



Medicinal Chemistry in Modern Drug Discovery: Rational Design, Structure–Activity Relationships, And Future Perspectives

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Abstract:

Medicinal chemistry is a key field in contemporary drug discovery, bringing together the knowledge and understanding of chemical structures and biological activity, therapeutic efficacy, selectivity, pharmacokinetics and safety. The focus of this review is on rational molecular design, structure–activity relationships (SAR), molecular optimisation, structure-based and fragment-based drug discovery, pharmacogenomics, human-relevant models and biomarkers, and how this transition has occurred over the last few years from an empirical approach towards a rational, structure-driven, computational and precision drug design. The evidence reviewed suggests that these methods can be used to enhance target validation, molecular optimisation, compound prioritisation, patient selection, and clinical translation. The molecularly targeted drug designs in human clinical examples such as osimertinib, venetoclax and sotorasib show how important these methods are for human drug discovery, and the upcoming clinical study of rentosertib, an AI-generated inhibitor of TNIK, illustrates the promise of generative AI in the field of modern drug discovery. But there are significant challenges to address, such as biological complexity, patient heterogeneity, drug resistance, computational bias, limited model interpretability and rigorous experimental and clinical validation. As a whole, modern medicinal chemistry is making a transition to an integrated and human-relevant approach in which all aspects of drug development, including chemical, biological, computational, genetic and clinical data, are used to guide more precise, efficient and clinically relevant drug development.

Keywords: Medicinal Chemistry; Rational Drug Design; Structure–Activity Relationships; Molecular Optimisation; Artificial Intelligence; Precision Drug Discovery.

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1. INTRODUCTION

Medicinal chemistry has become a central discipline in the field of drug discovery due to its contribution in linking the structure of a chemical to its biological activity, therapeutic efficacy, selectivity, pharmacokinetics, and safety¹. The field has been slowly moving from empirical

screening of chemical compounds to rational, target-directed, structure-based, and computational approaches. Target validation, molecular modelling, structure–activity relationship (SAR) analysis, fragment-based drug discovery, computer-aided drug design, artificial intelligence (AI), pharmacogenomics and biomarker-based drug development combine to uncover and optimise potential therapeutic agents. These methods have led to the discovery of targeted drugs for a number of human diseases and have become more and more useful for more precise and patient-oriented drug discovery.

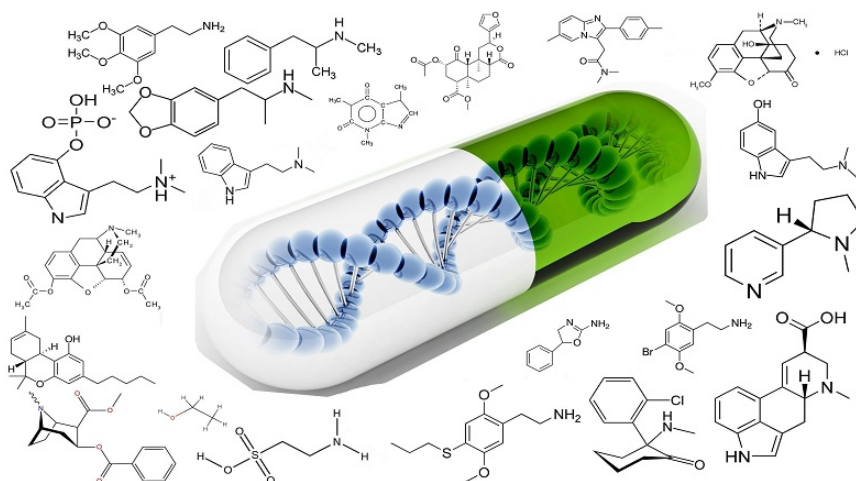


Figure 1: Modern Medicinal Chemistry and Drug Discovery²

The scope of medicinal chemistry has further expanded with the recent progress in structural biology, computational chemistry, molecular genetics and clinical pharmacology. Certain techniques, such as molecular docking, pharmacophore modeling, quantitative structure–activity relationship (QSAR) analysis, virtual screening, molecular dynamics, and AI-driven molecular generation, can help researchers identify potential compounds and predict their properties. Simultaneously, human genetic information and clinical biomarkers will be used to further validate targets and further select patient populations likely to be more responsive to a targeted drug. While these strides have been made, there are still obstacles to be overcome, such as biological complexity, drug resistance, patient variability, limited translation and predictive power, computational bias, and the need for careful experimental and clinical validation³. Thus, knowledge of the evolution and incorporation of the latest medicinal chemistry approaches is essential in assessing their role in the modern drug discovery process.

1.1 Background Information and Context

Empirical screening and iterative chemical modification were the traditional approaches used in drug discovery, and these methods could be time-consuming and offered limited information regarding the molecular mechanisms. The use of molecular biology, structural biology and computational chemistry helped determine specific therapeutic targets and more rational compound design, and SAR studies proved useful in elucidating the relationship between structural modifications and potency, selectivity, and pharmacological properties⁴. Leveraging structure-based design, fragment-based discovery, computational tools, AI, human genetics, pharmacogenomics, and biomarker usage, modern medicinal chemistry now follows an integrated approach comprising of target identification, molecular design, synthesis, biological evaluation, SAR analysis, optimisation, and clinical evaluation. While these methods have

enhanced precision drug discovery, they have enabled a better understanding of therapeutic response, drug exposure, and therapeutic side effects, and although drug development may be successful with these approaches, other factors such as efficacy, selectivity, pharmacokinetics, safety, and human clinical relevance must be considered.

1.2 Objectives of the Review

The key aims of this review are:

- To provide an overview of the major principles and approaches of modern medicinal chemistry in drug discovery.
- To examine the role of rational molecular design and target validation in therapeutic development.
- To discuss the importance of structure–activity relationships and molecular optimisation in lead development.
- To review the contribution of structure-based, fragment-based, computational, and AI-assisted approaches to drug discovery.
- To examine the relevance of human genetics, pharmacogenomics, and biomarkers in precision drug development.
- To evaluate the major strengths, limitations, challenges, and future perspectives of modern medicinal chemistry.

1.3 Importance of the Topic

The modern medicinal chemistry is very important because of the ability of enhancing the efficiency, selectivity, precision and scientific understanding of drug discovery. Systematic optimisation of chemical structure can be achieved through rational molecular design and SAR studies and detailed information on drug–target interactions and molecular properties can be obtained through structure-based, fragment-based and computational approaches. AI and machine learning can help further explore chemical space, prioritise compounds and optimise leads, while human genetic information, pharmacogenomics and biomarkers can bolster target validation and patient selection⁵. These strategies can be used as a unified strategy to create therapeutic agents with better pharmacological properties. The significance of medicinal chemistry, though, is not only in the discovery of high potency molecules, but also the development of clinically useful drug candidates which must exhibit the appropriate selectivity, pharmacokinetic parameters, safety, tolerability and human clinical activity. As a result, the blending of chemical, biological, computational, genetic and clinical information is becoming an essential part of the modern drug discovery process. To tackle the current limitations, to recognize gaps in research and to move forward in the field of medicinal chemistry towards more targeted, streamlined, human-relevant and clinically-potent drug development, it is essential to have a comprehensive understanding of these developments.

2. MODERN MEDICINAL CHEMISTRY APPROACHES

Medicinal chemistry has shifted from a trial-and-error approach to screening compounds to a structure-guided, computational and precision-based strategy. The state-of-the-art approach to drug discovery combines molecular targets with structure–activity relationships (SAR),

computational modelling, or artificial intelligence (AI), pharmacogenomics, biomarkers, and human clinical evidence⁶. These approaches enable the maximisation of drug potency, selectivity, pharmacokinetics, safety, and clinical relevance. The targeted therapies osimertinib, venetoclax and sotorasib are examples of rational medicinal chemistry that have been used in human clinical trials.

2.1 Rational Drug Design and Target Validation

Rational drug design is the process of designing and/or modifying compounds based on knowledge of a specific biological target and its molecular interactions. It involves target identification, target validation, structural analysis, hit identification, lead optimisation, SAR analysis, selectivity optimisation and clinical validation⁷. Human genetics and pharmacogenomics are gaining significance in the field of target validation since genetic variations can give clues to disease mechanisms and variation of treatment response.

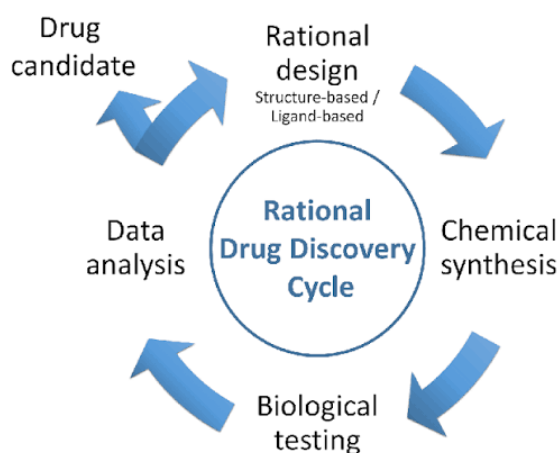


Figure 2: Rational Drug Discovery Cycle⁸

There are some important examples of this approach from human clinical evidence. For example, osimertinib is active against patients with EGFR-mutated non-small-cell lung cancer (NSCLC). The TREM study had an objective response rate of ~60% and 28% for T790M positive and negative patients, respectively, and a median PFS of 10.8 months and 5.1 months, respectively. These results proved the importance of molecular markers in targeted therapy for the clinical practice.

Strengths

- Target-specific molecular design
- Incorporation of human genetic information
- Improved patient selection
- Stronger mechanistic rationale

Weaknesses

- The relevance of your target may not be clear.
- In human diseases there may be several pathways involved.

- The presence of genetic associations does not imply that the genes are causing the disease.
- Reaction to treatment may be different among patients

2.2 Structure–Activity Relationship and Molecular Optimisation

Structure–activity relationship (SAR) is an essential part of medicinal chemistry. It explores the relationship between structure and biological activity and can be used to determine structural elements that are responsible for potency and selectivity⁹. Aromatic rings and heterocycles, alkyl groups, halogens, hydrogen bonding groups, stereochemical centres, linkers and other portions of the molecule can all be modified by medicinal chemists.

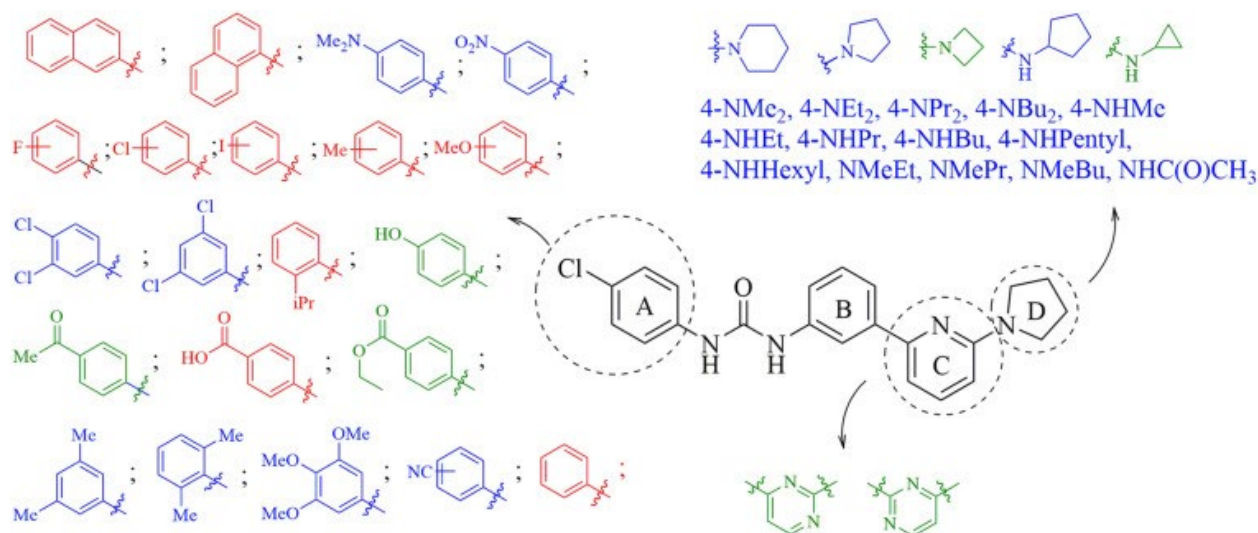


Figure 3: Structure–Activity Relationship (SAR)¹⁰

Human clinical development of venetoclax illustrates the critical need for molecular potency and clinical safety. Venetoclax is a selective BCL2 inhibitor that has shown to have significant efficacy in patients with relapsed chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). Tumour lysis syndrome, however, did pose a clinical management issue during development. It showed that in order to be successful in Medicinal Chemistry, you must strike a balance between target potency, target selectivity, exposure, dosing, and safety.

Strengths

- Systematic molecular optimisation
- Identification of important structural features
- Improvement of potency and selectivity
- Supports multi-parameter optimisation

Weaknesses

- Structural changes can affect several properties simultaneously
- Potency does not necessarily predict clinical efficacy
- Extensive chemical optimisation may be required

- Molecular responses may differ among patient populations

2.3 Structure-Based and Computational Drug Design

In the structure-based drug design, 3D information of the biological targets is used for molecular optimization. Information regarding the ligand–target interactions can be acquired through X-ray crystallography, nuclear magnetic resonance, cryo-electron microscopy, molecular docking, pharmacophore modelling, and molecular dynamics and binding-site analysis¹¹.

Virtual screening, QSAR, molecular-property prediction and computational optimisation are other aspects of computer-aided drug design. These approaches can be used to predict compounds that may possess desirable activity without a large amount of experimentation.

Important computational applications include:

- molecular docking;
- pharmacophore modelling;
- virtual screening;
- molecular dynamics;
- QSAR;
- molecular-property prediction.

Sotorasib is an example of structure-based medicinal chemistry for a clinically relevant compound. This drug is selectively active against KRAS G12C, and forms an irreversible covalent bond with the mutated cysteine. The overall objective response rate for patients with advanced KRAS G12C-mutated NSCLC was ~37% in a phase II study of patients with advanced KRAS G12C-mutated NSCLC, and median PFS was ~6.8 months¹². The clinical success of sotorasib represents the power of molecularly specific and covalent drug design in a therapeutic area that has proven to be challenging.

Strengths

- Includes a lot of information about molecular interactions
- Optimises rational compounds
- Enables virtual screening
- Saves time and resources by minimizing resource usage
- Ability to support challenging target drug discovery

Weaknesses

- Numerical simulations must be tested against experiments
- Can't always rely on docking scores for clinical activity prediction.
- Molecular models may not be representative of complete human biology.

- The results are very sensitive to the quality of the dataset and the model.

2.4 Artificial Intelligence, Pharmacogenomics and Precision Drug Discovery

AI is increasingly emerging in medicinal chemistry via machine learning, deep learning, generative molecular design, virtual screening, SAR prediction, molecular optimisation, biomarker identification and patient stratification¹³. Generative AI can suggest alternative molecule structures based on user-specified goals including potency, selectivity, physical-chemical characteristics, and synthetically viable.

One of the recent advances has been the clinical testing of rentosertib, a TNIK inhibitor identified using a generative-AI-based drug-discovery strategy for idiopathic pulmonary fibrosis. The compound was tested in a human clinical trial – a randomized phase 2a – that serves as a prime example of AI-driven molecular discovery moving into human clinical trials.

Pharmacogenomics works alongside AI and medicinal chemistry to uncover genetic variations that can affect drug metabolism, drug exposure, drug response and drug adverse effects¹⁴. Biomarkers may also help to select patients who are likely to respond to particular molecular treatments.

Strengths

- Rapid exploration of chemical space
- Generation of novel molecular structures
- Integration of genomic and clinical information
- Supports patient-specific drug development
- Potential acceleration of lead discovery and optimisation

Weaknesses

- AI models depend heavily on training data
- Dataset bias can affect predictions
- Some models have limited interpretability
- Generated molecules require experimental validation
- Human clinical evidence for AI-designed drugs remains comparatively limited

When combined, AI, pharmacogenomics, and biomarkers are helping drive the shift from traditional drug discovery to precision medicinal chemistry in which molecular design is becoming more closely linked to the biology and genetics of specific populations of patients¹⁵.

3. THEMATIC APPLICATIONS OF MODERN MEDICINAL CHEMISTRY IN DRUG DISCOVERY

Rational molecular design, SAR, structure-based approaches, artificial intelligence, human genetics, biomarkers and human-relevant models are all integrated aspects of modern medicinal chemistry for the enhancement of drug discovery¹⁶. These strategies facilitate

improved target selection, molecular optimisation, precision treatment, and clinical translation while acknowledging the need for experimental and human clinical validation.

3.1 Rational Molecular Design

Rational molecular design is an evolution from hit-hunting, empirical discovery to hypothesis-based medicinal chemistry. It combines target validation, structural biology, molecular modelling, pharmacophore identification, SAR analysis and experimental validation for the design of molecules with desired biological activity. The method allows researchers to comprehend the interaction between defined chemical structures and molecular targets and the impact of structural changes on potency and selectivity¹⁷. This approach has proven to be effective in targeted therapies, as molecular traits of the patient influence the therapeutic response. Human clinical research has already shown that this is the case in targeted therapies.

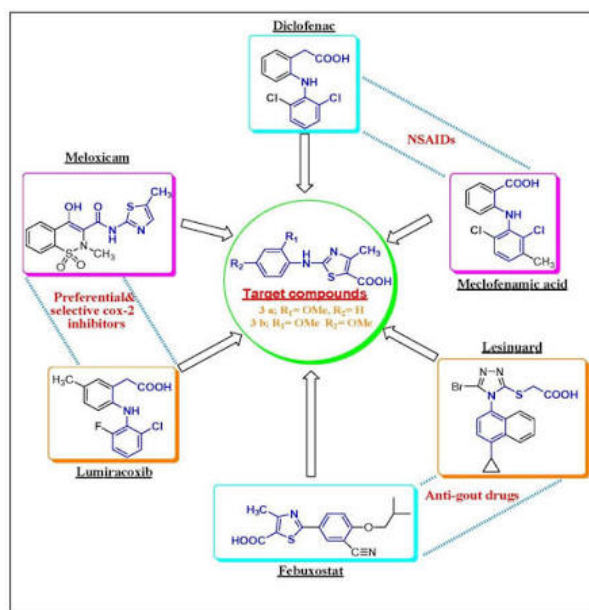


Figure 4: Rational Molecular Design¹⁸

One of the biggest advantages of a rational molecular design is that it can give a mechanistic explanation for drug development, and thus diminish the need for random compound screening. Molecular interactions, however, exist within complex biological systems and predictions from isolated targets may not fully describe the biology of the disease in humans. Compensatory pathways, drug exposure, resistance mechanisms and genetic variation can affect outcomes, as can patient heterogeneity. Thus, rational design must be based on human experimental evidence, pharmacological studies, bio-markers and clinical validation.

3.2 SAR and Lead Optimisation

Structure–activity relationship (SAR) analysis is a basic issue in medicinal chemistry and is employed to draw the structural–biological correlations. Modern lead optimisation takes into account the potency, as well as selectivity, solubility, permeability, metabolic stability, pharmacokinetics, safety, and target engagement¹⁹. This multi-dimensional approach aids in the design of compounds in addition to possessing a balanced pharmacological profile that is appropriate for human therapeutic use.

Clinical development has been shown to be useful for determining the molecular potency in combination with safety and pharmacological behaviour. The clinical activity of Venetoclax by selectively blocking BCL2 in chronic lymphocytic leukaemia (CLL) patients provided a clinically relevant example of its activity, and its development also emphasized the need to address treatment-associated safety issues. Therefore, SAR can be used as an effective tool for optimizing the lead, however, compromises in properties may occur during structural optimization. Experimental testing is always required, as changes that enhance one property might adversely impact another²⁰.

3.3 Structure-Based and Fragment-Based Drug Discovery

Structure-based drug design relies on the 3-D structure of biological targets to screen and optimise the structure of compounds that can bind to a specific site within the target. Molecular interactions can be provided in detail using techniques like X-ray crystallography, cryo-electron microscopy, nuclear magnetic resonance, molecular docking and pharmacophore modelling²¹. In addition to this, fragment-based drug discovery (FBDD) involves screening small chemical fragments and optimizing their binding affinity through fragment growing, linking and merging. The overlay strategy can be used to effectively cover chemical space and find new leads for drug development.

The great benefit is that the structure information can be used to direct accurate molecular optimization and to gain insight into drug–target interactions. However, in many cases binding of the fragments is relatively low and they can need significant optimisation to become a drug candidate in clinical trials²². Structural information alone also gives no prediction of human efficacy, pharmacokinetics, tolerability or safety and therefore experimental or clinical validation is crucial.

3.4 Computational and AI-Assisted Drug Discovery

Incorporating computational methods has broadened medicinal chemists' chemical space exploration capabilities and compound prioritization for experimental testing. The generation of molecules, prediction of molecular properties, prioritisation and optimisation of lead molecules can be supported through molecular docking, virtual screening, pharmacophore modelling, molecular dynamics, QSAR, machine learning, and deep learning²³. AI can also process intricate, complex bio and clinical data and uncover relationships that might not be recognisable using traditional methods. Using these technologies, it is possible to therefore evaluate large number of potential compounds in lesser time and resources.

A new human example is the development of a TNIK inhibitor, rentosertib, which was found via a Generative-AI-assisted process and tested in a Randomised Phase 2a clinical trial for IPF. This is a demonstration of the capabilities of computational technologies for a drug-development process from the generation of molecules to human clinical evaluation. But AI systems are still reliant on the quality and variety of the data they are trained with, and issues with dataset bias, interpretability, reproducibilities, and prediction errors can reduce the system's reliability²⁴. As a result, predictions created with AI need to be tested in experiments and by clinical humans.

3.5 Human Genetics and Precision Medicine

Human genetics will be an important tool to help identify and validate therapeutic targets and differences in response to treatment between people. Genetic variants, disease-associated mutations, gene-expression patterns and pharmacogenomic information can aid in the identification of biologically relevant targets and patient populations²⁵. Pharmacogenomics can also yield insights on variation in efficacy, exposure, adverse effect, metabolism, transporter activity and dose requirements. Combination of these data with medicinal chemistry can assist in the development of medicines targeted at particular molecular properties of patients.

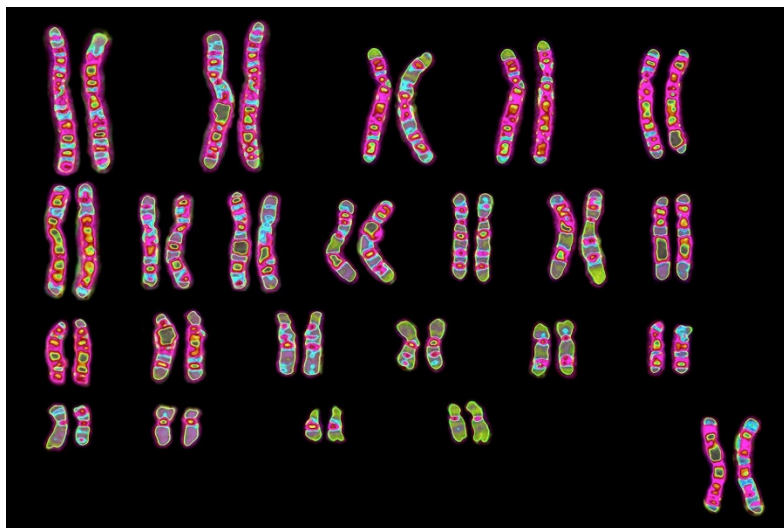


Figure 5: Human Genetics²⁶

In targeted oncology, the potential for targeted therapies to be developed for tumours with particular molecular changes has made precision medicine more relevant than ever. Examples of where molecular features are being used in therapeutic development and patient selection include EGFR-mutated cancers or KRAS G12C-mutated cancers. The variability of therapeutic responses is not, however, exclusively linked to the genetic information because other molecular changes, environmental factors, concurrent treatments and disease stage may also play a role. Consequently, precision medicinal chemistry is becoming increasingly humanized by incorporating human genetics, biomarkers, pharmacology, structural biology and clinical evidence.

3.6 Biomarker-Guided and Human-Relevant Drug Development

Biomarkers are measurable values that give information about disease biology, target engagement, therapeutic response, prognosis and treatment-related safety. They can help with patient selection, show if a drug has a desired effect on a target, track pharmacodynamic responses and understand clinical results. In precision medicine, the identification of patients at greater risk of response to a certain treatment is of special interest, which is why the use of predictive biomarkers is so crucial. Targeted oncology has already shown how molecular biomarkers can be directly linked to patient selection and clinical decision-making, via medicinal chemistry.

The human-relevant approach to drug discovery further reinforces the approach by bringing patient-derived cells, human tissues, organoids, cell models derived from iPS cells, human genetic data, clinical markers, and clinical pharmacology data. These approaches can deliver biologically relevant human information and may help to enhance disease heterogeneity, drug

sensitivity and resistance understanding. However, there are models that can't be generated by a man-made model of a human being and can't replicate all aspects of human physiology or disease²⁷. The integration of human-relevant models, computational science, molecular design, biomarkers, pharmacogenomics and clinical evidence is therefore required to advance future medicinal chemistry to ensure relevance to the human and to aid the development of better drugs.

4. MOLECULAR OPTIMISATION STRATEGIES IN MODERN MEDICINAL CHEMISTRY

Molecular optimisation is an important aspect of modern medicinal chemistry which deals with optimization of an initial hit/lead compound to make it a drug candidate with better biological and pharmacological properties²⁸. Their iterative chemical alterations include systematic modifications to the chemical structure to optimize potency, selectivity, solubility, permeability, metabolic stability and safety. Structure–activity relationship (SAR) studies are very important because they help to identify chemical groups involved in the desirable or undesirable biological effects. By repeating the cycle of chemical synthesis, biological testing and SAR (structure activity relationship) interpretation, medicinal chemists can continually improve lead molecules.

Structure-based drug design and computers have become popular tools in modern molecular optimisation to inform chemical modifications. The use of molecular docking, pharmacophore modelling, molecular dynamics, QSAR and virtual screening can aid in the prediction of the effect of structural changes on target binding and molecular properties. Small chemical fragments can also be identified using fragment-based methods which can then be grown, linked, or fused to create more potent compounds. These methods will enhance the use of chemistry in the search process and can give detailed insights into drug–target interactions.

The other major breakthrough is the use of AI and machine learning in molecular optimisation. AI tools can help predict molecular properties, identify promising structural modifications, prioritise compounds and come up with new chemical structures. Such technologies can help to minimize the number of compounds that need to be tested in the lab, and can contribute to the optimization of multiple properties at once²⁹. Computational predictions, however, rely on the quality and representativeness of data available and thus need to be corroborated by experiments.

Table 1: Summary of Selected Literature on Modern Medicinal Chemistry³⁰

Author(s) & Year	Study Focus	Methodology/Model	Key Findings
Wang et al. (2021) ³¹	Peptide-based PPI inhibitors	Rational peptide design and structural analysis	Rational design improved peptide binding and selectivity; stability and delivery remained challenges.
Ding & Xue (2024) ³²	Modification of bioactive natural products	Chemical modification and SAR analysis	Structural optimisation improved potency,

			selectivity, stability, and drug potential.
Talevi (2023)³³	Computer-aided drug discovery	Molecular modelling, docking, virtual screening, and pharmacophore approaches	Computational methods supported compound screening and lead optimisation but required validation.
Prasher & Sharma (2021)³⁴	Indane and its analogues	Structural modification and SAR evaluation	Indane derivatives provided useful scaffolds for biological activity and molecular optimisation.
Hemmerich & Ecker (2020)³⁵	In silico toxicology	SAR, deep learning, and adverse outcome pathways	Computational and deep-learning approaches strengthened toxicity prediction, subject to data quality and validation.

Human relevant information, such as pharmacogenomics, biomarkers, human derived cells and clinical pharmacology data are also now increasingly included in modern optimisation. This information may contribute to understanding the variation in drug response, drug exposure, drug toxicity and therapeutic effectiveness between patients. The effective molecular optimisation is no longer just to find compounds that are more potent, but compounds that have an optimized balance of efficacy, selectivity, pharmacokinetics, safety, and patient-specific therapeutic relevance.

5. DISCUSSION

This discussion critically evaluates the findings reviewed on the current role of medicinal chemistry in drug discovery, focusing on rational molecular design, structure–activity relationships, molecular optimisation, computational methods, artificial intelligence, human genetics, pharmacogenomics and biomarkers³⁶. The evidence reviewed demonstrates that medicinal chemistry has moved beyond mere compound screening to more target oriented, structure-guided, computational and precision oriented approaches. Human clinical examples with osimertinib, venetoclax and sotorasib highlight the potential of molecular design and optimisation for future targeted therapeutic applications, and the novel approaches that can be used to accelerate drug discovery, such as rentosertib powered by AI.

5.1 Interpretation and Analysis of Current Findings

The results suggest that rational molecular design and SAR are still essential to contemporary medicinal chemistry. Target validation, structural analysis, molecular modelling, and systematic chemical modification enable the relationship between molecular structure, target interaction, potency and selectivity to be established³⁷. In the case of the treatment of lung cancer, for instance, there is strong clinical evidence that linking molecules with treatment response, like osimertinib in EGFR-mutated lung cancer and sotorasib in KRAS G12C-mutated cancers, is crucial. But the molecular activity is not a rule of clinical success, as pharmacokinetics, safety, patient variability, resistance and biological complexity may impact success.

5.2 Clinical Implications and Significance

The new concepts of medicinal chemistry are relevant to clinical drug development, since molecular optimisation now takes into account not only potency but more properties. The parameters involved in the lead optimisation process include selectivity, solubility, permeability, metabolic stability, pharmacokinetics, safety and target engagement³⁸. Venetoclax is an example of the critical need to balance molecular activity with safety and appropriate clinical management in the clinical development of a drug. Likewise, pharmacogenomics and biomarkers can guide patient selection and explain variability in efficacy and drug exposure, as well as adverse effects, further bolstering precision drug development.

5.3 Research Gaps and Limitations

Although a great deal has been accomplished, there are some remaining drawbacks to the state of modern medicinal chemistry. Predictions relying on computational and AI methods are highly dependent on the quality and variety of the available datasets, and problems with datasets such as bias, limited interpretability, or lack of experimental validation can impact prediction reliability. Structural and computational models can also lack an accurate representation of the full complexity of the human body³⁹. In addition, differences in therapeutic response cannot be entirely attributed to genetic information and biomarkers as others molecular differences, disease heterogeneity, environmental factors and/or concurrent therapies may play a role. These restrictions underscore the need for more robust chemical, biological, genetic, computational and clinical validation and integration.

5.4 Future Research Directions

Future research should involve the incorporation of rational molecular design, SAR, structure-based approaches, AI, pharmacogenomics, biomarkers, and human-relevant models into a single drug-discovery process. Using patient-derived cells, human tissues, organoids, iPSC-derived models, human genetic data, and clinical pharmacology data could enhance translational relevance⁴⁰. The use of AI and computational technologies should be supported by experimental proof and human clinical validation, whereas the molecular optimisation should aim at achieving a profile with a compromise between efficacy, selectivity, pharmacokinetics, safety and patient-relevant therapeutic relevance. The integrated approaches could lead to improved drug development in more precise, efficient and clinically effective ways.

6. CONCLUSION

The present work demonstrates that the current medicinal chemistry has shifted the approach to drug discovery from an empirical screening process to structure-based rational drug design, computational and precision drug design. Combination of rational drug design, structure-activity relationship (SAR) analysis, molecular optimisation, structure-based drug discovery and fragment-based drug discovery, computational modelling, artificial intelligence, pharmacogenomics and biomarkers has enhanced patient selection, compound prioritisation, lead optimisation and target validation. Human clinical examples of molecularly targeted drug development with osimertinib, venetoclax, and sotorasib, and the emerging clinical investigation with rentosertib, illustrate the clinical relevance of molecularly targeted drug

development and how AI-assisted drug discovery works. But, the study also suggests that potency is not enough to assure the treatment's success, since the pharmacokinetics and safety profile of the drug, resistance, biological complexity, patient heterogeneity and biological variability are all factors that must be taken into consideration. The computational and AI-based solutions also demand high-quality data, experimental validation and clinical validation by humans. Hence, future drug discovery must combine medicinal chemistry with human genetics, pharmacogenomics, markers, human-relevant models, computational technologies and clinical data to create drug candidates that are balanced, both in efficacy and selectivity, in terms of their pharmacokinetics, safety and relevance to human patients.

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