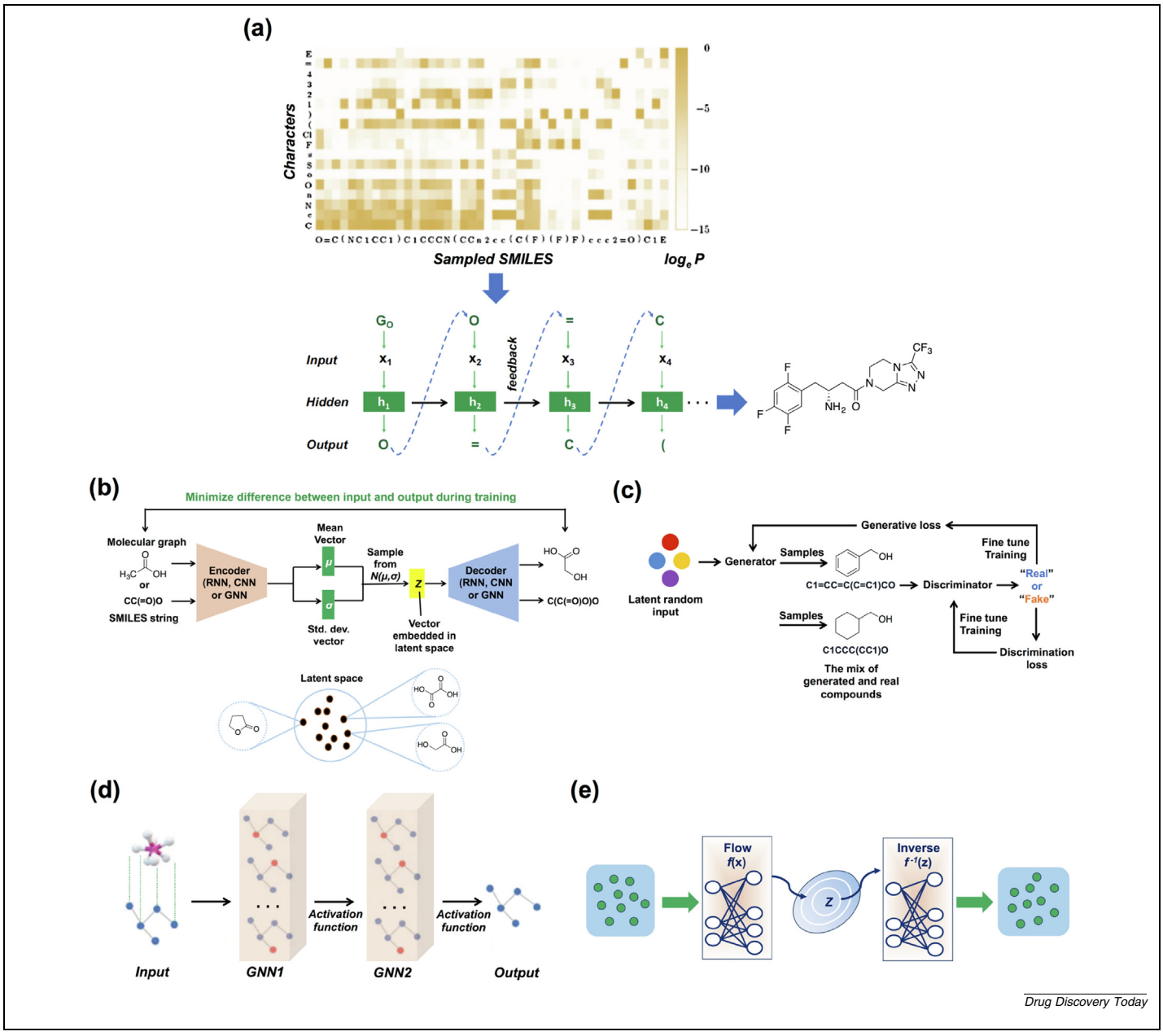

FIGURE 1

Examples of common types of DGMs for *de novo* drug design. a. Recurrent neural network (RNN); **b.** Variational Autoencoder (VAE); **c.** Generative adversarial network (GAN); **d.** Graph neural network (GNN); and **e.** Normalizing flow.

of CVAEs for conditional molecular generation, establishing it as a valuable tool in *de novo* molecular design and other drug discovery applications. Examples include creating molecules with desired SMILES strings,[p38] employing Transformers for conditional molecular generation,[p39] and generating molecules with specific fingerprint properties.[p40] Recently, Kotsias *et al.*[p41] demonstrated that molecular property constraints can be integrated into RNN-based DGMs as side information, so that the generated molecules tend to meet the constraints of the input. The semi-supervised VAE (SSVAE) is a powerful tool for generating molecules when only a portion of the dataset is labeled with properties.[p42] SSVAEs combine molecule generation and property prediction into a single network, making them efficient and versatile. The SSVAE architecture utilizes three bidirectional RNNs for encoding, decoding, and predicting. During training, the model can leverage both labeled and unlabeled molecules, making it practical for real-world applications where property data are limited. When applied to SMILES string generation, SSVAEs have demonstrated superior performance in terms of generating molecules that have greater chemical diversity when compared the molecules generated by models that solely rely on property co-learning from the latent space.[p43]

Adversarial AEs (AAEs) represent an alternative to VAEs and utilize adversarial training to shape the latent space. In this framework, the encoder transforms its input into a unique point within the latent space. Simultaneously, a discriminator network is deployed to differentiate between samples drawn from a predefined statistical distribution and the encoded points produced by the encoder. Essentially, the encoder takes on a dual role as a generator engaged in a competitive interplay with the discriminator, striking a delicate balance between minimizing reconstruction error and outsmarting the adversarial component.[p44] This amalgamation of GANs and AEs synergizes the strengths of both frameworks, offering a diverse range of techniques for generating novel molecules with desired properties and efficiently exploring the molecular space for drug discovery and design. AAEs have demonstrated proficiency in new molecule generation using both SMILES[p45],[p46] and fingerprint representations.[p47],[p48]

Unlike VAEs, GANs do not rely on an explicit probability density function. Rather, GANs employ an adversarial training framework, comprising a generator and a discriminator (Figure 1c). The discriminator trains a classification model with the goal of maximizing the error rate of synthetic molecules generated by the generator, closely resembling actual data. The generator and discriminator undergo simultaneous training in an adversarial, zero-sum game until the discriminator is deceived, signifying that the generator network is producing credible (i.e., seemingly authentic) molecules.[p49] Early applications of GAN for generating molecular structures include the ORGAN[p50] and ORGANIC[p51] algorithms. The RANC[p52] and ATNC[p53] algorithms integrate GAN, Reinforcement Learning (RL), and differential neural computing (DNC), an advanced version of the GRU network, to process long-term memory for structure generation. The LatentGAN algorithm[p54] combines an AE with the GAN algorithm for molecular design. Instead of using SMILES directly as the GAN input, as in the ORGANIC model, the hidden variables generated by the AE serve as the input to the GAN. The results indicate that GANs have the capability to generate a significant number of new structures, with some molecules even featuring novel scaffolds. In a recent application, GANs were fine-tuned on the basis of the desired gene expression signatures, enabling the generation of molecules that have specific properties linked to gene expression.[p55] This innovative approach holds promising potential for future applications in personalized medicine.

Graph neural networks (GNNs) represent an extension of convolutional neural networks (CNNs).[p12] CNNs are tailored for processing data with a regular structure, whereas GNNs exhibit proficiency in handling data that are represented on graphs, which are typically composed of sets of vertices referred to as nodes connected by directed edges. The methodology involves pairwise message passing, in which network nodes iteratively update their representations by exchanging information with neighboring nodes[p56] (Figure 1d). Biomedical data, such as protein–protein interactions, protein–drug interactions, drug–disease interactions, and drug repurposing data, are inherently interconnected, making them highly suitable for graph representation. Graphs also serve to illustrate small molecule drugs, portraying atoms as nodes and chemical bonds as edges. Knowledge graphs showcase intricate connections among pharmaceuticals, adverse reactions, repurposed drugs, and related outcomes, contributing to the formulation of innovative ideas.[p57] The trainable nature of these models empowers them to generate novel molecular graphs when provided with a database of existing structures. The process of transfer learning (TL) introduces an additional layer of sophistication, enabling the transfer of expertise from one domain to enhance outcomes in another. Within this domain, a noteworthy strategy is conditional generation,[p43] which involves the incorporation of vectors representing desired chemical properties (such as reduced toxicity or improved solubility) into the inputs of the generative process. The application of conditional generation seamlessly extends to various DGMs. Nevertheless, a drawback of this technique lies in the interdependence of data distribution and the distribution of the conditioning vectors, introducing an undesirable element into the process. Another issue associated with this approach pertains to the model's tendency to yield low novelty scores. This inclination arises because the model often places more emphasis on the conditioning vector rather than on the latent vector, opting for a solution that is perceived as an easier task.[p58] VAE and GAN, while serving distinct purposes, share the commonality of not directly representing the actual probability density function. VAE subtly enhances the log likelihood of the data by optimizing the lower bound of a likelihood function. Conversely, GAN takes a different route by sidestepping the explicit modeling of the distribution, adopting an adversarial approach to distinguish between valid and synthetic molecules.

Recent advancements in DGMs have seen the rise of deep flow-based approaches,[p59] marked by their prowess in explicitly defining densities within a given dataset (Figure 1e). The normalizing flows method, a simple yet powerful technique, excels in transforming the densities of intricate data into more manageable forms through bijective (i.e., invertible) transformations and a differentiable series of functions. Once the data has undergone this transformation to a simpler distribution, techniques such as Gaussian mixture modeling and maximizing the log likelihood can be applied, which is particularly beneficial for classification problems. Normalizing flow models offer several advantages over GANs and VAEs. Notably, they do not necessitate the addition of noise to the output, allowing for the utilization of more robust local variance models. In addition, the training procedure for a flow-based model exhibits greater stability than that used to train GANs, as it requires meticulous adjustment of the hyperparameters for both generators and discriminators. In terms of convergence properties, normalizing flows outperform both GANs and VAEs.[p60] Normalizing flow models have been used to create molecular graphs by building adjacency and feature matrices for the molecules.[p61] An autoregressive version allows for step-by-step growth of the molecular graph during generation, enhancing validity checks and quality metrics for the generated molecules.[p62],[p63] Guiding molecule generation using gradient ascent on a property predictor[p61] or RL[p62],[p63] are alternative approaches. Graph Flow-VAE[p64] combines a VAE-encoder and a flow-based decoder, capitalizing on the strengths of both approaches in molecular generation.

Diffusion-based models have also attracted considerable traction.[p65],[p66] Unlike flows, diffusion processes eliminate the

need for invertible transformations. These models operate in two phases: during the forward pass, samples from the data undergo stochastic noise injection in a Markov chain setup, eventually converging to a Gaussian distribution (Figure 2a). Remarkably, the forward pass involves no trainable parameters. In the backward pass, the objective is to transform samples from the Gaussian distribution into data-like samples using denoising steps executed by deep networks. The Equivariant Diffusion Model (EDM)[p65] operates on categorical atom types and continuous atom coordinates, generating 3D molecules via a denoising network that is equivariant to Euclidean transformation. However, diffusion processes suffer from computational intensity and time constraints during training and sampling.

Transformers, which are widely used in DGMs such as diffusion models, excel in generating high-quality samples by learning the data's underlying probability distribution.[p67] Leveraging the self-attention mechanism,[p68] Transformers capture long-range dependencies and contextual information. This mechanism weights each input sequence element based on its relative position, akin to how the positions of atoms or neighboring atoms affect the molecular properties of a structure. Transformers consist of attention layers with normalization and dense layers in 'blocks', housing billions of trainable parameters (Figure 2b). Learned embeddings occupy a well-organized latent space, promoting clustering of similar molecules through unsupervised training.[p69] AEs and Transformers encode molecules into this latent space and decode vectors back into small molecules, aiding generative exploration for small molecule design and drug discovery.[p40] Recently, Transformers have been pivotal in developing DGMs. Yang *et al.*[p70] constructed a Transformer-based model for exploring novel BRAF inhibitors, employing both RL and TL. Generative Pretrained Transformers (GPTs) are commonly used for *de novo* molecular design.[p71] Li *et al.*[p72] combined Transformers with objective-reinforced GANs to create molecules with desired properties. Liao *et al.*[p73] developed Sc2Mol, a hybrid Transformer-VAE model, yielding promising outcomes. These Transformer-based methods share a common goal of producing string-based structures, underlining their versatility and efficacy in molecular generation tasks.

Additional techniques that are commonly employed in generative DL for drug discovery include TL and RL. TL operates on the premise that mastering one task can enhance the subsequent learning of related tasks.[p74] This technique proves particularly valuable in low-data regimes, where training data are scarce for the specific learning task but abundant for a more generalized task. In the context of drug discovery, TL can be applied in pretraining a model on an extensive, generalized dataset containing therapeutic molecules. Subsequently, fine-tuning is conducted on a smaller dataset comprising molecules that have distinct activities.[p75] This two-step process enables the extraction of molecules with desired properties from the latent space (Figure 2c). Various optimization techniques, including RL,[p21] Sparse Gaussian Process modeling properties/Bayesian optimization,[p36],[p76],[p77] conditional latent (attribute) space sampling,[p78] genetic algorithms,[p79] particle swarm optimization,[p80] and generative topographic mapping[p79] can be employed to enhance the effectiveness of the model.

RL represents a ML paradigm that enables AI-based systems to adapt dynamically to changing environments by iteratively maximizing group rewards through feedback from individual actions. In RL, two primary methods are employed to derive a policy: policy-based RL and value-based RL. The objective of value-based RL is to learn a value function that characterizes the predicted return from a given condition. Once this function is understood, a policy is established to optimize the predicted value that results from specific actions. By contrast, policy-based RL aims to acquire a policy directly. Several RL-based methods have been proposed for *de novo* drug design. These encompass SMILES-based approaches that employ two RNN models with an exploration/exploitation strategy to ensure greater chemical diversity,[p81] the actor–critic method,[p82] the REINFORCE algorithm[p83],[p84] and the ORGAN model.[p85] In addition, graph-based representations, which offer a simpler way to depict molecules and to enable intermediate validity checks, include the REINVENT algorithm,[p83],[p86] the Graph Convolutional Policy Network (GCPN) utilizing the Proximal Policy Optimization algorithm,[p87] and Molecule Deep Q-Networks (MolDQN).[p88] RL has also been applied to improve the synthetic accessibility of generated molecules via reaction-based generation.[p89] In AEs, a RL-based decoder with an extra loss term and a 'reward network' ensures the decoded graph validity.[p90] The RL-VAE method, which uses a GNN encoder and a MolDQN-based decoder, exemplifies RL in graph-based decoding.[p90] For a brief insight into the differences between architectures, Table 1 contrasts a diverse array of techniques.

The various DGMs described above have emerged as promising alternatives to rule-based methods for *de novo* molecular generation, but they come with significant challenges. One primary challenge arises from the possibility that DGMs may propose molecules that are excessively complex or even impossible to synthesize. Therefore, it is imperative to verify the synthesizability of the generated molecules before progressing to the evaluation and optimization stages. In this regard, it must also be noted that the synthesizability of AI-generated molecules also depends on other factors, such as the training data of the models and the type of DGMs used to generate the molecules. The type of model is important because RNNs, for instance, learn to generate molecules on the basis of sequential data analysis, much like the natural language processing (NLP) arm of AI. On the other hand, GANs involve adversarial training, which provides ample chances of generating different types of molecule based on the underlying process of modeling the input data. As rightly mentioned by Segler *et al.*,[p91] DL is not a cure-all tool, and mere approximation in molecule generation is not adequate in chemistry, where precision is crucial. The model proposed by Segler *et al.*[p91] can rediscover key molecules, suggesting that DGMs can complement existing drug discovery methods. Although recent advances justify exploring novel approaches, the ultimate success of DGMs hinges on the determination of their effectiveness by wet lab results.[p91] Furthermore, one notable drawback, encountered especially in GANs, is mode collapse.[p92] Mode collapse occurs when the GAN generates an insignificant assortment of images or compound structures that is characterized by numerous duplicates. The reason behind this duplication

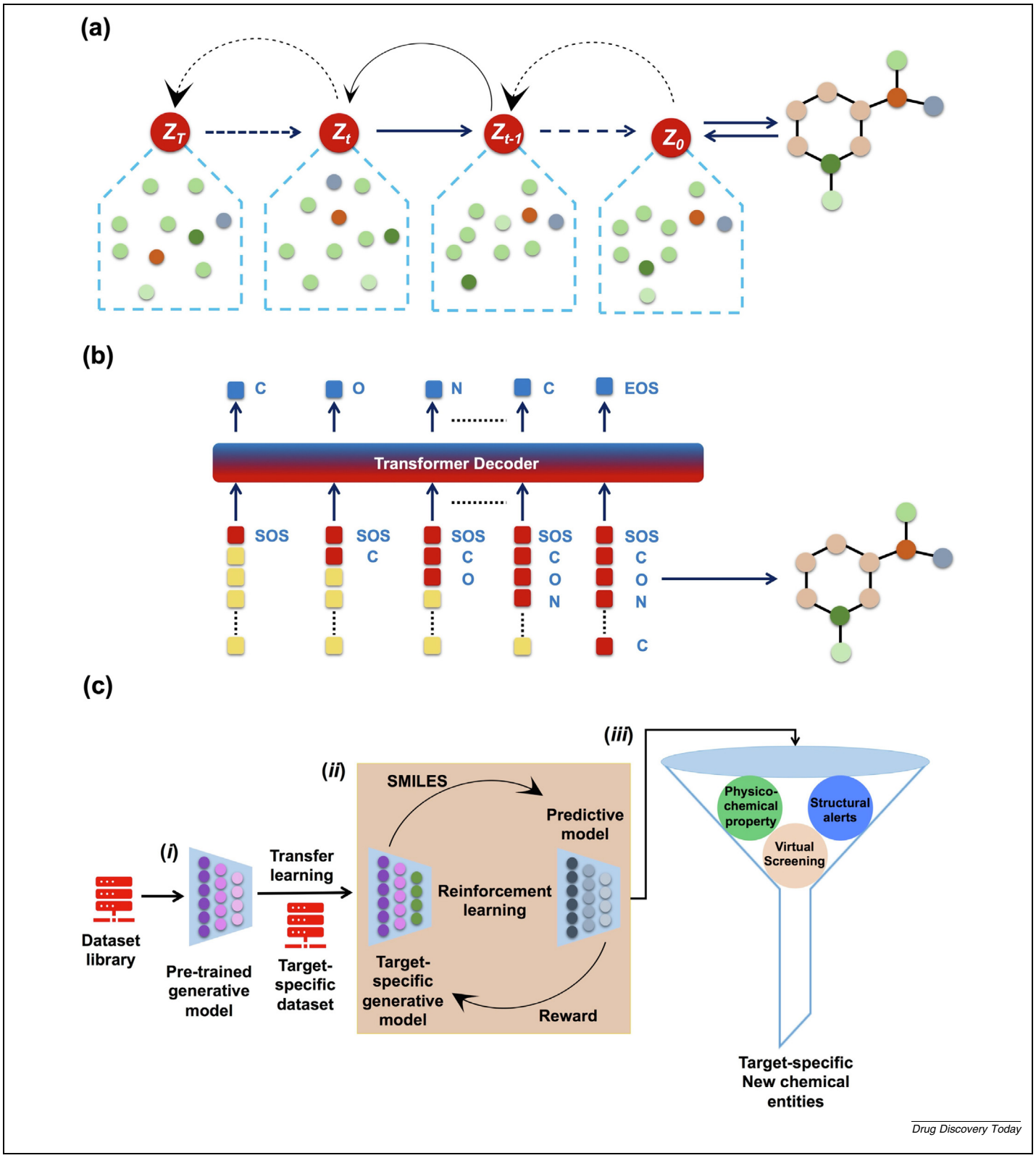

FIGURE 2

Common DGMs for *de novo* drug design. a. A diffusion-based model introduces noise in the forward process (curved arrows in the figure), aligning the data with a Gaussian distribution. The reverse process (straight arrows) generates samples from data derived from noise distribution sampling. **b.** A Transformer-based model process begins with start of sentence (SOS) input into the decoder and generates subsequent tokens until end of sentence (EOS) output is generated, resulting in a generated molecule. **c.** A *de novo* molecular design workflow integrates TLto address data scarcity in generating small molecules for specific receptors. Steps include (i) pre-trained DGM implementation; (ii) TL for acquiring compound characteristics coupled with RL for property refinement; and (iii) the application of filters for molecule selection.

TABLE 1

Comparison of different DGMs in terms of efficacy, accuracy, strengths, weaknesses and applications in drug discovery

Model	Efficacy	Accuracy	Strengths	Weaknesses	Drug discovery applications
RNNs	Medium	Medium	Sequential data modeling, temporal dependencies	Gradient vanishing, limited context	Drug–target interaction prediction, sequence generation
VAEs	Medium to high	High	Latent space representation, generative modeling	Mode collapse, blurry images	Molecular generation, drug design optimization
CVAE	Medium to high	High	Conditional generation, improved VAEs	Mode collapse, computational complexity	Conditional molecular generation, property prediction
AAE	Medium to High	High	Adversarial training, disentangled representations	Mode collapse, training instability	Data augmentation, molecule generation
GANs	High	High	High-quality image generation, diversity	Mode collapse, training instability	Molecular design, property prediction, generative modeling
GNNs	Medium to high	High	Graph structure modeling, node embeddings	Overfitting, limited scalability	Drug–protein interaction prediction, molecular graph analysis
Normalizing flows	High	High	Exact likelihood, invertibility	Computational cost, complex architectures	Molecular generation, density estimation
Diffusion models	High	High	Modeling complex data distributions, generative modeling	Computational cost, training complexity	Molecular generation, generative modeling
Transformers	High	High	Attention mechanism, parallel processing	Training data size dependency, interpretability	Molecular sequence generation, property prediction
TL	Medium to high	Medium to high	Knowledge transfer, leveraging pre-trained models	Task-specific fine-tuning, domain mismatch	Molecular property prediction, model generalization
RL	Medium to high	Medium to high	Sequential decision making, exploration–exploitation	Training instability, sample inefficiency	Molecular design optimization, drug discovery process

issue lies in the generator component's struggle to comprehend a rich feature representation. Essentially, GANs may inadvertently link identical outputs to various inputs during the learning process, leading to a limited diversity in the generated results. A similar kind of mode collapse is also observed with RNNs, as they may converge to one molecule, and therefore a bucket or a diversity filter is introduced to avoid this issue. Even RL methods are known to be susceptible to mode collapse as they often generate a single solution or a small family of similar solutions.

Successful applications of DGMs for *de novo* drug design

De novo drug design is undergoing a profound transformation thanks to DGMs. These models play a crucial role in designing chemical compounds with desirable properties such as a strong binding affinity for specific protein targets. They enhance drug-like features by fine-tuning molecular aspects such as solubility, thereby addressing longstanding challenges in designing novel drug candidates. Beyond the generation of structures, the utility of DGMs extends to predicting the synthesis route for generated molecules and bridging the conceptual design phase with the practical aspects of synthesis. Noteworthy contributions are observed in domains such as polypharmacology,[p93] drug repurposing (exploring new applications for existing drugs), and multi-target drug design. Notably, these models facilitate the early identification of potential side effects during drug development. Moreover, DGMs contribute to unraveling the molecular mechanisms of drug action, automating molecule generation for HTS, and predicting various molecular features, including ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles. In essence, DGMs are not only rapidly advancing the discovery of novel drugs but also enriching our understanding of drug–target interactions and optimizing the overall efficiency of the drug development process.

Several researchers have explored the use of DGMs for designing molecules, particularly in response to the SARS-CoV-2 pandemic, which prompted significant progress in DL-based *de novo* drug design. Multiple methods were proposed within a short timeframe. For example, Bung *et al.*[p94] improved a stacked RNN model with TL. This model was initially trained on more than 1.5 million molecules from ChEMBL to identify potential ligands for the SARS-CoV-2 protease. The model was further fine-tuned with 2,500 compounds against the protease. Using RL as a conditional model, the authors optimized the quantitative estimate of drug-likeness (QED), molecular weight, synthetic accessibility score (SA score), and logP. After conducting docking simulations to test the generated compounds, the team identified 31 promising leads.[p94] In another approach, a team of researchers utilized Rosalind and an internal model based on SMILES to design compounds targeting the SARS-CoV-2 major protease Mpro.[p95] After screening for binding affinity, QED, molecular weight, structural alerts, and toxicity, the team shared 40 compounds. Chenthamarakshan *et al.*[p78] employed CLaSS (conditional latent attribute space sampling) in a SMILES-based VS environment to design compounds that preferentially bind to three essential SARS-CoV-2 target proteins.[p78] Filtering for retrosynthesis prediction, toxicity, and docking-based target binding affinity resulted in the identification of 3,500 potential leads. Zhavoronkov *et al.*[p96] generated compounds targeting the SARS-CoV-2 major protease Mpro using 28 models with varied molecular representations. Born *et al.*[p97] adapted the PaccMannRL framework to generate SARS-CoV-2-targeting

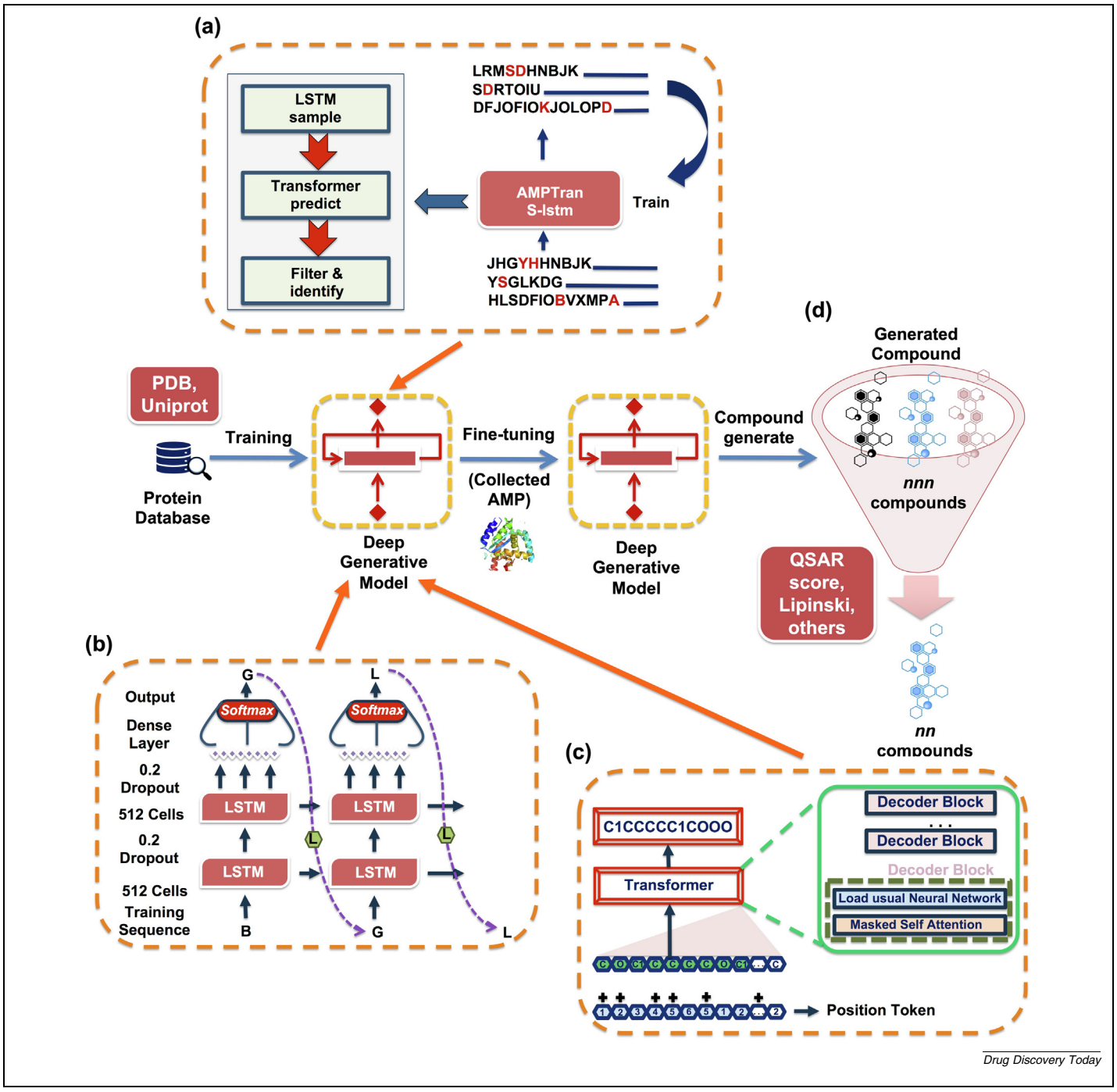

FIGURE 3

Workflow for generating candidate antimicrobial peptides (AMPs) with diverse antimicrobial properties using the AMPTrans-lstm deep generative network. The deep generative network (a), consists of three modules: the long short-term memory (LSTM) sampler (b), the Transformer converter (c), and identifying part (d). The Transformer and LSTM models were pretrained on a large dataset and fine-tuned on a smaller one. In the process of generating new samples, peptide sequences were created through LSTM sampling and then inputted into the Transformer model for decoding the novel sequence. Finally, the trained QSAR (Quantitative Structure-Activity Relationships) model predicted the function of the peptide sequences.

compounds using SELFIES instead of SMILES. In summary, the AI-based VS methods discussed here represent a departure from classical experimental and docking-based screening. They typically encode molecules into vectors and establish mapping relationships to their properties, facilitating rapid searches through large molecular libraries containing 10^6–10^9 molecules, which would be time-consuming if traditional methods were used. This capability addresses urgent challenges such as combating emerging viral threats like SARS-CoV-2.

Researchers have used RNNs, trained on extensive SMILES strings, to create novel and valid SMILES sequences.[p91] These models produced approximately 20% unique true actives against *Staphylococcus aureus* and 30% against *Plasmodium falciparum*. Jaques *et al.*[p98] used deep Q-learning with RNNs to generate

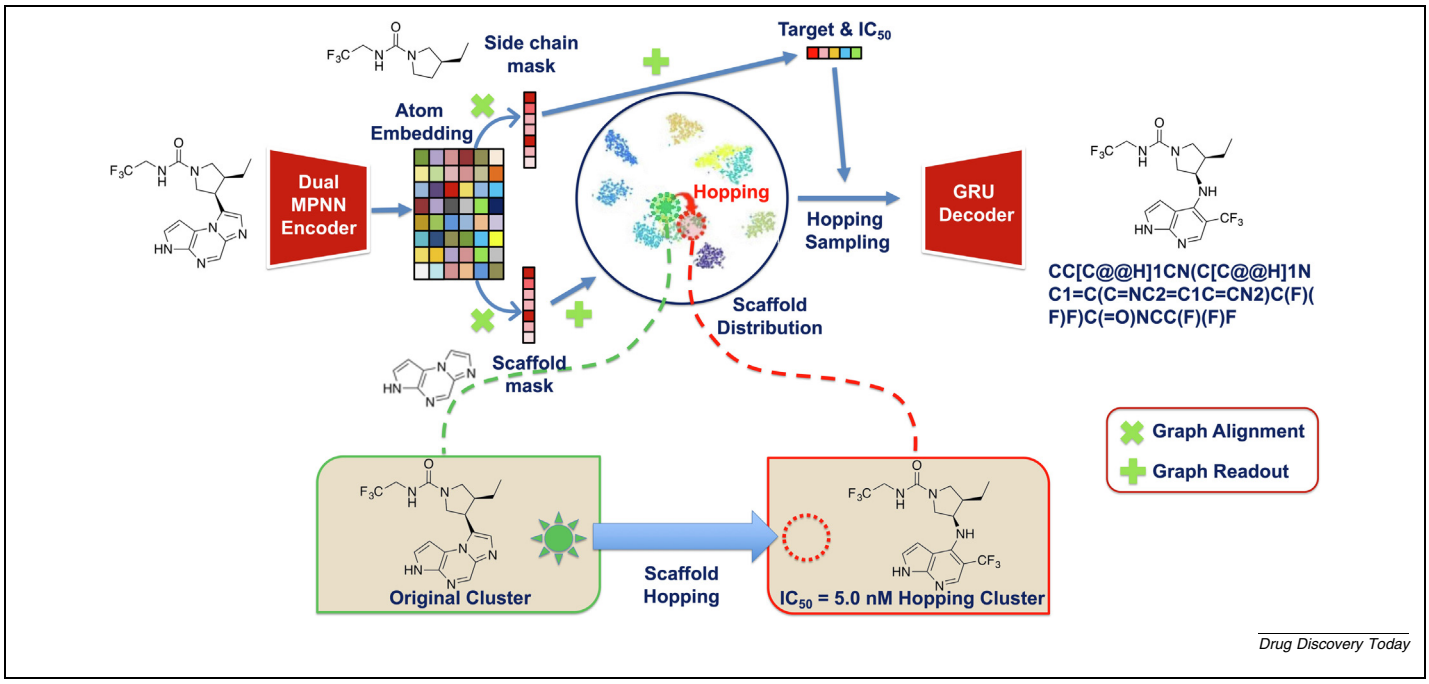

FIGURE 4

The Graph-GMVAE, a DL model for controlling scaffold hopping in generative chemistry. The dual message passing neural networks (Dual-MPNN) encoder captures node information and topologies, creating node embeddings. These embeddings are then utilized to derive side-chain and scaffold embeddings through masks. A Gaussian mixture layer facilitates the resampling of molecule embeddings, which are subsequently input into a gated recurrent unit (GRU) decoder that reconstructs the corresponding SMILES.

SMILES with desired molecular attributes. Others developed policy-based RL techniques to fine-tune pre-trained RNNs.[p83] Mao *et al.*[p99] recently introduced AMPTrans-lstm, a combination of LSTM and transformer models designed to customize peptides with different antimicrobial properties (Figure 3). The team trained AMPTrans-lstm using antimicrobial peptide (AMP) datasets along with a public database. Comparing the generated peptides to known AMPs revealed that the sequences produced by AMPTrans-lstm were more assorted and distinct than the training data while retaining essential AMP properties. When assessed using various ML models, the sequences that were generated by AMPTrans-lstm were more likely to be identified as antimicrobial agents than were randomly generated sequences. Despite its various benefits, the model faces some challenges. First, the training stability of the transformer module needs improvement to reduce training expenses. Second, additional validation is required to confirm that AMPTrans-lstm responds to changes in target microorganisms and accurately predicts target mechanisms. Last, the incorporation of more quantitative methodologies into model development and result comparisons is essential for evaluating the quality of DGMs.

Blaschke *et al.*[p46] employed VAE to design dopamine receptor type 2 antagonists. Yu *et al.*[p100] developed a graph-based VAE with Gaussian mixture hidden space (GraphGMVAE) for scaffold hopping, producing compounds with high accuracy and unique scaffolds (Figure 4). The study also introduced a strategy for ranking the generated molecules to enhance validation. To validate GraphGMVAE, the FDA-approved human Janus kinase 1 (JAK1) inhibitor upadacitinib was used as a reference, demonstrating the model's ability to generate molecules with novel scaffolds swiftly. The subsequent synthesis of seven compounds in a wet lab allowed for biochemical tests that assessed the efficacy of the generated molecules. Notably, the most active molecule exhibited a 5.0 nM activity against JAK1 kinase, demonstrating that the capability of GraphGMVAE to design molecules is akin to that of human experts, but with enhanced efficiency and accuracy. Nevertheless, it is essential to note that the assertion that GraphGMVAE has compound development capability comparable to that of human experts overlooks the broader context of the similarity principle in medicinal chemistry. The fast follower approach, which involves modifying a known drug to enhance its therapeutic profile, is a well-established strategy in drug development. Although the molecular generators function as intended, their effectiveness should be evaluated in light of established medicinal chemistry principles.

Kadurin *et al.*[p101] used AAE and later druGAN, a GAN combined with RL, to generate novel compounds. In graph representations, Kusner *et al.*[p36] and Dai *et al.*[p37] integrated grammar constraints into SMILES strings. You *et al.*[p102] introduced a graph convolutional policy network (GCPN) using deep RL to generate molecules with 100% validity.

In a different study, a multi-objective RL RNN-based *de novo* molecular design approach called DrugEx (in its initial version)[p103] was trained to generate compounds that exhibit activ-

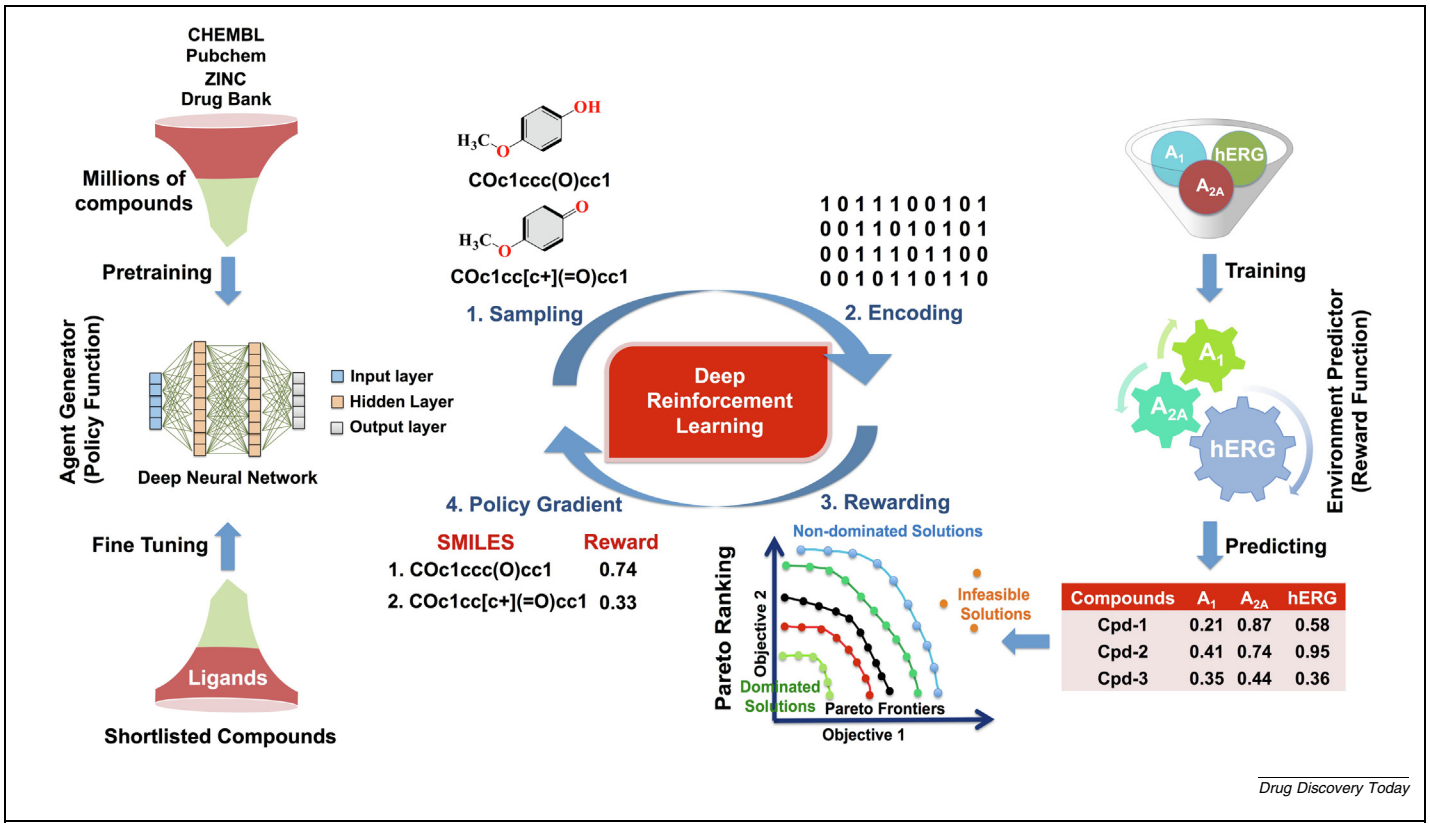

FIGURE 5

Workflow of the training process for the DL-based molecule generator DrugEx2 using RL. After pre-training/fine-tuning, the generator generates batches of SMILES sequentially through step-wise token sampling based on calculated probabilities (**1**). Valid SMILES are parsed into molecules, encoded into descriptors, and used to predict bioactivities as pX (where pX represents pKi, pK_d, pIC_{50}, or pEC_{50}) with predictors (**2**). Predicted pX values are combined into a single reward for each molecule using Pareto optimization (**3**). SMILES sequences and their rewards are then sent back to the generator for training using policy gradient methods (**4**).

ity against G protein-coupled receptors (GPCRs), with a specific focus on the adenosine A_{2A} receptor, an important target for cardiovascular and inflammatory diseases. During training, the DrugEx model creates SMILES strings in each iteration, introducing a random element to the process. The RNN single-task agent of a GRU network was initially pre-trained using a large set of chemical SMILES obtained from the ZINC 15 database, before being used in RL training. Both exploration and exploitation networks were derived from this pre-trained network. In RL training, the exploitation network was trained with a predetermined probability at each repetition, and the exploration network was consulted for the subsequent token. This approach allowed for extensive exploration of the chemical space during training, after which, the exploration network was phased out and only the exploitation network was used to generate novel compounds. The researchers highlighted the capability of the RNN agent to develop diverse molecules, demonstrating that machine-generated actives covered all groups generated by fingerprint-based clustering of reported adenosine A_{2A} receptor actives. In the second version of DrugEx, the authors upgraded the GRUs of the RNN single-task agent to LSTM units (Figure 5).[p104] This update also involved the introduction of multi-objective optimization (MOO)-based RL and an enhanced exploitation-exploration strategy. In its third version,[p105] generators based on a variant of the transformer and a novel graph-based encoding were introduced, enabling the sampling of molecules with specific substructures.

Although numerous studies have presented DGMs, few have explored the synthesis of *de novo*-generated molecules. Evaluations of their effectiveness in *in vitro* tests have generally been positive, motivating further research in this evolving field. For instance, in 2018, Merk and colleagues reported one of the earliest findings detailing the synthesis and subsequent biological testing of compounds generated using a DL model.[p106] The DL algorithm successfully designed retinoid X receptor (RXR) agonists and peroxisome proliferator-activated receptor (PPAR) agonists. Using an encoding of chemical space containing 50,000 molecules comparable to drug molecules, the researchers developed a DGM based on the known activities of 25 PPAR and RXR agonists. The DL model recommended five compounds, and subsequent biological tests revealed two molecules that inhibited RXR and PPAR with half-maximal effective concentration values ranging from 60 nM to 13 M. Several additional studies are presented in Table 2.

The integration of genetic algorithms and DL methodologies has revolutionized *de novo* molecular design, enabling the cre-

TABLE 2

Experimental endorsement of *de novo*-generated molecules

Receptor	Method type	Activity confirmation			Reference
		In silico	*In vitro*	*In vivo*	
PPAR, RXR	TL	SPiDER	Out of five synthesized molecules, four were found to be active, with two molecules inhibiting both PPAR and RXR.	—	(p140)
RXR	TL	SPiDER WHALES	Reported: four synthesized; two active.	—	(p106)
JK3 selective	RL	Docking	One synthesized molecule was found to be selectively active for JK3.	—	(p45)
Inhibitors of kinases	RL		Out of five purchased molecules, seven were reported to be active.	—	(p141)
DRD2, 5-HT1A, 5-HT2A	TL	MT-DNN on ECFP4	One molecule, synthesized along with six analogs, was found to be active for three targets.	One molecule was tested and found to be active and safe.	(p142)
VEGFR-2	Train on actives	Docking	Out of five synthesized molecules, three were reported to be active and noncytotoxic.	—	(p143)
DDR1	RL	SOM Pharmacophore	Only two actives were reported out of a total of six synthesized.	One molecule was tested, and its half-life was found to be 3.5 h.	(p21)
p300/CBP inhibitors	TL	Docking	One molecule, synthesized along with 26 analogs, was found to be active and selective.	Good bioavailability, efficacy, and safety	(p144)
LXR agonists	TL		Besides synthesizing 25 compounds, three were purchased. A total of 12 compounds showed a positive response.	—	(p145)

ation of novel, drug-like molecules that have desired properties. Notably, GARel (genetic algorithm-based receptor-ligand interaction generator) enhances DGMs by focusing on compounds that have unique scaffolds and highly drug-like profiles. Leveraging dense net, GARel efficiently updates parameters, yielding molecules that have diverse scaffolds, favorable properties, and improved docking scores for targets such as AA2AR, EGFR, and SARS-Cov2.(p107) In addition, the GENERA algorithm combines DL with genetic algorithms, yielding promising drug candidates for the ACE2 target by effectively performing multiobjective optimizations based on Pareto dominance.(p108) Evolutionary design methodology has further advanced by integrating DL models to guide molecular evolution while ensuring chemical validity. This approach involves evolving Morgan fingerprint vectors via mutation and crossover within a genetic algorithm, followed by reconstruction into molecular structures using an RNN. When successfully applied to modify the light-absorbing wavelengths of organic molecules, this methodology accelerated the design process.(p109)

Benchmark datasets and tools

In evaluating benchmark datasets for drug discovery, it is essential to differentiate between DGMs and QSAR (Quantitative Structure-Activity Relationships) models. DGMs aim to generate novel molecular structures that have desired pharmacological properties, relying on diverse training datasets to emphasize structural diversity and including information on molecular interactions, target specificity, and bioactivity profiles. Common data sources include repositories such as PubChem,(p110) ChEMBL,(p111) and proprietary pharmaceutical datasets.

The performance of DL models depends on the quality of the experimental data used during training, which is affected by factors such as dataset size, coverage of chemical and property space, diversity, and error presence. Although the volume of publicly available data is increasing, public datasets tend to be smaller than proprietary 'in-house' datasets, which still exhibit biases and lack systematic exploration, which impacts model performance. Addressing challenges such as class imbalances and non-uniform property distributions in public data often involves combining data from multiple sources, leading to increased dataset heterogeneity. Merging data sources can, however, introduce potential biases, redundancies, and errors, which directly affect model performance.(p112) Standardized assay protocols in the pharmaceutical industry typically generate more homogeneous datasets, but integrating diverse data sources remains complex due to legacy systems, evolving protocols, and differences in annotations. Consequently, careful curation and homogenization are crucial for the successful application of DGMs.(p113)

Public bioactivity datasets often lack negative or inactive data, creating imbalances when compared to HTS. Strategies such as adding putative negative examples or decoys are employed to improve model training.(p114)

Benchmark platforms for DGMs assess the quality, validity, novelty, and diversity of generated molecular structures, using metrics such as validity, uniqueness, novelty, diversity, and controllability (Table 3). Tools such as MOlecular SEtS (MOSES)(p115) and GuacaMol(p116) are commonly used for benchmarking, offering the ability to assess drug-likeness, synthetic feasibility, and target specificity, although challenges include balancing novelty with drug-likeness and defining meaningful generative metrics. Nevertheless, these platforms play a crucial role in facilitating

TABLE 3

Some common parameters used to assess DGMs

Type	Assessment parameters
Molecule set	Validity
	Novelty
	Uniqueness
	Controllability
	Nearest neighbor similarity
	Scaffold similarity
	Internal diversity
	Fragment similarity
	Fréchet ChemNet Distance[p146]
	Completeness, uniformity, closedness[p147]
Molecules	Physicochemical property
	Synthetic accessibility score (SA score)
	Natural product likeness score
	QED
	Jointly score[p148]
Integrated benchmark	GuacaMol[p33]
	MOSES[p149]

early-stage drug discovery. The study by Arús-Pous *et al.*[p117] showcased the use of RNNs to sample chemical space using SMILES notation, demonstrating the potential of the method for benchmarking DGM architectures.

By contrast, QSAR predictive models establish the quantitative relationship between chemical structures and properties or activities, and are trained using datasets comprising molecular descriptors, physicochemical properties, structural features, and experimental activity data from repositories such as ChEMBL[p111] and PubChem.[p110] Evaluation involves the assessment of accuracy, robustness, and predictive power using metrics such as root mean square error (RMSE), coefficient of determination (R^2), sensitivity, specificity, and area under the curve (AUC) or classification tasks. Software tools such as RDKit and Cheminformatics Toolkit aid in evaluating model performance, with outputs including property predictions such as solubility, bioactivity, toxicity, or ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters for given molecular structures. Challenges in QSAR model benchmarking include dataset selection, addressing biases, and validating predictions across various chemical classes. QSAR benchmark platforms aid in VS, compound optimization, toxicity prediction, and structure–activity relationship (SAR) analysis, enabling researchers and pharmaceutical companies to assess model reliability and applicability across various properties.

In a study by Kwapien *et al.*,[p118] the predictability of key drug design properties was investigated using different datasets and ML algorithms. The results suggest that additive data are easier to predict, highlighting the complexity of predicting properties during scaffold hopping. Despite the suitability of DL models for nonlinear events, they did not outperform classical methods in this regard. Activity cliffs, where similar molecules exhibit potency differences, were addressed by platforms such as MoleculeACE, which benchmarked 24 ML and DL methods using bioactivity data from 30 targets. All of the methods struggled with activity cliffs, but ML based on molecular descriptors outperformed DL methods, underscoring the need for specialized metrics and algorithms to handle such challenges effectively.[p119],[p120]

The assessment of model generalizability requires careful data splitting and selection procedures to avoid overly optimistic or pessimistic results.[p121] Time-based splits, which reflect real-world scenarios, are preferred in industry settings. However, public datasets often lack temporal information, limiting their use in academic settings. Recent literature highlights the importance of assessing model performance in the presence of structure–activity or property discontinuities such as non-additivity[p118] and activity cliffs.[p119],[p120] A minimum quality standard must be established before model deployment and it is essential that multiple metrics aligned with specific applications are employed. In industry, models are evaluated using metrics that are relevant to actual users, with a focus on understanding model decisions, especially for DL models treated as black boxes. Explainable AI approaches are pivotal for understanding model learning, assessing robustness, and identifying data-driven features that are related to specific effects, such as toxicophores.[p122],[p123] These investigations are instrumental in instilling trust in ML models that are deployed for drug discovery and development.

Collaborations between AI and pharma companies

With the increasing use of DL in healthcare, numerous pharmaceutical companies have entered financial agreements or joint ventures to enhance healthcare services and streamline clinical trials.[p124] These collaborations span diagnostics, biomarkers, drug/target discovery, molecular property prediction, *de novo* drug design, repositioning, and more.[p125] A summary of recent deals, including major financial pacts, is presented in Table 4. These partnerships emphasize the value of AI in exploring a broader molecular design space and discovering uncommon molecules that have desirable features, which are challenging to find through traditional research methods.

Insilico Medicine, an AI-based organization dedicated to comprehensive drug discovery using AI at every stage, has introduced a unique GAN-based approach for *de novo* drug design. The company also developed chemotypes against the SARS-CoV-2 main protease.[p96] In another study, Insilico Medicine utilized GENTRL to generate molecules for fibrosis treatment through inhibition of discoidin domain receptor 1 (DDR1).[p21] Clinical trials for these compounds are underway, with ISM001-055, a compound targeted against idiopathic pulmonary fibrosis, claimed as the world's first instance in which both the target and the drug candidate were developed from scratch using AI. This compound underwent a phase I clinical trial in February 2022,[p124] with a second compound, INS018-055, showing undergoing a successful phase I trial for activity against fibrotic disease in January 2023.[p126] Recently, the company developed its fifth pipeline candidate (ISM5411), a potential first-line ther-

TABLE 4

Recent deals and funding rounds between AI and pharma companies

Date	Collaborators	Deal summary
March 2019	Iktos and Merck	Merck partners with Iktos to access AI tech for three drug discovery projects. The collaboration aims to expedite drug development, aligning with Merck's innovation strategy in healthcare.
June 2019	Atomwise and Eli Lily	Eli Lilly teams up with Atomwise, with Eli Lilly investing up to US$ 560 million to develop ten drug targets by leveraging Atomwise's AI technology.
April 2020	Atomwise	Atomwise secured $123 M in Series B funding led by B Capital Group and Sanabil Investments, with other notable investors participating.
February 2021	Verge Genomics and Sheffield Institute for Translational Neuroscience	The primary focus of this partnership is to identify new pharmacological targets against Parkinson's disease.
March 2021	Insitro	The Canada Pension Plan Investment Board led a US$ 400 million funding round for Insitro.
April 2021	Recursion	Recursion successfully raised US$ 436 million in an initial public offering (IPO).
May 2021	Exscientia and Bristol Myers Squibb	Exscientia and Bristol Myers Squibb are collaborating to discover drug candidates for various therapeutic areas, with an initial payment of US$ 50 million made to Exscientia.
June 2021	Insilico Medicine	Insilico Medicine secured US$ 225 million through a financing transaction led by Warburg Pincus.
July 2021	Verge Genomics and Eli Lilly	Eli Lilly and Verge Genomics are using Verge's AI platform to find ALS treatments. Verge may get up to US$ 694 million in milestone payments, US$ 25 million in upfront equity, and near-term payouts under the deal.
August 2021	XtalPi	HOPU Investments and OrbiMed Healthcare Fund Management led a series D fundraising round for XTalPi, raising US$ 400 million.
October 2021	Exscientia	Exscientia raised US$ 510 million through an IPO of US$ 350 million and a private placement of US$ 160 million led by SoftBank.
December 2021	BenevolentAI	The merger between BenevolentAI and Odyssey Acquisition is estimated to generate around € 390 million.
December 2021	Recursion and Genentech/Roche	Recursion, Roche, and Genentech collaborate to use Recursion's AI-driven screening tech for cancer and neuroscience targets. Recursion could earn up to US$ 300 million for each of up to 40 research projects, with an initial payment of US$ 150 million.
January 2022	Exscientia and Sanofi	Sanofi partners with Exscientia to develop 15 therapeutic candidates in cancer and immunology, with an initial payment of $100 million.
April 2022	Atomwise and Sanofi	Sanofi's US$ 1.2 billion collaboration with Atomwise includes a $20 million upfront payment. It aims to use Atomwise's AtomNet platform to research small molecules targeting up to five drug targets.
June 2022	CHARM Therapeutics and others	CHARM Therapeutics, a 3D deep-learning company, secured US$50 million funding to advance drug discovery with their DragonFold platform, targeting cancer and other diseases by combining deep-learning with drug development expertise.
September 2022	Insilico Medicine and Ministry of Investment, Saudi Arabia	A memorandum of understanding (MoU) was signed to support the development of a robust AI-driven biotech industry in the Kingdom.
October 2022	XtalPi and Janssen	XtalPi will deliver validated small molecule hits meeting predefined criteria to Janssen. Utilizing its Inclusive Digital Drug Discovery & Development (ID4) platform, XtalPi aims to optimize the 'Design-Make-Test-Analyze' cycle.
November 2022	Exscientia and The University of Texas MD Anderson Cancer Center	This partnership aims to accelerate the development of innovative small molecules against cancer by combining Exscientia's patient-centric AI capabilities.
November 2022	XtalPi and CK Life Sciences	XtalPi and CK Life Sciences are collaborating to develop an advanced AI platform for tumor vaccines and vaccine development.
November 2022	Insilico Medicine and Sanofi	Sanofi announced a strategic research collaboration with Insilico Medicine to enhance its drug discovery pipeline using the Pharma.AI platform.
November 2022	Insilico Medicine	Insilico Medicine is using its AI platform to create non-hormonal contraceptive solutions for women with a US$ 700,000 grant.
May 2023	CharmTherapeutics and NVIDIA	CHARM Therapeutics has secured investment from NVentures, NVIDIA's venture arm, to fuel growth and leverage NVIDIA's computing platform. This accelerates CHARM's oncology research and development, harnessing DL for novel cancer therapeutics.
January 2024	Isomorphic Labs and Eli Lily	Isomorphic Labs is to receive a US$ 45 million upfront payment for collaboration on small molecule therapeutics research. It will then be eligible for up to US$ 1.7 billion in milestone payments, excluding royalties on net sales.
January 2024	Isomorphic Labs and Novartis	Isomorphic Labs partners with Novartis for small molecule therapeutics against three targets, securing $37.5 million upfront and up to US$1.2 billion in milestone payments.
March 2024	Iktos and Elsevier	Elsevier and Iktos join forces to integrate AI into Reaxys, optimizing early-stage research with predictive models, stereochemistry support, and rapid route identification, thus accelerating drug discovery while minimizing costs and time.
March 2019	Iktos and Merck	Merck partners with Iktos to access AI tech for three drug discovery projects. The collaboration aims to expedite drug development, aligning with Merck's innovation strategy in healthcare.

(continued on next page)

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November 2022	Insilico Medicine	Insilico Medicine is using its AI platform to create non-hormonal contraceptive solutions for women with a US$ 700,000 grant.
May 2023	CharmTherapeutics and NVIDIA	CHARM Therapeutics has secured investment from NVentures, NVIDIA's venture arm, to fuel growth and leverage NVIDIA's computing platform. This accelerates CHARM's oncology research and development, harnessing DL for novel cancer therapeutics.
January 2024	Isomorphic Labs and Eli Lily	Isomorphic Labs is to receive a US$ 45 million upfront payment for collaboration on small molecule therapeutics research. It will then be eligible for up to US$ 1.7 billion in milestone payments, excluding royalties on net sales.
January 2024	Isomorphic Labs and Novartis	Isomorphic Labs partners with Novartis for small molecule therapeutics against three targets, securing $37.5 million upfront and up to US$1.2 billion in milestone payments.
March 2024	Iktos and Elsevier	Elsevier and Iktos join forces to integrate AI into Reaxys, optimizing early-stage research with predictive models, stereochemistry support, and rapid route identification, thus accelerating drug discovery while minimizing costs and time.

Sources: Company websites (Media/Announcement sections).

TABLE 5

AI-assisted drug candidates under clinical investigation

Organization(s)[a]	Name and status of the compound under investigation	Description (target and indication)[b]	Reference (s)
Exscientia & Sumitomo Dainippon Pharma (which has expertise in GPCR drug discovery) [Centaur Chemist]	DSP-1181 (Phase I)	A potent full serotonin 5-HT1A receptor agonist with a lengthy half-life against obsessive–compulsive disorder.	(p128),(p129)
	DSP-0038 (Phase I)	A dual-targeted agonist/antagonist for the 5-HT1a and 5-HT2a receptors against Alzheimer's psychosis.	(p133)
Exscientia & Evotec [Centaur Chemist]	EXS-21546 (Phase I)	An adenosine A2a receptor antagonist for immuno-oncology therapy for several tumor types.	(p132),(p133)
Exscientia & one co-owner	GTAEXS617 (Phase I)	A selectively potent CDK7 inhibitor under investigation for its efficacy against transcriptionally addicted cancers.	(p150),(p151)
Exscientia & Bristol Myers Squibb	EXS4318 (Phase I)	A PKC-θ inhibitor for use against inflammatory diseases.	(p152)
Exscientia under a collaboration with Sumitomo Pharma, referred to as design as a service (DaaS)	DSP-2342 (Phase I)	A bispecific small molecule dual 5-HT2A and 5-HT7 antagonist, with broad potential in psychiatric disease.	(p153)
Recursion [Recursion OS]	REC-2282 (Phase 2/3)	A possibly first-in-disease, orally active, central nervous system penetrant small molecule histone deacetylase (HDAC) inhibitor, the potential to treat progressive neurofibromatosis type 2 (NF2)-mutated meningiomas.	(p135),(p150)
	REC-4881 (Phase 2)	Orally effective MEK1 and MEK inhibitors, non-ATP-competitive allosteric small molecule for the treatment of familial adenomatous polyposis.	(p135)
	REC-994 (Phase 2)	A small molecule superoxide scavenger, acting on CCM2, for the treatment of cerebral cavernous malformation.	(p154)
Insilico Medicine 3 [Pharma.AI platform (PandaOmics3.0 for novel target discovery, Chemistry42 2.0 for molecule generation and optimization with ADMET prediction, InClinico 1.0 for clinical trial prediction)]	ISM001-055 and INS018-055 (Phase 1 and 2, respectively)	Compounds for use against idiopathic pulmonary fibrosis.	(p126)
	ISM3091 (Phase I)	A selective inhibitor of ubiquitin-specific protease 1 (USP1) that holds the potential to enhance the outcomes of cancer therapy by reducing survivin levels and increasing DR5 through miR-216a-5p.	(p155),(p156)
	ISM8207 (with Fosun Pharma) (Phase I)	A first-in-class small molecule inhibitor of QPCTL to treat advanced stage malignant tumors.	(p157)
	ISM5411 (Phase I)	A potential first-line therapy for inflammatory bowel disease (IBD) that works by blocking the prolyl hydroxylase domain (PHD).	(p127)
Verge Genomics 4–5 [CONVERGE]	VRG50635 (Phase I)	A PIKfyve inhibitor to treat amyotrophic lateral sclerosis.	(p158)
BenevolentAI [Benevolent Platform]	BEN-2293 (Phase I)	A topical pan-tyrosine kinase inhibitor targeting Trk, for the treatment of atopic dermatitis.	(p135)
	BEN-8744 (Phase I)	Small molecule PDE10 inhibitor for the treatment of ulcerative colitis.	(p154)
BenevolentAI [Benevolent Platform] and Sheffield Institute for Translational Neuroscience (SITraN) at the University of Sheffield	BEN-34712 (Phase I)	An orally administered, potent, and selective brain-penetrating RARαβ (retinoic acid receptor alpha beta) biased agonist.	(p159)
Relay Therapeutics [Dynamo Platform]	RLY-1971/RG-6433 (Phase 1)	Targeting SHP2 for the treatment of solid tumors.	(p135)
	RLY-4008 (Phase 1/2)	Inhibitor targeting FGFR2, intended for the treatment of FGFR2-altered cholangiocarcinoma.	(p154),(p160)
	RLY-2608 (Phase 1)	Targeting PI3Kα for the treatment of solid tumors.	
Nimbus Therapeutics	NDI-010976/GS-0976 (Phase 2)	Targeting ACC, for the treatment of non-alcoholic steatohepatitis (NASH).	
Pharos iBio [Chemiverse]	PHI-101 (Phase I)	Targeting FLT3 for the treatment of acute myelogenous leukemia, platinum-resistant refractory ovarian cancer, and other cancers.	
Schrödinger	SGR-1505 (Phase 1)	Targeting MALT1 for the treatment of Non-Hodgkin's lymphoma.	
Valo Health	OPL-0301 (Phase 2)	Targeting S1P1 for the treatment of post-myocardial infarction acute kidney injury.	
	OPL-0401 (Phase 2)	Targeting ROCK1/2 for the treatment of diabetic retinopathy and diabetic complications.	
Structure Therapeutics	GSBR-1290 (Phase 1)	Targeting GLP1R for the treatment of type 2 diabetes and obesity.	
	ANPA-0073 (Phase 1)	Targeting APLNR for the treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis.	

[a] The name of AI platforms mentioned in parenthesis [] are registered trademarks or properties of the respective companies.
[b] Indications retrieved from the company pipeline.

apy for inflammatory bowel disease (IBD) that blocks the prolyl hydroxylase domain (PHD), using DGMs.[p127] Two more clinical assets of the company are mentioned in Table 5.

Exscientia, a UK-based company employing DL in drug discovery, developed DSP-1181 against obsessive–compulsive disorder (OCD) within 12 months, significantly faster than the average 4-year timeline to clinical trials (phase I in January 2020).[p128],[p129] Utilizing in-house AI tools, such as Centaur Chemist and Centaur Biologist, Exscientia optimizes various SARs in a structured manner. For DSP-1181, data from the ChEMBL repository was used to develop Bayesian models of ligand action spanning 784 human protein targets, including GPCRs. These models aim to find molecules that have multi-target effects while limiting off-target effects.[p130],[p131] Another asset from the company's AI platform, EXS21546, is undergoing phase I clinical study as an immuno-oncology therapy for various tumor types.[p132],[p133] In addition, Exscientia initiated phase I clinical studies of DSP-0038, the third DL-generated molecule, in the United States in May 2021. This molecule, a dual-targeted agonist/antagonist for the 5-HT_{1a} and 5-HT_{2a} receptors, resulted from a partnership with Sumitomo Dainippon Pharma.[p133] Three more clinical assets of the company are mentioned in Table 5.

Another AI company, BenevolentAI, specializes in a drug discovery strategy that utilizes knowledge graphs for biological data to propose novel drugs. The company identified baricitinib, a rheumatoid arthritis medicine, as a potential COVID-19 therapy that inhibits adaptor-associated protein kinase 1, reducing the cytokine storm (AAK1). The company completed this study by February 2020, leveraging its information base. Eli Lilly and BenevolentAI concluded clinical trials for COVID-19 treatment by November 2020 and obtained emergency use approval for this indication from the FDA.[p134] The company's DL-driven molecule, BEN-2293, is currently undergoing clinical trials for atopic dermatitis.[p135]

Verge Genomics is yet another company utilizing DL and human data to generate improved treatments for specific diseases. Their end-to-end drug development platform, CONVERGE, incorporates several technical advancements. Notably, the company has a clinical candidate in phase I (VRG50635), a PIKfyve inhibitor designed to treat amyotrophic lateral sclerosis (ALS). This candidate addresses a novel target discovered through the platform.

Recursion is a pioneering clinical-stage biotechnology organization that is transforming the quest for medicinally active molecules through innovative approaches to biology. The Recursion Operating System, a platform developed across multiple technologies, continuously expands one of the world's largest private biological and chemical datasets, known as the Recursion Data Universe, to fulfill its purpose. At present, two molecules from the company are undergoing clinical trials (Table 5).

Various other organizations are actively engaged in this domain, aiming to expedite the development of more cost-effective drugs through DL. The application of DL varies among companies, depending on the specific context of their discovery efforts. For instance, Relay Therapeutics and Turbine employ DL for discovering novel targets or mechanisms of action. By contrast, companies such as Aria Pharmaceuticals, Collaborations Pharmaceuticals, and Healx, leverage DL to explore potential opportunities for drug repurposing. Some organizations opt for a combination of multiple AI technologies to tackle a wide range of issues encountered throughout the drug discovery process.[p136] Additional drug candidates derived through DL that are currently under investigation and undergoing clinical trials are detailed in Table 5, including information on clinical stage, targeted diseases, specific targets, and the names of proprietary AI platforms (wherever available).

Successes and failures of AI-powered drugs in pharmaceutical industries

In the past year, several drug candidates developed through AI have faced setbacks or have been deprioritized in clinical trials. Among the companies affected are UK-based Exscientia, which recently announced the winding down of a Phase I/II study for its cancer drug candidate EXS-21546,[p132],[p133] and BenevolentAI, whose dermatitis drug BEN-2293 fell short in clinical trials.[p135],[p137] Meanwhile, Recursion Pharmaceuticals, although not experiencing trial failures, has encountered clinical setbacks. Despite initial enthusiasm surrounding AI-driven drug discovery, these developments underscore the challenges and uncertainties inherent in pharmaceutical R&D, raising questions about the efficacy of AI in improving the success rate of drug development. Clinical failures are not uncommon in biotech, but the 0-for-3 start for AI-powered drug candidates raises questions about the efficacy of AI in increasing the success rate of drug development. Executives from these companies emphasize that it is premature to assess whether AI enhances the likelihood of success, given the high failure rate of drug candidates, regardless of their development method. The companies have collectively invested over US$ 1.5 billion in AI-powered drug discovery efforts, highlighting the substantial resources involved in these endeavors. Moreover, the challenges faced by these first-generation biotechs, coupled with market volatility, have led to significant declines in their stock prices.

One important aspect to highlight is that discouraging results from AI-driven drug discovery efforts do not solely reflect the limitations of the AI models alone. Improperly curated training data also play a significant role in contributing to the poor performance of AI models. In addition, the accuracy of QSAR data is an equally crucial consideration, as the main challenge often lies in the deficiencies of QSAR accuracy. It is worth noting that the development and application of DL-derived predictive models have not always yielded the anticipated success, as indicated in various studies.[p118],[p119],[p120] Despite these setbacks, ongoing efforts are being made to refine AI-driven approaches and improve translational models to enhance the probability of success in clinical trials. As the pharmaceutical industry continues to evolve, it is imperative to critically evaluate the role and impact of AI-powered drugs in shaping the future of drug development.

To conclude, the potential impact of AI in drug discovery includes increased productivity, faster and cheaper innovation, and improved patient outcomes. Moreover, if the success percentage (i.e. the number of molecules successfully passing various clinical stages out of total number of molecules generated) of AI efforts matches that of the industry historically, then this

would be a positive sign. As more clinical data become available, ongoing research will continue to shape the future impact of AI-powered discovery on clinical success rates.

Challenges

DGMs have made significant progress in drug development, albeit they face several crucial challenges before reaching their full potential. Although no commercially available drugs have yet been developed using DGMs, there is continuous innovation in methods and approaches, inspiring anticipation that a generative AI-based drug may emerge in the future. Stakeholders express optimism about the transformative impact that generative design can have on the drug discovery pipeline, recognizing its limitations in designing newer drugs. The following section discusses some of main challenges faced by DGMs in drug discovery, along with recent solutions aimed at broadening the acceptance of DGMs in the field. Many challenges are interconnected, and addressing one has the potential to benefit others. These issues may also resonate with digital leaders in other sectors.

One of the primary challenges is the generation of chemically valid and synthetically accessible molecules. DGMs, such as VAEs and GANs, often struggle to produce molecules that adhere to the complex rules of chemistry. This limitation stems from the inherent difficulty in encoding and enforcing chemical constraints during the generative process. As a result, many generated molecules may exhibit unrealistic structures or lack the necessary functional groups for binding to biological targets. Another serious issue is the reliability and interpretability of generated molecules. DGMs operate in high-dimensional spaces, making it challenging to interpret the underlying factors that influence molecule generation. This lack of interpretability hinders the ability of researchers to understand why certain molecules are generated, limiting their confidence in the potential biological activity and pharmacokinetic profile of the generated molecules. Furthermore, the scalability of DGMs in drug discovery remains a significant concern. Training DGMs requires large amounts of high-quality data, which may not always be readily available, especially for rare diseases or niche therapeutic targets.

Drug development suffers from a scarcity of high-quality, relevant data for training DL models, unlike other fields such as image analysis or language translation where data are abundant. Public repositories such as PubChem[p110] and ChEMBL[p111] have limited data points, and proprietary data are often inaccessible. In addition, the computational resources and expertise needed to train and deploy these models effectively pose barriers for many research groups and organizations.

Yet another challenge is the complexity of drug discovery processes, which poses a significant challenge for DGMs. Optimizing compound design and predicting molecular interactions accurately in intricate biological systems require sophisticated algorithms that are capable of navigating complex chemical spaces and predicting compound behaviors with precision, a task that remains a significant hurdle for current generative AI technologies.

The next challenge involves the resemblance of generated molecules to existing drugs, (lack of novelty) which discourages researchers. Another challenge pertains to choosing an interpretable molecular representation, which can be complex given the trade-off between simplicity and expressiveness.

To overcome these challenges and unlock the full potential of generative AI in drug discovery, several strategies can be considered. Below, we succinctly describe them in the same order as the challenges outlined above. First, advancements in cheminformatics and ML algorithms can improve the generation of chemically valid molecules by incorporating domain knowledge and constraints into the DGMs. Techniques such as RL-based optimization and multi-objective optimization can guide the generation process towards synthesizable and biologically relevant compounds. Moreover, enhancing the interpretability of DGMs through techniques such as attention mechanisms and feature visualization can provide researchers with insights into the structural characteristics of the generated molecules and their relevance to target binding. Validation in thorough experimental trials is crucial, even though it requires significant time and resources. Potential remedies include boosting the quality of the training data through partnerships and advanced augmentation techniques, as well as enhancing model interpretability with explainable AI. In this context, it is imperative for researchers, pharmaceutical companies, and regulatory agencies to collaborate in setting guidelines and standards and in promoting data exchange to accelerate advancements in generative AI for drug discovery.

Addressing scalability issues requires innovative data generation strategies, including data augmentation techniques. Some of the methods used to address data scarcity include active learning, TL, one shot learning, federated learning (FL) (to address data privacy issue). One recent research project came up with a novel DL algorithm (in low-data regimes) for the automated design of drug-like analogs (DeLA-Drug). It consists of an RNN that has two LSTM layers and that was conceived for the data-driven generation of similar-to-bioactive compounds. DeLA-Drug captures the syntax of SMILES strings, employing a new strategy called sampling with substitutions (SWS). Remarkably, the algorithm preserves the drug likeness and synthetic accessibility of the known bioactive compounds.[p108]

Collaborative platforms and data-sharing initiatives within the scientific community can facilitate access to diverse and representative datasets, fostering the development of more robust and generalizable DGMs for drug discovery. In this regard, it is interesting to note that the Machine Learning Ledger Orchestration for Drug Discovery (MELLODDY) consortium, comprising 10 European pharmaceutical companies, has successfully explored methods to utilize distributed data while maintaining confidentiality.[p138] Employing FL techniques, MELLODDY aimed to enhance the performance of ML models by leveraging compound data from multiple pharmaceutical companies without sharing raw data. It is important to note, however, that compound libraries can vary significantly among pharmaceutical companies. As a result, the compound datasets from each company often exhibit large label biases, leading to significant differences in label distributions across companies. This discrepancy poses a challenge in developing accurate QSAR models. Furthermore, FL may exhibit suboptimal performance in such scenarios, particularly in settings that are not independently and identically distributed.[p139]

To tackle the complexity of drug discovery processes for DGMs, we propose a multi-faceted approach that includes integrating domain knowledge into algorithms, utilizing advanced techniques such as RL and TL, employing ensemble modeling for robust predictions, implementing iterative optimization with feedback loops, and fostering interdisciplinary collaborations. These strategies collectively enhance model accuracy, navigate complex chemical spaces efficiently, and improve predictions of compound behaviors and molecular interactions in intricate biological systems. The lack of novelty issue can be solved by encouraging the exploration of novel chemical space through techniques such as diversity-promoting objectives and enforcing dissimilarity constraints during the generative process. By prioritizing the generation of structurally distinct molecules that possess unique chemical features, DGMs can produce more innovative and potentially therapeutically valuable compounds. Interpretable molecular representation is crucial, and solutions can involve leveraging graph-based representations that capture the intricacies of molecular structures while maintaining interpretability. In addition, techniques such as attention mechanisms and feature visualization can enhance model interpretability by highlighting important molecular features and their contributions to generated compounds. By striking a balance between simplicity and expressiveness in molecular representations and leveraging advanced interpretability methods, researchers can gain deeper insights into the characteristics and potential biological activities of generative AI-generated molecules.

To sum up, by embracing interdisciplinary collaborations, advancing algorithmic innovations, and promoting data accessibility and transparency, the field can overcome the hurdles that it faces at present, paving the way for more efficient, effective, and ethical drug development processes.

Summary and future outlook

The transformative impact of AI on drug discovery, specifically in *de novo* drug design, is unequivocal. This review underscores significant strides in leveraging DGMs, which have become integral to the crafting of innovative drug candidates. These advancements showcase the potential of DGMs not only to optimize the drug development process but also to unveil uncharted territories for therapeutic exploration. However, the review also sheds light on formidable challenges, including the imperative need to ensure data quality, enhance model interpretability, and grapple with other complexities.

A pivotal element for successfully utilizing DGMs in drug development lies in the meticulous development of annotated labeled datasets, a task that necessitates collaborative efforts across several disciplines. There is a call for the pharmaceutical community, in tandem with AI experts, to establish a comprehensive molecule database and more robust benchmarks, analogous to the extensive ImageNet dataset used in training advanced DL models in computer vision. Current AI methodologies often prioritize addressing the symptoms and effects of diseases, rather than delving into their underlying causes. Unraveling the causative pathways and revealing genetic predispositions hold the potential to empower interventions and even reverse disease progression. In this vein, it is anticipated that seasoned AI experts will play a pivotal role in designing DL models that are capable of effectively modeling diseases, thereby improving outputs, particularly in toxicity profiles, to mitigate the long-standing challenge of late-stage failures in clinical trials. This strategic approach will contribute significantly to the development of robust DGMs for drug discovery.

The future promises a cultural shift whereby stakeholders enthusiastically embrace AI tools in drug discovery projects, actively contributing data for training DL models through FL. To unlock the full potential of data science in the healthcare sector, concerted research efforts and cooperative ventures involving industry, academia, and stakeholders are imperative. Given the rapid pace of technological advancement, continuous upskilling and reskilling across all educational and experience levels is inevitable. There is a pressing need to train individuals with a comprehensive understanding of both medicine and computer science. In the upcoming years, workshops, short-term courses, and comprehensive degree programs tailored for existing professionals and the younger workforce will be essential. Further, competitions such as the Merck Molecular Activity Challenge, Tox21 Challenge, CACHE, CASP and DREAM are advocated to encourage the development of new AI tools for handling the intricate chemical and biological data intrinsic to drug discovery projects. These competitions foster collaboration among specialists from diverse fields. In addition, the development of more user-friendly DGMs, as well as tutorials, will aim to bolster the confidence of stakeholders in integrating these models across various drug discovery stages. Initiatives such as the collaborative MELLODDY[p138] project are positioned as the norm, urging all stakeholders to unite for the greater societal interest.

Looking ahead, the integration of AI with traditional drug discovery processes is ushering in a transformative era in pharmaceutical research, driven by emerging trends and groundbreaking advancements. The role of AI in analyzing vast datasets from HTS methods accelerates the identification of potential drug candidates, streamlining the drug development pipeline. Recent breakthroughs in AI algorithms, particularly in predicting drug-target interactions, are fundamentally reshaping drug discovery, promising enhanced personalized medicine and tailored treatments. Nevertheless, several challenges persist in AI-driven drug discovery. Data privacy and security issues are significant concerns, given the sensitive nature of health-related data and the imperative to safeguard patient information. Ensuring the availability of standardized, high-quality datasets for training AI models remains a pressing concern, as the efficacy and reliability of AI-driven insights depend on the quality of the data inputs. Moreover, the inherent black-box nature of some AI models poses challenges in interpreting their predictions, necessitating the development of more transparent and interpretable AI models for improved decision-making in drug discovery processes. Addressing these multifaceted challenges requires a collaborative effort involving researchers, healthcare professionals, and policymakers to establish robust frameworks and guidelines.

Although the integration of AI into the pharmaceutical industry is still in its nascent stages, numerous unexplored applications hold immense potential. For example, the predictive

capabilities of AI could be leveraged to forecast the pharmacokinetics and pharmacodynamics of novel drug candidates, potentially accelerating the drug development timeline and reducing associated costs. Similarly, AI-driven approaches could facilitate the identification of novel drug targets, unlocking new avenues for therapeutic intervention and innovation. Alongside these opportunities come new challenges, however, such as the need for rigorous validation methods to ensure the accuracy and reliability of AI-generated predictions in real-world clinical settings. As the field progresses, addressing these challenges comprehensively will be essential to harnessing the full potential of AI in revolutionizing drug discovery and ultimately improving patient outcomes. The collaborative efforts of stakeholders across academia, industry, and regulatory bodies will be pivotal in navigating these complexities and in advancing the integration of AI as a cornerstone of modern drug development strategies. These developments suggest a shift towards more holistic and integrated approaches in drug development. The future path of generative AI in drug discovery is expected to be characterized by ongoing technological progress and a deeper comprehension of both the capabilities and limitations of DGMs. To harness fully the potential of AI, a collective effort to enhance data quality, model transparency, and interdisciplinary collaboration is imperative. This collective push is poised to yield more sophisticated AI tools, capable not only of expediting the drug discovery process but also of making it more cost-effective. In essence, AI stands at the cusp of revolutionizing drug discovery, promising to deliver groundbreaking treatments faster and more efficiently than ever before.

Conflicts of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Amit Gangwal: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Antonio Lavecchia:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization.

Data availability

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