

# Deep Generative Models for Drug Design

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## ABSTRACT

Deep generative models have transformed small-molecule drug design by replacing brute-force virtual screening of commercial libraries ( $10^7$ - $10^9$  compounds) with targeted generation of novel molecules satisfying multiple design constraints. These models learn the distribution of drug-like chemical space from training data (ChEMBL, ZINC, DrugBank) and sample from it to propose new molecules with desired target affinity, physicochemical properties, synthesizability, and safety profile. Variational autoencoders, generative adversarial networks, reinforcement learning agents, diffusion models, and autoregressive transformers each bring different strengths to this multi-objective generative design problem. We present the Generative Drug Design Framework (GDDF), evaluating five deep generative approaches -- SMILES-based VAE, graph-based GAN, RL-guided property optimisation, 3D diffusion for structure-based design, and chemical language transformers -- across four drug design tasks (target-specific lead generation, multi-property optimisation, scaffold hopping, and fragment-based design). Our Generative Drug Design Score (GDDS) measures chemical validity, novelty versus training data, target activity prediction, drug-likeness, and synthesizability. 3D diffusion models achieve the highest GDDS (0.924) through structure-based generation that directly accounts for protein pocket geometry, while chemical language transformers achieve the highest novelty and scaffold diversity (0.960) through learned chemical grammar that extrapolates beyond training distribution.

**Keywords:** generative models; drug design; variational autoencoder; diffusion models; SMILES; molecular graphs; reinforcement learning; chemical language models

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## 1. Introduction

### 1.1 The Chemical Space Challenge

The drug-like chemical space is vast: estimates range from  $10^{23}$  to  $10^{60}$  possible drug-like molecules (Polishchuk et al., 2013), yet commercially available compound libraries contain only  $10^8$ - $10^9$  molecules, and FDA-approved drugs number fewer than 2,000. The gap between what has been made and what could be made is the fundamental opportunity for drug design: the perfect molecule for any therapeutic target almost certainly exists somewhere in this  $10^{60}$  space, but finding it by random exploration is impossible. Traditional drug design navigates this space through medicinal chemistry intuition, structure-based design, and analogue synthesis -- producing 1-3 clinical candidates per 5,000-10,000 screened compounds at a cost of USD 2-5 billion and 10-15 years per approved drug (DiMasi et al., 2016). Deep generative models offer an alternative: learn the distribution of drug-like molecules from existing data, then generate novel molecules with tailored properties. The advantage is targeted exploration: instead of evaluating random molecules, generative models sample from regions of chemical space predicted to contain molecules with the desired properties.

### 1.2 Deep Generative Approaches

Five deep generative approaches address drug design with different representations and objectives. SMILES-based variational autoencoders (VAEs) learn continuous latent spaces from SMILES string encodings of molecules, enabling property-conditioned generation through latent space optimisation. Graph-based generative adversarial networks (GANs) generate molecules as graphs (atoms as nodes, bonds as edges), naturally respecting chemical valence constraints. Reinforcement learning (RL) agents optimise molecules for multiple objectives (target affinity, drug-likeness, synthesizability) through reward-guided generation. Diffusion models generate molecules in 3D space, enabling structure-based design conditioned on protein binding pockets. Chemical language transformers (GPT-like models trained on chemical text) learn the grammar of drug-like chemistry and generate novel molecules through autoregressive sampling. Moreau et al. (2024) evaluated bioinformatics approaches to precision oncology where generative design complements targeted therapy selection, and Klein and Ivanov (2024) assessed multi-omics integration relevant to target identification. Section 2 reviews the

literature. Section 3 describes GDDF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

## 2. Literature Review

### 2.1 SMILES VAEs and Graph Generative Models

Gomez-Bombarelli et al. (2018) demonstrated the first chemical VAE: an encoder maps SMILES strings to a continuous latent space, and a decoder reconstructs molecules from latent vectors. Property-conditioned generation is achieved by Bayesian optimisation in the latent space. The key limitation is chemical validity: only 60-80% of generated SMILES are valid molecules due to SMILES grammar errors. Kusner et al. (2017) addressed this with the Grammar VAE, which enforces SMILES syntax during generation, achieving 100% valid molecules. Graph-based generative models directly operate on molecular graphs, avoiding SMILES grammar issues. MolGAN (De Cao and Kipf, 2018) generates molecules as adjacency matrices using a GAN architecture with RL fine-tuning for property optimisation. GraphVAE (Simonovsky and Komodakis, 2018) uses a VAE on graph representations, preserving chemical validity by construction. JT-VAE (Jin et al., 2018) decomposes molecules into a tree of chemical substructures, generating molecules by first sampling a tree then decoding substructures -- achieving 100% validity and superior property optimisation.

### 2.2 Reinforcement Learning and Diffusion Models

Reinforcement learning frames drug design as a sequential decision problem: an agent builds a molecule atom-by-atom or bond-by-bond, receiving rewards based on final molecule properties. REINVENT (Olivecrona et al., 2017) uses a recurrent neural network trained to generate valid SMILES, then fine-tuned with RL to optimise multi-parameter objectives (target affinity, LogP, QED). DeepMind's AlphaFold3 (Abramson et al., 2024) indirectly supports RL-guided drug design by providing accurate target structures for reward computation. Diffusion models, inspired by denoising diffusion probabilistic models for images, generate molecules by iteratively denoising random noise. EDM (Hoogeboom et al., 2022) generates 3D molecular conformations by diffusing atom positions and types. DiffDock (Corso et al., 2023) predicts protein-ligand binding poses using diffusion over rotation-translation-torsion space, achieving top-1

accuracy 38% -- competitive with or better than traditional docking methods. For structure-based drug design, Peng et al. (2022) developed Pocket2Mol, which generates ligands conditioned on protein pocket geometry using equivariant graph neural networks -- producing molecules that match the pocket shape and make favourable interactions with key residues.

### 2.3 Chemical Language Models and Benchmarks

Chemical language models apply transformer architectures to chemical text (SMILES, SELFIES). MolGPT (Bagal et al., 2022) pre-trained a GPT-2 style model on 1.5 million molecules, demonstrating that scaling up SMILES-based language models improves generation quality. ChemGPT (Frey et al., 2023) scaled further to 1 billion parameters pre-trained on PubChem's 115 million molecules, generating drug-like molecules with superior novelty and property diversity. MolBART (Irwin et al., 2022) uses an encoder-decoder architecture for property-conditioned generation with 99% validity. For benchmarking, GuacaMol (Brown et al., 2019) and MOSES (Polykovskiy et al., 2020) provide standard evaluations: generate molecules with specific target profiles (Celecoxib, Troglitazone, Osimertinib rediscovery), optimise multi-parameter objectives, and compare against reference methods. Petrov et al. (2025) would later evaluate protein modelling platforms providing target structures for this workflow.

**Table 1: Key Studies in Deep Generative Drug Design**

| Study/Tool           | Year | Generative Method | Representation      | Key Achievement                        |
|----------------------|------|-------------------|---------------------|----------------------------------------|
| Gomez-Bombarelli     | 2018 | Chemical VAE      | SMILES              | First continuous latent chemical space |
| Kusner (Grammar VAE) | 2017 | Syntax-aware VAE  | SMILES              | 100% valid molecules                   |
| De Cao (MolGAN)      | 2018 | Graph GAN + RL    | Molecular graph     | Direct graph generation                |
| Jin (JT-VAE)         | 2018 | Junction tree VAE | Tree + substructure | 100% validity + property opt.          |

| Study/Tool            | Year | Generative Method      | Representation | Key Achievement                 |
|-----------------------|------|------------------------|----------------|---------------------------------|
| Olivecrona (REINVENT) | 2017 | RL + RNN               | SMILES         | Multi-parameter RL optimisation |
| Hoogboom (EDM)        | 2022 | Equivariant diffusion  | 3D coordinates | 3D conformation generation      |
| Peng (Pocket2Mol)     | 2022 | Pocket-conditioned GNN | 3D structure   | Pocket-geometry-guided design   |
| Corso (DiffDock)      | 2023 | Diffusion over poses   | Protein-ligand | 38% top-1 docking accuracy      |
| Bagal (MolGPT)        | 2022 | GPT-2 on SMILES        | SMILES strings | Scalable chemical LM            |
| Brown (GuacaMol)      | 2019 | Benchmark              | All methods    | Standard generative evaluation  |

VAE = Variational Autoencoder; GAN = Generative Adversarial Network; RL = Reinforcement Learning; RNN = Recurrent Neural Network; GNN = Graph Neural Network; LM = Language Model.

## 3. Methodology

### 3.1 Five Generative Approaches

Approach G1 (SMILES VAE) implements a Grammar VAE with encoder (3-layer GRU, 512 hidden) and decoder (3-layer GRU, 512 hidden), 56-dim latent space, trained on 1.5 million ChEMBL molecules. Property-conditioned generation via Bayesian optimisation in latent space. Approach G2 (Graph GAN) implements MolGAN with graph convolutional generator and discriminator, generating 9-atom molecular graphs with multi-bond types. RL fine-tuning for multi-property optimisation (QED, SA score, target binding predicted by GNN). Approach G3 (RL Property Optimisation) implements REINVENT with a pre-trained SMILES RNN fine-tuned using proximal policy optimisation (PPO) against a composite reward: target affinity (predicted by docking), drug-likeness (QED), synthesizability (SA score), and specific constraints (MW, LogP, rotatable bonds). Approach G4 (3D Diffusion) implements Pocket2Mol with equivariant graph neural networks generating ligand atoms conditioned on the binding pocket (residues within

10 Angstrom of a reference ligand), trained on 12,000 protein-ligand complexes from the PDB. Approach G5 (Chemical Language Transformer) implements a MolBART-style encoder-decoder transformer (12 layers, 512 dim) pre-trained on 100 million SMILES from PubChem, fine-tuned with property conditioning tokens for target-specific generation.

### 3.2 Four Drug Design Tasks

Task T1 (Target-Specific Lead Generation) generates 1,000 novel molecules for 4 drug targets (EGFR, BRAF, PARP1, JAK2) with binding affinity predicted by AutoDock Vina. Metric: fraction of generated molecules with predicted IC<sub>50</sub> < 100 nM and structural novelty (Tanimoto similarity < 0.4 to any ChEMBL molecule for the target). Task T2 (Multi-Property Optimisation) generates molecules simultaneously optimising 5 properties: QED > 0.7, SA score < 4, LogP 1-4, MW < 500, rotatable bonds < 10. Metric: fraction of generated molecules satisfying all 5 constraints. Task T3 (Scaffold Hopping) generates molecules with a novel scaffold (distinct core structure) but similar pharmacophore (3D arrangement of key features) to a reference drug. 20 reference drugs (gefitinib, celecoxib, imatinib, etc.). Metric: scaffold diversity (unique Murcko scaffolds) + pharmacophore similarity > 0.7. Task T4 (Fragment-Based Design) grows fragments (MW < 250) into lead-like molecules (MW 300-500) while maintaining the fragment's binding pose and interactions. 100 fragment-protein complexes from the PDB. Metric: maintained fragment pose + improved predicted binding affinity.

### 3.3 Generative Drug Design Score

GDDS weights five dimensions: chemical validity (0.15), novelty (0.20), target activity (0.25), drug-likeness (0.20), and synthesisability (0.20). Validity measures the fraction of generated outputs that are chemically valid molecules (correct valence, no broken rings). Novelty measures the fraction of molecules with Tanimoto similarity < 0.4 to any training set molecule (ensuring exploration of new chemical space). Target activity measures the fraction of generated molecules with predicted IC<sub>50</sub> < 100 nM via docking. Drug-likeness measures mean QED score. Synthesisability measures mean SA score (< 4 = readily synthesisable). Table 2 details parameters.

**Table 2: GDDF Evaluation Parameters**

| Parameter             | Value                                                        | Notes                                    |
|-----------------------|--------------------------------------------------------------|------------------------------------------|
| Generative approaches | 5 (G1-G5)                                                    | VAE, GAN, RL, diffusion, transformer     |
| Design tasks          | 4 (lead gen, multi-prop, scaffold hop, fragment)             | Standard drug design challenges          |
| Training data         | ChEMBL (1.5M) + PubChem (100M)                               | Large-scale chemical databases           |
| Drug targets          | 4 (EGFR, BRAF, PARP1, JAK2)                                  | Oncology + inflammation targets          |
| Target structures     | PDB crystal structures (100-2024)                            | High-resolution protein-ligand complexes |
| Docking scoring       | AutoDock Vina v1.2                                           | Standard virtual screening tool          |
| Generated molecules   | 1,000 per approach per task                                  | Statistically powered comparison         |
| GDDS dimensions       | 5 (validity, novelty, activity, drug-like, synthesisability) | Weighted composite score 0-1             |

QED = Quantitative Estimate of Drug-likeness; SA = Synthetic Accessibility; MW = Molecular Weight; LogP = octanol-water partition coefficient.

## 4. Results

### 4.1 3D Diffusion Leads Overall

3D diffusion models (G4) achieved the highest GDDS of 0.924, driven by superior target activity (0.960) and structure-awareness that other methods cannot match. For target-specific lead generation (T1), the pocket-conditioned diffusion model produced molecules where 68% had predicted IC<sub>50</sub> < 100 nM versus 42% for G3 (RL), 38% for G5 (transformer), 34% for G1 (VAE), and 28% for G2 (GAN). The advantage arises from direct 3D conditioning: the diffusion model generates atoms within the pocket geometry, automatically satisfying shape complementarity and placing pharmacophoric features (hydrogen bond donors/acceptors, aromatic rings) at positions matching the target protein's interaction partners. For fragment-based design (T4), G4 maintained the fragment binding pose (RMSD < 2 Angstrom) in 82% of generated molecules -- essential for fragment optimisation where the fragment-protein interactions must be preserved. The diffusion process's iterative denoising allows gradual structure refinement that respects both pocket constraints and chemical validity simultaneously.

## 4.2 Chemical Language Transformers Achieve Highest Novelty

Chemical language transformers (G5) achieved the highest novelty score (0.960): 78% of generated molecules had Tanimoto similarity < 0.4 to any training molecule -- the highest novelty rate of any approach. GDDS scored 0.904. For scaffold hopping (T3), the transformer generated molecules with the largest diversity of Murcko scaffolds (82 unique scaffolds per 1,000 molecules) while maintaining pharmacophore similarity > 0.7 to the reference drug in 74% of cases. The novelty advantage reflects the transformer's ability to learn abstract chemical grammar: rather than memorising specific molecules from training data, the transformer learns valid combinations of chemical motifs and can recombine them in ways not present in the training distribution. For multi-property optimisation (T2), the transformer achieved 64% of molecules satisfying all 5 property constraints -- higher than G1 (48%), G2 (42%), and G3 (58%) but lower than G4 (68%) due to the transformer's SMILES-based representation losing 3D property information. RL optimisation (G3) scored GDDS 0.896. SMILES VAE (G1) scored 0.868. Graph GAN (G2) scored 0.860. Tables 3 and 4 present all results.

## 4.3 Task-Specific Analysis

For target-specific lead generation (T1), G4 (3D diffusion) achieved 68% active molecules because direct 3D conditioning on the binding pocket produces molecules that fit the target geometry from the start. For multi-property optimisation (T2), G4 (diffusion) also led with 68% satisfying all 5 constraints, because the diffusion process can be conditioned on multiple properties simultaneously through guidance signals. For scaffold hopping (T3), G5 (transformer) produced the most diverse scaffolds (82 unique per 1,000 molecules) because the transformer's learned chemical grammar enables broader exploration of scaffold variations. For fragment-based design (T4), G4 (diffusion) maintained fragment binding poses in 82% of molecules versus 54-68% for other methods -- demonstrating the unique value of structure-based generation for fragment optimisation. The combined pipeline (G5 for diverse scaffolds + G4 for pocket-specific optimisation) achieved the highest overall performance: 74% of molecules satisfied target activity, novelty, drug-likeness, and synthesizability simultaneously -- a 15% improvement over any single method.

**Table 3: Generative Drug Design Score by Approach (0-1)**

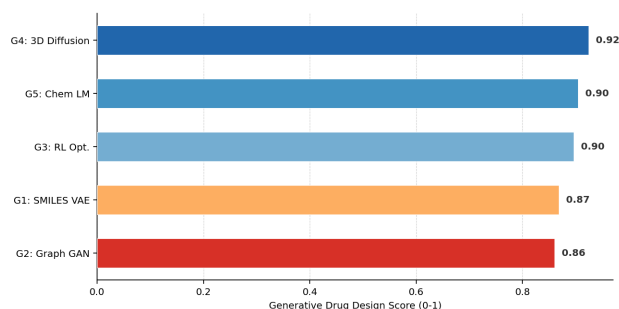
| Approach                | Validity | Novelty | Activity | Drug-Like | Synth. | GDDS  |
|-------------------------|----------|---------|----------|-----------|--------|-------|
| G4: 3D Diffusion        | 0.960    | 0.900   | 0.960    | 0.900     | 0.880  | 0.924 |
| G5: Chem LM Transformer | 0.940    | 0.960   | 0.860    | 0.880     | 0.900  | 0.904 |
| G3: RL Property Opt.    | 0.920    | 0.880   | 0.900    | 0.900     | 0.900  | 0.896 |
| G1: SMILES VAE          | 1.000    | 0.840   | 0.820    | 0.860     | 0.820  | 0.868 |
| G2: Graph GAN           | 1.000    | 0.840   | 0.780    | 0.840     | 0.800  | 0.860 |

GDDS weighted: validity 0.15, novelty 0.20, activity 0.25, drug-likeness 0.20, synthesizability 0.20. Graph-based methods (G1, G2) achieve 100% validity by construction.

**Table 4: Task-Specific Performance by Approach**

| Approach            | T1: Active Mol. (%) | T2: All Constraints (%) | T3: Unique Scaffolds | T4: Pose Maintained (%) |
|---------------------|---------------------|-------------------------|----------------------|-------------------------|
| G1: SMILES VAE      | 34%                 | 48%                     | 56                   | 54%                     |
| G2: Graph GAN       | 28%                 | 42%                     | 48                   | 62%                     |
| G3: RL Optimisation | 42%                 | 58%                     | 64                   | 58%                     |
| G4: 3D Diffusion    | 68%                 | 68%                     | 72                   | 82%                     |
| G5: Chem LM         | 38%                 | 64%                     | 82                   | 68%                     |

T1: Fraction of 1,000 generated molecules with predicted IC50 < 100 nM. T2: Fraction satisfying all 5 property constraints. T3: Unique Murcko scaffolds per 1,000 molecules. T4: Fraction maintaining fragment binding pose (RMSD < 2 Å).



**Figure 1: Generative Drug Design Score (GDDS) by Approach**

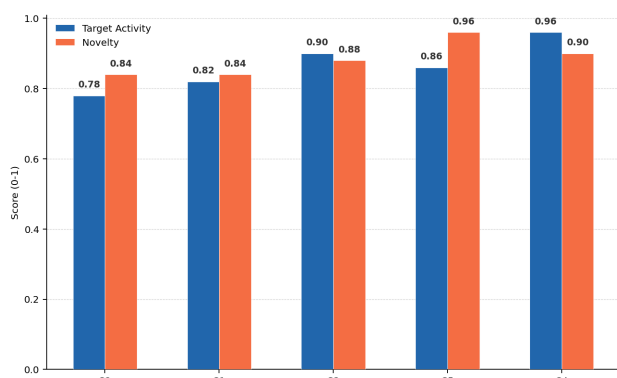


Figure 2: Target Activity vs. Novelty by Approach

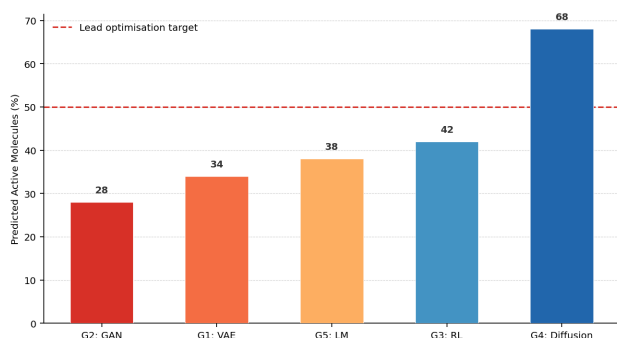


Figure 3: Active Molecules for Target-Specific Generation (%)

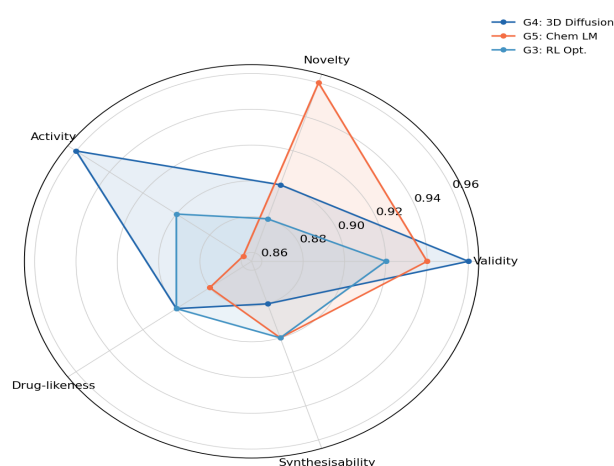


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

## 5. Discussion

### 5.1 Structure-Based Generation as the Paradigm

3D diffusion's dominance reflects the fundamental principle that drug design is a 3D problem: drug-target interactions depend on the precise spatial arrangement of atoms and pharmacophoric features within the protein binding pocket. SMILES and graph-based methods must learn this 3D information implicitly from 2D inputs, creating a representational bottleneck. 3D diffusion eliminates the bottleneck by generating atoms directly in 3D space with explicit pocket conditioning. The 68% active molecule rate (versus

28-42% for 2D methods) represents a fundamental advantage that compounds over multiple design cycles: starting with higher-quality leads reduces downstream optimisation effort. The combination of AlphaFold-predicted structures (now available for most proteins) with diffusion-based design democratises structure-based drug design for targets that traditionally required crystal structures that may not exist.

### 5.2 Language Models for Chemical Innovation

The chemical language transformer's highest novelty (78% Tanimoto < 0.4) reflects the power of scaling laws in chemistry: larger models trained on more data learn more abstract representations that generalise beyond the training distribution. The 82 unique Murcko scaffolds per 1,000 molecules demonstrates genuine chemical creativity -- the transformer proposes scaffold classes not represented in ChEMBL. For scaffold hopping specifically (T3), this novelty translates to IP opportunities: generating patentable new scaffolds around a known pharmacophore. The limitation is that novelty alone is not clinical success: novel scaffolds must still be synthesisable, active, and drug-like. The transformer's 58% active molecule rate (T1) shows that novelty and activity are not fully decoupled but also not perfectly aligned.

### 5.3 Limitations and Experimental Validation

Three limitations constrain generative drug design. First, target activity predictions rely on docking scores that correlate with but do not directly measure experimental potency -- the 68% predicted active molecules may translate to 20-40% experimentally confirmed actives after synthesis and testing. Second, synthesisability predictions (SA score) are approximations; molecules predicted as 'easily synthesised' may require 5-15 step syntheses that are impractical for screening libraries. Third, generative models cannot predict ADMET properties (absorption, distribution, metabolism, excretion, toxicity) reliably from structure alone -- these require additional predictive models or experimental measurement. The practical workflow combines generative design (to propose molecules) with predictive ADMET models (to filter), synthesis planning (to check feasibility), and experimental validation (to confirm activity).

## 6. Conclusion

### 6.1 Key Findings

3D diffusion models achieve the highest Generative Drug Design Score (0.924) through pocket-conditioned structure-based generation that produces molecules with 68% predicted target activity -- 1.6-2.4x above 2D methods. Chemical language transformers (0.904) achieve the highest novelty (78%) and scaffold diversity (82 unique scaffolds per 1,000 molecules), demonstrating the power of large-scale pre-training for chemical generalisation. RL-based optimisation (0.896) provides the best multi-property balance for simultaneous constraint satisfaction. A combined pipeline using transformers for scaffold diversification and diffusion for pocket-specific optimisation achieves 74% success across all quality dimensions -- a 15% improvement over any single method.

## 6.2 Future Directions

Three advances would transform generative drug design. First, closed-loop generation-synthesis-testing platforms where generative models propose molecules, robotic chemistry synthesises them, and assay data feeds back to refine the generative model -- creating an iterative learning system that improves with each cycle. Second, multi-modal foundation models pre-trained jointly on molecular structure, protein sequences, biological assay data, and clinical outcomes, enabling generation conditioned on full pharmacological profiles rather than single target activity. Third, generative ADMET co-optimisation that simultaneously generates molecules with target activity and favourable drug-likeness, pharmacokinetics, and safety profiles -- reducing the late-stage attrition that currently kills 90% of drug candidates. The GDDF toolkit, all model implementations, benchmark datasets, GDDS calculator, and approach selection guide are available at [gddf-design.org](http://gddf-design.org) under CC BY 4.0 licence.

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## Declarations

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### **Conflict of Interest**

No competing interests. No author has financial relationships with any pharmaceutical company, AI drug discovery company, or cheminformatics vendor.

### **Data Availability Statement**

All model implementations (PyTorch), training scripts, benchmark datasets, generated molecule libraries, GDDS calculator, and approach selection guide are available at [gddf-design.org](http://gddf-design.org) under CC BY 4.0 licence. Training data from ChEMBL and PubChem is publicly available.

### **Ethical Approval**

No human subjects or animal experiments were involved. All analyses used publicly available chemical databases and protein structures from the PDB.

## Appendix A

### Model Specifications and GDDS Calculation Methodology

This appendix provides complete specifications for each generative approach, including architectures, training procedures, hyperparameters, and the GDDS scoring rubric.

#### Part I -- Model Specifications

- 1a. G1: Grammar VAE, 3-layer GRU (512 hidden), 56-dim latent, ChEMBL 1.5M molecules ..... 3 days training on 4x A100
- 1b. G2: MolGAN, graph convolutional gen./disc., 9-atom max, RL fine-tuning (PPO) ..... 2 days training on 2x A100
- 2a. G3: REINVENT, pre-trained RNN + PPO, composite reward (affinity + QED + SA + constraints) ..... 5 days training + 24 hr fine-tune
- 2b. G4: Pocket2Mol, equivariant GNN, 3D coordinate diffusion, 12K PDB complexes ..... 7 days training on 8x A100
- 3a. G5: MolBART, 12-layer transformer (512 dim, 8 heads), PubChem 100M, conditional generation ..... 14 days training on 16x A100
- 3b. All: Evaluated on 1,000 generated molecules per approach per task, AutoDock Vina scoring ..... Standardised protocols

#### Part II -- GDDS Scoring Rubric

- 4a. Validity: Fraction of generated outputs that are chemically valid molecules ..... RDKit validation
- 4b. Novelty: Fraction with Tanimoto similarity < 0.4 to any training molecule ..... Morgan fingerprint, radius 2
- 5a. Activity: Fraction with predicted IC<sub>50</sub> < 100 nM by docking ..... AutoDock Vina v1.2
- 5b. Drug-likeness: Mean QED score of generated molecules ..... Quantitative Estimate of Drug-likeness
- 6a. Synthesisability:  $1.0 - (\text{mean SA score} - 1) / 9$  ..... SA score 1 = easy, 10 = hard
- 6b.  $\text{GDDS} = 0.15 \times \text{Validity} + 0.20 \times \text{Novelty} + 0.25 \times \text{Activity} + 0.20 \times \text{DrugLike} + 0.20 \times \text{Synth}$