



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Lead Optimization: Integrating Experimental, Computational, and AI/ML Approaches

S. D. Chavan*, D. D. Chede, A. R. Shitole

Delonix Society's Baramati College of Pharmacy, Baramati, Pune, Maharashtra, India 413102

ARTICLE INFO

Published: 04 Aug 2025

Keywords:

Lead, Docking, AI, ML,
Case study

DOI:

10.5281/zenodo.16737592

ABSTRACT

One of the most important and complex phases of drug development is lead optimization (LO), which turns early "hit" molecules into promising therapeutic candidates. The goal of this iterative approach is to reduce possible toxicity while improving a molecule's potency, selectivity, pharmacokinetics (ADME), and safety. In the past, LO depended on resource-intensive, empirical techniques. However, computational methods, especially virtual screening (VS), which includes structure-based (molecular docking and dynamics) and ligand-based (QSAR, pharmacophore modeling) approaches, have completely changed the area. These technologies aid in the logical design and synthesis of novel analogues by forecasting binding affinities and interaction patterns. Recent developments in artificial intelligence and machine learning are having a significant impact on LO, despite obstacles like precisely simulating receptor flexibility and desolvation effects. Generative Therapeutics Design (GTD) and Query-based molecular optimization (QMO) are two AI/ML-driven approaches that facilitate more effective chemical space exploration, improve the precision of molecular property predictions, and speed up the development of novel chemical entities. In order to overcome previous constraints and expedite the delivery of improved, safer, and more effective therapeutic candidates, this review examines the synergistic application of classic experimental, advanced computational, and transformative AI/ML approaches.

INTRODUCTION

A crucial and intricate stage of drug discovery is lead optimization (LO), which turns early "hit" molecules into promising therapeutic prospects. In order to improve the potency, selectivity,

pharmacokinetics (ADME properties: Absorption, Distribution, Metabolism, Excretion), and safety of promising molecules, this iterative process improves their physicochemical and pharmacological characteristics while also addressing potential drawbacks like toxicity.

***Corresponding Author:** S. D. Chavan

Address: *Delonix Society's Baramati College of Pharmacy, Baramati, Pune, Maharashtra, India 413102*

Email ✉: snehachavan280@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



Finding a molecule with the ideal ratio of these characteristics to advance into preclinical and clinical development is the ultimate objective.

Lead optimization has historically been a laborious and resource-intensive process that mostly relies on empirical techniques and trial-and-error testing. However, with the use of computer approaches and, more recently, AI and machine learning (ML) tools, the field of drug development is changing quickly. In order to find potential candidates, virtual screening (VS), which includes both ligand-based (such as QSAR and pharmacophore modeling) and structure-based techniques, is essential. In order to direct the synthesis of novel analogues, these computational methods seek to anticipate binding affinities, interaction modalities, and ADMET profiles.

Lead optimization still faces several obstacles despite notable progress, including as precisely taking into consideration receptor flexibility, desolvation effects, and the intrinsic intricacy of ligand-receptor interactions. This stage is being completely transformed by the advent of AI/ML-driven techniques like Generative Therapeutics Design (GTD) and Query-based molecular optimization (QMO), which allow for more effective chemical space exploration, more accurate molecular property prediction, and faster creation of new chemical entities. In order to produce optimal drug candidates, this study will explore the various approaches used in lead optimization, emphasizing the complementary use of cutting-edge computational tools, conventional experimental methodologies, and the revolutionary effects of artificial intelligence and machine learning.

Virtual Screening :

By using the Ligand for ligand-based high-throughput virtual screening, an internal library of FAD structural analogues was produced.^[27]

Accurate ranking to drive analog synthesis and correct ligand orientation within the active site are both necessary for lead optimization by virtual screening.

Substructures found in at least 5% of CNS medications were detected using SARvision, and their relative prevalence in non-CNS medications determined whether they were classified as equally preferred, non-CNS favored, or CNS-favored (C).^[28]

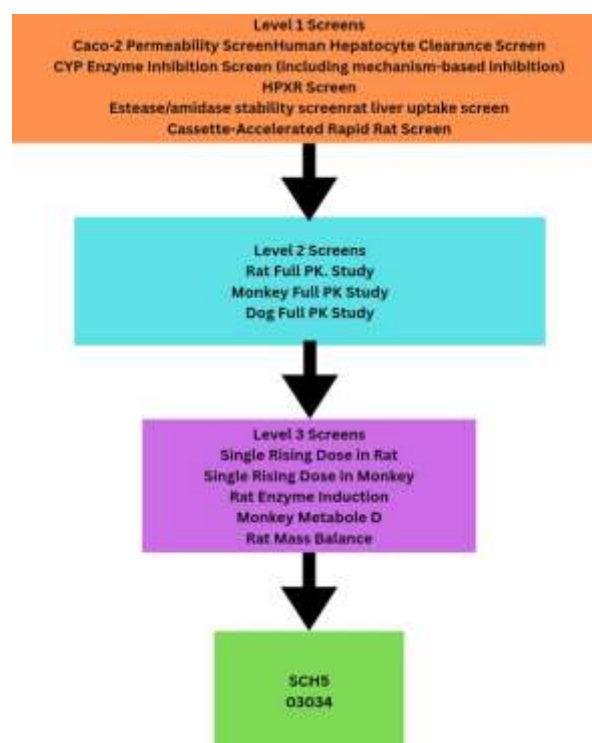


FIGURE 1. Application of the DMPK screening paradigm to the selection of HCV compounds as a component of the lead optimization and candidate selection process.

The prominent alternative to de novo design involves virtual screening of compound libraries via docking methodologies."

"Our initial docking attempts failed to yield active compounds but indicated a promising lead series with potent anti-HIV activity."

"Continuing efforts focused on the highest-ranked library compound, the inactive oxadiazole 3, which appeared to possess a suitable core."

"A subsequent virtual screening initiative demonstrated significant success."

"Notably, 11 compounds effectively inhibited protein-protein interactions in the micromolar range, with four exhibiting IC₅₀ values under 5 μ M." [20]

Steps

1. Ligand Preparation: Following geometry tests, ligands were protonated at N1 after being drawn identically in Sybyl.

2. Protein Preparation: Hydrogens were added, charges were calculated, sidechain orientations were adjusted (if necessary), and cofactors and ligands were combined to create PDB structures and homology models (such as LcDHFR).

3. Protein Minimization: The Amber force field was used to reduce the resulting protein-ligand-cofactor complexes, either completely or within a 3.5 Å radius of the ligand.

4. MD Ensemble Generation: Every 500 fs, conformational snapshots were produced via a 10,000 fs MD simulation at 300 K.

5. Definition of Active Sites and Minimization: After defining active sites (3.5 Å around the ligand/pteridine ring), the resulting MD ensemble structures were reduced using Amber. Geometry and charge verification came next. [21]

Ligand-based virtual screening:

Easy to use and efficient when ligands are known to exist; it finds similar binders but is constrained by a lack of data. De novo design is not the best option.

Essential Methods:

- **QSAR:** Predicts the behavior of novel molecules by relating structure to activity/toxicity.
- **Pharmacophore modeling** is a technique that finds new, comparable compounds by identifying key molecular characteristics from known ligands.

Structure-based virtual screening :

- **Utilizes 3D structures:** Even in the absence of known ligands, this method depends on known (experimental or computational) 3D structures of the drug and target.
- **Molecular Docking:** Assists with comparison and interaction quality by predicting binding modes. The best method for narrowing down candidate lists is to use molecular simulations (MD/Monte Carlo), which are computationally demanding and can predict structural, thermodynamic, and kinetic aspects of interactions.
- **Free Energy Estimation:** Using techniques such as Alchemical Free Energy, Thermodynamic Integration, or Free Energy Perturbation, binding free energy is frequently predicted.

Limitation :

1. Most VS tools are applicable to specific case studies.
2. Weakness in accurately incorporating water and receptor structural flexibility in docking calculations



3. The complicated ligand-receptor interactions and approximate desolvation/entropic terms make it difficult to score precise binding poses/rankings.
4. Increased rates of false results could be caused by anticipated protein structures from homology modeling and predicted protein-ligand complexes. ^[5]

Molecular Docking and Dynamics :

Maestro v9.2 was used to preprocess the ligands and MurB reductase for molecular docking. At the allosteric site, a three-phased Glide v5.7 docking approach (VHTS, SP, XP) was employed. In order to find strong binders, the XP technique produced and ranked 10,000 poses per ligand using XPGscore, excluding those with positive scores.

To assess stability and conformational changes, MD simulations of the MurB reductase-lead1 complex were carried out using Desmond v3.0 in Maestro v9.2. Before a 5000 ps NPT simulation at 310 K, the system, which contains about 40,914 atoms, underwent multi-step reduction and brief relaxation simulations (NVT, NPT). Hydrogen bonding interactions, stability, RMSD, and RMSF were then examined. ^[27]

In vitro phenotypic experiments, as well as assays for enzyme inhibition and IC₅₀ measurement, can employ N,8-dihydroxy-8-(naphthalen-2-yl) octanamide. ^[18]

Docking accuracy is improved by receptor flexibility.

All ligands were docked against a receptor library in Sybyl 7.2 using the Surflex-Dock docking protocol. Probes were used to determine active sites, and the software created ligands in a sequential fashion, producing 200 postures for each ligand.

Pose selection and scoring: The pose with the highest score and the conserved geometry of the 2,4-diaminopyrimidine ring was chosen as "correct." Docking scores were a weighted average of several atomic interactions and were reported in $-\log_{10}$ (K d) units, where larger denotes stronger affinity.

Ensemble Averaging: It was discovered that this method was better than Boltzmann distribution averaging for receptor ensembles, therefore the individual docking scores for each ensemble member were averaged to get a single overall docking score for each ligand.

Ligands were binned by affinity, and a score of 1 was assigned if the docked ligand fell into the same or an adjacent bin based on the docking score. Improper Orientation Rate (%IO - Ligand Orientation Accuracy): This metric measures the proportion of ligands where the top-scoring pose did not have the correct 2,4-diaminopyrimidine orientation; Grouped Ranking Score (Ligand Ranking Accuracy): This metric evaluates how well docking predicts the tightest-binding ligands. ^[3]

Methods :

Utility of AI\ ML Methods in Lead optimization

1. GTD: Workflow with 2D ML models
2. GTD: Modified workflows with pharmacophore models

The ability of GTD to produce pertinent and effective inhibitor concepts was greatly enhanced by the use of a 3D pharmacophore model, which represents crucial inhibitory properties.

The iterative process of GTD enabled the successful synthesis of desired substructures, such as amino pyrazines, that were first overlooked and



a wider exploration of the chemical space by gradually activating restrictions.

Even with challenges, GTD successfully produced hundreds of diverse molecular ideas that fit the pharmacophore and physicochemical property models, demonstrating its potential for lead optimization. [33]

LOMAP Method

1. Design goals

1. Atomic deletions and insertions should be minimized by making the compounds under comparison as comparable as possible.
2. Rings ought to be kept as long as possible.
3. Ligands must have the same net charge in order to be compared.
4. Only if rings are planar can parts of multi-ring systems be removed, hence this should be avoided wherever feasible.
5. Each molecule needs to participate in a minimum of one closed thermodynamic cycle.
6. Only a small number of computations should cover the set of intended calculations.

2. Algorithm

3. Our implementation is in Python Simulation methods:

1. Topology construction
2. Simulation protocols

4. Results [23]

Methods for Safety Risk Assessment

Both quantitative (statistical) and qualitative (judgment-based) techniques are used in construction risk measurement to measure and reduce dangers. Researchers have created a number of strategies to include safety, including activity-based quantification techniques and the risk assessor model (RAM). There are two types of safety risk assessment methods: activity-based and job-based. This study focuses on the latter. The QASR framework for TCSO analysis is presented in this research.

QSAR \ QSPR Modelling :

Through developments in de novo design, virtual screening, pharmacologically significant property prediction, and protein-ligand binding affinity estimate, computational chemisthas made a substantial contribution. [20]

Drug discovery is effectively being impacted by artificial intelligence, especially machine learning techniques like QSAR, SVMs, and Random Forests. In benchmark experiments, new developments in neural networks—particularly deep learning—improve property predictions even more, surpassing traditional techniques [19]

Steps

- Step 1) Identification of significant safety risks
- Step 2) Likelihood and severity evaluation of the risks
- Step 3) Overall evaluation of the risks

SAR of an HIV-1 Vif-APOBEC3G Axis Inhibitor.



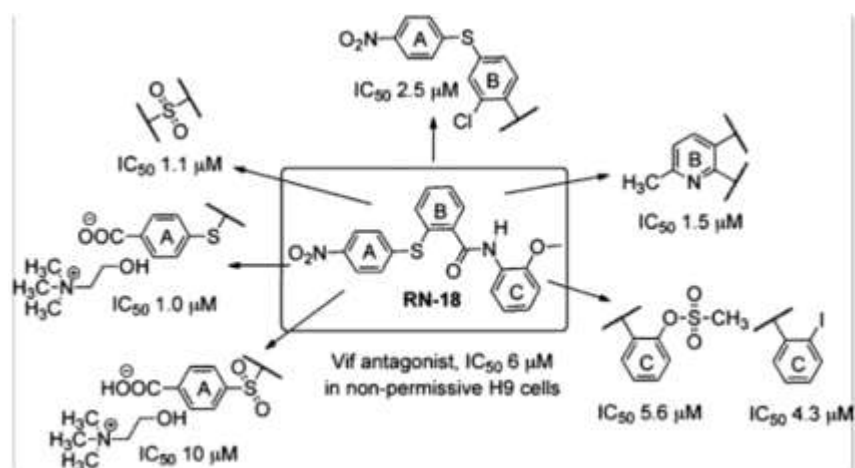


Figure 2 :SAR and lead optimization of HIV-APOBEC3G Axis inhibitor

Ring C: It is preferable to have a methyl at R1. Good activity was demonstrated by the analogues of 2-iodo (4g) and methanesulfonate (4i); methyl carboxylate (4f) at R2 also maintained action.

Bridge A-B: Other linkers (CH₂ extension, amide, and urea) decreased efficacy, while sulfone (5) demonstrated five times the activity of sulfide (1).

Ring B: Methyl at position 6 (8b) increased activity, while pyridine analogues (8a, 8b) were well tolerated. During S-arylation, a novel and surprising reaction was noted.

Ring B/Bridge A-B Position: Strong analogue 11 was produced by switching the thioether attachment to para on ring B with an ortho chloro group. Compounds were rendered inactive by employing methyl/benzyl moieties or by removing ring A and bridge A-B (12).

Ring A: The water-soluble choline carboxylate (17) shown strong antiviral action, but carboxylic acid and methyl carboxylate on ring A did not. Additionally active was its oxidized sulfone analog (19).

Additional SAR concentrated on:

Ring A has a nitro group, and bridges A-B are made of sulfone. Methylene 4-mercaptobenzoate,

CuI, K₂CO₃, SOCl₂, o-anisidine, Et₃N, KMnO₄/MnO₂, (CH₃)₃SnOH, and choline base were among the synthesis-related reagents.^[16]

ADME

Table 1 : Propertis and their Definitions

Terms	Requirement
Potency	Strength the innate ability of a substance to produce the intended pharmacological action.
Bioavailability	The ability of a compound to pass through multiples barriers, such as the GI tract and the liver in order to reach the target
T _{1/2}	The ability of a substance to remain in the bloodstream long enough to provide a notable pharmacological effect.
Safety	In order to develop an appropriate therapeutic index, the chemical must demonstrate adequate selectivity for its intended therapeutic action while limiting unwanted consequences.
P. Acceptability	Among other pertinent qualities, the compound should have the following suitable pharmaceutical properties: a feasible synthesis pathway, adequate water solubility, a satisfactory rate of dissolution, and strong chemical stability.



Figure 3: Diagram illustrating the iterative process of lead optimization that results in a candidate.

AI Machine Learning :

Quantitative structure-activity relationship (QSAR) models are frequently created using machine learning (ML) methods, which may identify mathematical relationships between chemical characteristics and the relationship between chemical activity and property can be classified as either categorical (active, inactive, toxic, nontoxic, etc.).^[11]

Conventional Approaches against AI-Powered Lead Optimization:

Traditional drug lead optimization utilizes empirical methods and is sluggish and resource-intensive, yet it works well for medications like statins and aspirin. This is being changed by AI-driven strategies that use machine learning and computational methods to speed up drug discovery. Large datasets are analyzed by these techniques in order to forecast good candidates and even suggest new chemical structures. Through virtual screening and QSAR modeling, artificial intelligence greatly broadens the scope of chemical space exploration. It lessens the need for experimental validation by assisting in the prediction of important characteristics like binding affinity and ADMET. AI also provides scalability and automation, which facilitates better decision-making and lowers expenses. Lead discovery, optimization, and even re-identifying therapeutic

prospects are being successfully accomplished with the help of tools such as BIOVIA Generative Therapeutics Design (GTD). Enhancing molecular attributes such as drug-likeness and solubility is a strong suit for the Query-based molecular Optimization (QMO) framework.

Enhancing molecular attributes such as drug-likeness and solubility is a strong suit for the Query-based molecular Optimization (QMO) framework. Through protein structure prediction and the creation of new compounds, the combination of AlphaFold2 and Chemistry42 has proved crucial in the discovery of new inhibitors.^[31]

ML:

These scoring functions (SFs) are evaluated using benchmarks such as the PDBbind datasets (CASF-2007, 2013, 2016), where the main metric is the Pearson correlation coefficient (R_p). Deep Neural Networks (DNNs), like DLSCORE, have been developed, and they achieve high R_p values by using a variety of descriptors. Other CNN-based SFs, like Pafnucy, and graph CNN-based SFs, like PotentialNet, offer advantages by directly generating features from crystal structures, avoiding manual feature engineering. Machine learning (ML) techniques, such as Random Forest (RF) and Gradient Boosting Decision Tree (GBDT), consistently outperform classical SFs.

Hybrid SFs, which combine features from multiple SFs or integrate ML algorithms, frequently exhibit improved predictive performance. Newer SFs, like Δ vinaXGB and FFT-BP incorporate

To improve accuracy, more sophisticated elements like explicit water molecules and protein stiffness changes are incorporated into newer SFs like Δ vinaXGB and FFT-BP. Calibration on docked poses can further correct the relatively minimal influence of pose generating mistake on SF performance. Importantly, compared to classical SFs, ML-based SFs show better performance with more training data, underscoring the need of expanding datasets for future developments. [32]

CASE STUDIES :

Four Takeaways from an Effective Lead Optimization Case Study

1. A realistic picture of model performance and builds is provided by regular time-based and series-level evaluation ml models can be trusted to be used as a tool during the design process.
2. The best model is due to training using a combination of "local" program data and "global" curated data performance
3. As a program transitions into a new chemical space, frequent model retraining enables ml models to learn local sar. and faced cliffs in activity
4. In order to have the most possible influence on the design process, ml models ought to be interactive, interpretable, and linked with additional tools [29]

GPCR :

Case Study 1: Identification of specific 5-HT_{2C} agonists to treat metabolic diseases

Case study 2: Fighting obesity with a sugar-based library

Case study 3: Identification of strong and specific antagonists of the OX₂ receptor^[14]

The first step in target-based treatments is to identify a crucial enzyme or pathway that is ideally unique to the parasite. Following the creation of a biochemical assay in vitro, an HTS (high-throughput screen) can be used to determine which chemicals are hit.^[4]

Toxic effects of lead:

Lead poisoning rarely manifests as traditional colic and constipation in affluent nations; instead, patients frequently have vague symptoms including exhaustion, joint and muscle pain, and stomach discomfort.

1. Neurological
2. Biochemical and haematological: Inhibits sulphydryl dependent enzymes
3. Renal : Chronic renal failure and interstitial nephritis are brought on by prolonged exposure to lead. Proximal tubular formation may result from acute, severe lead exposure. dysfunction accompanied by aminoaciduria, hyperphosphaturia, and glycosuria

Treatment : use of chelating agents polyaminocarboxylic acids, of which sodium calcium edetate (EDTA) is particularly effective for lead poisoning [6]

FUTURE DIRECTION :

Present achievements and future directions

Although automation and task consolidation are the main goals of workflow optimization in the imaging department, several additional aspects should be taken into account, such as the stochastic



task characteristics, human resource availability, and the particular technology being used. Workflow software, fully integrated electronic medical records, and macro-level data consolidation fueled by multi-facility networks aiming for financial and operational savings will be the main sources of future productivity increases.^[2] The foundation of the combinatorial optimization model is the idea that resources and activities, like people, machines, and airplanes, are often indivisible in real-world scenarios.

Impact of Formulation: The time required to identify an optimal solution is greatly influenced by the mathematical formulation of a combinatorial optimization issue.

LP Relaxation: Although LP relaxation is a popular approximation that eliminates integrality constraints, its solution may differ significantly from the actual integer answer.

"Good" Formulation Strategies: A "good" formulation could include prioritizing identical objects, disaggregating limitations, adding limits (cutting planes), or raising variables or constraints.

Tight Bounds Are Important: Since loose bounds result in bigger coefficients and weaker LP relaxations, it is imperative to provide tight bounds for variables.

Automatic Reformulation: Most software packages now incorporate "automatic" reformulation or preprocessing processes to enhance solvability because of the crucial role that formulation plays.^[24]

AL is mostly utilized for compound screening, but it can also be used to optimize hits that are found, which is a field that is ideal for investigation.^[12]

RESULT

The repeated drug development process known as "lead optimization" improves "hit" molecules for safety, ADME, and potency. For directing chemical alterations, computational techniques like as molecular dynamics and virtual screening are essential, as is Structure-Activity Relationship (SAR) analysis. This method is being revolutionized by AI/ML tools, which improve property predictions and speed up chemical space research. Finding a substance that is appropriate for use in pharmaceuticals and has the best possible balance between safety and efficacy is the ultimate objective.

DISCUSSION

Lead optimization is changing dramatically, shifting from time-consuming empirical techniques to more complex computational and AI/ML-driven methodologies. Virtual screening and molecular dynamics now provide previously unheard-of efficiency and insight into molecular interactions, even though conventional methods like SAR and experimental tests are still essential. Despite persistent issues with data quality and model accuracy, the incorporation of AI/ML, especially in generative design and predictive modeling, promises to significantly speed up the development of drug candidates with optimal potency, ADME, and safety profiles. In order to navigate the diverse chemical landscape and provide effective medicines more quickly, this synergistic strategy is crucial.

ACKNOWLEDGMENT

The authors would like to express their gratitude to Prof. A. R. Shitole, Principal of the Delonix Society Baramati College of Pharmacy, for his unwavering support during the writing of this work, as well as to the college for its excellent facilities.



REFERENCES

1. Priyadarshini V, Pradhan D, Munikumar M, Umamaheswari A, Rajasekhar D, Srinivasa Rao PV. Docking and molecular dynamic simulations of *Legionella pneumophila* MurB reductase for potential inhibitor design. *Biochem & Anal Biochem*. 2011;1(101):2161-1009.
2. Ghose AK, Herbertz T, Hudkins RL, Dorsey BD, Mallamo JP. Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. *ACS chemical neuroscience*. 2012 Jan 18;3(1):50-68.
3. Jorgensen WL. Efficient drug lead discovery and optimization. *Accounts of chemical research*. 2009 Jun 16;42(6):724-33.
4. Bolstad ES, Anderson AC. In pursuit of virtual lead optimization: the role of the receptor structure and ensembles in accurate docking. *Proteins: Structure, Function, and Bioinformatics*. 2008 Nov 15;73(3):566-80.
5. Lionta E, Spyrou G, K Vassilatis D, Cournia Z. Structure-based virtual screening for drug discovery: principles, applications and recent advances. *Current topics in medicinal chemistry*. 2014 Aug 1;14(16):1923-38.
6. Guimarães CR, Cardozo M. MM-GB/SA rescoring of docking poses in structure-based lead optimization. *Journal of chemical information and modeling*. 2008 May 27;48(5):958-70.
7. Singh R, Pandey PN. Molecular docking and molecular dynamics study on SmHDAC1 to identify potential lead compounds against Schistosomiasis. *Molecular biology reports*. 2015 Mar;42(3):689-98.
8. Singh J, Ator MA, Jaeger EP, Allen MP, Whipple DA, Solowey JE, Chowdhary S, Treasurywala AM. Application of genetic algorithms to combinatorial synthesis: A computational approach to lead identification and lead optimization. *Journal of the American Chemical Society*. 1996 Feb 21;118(7):1669-76.
9. Bleicher LS, van Daelen T, Honeycutt JD, Hassan M, Chandrasekhar J, Shirley W, Tsui V, Schmitz U. Enhanced utility of AI/ML methods during lead optimization by inclusion of 3D ligand information. *Frontiers in Drug Discovery*. 2022 Dec 19;2:1074797.
10. Liu S, Wu Y, Lin T, Abel R, Redmann JP, Summa CM, Jaber VR, Lim NM, Mobley DL. Lead optimization mapper: automating free energy calculations for lead optimization. *Journal of computer-aided molecular design*. 2013 Sep;27(9):755-70.
11. Hessler G, Baringhaus KH. Artificial intelligence in drug design. *Molecules*. 2018 Oct 2;23(10):2520.
12. de Souza Neto LR, Moreira-Filho JT, Neves BJ, Maidana RL, Guimarães AC, Furnham N, Andrade CH, Silva Jr FP. In silico strategies to support fragment-to-lead optimization in drug discovery. *Frontiers in chemistry*. 2020 Feb 18;8:93.
13. Deng J, Yang Z, Ojima I, Samaras D, Wang F. Artificial intelligence in drug discovery: applications and techniques. *Briefings in Bioinformatics*. 2022 Jan 17;23(1).
14. Crucitti D, Pérez Míguez C, Díaz Arias JÁ, Fernandez Prada DB, Mosquera Orgueira A. De novo drug design through artificial intelligence: an introduction. *Frontiers in hematology*. 2024 Jan 25;3:1305741.
15. Mohammed I, Parai MK, Jiang X, Sharova N, Singh G, Stevenson M, Rana TM. SAR and lead optimization of an HIV-1 Vif-APOBEC3G axis inhibitor. *ACS medicinal chemistry letters*. 2012 Jun 14;3(6):465-9.
16. Niazi SK, Mariam Z, Magoola M. Optimizing lead compounds: the role of artificial intelligence in drug discovery.



17. Li H, Sze KH, Lu G, Ballester PJ. Machine-learning scoring functions for structure-based drug lead optimization. *Wiley Interdisciplinary Reviews: Computational Molecular Science*. 2020 Sep;10(5):e1465.
18. Rich AS, Chan YH, Birnbaum B, Haider K, Haimson J, Hale M, Han Y, Hickman W, Hoeflich KP, Ortwine D, Ozen A. Machine Learning ADME Models in Practice: Four Guidelines from a Successful Lead Optimization Case Study. *ACS Medicinal Chemistry Letters*. 2024 Jul 25;15(8):1169-73.
19. Heifetz A, James T, Morao I, Bodkin MJ, Biggin PC. Guiding lead optimization with GPCR structure modeling and molecular dynamics. *Current opinion in pharmacology*. 2016 Oct 1;30:14-21.
20. K Chatterjee A, KS Yeung B. Back to the future: lessons learned in modern target-based and whole-cell lead optimization of antimalarials. *Current topics in medicinal chemistry*. 2012 Mar 1;12(5):473-83.
21. Gordon JN, Taylor A, Bennett PN. Lead poisoning: case studies. *British journal of clinical pharmacology*. 2002 May;53(5):451.
22. Reiner B, Siegel E, Carrino JA. Workflow optimization: current trends and future directions. *Journal of Digital Imaging*. 2002 Sep;15(3):141-52.
23. Hoffman KL. Combinatorial optimization: Current successes and directions for the future. *Journal of computational and applied mathematics*. 2000 Dec 1;124(1-2):341-60.
24. Deng J, Yang Z, Ojima I, Samaras D, Wang F. Artificial intelligence in drug discovery: applications and techniques. *Briefings in Bioinformatics*. 2022 Jan 17;23(1).
25. Afshar A, Dolabi HZ. Multi-objective optimization of time-cost-safety using genetic algorithm. *International journal of optimization in civil engineering*. 2014 Jan 1;4(4):433-50.
26. Zhang O, Lin H, Zhang H, Zhao H, Huang Y, Hsieh CY, Pan P, Hou T. Deep lead optimization: leveraging generative AI for structural modification. *Journal of the American Chemical Society*. 2024 Nov 5;146(46):31357-70.
27. Dartois V, Barry 3rd CE. A medicinal chemists' guide to the unique difficulties of lead optimization for tuberculosis. *Bioorganic & medicinal chemistry letters*. 2013 Sep 1;23(17):4741-50.
28. Hoffer L, Voitovich YV, Raux B, Carrasco K, Muller C, Fedorov AY, Derviaux C, Amouric A, Betzi S, Horvath D, Varnek A. Integrated strategy for lead optimization based on fragment growing: the diversity-oriented-target-focused-synthesis approach. *Journal of medicinal chemistry*. 2018 Jun 8;61(13):5719-32.
29. Lavecchia MJ, De La Bellacasa RP, Borrell JI, Cavasotto CN. Investigating molecular dynamics-guided lead optimization of EGFR inhibitors. *Bioorganic & Medicinal Chemistry*. 2016 Feb 15;24(4):768-78.
30. Cheng KC, Korfmacher WA, White RE, Njoroge FG. Lead optimization in discovery drug metabolism and pharmacokinetics/case study: the hepatitis C virus (HCV) protease inhibitor SCH 503034. *Perspectives in Medicinal Chemistry*. 2007 Jan;1:1177391X0700100001.

HOW TO CITE: S. D. Chavan, D. D. Chede, A. R. Shitole, Lead Optimization: Integrating Experimental, Computational, and AI/ML Approaches, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 8, 309-319. <https://doi.org/10.5281/zenodo.16737592>

