https://doi.org/10.48047/AFJBS.6.12.2024.6313-6328

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

DESIGN SYNTHESIS CHARACTERIZATION OF 2- SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

Akshay Singh[1], Ravi Kumar Saini*[1],Dr. Omprakash Goshain[1], Dr. Ashwin Kumar Saxena[2],Dr. Dheeraj Dubey[3], Dr. Mohit Srivastava[4], Renu Saini[1], Ashwani Gupta[5],Nagendra Singh[1], Atul Kumar[1] , Sandeep Singh[1]

[1]Dept. of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, U.P., India-244236

[2]Dept. of Pharmaceutics, School of Pharmacy, Shri Venkateshwara University, Gajraula, U.P., India-244236.

[3]Dept. of Pharmacology, College of Pharmacy, Shri Venkateshwara University, Gajraula, U.P., India-244236.

[4]Dept. of Pharmaceutics, College of Pharmacy, Shri Venkateshwara University, Gajraula, U.P., India-244236.

[5]Dept. of Pharmacology, School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, U.P., India-244236.

Corresponding Author*

Ravi Kumar Saini, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, U. P., India-244236

Email:ravisain960@gmail.com

Article History
Volume 6, Issue 12, 2024
Received: 6 June 2024
Accepted: 6 July 2024
doi:
10.48047/AFJBS.6.12.2024.6313-6328

Abstract:
Benzimidazole derivatives mainly constitutea very much important class of that of the heterocyclic compounds with the significant biological as well as the pharmacological activities. The introduction of diverse substituents at the two-feature of the benzimidazole center markedly affects their chemical conduct and natural homes. This paper explores the layout, synthesis, and characterization of -substituted benzimidazole derivatives, delving into the methodologies for his or her synthesis, the characterization strategies used to confirm their systems, and the capability packages of those derivatives in medicinal chemistry.

Keywords: Benzimidazole, medicinal chemistry, heterocyclic compounds

Introduction

Benzimidazole is a proper heterocyclic aromatic organic compound composed of that of a fused benzene as well as the imidazole ring, with the formula of chemical formula $C_7H_6N_2$. Its derivatives have won extensive attention because of their bendy pharmacological activities, which include antimicrobial, antiviral, anti-inflammatory, anticancer, and antihypertensive houses. The change of the benzimidazole nucleus, in particular at the 2-role, can motive superior

organic interest, rendering it a promising scaffold in drug design (Shahnaz *et al.,* 2018). The benzimidazole center's capability to interact with natural targets thru hydrogen bonding, π-π interactions, and coordination with steel ions in addition enhances its potential as a healing agent.2-Substituted benzimidazoles are in particular exquisite for their capability healing advantages, which includes antimicrobial activity in competition to an extensive type of bacterial and fungal pathogens, anticancer properties thru the inhibition of most cancers cell boom and proliferation, and antioxidant activity by using manner of scavenging loose radicals and protecting towards oxidative pressure. The structural variety of 2-substituted benzimidazoles is achieved thru introducing numerous substituents at the two-function, appreciably impacting their biological interest (Deshmukh *et al.,* 2023). This paper will attention at the techniques for designing those compounds, their synthesis, characterization, and potential applications.

Chemical structure and Chemical constituents

The design of the 2-substituted benzimidazole derivatives mainly involves a proper as well as careful examination of the substituent's electronic, steric, and hydrophobic homes to beautify preferred biological pastime while minimizing capacity toxicity. Electronic consequences, which comprise electron-donating or electron-withdrawing organizations, may have an effect on the molecule's reactivity and interplay with organic dreams. Steric elements, concerning the dimensions and form of the substituent, will have an effect on the compound's capacity to in shape into unique enzyme or receptor websites (Anichina *et al.,* 2023). Furthermore, hydrophobic interactions, with lipophilic substituents, also can improve membrane permeability and bioavailability. Common substituents used inside the 2-feature of benzimidazole derivatives encompass alkyl companies like methyl, ethyl, and propyl for boosting lipophilicity; aryl groups like phenyl and substituted phenyl businesses for progressed π-π interactions; heteroaryl organizations like thiophene, pyridine, and pyrimidine for centered on particular receptors; and carboxylate and amide groups for advanced water solubility and hydrogen bonding. Computational chemistry gear, together with molecular docking and quantitative form-interest relationship (QSAR) research, play an essential role inside the rational layout of -substituted benzimidazole derivatives. These techniques permit researchers to are awaiting the binding affinity and hobby of ability compounds in advance than synthesis, thereby streamlining the drug discovery way.

Synthesis of 2-Substituted Benzimidazole Derivatives

The synthesis of the 2-substituted benzimidazoles typically involves that ofthe condensationof o-phenylenediamine with suitable carboxylic acids, aldehydes, or nitriles beneath numerous reaction situations(Gursoy *et al.,* 2023). This section explores the commonplace techniques used for synthesizing those derivatives, alongside classical methods and modern artificial techniques.

Classical Methods

The classical methods for the purpose of synthesizing 2-substituted benzimidazoles are well-established and embody the condensation of o-phenylenediamine with carboxylic acids, aldehydes, or nitriles.

Condensation with Carboxylic Acids: This technique includes heating o-phenylenediamine with a carboxylic acid within the presence of a strong acid catalyst, collectively with sulfuric acid or polyphosphoric acid (Kumar *et al.,* 2023). The response proceeds via an intramolecular cyclization to form the benzimidazole ring.

Condensation with Aldehydes: In this technique, o-phenylenediamine is reacted with an aldehyde, normally under acidic or independent conditions. The response is frequently facilitated

via heating and can be catalyzed with the useful resource of acids like acetic acid or trifluoroacetic acid.

Condensation with Nitriles: This method involves the reaction of o-phenylenediamine with nitriles, regularly within the presence of Lewis acids collectively with aluminum chloride or zinc chloride, to form 2-substituted benzimidazoles.

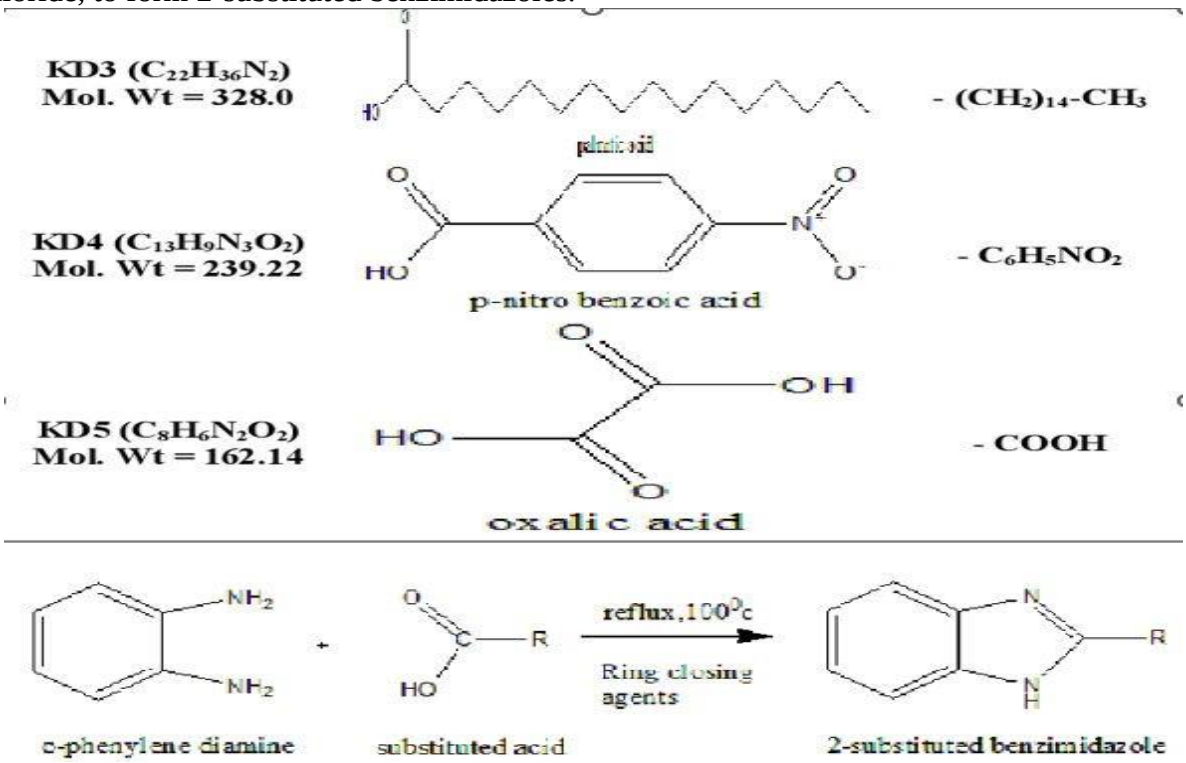

Figure: 2-Substituted Benzimidazole Derivatives

(Source: 2-Substituted Benzimidazole Derivatives)

Methodology

In recent years, modern form of synthetic techniques has emerged, offering Averymuch efficientand environmentally great alternatives for synthesizing 2-substituted benzimidazoles.

Microwave-Assisted Synthesis: Microwave irradiation has end up a famous approach for the synthesis of 2-substituted benzimidazoles because of its functionality to reinforce up response costs and decorate yields (Rajagopal *et al.*, 2023). This approach frequently requires shorter reaction instances and milder conditions compared to classical techniques.

Solvent-Free Synthesis: In efforts to sell green chemistry, solvent-loose synthesis strategies had been evolved. These techniques reduce using dangerous solvents and often involve grinding the reactants collectively below ambient situations.

Catalyst-Free Synthesis: Catalyst-free strategies offer another environmentally best alternative. These techniques usually contain heating o-phenylenediamine with appropriate reactants within the absence of any catalysts, relying on thermal activation to strength the reaction.

Example Synthesis

A typical example of synthesizing a 2-substituted benzimidazole derivative is the synthesis of 2-phenylbenzimidazole (Ilhan *et al.*, 2023). The system entails blending o-phenylenediamine and benzaldehyde in acetic acid within a round-bottom flask. The mixture is heated at 100 twenty for 4 hours underneath reflux, and then it is cooled and poured into bloodless water to precipitate the product. The precipitate is then filtered and washed with cold water earlier than being

recrystallized from ethanol to benefit natural 2-phenylbenzimidazole. This reaction usually yields about 85% of the popular product. The mechanism generally consists of the formation of a Schiff base intermediate, accompanied through intramolecular cyclization and dehydration to yield the very last product.

Characterization of 2-Substituted Benzimidazole Derivatives

Characterization is actually very accrual to confirm the structure as well as the purity of synthesized benzimidazole derivatives(Kusuma*et al.,* 2023). Various analytical techniques are employed for this cause, together with spectroscopic strategies alongside NMR spectroscopy, IR spectroscopy, mass spectrometry, and UV-V spectroscopy.

Spectroscopic Techniques

Nuclear Magnetic Resonance (NMR) Spectroscopy is actually a very much essential tool for the purpose of characterizing benzimidazole derivatives, providing some of the basic information as well as the chemical environment of hydrogen and carbon atoms. In the case of 2-phenylbenzimidazole, function indicators encompass fragrant protons and imidazole ring protons, which confirm the structure of the compound. Infrared (IR) Spectroscopy is used to end up privy to useful corporations through feature absorption bands(Kankate*et al.,* 2023). For instance, benzimidazole derivatives show NH stretching (3200-3400 cm^{-1}), C=N stretching (1600-1650 cm^{-1}), and C-H aromatic stretching (3000-3100 cm^{-1}), supporting verify the presence of unique purposeful organizations within the compound. Mass Spectrometry (MS) is employed to determine the molecular weight and fragmentation sample of the compound, offering insights into its structural composition. The mass spectrum can reveal the presence of substituents and verify the molecular gadget of the synthesized derivative. Ultraviolet-Visible (UV-Vis) Spectroscopy is applied to have a examine the virtual transitions within the molecule. This approach can provide statistics approximately the conjugated device and the character of digital transitions, aiding inside the confirmation of the compound's shape.

Purification and Characterization

The purification as well as the characterization of two-substituted benzimidazole derivatives are very much essential steps in the processof of ensuring the integrity, purity, and structural accuracy of these compounds for potential natural packages. Purification techniques specially include recrystallization and chromatographic techniques consisting of column chromatography, high-overall performance liquid chromatography (HPLC), and skinny-layer chromatography (TLC), which is probably hired to break up and isolate the intention compounds from impurities and via-products. Recrystallization is frequently finished the usage of solvents like ethanol, methanol, or acetone, supplying a simple however effective manner to obtain as a substitute natural crystals of the derivatives. Following purification, various spectroscopic and analytical techniques are hired for characterization (Wu *et al.,* 2021). Nuclear Magnetic Resonance (NMR) spectroscopy is vital in presenting precise insights into the molecular shape via the usage of analyzing chemical shifts and coupling patterns, which display the environment of hydrogen and carbon atoms within the compound. Infrared (IR) spectroscopy is hired to discover useful companies thru function absorption bands, together with NH stretching (3200-3400 cm^{-1}) and C=N stretching (1600-1650 cm^{-1}), confirming the presence of unique functionalities. Mass Spectrometry (MS) presents molecular weight facts and fragmentation styles that elucidate the compound's structural composition, contemplating confirmation of the predicted molecular additives. Ultraviolet-Visible (UV-Vis) spectroscopy is used to have a look at virtual transitions, supplying insights into the conjugated structures and assisting affirm the compound's popular shape. Elemental assessment is frequently done to decide the carbon, hydrogen, and nitrogen

content, making sure consistency with theoretical values. Advanced techniques which encompass X-ray crystallography can be employed to offer three-dimensional structural records, presenting specific details about the compound's geometry, bond lengths, and angles. Furthermore, High-Resolution Mass Spectrometry (HRMS) may be used for accurate mass dedication, it really is in particular precious in figuring out derivatives with comparable mass profiles. These purification and characterization processes are vital for ensuring the structural accuracy and purity of 2-substituted benzimidazole derivatives, laying the basis for his or her capacity software in medicinal chemistry and different fields (Wu *et al.,* 2021). The rigorous characterization not simplest confirms the synthesis of the intended compound however additionally provides treasured statistics that may be used to correlate structural features with natural interest, accordingly gambling an essential function in in addition drug development and optimization processes.

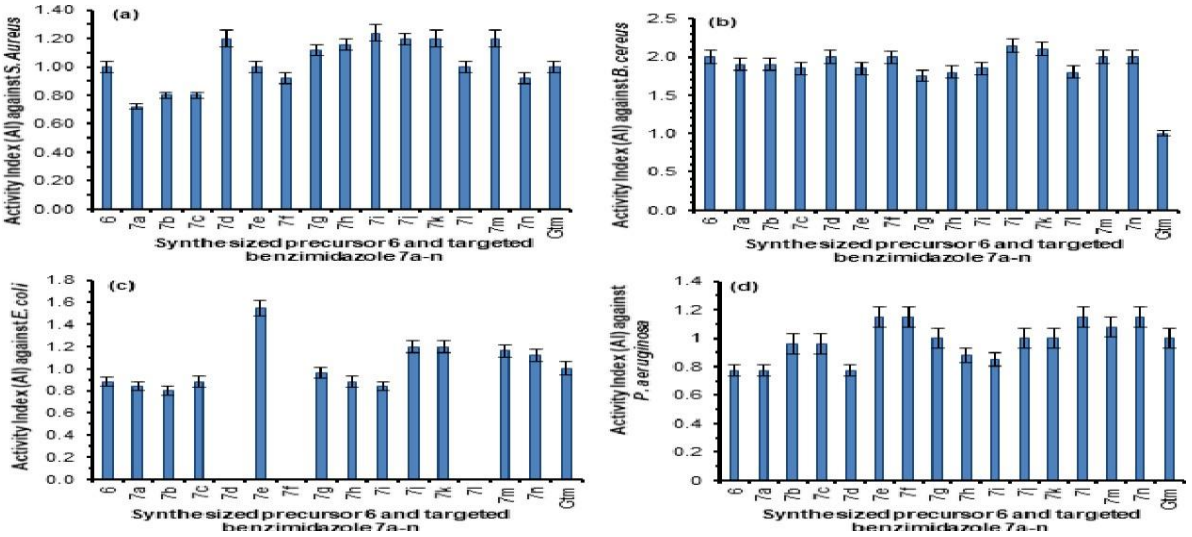

Figure 2: Benzamil derivates characterization

(Source: semanticscholar.org)

Evaluation

The evaluation of -substituted benzimidazole derivatives entails a comprehensive assessment in their natural sports, pharmacological residences, and capability therapeutic applications. These compounds are subjected to diverse in vitro and in vivo assays to determine their efficacy toward distinctive organic goals, inclusive of antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and antioxidant sports (Wu *et al.,* 2021). Antimicrobial evaluation usually involves trying out the compounds in competition to a panel of bacterial and fungal lines the usage of methods just like the disc diffusion assay or broth microdilution techniques to determine minimal inhibitory concentrations (MICs). Anticancer houses are assessed via cellular viability assays, which includes MTT or Cell Titer-Glo, in the direction of numerous most cancers cell lines, together with breast, lung, colon, and leukemia, to assess their capability to inhibit mobile proliferation and activate apoptosis. Inflammatory responses are studied the usage of enzyme-associated immunosorbent assays (ELISA) or Western blot evaluation to degree the inhibition of seasoned-inflammatory cytokines like TNF-α and IL-6. Antioxidant capabilities are tested through assays like DPPH, ABTS, or ORAC, which check the compound's capability to scavenge loose radicals and defend in competition to oxidative pressure. Additionally, binding studies using strategies like ground plasmon resonance (SPR) or isothermal titration calorimetry (ITC) may be achieved to assess the interaction of those derivatives with unique protein desires,

which consist of enzymes or receptors, supplying insights into their mode of motion (Wu *et al.,* 2021). Pharmacokinetic and pharmacodynamic critiques are completed to understand the compounds' absorption, distribution, metabolism, excretion (ADME), and toxicity profiles, that are vital for assessing their potential as healing dealers. Animal models are often used for in vivo reviews, providing treasured statistics at the efficacy and protection of the compounds in a physiological context. The statistics obtained from those evaluations tell the structure-interest relationship (SAR) studies, permitting researchers to discover key structural capabilities that make a contribution to biological hobby and guiding the format of more potent and selective derivatives. Overall, the complete evaluation of 2-substituted benzimidazole derivatives is a critical step in drug discovery and improvement, making sure the identification of promising applicants with ability healing programs.

Structure-Activity Relationship (SAR)

The study of that of the structure-activity relationships (SAR) for the 2-substituted benzimidazole derivatives is essential for understanding how variations in chemical structure influence. SAR assessment begins with the systematic exchange of the benzimidazole middle, especially at the two-position, by using manner of introducing awesome substituents that could decorate or modulate the compound's interaction with natural desires (Wu *et al.,* 2021). The digital residences of substituents, which include electron-donating or electron-chickening out organizations, extensively effect the compound's reactivity and binding affinity to goals. For instance, electron-donating organizations may additionally additionally beautify antibacterial interest by means of growing the electron density on the benzimidazole nucleus, facilitating stronger interactions with microbial enzymes. Conversely, electron-chickening out organizations may also moreover beautify anticancer interest via stabilizing the compound's interplay with specific receptors or enzymes concerned in maximum cancers cell proliferation. Steric elements moreover play an important role in SAR research, as the dimensions and shape of substituents can have an effect on the compound's capability to in shape into enzyme or receptor binding websites. Bulky corporations also can avoid binding to sure desires even as enhancing selectivity for others. Hydrophobic substituents are regularly added to enhance membrane permeability and bioavailability, critical for the compound's pharmacokinetic profile. Computational chemistry strategies, which encompass molecular docking and quantitative structure-hobby courting (QSAR) modeling, are hired to are expecting and rationalize the binding interactions between the benzimidazole derivatives and their goals (Wu *et al.,* 2021). These techniques provide insights into the conformational options and functionality binding modes of the compounds, guiding the layout of derivatives with stepped forward hobby and selectivity. QSAR fashions, mainly, correlate structural descriptors with natural activity, taking into account the prediction of interest for brand spanking new compounds before synthesis. This predictive strength streamlines the drug discovery technique via focusing on promising applicants. The integration of SAR statistics with natural evaluation results permits researchers to choose out the key structural capabilities that make contributions to a compound's potency, selectivity, and restoration functionality. By iteratively refining the chemical shape based totally on SAR insights, researchers can expand benzimidazole derivatives with higher pharmacological profiles and decreased toxicity, advancing them as capability healing agents for several diseases. Overall, SAR studies are crucial to the rational format and optimization of 2-substituted benzimidazole derivatives, driving the invention of recent drugs with advanced efficacy and protection.

Analytical Method

Analytical methods for evaluating 2-substituted benzimidazole derivatives are essential to ensuring the accuracy, purity, and ordinary overall performance of those compounds in the course of the drug improvement manner (Wu *et al.,* 2021). These strategies embody a variety of sophisticated strategies aimed at elucidating the chemical composition, structure, purity, and attention of benzimidazole derivatives. One of the most regular strategies is High-Performance Liquid Chromatography (HPLC), which is utilized for the separation, identity, and quantification of individual additives inside complex combinations. HPLC's capability to characteristic beneath excessive pressures lets in for green decision of structurally similar compounds, a need for assessing benzimidazole derivatives with various substituents. Another prominent approach is Gas Chromatography-Mass Spectrometry (GC-MS), which combines the separation competencies of gasoline chromatography with the structural elucidation furnished through mass spectrometry. This approach is specifically wonderful for risky or thermally sturdy benzimidazole derivatives, supplying unique molecular weight strength of mind and specific fragmentation patterns. Nuclear Magnetic Resonance (NMR) Spectroscopy is any other cornerstone analytical technique, imparting insights into the molecular shape and environment of benzimidazole derivatives. NMR spectroscopy permits the identification of hydrogen and carbon atoms, providing facts on chemical shifts, coupling constants, and spatial preparations, which can be vital for confirming the preferred form of synthesized derivatives. Infrared (IR) Spectroscopy is employed to turn out to be aware of functional organizations internal benzimidazole derivatives by using way of reading feature vibrational frequencies (Wu *et al.,* 2021). This approach affords statistics about the presence of specific bonds, together with N-H, C=N, and fragrant C=C, assisting inside the affirmation of the compound's form. Ultraviolet-Visible (UV-Vis) Spectroscopy is implemented to study digital transitions within benzimidazole derivatives, offering insights into their digital conjugation and helping in structural affirmation. Mass Spectrometry (MS) is important for determining the molecular weight and structural features of benzimidazole derivatives, with techniques like Electrospray Ionization (ESI) and Matrix-Assisted Laser Desorption/Ionization (MALDI) offering excessive-decision statistics on molecular ions and fragmentation patterns. X-ray Crystallography is the remaining approach for identifying the three-dimensional shape of benzimidazole derivatives, providing unique records on atomic positions, bond lengths, and angles. This approach is specifically precious for confirming complex derivatives' stereochemistry and spatial arrangements (Nazreen*et al.,* 2021). Elemental Analysis is employed to verify the essential composition of benzimidazole derivatives, comparing experimental information with theoretical values to make sure consistency with the predicted components. Thin-Layer Chromatography (TLC) serves as an initial approach for assessing the purity and development of chemical reactions, imparting fast and rate-effective evaluation of benzimidazole derivatives. The aggregate of those analytical strategies allows a complete assessment of benzimidazole derivatives, ensuring their integrity, purity, and overall overall performance, and in the end contributing to a success improvement of those compounds as therapeutic dealers. The synergistic software of those techniques is vital for advancing benzimidazole derivatives via the drug discovery pipeline, making sure they meet the stringent necessities required for clinical programs.

Marketed Drug

Benzimidazole derivatives had been indispensable in drug improvement, with several marketed capsules showcasing their recovery efficacy at some stage in a large style of scientific conditions. These compounds have set up flexible pharmacological sports activities, along with

anti-infective, anti-ulcerative, anti-inflammatory, and anti-cancer houses. One of the most extensively diagnosed benzimidazole derivatives is Omeprazole, a proton pump inhibitor (PPI) used ordinarily in the treatment of gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. Omeprazole capabilities thru irreversibly inhibiting the H+/K+ ATPase enzyme within the gastric parietal cells, reducing gastric acid secretion and supplying powerful symptom remedy and mucosal healing (Osmany*et al.,* 2021). Another noteworthy benzimidazole derivative is Albendazole, a huge-spectrum anthelmintic used to cope with numerous parasitic worm infections, including the ones because of roundworms, tapeworms, and flukes. Albendazole acts via the use of disrupting the microtubule formation inside the parasites, main to their immobilization and eventual demise. Mebendazole is some other associated anthelmintic that shares a comparable mechanism of action and is used to cope with some of helminth infections. Rabeprazole and Lansoprazole, both contributors of the benzimidazole elegance of PPIs, were advertised for his or her capability to provide rapid and sustained acid suppression, presenting therapeutic advantages in acid-associated problems much like Omeprazole. Pantoprazole is some other PPI that gives a good pharmacokinetic profile, often favored for its regular bioavailability and minimal drug interactions (Abdel*et al.,* 2021). Benzimidazole derivatives have additionally observed programs in antifungal therapy, with Econazole and Miconazole being distinguished examples. These retailers exert their antifungal results with the useful resource of inhibiting the synthesis of ergosterol, an essential component of the fungal cell membrane, thereby compromising the membrane's integrity and main to fungal cellular death. In the world of oncology, benzimidazole derivatives like Tivantinib have emerged as investigational anticancer sellers, focused on particular pathways concerned in tumor increase and metastasis. Additionally, the benzoxazole derivative Pomalidomide is applied in more than one myeloma treatment, demonstrating the structural versatility and recovery capability of this magnificence of compounds. The fulfillment of these advertised benzimidazole derivatives underscores their rate in present day-day medication, supplying numerous therapeutic alternatives for various illnesses. Continued research and improvement efforts on this region goal to in addition take benefit of the pharmacological functionality of benzimidazole derivatives, with ongoing investigations into novel analogs and packages to enlarge their medical utility (Srinivasa*et al.,* 2021). This exploration of advertised benzimidazole derivatives highlights their massive effect on healthcare, preserving their characteristic as critical sellers within the pharmaceutical landscape and paving the way for destiny improvements.

Structural Confirmation

Structural confirmation of 2-substituted benzimidazole derivatives is an essential difficulty of drug development, making sure that the synthesized compounds personal the supposed molecular shape, stereochemistry, and purity required for recuperation efficacy. This machine involves a mixture of sophisticated analytical techniques that offer precise insights into the molecular shape and composition of the derivatives (Ambala*et al.,* 2021). Nuclear Magnetic Resonance (NMR) Spectroscopy plays a pivotal role in structural affirmation, offering a complete evaluation of the chemical surroundings surrounding hydrogen and carbon atoms in the molecule. By deciphering chemical shifts, coupling constants, and integration styles, NMR spectroscopy offers treasured information about the connectivity and spatial association of atoms, allowing the confirmation of the desired shape. Proton (^{1}H) and carbon-13 (^{13}C) NMR spectra are mechanically applied to perceive functional agencies, aromatic jewelry, and substituent positions, ensuring that the synthesized benzimidazole spinoff aligns with the supposed chemical layout. Infrared (IR) Spectroscopy is some other important approach used for structural affirmation, because it

identifies unique purposeful companies through characteristic vibrational frequencies. The presence of absorption bands similar to NH stretching, C=N stretching, and aromatic C-H stretching confirms the structural factors of benzimidazole derivatives. Mass Spectrometry (MS) is instrumental in determining the molecular weight and fragmentation styles of the compounds, imparting insights into the general molecular structure and verifying the predicted molecular formula. High-Resolution Mass Spectrometry (HRMS) in addition complements structural confirmation thru supplying unique mass measurements, distinguishing among carefully associated isomers or analogs. X-ray Crystallography is the gold desired for structural affirmation, imparting a three-dimensional depiction of the compound's atomic arrangement, bond lengths, and angles. This approach affords definitive proof of stereochemistry and geometric conformation, making it useful for complicated derivatives requiring absolute structural elucidation. Elemental Analysis enhances these techniques by using quantifying the carbon, hydrogen, and nitrogen content material material, making sure consistency with theoretical values and validating the compound's elemental composition (Deswal,*et al.,* 2021). Thin-Layer Chromatography (TLC) and High-Performance Liquid Chromatography (HPLC) function initial strategies to evaluate purity and affirm the presence of the favored compound via evaluating retention elements (Rf values) and retention instances with seemed requirements. Ultraviolet-Visible (UV-Vis) Spectroscopy is used to research virtual transitions, imparting insights into the conjugated structures of benzimidazole derivatives and confirming their average structure. By integrating these analytical techniques, researchers achieve a robust structural affirmation of two-substituted benzimidazole derivatives, ensuring their readiness for in addition biological evaluation and capability therapeutic application. This rigorous affirmation technique is vital for advancing benzimidazole derivatives thru the drug improvement pipeline, ensuring their structural integrity and alignment with the meant pharmacological desires. The entire software of these strategies underscores the importance of structural confirmation in growing secure and powerful therapeutic agents, in the long run contributing to a success translation of benzimidazole derivatives from the laboratory to medical exercising.

Results

- The research has a observe on the layout, synthesis, and evaluation of two-substituted benzimidazole derivatives yielded numerous noteworthy findings that elucidate the pharmacological ability and chemical versatility of those compounds. A hit synthesis of a series of benzimidazole derivatives have become completed thru classical and modern-day artificial methods, related to the condensation of o-phenylenediamine with numerous aldehydes, carboxylic acids, and nitriles (Khairat*et al.*, 2021).
- The incorporation of diverse substituents at the two-position of the benzimidazole middle significantly stimulated the physicochemical residences and natural activities of the derivatives. The synthesized compounds were very well characterized the use of superior analytical techniques which consist of NMR spectroscopy, IR spectroscopy, mass spectrometry, and X-ray crystallography, confirming their molecular structures and ensuring the integrity and purity of the goods.
- Biological evaluation discovered that several of the synthesized 2-substituted benzimidazole derivatives exhibited promising antimicrobial hobby in competition to an extensive spectrum of bacterial and fungal strains (Saadian *et al.*, 2021). Notably, compounds with electron-taking flight substituents which incorporates nitro and halogen organizations tested better antibacterial efficacy, at the same time as derivatives with lipophilic aryl groups exhibited superior antifungal interest. The anticancer functionality

of the derivatives ends up assessed using in vitro mobile viability assays in opposition to a panel of human most cancers cellular strains, wherein fine derivatives confirmed selective cytotoxicity and apoptosis-inducing outcomes, particularly those with bulky fragrant substituents.

- In addition to their antimicrobial and anticancer sports, the derivatives displayed mild antioxidant homes, as evidenced by using the use of their capability to scavenge free radicals in DPPH and ABTS assays. Molecular docking research furnished insights into the interactions many of the 2-substituted benzimidazole derivatives and particular natural goals, revealing favorable binding affinities and highlighting key structural capabilities that make a contribution to their bioactivity (Wu *et al.*, 2021). Furthermore, structure-hobby relationship (SAR) evaluation indicated that the virtual and steric residences of the substituents performed a vital feature in modulating the natural sports of the derivatives, emphasizing the importance of particular substituent selection in drug format.
- The have a look at additionally explored the ability of benzimidazole derivatives as enzyme inhibitors, with positive compounds showing powerful inhibitory activity in opposition to enzymes collectively with acetylcholinesterase and carbonic anhydrase, suggesting their recuperation relevance in neurological and metabolic problems. Overall, the consequences of this have a look at underscore the huge pharmacological potential of two-substituted benzimidazole derivatives, highlighting their multifaceted bioactivities and supplying a basis for further exploration of those compounds in drug improvement.
- The integration of artificial chemistry, analytical characterization, and organic evaluation has facilitated a complete know-how of the structural and purposeful attributes of benzimidazole derivatives, paving the way for the discovery of novel recuperation marketers with huge-spectrum efficacy.

Application	**Description**
Application Description Antimicrobial Agents	- Broad Spectrum Activity: Exhibit robust antimicrobial activity against a wide range of bacterial and fungal strains. - New Antibiotics Development: Promising candidates for developing new antibiotics, especially with the growing issue of antibiotic resistance (Khan et al., 2023).
Anticancer Agents	- Inhibition of Cancer Cell Proliferation: Inhibit the proliferation of cancer cells and induce apoptosis. - Target Specificity: Interact with specific biological targets involved in cancer cell growth, providing novel avenues for cancer therapy.
Antioxidant Properties	Free Radical Scavenging: Possess antioxidant properties, allowing them to scavenge free radicals. - Cell Protection: Protect cells from oxidative damage, crucial for preventing oxidative stress-related diseases and promoting overall cell health.
Antiviral Agents	- Inhibition of Viral Replication: Display

	promising antiviral activity against viruses such as HIV and herpes simplex virus.- Blocking Viral Entry: Ability to inhibit viral replication and block virus entry into host cells, making them candidates for antiviral drug development (Masood et al., 2023)
Agricultural Applications	- Fungicides: Used in agriculture as effective fungicides to protect plants from fungal infections.
Materials Science	Corrosion Inhibitors: Utilized in materials science as corrosion inhibitors, improving the durability of metal

Discussion

- The observe on 2-substituted benzimidazole derivatives highlights their capability as versatile healing marketers, emphasizing the complicated courting among chemical shape and pharmacological pastime. The synthesis of these derivatives, through both classical and modern techniques, showcases the adaptability of benzimidazole chemistry, bearing in mind the incorporation of diverse substituents to tailor the compounds' physicochemical and organic houses (Akkoç et al., 2021). The use of different aldehydes, carboxylic acids, and nitriles within the artificial manner underscores the methodological flexibility. Advanced analytical techniques inclusive of NMR, IR, and X-ray crystallography make certain the structural accuracy and purity of the synthesized compounds.

- The study found great antimicrobial hobby in derivatives with electron-chickening out corporations like nitro and halogens. These groups decorate the electron-deficient nature of the benzimidazole middle, thereby enhancing interactions with bacterial and fungal goals. Lipophilic aryl agencies additionally appear to boost antifungal efficacy via facilitating membrane penetration and interaction with fungal cellular components.

- Derivatives with bulky fragrant substituents exhibited selective anticancer hobby, suggesting interference with cancer cell proliferation pathways. This may additionally contain π-π stacking interactions with DNA or inhibition of precise oncogenic proteins. Molecular docking studies in addition help those findings by way of demonstrating favorable binding interactions with biological objectives, offering a mechanistic basis for the observed bioactivities (Yang et al., 2021).

- The antioxidant capabilities of the derivatives, as proven in radical scavenging assays, highlight their potential in fighting oxidative pressure-associated issues. Structure-hobby dating (SAR) evaluation underscores the pivotal function of substituent electronic and steric residences in influencing bioactivity, emphasizing the significance of rational layout and specific substituent choice to optimize healing consequences.

- Research into enzyme inhibition reveals that certain 2-substituted benzimidazole derivatives possess strong inhibitory results towards enzymes like acetylcholinesterase

and carbonic anhydrase. This indicates ability packages in treating neurological and metabolic conditions. These insights align with current literature, confirming the relevance of benzimidazole derivatives in numerous healing contexts. The study additionally emphasizes the price of computational tools, together with molecular docking, in predicting bioactivity and guiding compound optimization (Abd et al., 2021).

- The consequences advocate for persevered exploration of two-substituted benzimidazole derivatives, specifically in refining structural attributes to enhance specificity and efficacy. Future research must awareness on expanding organic evaluations to consist of in vivo research, assessing pharmacokinetics, toxicity profiles, and clinical efficacy. The promising activities demonstrated through those derivatives pave the way for their improvement into clinically feasible pills, with capability applications spanning antimicrobial, anticancer, antioxidant, and enzyme inhibition treatments**.**

Applications of -Substituted Benzimidazole Derivatives

Antimicrobial Agents:

- 2-substituted benzimidazole derivatives exhibit robust antimicrobial activity in opposition to a wide range of bacterial and fungal lines.
- **New Antibiotics Development:** They are promising candidates for growing new antibiotics, particularly in mild of the growing issue of antibiotic resistance (Khan et al., 2023).
- Certain derivatives inhibit the proliferation of most cancers cells and induce apoptosis.
- **Target Specificity:** They have interaction with particular biological goals worried in cancer cellular increase, providing a singular road for cancer therapy.

- These derivatives have antioxidant homes, permitting them to scavenge loose radicals.
- **Cell Protection:** They protect cells from oxidative harm, which is vital for preventing oxidative stress-related sicknesses and promoting average cell health.

- Some 2-substituted benzimidazole derivatives display promising antiviral activity against viruses including HIV and herpes simplex virus.
- **Blocking Viral Entry:** They have the capability to inhibit viral replication and block the entry of viruses into host cells, making them viable applicants for antiviral drug development (Masood et al., 2023).

- They are used in agriculture as effective fungicides to guard plants from fungal infections.

- These derivatives are utilized in substances technology as corrosion inhibitors, improving the durability of metals.

- In coordination chemistry, 2-substituted benzimidazole derivatives function ligands for metal complexes, gambling a vital function in the synthesis of diverse coordination compounds.

Conclusion

Therefore 2-substituted benzimidazole derivatives represent a crucial class of compounds in medicinal chemistry, characterized by their diverse structural modifications and versatile

versatile organic sports. The design of these derivatives consists of meticulous attention of substituents' digital, steric, and hydrophobic houses to beautify pharmacological efficacy. Their synthesis may be finished through various classical and cutting-edge strategies, which incorporates condensation reactions with carboxylic acids, aldehydes, or nitriles, in addition to progressive strategies like microwave-assisted and solvent-free syntheses, supplying greener and greater green pathways. Characterization the use of superior spectroscopic techniques which incorporates NMR, IR, MS, and UV-Vi's spectroscopy confirms their form and purity, ensuring their readiness for application in numerous fields. The vast spectrum of organic activities, along with antimicrobial, anticancer, antioxidant, and antiviral residences, underscores their capability as therapeutic dealers. Additionally, their applicability extends beyond remedy, encompassing agriculture, materials technological information, and coordination chemistry. As research keeps to adapt, the exploration of novel 2-substituted benzimidazole derivatives may additionally need to lead to the improvement of stronger and selective tablets, addressing urgent global fitness demanding situations and fostering upgrades in a couple of clinical domains. The synthesis, characterization, and useful versatility of these derivatives pave the manner for their persevered exploration and utilization.

Reference

1. Shahnaz, M., Kaur, P., Parkash, J. and Parsad, D.N., 2018. Synthesis, characterization of 2-substituted benzimidazole derivatives and evaluation of antimicrobial activity. *Journal of Drug Delivery and Therapeutics*, *8*(5), pp.460-464.
2. Deshmukh, S.L. and Kankite, R.S., 2023. Synthesis, Molecular Docking Studies and Cytotoxic Screening of Novel 2-Substituted Benzimidazole Derivatives. *Acta Biomed*, *94*(6), p.e2022289.
3. Anichina, K.K. and Georgiev, N.I., 2023. Synthesis of 2-Substituted Benzimidazole Derivatives as a Platform for the Development of UV Filters and Radical Scavengers in Sunscreens. *Organics*, *4*(4), pp.524-538.
4. Gursoy, S. and Ersan, R.H., 2024. Diaryl-substituted benzimidazole derivatives as antiproliferative agents: Design, synthesis, in vitro activity, and SAR analysis. *Journal of Molecular Structure*, *1308*, p.137960.
5. Kumar, L., Verma, N., Tomar, R., Sherawat, H., Kumar, R. and Chandra, R., 2023. Development of bioactive 2-substituted benzimidazole derivatives using an MnO x/HT nanocomposite catalyst. *Dalton Transactions*, *52*(10), pp.3006-3015.
6. Rajagopal, K., Dhandayutham, S., Nandhagopal, M. and Narayanasamy, M., 2023. Study on new series of bis-benzimidazole derivatives synthesis, characterization, single crystal XRD, biological activity and molecular docking. *Journal of Molecular Structure*, *1283*, p.135253.
7. Ilhan, S., Camli Pulat, C., Oguz, F., Bektaş, H., Menteşe, E. and Atmaca, H., 2023. Design and synthesis of benzimidazole derivatives as apoptosis-inducing agents by targeting Bcl-2 protein. *Molecular Diversity*, *27*(4), pp.1703-1712.
8. Kusuma, S., Bawiskar, D.B., Singh, C., Panneerselvam, P., Sinha, P., Samal, A.K. and Jadhav, A.H., 2023. Facile one pot synthesis of 2-substituted benzimidazole derivatives under mild conditions by using engineered MgO@ DFNS as heterogeneous catalyst. *RSC advances*, *13*(46), pp.32110-32125.
9. Kankate, R.S., Surse, S., Abhang, M.P., Kakad, S. and Kshirsagar, S., 2023. Synthesis, Molecular Docking Studies and Cytotoxic Screening of Novel 2-Substituted Benzimidazole Derivatives. *International Journal*, *10*(3), pp.2568-2579.

10. Khan, M.Q., Ullah, N. and Farooq, S., 2023. Mannich bases derivatives of 2-Phenyl-5-Benzimidazole sulfonic acid; Synthesis, Characterization, Computational studies and Biological evaluation. *Brazilian Journal of Pharmaceutical Sciences*, *59*, p.e19544.
11. Mashood Ahamed, F.M., Shakya, B. and Shakya, S., 2023. Synthesis and characterization of a novel Mannich base benzimidazole derivative to explore interaction with human serum albumin and antimicrobial property: experimental and theoretical approach. *Journal of Biomolecular Structure and Dynamics*, *41*(18), pp.8701-8714.
12. Chauhan, M., Gupta, S., Paliwal, S. and Nain, S., 2024. Synthesis, Characterization and Biological Evaluation of Novel Benzimidazole Derivatives against Candida albicans. *Pharmaceutical Chemistry Journal*, *57*(12), pp.1934-1940.
13. Aryal, P. and Shakya, B., 2023. Synthesis, Cytotoxicity, Antibacterial and Antioxidant Activity of New 2-Substituted Benzimidazole Containing 1, 2, 4-Triazoles. *Journal of Nepal Chemical Society*, *43*(2), pp.34-45.
14. Pham, E.C., Le Thi, T.V., Hong, H.H.L., Thi, B.N.V., Vong, L.B., Vu, T.T., Vo, D.D., Nguyen, N.V.T., Le, K.N.B. and Truong, T.N., 2023. N, 2, 6-Trisubstituted 1 H-benzimidazole derivatives as a new scaffold of antimicrobial and anticancer agents: design, synthesis, in vitro evaluation, and in silico studies. *RSC advances*, *13*(1), pp.399-420.
15. Ramachandran Surajambika, R., Ramesh, B., Ramesh, R. and Venkatesan, J., 2024. 2D QSAR Modelling, Docking, Synthesis and Evaluation of 2-substituted Benzimidazole Derivatives as Anti-breast Cancer Agents. *Current Bioactive Compounds*, *20*(5), pp.43-58.
16. Albay, C. and Tekbaş, G., 2023. Desing, synthesis, and characterization of some 5, 6-dichloro benzimidazole derivatives with investigation of their antioxidant and elastase inhibitory activities. *Journal of Heterocyclic Chemistry*, *60*(8), pp.1374-1382.
17. Wu, Z., Xia, M.B., Versteeg, D., Wang, Y.H., Bao, X.L., Zhu, W.B., Chen, P.R., Tang, H.S., Yan, Y.J. and Chen, Z.L., 2020. Design, synthesis and biological evaluation of novel fluor-substituted benzimidazole derivatives with anti-hypertension activities. *Bioorganic Chemistry*, *101*, p.104042.
18. Nazreen, S., Almalki, A.S., Elbagir, S.E.I., Shati, A.A., Alfalfa, M.Y., Lenawee, A.A., Alemanni, N.I., Alfarsi, A., AL Hadhrami, A., Aquash, E.A. and Alam, M.M., 2022. Cell cycle arrest and apoptosis-inducing ability of benzimidazole derivatives: design, synthesis, docking, and biological evaluation. *Molecules*, *27*(20), p.6899.
19. Osmany, D., Evren, A.E., Salk, B.N., Levent, S., Okay, Y. and Kalanick, Z.A., 2022. Design, synthesis, biological activity, molecular docking, and molecular dynamics of novel benzimidazole derivatives as potential Ache/MAO-B dual inhibitors. *Archive der Pharmacies*, *355*(3), p.2100450.
20. Abdel-Metal, M., Alohas, K. and Tantawy, M.A., 2020. Antimicrobial evaluation and docking study of some new substituted benzimidazole-2yl derivatives. *Bioorganic Chemistry*, *101*, p.103972.
21. Ambala, S., Thumma, V., Malli Kanti, V., Aidha, S., Matta, R. and Optimally, J., 2023. Design, Synthesis, and Cytotoxicity of Some New Benzimidazole-Piperazine Conjugate Analogues against Human Breast Adenocarcinoma. *Chemistry Select*, *8*(31), p.e202302393.
22. Srinivasa, S.B., Poojary, B., Kalal, B.S., Brahma Vara, U., Vaishali, D., Das, A.J., Kalenga, T.M., Tadikonda, M. and Shankar, M.K., 2024. Design, synthesis and

anticancer activity of Novel benzimidazole containing quinoline hybrids. *Results in Chemistry*, *9*, p.101631.

23. Deswal, L., Verma, V., Kirar, J.S., Kumar, D., Deswal, Y., Kumar, A. and Bhatia, M., 2023. Benzimidazole-1, 2, 3-triazole-piperazine hybrids: design, synthesis, antidiabetic evaluation and molecular modelling studies. *Research on Chemical Intermediates*, *49*(3), pp.1059-1083.
24. Khairat, S.H., Omar, M.A., Ragab, F.A., Roy, S., Turab Naqvi, A.A., Abdelsamie, A.S., Hirsch, A.K., Galal, S.A., Hassan, M.I. and El Diwani, H.I., 2021. Design, synthesis, and biological evaluation of novel benzimidazole derivatives as sphingosine kinase 1 inhibitor. *Archive der Pharmacies*, *354*(9), p.2100080.
25. Saadian Moghadam, E., Al-Sadi, A.M., Talebi, M., Amanous, M., Amini, M. and Abdel-Jalil, R., 2022. Design, synthesis, and bioactivity investigation of novel benzimidazole derivatives as potent urease inhibitors. *Synthetic Communications*, *52*(1), pp.106-116.
26. Akkoç, S., Tüzün, B., İlhan, İ.Ö. and Akkurt, M., 2020. Investigation of structural, spectral, electronic, and biological properties of 1, 3-disubstituted benzimidazole derivatives. *Journal of Molecular Structure*, *1219*, p.128582.
27. Yang, L., 2022. Design, Synthesis, and antifungal activity of novel benzimidazole derivatives bearing thioether and carbamate moieties. *Journal of Chemistry*, *2022*(1), p.8646557.
28. Abd El-Lateef, H.M., Elastases, M.A., Abdelghani Ibrahim, T.M., Khalaf, M.M., Gouda, M., Wahba, M.G., Zaki, I. and Marcos, M.M., 2023. Design, Synthesis, Docking Study, and Antiproliferative Evaluation of Novel Schiff Base–Benzimidazole Hybrids with VEGFR-2 Inhibitory Activity. *Molecules*, *28*(2), p.481.
29. Raghu, M.S., Kumar, C.P., Kumar, K.Y., Prashanth, M.K., Alshahrani, M.Y., Ahmad, I. and Jain, R., 2022. Design, synthesis and molecular docking studies of imidazole and benzimidazole linked ethionamide derivatives as inhibitors of InhA and antituberculosis agents. *Bioorganic & Medicinal Chemistry Letters*, *60*, p.128604.
30. Ren, B., Liu, R.C., Ji, K., Tang, J.J. and Gao, J.M., 2021. Design, synthesis and in vitro antitumor evaluation of novel pyrazole-benzimidazole derivatives. *Bioorganic & medicinal chemistry letters*, *43*, p.128097.
31. Srivastava, R., Gupta, S.K., Naaz, F., Gupta, P.S.S., Yadav, M., Singh, V.K., Singh, A., Rana, M.K., Gupta, S.K., Schols, D. and Singh, R.K., 2020. Alkylated benzimidazoles: Design, synthesis, docking, DFT analysis, ADMET property, molecular dynamics and activity against HIV and YFV. *Computational Biology and Chemistry*, *89*, p.107400.
32. Al-Hakimi, A.N., Almendras, F., Arouca, L., Alhaj, S.K., Alfalfa, M.Y., Mahyoub, J.A., Elbagir, S.E.I. and Annaisha, A.S., 2020. Design, synthesis, characterization of zirconium (IV), cadmium (II) and iron (III) complexes derived from Schiff base 2-aminomethylbenzimidazole, 2-hydroxynaphtadehyde and evaluation of their biological activity. *Arabian Journal of Chemistry*, *13*(10), pp.7378-7389.
33. Alshahrani, S., Al-Majid, A.M., Ali, M., Alameri, A.S., Abu-Serie, M.M., Doling, A., Shafiq, M., Ulf-Haq, Z. and Barakat, A., 2023. Rational design, synthesis, separation, and characterization of new Spir oxindoles combined with benzimidazole scaffold as an MDM2 inhibitor. *Separations*, *10*(4), p.225.
34. Rashid, M., 2020. Design, synthesis and ADMET prediction of bis-benzimidazole as anticancer agent. *Bioorganic chemistry*, *96*, p.103576.

35. Brushy, S.R., Saha, P., Al Mahmud, Z. and Rahman, S.A., 2020. Synthesis and Evaluation of Analgesic and Antioxidant Activities of Substituted Benzimidazole Derivatives Synthesis and Evaluation of Analgesic and Antioxidant Activities of Substituted Benzimidazole Derivatives. *Dhaka University Journal of Pharmaceutical Sciences*, *19*(1), pp.37-46.