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Advances in Medicinal Chemistry: Bridging Natural Products and Modern Drug Discovery

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ABSTRACT

Medicinal chemistry has emerged as a dynamic discipline that integrates synthetic chemistry, pharmacology, computational modeling, and systems biology to accelerate drug discovery. Natural products remain indispensable due to their unparalleled structural diversity and biological relevance, serving as scaffolds for modern therapeutics. Recent advances in artificial intelligence (AI), computer-aided drug design (CADD), and ADMET prediction have transformed the evaluation and optimization of natural compounds, reducing attrition rates in clinical trials. Moreover, network pharmacology provides a systems-level framework to understand multi-target interactions, particularly relevant for complex diseases such as cancer and neurodegenerative disorders. This review highlights the synergy between natural product research and modern medicinal chemistry, emphasizing sustainable discovery strategies, computational innovations, and pharmacokinetic modeling. By bridging traditional wisdom with cutting-edge science, medicinal chemistry is positioned to deliver safer, more effective, and personalized therapeutics, marking a paradigm shift in drug discovery and development.

Keywords: Medicinal Chemistry, Natural Products, Drug Discovery, Computational Approaches, ADMET Prediction, Network Pharmacology

INTRODUCTION

Medicinal chemistry has historically been the backbone of drug discovery, combining chemical synthesis with biological evaluation to design molecules that address unmet medical needs. In recent years, the discipline has advanced significantly, with novel molecular entities approved between 2024 and 2025 reflecting precision targeting and sustainable synthesis strategies (Nair & Jain, 2026). Natural products, which have long served as the foundation of medicine, continue to inspire modern drug discovery. Their structural diversity and biological relevance make them indispensable scaffolds for therapeutic innovation, with nearly 10% of global drug approvals between 2014 and 2024 derived from natural sources (Butler et al., 2026).

The integration of computational approaches has revolutionized medicinal chemistry. AI and CADD now enable virtual screening of billions of compounds, accelerating hit identification and lead optimization.

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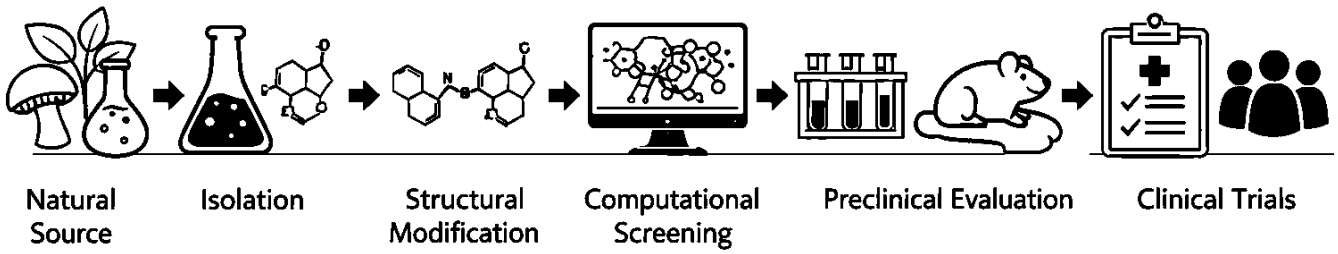

Figure 1. Workflow of natural product drug discovery integrated with medicinal chemistry

These tools complement traditional medicinal chemistry by predicting binding affinities, identifying cryptic pockets, and guiding rational drug design. Such innovations reduce costs and timelines while enhancing the probability of clinical success (Path, 2025).

Furthermore, ADMET prediction and drug-likeness evaluation have become critical in early-stage discovery. Machine learning models now outperform traditional QSAR methods, offering rapid and reliable assessments of pharmacokinetic properties and toxicity risks (Bang et al., 2025). Together, these advances highlight a new era in medicinal chemistry, where natural products and computational science converge to deliver safer, more effective therapeutics.

2. Natural Products in Modern Drug Discovery

Natural products remain a vital source of bioactive compounds, contributing significantly to drug approvals and clinical pipelines. Between 2014 and 2024, 56 natural product-derived drugs were approved globally, including antibiotics, anticancer agents, and immunomodulators (Butler et al., 2026). Their chemical diversity—spanning alkaloids, terpenoids, glycosides, and polyketides—provides unique scaffolds for medicinal chemistry. Unlike synthetic molecules, natural products often exhibit multi-target activity, making them particularly valuable for complex diseases such as cancer and neurodegenerative disorders.

Recent strategies emphasize sustainable discovery, including bioassay-guided isolation, semi-synthetic modification, and green chemistry approaches. Advances in metabolomics and high-throughput screening have expanded the accessible chemical space, enabling identification of novel pharmacophores. Importantly, natural products demonstrate higher progression rates in clinical trials compared to synthetic counterparts, underscoring their therapeutic relevance (Worm et al., 2024).

Figure 1 illustrates the sequential stages that connect traditional natural product research with modern medicinal chemistry, forming a comprehensive pipeline for drug discovery. The process begins with Natural Source, where plants, marine organisms, fungi, and microorganisms serve as reservoirs of bioactive molecules. These sources provide structurally diverse compounds that often exhibit pharmacological potential unmatched by synthetic analogs (Butler et al., 2026).

The next stage, Isolation, involves extracting and purifying active constituents using chromatographic and spectroscopic techniques. This step ensures that individual molecules responsible for biological activity are identified and characterized. Once isolated, Structural Modification follows, where chemists alter functional groups or molecular frameworks to enhance potency, selectivity, and pharmacokinetic properties. Semi-synthetic derivatives of natural compounds have historically led to breakthrough drugs such as paclitaxel and artemisinin (Nair & Jain, 2026).

Computational Screening integrates artificial intelligence and computer-aided drug design (CADD) to predict molecular interactions with biological targets. Docking simulations, pharmacophore modeling, and QSAR analyses accelerate lead identification and reduce experimental costs (Path, 2025). Subsequently, Preclinical Evaluation assesses the compound's efficacy, toxicity, and pharmacokinetics in vitro and in vivo, ensuring safety before human trials.

3. Computational Approaches in Medicinal Chemistry

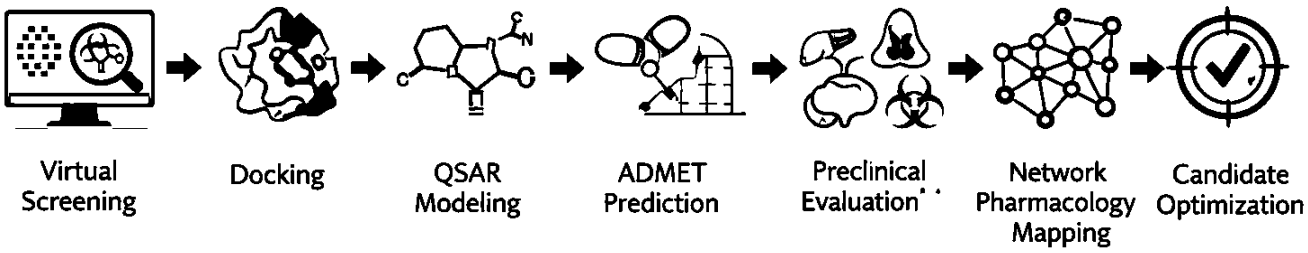

Figure 2. Integration of computational approaches and ADMET prediction in modern drug discovery.

Computational drug design has transformed medicinal chemistry by enabling large-scale virtual screening and predictive modeling. Platforms such as Schrödinger and MOE now allow docking of billions of compounds against specific targets, yielding diverse hits with high binding affinities. Deep learning-based protein structure prediction has further enhanced target identification, while free energy perturbation methods provide accurate binding affinity estimates during lead optimization (Path, 2025).

AI-driven approaches also integrate pharmacophore modeling, QSAR, and molecular dynamics simulations, offering robust insights into drug-target interactions. These computational tools reduce reliance on costly experimental assays, streamline discovery pipelines, and improve success rates. Recent applications include kinase inhibitors for resistant cancers and novel antivirals for infectious diseases. Collectively, computational methods bridge natural product research with modern medicinal chemistry, enabling rational design of multi-target therapeutics (Joshi et al., 2024).

4. ADMET Prediction and Network Pharmacology

ADMET properties—absorption, distribution, metabolism, excretion, and toxicity—are critical determinants of drug success. Recent advances in machine learning have revolutionized ADMET prediction, offering rapid, cost-effective, and accurate assessments of pharmacokinetic profiles. AI-driven models now integrate multi-task learning to capture interdependencies among ADME processes, significantly improving drug-likeness classification (Bang et al., 2025; Sucharitha et al., 2013). These tools filter out unsuitable candidates early, reducing attrition rates in clinical development.

Network pharmacology complements ADMET prediction by adopting a systems-level approach to drug discovery. Unlike traditional one-drug-one-target paradigms, network pharmacology maps drug-target-disease interactions, enabling identification of multi-target therapeutics for complex disorders. This integrative framework is particularly relevant for natural products, which often act on multiple pathways simultaneously. By combining computational modeling with network pharmacology, medicinal chemistry advances toward personalized and polypharmacological therapies (Joshi et al., 2024; Gujjeti et al., 2017).

Figure 2 presents a streamlined schematic of how computational tools and pharmacokinetic modeling converge to accelerate modern drug discovery. The process begins with Virtual Screening, where large chemical libraries are computationally evaluated to identify potential bioactive molecules. Artificial intelligence (AI) and machine learning algorithms now enable screening of millions of compounds in silico, drastically reducing time and cost compared to traditional wet-lab methods (Path, 2025).

The next stage, Docking, simulates the interaction between candidate molecules and target proteins. This step predicts binding affinities and orientations, helping chemists prioritize compounds with optimal receptor compatibility. Docking results feed into QSAR Modeling (Quantitative Structure–Activity Relationship), which correlates molecular descriptors with biological activity. QSAR models refine lead selection by predicting potency and selectivity based on structural features (Bang et al., 2025).

Following QSAR analysis, ADMET Prediction evaluates absorption, distribution, metabolism, excretion, and toxicity profiles. Machine learning-based ADMET models now integrate multi-task learning to capture complex

interdependencies among pharmacokinetic parameters, ensuring early elimination of unsafe or ineffective candidates (Venkataraman et al., 2025; Swapna et al., 2024; Munipally et al., 2020).

The workflow then advances to Network Pharmacology Mapping, which visualizes drug–target–pathway relationships across biological systems. This systems-level approach identifies multi-target interactions, particularly relevant for natural products and polypharmacological agents (Joshi et al., 2024). Finally, Candidate Optimization refines promising molecules through iterative computational and synthetic modifications, improving efficacy, bioavailability, and safety before preclinical validation.

5. Conclusion

Medicinal chemistry is undergoing a paradigm shift, driven by the integration of natural products, computational approaches, ADMET prediction, and network pharmacology. Natural products continue to provide unique scaffolds and therapeutic leads, while AI and computational tools accelerate discovery and optimization. ADMET modeling ensures safety and efficacy, and network pharmacology expands therapeutic potential by addressing complex diseases through multi-target strategies. Together, these advances bridge ancient wisdom with modern science, paving the way for evidence-based herbal therapeutics and innovative drug discovery. The future of medicinal chemistry lies in this synergy—where sustainability, precision, and systems biology converge to deliver safer, more effective, and personalized medicines (Butler et al., 2026; Venkataraman et al., 2025; Gujjeti et al., 2014; Lunavath et al., 2010; Namthabad et al., 2014; Porika et al., 2014).

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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