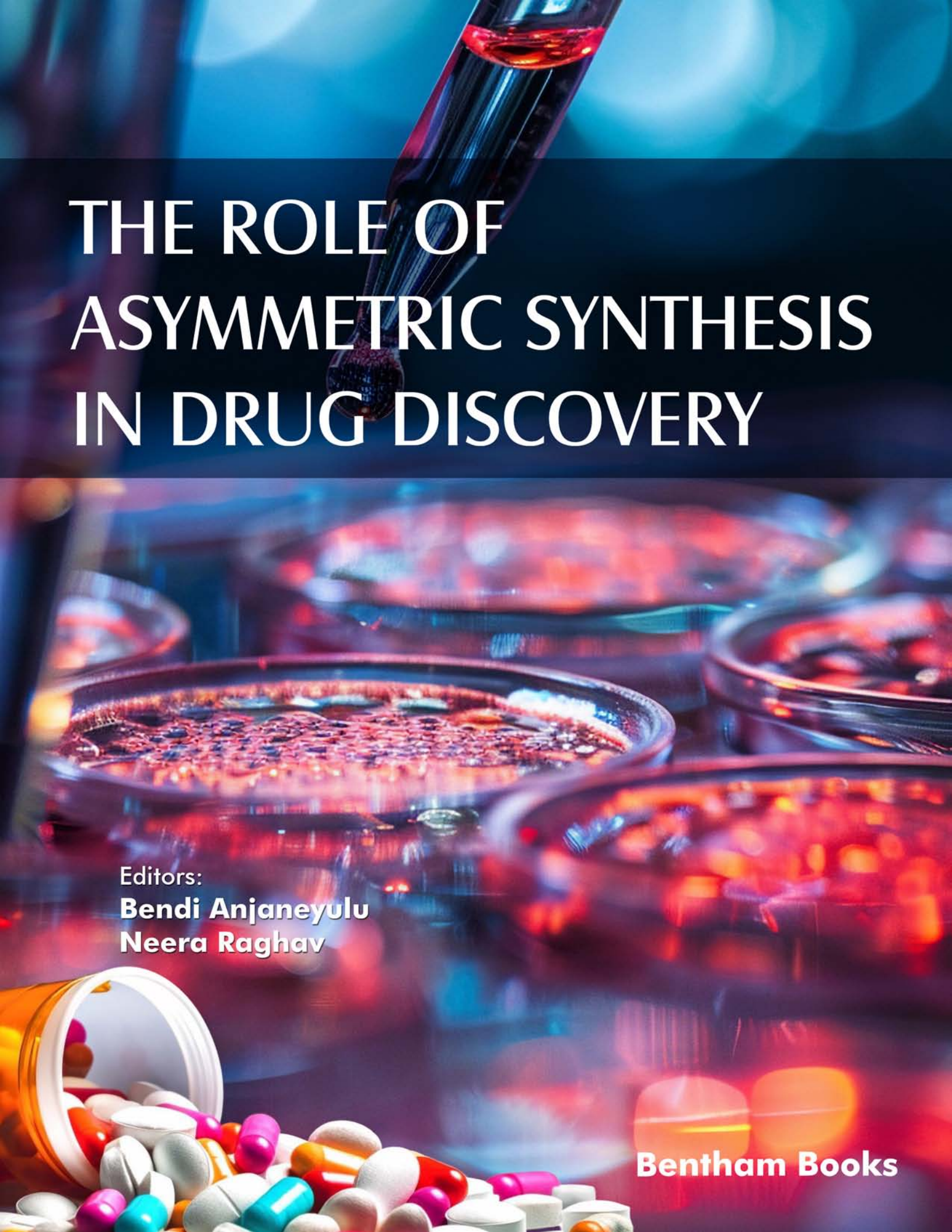
THE ROLE OF
ASYMMETRIC SYNTHESIS
IN DRUG DISCOVERY
Editors:
Bendi Anjaneyulu
Neera Raghav
Bentham Books

The Role of Asymmetric Synthesis in Drug Discovery

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FOREWORD

It is my pleasure to write foreword for the book entitled ***The Role of Asymmetric Synthesis in Drug Discovery*** edited by ***Anjaneyulu Bendi***, and ***Neera Raghav***. The editors are esteemed researchers with a wealth of experience across various domains of organic and medicinal chemistry. Their collective expertise spans a wide range of research areas, earning them high regard within the academic community

The quest for novel therapeutic agents has been a central pursuit in medicinal chemistry. The importance of chirality in drugs is now universally recognized. The profound differences in the biological activity of enantiomers can determine the success or failure of a drug candidate. Asymmetric synthesis has become the linchpin in modern drug discovery, offering precision in creating structurally sound and biologically efficacious chemical compounds.

This book offers an in-depth exploration of the molecular advancements in applying asymmetric synthesis to drug discovery. Each chapter covers the transformative potential of asymmetric synthesis in crafting a variety of heterocycles as drug candidates. Asymmetric synthesis is increasingly pivotal in tailoring medications to specific biological targets in an era of rapidly advancing precision medicine. This book equips researchers, scientists, and students with the insights necessary to leverage stereochemistry effectively in the quest for safer, more effective, and superior therapeutics.

I am confident that the book **The Role of Asymmetric Synthesis in Drug Discovery** will be an invaluable resource for researchers, practitioners, and policymakers, fostering further exploration and contributing more to drug discovery and development through asymmetric synthesis.

I hope that the book will be well received by the scientific community.

M.P. Kaushik
Amity University, Gwalior, M.P
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PREFACE

Is asymmetric synthesis essential for modern drug discovery?

Asymmetric synthesis is essential for modern drug discovery, playing a pivotal role in developing safer and more effective therapeutics by enabling the selective production of a single enantiomer. Since many biological molecules, including drug targets, are chiral, the three-dimensional arrangement of atoms in a drug can significantly influence its biological activity, efficacy, and safety. Asymmetric synthesis offers the precise control necessary to produce the desired enantiomer, minimizing side effects and enhancing the therapeutic potential of drugs. This level of precision is fundamental in the era of precision medicine, where treatments are tailored to interact optimally with specific biological targets.

This book showcases cutting-edge experimental research on synthesizing various heterocyclic drugs using the principles of asymmetric synthesis, summarized across ten chapters. In **Chapter 1**, the authors have briefly discussed the basic principles of enantioselective synthesis, underscoring its critical importance in drug discovery and development, and highlighted the biological significance of chiral heterocycles, focusing on chiral amines and other related compounds. The asymmetric synthesis of bioactive chiral alkaloids and terpenoids has been discussed in **Chapter 2**.

Chapter 3 describes the synthesis of pharmacologically active spirooxindoles through asymmetric synthesis. A brief discussion of the chemistry of medicinally important chiral dihydropyrimidinones has been presented in **Chapter 4**.

In **Chapter 5**, the authors have a special focus on exploring the procedures for the asymmetric synthesis of biologically active piperazine and its derivatives. **Chapter 6** deals with up-to-date improvement and novel trends in the green alternative synthesis of asymmetric oxazines. The chemistry of chiral triazoles and their biological significance have been discussed in **Chapter 7**. In **Chapter 8**, the authors have provided a comprehensive overview of the synthetic strategies and biological evaluations of chiral benzimidazole derivatives, underscoring their potential in pharmaceutical applications. **Chapter 9**, gives an insight into the chemistry of chiral pharmaceuticals, discussing the different classes of compounds that have been synthesized using asymmetric methods.

In conclusion, the goal of this book is to provide an overview of the research being conducted on the role of asymmetric synthesis in drug discovery. We hope the content will captivate aspiring researchers and inspire them to further explore novel chiral heterocycles for the treatment of various diseases. Additionally, we believe this book will be a valuable resource for researchers, academics, and industry professionals with a deep interest in this field.

We want to express our sincere admiration and gratitude to all the authors for their dedicated efforts in preparing the content of this book. We also extend our heartfelt thanks to the publishers and their team for efficiently handling the project at every stage. Lastly, we are deeply grateful to our family members for their unwavering support throughout this journey.

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CHAPTER 1

Asymmetric Synthesis: A Boom to Medicinal Chemistry

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Abstract: Asymmetric synthesis is a foundational aspect of medicinal chemistry, offering essential insights into developing chiral molecules with high enantioselectivity. This chapter thoroughly introduces the basic principles of enantioselective synthesis, underscoring its critical importance in drug discovery and development. The ability to selectively produce single enantiomers is vital, given that the biological activity of many pharmaceutical agents is closely tied to their chirality and exploring the advantages of utilizing asymmetric synthesis, such as improved drug efficacy and reduced side effects, which are vital to advancing personalized medicine. The chapter also highlights the biological significance of chiral heterocycles, focusing on chiral amines and other compounds, and presents detailed examples of their synthetic schemes. By examining these aspects, the chapter illustrates how asymmetric synthesis facilitates the creation of more effective drugs and contributes to the ongoing innovation in medicinal chemistry.

Keywords: Asymmetric synthesis, Biological activity, Chiral drug molecules, Medicinal chemistry.

INTRODUCTION

The development of new therapeutic compounds has always been at the forefront of medicinal chemistry. Over the last few decades, the landscape of drug discovery has changed dramatically, owing to breakthroughs in organic chemistry, notably asymmetric synthesis. Asymmetric synthesis, or the production of chiral compounds with defined three-dimensional topologies, has emerged as an important component in the design and development of pharmacologically active pharmaceuticals [1 - 4]. The importance of chirality in drug design cannot be und-

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erstated, since enantiomers of a chiral compound can have significantly distinct pharmacokinetic, pharmacodynamic, and toxicological characteristics. This understanding has resulted in a paradigm change in medicinal chemistry, with precise control of stereochemistry being deemed essential to producing effective and safe medications.

Historical Context of Asymmetric Synthesis in Medicinal Chemistry

When Louis Pasteur discovered tartaric acid's optical activity in the 19th century, he presented the idea of chirality for the first time [5]. However, it was not until the twentieth century that the fundamental implications of chirality in biological systems were fully appreciated. The Thalidomide disaster of the 1960s, in which one enantiomer of the medicine caused severe birth deformities while the other had therapeutic effects, demonstrated the need for enantioselective synthesis in drug research. This terrible incident served as a watershed moment, sparking extensive study into ways for manipulating pharmacological compounds' stereochemistry.

The area of asymmetric synthesis gained traction in the 1970s, with the introduction of chiral auxiliaries and catalysts that could preferentially promote the creation of one enantiomer over another. The development of chiral ligands, such as BINAP and DIPAMP, revolutionized the field by enabling the synthesis of a wide spectrum of enantiomerically pure compounds. These advancements paved the way for the use of asymmetric synthesis in medicinal chemistry, enabling the development of medications with increased efficiency and fewer adverse effects.

Significance of Chirality in Drug Action

The three-dimensional nature of biomolecules has a significant impact on the connection between chirality and biological activity. Enzymes, receptors, and other biological macromolecules are intrinsically chiral, and their interactions with drug molecules are extremely stereospecific. As a result, the two enantiomers of a chiral medication may interact differently with their target sites, resulting in differences in their pharmacological effects [6 - 11].

One of the most dramatic examples of this phenomenon is found with beta-blockers such as propranolol. Propranolol's beta-adrenergic blocking effect is attributed to its S-enantiomer, whereas its R-enantiomer is much less active. Similarly, in the case of ibuprofen, the S-enantiomer is the active form that has anti-inflammatory benefits, whilst the R-enantiomer is essentially inert [12 - 15]. These examples demonstrate the vital relevance of managing stereochemistry during the drug development process in order to maximize therapeutic effects.

Advancements in Asymmetric Synthesis Techniques

Asymmetric synthesis methods have advanced dramatically in recent decades. These techniques may be split into three types: chiral pool synthesis, chiral auxiliary-based synthesis, and catalytic asymmetric synthesis [16 - 32].

- ***Chiral Pool Synthesis*:** This method starts with naturally occurring chiral molecules and then uses them to synthesize complicated chiral compounds. The intrinsic chirality of the starting materials allows for selective transformation into the required enantiomerically pure products, which is the benefit of this approach. However, the scarcity of acceptable chiral precursors and the limited range of reactions that may be conducted on them have limited the application of chiral pool synthesis in medicinal chemistry.
- ***Chiral Auxiliary-Based Synthesis*:** Chiral auxiliaries are non-racemic, enantiomerically pure chemicals that can be briefly linked to a substrate to generate chirality in later reactions. The auxiliary can then be eliminated, leaving behind only the required chiral product. This approach has been widely used in the manufacture of complex natural products and pharmaceutical intermediates. Evans' oxazolidinone auxiliaries and Meyers' pseudoephedrine-based auxiliaries have greatly enlarged the repertory of high-enantioselectivity reactions.
- ***Catalytic Asymmetric Synthesis*:** Catalytic techniques, which utilize chiral catalysts to enhance the creation of one enantiomer over the other in a chemical process, have resulted in the most important advances in asymmetric synthesis to date. Catalytic asymmetric synthesis has various benefits to chiral auxiliary-based techniques, including increased efficiency, cheaper cost, and lesser environmental effect. Chiral catalysts are divided into three categories: organocatalysts, biocatalysts, and metal-based catalysts each having its own set of processes and uses.

Organo-catalysis, in particular, has gotten a lot of attention in recent years due to its simplicity, versatility, and eco-friendliness. Organo-catalysts such as proline, cinchona alkaloids, and chiral amines have been successfully used to catalyze a wide range of enantioselective processes, including aldol reactions, Michael additions, and Diels-Alder reactions.

Applications of Asymmetric Synthesis in Drug Discovery

Asymmetric synthesis has become an important aspect of the drug development process, allowing for the synthesis of chiral compounds with the necessary stereochemistry. The capacity to selectively synthesize a single enantiomer has significant implications for the effectiveness and safety of novel medications. Several blockbuster medications have been produced utilizing asymmetric

CHAPTER 2

Asymmetric Synthesis of Bioactive Chiral Alkaloids and Terpenoids

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Abstract: Terpenoids are vital components in the interactions and defence mechanisms among plants, microorganisms, and animals. These compounds hold considerable ecological significance, not only by protecting plants but also by influencing environmental factors that drive the evolution of plant communities and ecosystems. Their economic potential is also becoming increasingly recognized due to their wide application in human industries, including pharmaceuticals, food production, and chemical manufacturing. Additionally, terpenoids are emerging as biofuel candidates. Advances in synthetic biology, utilizing genomic resources and innovative tools, have improved the metabolic engineering of high-value terpenoids in both plants and microorganisms. Furthermore, their ecological importance has been underscored in developing sustainable pest control methods and enhancing plant resilience against environmental stresses. The continued exploration of the intricate metabolic and regulatory networks governing terpenoid biosynthesis is essential for realizing their full potential. This review provides an updated overview of the organization, regulation, and diversification of both core and specialized terpenoid metabolic pathways, while highlighting their prominent roles in therapeutic applications. In parallel, alkaloids, another significant class of natural compounds, are being synthesized using highly efficient methods. Recent approaches enable the enantioselective synthesis of complex alkaloids, such as yohimbine and tetrahydroprotoberberine, through innovative catalytic processes. These techniques facilitate access to a wide array of stereoisomeric forms, thus opening doors to novel biomedical research opportunities. The integration of flow chemistry and catalytic enantioselective reactions has streamlined the production of diverse alkaloid structures, enhancing the scope of both natural and synthetic analogues for therapeutic and pharmaceutical development.

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Keywords: Alkaloids, Bio-active, Catalysts, Diversification, Pharmaceuticals, Therapeutics, Terpenoids.

INTRODUCTION

Terpenoids, the largest class of plant secondary metabolites, are synthesized through the action of the enzyme Terpene Synthase (TPS). This enzymatic process produces basic backbone structures that are then modified through various reactions, such as hydroxylation, dehydrogenation, acylation, or glycosylation, resulting in a broad range of terpenoid compounds [1]. These compounds are not only integral to plant biology but also have commercial significance, including the production of terpenoid-based biofuels and high-quality natural rubber. Additionally, some terpenoids contain isoprenoid chains embedded within other metabolic groups. For example, in furanocoumarin derivatives, the furan ring originates from dimethylallyl diphosphate, although the traditional C5 moiety is no longer evident in the structure [2]. Shikonin derivatives contain a naphthalene ring, which originates from geranyl diphosphate. Additionally, certain indole alkaloids are known to incorporate isoprenoid residues into their structures. Within the terpenoid family, plant-derived volatile organic compounds primarily consist of monoterpenoids and sesquiterpenoids. Their biosynthetic processes and accumulation have been extensively investigated. In some species, these compounds are stored in non-volatile forms, such as monoterpene glycosides [3]. Upon tissue damage, for example, during an insect attack, these glycosides are enzymatically converted into volatile compounds. Terpenoid compounds studied (Fig. **1**) include geraniol, menthol, limonene, vitamin A, farnesol, and guaiazulene [4]. Complex reactions involving the cleavage of carbon-carbon (C–C) sigma bonds, like Baeyer–Villiger oxidation, Grob fragmentation, and other rearrangement processes, are commonly used in the synthesis of biologically active and structurally complex molecules. Beyond traditional methods, transition metal-catalysed C–C bond activation allows relatively inert C–C bonds to become reactive under redox conditions, offering novel pathways for constructing intricate molecular frameworks from simpler compounds [6]. Alkaloids extracted from various species of *Corydalis* and *Stephania* are naturally occurring members of the tetrahydro protoberberine alkaloid family. These compounds exhibit a remarkable spectrum of biological activities, such as antimicrobial, anti-inflammatory, antipsychotic, and analgesic effects, which have garnered substantial research interest. Certain tetrahydro protoberberine alkaloids have emerged as promising leads in the development of novel antagonists targeting the α1A-adrenoceptor, D2/D1 dopamine receptor, and 5-HT1A receptor. This interest has led to numerous derivatization and analogue development programs, with several compounds progressing to clinical trials [7]. Alkaloids, classified as secondary metabolites, are characterized by the presence of a basic nitrogen atom

and are widespread in both nature and medicinal applications. The high prevalence of these compounds in pharmaceuticals and the growing interest in exploring sp^3 carbon-rich molecules for drug discovery underscore the need for efficient methods to construct complex nitrogen-containing heterocycles with precise enantiocontrol [8]. Furthermore, the design of versatile synthetic routes that provide rapid access to a diverse range of structurally similar compounds is equally important. These alkaloids exhibit significant activity within the Central Nervous System (CNS). Although structural differences among diastereomeric subfamilies may be minimal, they can result in notable variations in pharmacological properties. Therefore, developing concise, modular, and stereoselective synthesis methods for these alkaloids is essential for enabling comprehensive studies of their structural analogues [9]. Traditional synthetic routes for yohimbines follow methodologies established by Woodward and colleagues in their groundbreaking synthesis of reserpine. This approach involves creating a fully functionalized E-ring precursor, followed by the incorporation of the tryptamine subunit and subsequent ring closure. While this strategy has successfully facilitated the synthesis of specific natural products, the critical β-carboline pharmacophore is typically introduced in the later stages of the synthesis. As a result, efficient access to related analogues with potential biomedical applications is constrained, necessitating modifications in the early synthesis stages to introduce variations in the terpenoid component of the molecule. Alternative synthetic approaches that postpone the introduction of the E-ring could provide greater access to a wider array of related alkaloids [10].

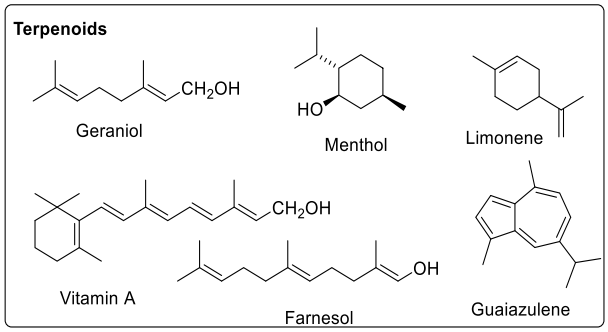

Fig. (1). Different terpenoids having useful applications in drug-related areas [11-15].

SYNTHESIS OF TERPENOIDS

In the year 2020, **Barry M. Trost *et al*.,** discovered a synthetic process producing a terpenoid from a diether unsaturated molecule **(1)** in a five-step reaction (Scheme **1**). The starting material can be easily achieved from propargyl alcohol, which reacts with n-BuLi and methyl chloroformate followed by the addition of an unsaturated aldehyde at the alkyne position to produce an unsaturated keto

CHAPTER 3

Asymmetric Synthesis of Pharmacologically Active Spirooxindoles

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Abstract: Spirooxindoles are a class of organic compounds characterized by a spirocyclic framework, where an oxindole moiety (which is a structure containing an indole fused to a carbonyl group) is connected to another ring system *via* a spiro carbon atom. These compounds have attracted significant interest in medicinal chemistry due to their diverse biological activities. They have been studied for their potential as anti-cancer, anti-inflammatory, and antimicrobial agents. The structural diversity of spirooxindoles allows for a wide range of pharmacological activities, making them valuable scaffolds in drug design. This chapter compiles the recent synthetic schemes on asymmetric synthesis of spirooxindoles and their significance as potential drug candidates. It discusses the different synthetic routes used to prepare chiral spirooxindoles and highlights the impact of chirality on their biological activities.

Keywords: Asymmetric synthesis, Biological activities, Chiral, Medicinal chemistry, Spirooxindoles.

INTRODUCTION

Chirality is crucial in chemistry because it determines how molecules interact with biological systems, where only one enantiomer of a chiral molecule might be biologically active or therapeutically effective [1]. This is especially important in pharmaceuticals, where the wrong enantiomer can cause harmful effects, as seen in historical drug cases like thalidomide [2]. Chirality also influences chemical reactions, where the selective production of a desired enantiomer is essential for synthesizing specific compounds [3]. Additionally, chiral molecules play a key role in molecular recognition, materials science, and even the fundamental understanding of symmetry in physics [4]. Thus, understanding and controlling chirality is vital for advancing chemical, biological, and medical sciences [5].

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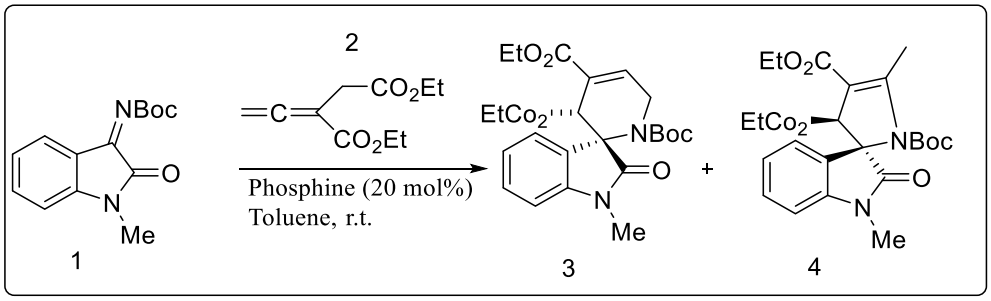
Spirooxindoles are a unique class of organic compounds characterized by a spirocyclic framework that includes an oxindole moiety. The spirocyclic structure refers to a molecular architecture where two or more rings are joined through a single atom, creating a highly strained and rigid system. In spirooxindoles, the oxindole nucleus—a bicyclic structure consisting of an indole fused to a lactam—forms the core, with the spiro atom typically being carbon, connecting this core to another ring [6]. This distinctive spiro configuration imparts significant structural complexity and three-dimensionality to spirooxindoles, making them interesting targets in synthetic organic chemistry [7]. They have attracted considerable attention due to their diverse and potent biological activities. This includes anticancer, antiviral, antimicrobial, and anti-inflammatory activities [8 - 11]. The structural diversity and rigidity contribute to their ability to interact with various biological targets, often with high specificity and affinity [12]. For instance, several spirooxindole derivatives have been identified as potent inhibitors of key enzymes involved in cancer cell proliferation, making them promising candidates for anticancer drug development [13, 14]. Additionally, the spirocyclic structure is often found in natural products with complex biological functions, further underscoring the importance of spirooxindoles in medicinal chemistry [15].

Chiral spirooxindoles are a subclass of spirooxindoles characterized by the presence of one or more chiral centers within their spirocyclic framework [16]. These chiral centers give rise to enantiomers. They are distinguished by their unique spiro-cyclic structures, featuring a spiro-ring connected at the oxindole core's C3-position. These compounds are prevalent in various natural alkaloids and pharmaceuticals, exhibiting a wide spectrum of biological functions, including anti-cancer, anti-bacterial, anti-HIV, anti-malarial, antiviral, anti-microbial, anti-inflammatory, fever-reducing properties, and the ability to block sodium channels [9, 11, 17, 18]. The synthesis of chiral spirooxindoles often requires highly selective methods to ensure the formation of the desired enantiomer. Asymmetric synthesis techniques, such as organocatalysis, metal-catalyzed reactions, and chiral auxiliary-based methods, are commonly employed to achieve enantioselective synthesis [19]. These methods allow for the precise control of stereochemistry during the formation of the spirocyclic structure, ensuring that the resulting compound has the desired chiral configuration. The stereochemistry of chiral spirooxindoles is vital because it can significantly influence the molecule's interactions with biological targets, such as enzymes, receptors, and nucleic acids [20]. The synthesis of these chiral, spiro-cyclic frameworks remains a significant challenge within the field of organic chemistry. Consequently, the development of efficient methods for synthesizing spirooxindoles, particularly through enantioselective processes, has captured the keen interest of both industrial and academic research communities. In this

chapter, we have compiled the method of asymmetric synthesis of spirooxindoles using various strategies.

RECENT SYNTHETIC SCHEMES ON ASYMMETRIC SYNTHESIS OF SPIROOXINDOLES

Sankar, M. G. *et al.,* employed an unprecedented mode of asymmetric [3+2]-annulation reaction that has been achieved by engaging allene-derived zwitterions. Catalytic addition of a chiral phosphine to an α-substituted allene ester generates a zwitterionic dipole. Under optimized conditions, this dipole reacts with isatin-derived N-Boc-ketimines in a novel [3+2] annulation, resulting in the formation of pyrrolinyl spirooxindoles. The reaction proceeds with high yields and excellent enantioselectivities, successfully constructing sp^3-rich, highly substituted 3,2'-pyrrolidinyl spirooxindoles with multiple chiral centers [21] (Scheme **1**).



Scheme 1. Synthesis of pyrrolidinyl-spirooxindoles derivatives 3 and 4.

Wang, B. *et al.,* synthesized chiral tetrahydronaphthalene-fused spirooxindoles. The reaction was carried out with 3-ylideneoxidole, 2-methyl-3-5-dinitrobenzaldehyde, and a catalyst in anhydrous CH_2Cl_2 at -10°C for 48 hours under nitrogen. The reaction mixture was purified directly using flash chromatography on silica gel to obtain the unprotected intermediate. This intermediate was then treated with TMSCl and imidazole in CH_2Cl at 0°C until the reaction was completed, as indicated by TLC. The product was purified by chromatography to yield the major isomer 8a. Finally, 8a was treated with HCl/EtOAc, quenched, and further purified by chromatography to obtain the deprotected spiro-oxindole derivative 8a as a white solid [22] (Scheme **2**).

CHAPTER 4

Asymmetric Synthesis of Medicinally Important Dihydropyrimidinones

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Abstract: The Biginelli reaction is considered one of the well-known examples of a multicomponent reaction that is useful in the synthesis of dihydropyrimidinones (DHPMs) using aryl aldehydes, urea, and esters and these are significant compounds in medicinal chemistry and chemical synthesis. DHPMs are considered vital compounds due to their diverse biological functions. Because of their remarkable and concentrated target-oriented biological activity, DHPMs have been the subject of large-scale and extensive research in the past few decades to determine how to synthesize them by using various catalysts and structural variations in a variety of solvents. Ionic liquids, Lewis acids, and organocatalysts are some of the chiral catalysts used in the enantioselective Biginelli reaction. This book chapter summarizes chiral reagents for asymmetric synthesis with particular absolute configuration.

Keywords: Asymmetric synthesis, Biologically activities, Chirality, Dihydropyrimidinones, Enantioselectivity, Medicinal chemistry.

INTRODUCTION

The chiral scaffold is essential to both nature and daily life as distinct stereoisomers of a chiral molecule can exhibit wildly disparate biological activity. In order to synthesise the intended enantiomer, synthetic chemists, therefore, strive to develop efficient and selective techniques. It is imperative for medicinal chemistry to aim toward the design, synthesis, and production of molecules that hold therapeutic significance for humans [1 - 5]. In the last ten years, there has been a dramatic rise in the quantity of chiral, non-racemic medications available on the market. Several novel single-enantiomer medications were developed to

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provide better therapy, more predictable pharmacokinetics, and lower toxicity by the use of an appropriate chiral switch [6 - 10] (Fig. **1**).

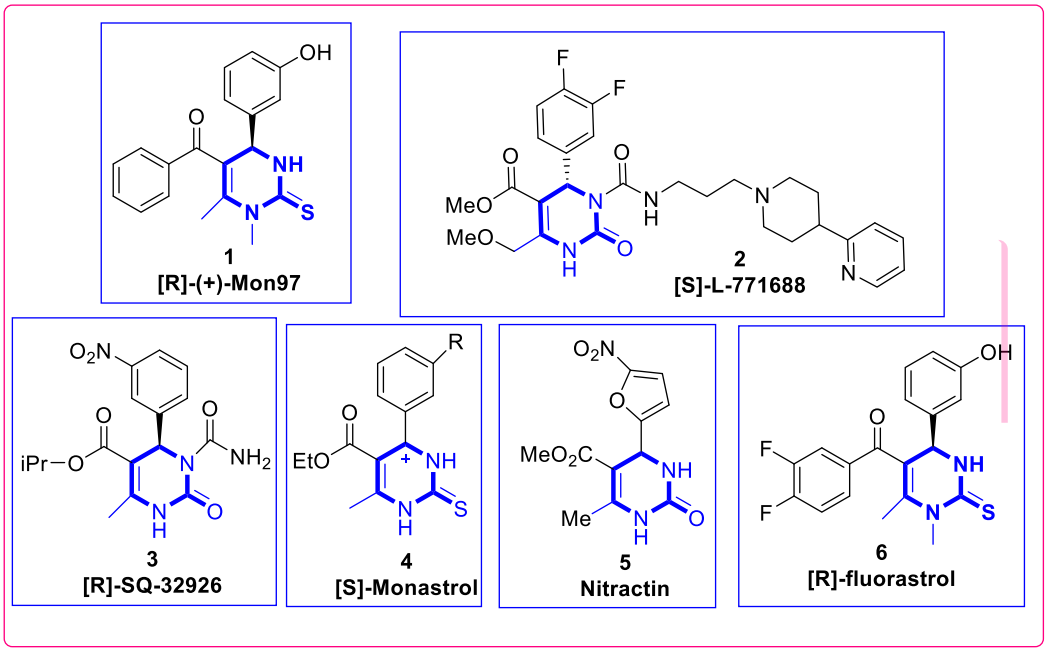
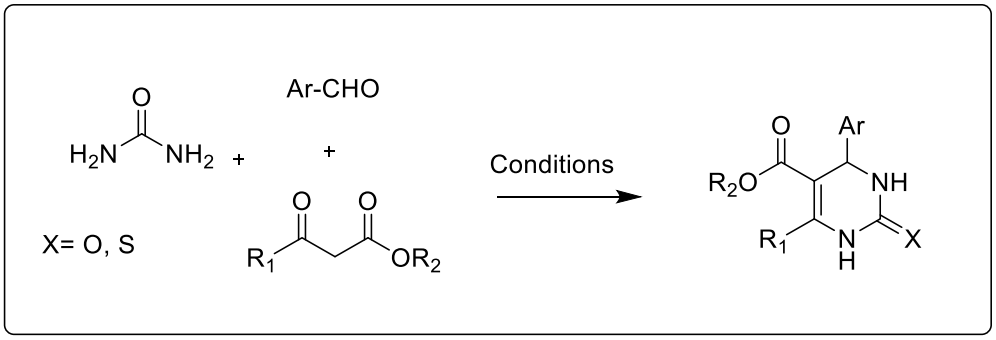


Fig. (1). Biologically active DHPMs.

Multi-component reactions represent one of the most active areas for the synthesis of heterocyclic complexes from easily accessible precursor materials [11 - 14]. Since its invention in 1893 by Italian scientist Pietro Biginelli, the Biginelli reaction is one of the most well-known examples of multi-component reactions for the production of Dihydropyrimidinone derivative (DHPM) by reacting urea or thiourea with different aldehyde derivatives and 1,3-dicarbonyl compounds *via* formation of iminium ion. As a nitrogen-contained heterocycle, DHPM exhibits a number of biological activities including antitubercular, antimalarial, anti-HIV, antitumor, antibacterial, anticonvulsant, anticancer, anti-inflammatory, and calcium channel antagonistic effects [15 - 19].

Chiral DHPMs have demonstrated a great deal of significance in pharmacological activities and have produced the essential structural components of numerous medications, including (S)-Monastrol, (S)-L-771688, (S)-SNAP-794130, (SQ 3292630, and (S)-L-771688, as well as some naturally occurring alkaloids [20 - 22]. Consequently, there has been a significant increase in interest in the many strategies for creating enantiomeric DHPMs *via* their asymmetric synthesis [23 - 26]. Chiral reagents like BINOL-phosphoric acids, Lewis acid catalyst containing

ytterbium, chiral primary and secondary amines, bifunctional primary amine thioureas, $NbCl_5$/primary amines, and SPINOL-phosphoric acid have been used by numerous research groups for stereoselective Biginelli reactions for the preparation of dihydropyrimidinones. Organic chemistry is very interested in the creation of ecologically friendly and effective chemical processes. For synthetic chemists, the biggest obstacles are the development and execution of significantly efficient methods for the synthesis of biologically active scaffolds [27 - 30] (Scheme **1**) (Fig. **2**).



Scheme 1. General synthesis of DHPMs.

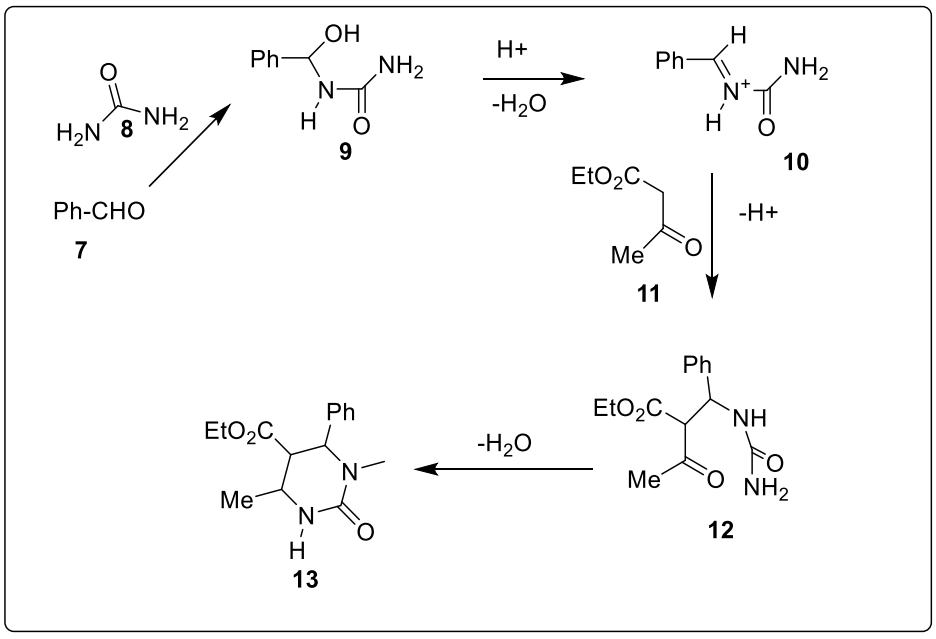


Fig. (2). Mechanism of Biginelli reaction.

CHAPTER 5

Asymmetric Synthesis of Biologically Active Piperazine Derivatives

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Abstract: An emerging area of interest in medicinal chemistry has highlighted heterocyclic moieties as some of the most promising compounds in organic chemistry. Piperazine is a notable six-membered saturated N-heterocyclic moiety with a wide range of bioactive applications in the pharmaceutical industry. Molecules containing the piperazine core unit have demonstrated numerous beneficial activities, such as antibacterial, analgesic, antiviral, antihypertensive, anti-allergic, antimalarial, antipsychotic, antidepressant, cardioprotective, antifungal, antioxidant, anti-inflammatory, and anticancer properties. The Food and Drug Administration (FDA) has approved various piperazine-based drugs for the treatment of several viral diseases, underscoring the pharmacological significance of piperazine analogues. In this chapter, we discuss in detail the procedures for the asymmetric synthesis of biologically active piperazine and its derivatives.

Keywords: Asymmetric synthesis, Bio-active molecules, Piperazine, Rearrangement reaction, Synthetic strategies.

INTRODUCTION

Nitrogen-containing heterocyclic compounds have attracted considerable interest in medicinal chemistry due to their diverse and potent therapeutic properties. In recent decades, research has increasingly focused on saturated nitrogen heterocycles, which have emerged as valuable scaffolds for the development of novel drug candidates, surpassing their aromatic or unsaturated counterparts in certain pharmacological contexts [1 - 4]. Among these, six-membered saturated ring systems bearing two nitrogen atoms specifically piperazine have proven particularly significant. Piperazine represents a key structural motif in the design

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of numerous bioactive molecules and is recognized as the third most frequently encountered nitrogen heterocycle in approved drug structures [5 - 8]. Its incorporation into pharmacophores has led to the development of a wide range of therapeutically relevant compounds.

Piperazine (1,4-hexahydropyrazine) is a saturated N-heterocyclic compound characterized by a six-membered ring containing two nitrogen atoms positioned opposite each other. With the chemical formula $C_4H_{10}N_2$, piperazine has emerged as a privileged scaffold in medicinal chemistry due to its broad spectrum of pharmacological activities, including antibacterial, analgesic, antiviral, antihypertensive, anti-allergic, antimalarial, antipsychotic, antidepressant, cardioprotective, antifungal, antioxidant, anti-inflammatory, and anticancer properties [9]. The presence of two nitrogen atoms significantly enhances the pharmacokinetic and biological properties of piperazine-containing drug molecules. These nitrogen atoms serve as hydrogen bond donors and acceptors, facilitating receptor interactions and improving aqueous solubility and bioavailability [10, 11]. Piperazine is commonly found in bioactive compounds and can interact with a wide variety of heterocyclic systems, contributing to the development of several commercially available drugs, as illustrated in Fig. (**1**).

Historically, piperazine was first introduced in medicine as a solvent for uric acid, and in 1953, it was adopted as an anthelmintic agent. Physically, it appears as small, hygroscopic crystals that readily absorb water and carbon dioxide and possess a mildly salty taste. Piperazine acts as a weak base, with pKb values of 5.35 and 9.73 at 25 °C, and is readily soluble in water and many organic solvents, though it is insoluble in diethyl ether [12]. A 10% aqueous solution of piperazine exhibits a pH range of 10.8 to 11.8. Furthermore, the nitrogen atoms in piperazine function as donor groups, making both piperazine and its analogues effective ligands in the formation of metal complexes. Substitution at one or both nitrogen atoms leads to the formation of symmetrical, monosubstituted, and disubstituted derivatives. This versatility allows for straightforward structural modification, making piperazine-based ligands highly adaptable for targeted pharmaceutical and coordination chemistry applications.

SYNTHESIS OF ASYMMETRIC PIPERAZINE DERIVATIVES

E. V. Pospelov and A. Y. Sukhorukov reported the synthesis of piperazine derivatives from primary amines *via* catalytic reduction of dioximes followed by cyclization [13]. For the preparation of substituted symmetrical dioximes (**2**), nitrosoacetate was added drop wise to a solution of the primary amine (**1**) in dichloromethane (DCM). The resulting reaction mixture was stirred at room temperature for 24 h. Subsequently, methanol was added, and the mixture was

further stirred vigorously for an additional 8 h to ensure complete conversion of the starting materials.

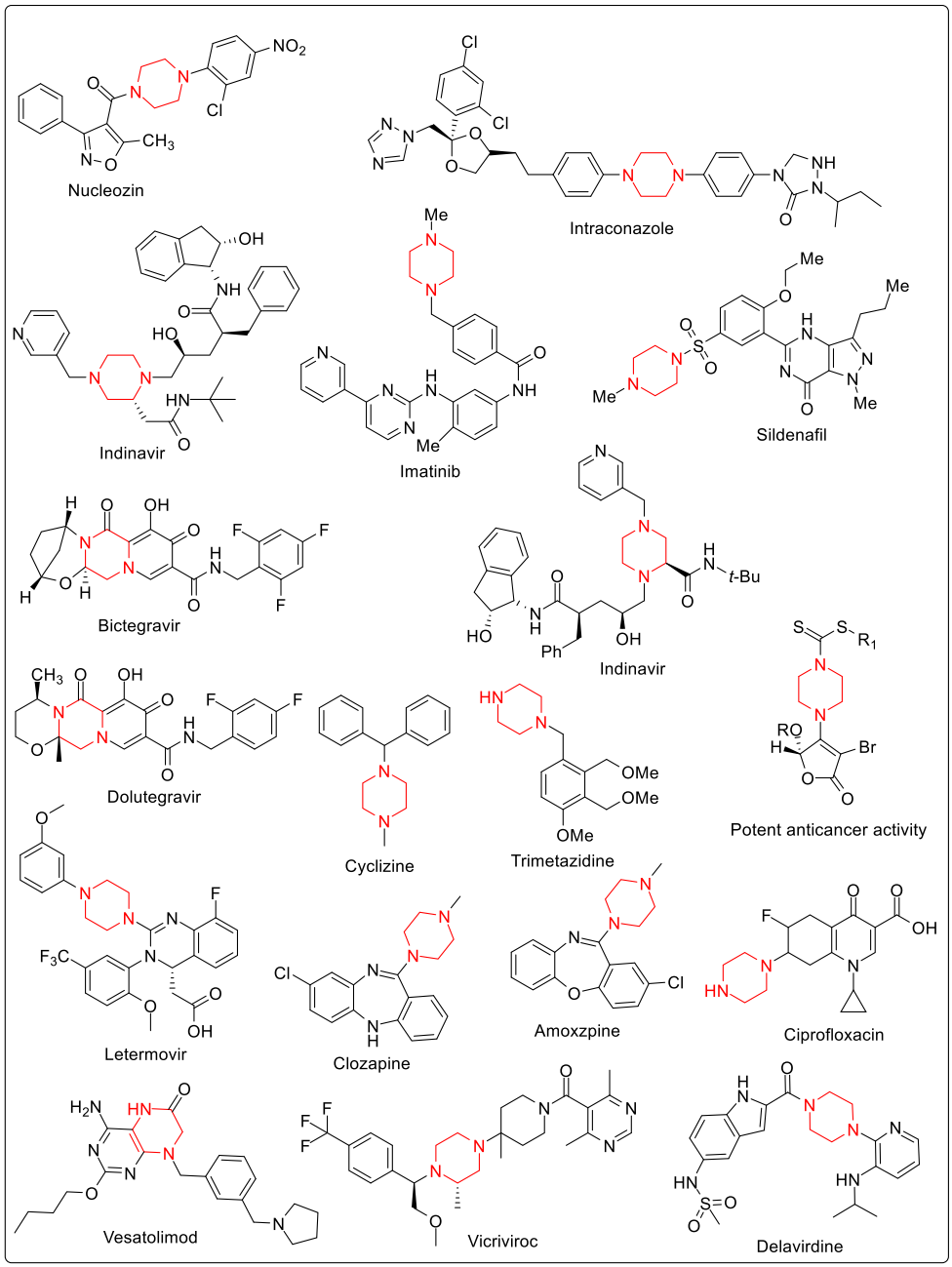

Fig. (1). Medicinally vital compounds holding piperazine core unit.

CHAPTER 6

Chemistry of Biologically Active Chiral Oxazine Derivatives

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Abstract: The utilization of naturally abundant resources is becoming more and more essential in the pursuit of green chemistry and sustainable development. Over the past two decades, the synthesis of organic compounds has increased interest in C-H functionalization. In organic chemistry, oxazine core unit molecules are renowned for their biological and synthetic significance along with numerous properties, such as ease of use, low cost, relative repeatability, stable products, and the absence of hazardous chemicals, high temperatures, pressures, or energies. The greener synthesis of oxazines is a step ahead of the preceding methodologies. In this book chapter, up-to-date improvements and novel trends in the green alternative synthesis of asymmetric oxazine have been highlighted and examined.

Keywords: Asymmetric synthesis, Asymmetric catalyst, Eco-friendly, Oxazine, Sustainable, Synthetic strategies.

INTRODUCTION

The chemistry of oxazines has sparked a new interest in the widespread global scientific community. Chemically, oxazines are heterocyclic compounds with six members that experience two double bonds along with one nitrogen atom, and one oxygen atom. The analogues of oxazine are noteworthy heterocyclic chemical compounds with a broad spectrum of biological properties. The oxazine core unit was categorized into three distinct types: 1,2-oxazines, 1,3-oxazines, and 1,4-oxazines based on the position of 'N' and 'O' atoms. The oxazines are named by the IUPAC nomenclature, which positions the number of oxygen atoms first followed by the nitrogen atom.

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The dihydro [1, 3]-oxazine ring system in molecules has demonstrated a broad range of pharmacological activities and adaptability as synthetic intermediates, leading to a recent increase in interest in 1,3-oxazine derivatives [1]. Additionally, compounds of naphthoxazine may be used therapeutically to treat Parkinson's disease [2]. An outstanding action against a range of HIV-1 mutant strains has been observed in trifluoromethyl-1,3-oxazine-2-one [3]. In order to study the synthetic methodology of 1,3-oxazine analogues, they were used with primary aliphatic and cyclic amines to undergo a three-component cyclo-condensation process with formaldehyde and substituted phenols [4]. Furthermore, diverse biological properties, together with those related to anti-diabetic, anti-cancer, anti-bacterial, anti-inflammatory, anti-tubercular, anti-oxidant, diuretic, analgesic and antiviral properties, have been documented as shown in Fig. (**1**). A significant class of chemical dyes, benzo-1,3-oxazines are also recognized to have pharmacological activity as depicted in Fig. (**2**) and they also exhibit significant biological activity [5 - 15].

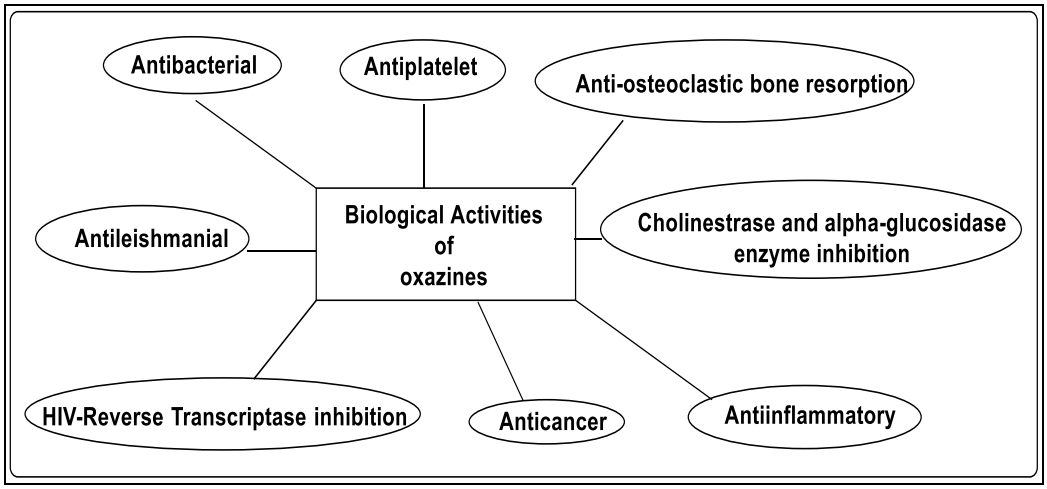

Fig. (1). Biological activities of oxazine derivatives.

SYNTHESIS OF CHIRAL OXAZINE DERIVATIVES

Marton Benedek Haznagy *et al.,* synthesized oxazine derivatives by using (S)-peryllaldehyde as the starting material. Initially, starting material(-)-(s)-peryllaldehyde (**6**) was reduced in the presence of Pt/C catalyst in solvent hexane-ethyl acetoacetate to synthesize a compound (S)-4-isopropyl-1-methylcyclo-ex-1-ene (**7**). In the next step, the synthesized compound **7** was converted into **8a-c** by reacting with amine derivatives in the presence of $NaBH_4$, and ethanol at room temperature for 2 h. In the third step, **8a-c** were protected by Boc_2O in the presence of DMAP and THF at room temperature to yield **9a-c**. The reaction

proceeded with OsO_4 in the presence of *tert*-BuOH, acetone-H_2O solvent at rt for 2 h to obtain **10a-c** and **11a-c**. Finally, **10a-c** intermediate underwent a reaction with HCl in diethyl ether overnight to obtain unprotected amine **12a-c** followed by the reaction with formaldehyde in diethyl ether to afford the desired fused oxazine derivative **13a-c** as described in Scheme **1** [16].

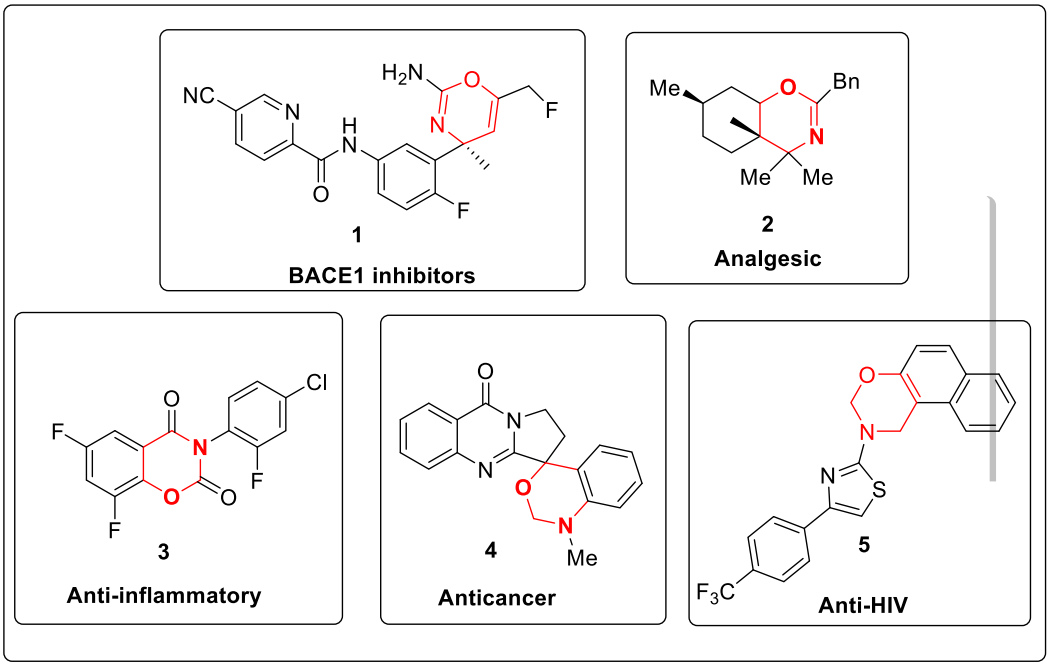

Fig. (2). Biologically important molecules containing oxazine core unit.

Pratap Kumar Mandal *et al.,* synthesized 1,4-oxazine derivatives *via* [3+3]annulation of α-amino cyclohexanones and enaldiazoaldehydes through γ-selective NHinsertion. In this reaction, diazoenol (**14**) reacted with 2-(l2-azaneyl)cyclohexan-1-one derivatives (**15**) in the presence of catalyst $Rh_2(OAC)_4$ and DCM at 25°C for 2h to attain the fused oxazine analogues as illustrated in Scheme **2** [17].

Seokhwi Park *et al.,* summarized ways of synthesizing chiral 1,3-oxazines- trans oxazoline (**21**), syn,syn-oxazine (**23**), syn, anti-oxazine (**24**), anti, syn-oxazine (**26**), and anti, anti-oxazine (**27**) with all possible conformations of anti and syn form. The authors described the one method in which anti and syn forms of amino alcohols (**18**), syn-amino alcohol (**22**), and anti-amino alcohol (**25**) were treated with different reagents K_2CO_3, CH_3CN, NaH, and THF in the presence of catalyst $Pd(PPh_3)_4$ at temperatures 0-40°C as illustrated herein Scheme **3** [18].

CHAPTER 7

Chemistry of Chiral Triazoles and their Biological Significance

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Abstract: Chiral triazoles are of considerable importance in medicinal chemistry due to their dual antifungal and antibacterial activities. The chiral configuration of these molecules enables them to interact selectively with specific microbial targets, enhancing their efficacy. In antifungal applications, chiral triazoles inhibit the enzyme lanosterol 14α-demethylase, disrupting ergosterol biosynthesis, which is essential for maintaining fungal cell membrane integrity. This inhibition leads to membrane destabilization and ultimately fungal cell death. In antibacterial contexts, chiral triazoles can disrupt essential bacterial processes, such as cell wall synthesis or protein function, by binding to key bacterial enzymes or receptors. The ability of chiral triazoles to effectively target both fungi and bacteria makes them promising candidates for the creation of antibacterial drugs with a broad spectrum, particularly in the fight against drug-resistant strains.

Keywords: Antibacterial activities, Antifungal activities, Chirality, Medicinal chemistry, Triazoles.

INTRODUCTION

Chirality and triazoles are significant in chemistry and pharmaceutical sciences due to their profound impact on biological activity and drug development. Chirality is the property of a molecule that prevents it from non-superimposing on its mirror image. This property produces enantiomers, or mirror-image molecules, which can have radically different biological consequences [1]. Triazoles are a family of heterocyclic compounds with five members that have three nitrogen atoms in them and are widely utilized in medicinal chemistry, particularly in antifungal and antiviral drugs [2]. Introducing chirality into triazole compounds enhances their specificity and effectiveness, as different enantiomers can interact

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uniquely with biological targets. This stereoselectivity is crucial for designing drugs that are not only potent but also safe, minimizing side effects, and improving therapeutic efficacy. Therefore, the combination of chirality with triazole structures plays a vital role in developing advanced pharmaceuticals, driving innovation in treatments for various diseases [3, 4].

Chiral triazoles have emerged as a cornerstone in the field of asymmetric synthesis, where they play a crucial role as catalysts or intermediates in the creation of other chiral molecules. Their unique ability to induce chirality in chemical reactions is indispensable for synthesizing complex natural products and Active Pharmaceutical Iingredients (APIs), which often require precise stereochemistry for their biological activity [5, 6]. The structural features of chiral triazoles, including stable chiral centers and versatile stereochemistry, contribute significantly to their widespread applicability. These characteristics are particularly important in the development of enantioselective processes, which are essential for producing pharmaceuticals with high efficacy and minimal side effects [7, 8].

In addition to their synthetic utility, chiral triazoles hold significant biological importance because they interact selectively with various biomolecules, making them invaluable in drug discovery and development [9]. Their chirality enables the design of enantiomerically pure compounds that can precisely target specific enzymes, receptors, and other biological targets, potentially leading to more effective and safer drugs. The triazole ring system further enhances these compounds' pharmacokinetic properties by providing stability and resistance to metabolic degradation. The combination of chirality and the versatile triazole scaffold makes these compounds highly valuable in developing new therapeutics with improved efficacy and reduced side effects [10, 11].

Moreover, the importance of chiral triazoles extends beyond their synthetic utility. These compounds hold significant biological relevance due to their ability to interact selectively with a variety of biomolecules, making them invaluable in the realms of drug development and discovery. The chirality of these molecules enables the design of enantiomerically pure compounds that can precisely target specific enzymes, receptors, and other biological targets. This precision in targeting not only enhances the effectiveness of the drugs but also reduces the potential for adverse side effects, leading to safer therapeutic options [12]. Additionally, the triazole ring system itself contributes to the pharmacokinetic properties of these compounds by providing enhanced stability and resistance to metabolic degradation. This combination of chirality and the versatile triazole scaffold underscores the significant value of these compounds in the development of new therapeutics, offering the potential for innovative treatments with

improved efficacy, safety, and overall patient outcomes [13, 14].

Triazoles have established themselves as vital components when treating bacterial and fungal infections, owing to their potent biological activity and selective interaction with key microbial targets. These compounds are particularly effective in disrupting essential processes within fungal and bacterial cells, making them indispensable in drug discovery and development [15]. For instance, triazoles inhibit the enzyme lanosterol 14α-demethylase in fungi, a critical step in ergosterol biosynthesis necessary to preserve the fungal cell membrane's integrity. This mechanism of action is the foundation for several widely used antifungal drugs, such as fluconazole [16], itraconazole [17], and voriconazole [18], which are employed in the therapy of several fungus-related illnesses, such as those brought on by the species *Aspergillus* and *Candida*. In antibacterial applications, triazoles can interfere with bacterial cell wall synthesis or other crucial metabolic pathways, thereby exerting a bacteriostatic or bactericidal effect [19]. The versatility of the triazole ring system, combined with its ability to enhance pharmacokinetic properties such as stability and resistance to metabolic degradation, makes these compounds highly effective in combating infections. The success of marketed drugs like posaconazole and isavuconazole, which have broad-spectrum antifungal activity, highlights the therapeutic potential of triazole-based compounds in treating infections that are increasingly resistant to other classes of antimicrobials. The ongoing development of new triazole derivatives continues to expand the arsenal of antifungal and antibacterial agents, offering hope for more effective treatments with improved safety profiles and reduced risk of resistance [20].

The primary medications used to treat fungal diseases that are invasive—miconazole, econazole, fluconazole, and ketoconazole contain 1-phenylethanol derivatives with triazolyl and imidazolyl substituents attached to the alcohol in the alpha position (Fig. **1**) [21, 22].

SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF CHIRAL TRIAZOLES COMPOUNDS

Synthesis of chiral triazole compounds employs several advanced strategies, each designed to achieve specific stereochemistry. A prominent method is asymmetric catalysis, which utilizes chiral catalysts to induce chirality during triazole ring formation, ensuring the selective production of the desired enantiomer. Another common approach involves enantioselective cycloaddition reactions, such as the functionalised alkynes and azides undergoing Huisgen 1,3-dipolar cycloaddition at high temperatures, yielding a combination of 1,5- and 1,4-replaced triazole regio isomers [23].

CHAPTER 8

Chiral Benzimidazoles and their Chemistry

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Abstract: Chiral benzimidazole derivatives have emerged as a significant class of compounds in pharmaceutical chemistry due to their wide range of potential biological and clinical applications. The present study explores the synthesis and biological potentialities of chiral benzimidazole derivatives, highlighting various synthetic approaches, including condensation, rearrangement, and green synthesis techniques. The chiral nature of these compounds, which is pivotal in their interaction with biological receptors, is discussed with a focus on methods for introducing and controlling chirality. Recent research findings highlight the remarkable biological activities of these derivatives, including carbonic anhydrase enzyme inhibition, antibacterial and antifungal properties, urease inhibition, ORL-1 antagonism, antitrypanosomal activity, antihypertensive effects, and inhibition of leukotriene biosynthesis. These activities position chiral benzimidazole derivatives as promising candidates for developing new therapeutic agents for a range of medical conditions. This study provides a comprehensive overview of the synthesis strategies and biological evaluations of chiral benzimidazole derivatives, underscoring their potential in pharmaceutical applications.

Keywords: Chiral, Condensation, Enantioselective synthesis, Pharmacological activity, Rearrangement.

INTRODUCTION

Compounds containing heterocyclic rings form a fundamental class of organic compounds that play a critical role in synthesizing various other organic substances, such as pharmaceuticals. These materials are complex due to the presence of heteroatoms, which confer a wide range of properties. Their significance extends beyond chemistry to human life, where they are pivotal. Additionally, heterocyclic compounds find applications in medicine, agriculture, and the synthesis of other organic substances and polymers. They are also employed in different industrial processes. Numerous heterocyclic moieties serve

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as drugs, including those used as hypnotics, anticonvulsants, antitumor agents, antihistamines, antiseptics, and antivirals [1 - 5].

Benzimidazoles, also known as 1,3-diazaindene, is an important class of aromatic heterocyclic compounds. Benzimidazole compound is a white solid that consists of a fusion between a benzene ring and an imidazole ring. This compound is also termed 1H-1,3-benzimidazole or 1H-benzo[d]imidazole, with a molecular formula $C_7H_6N_2$ shown in Fig. (**1a**) [6]. This was initially synthesized by Hoebrecker, followed by further synthesis by Ladenberg and Wundt between 1872 and 1878 [7]. N-ribosyl-dimethylbenzimidazole is a notable natural benzimidazole derivative that acts as an axial ligand for the Co metal atom in vitamin B_{12}, its structure is shown in Fig. (**1b**). The benzimidazole core is an essential structural motif in drug discovery and a vital component in clinical chemistry due to its diverse biological potentialities [8]. Its derivatives exhibit various biological activities, including antitumor, antiproliferative, antimicrobial, DNA binding, antiangiogenic, anthelmintic, antipsychotic, potassium-competitive acid blocking, and antifungal activity against serotoninergic 5-HT3 and 5-HT4 receptors. It has also shown antiviral, protein tyrosine phosphatase 1B inhibiting, anti-trypanosomatid, protein kinase inhibiting, JAK1-selective inhibiting, cytotoxic, and anti-estrogen breast cancer properties. Therefore, benzimidazole is highly significant in pharmaceutical applications due to its important bicyclic ring system [9-21].

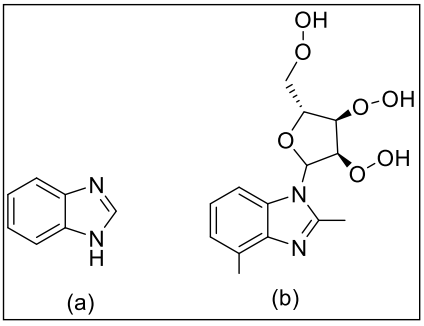

Fig. (1). Structure of 1*H*-benzo[d]imidazole (a) and natural benzimidazoles (b).

Various strategies have been developed for synthesizing benzimidazole derivatives, typically involving the reaction of ortho-phenylenediamines with aromatic and alkyl carboxylic acids, ketones, aldehydes, or their analogs under various conditions, both with and without catalysts. Specifically, the condensation of 1,2-phenylenediamines with carboxylic acids under acidic conditions with HCl is known as the Phillips method. Benzimidazole development *via* rearrangement involves the utility of a particular rearrangement method to form the desired

benzene-fused imidazole ring system. Additionally, benzimidazole and its different compounds have been synthesized using green techniques as alternatives to traditional chemical processes. For instance, microwave irradiation has been employed to develop benzimidazole by reacting aldehydes with *o*-phenylenediamine in the presence of certain amounts of CH_3COOH. This method offers several advantages, including short reaction times, the use of non-harmful solvents, and high product yields. Furthermore, ionic liquids have also been utilized for the green synthesis of benzimidazoles, highlighting the shift towards more environment-friendly approaches in chemical synthesis [22 - 26].

Chiral benzimidazoles are derivatives of benzimidazole that exhibit chirality, meaning they have a mirror image that cannot be superimposed onto the original because of an asymmetric carbon atom or another element of asymmetry within their arrangement. Chiral derivatives of benzimidazoles play a significant role in chiral processes due to their complex structure, ability to build hydrogen bonds, basic nature, robust stability, reactive properties, ease of incorporating asymmetric components, and the presence of pyrrole and pyridine-like N atoms connected to the benzene ring as the chiral nature of a compound influences its biological and pharmacological properties because asymmetric centers are crucial in biological processes. The interaction of these molecules with biological receptors depends on their fit in the active sites, which is greatly influenced by chirality. Using chiral chemicals as drugs, like antifungals, antiarrhythmics, antihistamines, anticancer agents, insecticides, and antimicrobials, can reduce undesirable side effects and environmental impact, as well as decrease unnecessary drug consumption [27 - 29].

The chirality of these compounds is significant because it can affect their biological activity and molecular interactions, in turn, making them valuable in pharmaceutical research and therapeutic development. The synthesis of chiral benzimidazoles can involve asymmetric synthetic techniques to introduce and control chirality. Asymmetric synthesis strategies of chiral benzimidazoles may include the use of chiral reactants, chiral auxiliaries, and asymmetric catalysis. One of the approaches involves using chiral starting materials, such as reacting a chiral carboxylic acid with o-phenylenediamine under acidic conditions to yield a chiral benzimidazole, transferring the chiral centre from the carboxylic acid to the C2 position of the benzimidazole. This method is relatively straightforward with often good yields but is limited by the availability of the corresponding chiral carboxylic acids. Another strategy is employing chiral auxiliaries, where a temporary chiral group is attached to the starting material to influence the reaction's stereochemistry, ensuring the formation of the desired enantiomer. For example, attaching a chiral oxazolidinone to a benzimidazole precursor can direct the stereochemistry of a subsequent alkylation or reduction step, resulting in a

CHAPTER 9

Chemistry of Chiral Pharmaceuticals

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Abstract: The chapter gives an insight into the chemistry of chiral pharmaceuticals, discussing the different classes of compounds that have been synthesized using asymmetric methods. It covers the synthetic routes used to produce chiral pharmaceuticals and discusses the impact of chirality on their pharmacological properties. The chapter discusses key challenges in developing enantioselective syntheses for complex drug molecules, particularly those with intricate structures and multiple stereo-enters. It examines issues like controlling stereoselectivity, optimizing reaction conditions, and scaling up for industrial use. Additionally, the chapter explores the biological activities of chiral heterocycles, emphasizing how their stereochemistry impacts drug potency, selectivity, and metabolism. It highlights both the importance of enantioselective synthesis and the critical role of chiral heterocycles in the effectiveness of modern pharmaceuticals.

Keywords: Asymmetric synthesis, Biological activities, Chiral compounds, Chiral pharmaceuticals.

INTRODUCTION

The various types of pharmacological activities demonstrated by heterocyclic compounds have made them potential life-saving substances for humankind [1, 2]. Among them, chirality plays an important role in defining the biological activity of a particular enantiomer, thereby making it important to consider chirality in drug development and its usage [3 - 5]. A simple way to define chiral pharmaceuticals is that they are drugs or heterocyclic compounds with a chiral molecule *i.e.*, they contain enantiomers. A chiral compound, molecule, or atom is

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defined as one that has a carbon atom attached to four groups that are different in nature, which in turn leads to the creation of mirror images that are non-superimposable to each other [6, 7]. These enantiomers, as mentioned earlier, may have different pharmacological properties as they may interact with the target differently, which leads to variations in efficiency, metabolism, and possible side effects that occur due to the intake of the drug. One of the common examples of chiral drugs or heterocycles is thalidomide in which one enantiomer causes birth defects whereas the other acts as a potential sedative [8, 9]. Another example is SQ-3296 in which the R- enantiomer shows more anti-hypertensive properties than the S enantiomer whereas the S-L-771688 had proven to be more active against adrenergic receptors when compared to its other enantiomer [10 - 12]. Other examples include Ibuprofen whose S-enantiomer shows anti-inflammatory activity, *S*-monastrol shows anti-cancerous activity and Omeprazole's S-enantiomer more actively reduces acid in stomach [13 - 15].

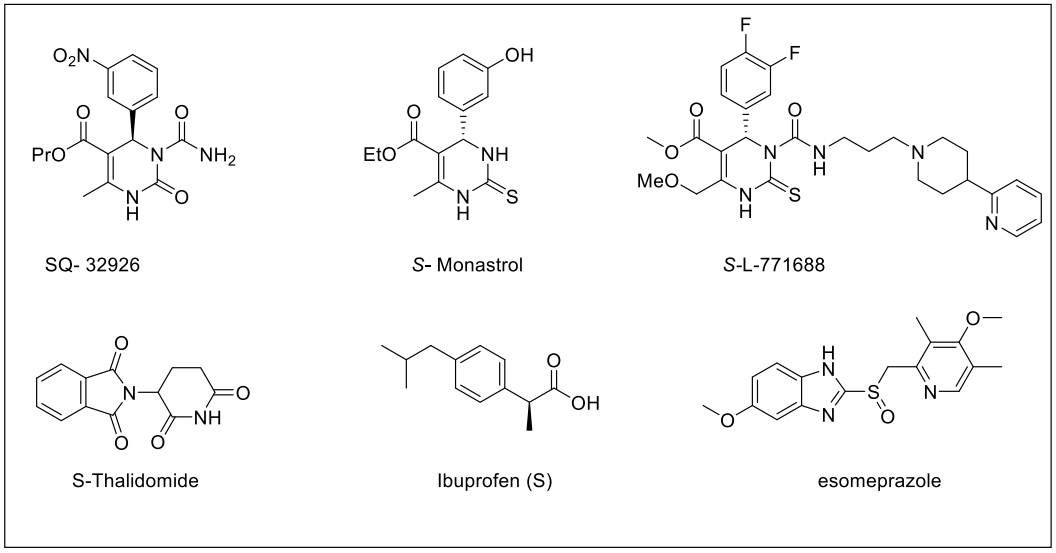


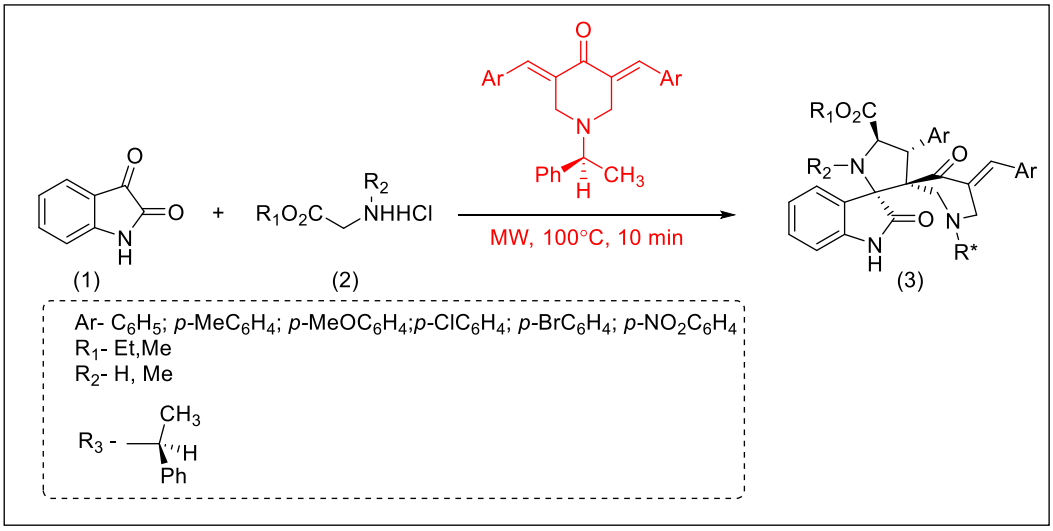
Fig. (1). Chiral pharmaceuticals.

These chiral pharmaceuticals are synthesized using the technique called asymmetric synthesis. An important process in modern-day synthetic chemistry, asymmetric synthesis involves the production of one enantiomer or diastereomer in a larger quantity than the other isomer [16]. Therefore, the process helps in creating desired chiral compounds having various biological activities. The process is generally achieved using chiral catalysts, chiral auxiliaries, and chiral reagents [17 - 20]. Apart form its wide scale application in pharmaceutical and drug development, it is also used in forming herbicides [21, 22], pesticides [23, 24] and in flavor [25, 26] and fragrances [27, 28] emitting compounds. Some of

the common name reactions that involve the process of asymmetric synthesis are sharpless asymmetric epoxidation [29, 30] and dihydroxylation [31, 32], Biginelli reaction [33, 34], Evans aldol reaction [35, 36], Jacobsen epoxidation [37, 38], Noyori asymmetric hydrogentaion [39, 40] and Corey-Bakshi-Shibata reduction [41].

ASYMMETRIC SYNTHESIS OF PHARMACOLOGICALLY ACTIVE COMPOUNDS

Jelizi *et al.*, synthesized tetracyclic dispirooxindolopyrrolidine consisting of piperidones in an asymmetric manner, thereby forming its pure enantiomer in the presence of methanol as solvent under microwave irradiation. The configuration of the synthesized compounds was evaluated using single-crystal XRD analysis. Furthermore, these compounds were tested as potential anti-microbial agents against various strains of bacteria and fungus. An exceptional anti-microbial activity against *P. aeruginosa, E.coli,* and *S.enterica* was achieved with MIC values of 12.1 µg/mL as compared to the standard drugs namely Ampicillin and Griseofulvin [42] (Scheme **1**).



Scheme 1. Asymmetric synthesis of tetracyclic dispirooxindolopyrrolidine consisting of piperidones.

Maqbali *et al.*, formed a novel series of triazole compounds having glucose moiety. A 1,3-dipolar cycloaddition process was employed to achieve the same where the Schiff base of carbohydrates was made to react with hydrazonyl chlorides. The crystal structure of one of the derivatives synthesized was examined using the single crystal X-ray method which confirmed the formation of *(S)*-isomer at the newly formed stereocenter. The compound was tested for their

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Bendi Anjaneyulu

Dr. Bendi Anjaneyulu is presently serving as Deputy Dean, Academic Affairs, and In-charge Dean, Faculty of Science, at Kalinga University, Naya Raipur, Chhattisgarh. He possesses over 18 years of experience in Academics, Administration and Research. Dr. Bendi earned his Ph.D. and M.Sc. in Organic Chemistry and qualified the CSIR-NET examination with all India rank of 30. His research career began as a Junior Research Fellow (JRF) at the Defence Research and Development Establishment (DRDE/DRDO), Gwalior, Madhya Pradesh. His primary research interests focus on exploring the chemistry of biologically active heterocycles through catalysis (including nanocatalysis), computational chemistry, and environmental remediation.

Dr. Bendi has made substantial contributions to the scientific community, authoring over 100 publications, including research papers, books, and book chapters. He has been granted one patent and has seven additional patents published, reflecting his commitment to translational and application-oriented research. In addition, he has actively organized and participated in national and international conferences, workshops and faculty development programs, contributing to the dissemination and exchange of scientific knowledge. He has also completed several internationally recognized certification courses that enhance his multidisciplinary expertise. Furthermore, he is an active member of several esteemed professional organizations, through which he continues to collaborate and engage with the broader scientific

Neera Raghav

Prof. (Dr.) Neera Raghav, Former Chairperson, Department of Chemistry, Coordinator Women in STEM Forum, Kurukshetra University Kurukshetra has dedicated her 29 years to teaching profession till now. Prof. Raghav has worked in diverse research areas like enzyme chemistry, drug delivery system, natural product formulations, biodegradable polymers etc. She had worked on a major research project, supervised a number of Ph.D. students, and had various national and international collaborations. She has >125 SCOPUS /WoS indexed publications. Since 2020 the cumulative impact factor of publications is more than ~400. Twenty-two published patent applications/granted in the field of enzyme inhibitors and drug delivery systems are also to her credit and has recently edited one book (Bentham publisher). Prof. Raghav has been placed in Top 2% researchers by SCHOLAR GPS in the research fields of Macromolecules, Bioorganic Chemistry and Non Steroidal Anti-inflammatory Drugs.