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Small Molecule Therapeutics in Drug Discovery: Current Trends and Future Directions

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Abstract:

The advantages of small molecule therapeutics, such as their good pharmacological properties and wide range of therapeutic uses, make them a mainstay of the modern drug discovery process. This review highlights the latest developments in the field of artificial intelligence (AI), machine learning, targeted protein degradation (PROTACs), covalent drug design, and fragment-based drug discovery (FBDD), which are revolutionizing small molecule drug discovery and development. It illustrates the accelerating rate at which leads can be identified, the ability to expand the druggable proteome, and the potential to improve drug design with these new approaches, as well as their benefits, drawbacks, and current clinical applications. Some of the major challenges are also highlighted, such as limited clinical validation, drug resistance, bioavailability concerns and regulatory issues, as well as future research directions to make small-molecule therapeutics more efficient, precise and clinically translatable. In summary, the application of computational intelligence in conjunction with the latest advances in medicinal chemistry is projected to have a significant impact on the future of precision medicine and drug development.

Keywords: Small-molecule therapeutics; Drug discovery; Artificial intelligence; PROTACs; Covalent inhibitors.

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1. INTRODUCTION

In spite of the advancement of biologics, gene therapy, and cell-based medicines, small molecule therapeutics are still the mainstay of the modern drug discovery process[1]. Small molecules can be

defined as an organic compound with a molecular weight of less than 900 Da which can easily pass through cell membranes, bind to intracellular targets and are typically orally administered. Due to their favourable pharmacokinetic properties, ease of synthesis, low production costs, and defined regulatory pathway, these molecules have become the preferred therapeutic approach for the treatment of cancer, cardiovascular, infectious, neurological, metabolic and inflammatory diseases.

Small molecules have been responsible for more than 50% of all the novel drug approvals by the U.S. Food and Drug Administration (FDA) in the last decade. The FDA's Center for Drug Evaluation and Research (CDER) approved 46 new therapeutic products in 2025, including 12 biologics, 34 New Molecular Entities (NMEs) and 31 small-molecule drugs (67.4%). About 35% of these approvals were for oncology indications, with cardiovascular and inflammatory disease showing continued clinical importance, demonstrating the continued clinical relevance of small molecule therapeutics.

Conventional small-molecule drug discovery is still a difficult, costly and time-consuming process, although it has been successful. The time involved for development of one drug is 10-15 years and the total cost of development for one drug is often figured at more than US$2 billion, including the costs of unsuccessful drug candidates. In addition, approximately 90% of drug candidates that enter clinical trials are rejected due to poor efficacy, safety, and/or unfavorable pharmacokinetics. Such challenges have generated significant interest in novel approaches to find more efficient methods to reduce cost and attrition.

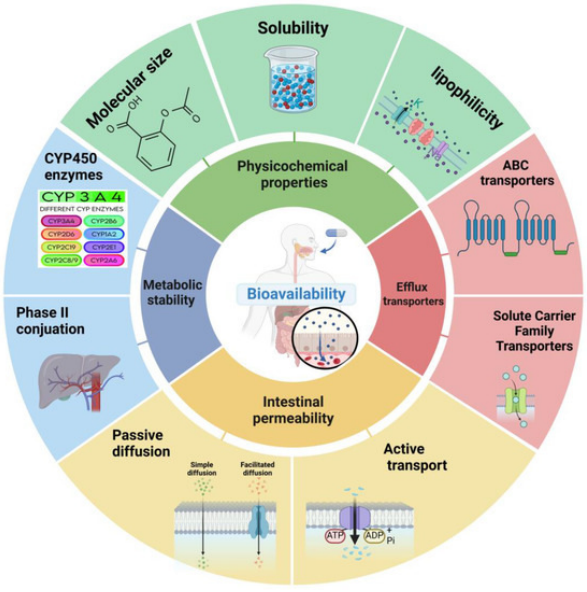

Figure 1: Small Molecule in Drug Delivery

Over the last several years, small molecule drug discovery has been profoundly changed by the advancements of computational science, artificial intelligence (AI), structural biology, medicinal chemistry and chemical biology. The range of druggable targets has been greatly increased thanks to the use of AI tools, virtual screening with machine learning and targeted protein degradation (TPD) approaches like PROTACs, covalent inhibitors, fragment-based drug discovery (FBDD), and DNA-encoded library (DEL) screening, which has led to faster identification and optimization of potential leads. These technologies can help researchers cover a wider landscape of chemical space, make more precise predictions for molecular properties, and find drug candidates faster than traditional experimental techniques[2].

In this way, the pharmaceutical sector is undergoing a paradigm shift from empirical drug discovery to integrated, data-driven and mechanism-based therapeutic development. Biologics are becoming more significant but recently, regulatory approvals and other evidence of their distinct advantages are evident that small molecules are the dominant therapeutic platform due to their versatility, scalability and targeting of intracellular disease mechanisms. Thus, knowledge of the newest technologies, trends and future developments in small-molecule therapeutics is vital to increasing the efficiency of drug discovery and meeting medical unmet needs in a wide range of disease areas.

1.1 Background and Context

Historically, small molecules (molecular weight < 900 daltons) have served as the backbone of therapeutics in the pharmaceutical industry, owing to their ability to easily penetrate cells, be orally bioavailable, be easily manufactured, and modulate intracellular targets that are inaccessible to biologics. In recent years, the emergence of new therapeutics such as monoclonal antibodies, antibody-drug conjugates, cell and gene therapy products, and oligonucleotide-based medicines has introduced a variety of new therapeutic modalities; however, small molecules remain the primary vehicles for new drug approvals by number, and underpin the bulk of the active pipeline within the pharmaceutical industry.

Traditional small molecule discovery is through iterative optimization of structure-activity relationships, high-throughput screening, and medicinal chemistry, which was historically slow, expensive and had high attrition[3]. The human proteome is estimated to contain many more proteins than are known to have deep binding pockets, and therefore are not easily targeted by conventional inhibitor design, and are considered to be “undruggable”. In the last five years, however, this paradigm has undergone a series of challenges and extensions, with the convergence of a number of innovations, including the use of generative and predictive artificial intelligence, event-driven pharmacology (e.g. targeted protein degradation), covalent and electrophile-based chemistry, and high throughput chemical library technologies (e.g. DNA-encoded libraries). All these advances

are changing the definition of a druggable target, and the pace at which candidate molecules can go from concept to clinic.

1.2 Objectives of the Review

This review aims to

- To synthesize recent peer-reviewed literature on the emerging methodologies and technological advancements shaping small-molecule drug discovery.
- To critically evaluate the strengths, limitations, and translational potential of key approaches, including artificial intelligence, targeted protein degradation, covalent inhibitors, fragment-based drug discovery, and DNA-encoded library technologies.
- To examine the current evidence supporting these methodologies and identify the major challenges limiting their successful clinical translation.
- To highlight existing research gaps and propose future directions that may enhance the efficiency, precision, and success rate of small-molecule therapeutic discovery and development.

1.3 Importance of the Topic

It is crucial to understand the current course of small-molecule discovery for a number of inter-related reasons. Small molecules are most easily accessed, most scalable worldwide therapeutic modality, especially for orally delivered, low cost medications required in the high and low resource world. Second, methodological efficiency gains, such as those enabled by artificial intelligence, new chemical modalities, and more advanced screening technologies, are not only of significant economic and public health impact for the pharmaceutical industry, but are also an issue of ever-growing R&D expenses and persistently high clinical attrition rates[4]. Third, new technologies that can target new drugs that were not previously druggable have direct implications for diseases which have little or no current treatment, such as many, if not most cancers, neurodegenerative conditions and rare genetic disorders. An honest balance between what has been achieved and what has yet to be realized is critical, therefore, for all stakeholders: researchers, funders, and policy makers.

2. CONTINUED CENTRALITY OF SMALL MOLECULES IN THE APPROVAL LANDSCAPE

Although earlier on it was thought that small molecules would increasingly be replaced by biologics, recent data from the FDA shows that small molecules are currently the primary modality

by volume. In 2025, the FDA's Center for Drug Evaluation and Research approved 46 novel drugs, with roughly two-thirds of these being small molecules (34) and the remaining third being novel biologics (12) – including ten small molecule kinase inhibitors across a range of oncology and non-oncology indications. A further analysis of these approvals by industry also suggests that over 70% of these small molecule approvals represented true novel mechanisms of action, including the use of allosteric inhibition, dispelling the notion that small molecule innovation is dying down. Selected 2025 approval parameters summarized in the table below are cited throughout the resources reviewed[5].

Table 1: Recent FDA Drug Approval Statistics Highlighting the Continued Dominance of Small-Molecule Therapeutics (CDER, 2025) [6]

Metric (CDER, 2025)	Value	Source
Total novel drug approvals	46 (34 NMEs + 12 BLAs)	FDA CDER 2025 Report
Small-molecule share of NMEs	31 of 46 (~67%)	New Drugs Approved by FDA in 2025
First-in-class approvals	~43-50%	FDA CDER / Industry analyses
Kinase inhibitors approved	10	New Drugs Approved by FDA in 2025
Small molecules with novel MoA	>70%	Biopharma PEG 2025 Analysis
Leading therapeutic area	Oncology (~35%)	FDA CDER 2025 Report

These numbers show that small molecule drug discovery is a living discipline in which new mechanisms, not sheer quantity, mark success.

2.1 Artificial Intelligence and Machine Learning in Small-Molecule Discovery

The use of artificial intelligence and machine learning has become crucial in the process of contemporary drug discovery owing to the fast analysis of biological and chemical data sets. The mentioned computational techniques support researchers in the whole process of drug discovery, including target identification, drug design, virtual screening, and pharmacokinetics optimization. AI analyzes the huge chemical library and finds the active compounds faster and more accurately than through traditional experimental methods.

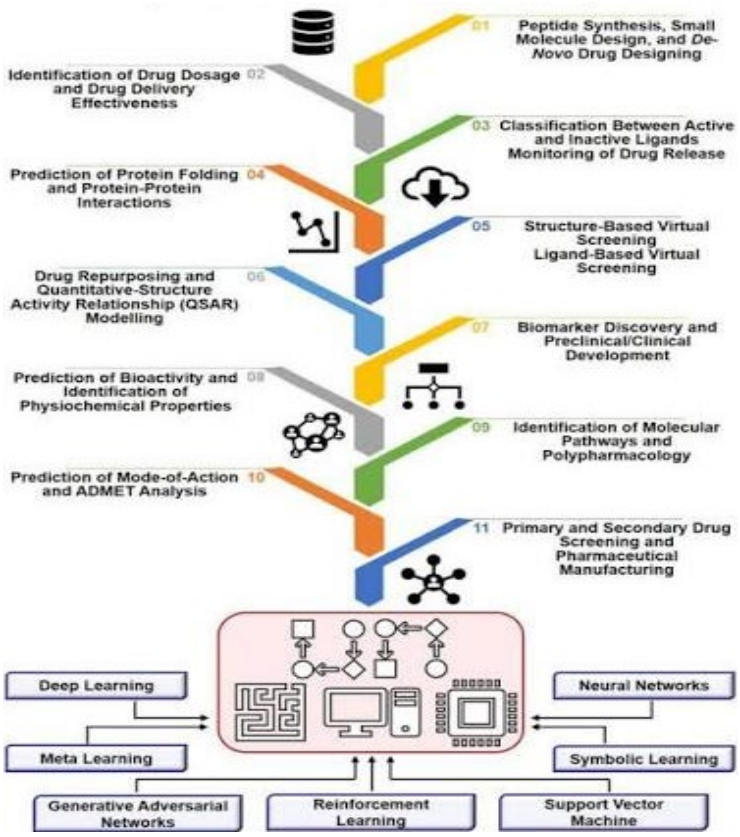

Figure 2: Artificial Intelligence in Small-Molecule Discovery

Machine learning has helped to improve ADMET properties and thus prevent failures of drugs at the later stages. Some pharmaceutical companies managed to apply AI-based platform, which helps them to decrease the time spent on drug discovery and expenses for research.

- Target identification and validation.
- Molecular de novo design.
- Virtual screening of the chemical libraries.
- ADMET and toxicity prediction.
- Lead optimization and drug repurposing.

Table 2: Applications of Artificial Intelligence in Small-Molecule Drug Discovery[7]

Application	Role in Drug Discovery	Major Benefit

Target Identification	Identifies disease-associated targets	Faster target validation
Molecular Design	Generates novel compounds	Reduced discovery time
Virtual Screening	Screens millions of compounds	Cost-effective lead selection
ADMET Prediction	Predicts pharmacokinetic properties	Lower clinical failure rates
Drug Repurposing	Identifies new indications	Reduced development cost

Artificial Intelligence has become an enabling technology in many different phases of drug discovery. The use of AI for data analysis has helped to select candidates while minimizing the experimental load and development timeframes[8].

2.2 Targeted Protein Degradation: PROTACs and Molecular Glues

The development of targeted protein degradation has been seen as an innovative treatment approach which involves the removal of disease-causing proteins and not just inhibition of their function. Whereas traditional inhibitors only prevent the proteins from being active, the Proteolysis-Targeting Chimeras (PROTACs) use E3 ubiquitin ligases for targeting the desired protein and degrading it via the process of ubiquitination. The molecular glue works in a similar way, except for the fact that it uses a single molecule to stabilize the interaction between the two.

Advantages

- Targets previously undruggable proteins.
- Catalytic mechanism allows repeated protein degradation.
- Reduced probability of resistance.
- Applicable to intracellular therapeutic targets.

Current Challenges

- Large molecular size.
- Limited oral bioavailability.
- Complex chemical synthesis.

- Need for improved tissue selectivity.

2.3 Covalent Inhibitors and the KRAS Paradigm

Covalent inhibitors have marked a significant milestone in precision medicine due to their ability to create permanent or slow-reversible bonds with a certain amino acid residue within target proteins.

The targeting of the KRAS G12C mutation has proven that certain proteins which were considered undruggable in the past could be successfully targeted through structure-based medicinal chemistry[9].

The approval of Sotorasib and Adagrasib for non-small cell lung cancer has confirmed the clinical value of covalent inhibition. Advances in modern docking and molecular dynamics have kept on contributing to the discovery of new covalent inhibitors.

Table 3: Clinically Important Covalent KRAS G12C Inhibitors[10]

Drug	Target	Therapeutic Indication	Clinical Status
Sotorasib	KRAS G12C	Non-Small-Cell Lung Cancer	FDA Approved
Adagrasib	KRAS G12C	Non-Small-Cell Lung Cancer	FDA Approved

Clinical development of the KRAS G12C inhibitors proves the efficacy of designing drugs through covalency for hitting those proteins that could not be accessed before and stresses the increasing role of structure-based medicinal chemistry.

2.4 Fragment-Based Drug Design and DNA-Encoded Libraries

Fragment-Based Drug Discovery (FBDD) and DNA-Encoded Libraries (DEL) techniques are useful technologies that allow efficient discovery of novel lead compounds. Fragment-Based Drug Discovery is based on screening of small molecular fragments with weak binding activity towards biological targets followed by optimization of these fragments into effective drugs by structure-based medicinal chemistry[11].

DNA-Encoded Libraries make it possible to screen millions to billions of chemically diverse molecules thanks to attachment of DNA barcodes to each compound.

- Highly efficient exploration of chemical diversity.

- Discovery of high-quality lead compounds.
- Structure-based drug discovery compatible technology.
- Fast hits discovery and optimization.

Thus, combination of FBDD and DEL technologies allows efficient optimization of lead compounds and chemical-space exploration, while the combination of these technologies with artificial intelligence and structural biology greatly improves small-molecule drug discovery[12].

Table 4: Summary of Representative Studies on Small-Molecule Drug Discovery and Therapeutic Development

Author(s) & Year	**Research Focus**	**Key Findings / Contribution**
Lee et al. (2019) [13]	Peptide drug development and design	Reviewed recent advances in peptide therapeutics, emphasizing rational peptide design, improved stability, drug delivery strategies, and the growing role of peptide-based medicines in modern therapeutics.
Quinn et al. (2017) [14]	Molecular networking in drug discovery	Demonstrated that molecular networking is a powerful computational strategy for natural product discovery, drug metabolism studies, biomarker identification, and precision medicine applications.
Xia et al. (2019) [15]	PD-1/PD-L1 immunotherapy	Summarized the clinical progress of PD-1/PD-L1 checkpoint inhibitors in advanced non-small-cell lung cancer and discussed future therapeutic opportunities for targeted cancer treatment.
Congreve et al. (2020) [16]	GPCR structural biology	Highlighted how recent advances in G protein-coupled receptor (GPCR) structural determination have accelerated structure-based drug design and facilitated the discovery of novel small-molecule therapeutics.
Sharma & Das (2019) [17]	Small molecule-derived carbon dots	Reviewed the synthesis and biomedical applications of carbon dots derived from small molecules, including their use in biosensing, bioimaging, drug delivery, and catalysis.

Table 4 contains papers that show how interdisciplinary the field of modern drug discovery is. The development of technologies such as peptide engineering, molecular networking, immunotherapy, structure biology of GPCRs, and nanotechnology-based drug delivery have contributed to improving modern pharmaceutical research and the number of options for treatment. These results emphasize the increasing use of computer-aided design and chemical technologies in modern drug discovery.

3. METHODOLOGIES AND FINDINGS

The progress made in the last years in computational sciences, medicinal chemistry, structural biology, and chemical biology has changed the field of small molecule drug discovery considerably[18]. In addition to the classic techniques using medicinal chemistry in an iterative fashion and high throughput screens, methods like artificial intelligence (AI), targeted protein degradation, covalent drug design, fragment-based drug discovery (FBDD), and DNA-encoded libraries (DEL) are gaining ground.

3.1 Generative AI and Machine Learning-Based Molecular Design

Artificial intelligence has now become an essential part of the process of drug discovery due to the fast molecular design and optimization provided by this technology. Deep learning methods such as graph neural networks, variational autoencoders, and reinforcement learning create new molecular structures with the desired characteristics before their synthesis in the lab. It allows reducing the costs and time that are needed for medicinal chemistry and leads to effective optimization[19].

There are several cases when companies implemented artificial intelligence in drug discovery. Exscientia created the first AI-designed drug candidate DSP-1181 which is now undergoing clinical trials, while Insilico Medicine developed Rentosertib (ISM001-055) for idiopathic pulmonary fibrosis in around 18 months.

Table 5: Representative AI-Based Drug Discovery Platforms[20]

Company	AI Platform	Drug Candidate	Therapeutic Area
Exscientia	Deep Learning	DSP-1181	Obsessive-Compulsive Disorder
Insilico Medicine	Generative AI	ISM001-055	Pulmonary Fibrosis

Recursion Pharmaceuticals	Machine Learning	Multiple Candidates	Oncology & Rare Diseases

AI platforms have significantly accelerated lead identification and molecular optimization, reducing discovery timelines while improving candidate selection.

3.2 Machine Learning-Guided Virtual Screening and ADMET Prediction

Machine learning has enhanced virtual screening through computational evaluation of millions of chemical compounds prior to laboratory experiments[21]. Additionally, AI-driven models for prediction of ADMET properties help to assess absorption, distribution, metabolism, excretion, and toxicity features at an early stage of drug development, thus reducing the risk of failure in later stages.

- Virtual screening of chemical libraries.
- Prediction of toxicity and pharmacokinetics parameters.
- Optimization of lead compounds on multiple parameters.
- Elimination of costs and time spent on experiments.

While these approaches have increased efficiency of drug discovery at an early stage, their predictability highly relies on the quality of experimental data.

3.3 Bifunctional Degrader Design: PROTACs and Molecular Glues

Targeted protein degradation technology is a relatively new treatment modality for getting rid of harmful proteins within cells. PROTAC technology uses a ligand for the target protein, ligand for the E3 ligase, and a linker, which causes ubiquitination and proteasomal degradation of the target protein. On the other hand, molecular glues enhance degradation of proteins through the stabilization of the association of target proteins and E3 ubiquitin ligases with just one small molecule[22].

PROTACs have been tested rapidly in clinical trials. ARV-110 is undergoing clinical trials for metastatic prostate cancer, while ARV-471 has entered phase III clinical trials for breast cancer. Linker-free PROTACs have been recently developed to increase drug stability and oral bioavailability.

Table 6: Clinical-Stage PROTAC Drug Candidates[23]

Drug Candidate	Target Disease	Clinical Phase
ARV-110	Prostate Cancer	Phase I/II
ARV-471	Breast Cancer	Phase III
ARV-393	Lymphoma	Phase I

The increasing number of clinical-stage PROTACs demonstrates the growing therapeutic potential of targeted protein degradation, particularly in oncology.

3.4 Covalent Structure-Based Drug Design: The KRAS G12C Case Study

Development of the covalent inhibitors that bind to nucleophilic amino acid residues in target proteins is currently one of the most important breakthroughs in the field of medicinal chemistry and drug design[24]. As opposed to traditional irreversible inhibitors, covalent inhibitors form a slowly or irreversibly cleavable bond with particular nucleophiles in the target protein such as cysteine residue, thus providing extended inhibition and increased efficacy of the drug. Discovery of the cryptic switch-II pocket adjacent to the mutant cysteine residue in KRAS G12C was a major step forward in the field of oncology that turned a previously undruggable protein into an accessible target.

The described scientific breakthrough made it possible to create Sotorasib and Adagrasib – the first KRAS G12C inhibitors successfully used for the treatment of patients with advanced NSCLC. These drugs proved the possibility of the selective targeting of a particular mutation without effecting normal cells. Besides, advancements in computational docking, molecular dynamics simulation and virtual screening methods were helpful in the search of new covalent scaffolds and optimization of drug leads for difficult targets.

However, there are still certain problems connected with the covalent inhibitors. These include formation of acquired mutations providing resistance to the inhibitor and inability to use them for the protein targets without reactive cysteine residue. Thus, further research should be directed at creating next-generation inhibitors, combinatory therapies and innovative computational techniques[25].

3.5 Fragment-Based Screening and DNA-Encoded Library Technologies

FBDD involves the discovery of fragments of molecules that interact very weakly with the therapeutic target followed by optimization to get potent leads. DNA-encoded libraries on the other

hand are used in the screening of billions of compounds tagged with DNA against biological targets for high affinity binders[26].

Table 7: Comparison of Emerging Small-Molecule Drug Discovery Approaches[27]

Methodology	**Major Advantage**	**Main Limitation**
Generative AI	Rapid molecular design	Limited clinical validation
Virtual Screening	Fast compound selection	Data dependency
PROTACs	Targets undruggable proteins	Poor bioavailability
Covalent Inhibitors	Strong target engagement	Drug resistance
FBDD & DEL	Efficient hit discovery	Specialized infrastructure

Each methodology contributes to different stages of the drug discovery pipeline. Their combined application has significantly improved lead identification, optimization, and the development of novel small-molecule therapeutics[28].

3. DISCUSSION

The speedy development of AI technology, computational techniques, and new medicinal chemistry practices has changed the field of small molecule drug discovery[29]. The papers analyzed in this review show that the modern technologies such as AI-based molecular design, machine learning assisted virtual screening, targeted protein degradation, covalent drug design, fragment-based drug discovery, and DNA-encoded libraries technology have greatly increased the effectiveness and efficiency of drug development[30]. Despite all the progress achieved due to these technologies, there are still some challenges in science, medicine, and regulation associated with the process. This section comments on the main results of the review, evaluates their implications, and describes the challenges facing the area.

3.1 Interpretation of Findings

In summary, the reviewed literature suggests that small molecule drug discovery is experiencing not a transformation but rather a consolidation of several different methodological trends[31]. AI is enabling the compression of early drug discovery timelines and expansion of chemical space; targeted protein degradation and covalent chemistry are broadening the definition of druggable targets by extending beyond simple active site occupancy; and FBLD and DEL technologies are

making the hit discovery process more efficient and rational. The common theme among all four methodologies is that feasibility of early stages, speed of timelines, size of libraries, and access to undruggable proteins has increased much more rapidly than late stage validation has. Several landmark successes (rentosertib, vepdegestrant, sotorasib) have shown that in certain instances, these technologies can yield clinical results, but there is still no evidence of an industry-wide increase in success rate.

3.2 Implications and Significance

There are several significant implications resulting from the findings of the review on the state of the art in early drug discovery[32]:

- Acceleration of Early Drug Discovery: The use of artificial intelligence (AI), machine learning (ML) and advanced screening techniques has resulted in shorter timelines in target identification, lead generation and optimization.
- Expansion of the Druggable Proteome: Novel approaches such as PROTACs, molecular glues, and covalent inhibitors allow targeting previously undruggable protein targets and thus provide additional treatment options for complex disorders.
- Improved Drug Design and Lead Candidate Selection: The use of computational approaches such as virtual screening and ADMET prediction is helpful in identifying high quality lead candidates at a lower cost and decreased risk of late-stage failure.
- Regulatory Issues: Increasing implementation of AI into the process of pharmaceutical research suggests that there is an urgent need for regulatory guidelines and validation of the use of such tools in drug development.
- Clinical Applications: Novel small molecule drugs show great results in oncology and are actively investigated in the field of neurological, autoimmune, infectious and rare genetic diseases.
- Future Developments in Pharmaceutical Industry: The use of computational approaches in combination with medicinal and structural biology should advance the field of precision medicine and personalized therapeutics[33].

3.3 Gaps and Future Research Directions

Even with great strides made, there are still some unresolved issues that need further investigations:

- **Proactive Clinical Validation:** While there have been great strides in reducing costs and increasing discovery rate, there needs to be proactive clinical validation on whether there are indeed improvements in clinical success rates[34].

- **Further Optimization of PROTAC Technology:** Further investigations should seek to optimize bioavailability, membrane permeability, stability of molecules, and the hook effect of existing PROTAC design[35].

- **Expanding Covalent Drug Discovery:** New computational approaches and medicinal chemistry approaches are needed in developing covalent inhibitors in those target proteins where there are no available reactive amino acid residues, like KRAS G12D[36].

- **Improvement of Machine Learning Models:** Better datasets are needed for better model predictions, robustness, and generalization of models[37].

- **Integration of DEL and Fragment Based Approaches:** Advanced computation tools need to be developed in order to improve hit selection, reduce false positives, and to facilitate lead optimization from large combinatorial libraries[38].

- **Biomarker Identification and Combination Therapy:** There is a need to identify predictive biomarkers and develop rationally driven combination therapies as means of overcoming drug resistance[39].

- **Multi-disciplinary Collaboration:** There will be a need for greater collaboration between computational scientists, medicinal chemists, structural biologists, clinicians, and regulatory agencies.

- **International Regulatory Agency Harmonization:** There needs to be set standards by international regulatory agencies to ensure validation, transparency, and ethical application of AI in drug discovery[40].

The above format is more concise, easier to understand and is consistent with the discussion format used in scientific papers like in Drug Discovery Today, Journal of Medicinal Chemistry, and Nature Reviews Drug Discovery.

4. CONCLUSION

The swift development of computational technology, artificial intelligence, and medicinal chemistry has led to a complete change in the field of drug discovery from small molecules. This paper highlights some of the important methodological advances and their application and issues

in terms of translating them into clinic. Through an analysis of existing literature, it is illustrated that the use of AI technologies, protein degraders, covalent drug design, fragment based drug discovery and DNA encoded libraries have led to the development of new drugs and increased druggability of certain targets. The below section will provide the main ideas discussed in this review along with its significance and future recommendations.

4.1 Summary of Main Insights and Conclusions

The development of small molecules as drugs remains an important aspect of contemporary medicine since it provides versatility, oral absorption, cost-effectiveness, and the possibility to affect the processes inside cells. This article will emphasize the importance of revolutionary technologies used in drug design, including artificial intelligence, machine learning-assisted virtual screening, PROTACs and molecular glues, covalent structure-based drug design, fragment-based drug discovery, and DEL technologies. These methods have provided faster identification of potential leads, broadened the list of druggable targets, and made the drug discovery process more efficient. Nevertheless, some difficulties, such as clinical validation, drug resistance, bioavailability problems, the accuracy of the model used for prediction, and standardization, still affect their clinical application.

4.2 Importance of the Review

This review is significant because:

- Gives an overview of advances made recently in small molecule drugs discovery that include: AI; machine learning; PROTACs; covalent inhibitors; FBDD; and DEL technologies.
- Illustrates the use of both computational and experimental techniques to show how these technologies make drug discovery more efficient.
- Shows the strengths and weaknesses of these emerging technologies, hence helping one to know how they can be used currently and possibly in the future.
- Puts emphasis on the significance of small molecule drugs in managing cancer; neurological diseases; infectious diseases; rare diseases; and many other complex diseases.
- Can act as an informative reference source to researchers, pharmaceutical experts, clinicians, and even regulatory bodies in modern drug discovery and development.
- Helps inform the future research work and innovations in the field.

4.3 Recommendations

Based on the findings of the present review, the following recommendations are suggested:

- Further strengthen clinical validation to examine the safety and efficacy of AI-assisted drug discovery methods over extended periods of time.
- Create new, accurate and easy-to-understand AI and machine learning algorithms employing large, varied and quality biological data sets.
- Enhance the properties of PROTAC and molecular glues, such as bioavailability, chemical stability and specificity.
- Implement the use of covalent drug discovery techniques to target proteins that lack suitable amino acid residues and develop resistance mechanisms.
- Use AI in combination with other techniques like FBDD, DEL and structure-based drug design.
- Foster collaboration between medicinal chemists, computer scientists, structural biologists, clinicians and regulators to advance the development of drugs.
- Formulate regulatory guidelines regarding validation, transparency and ethical use of AI-assisted drug discovery technologies on an international scale.
- Continue investing in novel technologies to create safe and effective small molecule therapeutics.

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