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Advancements in Synthetic Methods for Biologically Active 1-((1H-imidazol-2- yl)(phenyl)methyl)piperidine Derivatives

Vilas Kondiram Kamble¹, Prabhakar Ramrao Kute²

Department of Chemistry, Badrinarayan Barwale College, Jalna, India¹

Department of Chemistry, Pratishthan Mahavidyalaya, Paithan, Aurangabad, India²

ABSTRACT: Heterocyclic compounds, including 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine derivatives, are essential in pharmaceuticals and materials science due to their diverse biological activities. Pyrimidines, with a six-membered ring containing two nitrogen atoms, are foundational in numerous therapeutic agents, exhibiting antiviral, anticancer, and antimicrobial properties. Their synthesis involves several methods, including cyclization reactions like the Biginelli reaction, and multicomponent reactions (MCRs) such as the Hantzsch synthesis, which allow for efficient formation of substituted pyrimidines. Metal-catalyzed reactions and nucleophilic substitutions further enable the modification of pyrimidine rings, enhancing their functional diversity. This study underscores the importance of 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine derivatives and their synthesis in advancing drug development and scientific research.

KEYWORDS: Heterocyclic compound; pyrimidines derivative; Synthetic route; biomedical application.

I. INTRODUCTION

Heterocyclic compounds represent a diverse class of organic compounds that contain rings with at least one atom other than carbon. These atoms, known as heteroatoms, typically include nitrogen, oxygen, and sulfur [1, 2]. The presence of heteroatoms greatly impacts the chemical and biological properties of these compounds, making heterocyclic chemistry a crucial area in both organic and medicinal chemistry [3]. These compounds are widespread in nature and play essential roles in various biological processes. They are fundamental components of many biomolecules, such as nucleic acids, vitamins, hormones, and alkaloids [4]. The structural versatility of heterocyclic compounds allows for the creation of a wide range of molecular frameworks, each with distinct physical and chemical characteristics. In the field of pharmaceuticals, heterocyclic compounds are of utmost importance. A significant number of therapeutic agents are based on heterocycles, as they have the ability to interact specifically with biological targets like enzymes, receptors, and ion channels [5]. For example, heterocycles such as pyridine, pyrimidine, imidazole, and indole serve as core structures in numerous drugs used to treat various diseases, including cancer, infections, cardiovascular conditions, and neurological disorders [6]. The creation of heterocyclic compounds represents a crucial element of organic chemistry with significant implications for pharmaceuticals, agrochemicals, and materials science. Diverse strategies ranging from traditional approaches to cutting-edge methods utilizing sophisticated catalysts are utilized. Process involving cyclization, whether intramolecular or intermolecular, transform linear or branched precursors into ring structures. Other methods such as condensation reactions connect molecules by eliminating a small molecule, demonstrated by the Knorr and Paal-Knorr synthesis [7]. Multicomponent reactions (MCRs) like the Ugi and Hantzsch reactions are proficient in generating intricate heterocycles from multiple reactants [8]. Metal-catalyzed reactions such as palladium-catalyzed couplings and copper-catalyzed cycloadditions facilitate both ring formation and introduction of functional groups [9]. Electrophilic and nucleophilic substitutions play a role in altering heterocyclic cores by substituting atoms or groups with electrophiles or nucleophiles [10]. Cycloaddition reactions, including the Diels-Alder and 1,3-dipolar cycloadditions, are instrumental in producing rings by combining unsaturated molecules [11]. Progress in synthetic methods has facilitated the exploration of structure-activity relationships (SAR) and the enhancement of pharmacokinetic properties, leading to the discovery of potent and selective therapeutic agents [12]. The selection of the most suitable synthesis method depends on the specific heterocycle desired, initial starting materials, and necessary functional groups, with ongoing advancements in synthetic methodologies broadening the scope for the creation of novel and elaborate heterocyclic structures across various disciplines. Heterocyclic compounds are widely utilized

across various industries due to their diverse structures and unique chemical properties [13]. In pharmaceuticals, they play a crucial role in the development of therapeutic agents like anticancer drugs, antibiotics, antivirals, anti-inflammatory medications, and CNS agents [14-16]. Agriculture benefits from heterocyclic compounds in pesticides, herbicides, and fungicides, enhancing crop protection and yield [17]. Materials science utilizes heterocycles in creating conducting polymers, dyes, pigments, and organic semiconductors for electronic devices, sensors, and batteries [18, 19]. Biochemical research relies on these compounds as probes, markers, and enzyme inhibitors. Environmental science uses heterocyclic compounds in sensors for pollutant detection and bioremediation agents [20, 21]. The food industry employs heterocycles for flavor enhancement and preservation [22]. The wide-ranging applications of heterocyclic compounds underscore their importance and the continuous need for research and development in this field as depicted in Figure 1.

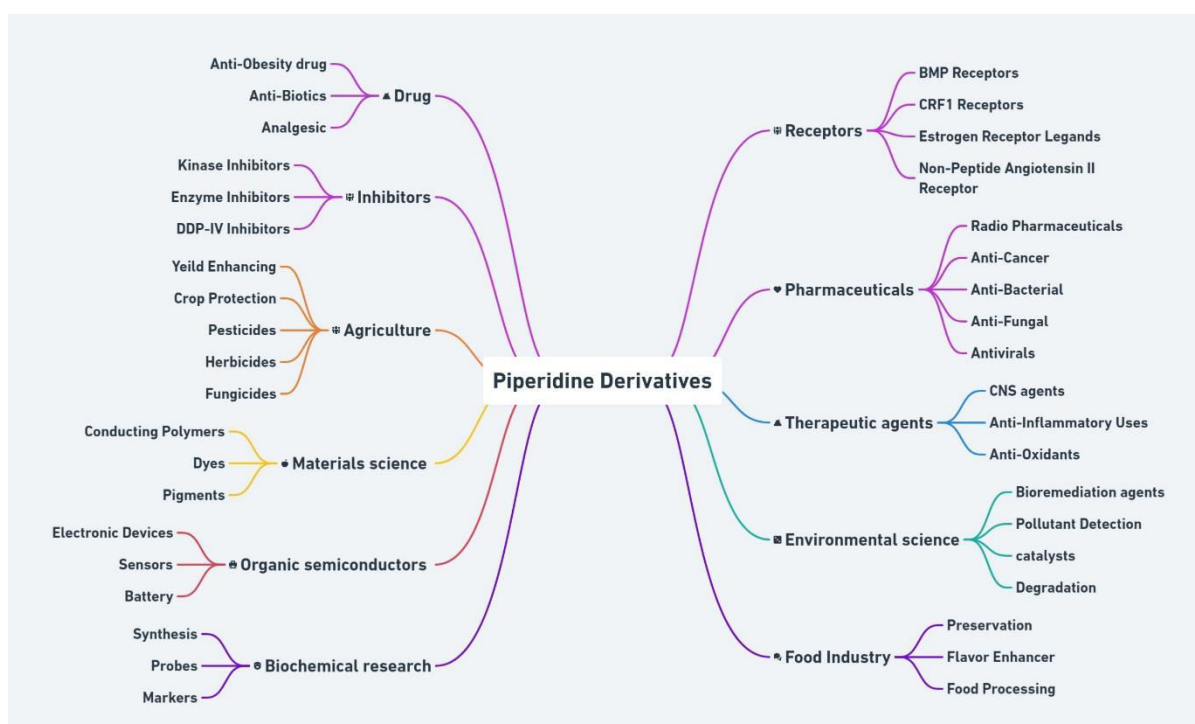


Figure 1 Various Applications of 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine

Polysubstituted derivatives of different heterocyclic compounds, including 4H-pyrans, benzothiazoles, imidazoles, 1,4-benzothiazinones, pyrazolines, xanthenes, benzoxanthenes, and indoles, demonstrate a broad spectrum of biological effects owing to their varied chemical structures [23, 24]. These compounds are recognized for their antimicrobial, anticancer, anti-inflammatory, and antioxidant properties [25]. For example, 4H-pyrans and pyrazolines exhibit efficacy against bacterial and fungal pathogens, as well as inhibit cancer cell growth and reduce inflammation [26]. Benzothiazoles and 1,4-benzothiazinones display strong activity against *Mycobacterium tuberculosis* and various cancer cells, while imidazole derivatives are commonly used as antifungal and antibacterial agents [27]. Xanthenes and benzoxanthenes are distinguished for their antioxidant and anticancer effects [28], whereas indole derivatives play crucial roles in regulating biological processes, showing promise in cancer treatment, microbial infections, and inflammatory conditions [29]. The diverse biological activities of these polysubstituted heterocycles make them significant in the field of drug discovery and development, underscoring their relevance in medicinal chemistry.

II. EXPERIMENTAL METHOD

Materials:

The synthesis of 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine derivatives requires a range of specific materials and reagents. The process begins with the formation of 2-phenylimidazole, which involves glyoxal, ammonium acetate, and aniline dissolved in a solvent such as ethanol or acetic acid. An acid or base catalyst may be used to

facilitate the reaction. The next step is alkylation, where 2-phenylimidazole reacts with benzyl bromide or benzyl chloride in the presence of a base like potassium carbonate or sodium hydride, using solvents such as acetone or DMF. Optional catalysts can enhance this reaction. For the final nucleophilic substitution, 2-benzyl-1-phenylimidazole is reacted with piperidine in a solvent like ethanol or THF, with a base such as sodium hydride aiding the process. Purification of the final product involves column chromatography and recrystallization, using solvents like methanol, dichloromethane, and acetone. Throughout the synthesis, personal protective equipment (PPE) and laboratory equipment, including reflux apparatus, magnetic stirrers, and analytical instruments for characterizing the product, are essential to ensure safety and efficiency.

III. GENERAL ASSUMPTION OF SYNTHESIS

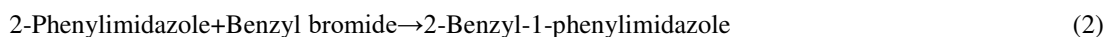
Synthetic route:

The synthesis of derivatives of 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine is a complex process that involves multiple steps including the formation of the imidazole ring, its functionalization, and the subsequent attachment of the piperidine group [30]. Initially, a 2-substituted imidazole is formed through the Debus-Radziszewski imidazole synthesis by combining glyoxal, ammonium acetate, and aniline in a suitable solvent like ethanol or acetic acid, followed by heating under reflux conditions [31]. The resulting 2-phenylimidazole is then isolated through filtration or extraction after cooling. After the formation of the imidazole ring, the next step is alkylation to introduce the phenylmethyl group [32]. The 2-phenylimidazole is dissolved in a solvent such as acetone or DMF, and benzyl bromide or benzyl chloride is added dropwise with stirring [33]. A base like potassium carbonate is added to neutralize the hydrogen halide by-product, and the mixture is stirred at room temperature or slightly elevated temperatures to ensure complete reaction. The benzylated imidazole derivative is then extracted and purified using column chromatography or recrystallization. The final step involves nucleophilic substitution to attach the piperidine group [34]. The benzylated imidazole derivative is dissolved in a suitable solvent like ethanol or THF, and piperidine is added along with a catalytic amount of sodium hydride or another appropriate base. The mixture is stirred at room temperature or under reflux conditions until the reaction is complete. The product, 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine, is isolated through extraction and further purified using column chromatography or recrystallization. The synthetic route can be succinctly described through the subsequent general reaction sequence as shown in **Figure 2**: Initially, the imidazole ring is formed by reacting glyoxal, ammonium acetate, and aniline, resulting in 2-phenylimidazole. Subsequently, 2-phenylimidazole is alkylated with benzyl bromide or benzyl chloride to yield 2-benzyl-1-phenylimidazole. Lastly, the nucleophilic substitution of 2-benzyl-1-phenylimidazole with piperidine leads to the desired product, 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine.

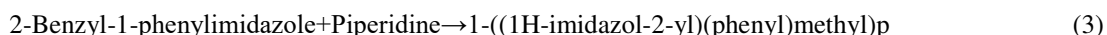
Imidazole Formation



Alkylation



Nucleophilic Substitution



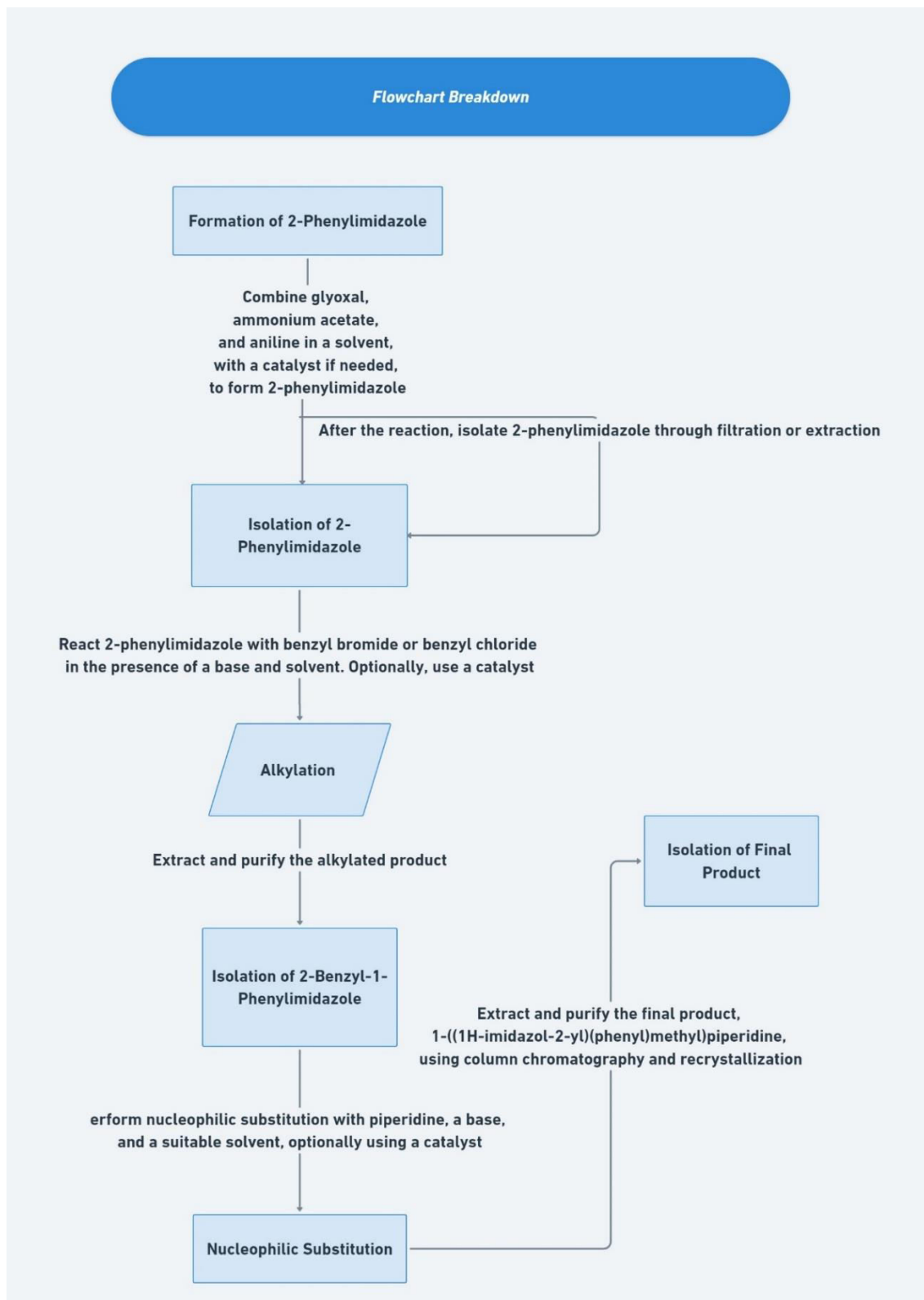
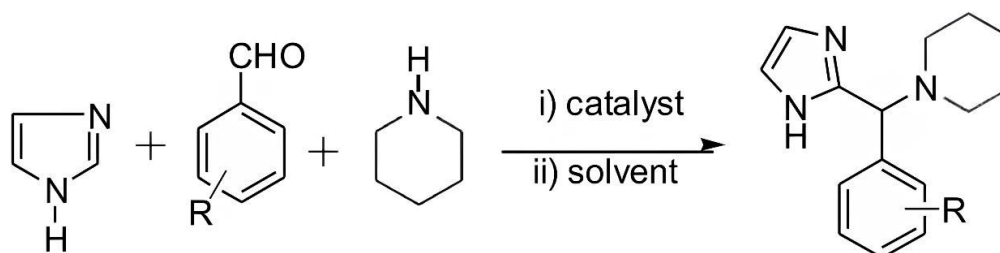


Figure 2 General Synthetic route for 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine

The illustration shows a chemical reaction involving three reactants: imidazole, substituted benzaldehyde, and piperidine. Imidazole is a five-membered ring with two nitrogen atoms at positions 1 and 3, making it a heterocyclic aromatic organic compound. The substituted benzaldehyde contains a benzene ring with an aldehyde group (-CHO) at one of its carbon atoms and an additional substituent (denoted as R) attached to another carbon atom [35]. Piperidine is a six-membered ring with one nitrogen atom, classifying it as a heterocyclic amine. In the reaction, these three reactants interact under the influence of a catalyst and solvent, which are unspecified in the diagram. The catalyst is used to accelerate the reaction rate without being consumed in the process, while the solvent provides a medium in which the reactants can dissolve and interact more freely [36]. The reaction depicted is a multi-component condensation reaction, which involves the combination of multiple reactants to form a single product with the elimination of small molecules like water. In this specific reaction, the aldehyde group of the substituted benzaldehyde reacts with the amine group of piperidine and the imidazole. This leads to the formation of a more complex heterocyclic structure where the imidazole and piperidine rings are connected to the benzene ring of the benzaldehyde. The substituent R remains attached to the benzene ring, indicating that the reaction does not affect this part of the molecule. The product formed from this reaction is a compound where the imidazole and piperidine are linked to a benzene ring, which retains the substituent R. This type of reaction is significant in the field of organic synthesis, particularly in the development of pharmaceuticals and fine chemicals. Heterocyclic compounds like the one formed in this reaction are often biologically active and can serve as key components in drugs and other bioactive molecules [37].

Scheme:



The reaction can be represented as:



IV. LITERATURE REVIEW

The literature survey indicates that heterocyclic chemistry is rapidly expanding due to the significant amount of research in this area. Heterocyclic chemistry is one of the most intriguing and applied branches of organic chemistry, with substantial practical and theoretical importance. 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine derivatives exhibit significant biological activities, particularly in medicinal chemistry. These derivatives are known for their broad-spectrum antifungal, antibacterial, and anti-inflammatory properties [38]. They hold promise in the treatment of fungal infections, which pose a global health problem and are especially dangerous for elderly individuals and patients with compromised immune systems due to conditions such as neutropenia, AIDS, diabetes, cancer, and post-organ transplant immunosuppression [39]. Andrés A. Trabanco et al. has worked on the the most potent and selective δ -opioid agonist 18a exhibited a K_i of 18 nM, with >258-fold and 28-fold selectivity over μ - and κ -receptors, respectively; the compound is a full agonist with an EC_{50} value of 14 nM [40]. Estelle Dubost et al. has reported the synthesis of substituted imidazo[1,2-a]-L-arabino-piperidinoses with various substituents. The compounds were evaluated for their inhibitory properties against β -glucosidase from almonds and β -galactosidase from *Escherichia coli*, with cyclohexylethyl and phenylethyl substituents showing the best results ($K_i = 2$ and 4 nM, respectively, against β -galactosidase). The synthesis and inhibitory potency of imidazo[1,2-a]-D-xylo-piperidinose against β -xylosidase from *Aspergillus niger* are also reported [41]. M.W. Bhade and P. R. Rajput et al. conducted a study on the synthesis and antibacterial activity of various imidazole derivatives, including those containing a phenyl group. They evaluated the compounds against several bacterial strains using standard antimicrobial methods [42]. N.C. Desai et al. synthesized

and assessed the antimicrobial potential of imidazole-substituted carbamates, showing significant activity against both bacterial and fungal strains [43]. P.G. Shobhashana et al. focused on imidazole-quinoline derivatives and their antimicrobial properties, demonstrating effectiveness against a range of pathogens [44]. The diverse biological activities of 1-((1H-imidazol-2-yl)(phenyl)methyl)piperidine derivatives make them valuable in the development of new therapeutic agents. Their ability to act against a wide range of pathogens highlights their potential in addressing various infectious diseases. Furthermore, ongoing research continues to explore and expand the applications of these derivatives in other areas of medicinal chemistry, emphasizing their importance in the field.

V. CONCLUSION

Pyrimidine derivatives play a vital role as inhibitors in medicinal chemistry, showing great promise for treating a wide array of diseases. Their versatility and therapeutic potential are evident in their ability to target various biological entities like enzymes, kinases, and receptors. These compounds have proven effective in managing complex health conditions such as cancer, viral infections, inflammatory diseases, and neurological disorders. The adaptability of pyrimidine derivatives allows for specific modifications to enhance their biological activity and selectivity. In cancer treatment, pyrimidine-based kinase inhibitors have been successful in disrupting crucial signalling pathways necessary for tumor progression and survival. In antiviral therapy, these derivatives can impede viral replication mechanisms, offering strong protection against different viral infections. Moreover, their anti-inflammatory properties make them valuable in controlling chronic inflammatory conditions by targeting specific inflammatory pathways. Neurological disorders like Alzheimer's disease, Parkinson's disease, and epilepsy also benefit from the inhibitory effects of pyrimidine derivatives on specific neural targets. This underscores the wide-ranging utility of these compounds in various therapeutic fields. Continuous research and innovation in synthesizing and functionalizing pyrimidine derivatives are essential for discovering novel therapeutic agents. Progress in synthetic chemistry, along with a deeper understanding of the structure-activity relationships (SAR) of pyrimidine compounds, have paved the way for developing inhibitors with enhanced efficacy, reduced toxicity, and improved pharmacokinetic properties. The impact of pyrimidine derivatives in drug discovery and development is significant, with numerous clinical applications showcasing their potential to enhance patient outcomes. Ongoing research advancements are expected to result in the discovery of novel pyrimidine-based inhibitors, which could potentially pave the way for the creation of enhanced and targeted medications, catering to unmet healthcare requirements and propelling progress in the medical field. To summarize, pyrimidine derivatives play a crucial role in medicinal chemistry, presenting a range of therapeutic options. The ongoing exploration and enhancement of these compounds offer hope for the introduction of groundbreaking therapies for various illnesses, ultimately improving the well-being of patients globally.

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