JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Artificial Intelligence in the Discovery and Optimization of Carboxamide-Containing Therapeutic Agents: A Theoretical and Comprehensive Review

Sushil Eknathrao Jamale[1*]

[1*] Department of Chemistry, S M D Mohekar Mahavidyalaya, Kalamb, Dharashiv, Maharashtra, India.

Abstract : The integration of artificial intelligence (AI) into drug discovery has revolutionized the identification and optimization of therapeutic agents, with carboxamide-containing compounds representing a particularly fruitful class for AI-assisted design. This review comprehensively examines the theoretical foundations and practical applications of AI methodologies in the discovery and optimization of carboxamide-based therapeutics. We explore the evolution from traditional computer-aided drug design to contemporary AI-driven approaches, highlighting key machine learning algorithms including quantitative structure-activity relationship models, support vector machines, artificial neural networks, and generative architectures. The review systematically analyses case studies across multiple therapeutic areas—oncology, infectious diseases, and inflammatory disorders—where AI has successfully facilitated the discovery of novel carboxamide derivatives. Particular attention is given to optimization strategies encompassing pharmacokinetic property prediction, toxicity assessment, and synthetic feasibility. Finally, we discuss current challenges, including data quality issues and model interpretability, while projecting future directions at the intersection of AI and carboxamide medicinal chemistry

Keywords: artificial intelligence, machine learning, carboxamide derivatives, drug discovery, QSAR, neural networks, computer-aided drug design

1. Introduction

The carboxamide functional group (-$CONH_2$) represents one of the most ubiquitous and versatile motifs in medicinal chemistry, appearing in numerous approved drugs and clinical candidates across diverse therapeutic indications. From anticancer agents to antibiotics and anti-inflammatory drugs, the carboxamide moiety contributes critically to target binding, metabolic stability, and pharmacokinetic profiles. The discovery and optimization of carboxamide-containing therapeutic agents have traditionally relied on medicinal chemistry expertise, structure-activity relationship (SAR) exploration, and high-throughput screening—approaches that are time-consuming, resource-intensive, and increasingly insufficient to address the growing demand for novel therapeutics [1].

In parallel, the past decade has witnessed an exponential acceleration in the application of artificial intelligence (AI) to pharmaceutical research and development. What began as computer-aided drug design (CADD) has evolved into a sophisticated ecosystem of machine learning (ML), deep learning (DL), and generative AI that is fundamentally reshaping how we discover new medicines [2]. As noted by Ferreira and Carneiro, "AI-driven drug discovery has transitioned from theoretical possibility to practical reality, with multiple AI-discovered molecules now entering clinical trials" [3].

This convergence—between the chemical richness of carboxamide-containing compounds and the computational power of AI—presents unique opportunities and challenges. Carboxamides exhibit structural diversity, predictable hydrogen-bonding patterns, and tuneable physicochemical properties that make them particularly amenable to computational modelling [4]. Simultaneously, the availability of large datasets on carboxamide bioactivity, coupled with advances in algorithm development, enables increasingly accurate predictions of biological activity and drug-like properties [5].

This review aims to provide a comprehensive examination of how AI technologies are being applied to discover and optimize carboxamide-containing therapeutic agents. We begin with a theoretical overview of AI methodologies relevant to drug discovery, followed by a systematic analysis of their application to carboxamide compounds across major therapeutic areas. We then explore optimization strategies, discuss current limitations, and offer perspectives on future directions. By synthesizing recent literature and case studies, we seek to provide medicinal chemists, computational scientists, and pharmaceutical researchers with an integrated understanding of this rapidly evolving field.

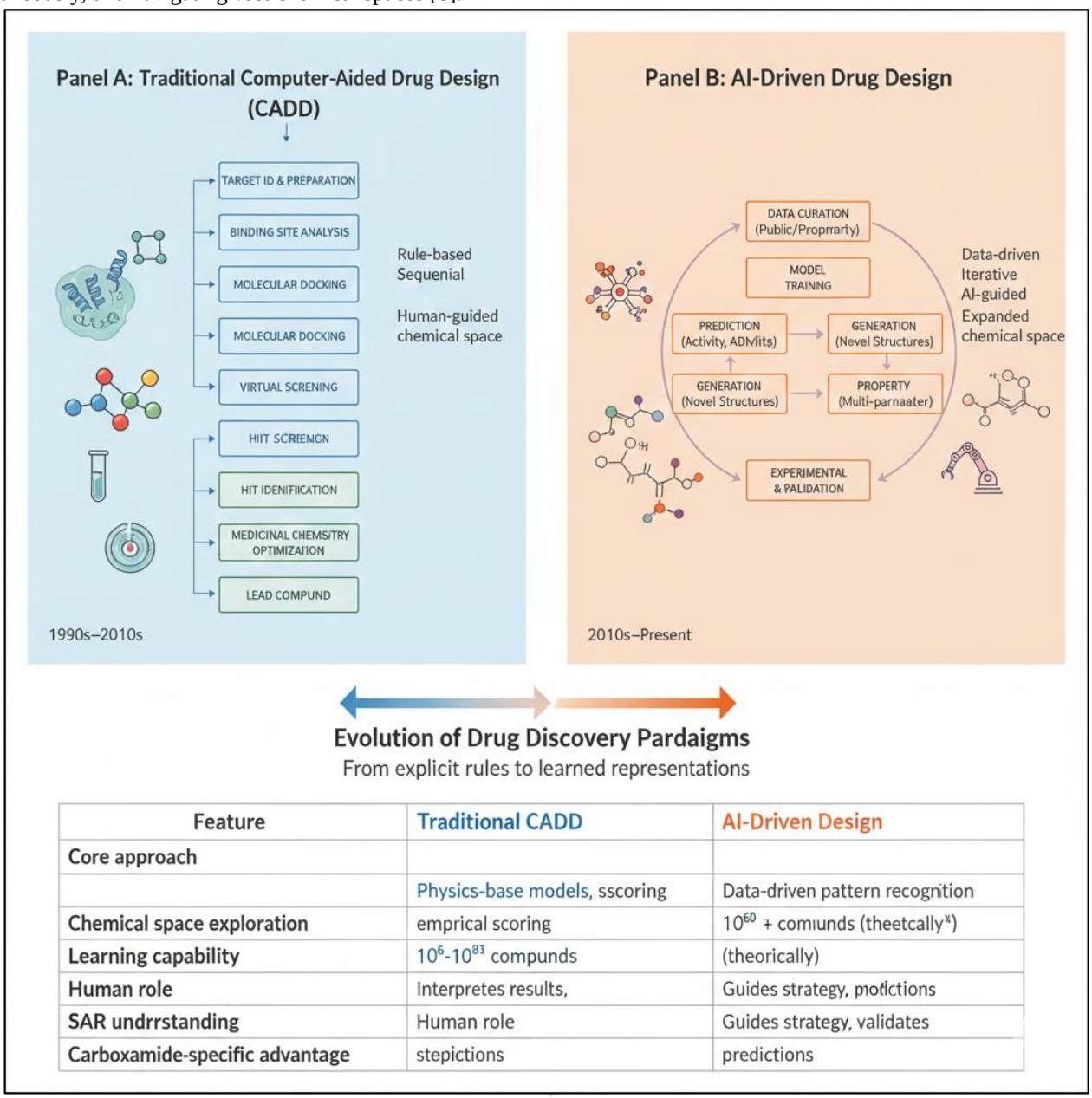
2. AI Methodologies in Drug Discovery: A Theoretical Framework

2.1 From Computer-Aided to Artificial Intelligence-Driven Design

The journey from traditional CADD to contemporary AI-driven drug design represents a paradigm shift in pharmaceutical research. Classical CADD approaches—including molecular docking, pharmacophore modelling, and molecular dynamics simulations—remain valuable tools but are inherently limited by their reliance on pre-defined rules, force fields, and human expertise

[4]. These methods, while powerful, often struggle to capture the complex, non-linear relationships between chemical structure and biological activity [6].

Wang and colleagues have articulated this evolution, noting that "AI drug design differs fundamentally from traditional CADD in its ability to learn directly from data, identify patterns imperceptible to human observers, and generate novel chemical entities without explicit programming of chemical rules" [7]. This learning capability enables AI approaches to address problems that resist analytical solutions, including predicting protein-ligand interactions, optimizing multiple pharmacokinetic parameters simultaneously, and navigating vast chemical spaces [8].



Feature	Traditional CADD	AI-Driven Design
Core approach		
	Physics-base models, sscoring	Data-driven pattern recognition
Chemical space exploration	emprical scoring	10^{60} + comiunds (theetcally[x])
Learning capability	10^{6}-10^{83} compunds	(theorically)
Human role	Interpretes results,	Guides strategy, mofictions
SAR undrrstanding	Human role	Guides strategy, validates
Carboxamide-specific advantage	stepictions	predictions

Figure 1: From Computer-Aided to AI-Driven Drug Design: A Paradigm Shift

2.2 Key Machine Learning Paradigms

2.2.1 Supervised Learning: QSAR and Beyond

Quantitative structure-activity relationship (QSAR) modelling represents the most established application of machine learning to drug discovery [9]. Traditional QSAR relied on linear regression and partial least squares, but contemporary approaches employ diverse algorithms including random forests, support vector machines (SVM), and gradient boosting machines [10]. These methods learn from datasets of compounds with known activities to predict the properties of novel molecules [11].

The theoretical foundation of QSAR lies in the similarity principle—structurally similar compounds tend to exhibit similar biological activities. Machine learning enhances this principle by identifying complex, non-linear relationships between molecular descriptors and activities that would escape traditional statistical methods [12]. For carboxamide-containing compounds, where subtle substitutions can dramatically alter activity, this capability is particularly valuable.

2.2.2 Unsupervised Learning and Chemical Space Exploration

Unsupervised learning methods, including principal component analysis, t-distributed stochastic neighbour embedding (t-SNE), and variational autoencoders, enable exploration of chemical space without requiring labelled activity data [13]. These approaches can identify structural patterns, cluster compounds by similarity, and reveal relationships that inform rational design [14]. For carboxamide libraries, unsupervised learning facilitates navigation of diversity-oriented synthesis spaces and identification of underrepresented chemotypes.

2.2.3 Deep Learning and Neural Networks

Deep learning, characterized by multi-layered neural networks, has emerged as a particularly powerful approach for drug discovery [15]. Convolutional neural networks (CNNs) excel at processing graph-based representations of molecular structures, while recurrent neural networks (RNNs) and transformers can generate novel chemical structures [16]. Gupta and colleagues emphasize that "deep learning architectures can automatically extract relevant features from raw molecular representations, eliminating the need for hand-crafted descriptors and potentially discovering new structural determinants of activity" [12].

Artificial neural networks (ANNs), the foundation of deep learning, have been applied extensively to carboxamide optimization. These networks consist of interconnected nodes organized in layers, with each connection weighted and adjusted during training. The ability of ANNs to approximate any continuous function makes them exceptionally suited for modelling complex SAR [17].

2.2.4 Generative Models for de Novo Design

Perhaps the most transformative AI application in drug discovery is generative modelling—algorithms that create novel chemical structures rather than merely predicting properties of existing ones [18]. Variational autoencoders (VAEs), generative adversarial networks (GANs), and flow-based models can generate molecules with desired properties by learning the underlying distribution of chemical space [7].

For carboxamide-containing compounds, generative models offer the ability to propose novel scaffolds while maintaining the essential pharmacophoric features of the carboxamide group. These approaches can explore regions of chemical space that medicinal chemists might overlook, potentially leading to breakthrough discoveries.

Table 1 summarizes the principal AI and machine learning paradigms currently applied in carboxamide-based drug discovery, highlighting their typical applications, advantages, and limitations.

Table 1: Key Machine Learning Algorithms in Carboxamide Drug Discovery

AI/ML Paradigm	Algorithms / Techniques	Application in Carboxamide Discovery	Key Advantage	References
Supervised Learning	QSAR, Random Forest, SVM	Predict biological activity, SAR modelling	High accuracy with labelled data	9–12
Unsupervised Learning	PCA, t-SNE, Clustering	Explore chemical space, scaffold clustering	Reveals structural patterns without labels	13–14
Deep Learning	ANN, CNN, RNN, Transformers	Feature extraction, activity prediction, de novo design	Learns complex, non-linear relationships	12,15–16
Generative Models	VAE, GAN	Novel scaffold generation, lead optimization	Creates new molecules maintaining pharmacophoric features	7,18

2.3 Data Resources and Representation

The performance of AI models depends critically on the quality, quantity, and representation of training data [5]. Public databases including ChEMBL, PubChem, and the Protein Data Bank provide extensive bioactivity data for carboxamide compounds [19]. Molecular representation—how chemical structures are encoded for machine learning—significantly impacts model performance. Common representations include molecular fingerprints (e.g., Morgan fingerprints, MACCS keys), graph-based representations, and SMILES strings [13]. Each representation captures different aspects of molecular structure, and the choice depends on the specific application.

3. Carboxamides in Medicinal Chemistry: Structural and Therapeutic Significance

3.1 Chemical and Structural Features

The carboxamide group (-$CONH_2$) and its substituted derivatives (-CONHR, -$CONR_2$) possess unique physicochemical properties that explain their prevalence in drug molecules [4]. The amide bond exhibits partial double-bond character due to resonance between the carbonyl and nitrogen lone pair, resulting in planar geometry and restricted rotation. This conformational constraint can pre-organize molecules for target binding, reducing entropic penalties upon interaction with proteins.

The hydrogen-bonding capacity of carboxamides is particularly significant for molecular recognition. The carbonyl oxygen serves as a hydrogen bond acceptor, while the amide protons (when present) act as donors. This dual functionality enables carboxamides to participate in networks of interactions with protein backbone and side chain atoms. Furthermore, the moderate polarity of the carboxamide group (LogP contribution approximately -1 to -2) contributes to favourable solubility while maintaining membrane permeability.

Figure 2 summarizes the key structural features and interaction capabilities of the carboxamide group that underpin its prevalence in therapeutic agents and its amenability to AI-driven design

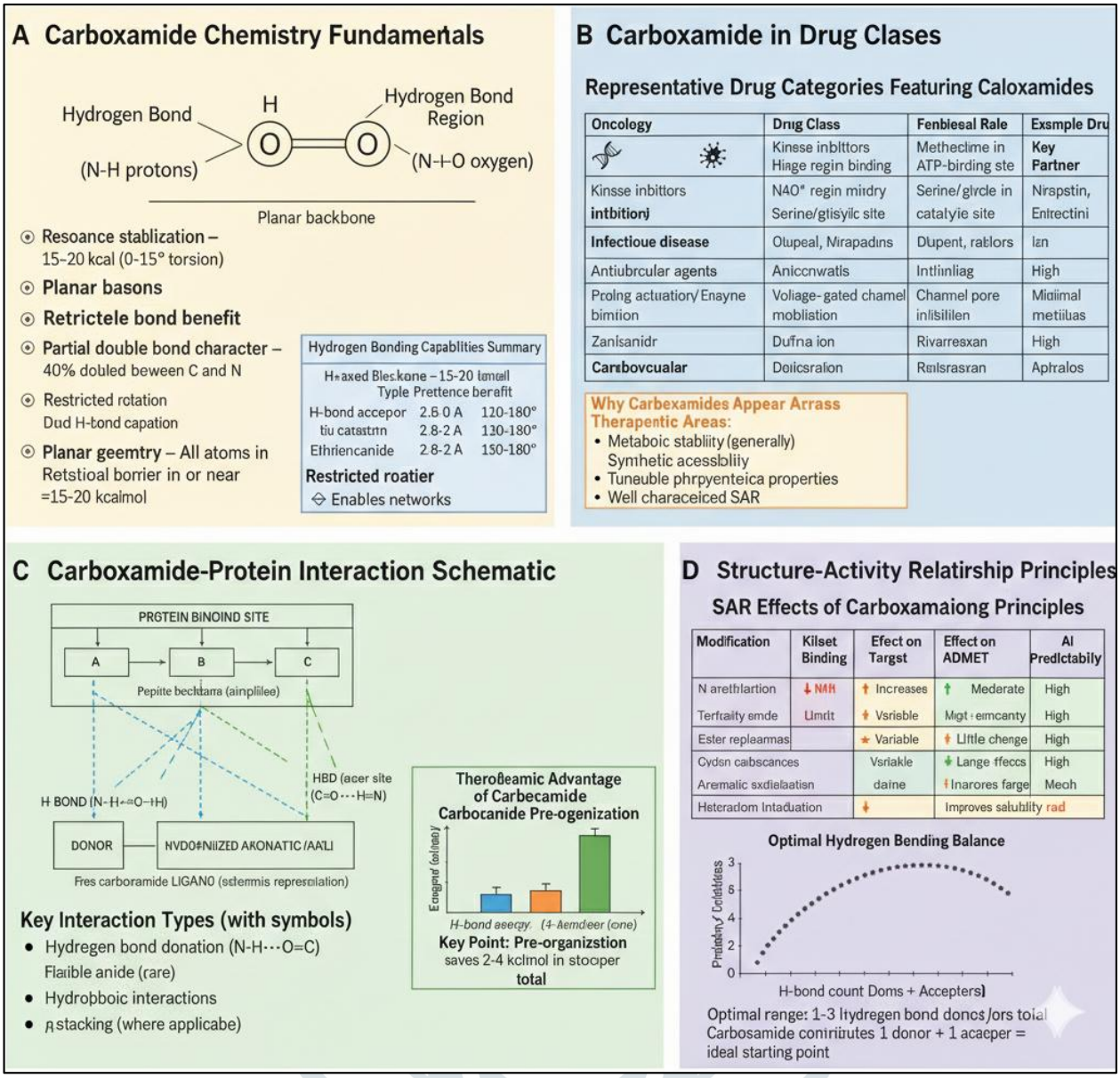


Figure 2. Structural and Functional Features of the Carboxamide Group in Drug-Target Interactions. Schematic overview of carboxamide chemistry and its role in therapeutic agents. **(A)** Carboxamide fundamentals illustrating hydrogen bond donor (N-H) and acceptor (C=O) regions, planar geometry, resonance stabilization, and restricted rotation. These features collectively enable predictable, high-affinity protein interactions. **(B)** Representative therapeutic categories utilizing carboxamide-containing drugs, including oncology (kinase inhibitors, PARP inhibitors), infectious diseases (antitubercular agents, antivirals), CNS disorders (anticonvulsants), and cardiovascular indications (anticoagulants). The table summarizes carboxamide functional roles and example drugs in each category. **(C)** Schematic protein-carboxamide interaction diagram showing hydrogen bond networks (dashed blue lines) between the carboxamide ligand (bottom) and protein binding site residues (top). Key interaction types include N-H···O=C hydrogen bond donation, C=O···H-N hydrogen bond acceptance, and hydrophobic contacts. The thermodynamic inset illustrates the entropic advantage (2-4 kcal/mol) conferred by carboxamide pre-organization compared to flexible amides. **(D)** Structure-activity relationship principles for carboxamide modifications presented as a heat map showing effects on target binding and ADMET properties. The graph demonstrates the optimal hydrogen bonding balance (1-3 donors/acceptors total) for drug-like molecules, with carboxamides providing an ideal starting point through their dual donor/acceptor capacity.

3.2 Therapeutic Applications

Carboxamide-containing compounds span virtually every therapeutic area. In oncology, drugs including imatinib (a benzamide), gefitinib, and numerous kinase inhibitors incorporate carboxamide motifs that engage critical hydrogen bonds with ATP-binding sites [15]. The PARP inhibitor Olaparib contains a phthalazinone moiety that functions as a cyclic carboxamide, while newer PARP1 inhibitors continue to explore carboxamide-containing scaffolds [20].

Anti-infective agents similarly leverage carboxamide functionality. Isoniazid, a mainstay of tuberculosis treatment for decades, is a simple pyridine carboxamide that undergoes metabolic activation to inhibit mycobacterial cell wall synthesis. More recently, pyrrolidine carboxamides have emerged as potent inhibitors of enoyl-ACP reductase (InhA) in *Mycobacterium tuberculosis* [19].

In neuroscience, carboxamides feature prominently in drugs targeting CNS disorders, leveraging the group's ability to balance polarity for blood-brain barrier penetration. Anticonvulsants, antidepressants, and antipsychotics frequently incorporate carboxamide motifs [16].

The diverse therapeutic relevance of carboxamide-containing compounds is illustrated in **Table 2**, which provides representative drugs, scaffold types, and primary molecular targets across major disease areas.

Table 2: Therapeutic Applications of Carboxamide-Containing Drugs

Therapeutic Area	Representative Drugs	Carboxamide Scaffold Type	Target / Mechanism	References
Oncology	Imatinib, Gefitinib, Olaparib	Benzamide, Phthalazinone	Kinase inhibition, PARP inhibition	15,20
Infectious Diseases	Isoniazid, Pyrrolidine carboxamides	Pyridine, Pyrrolidine	Mycobacterial inhibition (InhA)	19
CNS Disorders	Topiramate, Lamotrigine	Substituted carboxamides	Anticonvulsant, neurotransmitter modulation	16

3.3 Rationale for AI Application

The combination of structural diversity, well-characterized SAR, and therapeutic importance makes carboxamides ideal candidates for AI-assisted discovery [14]. The availability of extensive bioactivity data enables training of predictive models, while the modular nature of carboxamide synthesis facilitates rapid exploration of AI-generated suggestions. Moreover, the predictable hydrogen-bonding patterns of carboxamides simplify the interpretation of AI predictions, partially addressing the "black box" criticism of deep learning approaches.

4. AI in the Discovery of Carboxamide Therapeutics: Case Studies

4.1 Oncology Applications

4.1.1 ALK Inhibitors

Anaplastic lymphoma kinase (ALK) represents a validated target in multiple cancers, particularly non-small cell lung cancer. Zhang and colleagues recently reported a comprehensive AI-driven study of piperidine carboxamide derivatives as ALK inhibitors [22]. Employing 3D-QSAR modelling with Topomer CoMFA, the team developed robust predictive models validated through artificial neural network analysis ($q^2 = 0.597$, $r^2 = 0.939$). The integration of multiple computational approaches—including molecular docking, ADMET prediction, and molecular dynamics simulations—enabled rational design of 60 novel compounds. Notably, the lead compound identified through this workflow exhibited favourable binding interactions and drug-like properties, demonstrating the power of integrated AI approaches for carboxamide optimization.

4.1.2 PARP1 Inhibitors

Poly (ADP-ribose) polymerase 1 (PARP1) inhibitors have transformed the treatment of BRCA-mutant cancers, and thiophene carboxamide scaffolds have emerged as promising chemotypes. Singh and colleagues combined support vector machine classification with pharmacophore-based virtual screening to identify novel PARP1 inhibitors [23]. The integrated SVM model effectively distinguished active from inactive compounds, while pharmacophore filtering ensured identification of molecules with appropriate three-dimensional features for target engagement. This approach identified GK01172, a thiophene carboxamide compound with potential as a new PARP1 inhibitor chemotype, demonstrating how machine learning can complement structure-based methods.

4.1.3 LSD1 Inhibitors for Acute Myeloid Leukaemia

Lysine-specific demethylase 1 (LSD1/KDM1A) has emerged as a therapeutic target in acute myeloid leukaemia (AML). Borrello and colleagues synthesized tranylcypromine analogues containing carboxamide substitutions at the 4-position of the aryl ring [24]. These compounds exhibited potent sub-micromolar LSD1 inhibition and anti-proliferative activity against AML cell lines. While this work predates the most recent AI advances, it established carboxamide-containing scaffolds that subsequent computational studies have exploited. The predictable SAR of these compounds—where carboxamide substitution dramatically improves potency compared to unsubstituted tranylcypromine—exemplifies the type of structure-activity relationships that AI models can learn and exploit.

Additional studies by Borrello and colleagues further explored the synthesis of carboxamide-containing tranylcypromine analogues as LSD1 inhibitors for AML, demonstrating the continued interest in this chemotype [28].

4.2 Infectious Diseases

4.2.1 Antitubercular Agents

Tuberculosis remains a leading cause of infectious disease mortality, and the emergence of multi-drug-resistant strains necessitates novel therapeutic agents. Esmel and colleagues conducted structure-based design of pyrrolidine carboxamide inhibitors of InhA, a validated target in *Mycobacterium tuberculosis* [19]. Building QSAR models that correlated computed Gibbs free energies of complex formation with experimental IC_{50} values ($R^2 = 0.94$), the team generated a virtual combinatorial library exceeding 17 million compounds. Through ADME-focused filtering and pharmacophore screening, they identified candidates with predicted IC_{50} values as low as 5 nM. This work illustrates how computational approaches can efficiently explore enormous chemical spaces to identify promising carboxamide leads.

4.2.2 HPK1 Inhibitors for Immunotherapy

Hematopoietic progenitor kinase 1 (HPK1) has emerged as a target for cancer immunotherapy. Insilco Medicine recently employed their generative AI platform Chemistry42 to discover HPK1 inhibitors with a pyridine-2-carboxamide core [25]. The AI-driven workflow systematically identified and optimized compounds with enhanced potency and selectivity, with iterative design guided by AI models. The resulting candidates demonstrated improved kinase selectivity and pharmacokinetic properties compared to previous inhibitors. This case study exemplifies how generative AI can accelerate the optimization cycle while maintaining focus on developability parameters.

To provide a consolidated view of how diverse AI methodologies have been applied to carboxamide discovery, **Figure 3** presents integrated workflows from the three case studies discussed above. The figure illustrates supervised learning (ALK inhibitors), integrated classification with pharmacophore modeling (PARP1 inhibitors), and generative AI (HPK1 inhibitors) as parallel approaches sharing common data foundations and validation criteria. This comparative visualization highlights both the methodological diversity and the unifying principles that characterize AI-driven carboxamide optimization.

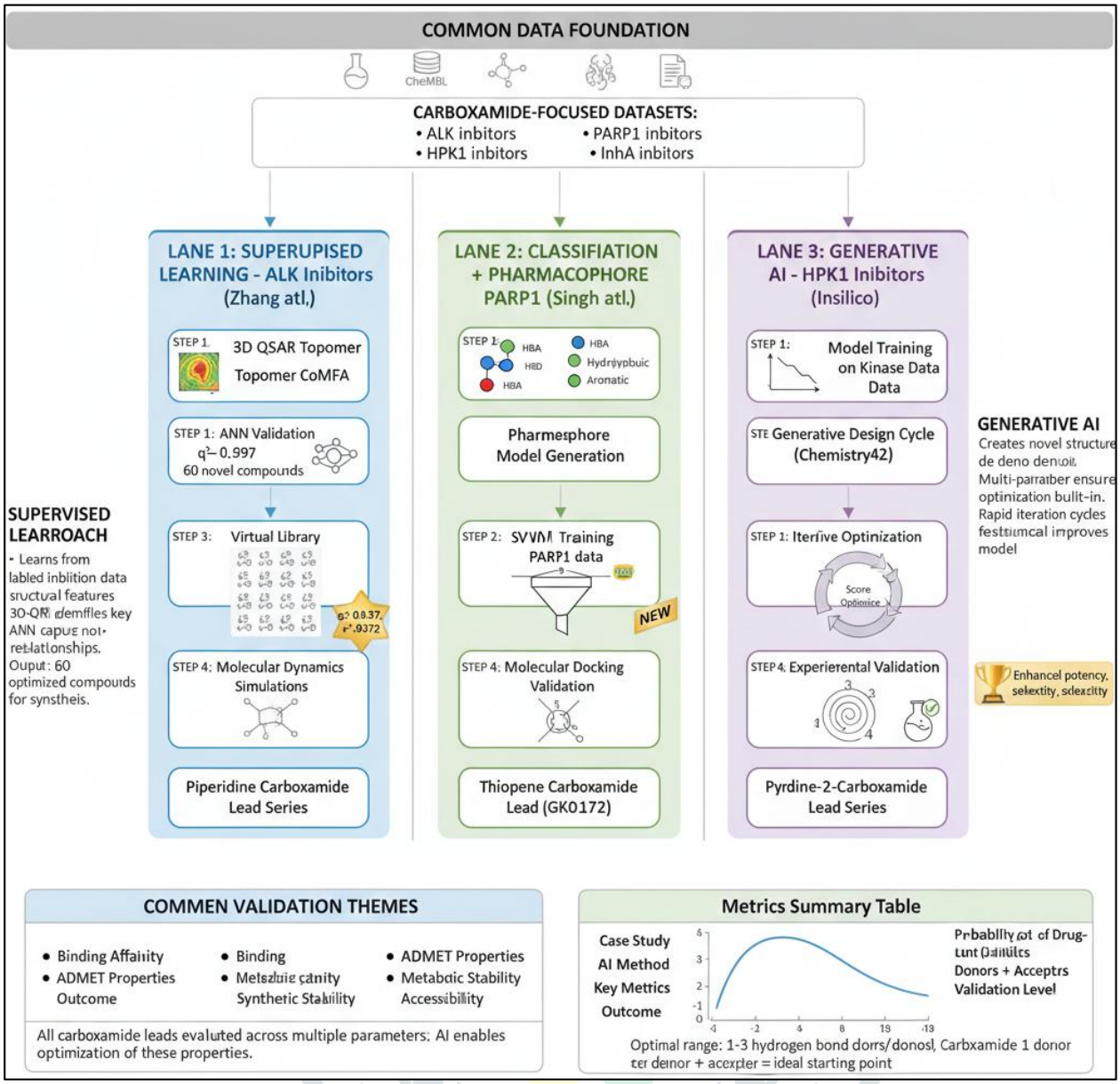


Figure 3: AI-Driven Discovery Workflows for Carboxamide Therapeutics: Case Study Integration

4.3 Anti-inflammatory and Other Applications

The RAGE (receptor for advanced glycation end products) pathway represents a therapeutic target for inflammatory disorders and diabetic complications. Patent literature reveals extensive exploration of carboxamide derivatives as RAGE modulators, with structural diversity encompassing aryl, heteroaryl, and cyclic carboxamides [26]. While much of this work predates modern AI, the structure-activity relationships established provide fertile ground for machine learning applications.

Recent computational studies have explored carboxamide derivatives for prostate cancer treatment. Anber and colleagues synthesized 18 carboxamide derivatives and evaluated their anti-proliferative activity against PC3 prostate cancer cells [27]. Combining quantum chemical calculations, molecular docking against prostate cancer-related proteins (3RUK and 3A99), and ADMET prediction, they identified compounds with significant activity and favourable predicted pharmacokinetics. This integrated experimental-computational approach demonstrates the value of combining multiple AI and computational chemistry techniques.

Table 3 consolidates key AI-driven case studies in carboxamide discovery, detailing the target, AI methodology, main findings, and supporting references.

Table 3: Case Studies: AI-Driven Discovery of Carboxamide Therapeutics

Case Study	Target / Indication	AI Approach	Key Findings	References
Piperidine Carboxamides	ALK inhibitors, NSCLC	3D-QSAR + ANN	Lead with high predicted potency, validated docking	22
Thiophene Carboxamides	PARP1 inhibitors	SVM + Pharmacophore	Novel chemotype identified (GK01172)	23
Pyridine-2-Carboxamides	HPK1 inhibitors, immunotherapy	Generative AI	Enhanced potency & selectivity, optimized ADMET	25
Pyrrolidine Carboxamides	Antitubercular (InhA)	QSAR + Virtual Library	IC_{50} as low as 5 nM, ADME filtering	19

5. AI-Driven Optimization Strategies for Carboxamide Derivatives

5.1 Prediction and Optimization of Pharmacokinetic Properties

Beyond target affinity, successful drugs must exhibit appropriate absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles [18]. AI models have proven remarkably effective at predicting these properties from molecular structure [8]. For carboxamide-containing compounds, particular attention must be paid to metabolic stability, as amide bonds can be susceptible to hydrolysis by peptidases and other hydrolases [14].

Machine learning models trained on large ADMET datasets can predict clearance, half-life, bioavailability, and tissue distribution with sufficient accuracy to guide medicinal chemistry optimization [17]. These models enable simultaneous optimization of potency and pharmacokinetics, addressing a major source of attrition in drug development. For carboxamides, AI predictions can identify compounds where amide hydrolysis may be problematic and suggest structural modifications to enhance metabolic stability.

5.2 Toxicity Prediction

Drug-induced toxicity remains a leading cause of late-stage attrition and post-marketing withdrawals [21]. AI models for toxicity prediction have advanced considerably, with deep learning approaches achieving performance comparable to or exceeding that of in vitro assays for certain endpoints [11]. For carboxamide-containing compounds, particular concerns include potential for bioactivation to reactive intermediates and off-target interactions [3].

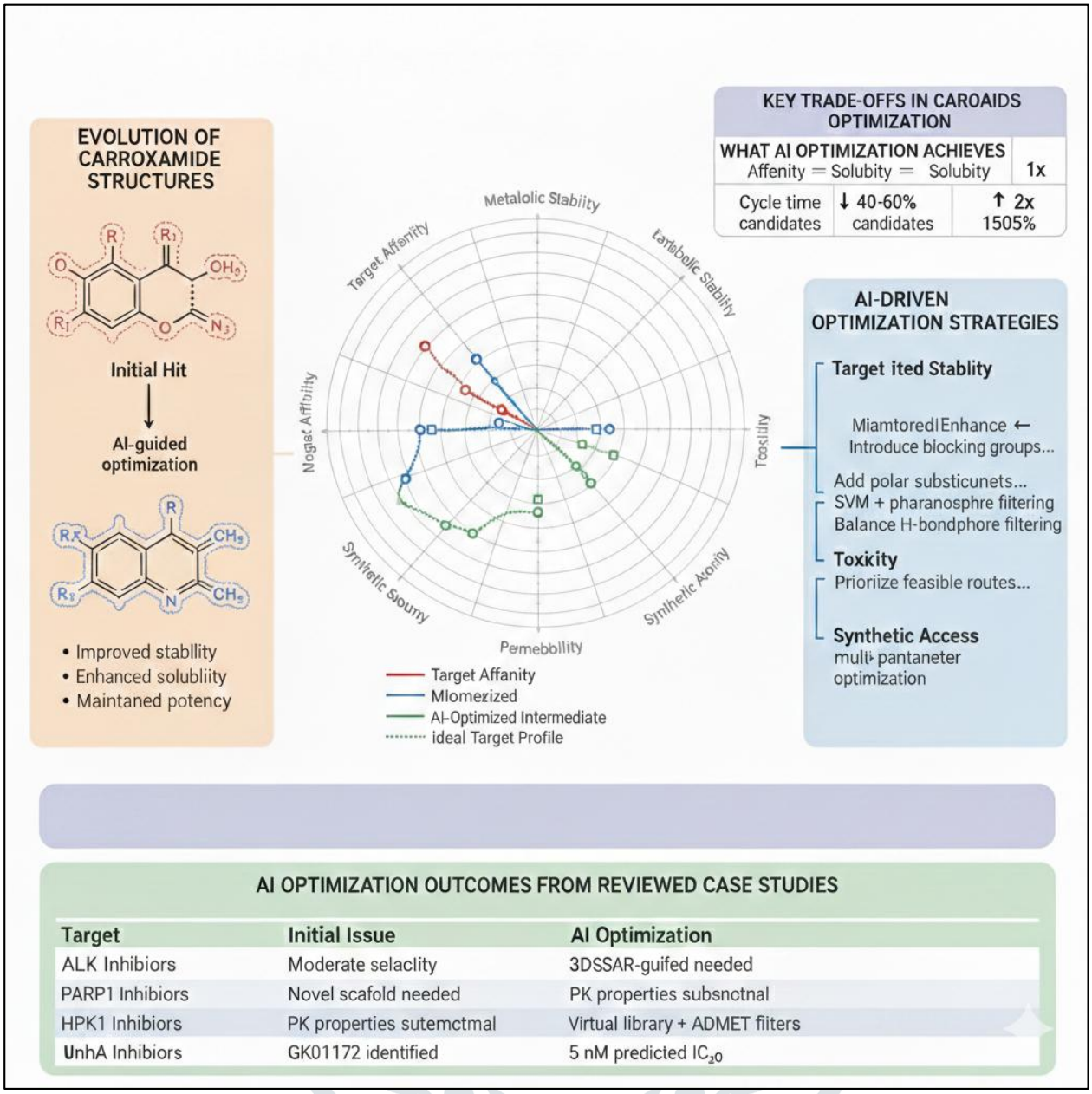
Contemporary AI toxicity models integrate multiple data types, including structural features, in vitro assay data, and in vivo observations, to provide comprehensive safety assessments [10]. These models can flag potential issues early in discovery, enabling medicinal chemists to design out toxicity while maintaining desired pharmacological activity.

5.3 Synthetic Accessibility Assessment

A significant challenge in AI-driven drug discovery is that generative models may propose molecules that are difficult or impossible to synthesize [7]. Synthetic accessibility prediction has therefore become an integral component of AI workflows [20]. Models trained on reaction databases can estimate the feasibility of proposed synthetic routes and suggest alternative, more accessible structures.

For carboxamide derivatives, synthetic accessibility is generally favourable due to well-established amide bond-forming reactions. However, complex substitution patterns or stereochemical requirements may present challenges. AI synthetic accessibility tools can prioritize compounds with favourable synthetic profiles, increasing the likelihood that computational predictions can be experimentally validated [9].

The preceding discussion has examined individual optimization dimensions—pharmacokinetics, toxicity, and synthetic accessibility—that determine the developability of carboxamide candidates. However, in practice, these parameters cannot be optimized in isolation; medicinal chemists must navigate complex trade-offs where improving one property may compromise another. **Figure 4** integrates these dimensions into a unified multi-parameter optimization landscape, comparing typical profiles of initial screening hits, AI-optimized intermediates, and ideal drug candidates. This radar plot visualization demonstrates how AI approaches enable simultaneous optimization across multiple axes, transforming imbalanced hits into balanced leads with improved probability of success. The supporting panels further illustrate the chemical evolution enabled by AI guidance (left), specific optimization strategies for each parameter (right), and outcomes from the case studies reviewed in Section 4 (bottom), providing a comprehensive view of how AI is reshaping carboxamide optimization.



AI OPTIMIZATION OUTCOMES FROM REVIEWED CASE STUDIES

Target	Initial Issue	AI Optimization
ALK Inhibiors	Moderate selaclity	3DSSAR-guifed needed
PARP1 Inhibiors	Novel scafold needed	PK properties subsnotnal
HPK1 Inhibiors	PK properties sutemctmal	Virtual library + ADMET fiiters
UnhA Inhibiors	GK01172 identified	5 nM predicted IC_{20}

6. Challenges and Limitations

6.1 Data Quality and Availability

Despite advances in AI methodologies, the quality and quantity of training data remain fundamental limitations [13]. Public databases contain substantial bioactivity data for carboxamide compounds, but these data are heterogeneous, generated across different assays, laboratories, and conditions [2]. Activity measurements may not be directly comparable, introducing noise that can limit model performance [6].

Furthermore, negative data—compounds tested and found inactive—are substantially underreported in the literature, creating biased datasets that may not accurately represent true structure-activity relationships [1]. Efforts to curate and standardize data, along with initiatives to encourage publication of negative results, are essential to address this limitation.

6.2 Model Interpretability

The "black box" nature of deep learning models presents challenges for medicinal chemists seeking to understand and act upon AI predictions [5]. While a model may accurately predict that a particular carboxamide derivative will be active, it may not reveal *why*—which structural features contribute to activity or what modifications might further improve potency [12].

Techniques for model interpretability, including attention mechanisms, SHAP values, and integrated gradients, are actively being developed and applied to drug discovery [23]. These methods can highlight molecular substructures or physicochemical properties driving predictions, providing insights that guide rational design.

6.3 Generalization to Novel Chemical Space

AI models perform best when predicting properties of compounds similar to those in the training set [24]. Their ability to generalize to truly novel chemical space—particularly scaffolds unlike any seen during training—remains uncertain [19]. For carboxamide discovery, this limitation may restrict the identification of truly innovative chemotypes in favour of incremental optimization of known scaffolds.

Strategies to address this limitation include multi-task learning, which leverages information across multiple endpoints, and active learning, which iteratively selects informative compounds for experimental testing [22]. These approaches can guide exploration of novel chemical space while maintaining model reliability.

7. Future Perspectives

7.1 Integration of AI with Emerging Technologies

The convergence of AI with other transformative technologies promises to accelerate carboxamide discovery [25]. Automated synthesis platforms, coupled with AI design tools, could enable closed-loop discovery cycles where computational predictions are rapidly tested experimentally [27]. High-throughput experimentation generates data that continuously improves AI models, creating virtuous cycles of increasing predictive accuracy.

Cryo-electron microscopy and other structural biology advances are generating high-resolution protein structures at unprecedented rates, providing rich data for structure-based AI approaches [15]. Integration of structural information with ligand-based models may further improve prediction accuracy and provide mechanistic insights.

7.2 Personalized Medicine Applications

As our understanding of disease heterogeneity advances, AI-driven discovery of carboxamide therapeutics will increasingly target patient subpopulations defined by genetic, proteomic, or metabolic biomarkers [16]. Machine learning models can integrate multi-omics data with chemical structure information to predict which patients are most likely to benefit from particular compounds, enabling precision medicine approaches from the earliest stages of discovery.

7.3 Ethical and Regulatory Considerations

The increasing role of AI in drug discovery raises important ethical and regulatory questions [3]. How should regulatory agencies evaluate AI-discovered molecules? What validation standards are appropriate for AI predictions that guide critical development decisions? [14]. Addressing these questions will require dialogue between computational scientists, medicinal chemists, regulators, and ethicists to establish frameworks ensuring that AI accelerates rather than compromises drug development.

8. Conclusion

The application of artificial intelligence to the discovery and optimization of carboxamide-containing therapeutic agents represents a convergence of chemical opportunity and computational capability [26]. Carboxamides, with their structural diversity, favourable properties, and extensive bioactivity data, are ideally suited to AI-driven approaches [21]. From QSAR models predicting ALK inhibition to generative algorithms designing HPK1 inhibitors, AI methodologies are demonstrating tangible impact across multiple therapeutic areas [28].

The case studies reviewed herein illustrate both the power and the current limitations of AI in this domain. When thoughtfully integrated with medicinal chemistry expertise, experimental validation, and an appreciation of data limitations, AI approaches can accelerate discovery, expand explored chemical space, and identify compounds that might otherwise remain undiscovered. The pyrrolidine carboxamide antitubercular agents, piperidine carboxamide ALK inhibitors, and thiophene carboxamide PARP1 inhibitors discussed in this review exemplify the potential of these approaches [19,22,23].

Looking forward, continued advances in algorithms, expansion of high-quality training data, and integration with complementary technologies will further enhance the role of AI in carboxamide discovery [8]. The ultimate measure of success, however, will be the translation of AI-discovered compounds into approved therapies benefiting patients [17]. As the first AI-discovered molecules enter clinical trials, the field stands at an inflection point where theoretical potential meets practical reality [3]. For carboxamide-containing therapeutics, this moment represents both an opportunity and a responsibility to harness AI in service of addressing unmet medical needs.

References

[1] Sahoo, A.; Dar, G. M. A comprehensive review on the application of artificial intelligence in drug discovery. *Appl. Biol. Chem. J.* **2021**, *2* (2), 34-48.

[2] Yang, X.; Wang, Y.; Byrne, R.; Schneider, G.; Yang, S. Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery. *Chem. Rev.* **2019**, *119* (18), 10520-10594.

[3] Ferreira, F. J. N.; Carneiro, A. S. AI-Driven Drug Discovery: A Comprehensive Review. *ACS Omega* **2025**, *10* (23), 23889-23903.

[4] Lee, J. W.; Maria-Solano, M. A.; Vu, T. N. L.; Yoon, S.; Choi, S. Big data and artificial intelligence (AI) methodologies for computer-aided drug design (CADD). *Biochem. Soc. Trans.* **2022**, *50* (1), 241-252.

[5] Niazi, S. K. Artificial Intelligence in Small-Molecule Drug Discovery: A Critical Review of Methods, Applications, and Real-World Outcomes. *Pharmaceuticals* **2025**, *18* (9), 1271.

[6] Zhang, L.; Tan, J.; Han, D.; Zhu, H. From machine learning to deep learning: progress in machine intelligence for rational drug discovery. *Drug Discovery Today* **2017**, *22* (11), 1680-1685.

[7] Wang, K.; Huang, Y.; Wang, Y.; You, Q.; Wang, L. Recent Advances from Computer-Aided Drug Design to Artificial Intelligence Drug Design. *RSC Med. Chem.* **2024**, *15*, 3978–4000.

[8] Zhu, H. Big Data and Artificial Intelligence Modeling for Drug Discovery. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 573-589.

[9] Han, R.; Yoon, H.; Kim, G.; Lee, H.; Lee, Y. Revolutionizing Medicinal Chemistry: The Application of Artificial Intelligence (AI) in Early Drug Discovery. *Pharmaceuticals* **2023**, *16* (9), 1259.

[10] Jarallah, S. J.; Almughem, F. A.; Alhumaid, N. K.; Fayez, N. A.; Alradwan, I.; Alsulami, K. A.; Tawfik, E. A.; Alshehri, A. A. Artificial intelligence revolution in drug discovery: A paradigm shift in pharmaceutical innovation. *Int. J. Pharm.* **2025**, *680*, 125789.

[11] Sarvepalli, S.; Vadarevu, S. Role of artificial intelligence in cancer drug discovery and development. *Cancer Lett.* **2025**, *627*, 217821.

[12] Gupta, R.; Srivastava, D.; Sahu, M.; Tiwari, S.; Ambasta, R. K.; Kumar, P. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. *Mol. Divers.* **2021**, *25* (3), 1315-1360.

[13] Tripathi, M. K.; Nath, A.; Singh, T. P.; Ethayathulla, A. S.; Kaur, P. Evolving scenario of big data and Artificial Intelligence (AI) in drug discovery. *Mol. Divers.* **2021**, *25* (3), 1439-1460.

[14] Tripathi, N.; Goshisht, M. K.; Sahu, S. K.; Arora, C. Applications of artificial intelligence to drug design and discovery in the big data era: a comprehensive review. *Mol. Divers.* **2021**, *25* (3), 1643-1664.

[15] Kashyap, K.; Siddiqi, M. I. Recent trends in artificial intelligence-driven identification and development of anti-neurodegenerative therapeutic agents. *Mol. Divers.* **2021**, *25* (3), 1517-1539.

[16] Pasrija, P.; Jha, P.; Upadhyaya, P.; Khan, M. S.; Chopra, M. Machine Learning and Artificial Intelligence: A Paradigm Shift in Big Data-Driven Drug Design and Discovery. *Curr. Top. Med. Chem.* **2022**, *22* (20), 1692-1727.

[17] Visan, A. I.; Negut, I. Integrating Artificial Intelligence for Drug Discovery in the Context of Revolutionizing Drug Delivery. *Life* **2024**, *14* (2), 233.

[18] Gholap, A. D.; Uddin, M. J.; Faiyazuddin, M.; Omri, A.; Gowri, S.; Khalid, M. Advances in artificial intelligence for drug delivery and development: A comprehensive review. *Comput. Biol. Med.* **2024**, *178*, 108702.

[19] Esmel, A.; Kouassi, A. F.; Megnassan, E.; N'Guessan, Y. T.; Keita, M.; Frecer, V.; Kone, M.; Miertus, S. Computer-Aided Design of Orally Bioavailable Pyrrolidine Carboxamide Inhibitors of Enoyl-Acyl Carrier Protein Reductase of Mycobacterium tuberculosis with Favorable Pharmacokinetic Profiles. *Int. J. Mol. Sci.* **2015**, *16*, 29744-29771.

[20] Noorain; Srivastava, V.; Parveen, B.; Parveen, R. Artificial Intelligence in Drug Formulation and Development: Applications and Future Prospects. *Curr. Drug Metab.* **2023**, *24* (9), 622-634.

[21] Suriyaamporn, P.; Pamornpathomkul, B.; Patrojanasophon, P.; Ngawhirunpat, T.; Rojanarata, T.; Opanasopit, P. The Artificial Intelligence-Powered New Era in Pharmaceutical Research and Development: A Review. *AAPS PharmSciTech* **2024**, *25* (6), 188.

[22] Zhang, Y.-K.; Tong, J.-B.; Luo, M.-X.; Xing, X.-Y.; Yang, Y.-L.; Qing, Z.-P.; Chang, Z.-L.; Zeng, Y.-R. Design and evaluation of piperidine carboxamide derivatives as potent ALK inhibitors through 3D-QSAR modeling, artificial neural network and computational analysis. *Arab. J. Chem.* **2024**, 105863.

[23] Singh, M.; Rajawat, J.; Kuldeep, J.; Shukla, N.; Mishra, D. P.; Siddiqi, M. I. Integrated support vector machine and pharmacophore based virtual screening driven identification of thiophene carboxamide scaffold containing compound as potential PARP1 inhibitor. *J. Biomol. Struct. Dyn.* **2021**, *40*, 8494-8507.

[24] Borrello, M. T.; Benelkebir, H.; Lee, A.; Tam, C. H.; Shafat, M.; Rushworth, S. A.; Bowles, K. M.; Douglas, L.; Duriez, P. J.; Bailey, S.; Crabb, S. J.; Packham, G.; Ganesan, A. Synthesis of Carboxamide-Containing Tranylcypromine Analogues as LSD1 (KDM1A) Inhibitors Targeting Acute Myeloid Leukemia. *ChemMedChem* **2021**, *16* (8), 1316-1324.

[25] Insilico Medicine. Generative AI against diseases: HPK1 inhibitors with pyridine-2-carboxamide core generated by Chemistry42. *Eur. J. Med. Chem.* **2024**.

[26] Carboxamide derivatives as therapeutic agents. Eur. Pat. EP 1377295 A2, 2004.

[27] Anber, A. M.; et al. Synthesis, Biological Evaluation, Antiproliferative Activity, and Computational Insights of Carboxamide Derivatives: A Computational and Experimental Approach. *J. Heterocycl. Chem.* **2025**.

[28] Borrello, T.; Tam, C. H.; Shafat, M.; Rushworth, S.; Bowles, K.; Bailey, S.; Crabb, S.; Packham, G.; Duriez, P. J.; Ganesan, P.; Benelkebir, H.; Douglas, L. Synthesis of Carboxamides Tranylcypromine Analogues as LSD1 (KDM1A) Inhibitors for AML. *ChemRxiv* **2020**.