REVIEW ARTICLE

Benzimidazoles in Medicinal Chemistry: Current Trends and Future Opportunities

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ABSTRACT

Because of their various pharmacological actions and structural plasticity, benzimidazoles, a class of heterocyclic molecules, have received much attention in medicinal chemistry. This review paper aims to provide a complete overview of the current developments and future possibilities of benzimidazoles as promising candidates for the creation of innovative therapeutic medicines. The introduction discusses the importance of benzimidazoles in medicinal chemistry, emphasizing their wide range of uses, which include antibacterial, anticancer, and central nervous system actions. The structural properties of benzimidazoles and the effect of substituent changes on their biological activity are investigated, as well as crucial structure-activity relationship (SAR) investigations. The review looks into the synthesis of benzimidazole derivatives, including both traditional and novel methods. The rise of microwave-assisted synthesis, green chemistry methodologies, and solid phase strategies for chemical manufacturing are explored. A thorough review of current breakthroughs in benzimidazole medicinal chemistry emphasizes the importance of target-based drug design, high throughput screening, and computational approaches in expediting drug discovery. As prospective directions for future research, the numerous applications of benzimidazoles in personalized medicine, nanotechnology-assisted medication delivery, and the examination of natural sources for chemical discovery are noted. However, concerns about toxicity, pharmacokinetic limits, and intellectual property difficulties have been raised, leading a cautious assessment of benzimidazole-based therapies. Benzimidazoles, medicinal chemistry, pharmacological activities, synthesis methodologies, structure-activity connection, drug discovery, and future possibilities are some of the keywords used in this study.

Keywords: Benzimidazoles, Pharmacological activities, Drug discovery, Nanomedicines.

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INTRODUCTION

Benzimidazoles are a well-known class of heterocyclic compounds that have received a lot of interest in the field of medicinal chemistry. Their distinct structural characteristics and a wide spectrum of pharmacological activity have driven them to the forefront of drug research and development. This study seeks to give an informative exploration into the multifarious world of benzimidazoles, delving into their structural complexities, emphasizing their amazing significance within medicinal chemistry, and clarifying the precise objectives and bounds of this thorough analysis. Benzimidazoles consist a fused heterocyclic ring structures with two nitrogen atoms. They are crucial therapeutic factors in the search for new drugs, numerous other medications have been developed from benzimidazole such as pracinostat (anticancer), lansoprazole (proton pump inhibitors), albendazole (anthelmintic), enviroxine (antiviral), lansoprazole (antiulcer), ridinilazole (antibacterial), flubendazole (antiparasitic), risperidone (Antipsychotic), etofylline (bronchodilator). Many new pharmaceutical drugs containing benzimidazole are anticipated to be available within the next few years as a result of the extensive therapeutic applications of benzimidazole and its derivatives. This has inspired many researchers to develop more pharmacologically active molecules bearing benzimidazole nucleus, expanding the scope of finding a remedy for other diseases. To highlight the benefits of employing benzimidazole in drug development, we outline pharmacological active benzimidazole hybrids in this review.

A Brief Overview of Benzimidazoles

Benzimidazoles, which have a fused benzene and imidazole ring structure, have an extraordinary capacity for structural variety due to selective substitution patterns. This basic structural motif serves as the foundation for a wide range of derivatives, each with potentially diverse biological features. The addition of multiple substituents provides adaptability, which underlines its application across a wide range of therapeutic domains.

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Medicinal Chemistry Importance

The extensive range of pharmacological effects of benzimidazoles emphasizes their importance in medicinal chemistry. Their adaptability allows them to have powerful impacts in areas such as antimicrobial defense, cancer treatment, and central nervous system modulation. The complicated interplay between the core structure and the added functional groups contributes to their ability to engage selectively with biological targets, placing them as prospective drug development options (Table 1).

This study seeks to provide a complete examination of the current state of benzimidazoles in medicinal chemistry, including their numerous applications, synthetic techniques, and future possibilities. We hope to provide a comprehensive view of the delicate interplay between structure and activity by deconstructing their structural properties and understanding their significance in distinct pharmacological situations. Furthermore, we aim to investigate the changing landscape of benzimidazole research, focusing on new trends and prospective discoveries that could affect the future of medicinal chemistry.

We intend to provide both researchers and practitioners with an informed perspective of the current landscape and the potential pathways ahead as we embark on this adventure into benzimidazoles. We hope to uncover the multifarious potential of benzimidazoles and encourage additional innovation in the quest for therapeutic interventions through a rigorous examination of available material.

Benzimidazole Structural Characteristics

Benzimidazoles, distinguished by their fused benzene and imidazole ring structure, contain a plethora of structural subtleties that play an important role in their pharmacological actions. This section dives into the fundamental structural characteristics of benzimidazoles, investigating the effect of substituent changes on biological activity and clarifying the structure-activity relationships (SAR) principles that regulate their interactions with biological targets.

Substituent variations and the core structure

A conjugated ring structure composed of a benzene ring fused with an imidazole ring is at the heart of benzimidazoles (Figure 1). This structure acts as a scaffold on which various functional groups can be attached, allowing the molecule's chemical and pharmacological properties to be tailored. Strategic substitutions increase structural diversity, which increases selectivity and affinity for certain target molecules, allowing for the construction of compounds with desired properties.

Substitution effects on biological activity

The kind and position of substituent on the core structure significantly impact the biological activity of benzimidazole derivatives. Substitutions can have a variety of impacts, such as increased solubility, higher binding affinity, changed metabolic stability, and altered pharmacokinetic profiles. An in-depth examination of substituent effects shows the delicate balance between desired biological activity and probable side effects, which guides the design and optimization of benzimidazole-based therapies.

Table 1: Common benzimidazole derivatives and their biological activities[1]

S. No.	*Benzimidazole derivative*	*Biological activity*
1	Albendazole	Antiparasitic, antihelminthic
2	Mebendazole	Antiparasitic, antihelminthic
3	Thiabendazole	Antifungal, antiparasitic
4	Flubendazole	Antiparasitic
5	Metronidazole	Antibacterial, antiprotozoal
6	Rabeprazole	Proton pump inhibitor
7	Omeprazole	Proton pump inhibitor
8	Lansoprazole	Proton pump inhibitor
9	Etofylline	Bronchodilator
10	Astemizole	Antihistamine, antiarrhythmic
11	Levamisole	Immunomodulator, anthelmintic
12	Domperidone	Antiemetic
13	Tegaserod	Serotonin receptor agonist
14	Meclizine	Antihistamine, antiemetic
15	Niclosamide	Anthelmintic, antiparasitic
16	Benzocaine	Local anesthetic
17	Albendazole sulfoxide	Antiparasitic, antihelminthic
18	Pantoprazole	Proton pump inhibitor
19	Carbendazim	Antifungal, antiparasitic
20	Oxibendazole	Antiparasitic, anthelmintic
21	Risperidone	Antipsychotic
22	Fenbendazole	Anthelmintic, antiparasitic
23	Mebendazole oxide	Antiparasitic, antihelminthic
24	Nimorazole	Antibacterial, antiprotozoal
25	Tinidazole	Antibacterial, antiprotozoal
26	Praziquantel	Anthelmintic
27	Ketoconazole	Antifungal
28	Itraconazole	Antifungal
29	Tiabendazole	Antiparasitic, antihelminthic
30	Oxfendazole	Antiparasitic, anthelmintic
31	Rabeprazole sulfide	Proton pump inhibitor
32	Clopidogrel	Antiplatelet
33	Astemizole oxide	Antihistamine, antiarrhythmic
34	Niclofolan	Anthelmintic
35	Lansoprazole sulfide	Proton pump inhibitor
36	Vardenafil	Erectile dysfunction treatment

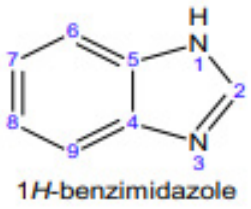

Figure 1: Benzimidazole structure with numbering

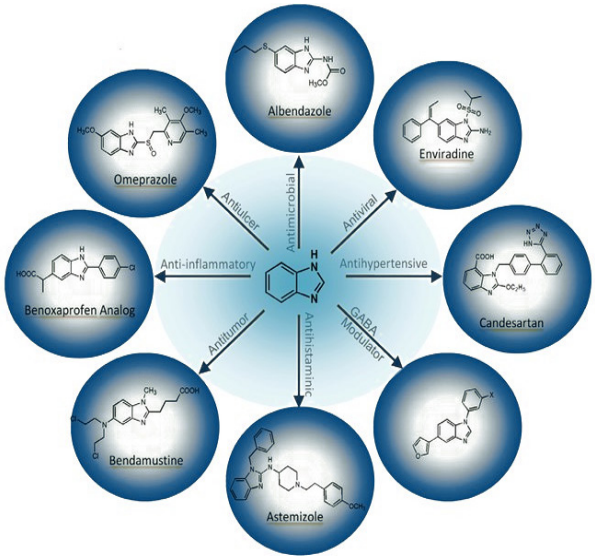

Figure 2: Drugs with benzimidazole molecule[5]

Studies on the structure-activity relationship

Understanding benzimidazoles' structure-activity relationship (SAR) is critical for unraveling the complex links between their structural properties and pharmacological effects. SAR studies provide vital insights into the best substituent placement and characteristics for generating targeted biological effects. Researchers can justify known effects, forecast the impact of alterations, and lead the production of compounds with improved efficacy and lower toxicity by evaluating the relationships between chemical structure and activity profiles.[2-4]

Benzimidazole Pharmacological Diversity

Benzimidazoles have a great pharmacological diversity, making them a significant class of chemicals with numerous therapeutic applications (Figure 2). This section goes into their various involvements in antimicrobial activities, including antibacterial, antifungal, and antiparasitic contributions.

Antimicrobial Properties

Benzimidazoles have exhibited outstanding efficacy as antimicrobial agents, demonstrating their diversity and potency. This section focuses on their contributions to antibacterial, antifungal, and antiparasitic actions.[6]

- *Antibacterial properties*

Certain benzimidazole compounds have high antibacterial activity, making them promising candidates for treating bacterial infections. These chemicals impede bacterial growth and survival by interfering with critical biochemical processes via interactions with important bacterial enzymes or cellular components. Antibacterial drugs based on benzimidazoles have shown potential against various pathogens, including gram-positive and gram-negative bacteria.

- *Antifungal action*

Benzimidazoles have emerged as drugs capable of fighting fungal infections in the field of antifungal treatments. Benzimidazole derivatives have fungicidal or fungistatic effects on a variety of fungal species *via* affecting fungal cell division, membrane integrity, or the manufacture of essential components. Because of their capacity to target both systemic and superficial fungal diseases, they are useful tools in the creation of antifungal drugs.[7]

- *Antiparasitic properties*

Benzimidazoles are crucial in antiparasitic interventions, providing effective treatment choices for a variety of parasitic illnesses. They impair parasites' cellular division and cause structural damage by interfering with their microtubule dynamics. As a result, benzimidazole derivatives are useful in combating parasitic infections such as nematodes and cestodes, making a substantial contribution to worldwide parasitic disease control efforts.[8]

Anticancer activity

Benzimidazoles have emerged as intriguing oncology candidates, demonstrating their potential as effective anticancer medicines. This section digs into their unique contributions to cancer therapy, concentrating on the fundamental mechanisms of their anticancer action and emphasizing current clinical uses.

- *Anticancer activity mechanisms*

Benzimidazole compounds have varied anticancer actions, indicating their capacity to target numerous disease markers. Some chemicals impede mitotic spindle formation and cause cell cycle arrest or death by interfering with microtubule dynamics. Others, such as angiogenesis, proliferation, and DNA repair, hinder essential enzymes or processes involved in cancer growth. Benzimidazoles have the potential to target a wide spectrum of cancer types due to their complex actions.[9]

- *Clinical applications in the present*

Several benzimidazole-based drugs have advanced from preclinical to clinical trials, indicating substantial progress in their development as anticancer medicines. The drugs' safety, effectiveness, and tolerability in cancer patients are assessed in these trials. Some benzimidazole compounds have shown promise in early stage trials, with encouraging responses in terms of tumor reduction, disease stabilization, or improved patient outcomes. These chemicals' different modes of action provide a foundation for their possible incorporation into multiple cancer treatment regimens.

The investigation of benzimidazoles' anticancer potential highlights their importance as agents with the potential to expand the arsenal of anticancer therapies. These chemicals provide new options for individualized and targeted cancer treatment by targeting certain cancer-associated pathways and processes. Benzimidazoles may emerge as transformational additions to the area of oncology as clinical trials proceed and our understanding of their mechanisms develops.

Benzimidazole Derivative Synthetic Strategies

The synthesis of benzimidazole derivatives is a critical component of their medicinal chemistry research (Figures 3 and 4). This section delves into the many synthetic tactics used to create these molecules, including traditional approaches,

contemporary methodology, and solid phase synthesis techniques.[10]

Approaches to Classical Synthesis

Traditional approaches for manufacturing benzimidazole derivatives frequently entail multistep processes, including functional group modification and the use of multiple chemicals. Among the fundamental routes are condensation reactions between ortho-diamines and aromatic carboxylic acids or their derivatives. While traditional methods provide a historical foundation for benzimidazole synthesis, they may be linked with lengthier reaction durations and significant difficulties in reaching high yields and purity (Table 2).

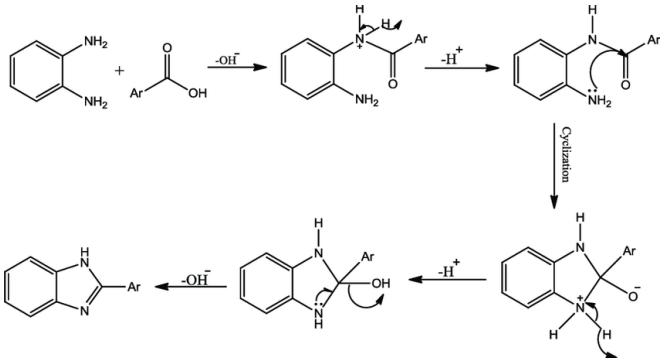

Figure 3: Synthetic scheme for benzimidazole

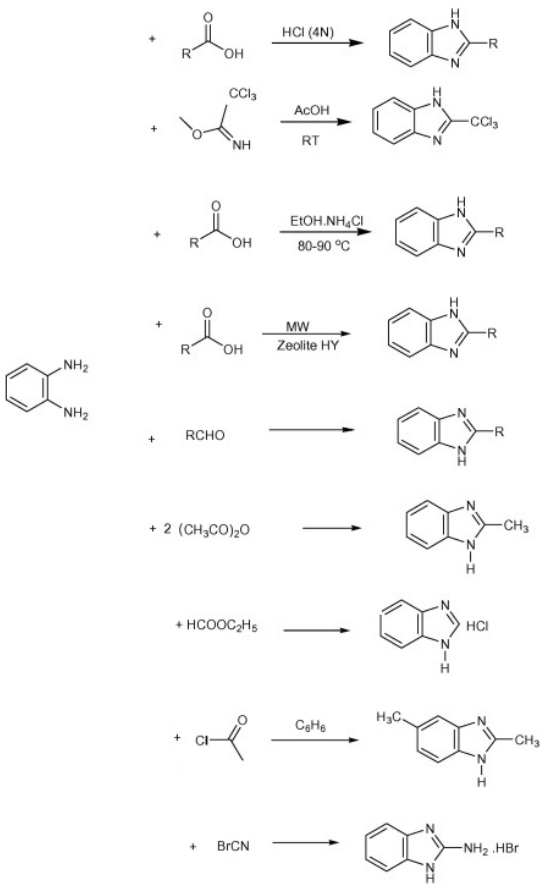

Figure 4: Different synthetic scheme for benzimidazole from o-phenylenediamine

Synthetic methods of today

- *Synthesis assisted by microwaves*

Microwave-assisted synthesis, for example, has revolutionized the creation of benzimidazoles. Microwave irradiation promotes quick heating and efficient energy transfer, resulting in shorter reaction times and higher yields. This method has simplified the synthesis of benzimidazole derivatives, making them more accessible for medicinal chemistry research.

- *Green chemistry methodologies*

Green chemistry ideas have also permeated benzimidazole synthesis, with a focus on sustainability and minimizing environmental effects. Solvent-free or water-based reactions, catalytic methods, and bio-inspired transformations aid in greening synthetic pathways. These methodologies align with the growing emphasis on ecologically benign approaches to chemical synthesis while ensuring the efficiency required for drug development operations.

Benzimidazole solid phase synthesis

Solid phase synthesis is a high throughput method for producing benzimidazole derivatives. Researchers can streamline purification operations and accelerate reactions by anchoring the initial components to a solid substrate. This method is well suited to the demands of combinatorial chemistry and parallel synthesis, allowing for the production of various chemical libraries for quick screening.

Traditional multistep techniques for the synthesis of benzimidazole derivatives have given way to novel and efficient technologies. The use of microwave-assisted techniques, green chemistry principles, and a solid phase procedure has not only made these molecules more accessible, but it has also facilitated their evaluation as possible therapeutic agents in medicinal chemistry research (Table 3).[20]

New Developments in Benzimidazole Medicinal Chemistry

In recent years, the discipline of benzimidazole medicinal chemistry has made great development thanks to novel techniques that have changed drug discovery and design. This section examines major recent achievements in this field, emphasizing the roles of target-based drug design, high throughput screening (HTS), and computational approaches in defining the landscape of benzimidazole research.

Targeted drug development

In benzimidazole research, molecular and structural biology advances have paved the way for target-based drug design. Researchers can customize benzimidazole derivatives to engage with specific binding sites or active pockets by understanding the three-dimensional structures of relevant proteins. Compounds can be optimized using rational design methodologies to achieve improved selectivity and affinity for target molecules, increasing the potential for therapeutic efficacy while decreasing off-target effects.[21]

Table 2: Different approaches to the synthesis of benzimidazole[11-19]

Method	*Reaction components*	*Catalyst/Conditions*	*Advantages*	*Disadvantages*	*Ref.*
Hantzsch synthesis	o-Phenylenediamine + Aldehyde	Acidic catalyst (e.G., Hcl, acetic acid)	Widely used, simple procedure	Limited scope of substituents requires reflux	11
Bischler-Napieralski reaction	1,2-Phenylenediamine + Ketone	Acidic catalyst, heat	Produces 2-aminobenzimidazole	Limited to ketones, low yield	12
Debus-Radziszewski reaction	o-Phenylenediamine + Formic Acid	Sulfuric acid, heat	Useful for 2-alkylbenzimidazoles	Requires high temperatures, formic acid handling	13
Duff reaction	o-Phenylenediamine + Aldehyde	Sulfuric acid, heat	Efficient for various substituents	Harsh reaction conditions	14
Cyclodehydration of diamides	Diamide + Phosphorous Oxychloride	Base, heat	Diverse substrate scope	Generation of POCl3 byproduct	15
Condensation with diaminomaleonitrile	Diaminomaleonitrile + Aldehyde	Base, heat	Provides functionalized benzimidazoles	Limited to specific starting materials	16
Microwave-assisted synthesis	Diamine + Aldehyde	Microwave irradiation	Rapid reactions, improved yields	Specialized equipment, limited scale	17
Green chemistry approaches	Diamine + Aldehyde	Solvent-free, water-based, catalysis	Environmentally friendly, reduced waste	Reaction optimization, substrate limitations	18
Solid-phase synthesis	Resin-bound amine + Aldehyde	Solid-phase conditions	High-throughput, efficient for combinatorial	Requires specialized equipment, specific resins	19

Table 3: Comparative analysis of classical and modern synthesis approaches for benzimidazole derivatives

Synthesis approach	*Advantages*	*Disadvantages*
Classical methods	Established protocols Widely available starting materials	Multistep procedures Limited regioselectivity Longer reaction times
Modern methods	Microwave assisted synthesis Rapid reaction rates High yields Energy efficient Green chemistry Approaches Reduced environmental impact Solvent free or water based reactions Catalytic processes	Limited to specific types of reactions Equipment requirements Reaction optimization Challenges Limited to certain reaction types Reaction optimization challenges
Solid phase synthesis	Parallel synthesis capability Enhanced purification Faster reaction rates	Limited to specific compounds Requires solid phase equipment Complexity in library synthesis

Efforts in high throughput screening

Rapid evaluation of vast chemical libraries has been made possible by high throughput screening technologies, permitting the identification of potential benzimidazole compounds with desirable biological activity. Researchers can quickly identify chemicals that demonstrate specific interactions with target proteins or pathways by exposing them to a battery of experiments. This speeds up the discovery of lead compounds, making the early phases of drug development more efficient.[22]

Computational methods for benzimidazole design

Computational approaches such as molecular docking, molecular dynamics simulations, and quantitative structure activity relationship (QSAR) investigations have become indispensable in the creation of benzimidazoles. These methods make predicting binding affinities, identifying binding modes, and investigating structure activity connections *in-silico* easier. Computational techniques help to speed up the identification of promising benzimidazole candidates by directing experimental efforts and assisting in the formulation of more powerful and selective molecules.[23]

The combination of target-based drug design, high throughput screening, and computational methods has catapulted benzimidazole medicinal chemistry into a new era of precision and efficiency. These breakthroughs enable researchers to harness the power of data-driven techniques, thereby speeding up the development and optimization of benzimidazole-based therapies. The synergy between experimental and computational methodologies will continue to determine the direction of benzimidazole research as technology evolves.

Future Prospects and Emerging Trends

The dynamic landscape of benzimidazole medicinal chemistry is evolving, driven by emergent developments that have the potential to reshape drug discovery and therapeutic interventions. This section investigates these tendencies and speculates on how they might affect the future of benzimidazole research.

Benzimidazole Therapeutics and Personalized Medicine

The era of personalized medicine has here, and benzimidazole therapies are ready to make a substantial contribution. Because of advances in genomes and biomarker identification, benzimidazole-based medicines can now be tailored to

individual patient profiles. Personalized benzimidazole medicines that target specific genetic variations or molecular signatures could improve efficacy while minimizing side effects, ushering in a new era of precision medicine.[24]

Polypharmacology and Multitarget Ligands

Benzimidazole compounds, which have the capacity to regulate numerous targets at the same time, are gaining popularity. Polypharmacology and multitarget ligands provide a strategic approach to treating complicated diseases with varied pathologies. Researchers can improve therapy outcomes and potentially overcome the limits of single-target techniques by developing molecules that interact with several pathways or proteins important to disease.[25]

Applications of Nanotechnology in Drug Delivery

Nanotechnology holds significant promise for improving the transport of benzimidazole compounds to their active sites. Drug delivery systems based on nanocarriers and nanoparticles provide increased bioavailability, controlled release, and superior targeting. These approaches not only maximize therapeutic effects but also minimize potential negative effects, transforming the pharmacokinetics and efficacy of benzimidazole-based medicines.[26]

Natural Sources Exploration for Benzimidazole Discovery

Nature continues to be a rich source of chemical variety. Exploration of natural products and bioactive molecules may lead to the discovery of novel benzimidazole derivatives with distinct characteristics and activities. Such molecules may serve as inspiration for medication development and give new therapeutic approaches.

These new developments portend an exciting future for benzimidazole medicinal chemistry. Researchers can unlock novel avenues for therapeutic development by embracing personalized medicine, utilizing multitarget approaches, leveraging nanotechnology, addressing resistance, and tapping into natural sources, ultimately leading to the discovery of innovative benzimidazole-based treatments for a variety of diseases.[27]

Limitations and Challenges

While benzimidazoles have enormous potential as therapeutic agents, various hurdles and constraints must be overcome before their clinical applications can be completely realized. This section looks at some of the most significant challenges that researchers and developers confront while working with benzimidazole molecules.

Concerns About Toxicity and Safety

It is critical to ensure the safety and minimize the potential toxicity of benzimidazole derivatives. Unintended off-target effects can occur when these substances interact with biological targets, resulting in unpleasant reactions or unwanted physiological responses. The potential for cytotoxicity, genotoxicity, and organspecific toxicity must be extensively examined during preclinical research to determine the drugs' safety profiles and create optimal dose regimens.[28]

Pharmacokinetic Difficulties

The pharmacokinetic characteristics of benzimidazole derivatives can make clinical translation difficult. Poor solubility, low bioavailability, rapid metabolism, and short half-lives can all have an impact on their therapeutic efficacy. Researchers continue to focus on developing techniques to improve druglike characteristics, improve absorption, lengthen circulation time, and optimize distribution to target tissues.[29]

Problems with Intellectual Property

Drug discovery and development are fraught with intellectual property (IP) issues. The potential of patent conflicts and challenges to exclusivity grows as the field of benzimidazole research expands. Creating a comprehensive intellectual property strategy that navigates current patents, protects novel compounds, and obtains commercial rights is critical for maintaining research efforts and encouraging investment in new therapeutic medicines.

Researchers, pharmacologists, chemists, and regulatory specialists must work together to address these issues. The discipline of benzimidazole medicinal chemistry can overcome these restrictions and pave the way for the successful creation of safe and effective medicines by addressing toxicity concerns, optimizing pharmacokinetics, and negotiating intellectual property challenges.

CONCLUSION

Benzimidazole compounds have emerged as versatile and promising entities in medicinal chemistry, with their various pharmacological activity and structural flexibility making them an important resource for drug discovery. This study has thoroughly examined benzimidazoles' many facets, emphasizing their structural properties, pharmacological diversity, synthetic methodologies, recent achievements, emerging trends, and problems.

Throughout this review, we studied the basic structure and substituent changes that define benzimidazoles, as well as their contributions to antibacterial activity, anticancer potential, and modulation of central nervous system functions. We looked at their synthesis processes, discussed current advances like target-based drug design and high throughput screening, and looked into the computational tools driving benzimidazole design. Personalized medicine, multitarget ligands, nanotechnology, resistance tactics, and natural sources for discovery were all highlighted.

Benzimidazole molecules have the potential to transform therapeutic interventions in a wide range of fields, from infectious diseases to cancer and neurological problems. Their distinct structural properties and modulatory mechanisms enable the development of personalized medicines with improved efficacy and fewer side effects. As more study reveals their complicated interactions with biological targets, the idea of producing benzimidazole-based therapies becomes more appealing.

We hereby conclude that medicinal chemistry has been revolutionized due to the many biological actions of

benzimidazoles. In this lead nucleus, researchers created useful hybrids by working through numerous mechanisms to cure a wide range of disorders. Researchers worldwide will benefit from compounds containing benzimidazole nuclei combined with a larger chemical space to create pharmacologically active molecules for various targets. It is anticipated that would open up new avenues for the study of benzimidazole-derived and inspire researchers to employ the potential heterocycle for additional biological research.

Dynamic shifts and discoveries characterize the future of benzimidazole medicinal chemistry. Personalized medicine promises therapies tailored to individual patients, made possible by genomes and biomarker identification advances. The study of multitarget ligands and polypharmacology paves the way for complicated disease therapies, while nanotechnology improves medication delivery precision. Understanding resistance mechanisms and utilizing natural sources for chemical development are difficulties that will drive novel approaches.

REFERENCES

1. Brishty SR, Hossain MJ, Khandaker MU, Faruque MR, Osman H, Rahman SM. A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. Frontiers in pharmacology. 2021 Nov 3;12:762807.
2. Feng LS, Su WQ, Cheng JB, Xiao T, Li HZ, Chen DA, Zhang ZL. Benzimidazole hybrids as anticancer drugs: An updated review on anticancer properties, structure–activity relationship, and mechanisms of action (2019–2021). Archiv der Pharmazie. 2022 Jun;355(6):2200051.
3. Satija G, Sharma B, Madan A, Iqubal A, Shaquiquzzaman M, Akhter M, Parvez S, Khan MA, Alam MM. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chemistry. 2022 Jan;59(1):22-66.
4. Moghadam Farid S, Noori M, Nazari Montazer M, Khalili Ghomi M, Mollazadeh M, Dastyafteh N, Irajie C, Zomorodian K, Mirfazli SS, Mojtabavi S, Faramarzi MA. Synthesis and structure–activity relationship studies of benzimidazole-thioquinoline derivatives as α-glucosidase inhibitors. Scientific Reports. 2023 Mar 16;13(1):4392.
5. Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: A review. Bioorganic & medicinal chemistry. 2012 Nov 1;20(21):6208-36.
6. Marinescu M. Benzimidazole-Triazole Hybrids as Antimicrobial and Antiviral Agents: A Systematic Review. Antibiotics. 2023 Jul 22;12(7):1220.
7. Moghimi S, Shafiei M, Foroumadi A. Drug design strategies for the treatment azole-resistant candidiasis. Expert Opinion on Drug Discovery. 2022 Aug 3;17(8):879-95.
8. Hernández-López H, Tejada-Rodríguez CJ, Leyva-Ramos S. A panoramic review of benzimidazole derivatives and their potential biological activity. Mini Reviews in Medicinal Chemistry. 2022 May 1;22(9):1268-80.
9. Chalkappa PK, Aralihalli S, Sudileti M, Aithal SJ, Praveen BM, Birjadar K. The medicinal panorama of benzimidazoles and their scaffolds as anticancer and antithrombotic agents: A review. Archiv der Pharmazie. 2023 Jul 13:e2300206.
10. Alaqeel SI. Synthetic approaches to benzimidazoles from o-phenylenediamine: A literature review. Journal of Saudi Chemical Society. 2017 Feb 1;21(2):229-37.
11. Walia R, Hedaitullah M, Naaz SF, Iqbal K, Lamba HS. Benzimidazole derivatives-an overview. Int. J. Res. Pharm. Chem. 2011;1(3):565-74.
12. Nagubandi S, Fodor G. The mechanism of the bischler-napieralski reaction. Journal of Heterocyclic Chemistry. 1980 Nov;17(7):1457-63.
13. Saxer S, Marestin C, Mercier R, Dupuy J. The multicomponent Debus–Radziszewski reaction in macromolecular chemistry. Polymer Chemistry. 2018;9(15):1927-33.
14. Masurier N, Moreau E, Lartigue C, Gaumet V, Chezal JM, Heitz A, Teulade JC, Chavignon O. New opportunities with the Duff reaction. The Journal of organic chemistry. 2008 Aug 1;73(15):5989-92.
15. Brusnakov MY, Golovchenko OV, Potikha LM, Brovarets VS. Condensed azole-based organophosphorus heterocycles. Chemistry of Heterocyclic Compounds. 2023 Jun 17:1-20.
16. Morja MI, Moradiya RB, Chikhalia KH. First-row transition metal for isocyanide-involving multicomponent reactions (IMCR). Molecular Diversity. 2022 Dec 20:1-40.
17. Hashem HE, Amr AE, Nossier ES, Anwar MM, Azmy EM. New benzimidazole-, 1, 2, 4-triazole-, and 1, 3, 5-triazine-based derivatives as potential EGFRWT and EGFRT790M inhibitors: microwave-assisted synthesis, anticancer evaluation, and molecular docking study. Acs Omega. 2022 Feb 18;7(8):7155-71.
18. Saif MJ, Abrar S, Hameed A, Idrees N, Asif M. Theoretical and Experimental Insights of Benzimidazole Catalyzed by the Epoxy–Acrylic Acid Reaction. Molecules. 2022 Nov 15;27(22):7900.
19. Pham W. Solid-Phase Chemistry. InPrinciples of Molecular Probe Design and Applications 2022 Sep 27 (pp. 201-237). Singapore: Springer Nature Singapore.
20. Ebenezer O, Oyetunde-Joshua F, Omotoso OD, Shapi M. Benzimidazole and its derivatives: Recent Advances (2020-2022). Results in Chemistry. 2023 Apr 7:100925.
21. Gaba M, Singh S, Mohan C. Benzimidazole: an emerging scaffold for analgesic and anti-inflammatory agents. European journal of medicinal chemistry. 2014 Apr 9;76:494-505.
22. Kumar A, Nimsarkar P, Singh S. Systems pharmacology aiding benzimidazole scaffold as potential lead compounds against leishmaniasis for functional therapeutics. Life Sciences. 2022 Nov 1;308:120960.
23. Mishra VR, Ghanavatkar CW, Mali SN, Qureshi SI, Chaudhari HK, Sekar N. Design, synthesis, antimicrobial activity and computational studies of novel azo linked substituted benzimidazole, benzoxazole and benzothiazole derivatives. Computational biology and chemistry. 2019 Feb 1;78:330-7.
24. Lee YT, Tan YJ, Oon CE. Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine. Acta Pharmaceutica Sinica B. 2022 Sep 21.
25. Ryszkiewicz P, Malinowska B, Schlicker E. Polypharmacology: promises and new drugs in 2022. Pharmacological Reports. 2023 Jun 6:1-6.
26. El-Sayed A, Abu-Bakr S, Swelam S, Khaireldin N, Shoueir K, Khalil A. Applying nanotechnology in the synthesis of benzimidazole derivatives: a pharmacological approach. Biointerface Research in Applied Chemistry. 2022;12:992-1005.
27. Lungu CN, Mangalagiu I. Editorial for Special Issue—" Research Progress and Applications of Natural Products". Molecules. 2023 Jul 17;28(14):5449.

28. Raducka A, Świątkowski M, Gobis K, Szymański P, Czylkowska A. In Silico ADME and Toxicity Prediction of Benzimidazole Derivatives and Its Cobalt Coordination Compounds. Synthesis, Characterization and Crystal Structure. Molecules. 2022 Nov 18;27(22):8011.

29. Abchir O, Daoui O, Belaidi S, Ouassaf M, Qais FA, ElKhattabi S, Belaaouad S, Chtita S. Design of novel benzimidazole derivatives as potential α-amylase inhibitors using QSAR, pharmacokinetics, molecular docking, and molecular dynamics simulation studies. Journal of Molecular Modeling. 2022 Apr;28(4):106.