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REVIEW ARTICLE

Applications of artificial intelligence in the synthesis, docking, and pharmacological profiling of coumarins

Yasser Fakri Mustafa*

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, 41001, Iraq

***Corresponding author:** Yasser Fakri Mustafa, Dr.yassermustafa@uomosul.edu.iq, http://orcid.org/0000-0002-0926-7428

ABSTRACT

Coumarins, a diverse class of benzopyrone derivatives, have long captivated researchers due to their broad spectrum of pharmacological activities and synthetic versatility. In recent years, the convergence of artificial intelligence (AI) with pharmaceutical sciences has redefined how researchers approach the synthesis, molecular docking, and pharmacological profiling of such bioactive compounds. This review explores the transformative potential of AI in the context of coumarin research, presenting a holistic view of how machine learning algorithms, deep learning models, and data-driven design strategies are reshaping drug discovery. Traditional synthesis of coumarins, often constrained by multistep protocols and environmental concerns, is now being revolutionized through AI-assisted reaction predictions and retrosynthetic analyses. AI enables the generation of synthetically accessible molecules with optimized structural features, significantly reducing time and resource investment. Furthermore, molecular docking, critical to understanding structure-activity relationships, is increasingly benefiting from AI-enhanced scoring functions and predictive modeling, thus improving the accuracy of ligand-receptor interaction predictions. Pharmacological profiling, both in vitro and in vivo, is becoming more streamlined with AI models capable of predicting bioactivity, toxicity, and pharmacokinetics, making the lead optimization process more efficient and reliable. Public databases, curated datasets, and integrative cheminformatics platforms now provide a rich foundation for data mining and drug-target interaction studies. This review not only highlights the successes of AI in coumarin-based drug design but also discusses existing challenges, including algorithm interpretability, data quality, and regulatory considerations. Ultimately, the synergy between AI and coumarin research presents an exciting frontier that holds immense promise for accelerating drug discovery and advancing personalized therapeutics.

Keywords: artificial intelligence; drug discovery; machine learning; molecular docking; pharmacological profiling

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1. Introduction to coumarins

Coumarins have found extensive application across multiple domains of medicine and industry due to their versatile biological and chemical properties[1]. Clinically, they are employed as anticoagulants[2], photoprotective agents[3], anti-inflammatory compounds[4], and skin depigmenting agents[5]. They have also demonstrated therapeutic utility in managing conditions such as biliary obstruction[6], hypertension[7], and osteoporosis[8]. Beyond pharmacological roles, coumarins serve as valuable tools in analytical chemistry, particularly as fluorescent chemosensors for the detection of metal ions, amino acids, and reactive sulfur-containing species[9].

In the food and cosmetic industries, coumarins are widely appreciated for their aromatic characteristics, contributing fragrance and flavor to various products. Naturally abundant in a range of

medicinal plants and aromatic herbs, coumarins continue to inspire the development of novel synthetic derivatives with enhanced therapeutic potential[10]. However, traditional synthetic strategies often pose challenges, including multi-step protocols, variable reactivity, and labor-intensive purification processes. The use of toxic metal catalysts, fluorinated reagents, and costly precursors further complicates their preparation. These limitations underscore the urgent need for greener, more cost-effective, and sustainable synthetic methodologies[11].

In the context of drug discovery, molecular docking plays a pivotal role in elucidating the interactions between ligands and biological targets, thereby advancing the understanding of structure–activity relationships. Nevertheless, conventional docking workflows often depend on large-scale molecular modeling efforts to construct diverse chemical libraries, which can be computationally intensive and time-consuming[12]. Generating vast libraries of three-dimensional ligand conformations and evaluating their docking poses across multiple targets requires significant computational resources. This becomes particularly limiting when exploring flexible ligand spaces[13]. Therefore, the development of efficient, accurate conformer generation techniques and reliable scoring functions remains a critical priority for accelerating virtual screening and identifying promising lead compounds with reduced computational burden.

2. Overview of AI in drug discovery

Drug discovery is an inherently intricate and time-consuming endeavor, requiring a sequential process that includes target identification, the generation of *de novo* hits, hit-to-lead optimization, and subsequent refinement into viable lead compounds. At the early stages, high-throughput screening of extensive combinatorial chemical libraries, often encompassing millions of candidates, serves as a foundational strategy across numerous drug design initiatives[14]. However, achieving a successful hit with favorable binding affinity metrics, such as a low dissociation constant or inhibitory concentration, depends heavily on simultaneously optimizing multiple physicochemical parameters. These typically include solubility, lipophilicity, molecular weight, hydrogen bond donors and acceptors, and structural flexibility[15,16].

Natural products, derived from diverse biological sources, have historically served as one of the richest reservoirs for identifying pharmacologically active scaffolds. Despite their success, significant limitations persist. The irregular availability of source organisms, laborious extraction and isolation procedures, and the structural complexity of natural molecules, often with poorly understood bioactivities, pose significant challenges to their widespread application in modern discovery pipelines[17,18]. To overcome these obstacles, AI has emerged as a transformative force in drug discovery. By integrating the triad of "maps" (chemical space exploration), "data" (compound and target information), and "knowledge" (biological and pharmacological insights), AI platforms are streamlining the hit identification process. These systems rapidly screen vast compound libraries, prioritize candidates, and reduce the time and cost traditionally associated with early-phase discovery[19].

The COVID-19 pandemic highlighted the potential of AI-driven methodologies in responding to emerging health crises. AI-enabled virtual screening of synthetic libraries led to the identification of vandetanib (**Figure 1**) as a dual-action candidate for COVID-19 prevention and treatment. Subsequent *in vitro* and *in vivo* evaluations confirmed its multitarget mechanism of action, as suggested by docking studies and molecular dynamics simulations[20]. Similarly, for other viral threats such as the Zika virus, hybrid strategies that combine network pharmacology with ligand-based design have shown promise. For instance, naturally derived and crystallographically characterized coumarins were used to explore fungi-preventive and antiviral potential[21]. Through similarity-based searching, *de novo* compound generation, and multi-objective optimization models, novel coumarin-based scaffolds, engineered as slow-release organic cages, were proposed as nanotherapeutics for SARS-CoV-2[22–24]. In this context, AI excels in extracting meaningful patterns from high-dimensional

datasets. Its ability to correlate, infer, and reconstruct biological relevance from complex databases exemplifies its role in accelerating modern drug discovery and transforming chemical innovation into therapeutic reality.

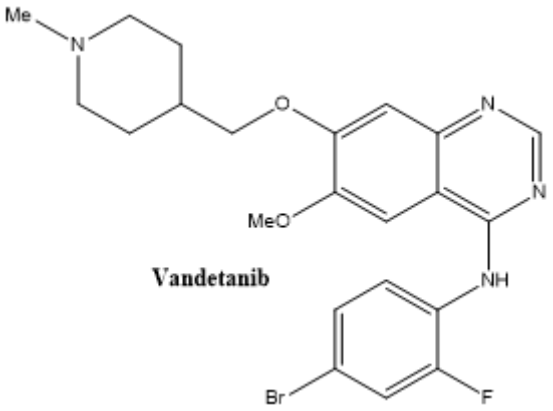

Figure 1. The chemical structure of vandetanib.

3. Synthesis of coumarins using AI

Designing novel compounds through in-house or outsourced synthesis remains a resource-intensive and intricate endeavor. However, AI has begun to transform this process by enabling the identification of viable synthetic starting points even before laboratory efforts commence. Leveraging extensive reaction databases that account for atom economy and mass balance, AI-driven models can construct reaction networks and propose routes predicted to be synthetically accessible within relatively short timeframes—often suggesting under 300 candidate molecules with anticipated synthesis completion in less than 30 days[25–27].

Crucially, these AI-generated candidates undergo further filtration using synthetic complexity indices and expert review to ensure practical feasibility. This integration of computational prediction with human oversight results in more efficient and economically viable drug discovery processes. In contrast to traditional deep generative models that focus solely on proposing new molecular structures, emerging AI frameworks in synthesis planning emphasize the generation of plausible synthetic routes, considering not just the molecular outcome but also the chemical logic and structural constraints involved in real-world synthesis[28–30].

Advanced machine learning (ML) techniques, such as random forest algorithms and gradient boosting methods, are increasingly being applied to analyze experimental reaction conditions. These models can map the structural attributes of a target molecule to feasible synthetic routes, encompassing reaction types that extend beyond well-characterized literature precedents. Moreover, by incorporating reaction informatics and historical synthesis data, these approaches can filter out impractical or low-probability routes, further refining the decision-making process[31–33].

Recent developments have also introduced generative systems capable of predicting reaction sequences by randomly selecting input reagents and transformation types, informed by transition state theory. These tools, coupled with expansive reaction knowledge bases and inference platforms, are now broadening the reach of AI-assisted synthesis design among medicinal chemists and synthetic researchers alike. Despite these advancements, challenges persist, particularly in automating decisions involving bond cleavage, stoichiometric adjustments, or multi-step pathway convergence. As AI continues to evolve in the realm of drug design and development, these obstacles represent active frontiers of research[34–36]. Nonetheless, the synergy between AI and synthetic chemistry holds great promise for accelerating the discovery of innovative therapeutics with greater precision and efficiency.

3.1. Machine learning approaches

ML encompasses a class of computational algorithms inspired by evolutionary and biological processes, designed to learn from data and generalize their understanding to predict outcomes for novel or hypothetical

samples. Its capacity to discern complex patterns from large datasets has made it an invaluable tool in fields such as biology, chemistry, and drug discovery. However, one of the enduring limitations of traditional ML approaches has been the difficulty in interpreting how models reach their conclusions, a limitation that has prompted renewed interest in explainable AI, which blends predictive performance with model transparency[37–39].

In the context of molecular docking, AI-driven algorithms have been developed and evaluated against several classical search strategies, including genetic algorithms, simulated annealing, particle swarm optimization, and blind docking protocols, particularly in the pursuit of lead compound identification[40]. Comparative studies have shown that representation-based docking approaches, particularly those incorporating homology modeling and threading techniques, can offer improved flexibility for large and complex molecular systems. Concurrently, enhancements to scoring functions have been introduced to reduce computational overhead associated with ligand re-docking and affinity evaluation[41].

To further address the limitations of conventional docking methods, modern AI strategies have been employed to train more efficient scoring functions and generate accurate three-dimensional pharmacophore libraries[42]. A notable example is the integration of Random Forest and Z-DOCK optimization techniques within a hybrid ML framework, which demonstrated a 6.3% improvement in the enrichment factor for top-ranking molecules such as 7-azaindoles and benzenes. Additionally, quantitative structure–property relationship models, which encode both structural and chemical features, have proven effective in refining three-dimensional molecular predictions[43]. Neural networks have played a critical role in mitigating over-fitting, particularly in modeling biological activity spectra and designing specific inhibitors, such as those targeting *Burkholderia* species[44]. Furthermore, simulation-based deep learning models combined with reinforcement learning techniques have been applied to generate molecule-centric representations, thereby enabling the design of novel, biologically active compounds through *de novo* approaches[45–47].

3.2. Predictive models for synthesis

Over the past few decades, one of the most promising applications of AI in drug discovery has been the prediction of synthetic pathways for target molecules, as illustrated in **Figure 2**. Despite its significance, synthesis prediction remains a challenging and underexplored area due to the complexity of organic reactions and the diversity of possible outcomes[48]. A primary challenge lies in identifying a suitable molecular representation that AI systems can interpret effectively. Traditionally, many synthesis models rely on linear string-based representations such as SMILES (simplified molecular input line entry system). These formats are popular because they are easy to use and supported by large datasets. However, SMILES-based models often oversimplify the underlying chemistry, failing to capture the nuanced relationships between reactants and products, and they typically struggle to scale with increasing data complexity[49]. In contrast, graph-based representations offer a more intuitive way to model molecular structures by treating atoms and bonds as nodes and edges. These graphical methods allow better extraction of structural and relational information, offering moderate interpretability and improved learning performance[50].

Another critical hurdle involves constructing accurate reaction prediction models. This area includes both retrosynthetic analysis (breaking down a complex molecule into simpler precursors) and forward synthesis (predicting the outcome of combining specific reactants). While AI tools for retrosynthetic prediction have advanced significantly and demonstrated strong performance on benchmark datasets, forward reaction prediction, which represents the bulk of practical synthetic work, remains comparatively less developed[51]. Some recent studies have attempted to tackle this using *ab initio* methods, but these approaches are computationally expensive and often require access to high-performance computing infrastructure[52]. Consequently, there is a pressing need to develop more affordable and efficient algorithms that maintain predictive accuracy while reducing computational cost[53].

Once a synthetic pathway is proposed, evaluating the feasibility of the route is essential. This concept, known as synthetic accessibility, has become a focal point in computational chemistry. Ideally, researchers aim to predict not just the feasibility but also the expected yield distribution of each reaction step. However, limited availability of high-quality yield data makes it difficult to train reliable models for yield prediction. Most current synthetic accessibility tools rely on separate models to estimate reaction difficulty and yield, which introduces additional complexity[54]. To address this, recent advancements have introduced unified models that can identify bottlenecks in a synthetic route. For instance, a decision tree-based model trained on over 115,000 experimentally validated and computationally predicted reactions successfully identified the most challenging steps in synthetic pathways. This model, built using density functional theory-derived features and Morgan412 fingerprints, offers a practical example of how AI can inform synthetic planning by highlighting steps that may require more intensive optimization or alternative strategies[55].

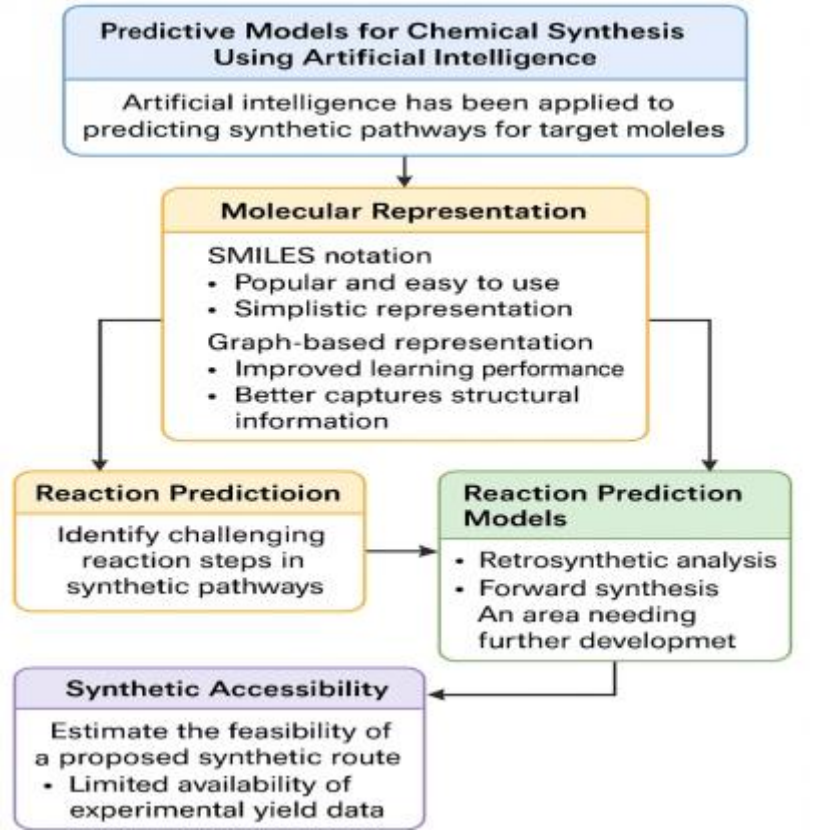

Figure 2. AI-driven flowchart for synthesis prediction and evaluation.

4. AI in molecular docking

Molecular docking is a widely used *in silico* technique designed to predict the optimal orientation and binding affinity between a ligand and a biological target, typically a receptor implicated in disease[56]. This computational approach has become a cornerstone in modern drug discovery, particularly for elucidating structure–activity relationships and informing the rational design of novel therapeutic agents. One of the key strengths of molecular docking lies in its ability to accommodate the structural flexibility of both ligands and receptor proteins[57]. By simulating protein–ligand interactions and accounting for factors such as solvation effects and conformational dynamics, docking enables researchers to explore the potential binding mechanisms and affinities of thousands, or even millions, of compounds for a specific molecular target[58–60].

Despite the speed and scalability of virtual screening, docking large libraries of compounds remains computationally intensive, sometimes requiring weeks or months of processing even with advanced high-performance computing systems. Furthermore, promising compounds identified through docking must still

undergo experimental validation to confirm their biological activity[61]. In addition to the time and labor, the financial costs of commercial software licenses, server infrastructure, and maintenance can be significant. To overcome these challenges, researchers have increasingly turned to complementary *in silico* strategies that leverage existing biological and structural data[62]. Structure-based drug design, virtual screening, and drug repurposing efforts benefit from databases of known protein-ligand complexes, enabling the identification of new therapeutic uses for existing compounds. These approaches can also reduce reliance on animal testing, minimizing associated ethical and regulatory hurdles[63–65].

Moreover, recent advances in data science and AI have enabled the development of predictive models that map molecular or sequence features directly to biological activity [66]. These models, based on ML algorithms for regression or classification, are reshaping how early-stage drug discovery is conducted. Reflecting this evolution, the American Chemical Society convened a virtual symposium on March 19–20, 2020 [Link], bringing together experts from its divisions of pharmaceutical sciences, chemical information, and computational chemistry. The event showcased the growing impact of data-driven techniques in lead discovery, compound optimization, and drug repurposing, highlighting the synergistic potential of integrating computational and experimental approaches in the drug development pipeline.

4.1. Docking algorithms and techniques

Molecular docking has emerged as one of the most widely adopted computational strategies in modern drug discovery and development. Its utility lies in predicting how ligands interact with biological macromolecules, particularly protein receptors[67]. Despite being extensively used, molecular docking still faces certain challenges that require ongoing research and refinement. At its core, docking involves generating potential binding poses for a ligand within a target binding site and then ranking these poses based on predicted binding affinities. While pose generation is often the most technically demanding step, scoring functions, used to estimate binding energies, are equally critical for accurate prediction[68–70].

The widespread popularity of molecular docking in both academic and industrial settings can be attributed to several key advantages. These include its broad applicability across diverse biological targets, the accessibility of various free and commercial software packages, straightforward post-docking analysis outputs, and the relatively low computational demands compared to other modeling techniques[71]. These strengths have contributed to a substantial number of publications utilizing docking methodologies across pharmaceutical sciences. Notably, molecular docking has transcended traditional pharmaceutical research and is now widely applied in fields such as molecular biology, biochemistry, biophysics, and environmental science[72]. The broad scope of docking applications includes virtual screening campaigns aimed at identifying lead compounds, followed by experimental validation of top-ranked candidates. In many workflows, docking is complemented or substituted by pharmacophore-based screening to further refine compound selection[73–75].

In addition to conventional applications, docking is increasingly used to predict potential ligand binding sites, broadening its role beyond pose prediction. Technological advances, such as the integration of graphics processing units, have significantly accelerated docking simulations, making them more suitable for high-throughput virtual screening[76]. A small yet growing body of literature even explores the philosophical dimensions of molecular docking, such as its implications in understanding molecular recognition and the nature of chemical interactions at a theoretical level[77].

4.2. Evaluating binding affinities

Molecular docking is commonly employed to predict the interaction between small-molecule ligands and target proteins by identifying the key amino acid residues involved in binding and estimating the binding free energy. These computational results are typically validated through experimental methods to assess the actual binding affinity[78–80]. One emerging tool in this domain is DockScreener (Dockscr), a Java-based spreadsheet-

integrated artificial neural network designed for quantitative structure–activity relationship modeling. This platform facilitates the prediction of docking affinities between small ligands and macromolecular targets[81]. In a recent study, a chemometric model was developed using a comprehensive set of 4,176 molecular descriptors, in conjunction with ligand data representing diverse chemical scaffolds. These ligands were previously docked to human serum albumin using the AutoDock 4.0 software, offering a robust dataset for model training and validation[82–84].

5. Pharmacological profiling of coumarins

Coumarins represent a structurally diverse and biologically active class of phytochemicals that have garnered significant attention in recent years due to their broad therapeutic potential[85]. Substituted simple coumarins, in particular, have demonstrated a wide range of pharmacological effects, including antiviral[86], anti-inflammatory[87], anticancer[88], antibacterial[89], antifungal[90], antidiabetic[91], and antispasmodic[92] activities. The coumarin scaffold is commonly found in various bioactive natural products that play crucial roles in the treatment of numerous diseases[93].

Beyond naturally occurring coumarins, extensive efforts have been made to design and synthesize a variety of coumarin-based analogs to explore and enhance their pharmacological profiles[94]. These synthetic derivatives have served not only as therapeutic agents but also as valuable lead structures in the drug discovery process[95]. Advances in biological sciences and medicinal chemistry have facilitated the structural optimization of coumarin derivatives, enabling the development of compounds with improved potency, selectivity, and safety profiles[96]. Coumarins have emerged as promising candidates for drug development, particularly in the context of challenging diseases such as breast cancer, pancreatic cancer, hepatocellular carcinoma, and prostate cancer[97]. The growing concerns about the toxicity and side effects of conventional synthetic drugs have further reinforced the interest in plant-derived compounds like coumarins, which offer favorable safety and efficacy profiles[98–100].

Moreover, computational techniques such as molecular docking and structure–activity relationship analyses have proven instrumental in understanding the interaction of coumarin analogs with biological targets[101]. These *in silico* approaches complement experimental studies and help guide the rational design of more effective coumarin-based therapeutics. A comprehensive review of the literature reveals that numerous coumarin compounds hold significant potential for pharmacological development[102]. By highlighting key examples and discussing emerging trends, this review aims to inspire further research into the therapeutic applications of coumarins and support the continued exploration of their diverse biological activities.

5.1. In vitro assays

Due to their wide pharmacological action, new coumarin derivatives have been designed, synthesized, and biochemically and pharmacologically evaluated. The synthetic chemistry and biological profiles of these newly synthesized coumarins have been reported[103]. Fluorescent, solubility, and octanol-water partition coefficient data for coumarins have been established. The *in vitro* biological activities of the prepared coumarin derivatives have been reported, and their mechanisms of action and structure-activity relationships were established[104–106].

Molecular docking has been widely applied in drug discovery to better elucidate the action of ligands at the target and evaluate their binding affinities and orientation in the active site of proteins. It predicts the conformation of a ligand when bound to a target of known three-dimensional structure. Currently, there are multiple commercial and non-commercial softwares employed for docking and scoring the best-docked poses. These tools can broadly be categorized into two classes: rigid and flexible docking. Typically, rigid docking is employed when docking small ligands to a large target, whereas flexible docking is used with larger ligands in the test series[107]. The present review article summarizes ten works, as recorded in **Table 1** and displayed

in **Figure 3**, on coumarins that employed molecular docking as a major methodology in their anticancer profiling; five works targeting caspase-7, while the others docked to carbonic anhydrase IX. Additionally, several docking software, some popular docking strategies, and the evaluation of docking methods have been discussed. It is hoped that this review will encourage researchers to explore molecular docking further for their new coumarin derivatives and other structures.

Table 1. Coumarins docked to specific enzymes as anticancer candidates.

Coumarin derivative	Targeted enzyme	Tested biological activity	Ref.
7-Hydroxy-4-methylcoumarin	Caspase-7	Potential anti-apoptotic agent for cisplatin-induced renal injury.	[108]
4-Methyl-7-methoxycoumarin			[109]
6,7-Dihydroxycoumarin			[110]
4-Methyl-7-hydroxy-8-methoxycoumarin			[111]
4,7-Dimethoxycoumarin			[112]
3-(4-Chlorophenyl)-6,8-dihydroxycoumarin	Carbonic anhydrase IX	Potential anticancer agent targeting tumor-associated enzyme.	[113]
3-(3,4-Dichlorophenyl)-6,8-dihydroxycoumarin			[114]
3-(3-Bromophenyl)-6,8-dihydroxycoumarin			[115]
3-(4-Methoxyphenyl)-6,8-dihydroxycoumarin			[116]
3-(4-Hydroxyphenyl)-6,8-dihydroxycoumarin			[117]

The biological evaluation of coumarins has been systematically explored by profiling their interactions with specific receptors, utilizing various computational and experimental approaches. These investigations typically consider the receptor or assay method, the structural identity of the coumarin derivative, the biological context of the study, observed outcomes, and insights into structure–activity relationships[118–120]. Initially, research efforts focused on screening coumarin compounds with relatively simple chemical structures and low toxicity profiles against individual biological targets. However, as interest in their pharmacological potential has grown, the structural complexity of coumarins and the diversity of their target profiles have increased, particularly with the use of combinatorial screening strategies targeting multiple receptors or pathways[121]. In recent years, substantial progress has been made in understanding the biological effects of specific coumarin derivatives across various physiological systems. These findings have been extensively reviewed, particularly with regard to their mechanisms of action[122]. The integration of computational tools such as molecular docking has significantly enhanced our ability to predict and interpret the structure–activity relationship of both synthetic coumarins and naturally occurring analogues, thereby accelerating the development of novel bioactive candidates[16,123,124].

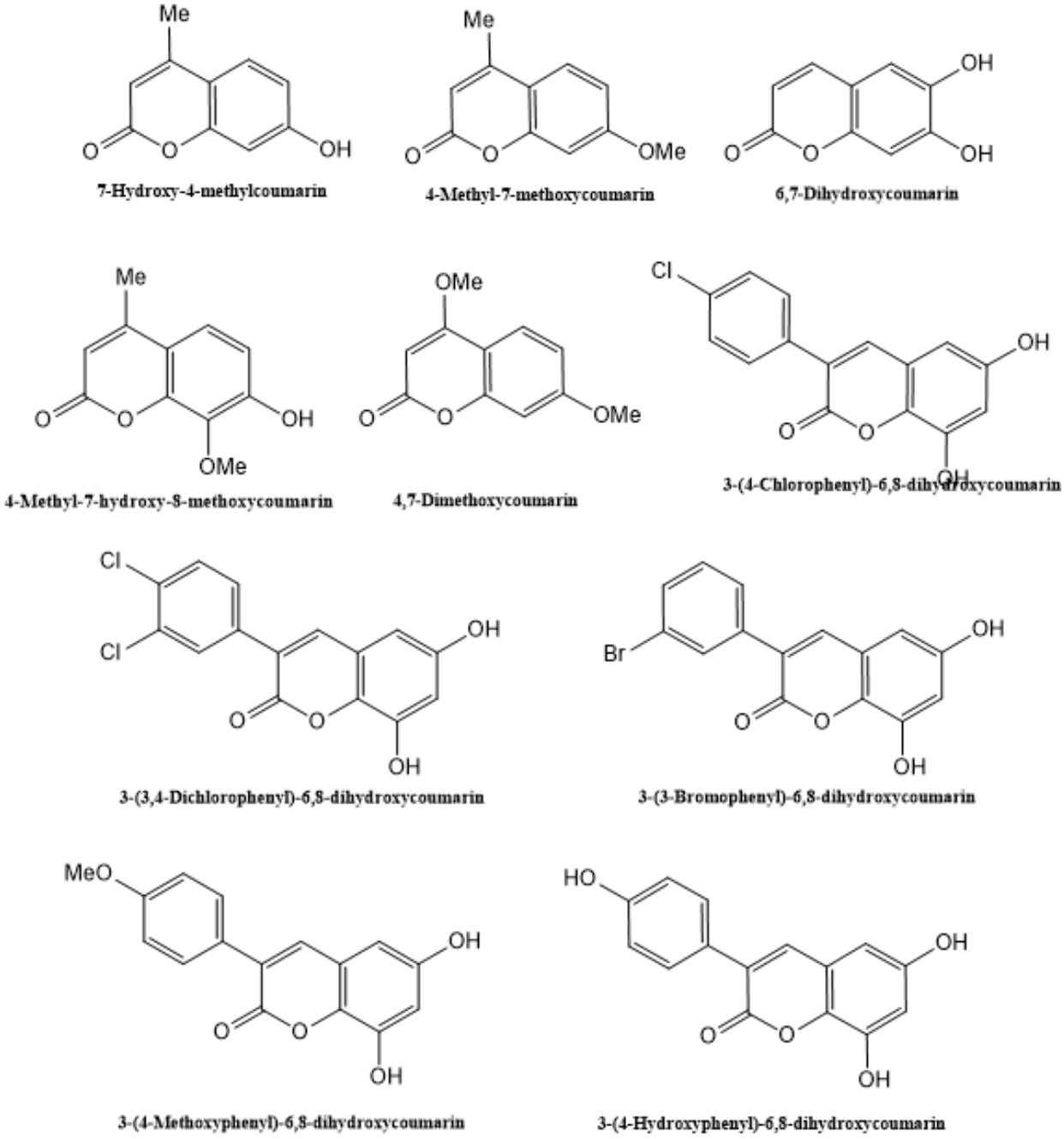

Figure 3. Some coumarins in silico tested as anticancer candidates.

5.2. In vivo studies

Coumarins have also shown promise in managing various infectious diseases. For example, 7-hydroxycoumarin derivatives have emerged as potential antitubercular agents, while several fused coumarin structures have demonstrated strong anti-HIV activity. In addition, many coumarin-based compounds have shown notable antimicrobial potential, including activity against malaria-causing parasites[125]. Motivated by the promising antimicrobial profile of these compounds, a recent study focused on synthesizing various analogs of 4-methylamino-7-hydroxycoumarin to evaluate their efficacy against *Bacillus subtilis* and *Staphylococcus aureus*. The pharmacokinetic and toxicity profiles of the most active analogs were also predicted using computational tools[126]. To support drug design efforts, predictive models were developed to estimate the biological activity of coumarin analogs against strains such as *Staphylococcus aureus* WNW138 and *Staphylococcus aureus* 85R3A3. This modeling effort employed artificial neural networks enhanced with

genetic algorithms, resulting in 60 predictive quantitative structure-activity relationship models. These models were rigorously validated using diverse datasets, including AppLis[127–130].

AI has been integrated into *in vivo* experimental design, particularly to study coumarin interactions with biological targets. For instance, docking studies revealed critical binding interactions between coumarins and human topoisomerase I, using ligands retrieved from the ChEMBL database with IC_{50} values below 1000 nM[131]. Advanced scoring algorithms such as VDL-POF were employed for docking, followed by ensemble docking using normal mode analysis to identify representative binding poses. Molecular dynamics simulations (50 nanoseconds) were subsequently conducted, which highlighted significant structural changes, particularly in analogs with high binding affinity[132]. Collectively, coumarin derivatives continue to demonstrate substantial therapeutic potential, as confirmed by both *in vitro* and *in vivo* studies across various biological systems[133–135].

6. Data mining and coumarin databases

The fast-paced evolution of computational chemistry and computer-aided drug design has created a growing reliance on AI to manage, interpret, and extract meaningful insights from vast datasets. In this context, automated data mining of archived computational analyses involving known ligands has emerged as a promising approach to enhance virtual screening and support lead optimization[136]. Recent innovations have introduced advanced methodologies that leverage ML as a strategic tool in medicinal chemistry. The ML algorithms are now routinely employed to process large ligand databases, enabling the generation of predictive three-dimensional models of molecular target sites[137]. Among the chemical scaffolds of interest, coumarins stand out due to their broad structural diversity and wide-ranging pharmacological activities. Their appeal lies in the ease of synthetic modification, which allows for the design of structurally rich analogs using molecular scribers[138].

Notably, dihydrocoumarin hybrids incorporating purine and pyrimidine moieties have been investigated for their therapeutic potential. In this study, novel coumarin derivatives featuring 2-amide-1,3-thiazole-5-carboxylic acid or its ethyl ester-linked peptides were synthesized and selected for further evaluation. The geometries of these molecules were optimized using density functional theory at the B3LYP/6-311G level to obtain accurate two-dimensional and three-dimensional representations[139]. To explore their potential against SARS-CoV-2, *ab initio* molecular dynamics and docking simulations were conducted, targeting key viral proteins. Prior to docking, molecular dynamics simulations were employed to stabilize the protein structures, ensuring more reliable interaction predictions. Additional investigations included binding affinity studies of coumarins with chiral guests using fluorescence-based techniques. Furthermore, the electrochemical and solvent-dependent photo-physical behaviors of coumarins and their substituents were characterized[140]. Molecular docking continues to serve as an essential tool in virtual screening, particularly for identifying selective candidates in the treatment of angiogenesis-related disorders. In this regard, structure–activity relationship studies of coumarins are often preceded by drug-likeness assessments to refine compound selection. Encouraging results have highlighted the strong binding affinity of coumarins to the active sites of angiogenic target proteins, reinforcing their therapeutic promise[141–143].

6.1. Publicly available databases

AI has undergone a remarkable transformation in recent years, becoming deeply integrated into everyday technologies such as smartphones, computers, smart TVs, and drones[144]. Despite its widespread presence, the intricacies of AI remain unfamiliar to many. In the realm of biomedical research, AI is emerging as a powerful ally to scientists, particularly in the field of drug discovery. A key application of AI lies in enhancing the exploration of chemical databases. These databases have matured significantly, allowing researchers to identify potential targets for small molecules using computational methods like molecular docking[145].

Additionally, AI-driven data mining techniques enable the repurposing of FDA-approved drugs by uncovering novel therapeutic indications and predicting possible side effects; an approach broadly referred to as pharmacological profiling[146].

Traditionally, the evaluation of a drug's role in a specific biological process or disease involves labor-intensive and costly experimental procedures that can take years to yield meaningful results. To circumvent these challenges, AI-based bioinformatics platforms have been developed to uncover previously unknown drug-target interactions[147]. One such strategy involves reverse docking, where existing drugs are computationally screened against a database of validated protein targets to identify new binding affinities. These computational predictions have shown promise, with selected drugs demonstrating antiproliferative activity and upregulating novel target proteins in experimental validation studies. Importantly, predicted side effects often align with those observed clinically, supporting the accuracy of these AI-driven insights[148–150].

Compared to conventional drug discovery methods, AI dramatically reduces the time and cost required to identify new drug-target pairs. For instance, a screening workflow involving FDA-approved compounds and a specific target can yield meaningful predictions in under an hour; however, there remain areas for refinement[151]. One limitation is that most structural targets in the protein data bank are complexed with ligands, which may not reflect the unbound state of proteins *in vivo*. Therefore, incorporating ligand-free protein structures from specialized databases could improve predictive accuracy. Moreover, attention must be paid to the binding sites around the target area, ensuring that drug interactions are physiologically relevant. To minimize false positives, known drug-target interactions should be excluded during screening[152].

6.2. Data curation techniques

The reliability and impact of structure–activity relationship studies are closely tied to the integrity and quality of the datasets used. In data-driven drug discovery, the meticulous curation of input datasets is arguably the most critical factor determining the success of predictive modeling efforts[153]. A common pitfall is the hasty aggregation of data from multiple open-access sources, which, while resulting in large datasets, often introduces inconsistencies, errors, or incomplete records. Such poorly constructed datasets can severely compromise the biological relevance of the findings and distort statistical analyses, ultimately undermining the credibility of the research[154–156].

Literature-based data mining holds significant promise as a source of high-quality information. However, unstructured or indiscriminate data collection strategies can mislead researchers, consuming valuable time and resources when inaccuracies become apparent during the modeling process. A more strategic approach involves working initially with smaller, well-validated datasets and rigorously evaluating the output from preliminary models before extending the analysis to broader systems. This not only helps identify dataset-specific pitfalls and anomalies but also enables more efficient allocation of research resources[157]. To highlight these challenges and opportunities, several focused case studies have been reviewed, offering practical insights that may benefit researchers in similar endeavors. The increasing availability of electronic datasets in open formats presents an opportunity to bypass some of the bureaucratic barriers traditionally associated with data access, facilitating more agile and informed research practices[158].

7. Case studies: Successful AI applications

The COVID-19 pandemic has emerged as a profound global health crisis, prompting an urgent need for effective medical countermeasures. While the rapid development and deployment of vaccines have significantly contributed to controlling the spread of this pandemic, the continued emergence of new viral variants has led to recurrent outbreaks, underscoring the necessity for additional therapeutic strategies[159]. Among these, the identification of novel antiviral agents remains a priority for both prevention and treatment. The entry of SARS-CoV-2 into host cells is mediated by the interaction between the receptor-binding domain

(RBD) of its spike protein and the angiotensin-converting enzyme 2 (ACE2) receptor on host cell surfaces. This molecular interaction is a critical step in the viral life cycle, making it a strategic target for therapeutic intervention[160]. Compounds that can disrupt the RBD–ACE2 binding have the potential to block viral entry, offering a promising approach for antiviral drug development.

In this context, a deep learning-assisted virtual screening pipeline was developed using the structural data of the RBD–ACE2 complex. This computational strategy was applied to screen a library of natural products to identify potential hit compounds capable of inhibiting this key interaction. Promising candidates from the virtual screen were subsequently subjected to *in vitro* validation to assess their inhibitory activity against the RBD–ACE2 interaction and their potential to prevent SARS-CoV-2 infection[161]. Detailed molecular interaction analysis further elucidated the key binding residues involved, providing critical insights for the rational design of future antiviral agents.

On the other hand, benzopyrones are known to interact with multiple molecular targets, such as cyclooxygenases, aldose reductases, histone deacetylases, protein kinase C, and thromboxane receptors[74]. However, no proof existed linking benzopyrones to activity against influenza A virus (IAV), particularly through inhibition of the RNA-dependent RNA polymerase (RdRp) complex. In a recent study, two benzopyrones that exhibit potent inhibitory effects on IAV-RdRp activity at low micromolar concentrations[162]. Mechanistic investigations suggested that these compounds interfere with the formation or stability of the viral polymerase complex, indicating a novel mode of action. These findings represent the first demonstration of benzopyrones as potential anti-IAV agents and provide a new foundation for high-throughput antiviral drug discovery[163]. Moreover, the identification of isomer-selective inhibitors introduces an opportunity for the development of next-generation antiviral therapies with improved specificity and efficacy[164–166].

7.1. Case I: Coumarin derivative development

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the deterioration of memory and cognitive functions, and attributed to the degeneration of cholinergic neurons in the basal forebrain. This neuronal loss is primarily driven by dysfunction in the cholinergic arousal system. Despite significant research efforts, current pharmacotherapies for AD offer only temporary symptomatic relief and fail to halt or reverse disease progression[167]. Recent advances have explored the potential of coumarin-based compounds as multitarget agents for AD treatment. Several derivatives have demonstrated inhibitory activity against key enzymes involved in AD pathology, including acetylcholinesterase, butyrylcholinesterase, monoamine oxidases A and B, and have shown the ability to chelate and inhibit the aggregation of β-amyloid peptides[168]. Molecular docking analyses have highlighted that some of these coumarin derivatives bind to acetylcholinesterase at sites distinct from classical inhibitors like galantamine and rivastigmine[169]. This alternative binding behavior suggests a novel mechanism of action and potential for improved selectivity towards acetylcholinesterase over butyrylcholinesterase[170]. These findings underscore the therapeutic promise of coumarins as acetylcholinesterase inhibitors and multifunctional agents in the development of anti-Alzheimer's therapeutics[171–173].

7.2. Case II: Target identification

Identifying the biological target of a compound is a critical step in the research and development pipeline, as it plays a central role in elucidating the compound's mechanism of action and shaping its pharmacological profile[174]. Understanding the primary target not only aids in evaluating potential off-target effects but also guides medicinal chemists in lead optimization and the rational design of analogues with improved efficacy or selectivity across various therapeutic indications. Traditionally, target identification has relied on binding affinity-based techniques, such as affinity chromatography[175]. However, the emergence of high-throughput and system-level methodologies has significantly expanded the toolkit available for probing molecular targets, incorporating approaches that interrogate interactions with diverse classes of biomolecules[176–178].

For researchers engaged in drug discovery, the growing array of available strategies presents a challenge: determining the most suitable approach to initiate target deconvolution. Several key factors influence this decision, chief among them being the compound's presumed mechanism of action and the biochemical nature of its prospective targets. Generally, successful target identification assumes the compound binds to a protein, unless a non-protein target has been hypothesized and experimentally supported[179]. A solid understanding of the compound's functional behavior is necessary to inform the design of the assay and the selection of an appropriate ligand library. In scenarios where the mechanism of action is unknown or ambiguous, researchers often employ chemically diverse, hypothesis-free libraries to probe potential interactions. While this unbiased approach increases the breadth of detectable interactions, it also introduces greater complexity, complicating downstream data analysis and interpretation[180–182].

To illustrate this multifaceted process, a case study is presented comparing four parallel strategies for target identification within a chemical library of uncertain bioactivity and exposure characteristics. This comparative analysis offers a flexible framework for drug discovery scientists seeking comprehensive yet efficient approaches to uncovering molecular targets, particularly in the context of structurally diverse or mechanistically undefined libraries. In modern drug discovery, these strategies are often employed in parallel to identify the biological targets of small molecules, particularly when the compound's mechanism of action is unknown or poorly understood[183]. One widely used approach involves affinity-based methods, such as affinity chromatography or pull-down assays, where chemically tagged compounds are used to capture and isolate their binding partners[184–186].

Another increasingly popular technique is the use of label-free methods like Drug Affinity Responsive Target Stability or Cellular Thermal Shift Assay, which detect shifts in protein stability upon compound binding, without the need for chemical modification of the molecule[187]. Additionally, omics-based profiling, including chemoproteomics, transcriptomics, and phosphoproteomics, provides a systems-level view by mapping how compounds influence global protein expression or post-translational modifications[188]. Finally, genetic perturbation approaches, such as CRISPR-Cas9 or RNA interference screens, help uncover genes or proteins essential for compound activity by observing phenotypic changes following genetic knockdown or knockout[189]. Together, these strategies, as illustrated in **Figure 4**, offer a versatile and synergistic toolkit for uncovering molecular targets in complex biological systems.

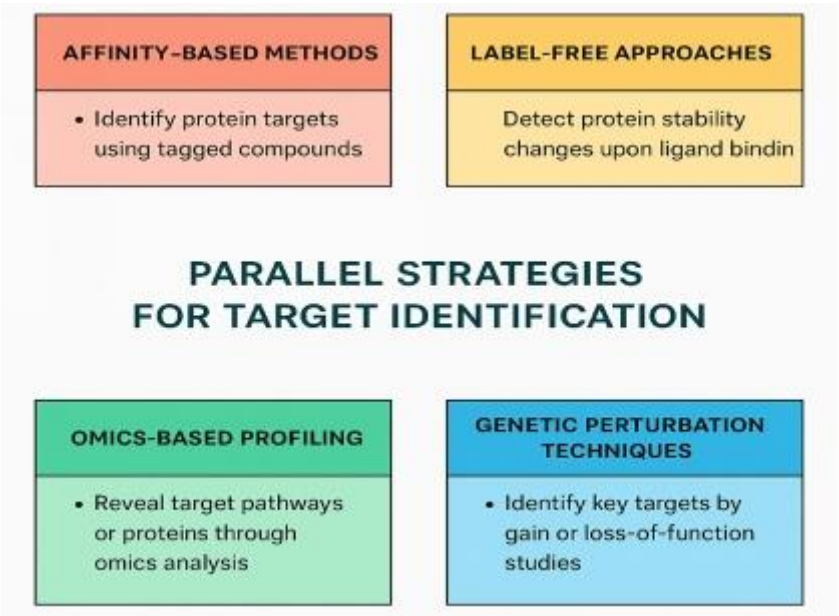

Figure 4. Four complementary strategies for molecular target identification in drug discovery.

8. Challenges in AI integration

The accelerated advancement of AI technologies has revolutionized the landscape of drug discovery, equipping researchers and pharmaceutical industries with innovative tools to explore new therapeutic options. Through reinforcement learning frameworks, AI systems have been trained to grasp the principles of molecular design, enabling the generation of structurally novel and biologically diverse compounds with promising predicted bioactivity[190]. One notable application of this approach was the development of an orally administered drug candidate for Parkinson's disease, marking a significant milestone in AI-driven drug development[191–193].

Since then, the application of AI in pharmaceutical research has grown exponentially, with over 150 studies contributing to the field. In this context, the current work categorizes AI applications in drug discovery into three major developmental stages: data mining and bioinformatics; molecular modeling and pharmacological evaluation; and AI-assisted molecular design and optimization. These stages reflect the evolution of AI's role in the field and offer a structured resource for advancing future innovations[194]. AI presents a transformative opportunity to reduce the timeframes of drug development and enhance the likelihood of success. The fusion of ML with chemoinformatics and bioinformatics has yielded predictive models capable of conducting *in silico* screenings of chemical libraries, thereby identifying promising candidate molecules for experimental validation. Moreover, these virtual hits can be further refined computationally to enhance their pharmacodynamic and pharmacokinetic profiles, including potency and selectivity[195–197].

However, effective integration of AI models into drug discovery pipelines necessitates careful consideration of their underlying data. These models are typically built from heterogeneous datasets derived from various experimental phases, each of which can be time-consuming and resource-intensive. As a result, available data is often sparse, heterogeneous, and may include both quantitative and categorical elements, making it vulnerable to noise and bias. This inherent complexity poses a challenge in constructing reliable and generalizable predictive models[198]. While deep learning architectures, such as neural networks, have demonstrated impressive predictive capabilities, their "black box" nature can hinder transparency and user trust. The inability to extract or rationalize internal learned features limits their acceptance in regulated and data-sensitive environments like drug discovery[199]. Therefore, improving the interpretability and accountability of AI models remains a crucial step toward their broader adoption in pharmaceutical research.

8.1. Data quality and availability

The integration of AI into drug discovery heavily depends on the availability of high-quality, well-curated datasets. Over the past decade, remarkable advancements in high-throughput sequencing, information technology, and AI methodologies have significantly boosted efforts to develop open-access databases tailored for pharmaceutical research[200]. These developments have ushered drug discovery into the era of big data, streamlining the once time-intensive processes of cognitive analysis and knowledge extraction. Fundamentally, successful AI-driven drug discovery begins with robust data acquisition. Various types of datasets now support this endeavor, encompassing chemical libraries of small molecules, oligonucleotides, protein sequences, and biological assay results. Each of these datasets contributes unique value to different stages of the drug development pipeline[201].

As new technologies emerge and evolve, there is an ongoing debate about the optimal direction for AI applications in drug discovery. This calls for a critical evaluation of existing data infrastructure. Limitations such as data heterogeneity, incomplete annotations, and lack of standardization pose significant challenges. Addressing these issues is essential for fostering collaboration among researchers and promoting the establishment of unified and scalable drug discovery pipelines[202]. Several publicly accessible databases now serve as central resources for chemical, biological, and bioactivity data. When properly annotated and

integrated, these multidimensional datasets enable comprehensive analyses of drug-target interactions, guide high-throughput screening strategies, and facilitate the development of predictive algorithms for drug-likeness, efficacy, and safety[203].

For instance, ChEMBL is a well-established and widely used platform that offers detailed information on bioactive compounds. Its content includes molecular structures, mechanisms of action, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, therapeutic uses, and target associations. Each entry provides extensive data on compound structure, pharmacological activity, and interaction networks[204]. Similarly, ChemDB incorporates cheminformatics tools that assist in compound evaluation, while COCONUT focuses on natural products by aggregating both characterized and predicted structures from diverse chemical sources. It allows users to search for compounds based on structure, name, or physicochemical properties[205].

Another vital resource is DGIdb (Drug–Gene Interaction database), which bridges genotypic data with phenotypic implications. It includes a repository of over 40,000 protein-coding genes and 10,000 small molecules, offering valuable insights into gene–drug relationships. Perhaps the most comprehensive is DrugBank, which provides detailed information on both FDA-approved and experimental drugs. It catalogs drug interactions, molecular targets, pharmacokinetics, mechanisms of action, and structural data, making it indispensable for modern pharmaceutical research[206]. Together, these databases form the foundation for AI-enhanced drug discovery, enabling researchers to harness data-driven insights and accelerate the journey from compound identification to clinical application.

8.2. Interpretability of AI models

The integration of AI into medicinal chemistry has grown remarkably in recent years[207]. However, many AI models remain largely opaque, with limited interpretability regarding how decisions are made. This has prompted the development of explainable artificial intelligence (XAI), a field focused on enhancing the transparency and interpretability of AI models. In the pharmaceutical sector, where regulatory scrutiny is high and the stakes are significant, this transparency fosters greater trust, understanding, and acceptance of AI-driven outputs[208]. While plant-based drug discovery can benefit from XAI advancements achieved in other disciplines, it also presents distinctive challenges. These include the need for rapid, high-level decision-making, defining and navigating a complex molecular design space, generating meaningful structural representations, and optimizing them effectively[209]. In such contexts, interpretable models are not just advantageous but necessary. They enable researchers to uncover the rationale behind AI predictions, helping to detect and minimize bias, reduce the risk of misleading results, and ensure fairness in decision-making[210].

XAI methodologies can provide insights into the relative importance of input features, ensuring that correct predictions are not coincidental or based on flawed logic. Moreover, explainability helps scientists extract meaningful knowledge about the underlying biological or chemical phenomena modeled by AI systems. A clearer understanding of the model's nature, capabilities, and limitations can reduce the risks of over-fitting and erroneous assumptions about the input data. Identifying the model's boundary conditions also contributes to defining realistic operational parameters[211]. Importantly, explainability also facilitates better communication and collaboration between interdisciplinary teams, including chemists, biologists, data scientists, and regulatory experts, bridging gaps in language and perspective. By promoting ethical and informed application of AI in medicinal chemistry, XAI has the potential to improve drug candidate success rates while reducing the likelihood of adverse effects and development failures[212].

9. Future directions in AI and coumarin research

The integration of AI into the study of coumarins remains in its early stages and stands to benefit from the diverse strategies already proven effective in other areas of drug discovery. Applying advanced computational tools—including ML algorithms from chemistry, bioinformatics, cheminformatics, computer

vision, and reinforcement learning—could significantly expand our understanding and exploitation of coumarins. There is immense potential to accelerate the design of novel coumarin-based compounds, smart formulations, and optimized therapeutic strategies by harnessing these cutting-edge technologies. To date, most AI-driven applications in pharmacokinetics have centered around ADMET modeling. These models often suffer from either overly complex feature spaces or minimalistic attribute sets, and have largely focused on conservative scaffold modifications that retain biological activity. In contrast, coumarins formulated in medium- to high-potency excipients have been scarcely explored, presenting a valuable opportunity to develop advanced predictive models to enhance drug delivery systems.

Despite the broad biological profiling of coumarins, AI-based simulations using physiologically relevant human models remain virtually nonexistent. This highlights a major gap that could be addressed through more targeted modeling efforts. Furthermore, the application of AI in ecological disposition modeling could aid in identifying biodiverse or endemic-rich environments, potential reservoirs for coumarin-rich plant species, thus opening new avenues for natural product research. Quantitative structure–activity relationship models, particularly those focusing on enzymatic targets such as coupling enzymes, could be instrumental in pre-screening natural coumarins before isolating them from source species. Given that the metabolic pathways involving coupling enzymes are relatively well characterized, ML could potentially use emission spectra or molecular fingerprints to classify coumarin compounds with both precision and speed.

The coumarin scaffold remains a compelling focus for researchers due to its versatile chemical, biological, and materials science attributes. Accumulated data from the past decade suggest there is a vast, largely untapped structure–activity landscape within this class of molecules, holding great promise for the discovery of new pharmacologically active leads. Therefore, coumarins present a prime opportunity for renewed research, particularly through the convergence of multi-scale experimental techniques and AI-enabled discovery pipelines. Realizing this potential, however, will depend on addressing the current underutilization of AI tools in this domain.

9.1. Emerging technologies

With remarkable advances in ML and computational modeling over the past few decades, AI methodologies have been integrated into nearly every stage of the drug discovery pipeline. These applications span from rational drug design and molecular docking to comprehensive pharmacological profiling. In the realm of natural product-inspired drug discovery, AI has shown particular promise. It has enabled progress in *de novo* drug design, prediction of target protein structures, and the assessment of drug-target interactions along with their binding affinities. While this prediction remains a central focus, recent reviews have expanded to highlight advancements in other aspects of natural product-based drug discovery, underscoring AI's transformative potential in this space.

Pharmacological profiling is critical for prioritizing drug candidates. Recent investigations have detailed how AI-driven strategies are revolutionizing this process, especially within the context of bioactive natural compounds. Notably, while AI applications in natural product synthesis are beyond the scope of this paper, they have been thoroughly addressed elsewhere in the literature. Coumarins exemplify the intersection of natural products and AI-driven drug discovery. These molecules are widespread in nature and possess a broad spectrum of pharmacological activities, including anticancer, antibacterial, antioxidant, antidiabetic, anti-inflammatory, antiviral, and neuroprotective properties. Their versatility has led to their use not only as therapeutic agents but also as components in agrochemicals, fragrances, and fluorescent materials.

9.2. Interdisciplinary approaches

Drug discovery is inherently a complex, interdisciplinary endeavor involving several critical stages, including target identification, hit identification, hit-to-lead optimization, and extensive preclinical and clinical

evaluations of novel chemical entities. Despite significant advancements, the traditional pipeline remains highly resource-intensive, both in terms of time and cost, and is burdened with a high attrition rate. To overcome these longstanding challenges, AI has emerged as a transformative tool, increasingly integrated into nearly every phase of drug development. AI technologies are now widely applied to enhance data mining, molecular design, and biological characterization. These applications rely on diverse strategies, including various molecular representations, three-dimensional structure-based approaches, and knowledge-driven algorithms to build predictive models with high efficiency and precision. Additionally, a growing number of open-access platforms and computational servers have been established to democratize AI-driven research in drug discovery and facilitate collaborative innovation.

Natural products have historically served as a prolific source of bioactive compounds and pharmacological leads. Advances in analytical chemistry and molecular biology have deepened our understanding of nature's vast chemical repertoire, revealing a wealth of structurally diverse compounds with therapeutic potential. However, the increasing volume and complexity of biological and chemical data have also introduced new analytical challenges. Traditional methods often fall short in efficiently extracting actionable insights from such expansive datasets. Moreover, the development of new therapeutics derived from natural products has been hampered by limited insights into their modes of action and the synthetic complexity involved in their modification. To address these issues, AI has been increasingly leveraged to streamline and enhance natural product-inspired drug discovery. Modern applications of AI in this field include *de novo* drug design, structural prediction of targets, computational modeling of drug-target interactions, and *in silico* estimation of binding affinities. These technologies, as displayed in **Figure 5**, are accelerating the identification and optimization of promising compounds, thereby improving the efficiency and success rates of the drug development process.

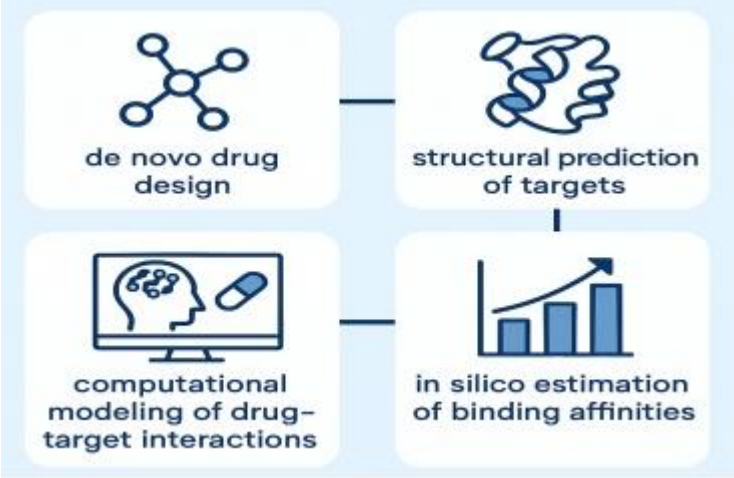

Figure 5. The AI applications in the field of drug discovery.

10. Conclusion

Coumarins, a class of naturally occurring and synthetically derived compounds, have long held scientific interest due to their diverse pharmacological and chemical properties. For more than two centuries, these molecules have been extensively studied for their potential therapeutic applications. Their broad spectrum of biological activities, including anti-inflammatory, antiviral, antibacterial, antitumor, and antiproliferative effects, has made them attractive candidates in the field of drug discovery. Beyond their pharmacological potential, coumarins have also shown promise in non-therapeutic domains such as fluorescent labeling, analytical chemistry, and molecular probe design. Despite the substantial research on coumarins, the pharmacodynamics and mechanisms of action of many derivatives remain incompletely understood. This gap highlights the opportunity for identifying new coumarin-based agents with novel biological activities.

Intriguingly, it is increasingly recognized that these compounds may exert their effects through multi-target interactions rather than acting on a single molecular pathway. This polypharmacological nature could enhance therapeutic efficacy, prolong drug action, and potentially mitigate the emergence of resistance in conditions such as cancer.

Driven by their wide-ranging bioactivity, coumarins have been studied for their interactions with key biomolecular targets, particularly proteins implicated in disease progression. Given the structural versatility of coumarin analogues, computational chemistry has emerged as a powerful tool to predict and rationalize their biological behavior. Approaches such as quantitative structure–activity relationship modeling, molecular docking, molecular dynamics simulations, and free-energy calculations are now routinely applied to explore the structure–activity relationships of these compounds. These approaches enable the correlation of molecular features with biological activity across large compound libraries, enhancing the efficiency of lead optimization. Coumarins are especially suited for such studies due to their amenability to structural modifications and their utility as core scaffolds in medicinal chemistry. In recent years, numerous *in silico* studies have expanded the understanding of coumarins across various biological targets. Comprehensive insights from three-dimentional quantitative structure–activity relationship, ligand-based design, and dynamic modeling, when integrated with experimental validation, offer a robust platform for advancing coumarin-based drug discovery.

Conflict of Interest

The authors declare no conflict of interest.

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