Transforming Drug Discovery: Generative Models and Electrostatic Complementarity

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1 Introduction

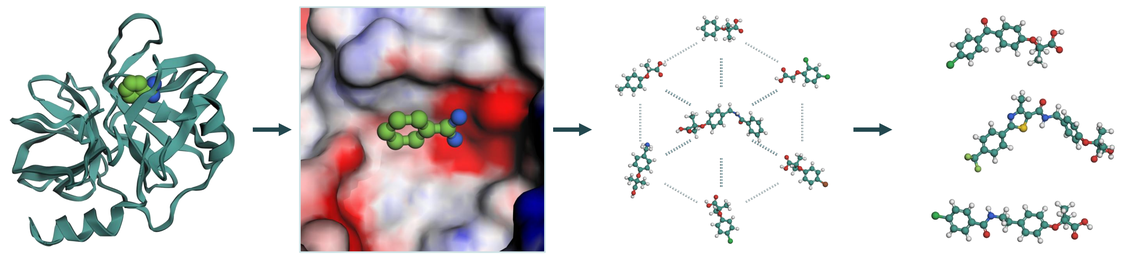
Generative AI is opening new avenues for structure-based drug design by enabling efficient exploration of chemical space. However, successful ligand design requires more than geometric complementarity: electrostatic interactions, hydrogen bonding, desolvation, and water displacement are critical determinants of protein–ligand affinity.

We investigate a generative design strategy that combines molecular expansion with explicit shape and electrostatic complementarity. Starting from docked fragments, the approach uses electrostatic representations and spherical-harmonic fingerprints to guide molecular generation and identify compounds with complementary physicochemical properties. The methodology is demonstrated on the DUDE-Z PPAR-α family and large-scale ligand databases such as ZINC22.

This framework aims to integrate physical interaction principles directly into AI-driven molecular design, providing a route toward more informed compound generation and prioritization.

2 Rational Drug Design and Generative AI

From structural biology to generative molecular design

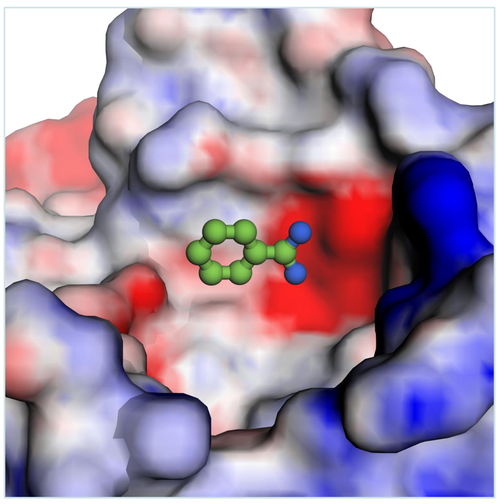


Structural biology
- Atomic-resolution structures
- Binding site characterization
- Fragment-based design

Physics-based insights
- Shape complementarity
- Electrostatic interactions
- Water and desolvation effects

Generative AI
- Fragment expansion
- Electrostatics-aware generation
- Prioritization of synthetically accessible candidate compounds

3 Why Electrostatics Matters



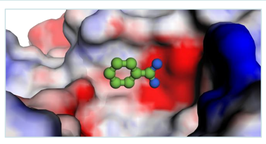
Electrostatic interactions are critical for:
- Binding affinity (coulombic attraction between ligand and protein residues)
- Desolvation energy optimization
- Water displacement and entropic effects

Compounds with weak activity might lack:
- Charge complementarity
- Polar/hydrogen bonding optimization
- Directionality in their dipole moment or partial charges

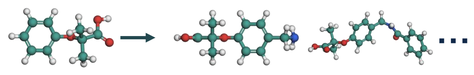
Modifying partial charges, dipoles, or introducing/removing charged/polar groups can significantly improve potency.

4 Electrostatics-Guided Generative Design Workflow

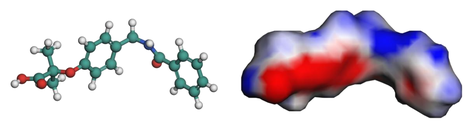
1 Fragment docking
Dock fragments into the binding site and evaluate shape and electrostatic complementarity.



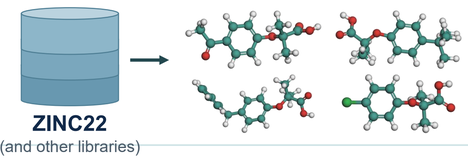
2 Fragment expansion (generative AI)
Generate molecular expansions from promising fragments using generative models and chemical rules.



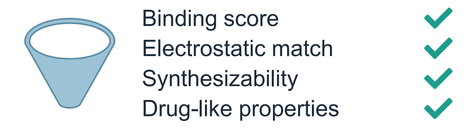
3 Electrostatic characterization
Compute shape and electrostatic representations (e.g., spherical harmonics).



4 Similarity search
Search large databases for molecules with similar shape and electrostatics.

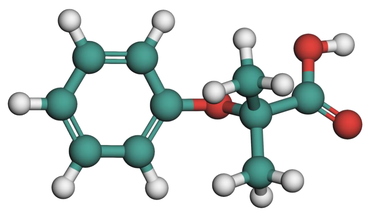


5 Selection and filtering
Prioritize compounds based on binding, electrostatic complementarity, and synthetic accessibility.

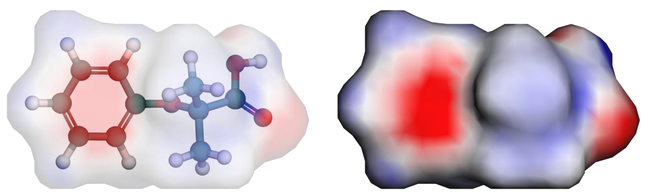


5 Case Study: DUDE-Z PPAR-α (Peroxisome proliferator-activated receptor alpha)

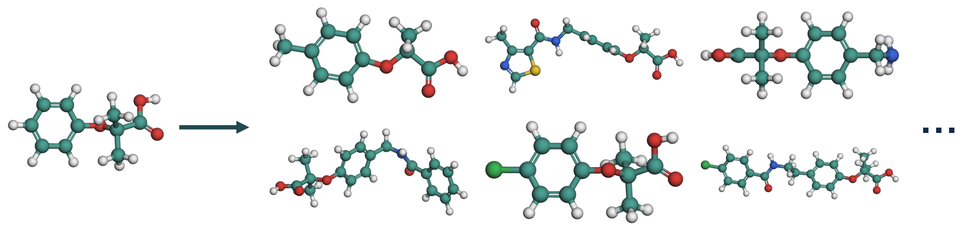
Initial docked fragment



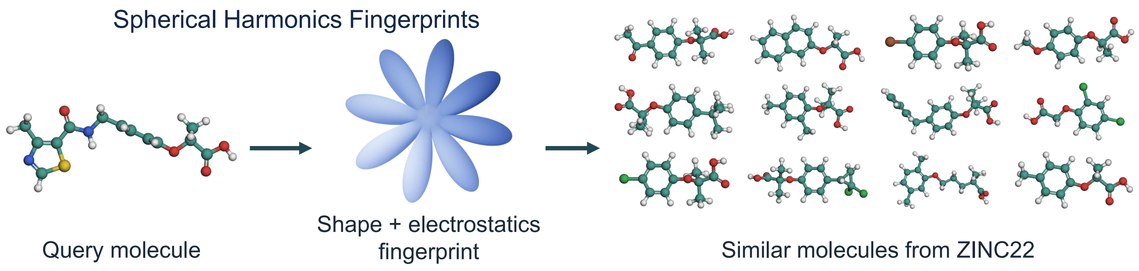
Fragment electrostatics



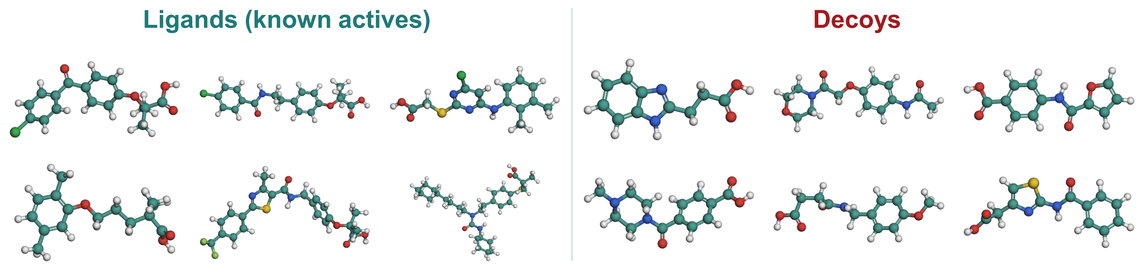
Molecular expansion



Database search for similar shape and electrostatics

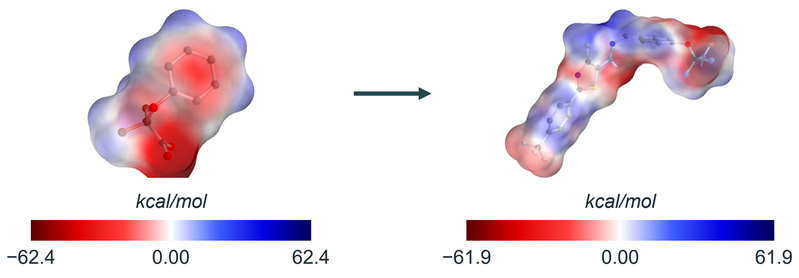


Examples of retrieved molecules

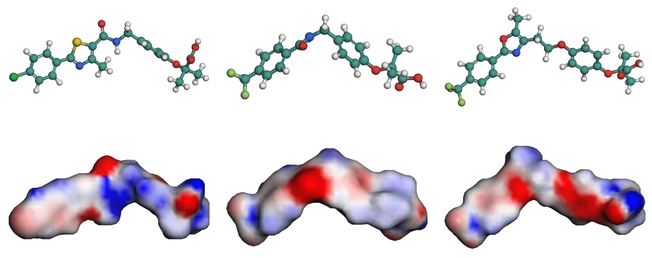


6 Results and Conclusions

From fragments to prioritized candidates



Representative generated compounds



Key takeaways

- Electrostatics-aware generative design supports the prioritization of potential ligands.
- Combining shape and electrostatic similarity enables efficient exploration of large chemical libraries.
- The approach generates chemically diverse, synthesizable compounds with complementary physicochemical properties.
- Integrating physical interaction principles into generative models provides a promising route toward more informed compound prioritization.