HETEROCYCLIC ANTI-INFLAMMATORY AGENTS:

A GUIDE FOR MEDICINAL CHEMISTS

Editors:
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Heterocyclic Anti-Inflammatory Agents: A Guide for Medicinal Chemists

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Heterocyclic Anti-Inflammatory Agents: A Guide for Medicinal Chemists

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FOREWORD

It is my pleasure to write the foreword for the book entitled ***"Heterocyclic Anti-Inflammatory Agents: A Guide for Medicinal Chemists"*** edited by ***Anjaneyulu Bendi, M. P. Kaushik, and Neera Raghav***. All the editors are well-known researchers working in different areas of organic and medicinal chemistry.

A large number of anti-inflammatory drugs are currently being used. However, many of these compounds are found to be highly unsafe for long-term use due to the associated toxicity. It has been established that the incorporation of heterocyclic moiety provides a useful tool for the modification of polarity, solubility, lipophilicity and hydrogen bonding capacity of such compounds. Going deeper into the book, the significance of heterocyclic compounds in the development of anti-inflammatory agents becomes apparent.

This book will be helpful for both, beginners and experimental researchers, working in the interdisciplinary areas involving chemistry, medicinal chemistry and pharmaceutical chemistry. It will also benefit the students who are pursuing a course involving the role of heterocyclic compounds in the development of medicinal agents in general, and of anti-inflammatory drugs in particular.

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

S. P. Singh
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PREFACE

Are anti-inflammatory agents really requisite?

In ancient Egypt, Ebers Papyrus suggested rubbing a decoction of dried myrtle leaves on the back and abdomen to alleviate womb rheumatic pains about 3,500 years ago. A thousand years later, Hippocrates suggested to use the willow bark juice to reduce the fever and labour pains, and also recommended to use the poplar tree juice to treat eye problems. Celsus identified the four primary symptoms of inflammation (rubor, calor, dolor, and tumor, or redness, heat, pain, and swelling) in A.D. 30 and used willow leaf extract to treat them. This journey of utilizing extracts from different natural sources to reduce inflammation laid the foundation for aspirants in the modern era to develop novel drugs to treat different kinds of inflammation. Nowadays, different heterocyclic compounds have been used as anti-inflammatory agents.

This book highlights the cutting-edge experimental research on a variety of heterocycles used as anti-inflammatory agents in ten chapters. In **Chapter 1**, authors have briefly discussed the role of pyrimidine and pyrimidinone derivatives in the reduction of inflammation. **Chapter 2** addresses the importance of 1,2,3- and 1,2,4- triazoles and their derivatives as anti-inflammatory agents. The chemistry of imidazole and benzimidazole derivatives to deal with the different kinds of inflammation has been discussed in **Chapter 3**.

Chapter 4 describes the synthesis of different oxazole, oxadiazole, isoxazoline, and oxazoline derivatives along with their biological evaluation as anti-inflammatory agents. A brief discussion of the chemistry of thiazole and thiazolidinone derivatives related to reducing inflammation has been described in **Chapter 5**.

In **Chapter 6**, authors have a special focus on exploring the chemistry of pyrazole and pyrazoline derivatives as anti-inflammatory agents. **Chapter 7** deals with the importance of carbazoles and their derivatives in reducing different kinds of inflammation. The chemistry of azipines, quinolines, and coumarins has been discussed as anti-inflammatory agents in **Chapter 8**, **Chapter 9** and **Chapter 10**.

In conclusion, we would like to say that the book's goal is to give an overview of the interesting research that is being done to design and make the new heterocycles as anti-inflammatory drugs. We hope that the content of this book will pique the interest of aspiring researchers everywhere and inspire them to continue their research in exploring novel heterocycles to treat different kinds of inflammation. We also hope that the book will be helpful to researchers, academics, and business people who have a strong interest in this research area.

We would like to express our admiration and gratitude for the efforts of all the authors who have worked enduringly on preparing the content of this book. We would also like to extend our heartfelt gratitude to the publishers and their employees for the efficient handling of the project at all stages. Lastly, we want to thank our family members for their unwavering support throughout the whole journey.

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CHAPTER 1

Pyrimidine and Pyrimidinone Derivatives as Anti-Inflammatory Agents

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Abstract: Heterocyclic compounds are one of the most significant sources of bio-active molecules. Pyrimidines and pyrimidinones are a class of nitrogen-containing heterocyclic compounds with significant biological activities. Among the different applications of these compounds in medicinal chemistry, their anti-inflammatory activities have attracted the attention of the scientific community to explore their chemistry. Some of these derivatives have been found to inhibit the production of pro-inflammatory cytokines and chemokine enzymes, which are involved in the recruitment and activation of immune cells at sites of inflammation. The chapter outlines the range of methods available to create different pyrimidine and pyrimidinone derivatives along with their anti-inflammatory activities.

Keywords: Anti-inflammatory agents, Biginelli reaction, Biological activity, Dihydropyrimidinones, Drug discovery, Heterocyclic compounds, Inflammation, Medicinal chemistry, Pharmaceuticals, Pyrimidines and pyrimidinones.

INTRODUCTION

Heterocyclic compounds have gained significant attention due to their vast synthetic studies, functional utility, and multiple biological applications [1, 2]. These compounds are found in more than 90% of novel drugs and fill the gap between biology and chemistry, where so much scientific discovery and their applications occur. These are also prevalent in macromolecules like enzymes, vitamins, natural products, and are regarded as potential scaffolds in medicinal chemistry [3, 4].

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Pyrimidine is a six-membered aza-aromatic compound that has profound biological applications in medicinal chemistry, which include anti-tumor, analgesic, anti-inflammatory, anti-fungal, anti-bacterial agents, *etc* [5]. Pyrimidines have been recently applied in coordination chemistry as electron-rich ligands that serve as interesting alternatives to pyridines [6]. The widespread applications are given a thought to further explore the chemistry of these compounds. Aside from the historical first syntheses by Brugnatelli and later by Kolbe [7], the Pinner synthesis had been the long-favored method for pyrimidines [8 - 10] (Fig. **1**).

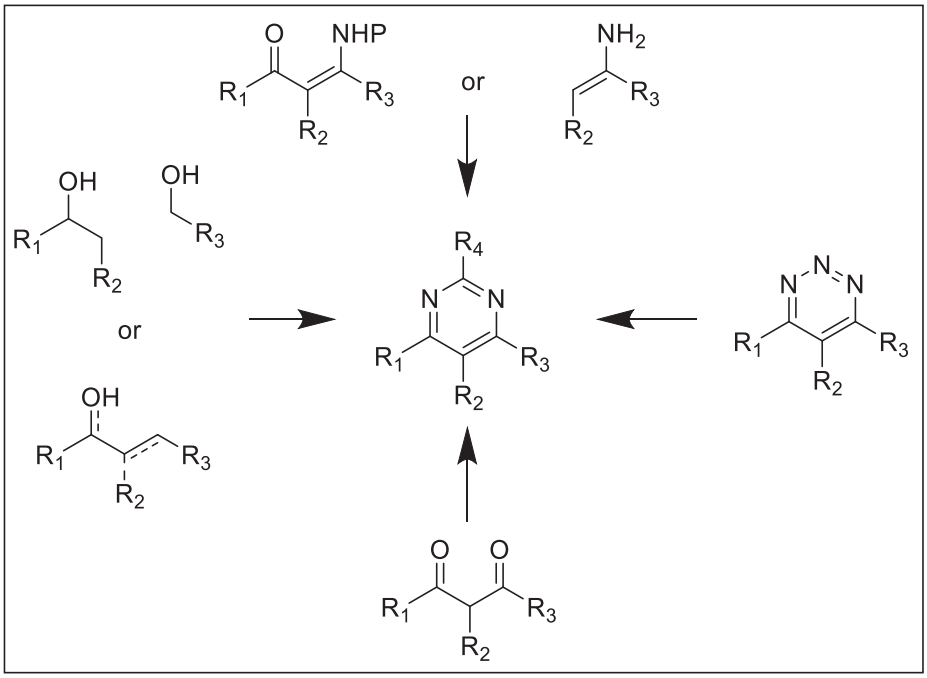
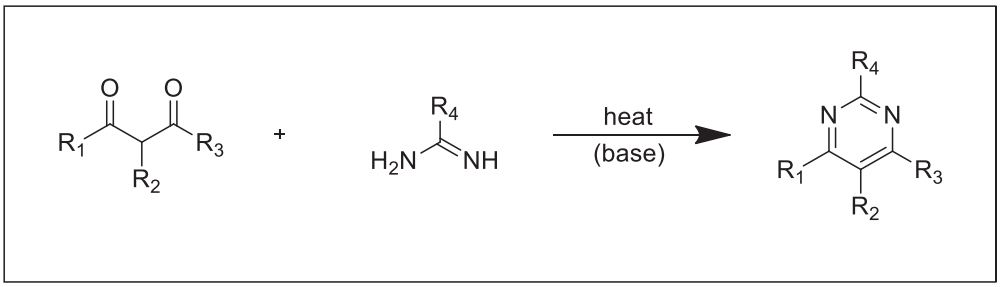


Fig. (1). Synthetic strategies directed towards pyrimidines.

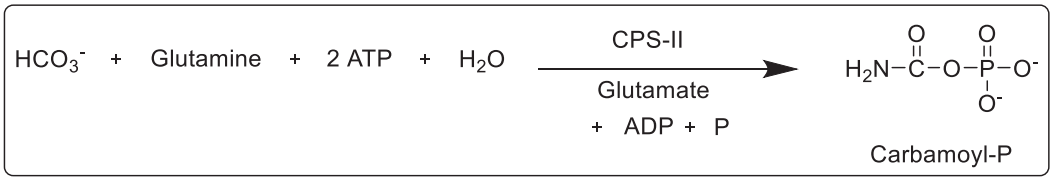
The historical Pinner reaction is a condensation reaction between amidine and 1,3-dicarbonyl compounds that makes a variety of substituted pyrimidines. However, harsh reaction conditions and low yields have frequently hampered the pinner's strategy. As a result, a wide range of strategies, ranging from cycloaddition reactions to multi-component and tandem processes, have been explored in order to broaden the scope and improve the yields of pyrimidines Scheme (**1**).



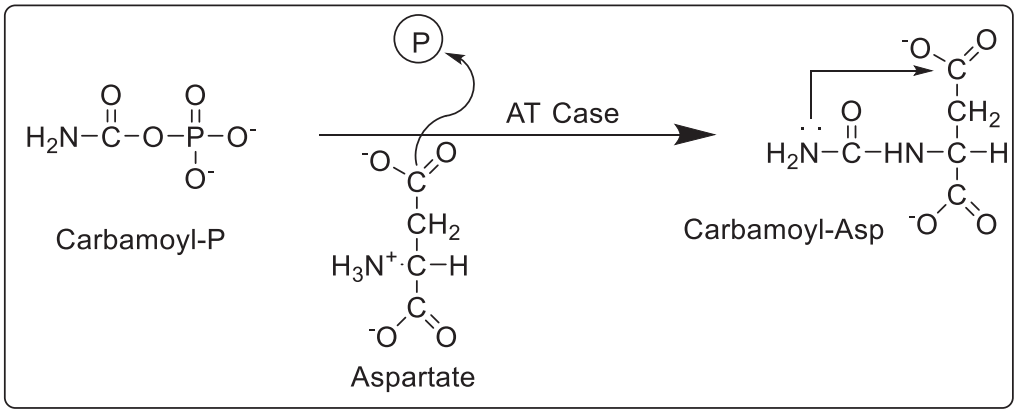
Scheme (1). Classical pinner synthesis.

The biosynthetic pathway of the pyrimidines was also observed along with their synthesis in laboratory conditions. The de-novo synthetic pathway is commonly used for the bio-synthesis of pyrimidines [11, 12]. The following steps are involved in their biosynthesis:

Step 1: Synthesis of carbamoyl phosphate from bicarbonate ion and the amide nitrogen of glutamine.



Step 2: Condensation of carbamoyl phosphate with aspartate to form carbamoyl aspartate.



CHAPTER 2

Triazoles and their Derivatives as Anti-Inflammatory Agents

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Abstract: Heterocyclic compounds are a large group of organic chemical compounds that have at least one and sometimes more than one heteroatom. For their anti-fungal, anti-inflammatory, anti-bacterial, anti-cancer, and other properties, heterocyclic compounds are used a lot in pharmaceuticals, agrochemicals, veterinary products, sanitizers, antioxidants, co-polymers, and other products. Triazoles are a type of chemical compound that has a five-membered heterocyclic ring with three nitrogen atoms and are used in a significant number of different pharmaceutical applications along with anti-inflammatory agents. Nowadays, a significant amount of research is being done on triazoles as potential anti-inflammatory agents. This chapter is mainly focused on the synthesis of triazoles and their various derivatives, along with their anti-inflammatory properties.

Keywords: Anti-inflammatory agents, Biological activity, Click chemistry, Drug discovery, Heterocyclic compounds, Inflammation, Medicinal chemistry, Pharmaceuticals, Triazoles.

INTRODUCTION

The word heterocyclic is derived from the Greek word ‘heteros’, which means different. Heterocycles are organic moieties containing at least one heteroatom other than carbon in their structural rings. The heterocyclic compounds are of stupendous importance, not only because of their prolific presence in natural products but also because of their array of biological activities. The heterocyclic compounds are found to have many biological applications, like anti-inflammatory, anti-cancer, anti-bacterial, antiviral, anti-tumor, anti-allergic, herbicidal,

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anti-convulsant, and many more. Medicinal chemistry has engrossed itself in heterocyclic compounds due to their wide applications in biological fields [1].

The name triazole was first given to the compounds with the formula $C_2H_3N_3$ in early 1885 by Bladdin, who first synthesized and described them [2]. Triazoles are aromatic and planar compounds with 6π-electrons aromatic systems having a distortion of π-system prompted by the annular nitrogen atoms (Fig. **1** and Scheme **1**).

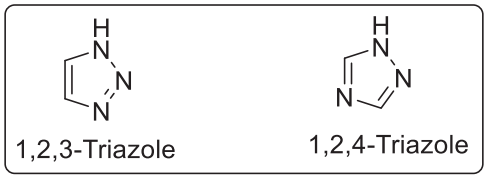
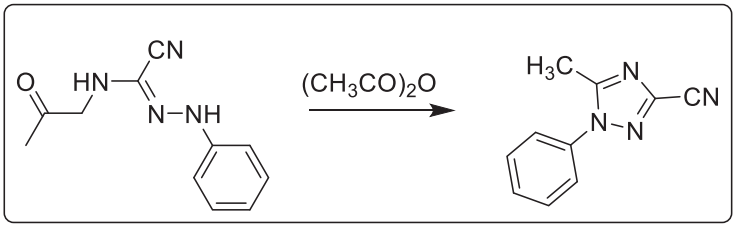


Fig. (1). Isomeric forms of triazoles.



Scheme (1). Synthesis of triazole by bladdin.

Triazole exists in two isomeric forms, *i.e.*, 1,2,3-triazole (vicinal triazoles) and 1,2,4-triazole (symmetrical) (Fig. **2**). Triazole compounds can form hydrogen bonds, which makes it easier to bind with biomolecular targets and shows enhanced solubility of the compounds [3, 4]. Triazole scaffolds imitate different functional groups very well, showing their wide participation as bio isosteres for the dynamic synthesis of new molecules [5]. In 1,2,3-triazoles, there are three replaceable hydrogen atoms at positions 1, 4, and 5, making it easier to undergo electrophilic substitution reactions. The 1,2,3-triazole exists in three tautomeric forms, *i.e.*, 1H, 2H, and 4H. The 1,2,4-triazole form exists in two tautomeric forms, *i.e.*, 1H and 4H.

Over the years, triazole derivatives have allured the scientists of agricultural and medicinal fields because of their extensive biological activities [6] such as anti-cancer [7], anti-tumor [8], anti-microbial [9], anti-inflammatory [10, 11], anti-bacterial [12], anti-malarial [13], anti-fungal [14], antiviral [15], anti-proliferative [16], neuroprotective [17], pesticidal [18], herbicidal [19], antioxidant [20], anti-HIV [21], analgesic [22], molluscicidal [23], anticonvulsant [24] and many more.

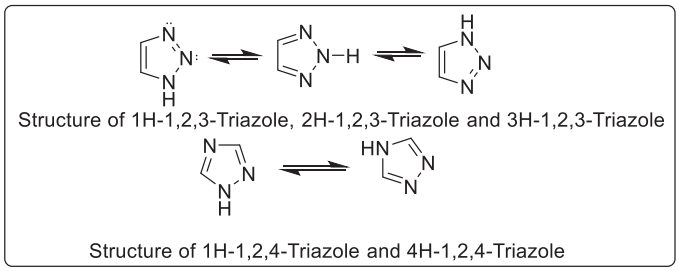
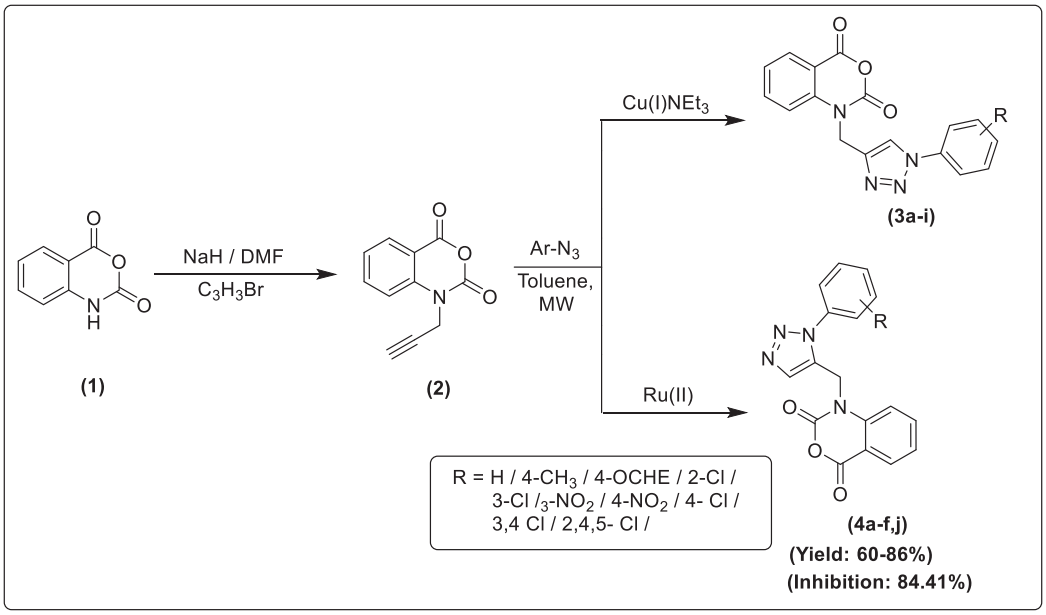


Fig. (2). Tautomeric forms of triazoles.

CHEMISTRY OF 1,2,3-TRIAZOLES AS ANTI-INFLAMMATORY AGENTS

Hammouda *et al*. deduced a new method for the synthesis of 1,2,3-triazole linked benzoxazine-2,4-dione conjugates with impressive anti-microbial, antioxidant, and anti-inflammatory activities. The synthesis began using a reaction mixture of copper iodide and trimethylamine in the presence of aryl azide and toluene under microwave irradiation at 250 W. Anti-inflammatory activities were observed on adult Wistar Swiss mice of both genders by using xylene induced ear oedema. The result showed that the compound without any substitution (3a) was most effective in the treatment of ear oedema which showed inhibition of 84.41% [25, 26] (Scheme **2**).



Scheme (2). 1,2,3-triazole linked benzoxazine-2,4-dione conjugates.

CHAPTER 3

Imidazole and Benzimidazole Derivatives as Anti-Inflammatory Agents

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Abstract: In current days, imidazoles and benzimidazoles are vital classes of N-heterocyclic compounds. One of the 5-membered heterocyclic compounds is imidazole ring structure through 3 carbon and 2 nitrogen atoms and in imidazole structure, N is occupied in 1st and 3rd location in five-membered ring system. It is planer in structure. The imidazole moiety is an essential of numerous significant natural products, together with histamine, purine, histidine and nucleic acid. On the other hand, benzimidazole covers six-membered benzene ring system fused with five-member imidazole ring systems. Benzimidazole core unit molecules continue to be the indispensable focus among the available heterocyclic compounds because of more than a few pharmacological and biological properties. Benzimidazoles achieve the center of attention due to their stability, outstanding bioavailability, and wide range of biological competence. The current study discloses and discusses the biological activities of imidazole and benzimidazole scaffolds widely used as anti-inflammatory agents.

Keywords: Anti-inflammatory, Benzimidazoles, Biological activity, Imidazoles medicinal chemistry.

INTRODUCTION

Heterocyclic scaffolds are the most outstanding and assorted range of organic compounds. A noteworthy number of heterocyclic molecules have been synthesized up to the peak point. Heterocyclic molecules are swiftly growing in number owing to widespread synthetic research and their enhanced biological activity. Such heterocyclic molecules have an extensive range of exercises in the field of medicinal chemistry. Biologically, dyestuff, sanitizers, electronics, corrosion inhibitors, optics, antioxidants, pharmacology, material sciences and

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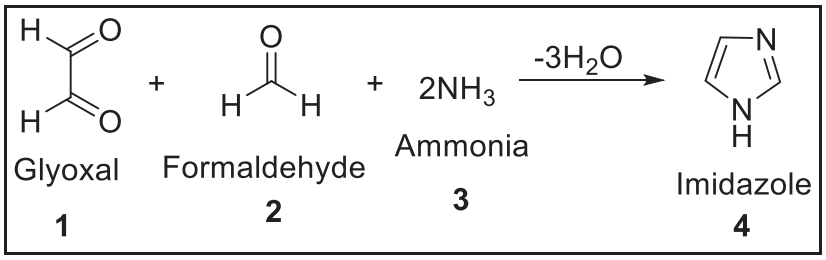
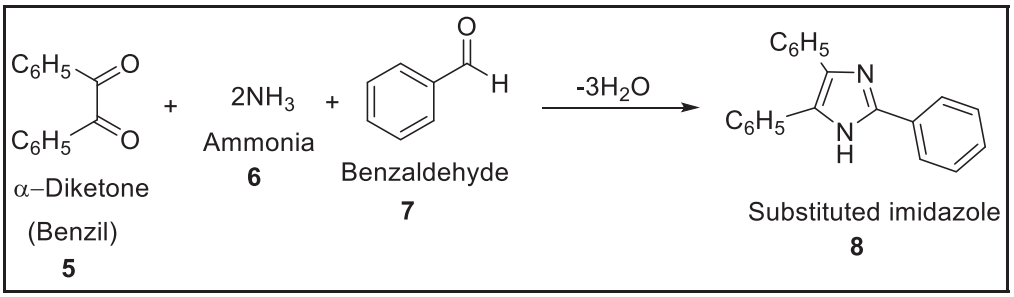
copolymer synthesis are supplementary renowned applications [1]. The heterocyclic core nucleus imparts a significant function in medicinal chemistry and provides as a vital core unit for the advance of a variety of newly exposed heterocyclic molecules and their derivatives. Inflammation is the resistance procedure of the organism to tissue damage; our immune system acts and initiates the healing process *i.e.* inflammation [2].

Imidazolidines (saturated imidazoles) are also acknowledged as tetrahydroimidazoles, holding two nitrogen atoms in an aromatic azole five-membered ring system. In the year 1858, Heinrich Debus, a German chemist, pioneered the first synthesis of imidazole using glyoxal, ammonia, and formaldehyde in low yield, as shown in (Scheme **1**) [3].



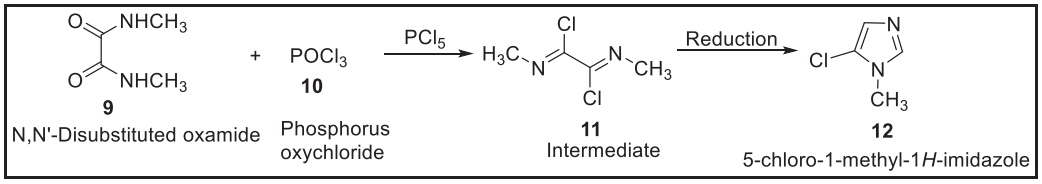
Scheme (1). Heinrich debus synthesis of imidazoles.

In the extension of the Debus synthesis, Radiszewski introduced the synthesis of substituted imidazoles [4] using aldehydes, 1,2-dicarbonyl compounds, and ammonia, as shown in (Scheme **2**).

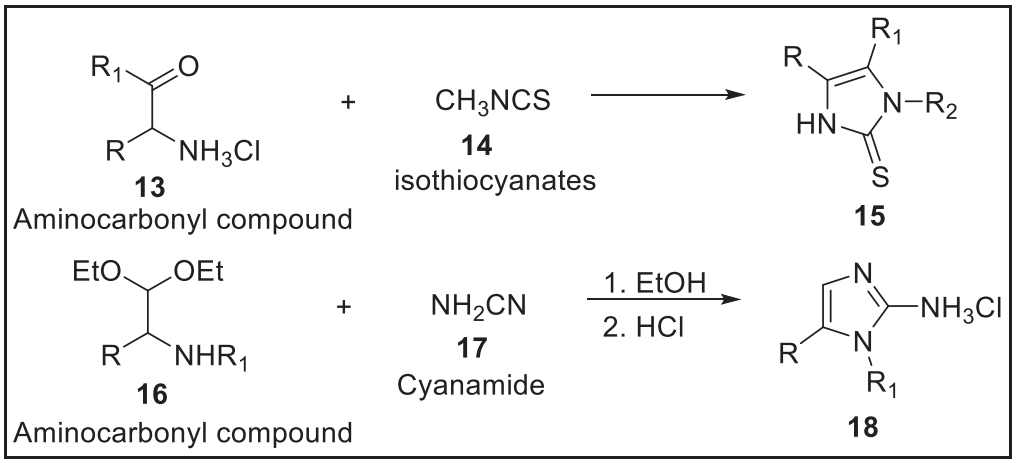


Scheme (2). Radiszewski synthesis of imidazoles.

Furthermore, the synthesis of a variety of substituted imidazoles is still employed by means of this process. The Wallach synthesis (Scheme **3**) [5] and the Marckwald synthesis (Scheme **4**) [6] are additional named reactions engaged in the synthesis of imidazoles.



Scheme (3). Wallach synthesis of imidazoles.



Scheme (4). Marckwald synthesis of imidazoles.

Imidazoles have established extraordinary consideration in modern years, which have been accounted as spin-trapping classes in the attractive appliance of drug designing with neuroprotective activity [7, 8]. They have been believed as chief moiety such as outstanding bioavailability, superior tissue penetrability and permeability and a comparatively low incidence of adverse and toxic effects, which recommended that they have considerable improvement potential in chemistry, medicinal chemistry and materials science [9] and intermediates for synthesis and designing of medicinal scaffolds with prospective cyclooxygenase-2 (COX-2) inhibition activity. On the other hand, imidazole is a planar 5-membered ring structure, which is dissolved in polar solvents as well as water. It is present in two corresponding tautomeric structures, the reason that the hydrogen atom can be situated on both of the two nitrogen atoms. Imidazole is an extremely polar system of 3.61D and is completely dissolved in water. The imidazole is noticed as aromatic character owing to the occurrence of a sextet of π-electrons, and it is amphoteric, *i.e*. it can be able to employed as an acid as well as a base. Moreover, imidazole can act as a hydrogen bond donor if it is not substituted at N1, and it can contribute to van der Walls interactions [10]. The available drug molecules that contain imidazole as core unit act as an effective inflammatory drug as shown

CHAPTER 4

Oxazole, Oxadiazole, Isoxazoline and Oxazoline Derivatives as Anti-Inflammatory Agents

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Abstract: Oxygen and Nitrogen containing five-membered heterocyclic compounds have been the target of intense investigation in the last two decades to discover potent biologically active compounds as anti-inflammatory agents. The related studies comprising of fascinating oxazole-based derivatives include oxazoles, isoxazoles, oxazolines, and oxadiazoles, as therapeutic agents, which have become an interesting topic.Therefore, noticeable achievements have been accomplished in the field of anti-inflammatory studies. This chapter will discuss some latest updates on the synthesis and anti-inflammatory studies of these oxazole-based derivatives, which we hope will be beneficial to synthetic organic and medicinal chemists.

Keywords: Anti-Inflammatory agents, Analgesic, Biological activities, Chemotherapeutic agents, Heterocyclic compounds, Isoxazoline, Inflammation, Medication, Oxazole, Oxadiazole, Oxazoline, Scaffold.

INTRODUCTION

The prevalence of health issues is proliferating, making it a pressing clinical concern. To address this, medicinal chemists are currently exploring novel drug options that can effectively and safely treat these conditions. There is a plethora of heterocyclic compounds that are presently in use for the treatment of infectious diseases. Heterocyclic systems comprise a vast number of drugs and biologically relevant molecules. Inflammation is the body's natural defense mechanism in response to injury and infection, and the intractable inflammatory cascades cause several diseases such as rheumatoid (RA), osteoarthritis (OA), inflammatory bowel disease, diabetic neuropathy, inflammation mediated by tumor initiation and progression [1].

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Oxazole-based compounds are considered prime scaffolds for anti-inflammatory activity studies in the drug discovery process owing to their unique structural nature exerting diverse weak interactions such as coordination bonds, hydrogen bonds, ion-dipole, π-π stacking, van der Waals force, hydrophobic effect, and so on [2]. Presently, various oxazole-based drugs have reached in clinics and some of them show anti-inflammatory properties [3] which are shown in Fig. (**1**).

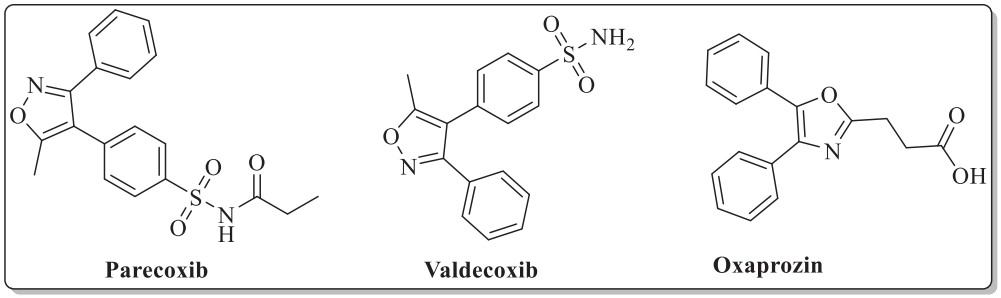
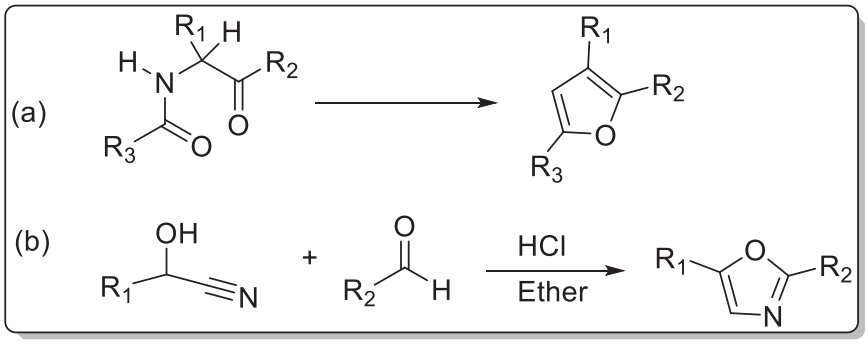


Fig. (1). Oxazole based anti-inflammatory drugs.

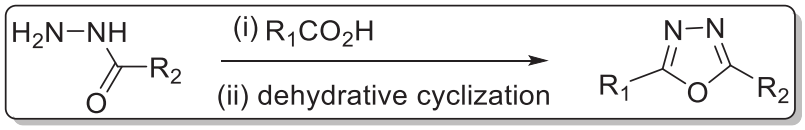
The **oxazoles** are heterocycles containing one oxygen atom and one nitrogen atom, extensively exhibited in natural products and synthetic molecules. Their structures bind to numerous receptors and enzymes through noncovalent interactions and are known as a prime skeleton for drug discovery [4]. There are several synthetic methods to prepare oxazoles in organic chemistry, and the most common ones include Robinson-Gabriel synthesis and Fischer oxazole synthesis. In the first method, 2-amino alcohols are condensed with α-halo ketones or α-halo aldehydes to form oxazoles. In contrast, cyanohydrin reacts with an aldehyde in the presence of anhydrous hydrochloric acid (Scheme **1**).



Scheme (1). General Methods for the synthesis of Oxazoles: (**a**) Robinson-Gabriel synthesis, (**b**) Fischer oxazole synthesis.

Oxazole-containing scaffolds, including anti-inflammatory activities, are essential in treating different diseases [5]. The therapeutic benefit of the oxazole ring system is actively utilized in marketing medications that include it.

Oxadiazoles are the heterocyclic five-membered ring containing one oxygen, two carbons, two nitrogen atoms, and two double bonds [6]. It is also referred to as azoximes, oxybiazole, biozole, diazoxole, furadiazole, and furoxans [7]. The most common synthetic route for oxadiazoles includes the cyclization between acid hydrazides (or hydrazine) and acid chlorides/carboxylic acids through direct cyclization [8] of diacyl hydrazines with a range of dehydrating agents (Scheme **2).**



Scheme (2). General method for the synthesis of oxadiazoles.

Oxadiazole motifs are commonly found in drug-like molecules and are known for their distinctive and impressive properties. As a result, they are frequently used in drug synthesis, including creating medications like fasiplon, butalamine, oxolamine, raltegravir, and pleconaril. The family of heterocyclic compounds consisting of substituted oxadiazole and its derivatives is vital due to their biological and pharmacological properties. These properties include antibacterial, fungicidal, antimicrobial, anti-inflammatory [9a, b], anticonvulsant, anticancer, antimalarial, and antidepressant activities. The heterocyclic ring of 1,3,4-oxadiazole is highly significant due to its diverse range of biological activities [10], making it one of the most critical heterocyclic structures. Oxidative stress and inflammation are intricately linked to the development of several severe human diseases, including cancer, atherosclerosis, diabetes, and its associated complications, such as diabetic nephropathy [11] and thus creating new and effective therapeutic medications to prevent diseases resulting from oxidative stress and inflammation is highly important [12].

Isoxazoline is part of the azole family and contains nitrogen and oxygen heteroatoms within the ring structure [13]. The general structure of isoxazoline is a five-membered heterocyclic ring with an endocyclic double bond that has adjacent nitrogen and oxygen atoms [14]. There are numerous methods for preparing isoxazolines and the most common ones include the cyclization cycloaddition of oximes to alkenes or alkynes, leading to various isoxazolines (Scheme **3**). After dehydrogenation, isoxazoline forms the derivative isoxazole [15].

CHAPTER 5

Thiazole and Thiazolidinone Derivatives as Anti-inflammatory Agents

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Abstract: The significant potential of thiazole and thiazolidinone derivatives as anti-inflammatory drugs can be observed in their ability to inhibit a variety of inflammatory mediators. These derivatives also inhibit factors that catalyze the synthesis of inflammatory mediators. The anti-inflammatory effects of the derivatives of thiazole and thiazolidinone demonstrated this potential. In addition, they have antioxidant properties that help to reduce oxidative stress and inflammation that the body experiences. These derivatives represent promising molecules for the development of new medications in the near future because they successfully reduce inflammation in various preclinical and clinical studies. The potential of thiazole derivatives as COX inhibitors and anti-inflammatory drugs has also been investigated, with promising results. Further research is needed to explore their mechanisms of action, optimize their therapeutic potential, and evaluate their safety and efficacy in clinical settings.

Keywords: Anti-inflammatory agents, COX1, COX2, NASIDs, Thiazole, Thiazolidinone.

INTRODUCTION

Heterocycles containing sulfur and nitrogen atoms in a five-membered ring represent thiazole and thiazolidinone derivatives. In the case of thiazole derivatives, the heterocyclic ring contains a carbon–carbon double bond and carbon–nitrogen double bond. Thiazolidinone derivatives have a carbonyl group attached to the nitrogen and sulfur atoms of the ring (Fig. **1**). Both types of compounds exhibit diverse pharmacological activities, including anti-inflammatory, antidiabetic [1], antioxidant, antibacterial [2], antifungal [3], and anticancer properties. Thiazole and thiazolidinone derivatives have been found to have the potential to treat various ailments, including inflammatory disorders, infectious diseases, and cancer [4, 5].

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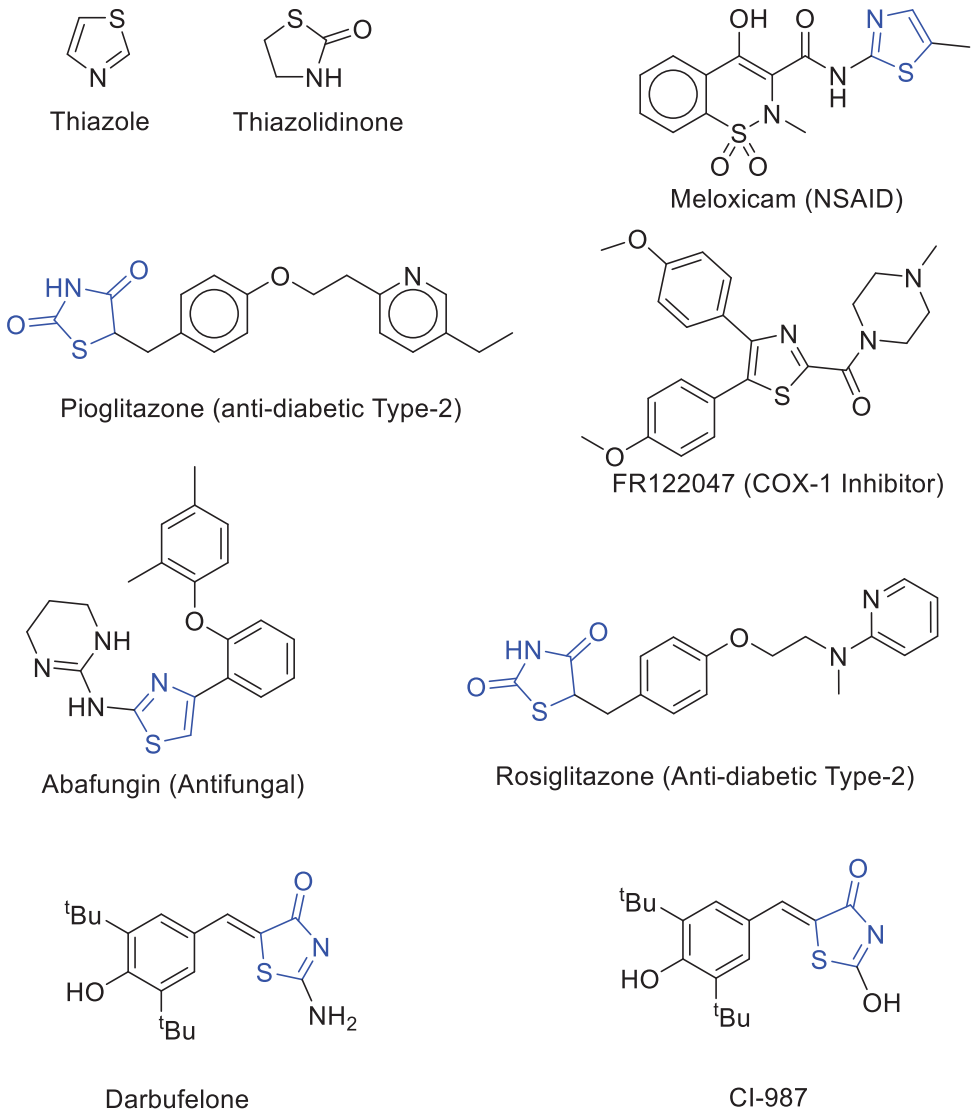

Fig. (1). Structures of thiazole and thiazolidine derivatives.

Many derivatives of thiazole and thiazolidine have been used clinically to treat inflammation and other diseases **(**Fig. **1)**.

Thiazole rings are structural components found in a wide variety of compounds, including vitamin B1 (thiamine), thiamine pyrophosphate (TPP), epothilones, carboxylase, and thiopeptide antibiotics like thiostrepton and micrococcin P1 [6].

CHEMISTRY OF THIAZOLE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

Burdulene and coworkers studied the anti-inflammatory activity of substituted succinic acids [7]. The thiazole-substituted succinic acid methyl ester showed moderate inflammatory activity in white male mongrel rats (Fig. **2**).

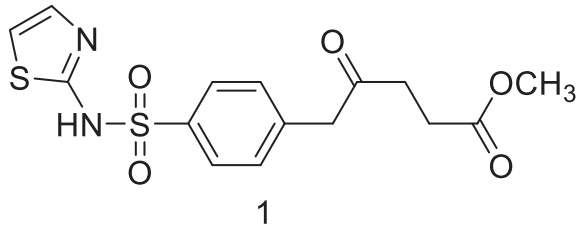

Fig. (2). Methyl ester of thiazole-substituted succinic acid.

Thore and coworkers converted phenylthiazole-4-carboxylate **6** to the corresponding carboxhydrazide **2** and carbonitrile **7** (Fig. **3**).

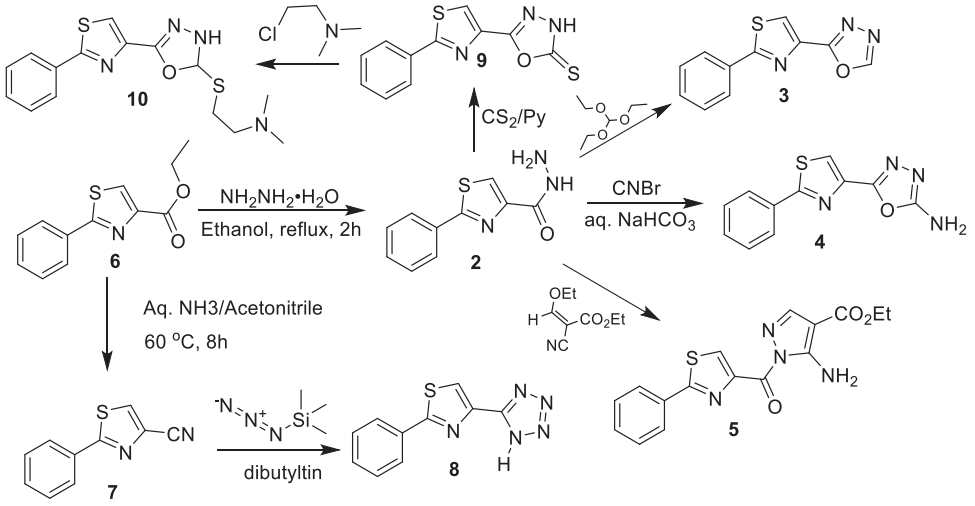

Fig. (3). Synthesis of ethyl-2-phenylthiazole-4-carboxylate derivatives as anti-inflammatory

Molecules **2** and **7** were modified even further by generating another heterocyclic moiety viz. oxadiazolinone, oxadiazole, oxadiazolinethione, tetrazole, and pyrazole moiety to the thiazole moiety at position 4. These molecules have the potential to act as anti-inflammatory agents, as established by the carrageenan-induced rat paw edema method and molecular docking studies against COX2 [8].

CHAPTER 6

Pyrazole and Pyrazoline Derivatives as Anti-Inflammatory agents

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Abstract: Heterocyclic compounds have provided significant contributions to the field of medicinal chemistry. Pyrazole and pyrazoline are a class of five-membered two adjacent nitrogen-containing compounds that are integral parts of a large number of commercial anti-inflammatory drugs. After an initial introduction to inflammatory response, mechanism involved therein, the chapter compiles recent synthetic schemes along with *in-vivo* and *in-vitro* studies of pyrazole and pyrazoline derivative as anti-inflammatory compounds on various established and recently recognized molecular targets.

Keywords: Anti-inflammatory agents, COX-1, COX-2, LOX, Carrageen paw edema, Cathepsins, Pyrazole, Pyrazoline.

INTRODUCTION

Response of the immune system involving white blood cells and related substances to foreign invaders like bacteria and viruses by activating a process involving a complicated biochemical reaction in vascular tissue to hostile stimuli like infections, irritants, or injured cells is inflammation [1, 2]. Mainly characterized by redness because of increased blood flow also involves increased cellular metabolism, vasodilatation and the release of soluble mediators, extravasation of fluids, and cellular influx that can lead to swollen joints and joint pain, stiffness and loss of joint function [3]. In the presence of an inflammatory agent, cell membranes activate phospholipase A2, which inhibits a cascade of reactions leading to the release of arachidonic acid and inflammatory mediators like cytokines, serotonin, histamine, prostaglandin and leukotrienes that increase vascular permeability and aid leukocyte migration to the site of inflammation [4, 5]. However, in conditions like arthritis, the immune system causes inflammation even in the absence of any foreign intruders. In the autonomic nervous system,

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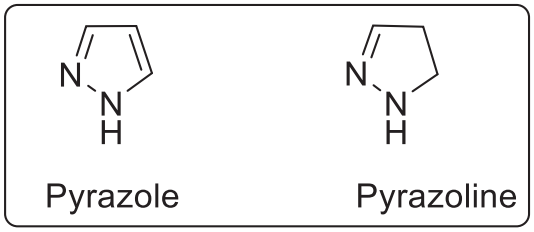
inflammation occurs when the immune system mistakes healthy tissues for infectious or abnormal ones and attacks them [6].

Vascular endothelial growth factor (VEGF), Tumor necrosis factor (TNF-α), and Interleukin-1 (IL)-1β are three pro-inflammatory cytokines that play key roles in the dynamic process of inflammation. Although inflammation is a protective strategy for the body to get rid of harmful stimuli with the help of a variety of substances that deplete B lymphocytes, inhibit the trafficking of lymphocytes into tissues, inhibit the activity of particular cytokines or their receptors, or block the binding of molecules on monocytes and lymphocytes, but still anti-inflammatory drugs can be a useful tool in easing the inflammation related conditions [7].

Salicylate-containing plant extracts have been used by humans for thousands of years to treat a variety of ailments, including pain, inflammation and fever. Felix Hoffman acetylated salicylic acid and developed aspirin 150 years ago [8]. Aspirin's ability to prevent the formation of prostaglandins and thromboxane, inflammatory mediators synthesized by the cyclooxygenase enzymes COX-1 and COX-2, still makes it the most widely utilized therapeutic medication in the world. Non-steroidal anti-inflammatory drugs (NSAIDs) have occupied second place to aspirin in effectiveness, which works by inhibiting cyclooxygenase-2 (COX-2) and other targets like the cytokine tumor necrosis factor-(TNF-α) [9].

In addition to the understanding of immunology during the last 20 years where more than 80 cytokines, 20 chemokines and their GPCRs have been characterized with 50 additional GPCRs with potential roles in inflammation and emerging targets for inflammatory agents like cathepsin focus on design and development of novel anti-inflammatory agents is increased enormously [10 - 12].

In this chapter, we are focusing on pyrazole (1), the term coined by Ludwig Knorr in 1883 and pyrazoline (2) based compounds with potential anti-inflammatory activities reported *via in-vivo* and *in-vitro* target inhibition studies [13].



One nitrogen atom is sp^2 hybridized and with lone pairs contributing to the forward aromaticity, whereas the second nitrogen is sp^3 hybridized with acidic

hydrogen as a substituent in pyrazoles (1), whereas pyrazolines (2) is reduced endocyclic pyrazole having only one double bond and it is basic in nature. Pyrazoles and pyrazolines are synthetically significant drug candidates because they:

• can alter the shape of molecular targets through hydrogen bonding and can exhibit different types of biological activities by interactions because of the presence of hydrogen donor and hydrogen acceptor sites [6, 14].

• can undergo nucleophilic and electrophilic substitution reactions such as halogenation , sulphonation, nitration, *etc*. and can afford extended sites for interaction with biological polymers, including molecular targets involved in various disease conditions.

• can be synthesized using a variety of reactions through various condensation and rearrangements exclusion reactions [15, 16] Fig. (**1**).

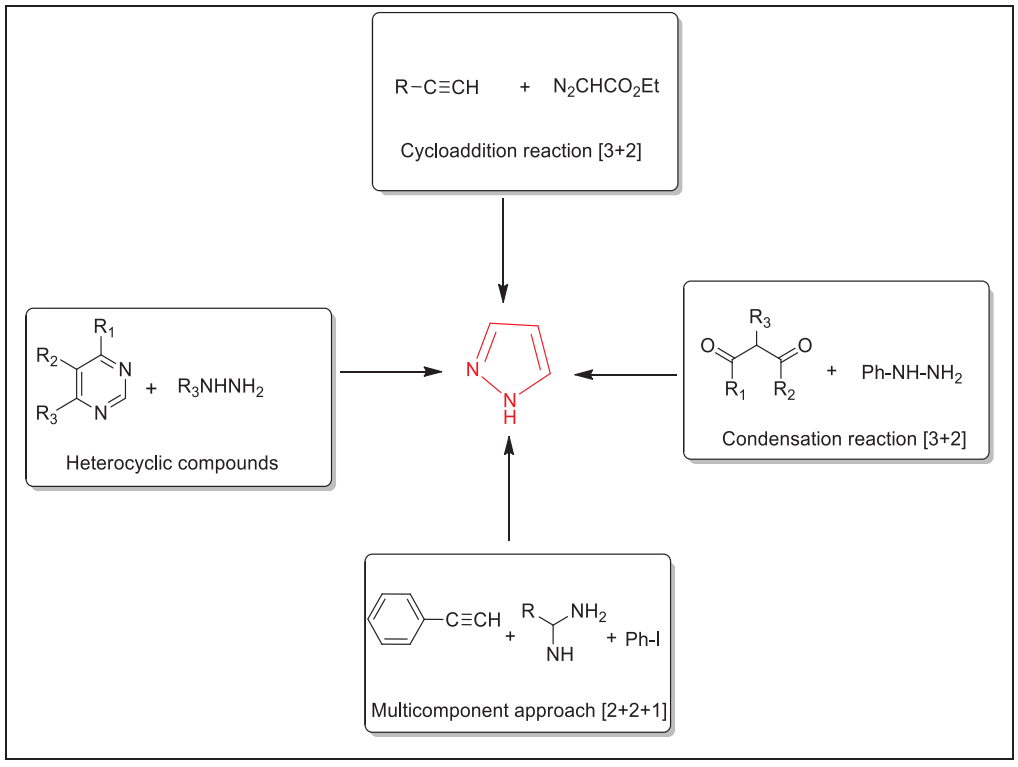


Fig. (1). Synthetic strategies for the synthesis of pyrazoles.

CHAPTER 7

Carbazoles and their Derivatives as Anti-inflammatory agents

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Abstract: Heterocyclic compounds refer to a defining class of organic compounds with vast biological applications. Heterocyclic compounds are of great significance to life for the reason that they are abundantly present in nature, such as in the form of antibiotics, hormones, vitamins, and many more. Among heterocyclic compounds, nitrogen-based heterocycles are of special biological use because of their boundless medicinal and biological applications. Carbazoles are one of several nitrogen-based, biologically active heterocyclic compounds with the chemical formula $C_{12}H_9N$. Carbazole moiety has diverse pharmaceutical applications, which have attracted the interest of chemists as well as biologists to study more about these chemical compounds. This chapter compiles the synthesis of a variety of carbazole-derived compounds and their anti-inflammatory applications.

Keywords: Anti-inflammatory agents, Biological activity, Carbazoles, Drug discovery, Heterocycles, Heterocyclic compounds, Inflammation, Medicinal chemistry, Pharmaceuticals.

INTRODUCTION

Carbazole is a tricyclic hydrocarbon with a carbon skeleton made of fluorene, naturally found in coal tar. Other sources of carbazoles are higher blue-green algae, actinomycetes, and filamentous algae [1]. The structure includes two six-membered benzene rings fused on one side of five-membered nitrogen-containing rings [2] (Fig. **1**).

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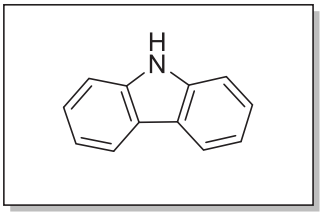

Fig. (1). General properties of carbazole.

IUPAC name: 9H-Carbazole, Structural formula: $C_{12}H_9N$, Calculated molecular weight: 167.206 g/mole, Density: 1.301 g/cm^3, Melting point: 246-248 ºC, Boiling point: 354-356 ºC, Physical shape: Off-shite crystals.

Carbazole and their derivatives constitute an important class of nitrogen-containing heterocyclics that are predominantly present in nature [3]. Over the last 50 years, the versatile biological activities of carbazole have gained the interest of chemists and biologists. Carbazole, as a pharmacophore, is used as a starting material for the synthesis of diverse biologically active chemical compounds [4]. The carbazole-derived commercially available drugs include carvedilol, carprofen, carazostatin, ellipticine, ollivacine, datelliptium, alectinib, celiptium, carbomycins, murrayafoline, and many more [5 - 8] (Fig. **2**).

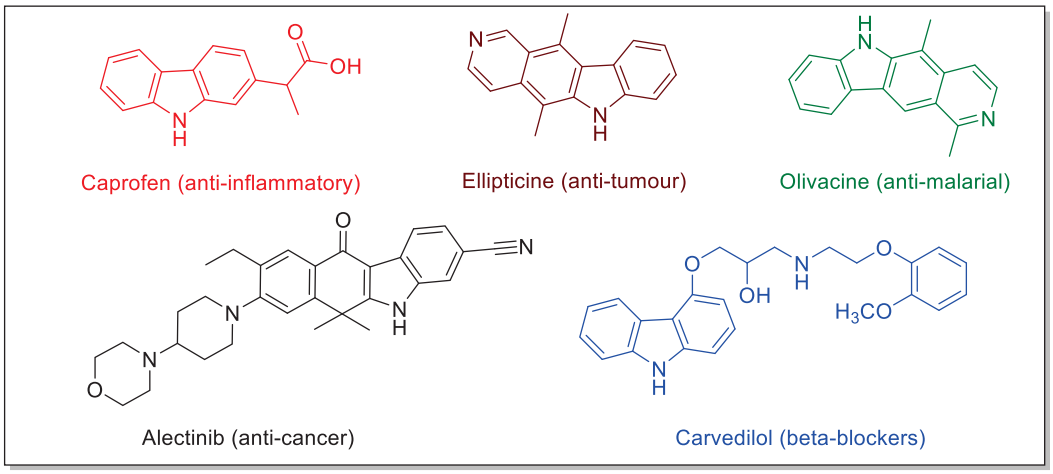

Fig. (2). Carbazole derived approved drugs.

The list of synthesized carbazole derived compounds includes oxazinocarbazoles, isoxazolocarbazolequinone, pyrido-carbazolequinone, tetrahydrocarbazoles, ben zocarbazoles, furo-carbazoles, pyridocarbazoles, purrolo-carbazoles, indolocar

bazoles, oxazolinyl, carbazoles, thienocarbazoles imidazo-carbazoles, thiazocar bazoles, benzopyrano-carbazoles, benzofurano-carbazoles, *etc* [9 - 22]. Various classes of carbazole include compounds as shown in Fig. (**3**).

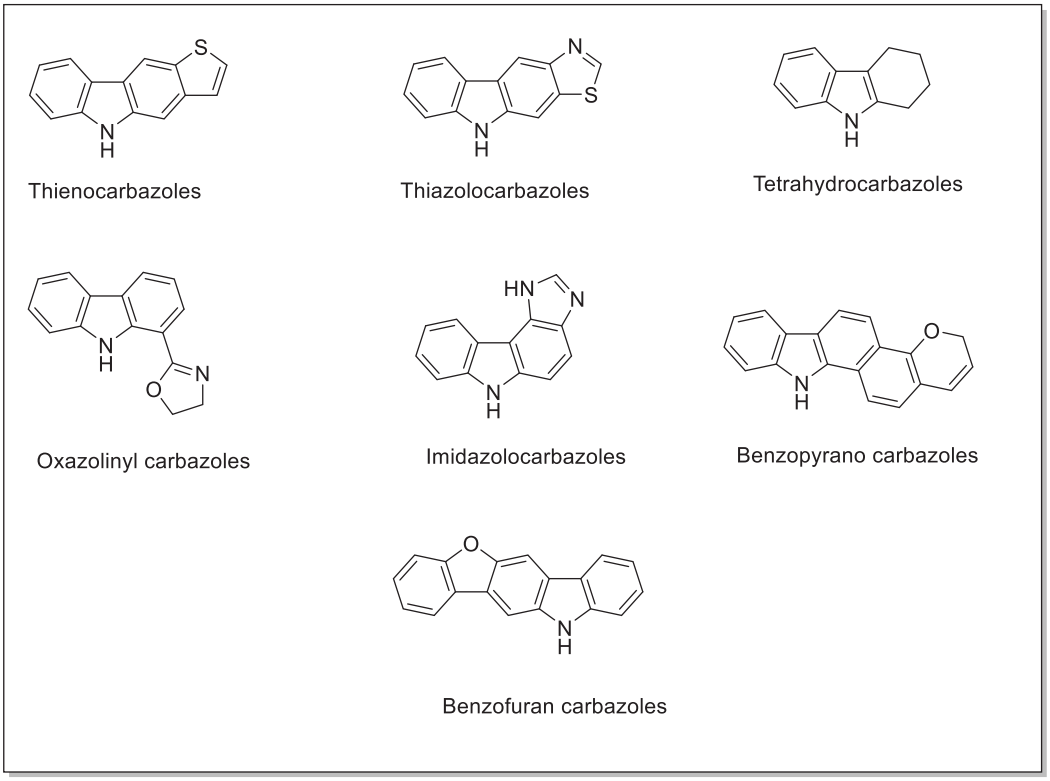

Fig. (3). Some classes of carbazoles.

CARBAZOLES AND THEIR DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

Yan-Hui-Fu *et al*. isolated three new carbazole alkaloids from the roots of *Zanthoxylum austrosinense Huang* (Rutaceae) and studied their anti-inflammatory and antiproliferative activities (Scheme **1**). The extraction was done using air-dried roots of *Z. austrosinense* using methanol six times, each for 3 days. The methanol extracted solution was then concentrated and reduced to obtain crude extract under lower pressure. The isolated compounds were found to exhibit pronounced inhibitory effects on NO production with IC_{50} value in the range of 0.89 ± 0.05 to 9.62 ± 0.15 μM, which was comparable with hydrocortisone taken as positive control [23].

CHAPTER 8

Azepines and their Derivatives as Anti-Inflammatory Agents

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Abstract: Heterocyclic compounds are of great interest today for scientists and chemists because of their various pharmaceutical applications. They have an exceptional ability to present both biomimetic and active pharmacophores, which makes them versatile pharmacophores for numerous drugs. Azepines are among the nitrogen-containing heterocyclic moieties with boundless medicinal and biological applications. This chapter is mainly focused on the synthesis and isolation of a variety of azepine based heterocyclic compounds with their anti-inflammatory activities.

Keywords: Anti-inflammatory agents, Azepines, Biological activity, Drug discovery, Heterocycles, Inflammation, Medicinal chemistry, Pharmaceuticals, Therapeutic drugs.

INTRODUCTION

Azepines are seven-membered monocyclic ring-structured, nitrogen-containing heterocyclic compounds. The researchers have concentrated more on creating the structure of 1,4-benzodiazepine based azepines while synthesizing seven-membered nitrogen-containing rings. A comprehensive range of azepine derivatives, such as isoxazole [4,5-c] azepines, isoxazole [5,4-b] azepines, and isoxazole [4,5-b] azepines have numerous pharmacological applications [1 - 3] (Fig. **1**). Naturally isolated and synthetically available azepines have been used as

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scaffolds for the design of pharmacological active profiles, including anti-inflammatory, anti-convulsant, HIV growth inhibitors, and anti-tumour activity [4 - 8].

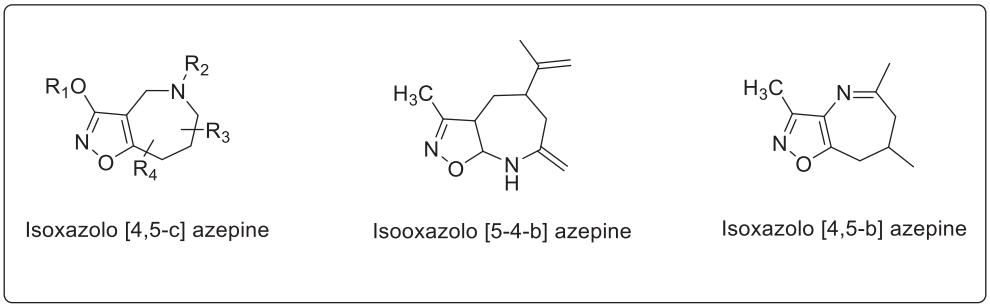

Fig. (1). Structure of biologically active isoxazole azepines.

Benzodiazepines are a key structure moiety containing azepine core unit with a broad range of pharmaceutical and agrochemical activities [9 - 12] as depicted in Fig. (**2**).

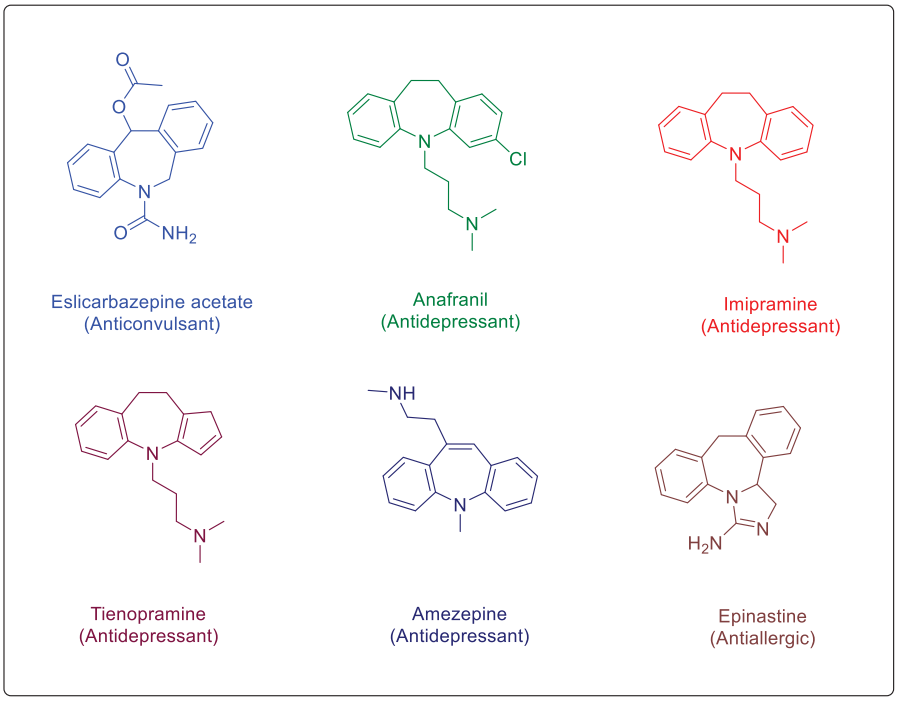

Fig. (2). Commercially available azepine-derived drugs.

Inflammatory diseases [13, 14] are a worldwide problem; hence, a major interest for chemists to develop more effective non-steroidal anti-inflammatory drugs (NSAIDs) and a variety of NSAIDs are aspirin, diclofenac, indomethacin, and COXIBs [15 - 18], but these were often found to cause cardiovascular side effects [19 - 22]. Consequently, the discovery of new anti-inflammatory agents with higher affiance and lower toxicity led to an increase in demand.

CHEMISTRY OF AZEPINES AS ANTI-INFLAMMATORY AGENTS

Li Xu *et al*. reported the synthesis of pyrrolinone-fused benzodiazepine alkaloids. The first step involves the reaction between mono-Ethyl malonate **(1)** with L-aspartic acid diethyl ester hydrochloride **(2)** in the presence of EDCl(1-[3-dimethylamino)propyl]-ethylcarbodiimide hydrochloride and 4-dimethylamino pyridine as a catalyst to yield the desired amiden **(3)**. The final pyrrolinone-fused benzodiazepine alkaloids were achieved in seven steps, with the key step being the intramolecular Friedel-Crafts reaction to form a unique tricyclic skeleton. The Asperazepanone B **(10)** exhibits not only potent inhibitory activity against NO production but also hindered potent LPS-induced expression of TNF-α and IL-6 at a concentration of 0.1 μM, thus proving to be a great anti-inflammatory drug [23] (Scheme **1**).

Yingying Gu *et al*. isolated a novel compound having pyrrole-azepine moieties from the plant *P. oleracea* along with six known compounds and the isolated compounds were examined for their anti-inflammatory activities. The results showed that the newly isolated compound with pyrrole-azepine moieties inhibits the IL-1β in RAW 264.7 cells induced by LPS at 50 μM (Scheme **2**) [24].

Demchenko *et al*. developed new triazole-azepine hybrid derivatives and screened for their anti-inflammatory activities using the Carrageenan-paw edema assay. In addition, the hybrid derivatives were also react with various (het)arene carbaldehydes along with ethanol and piperidine to obtain a new series of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5H- [1, 2, 4]triazolo[4,3-a]azepin-3-yl)acrylonitrile derivatives. The Carrageenan-paw edema assay revealed that the compound (7) had an inhibition of -18.50% whereas the standard drug Ketorolac had an inhibition of 49.77% at a dose of 25.0 mg/kg (Scheme **3**) [25].

CHAPTER 9

Quinoline and their Derivatives as Anti-Inflammatory Agents

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Abstract: Quinoline is one of the significant moieties in the construction of new pharmaceuticals since it is a notable scaffold among heterocyclic compounds. The derivatives of quinoline which are biologically active compounds, are acknowledged as prominent scaffolds in drug discovery. Quinoline-based heterocycle scaffolds have recently become very important in medicinal chemistry because of their important pharmacological and biological properties. These substances' importance in the finding and formation of pioneering medicines for the treatment of various diseases is an example of their value. Using literature that has been published in the last five years, the current study describes the synthesis of different quinoline-based heterocycle scaffolds and their advantageous medicinal uses, especially as anti-inflammatory agents.

Keywords: Anti-inflammatory agents, Azoimine, Biological properties, Heterocyclic compounds, Isoxazole, Ibuprofen, Medicinal chemistry, Molecular docking, Oxadiazole, Pyran, Pyrazolo quinoline, Pharmacological properties, Quinoline derivatives, Quinazolinones, Sulfonamides, Thiazolidinone, Triazine and triazole.

INTRODUCTION

Heterocycles with nitrogen atoms have grown significantly in medicinal chemistry because of the underlying composition and structure of many natural and synthetic compounds with potent biological activity [1, 2]. Due to a wide range of biological and pharmacological activities, which include anti-malarial [3, 4], anti-inflammatory [5, 6], anti-bacterial [7, 8], anti-cancer [9, 10] and anti-oxidant [11] activities, quinoline-based heterocycles have gained a lot of attention from scientists among all the different types of N-Heterocycles. The quinoline scaffolds, out of many anti-inflammatory drugs, have emerged as novel anti-

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inflammatory agents to treat diseases associated with acute and chronic inflammation with minimum side effects. These compounds are categorised on the basis of a number of substituents on the quinoline ring or compounds containing a quinoline ring with other heterocycles [12, 13]. Inflammation is an immune system defence mechanism that occurs when an organism sustains various wounds or is invaded by germs [14, 15]. Numerous autoimmune illnesses that are chronic are linked to this phenomenon, such as rheumatoid arthritis and inflammatory bowel disorders [16, 17] (Fig. **1**).

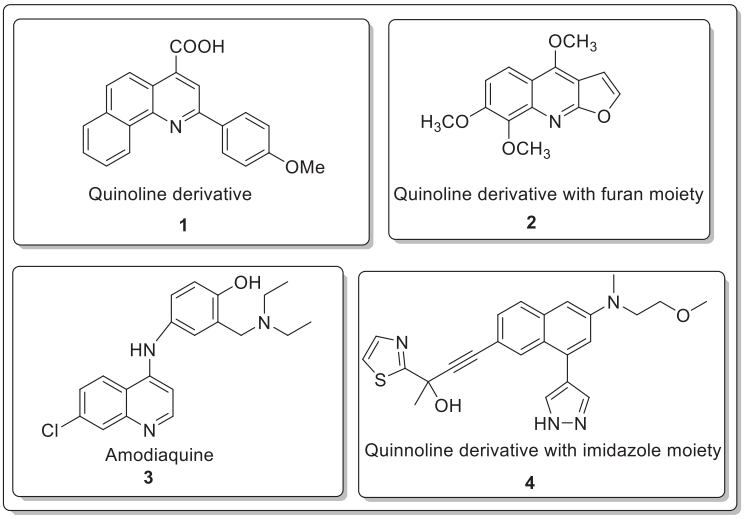


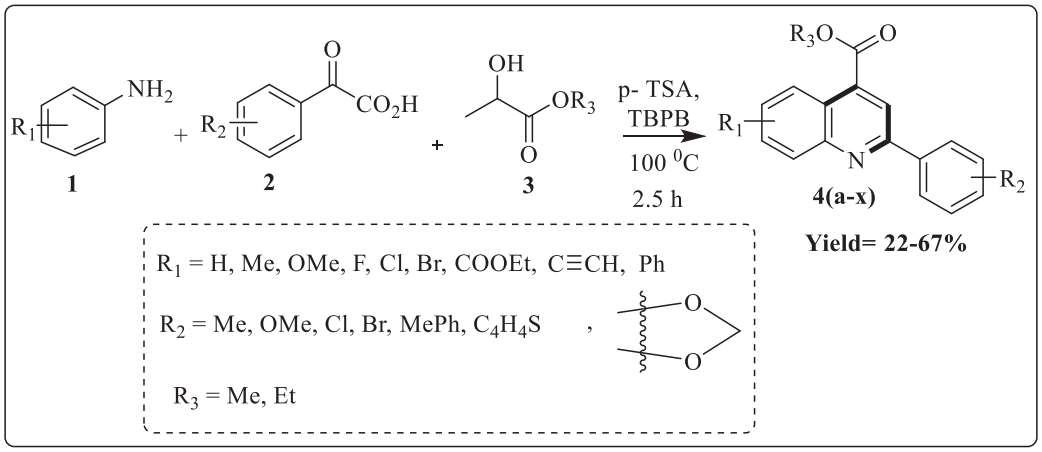
Fig. (1). Quinoline derivatives as anti-inflammatory agents.

CHEMISTRY OF QUINOLINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

Lizhu Huang *et al.* reported a new metal-free three-component method to prepare 2,4-disubstituted quinolines **4(a-x)** by reacting substituted anilines **(1)**, α-keto acids **(2)** and alkyl lactates **(3)** in the presence of p-TSA and TBPB followed by refluxing at 100˚ C for 2.5h.

All synthesized derivatives were screened for *in vitro* anti-inflammatory properties in RAW264.7 cell assays against standard quercetin and it was observed that compounds **4i** (R_1=OMe, R_2=Ph, R_3=Et), **4t** (R_1=H, R_2=Ph, R_3=Me) and **4x** (R_1=H,

R_2=PhMe, R_3=Me) were found to be most potent and could inhibit the release of NO from LPS induced RAW264.7 cells Scheme (**1**) [18].



Scheme (1). Synthesis of 2,4-disubstituted quinolines.

Siqi Xing *et al.* reported a protocol for the synthesis of new quinoline-based derivatives **(10-40)**. Initially, 8-quinolinesulfonyl chloride **(5)** and 3-nitroaniline **(6)** were reacted in the presence of triethylamine (TEA) and tetrahydrofuran (THF) in DCM to synthesize **(7)** followed by a reduction in methanol in the presence of Pd/C and hydrazine hydrate to yield **(8)**. Finally, in pyridine solvent, compound **(8)** was reacted with substituted benzenesulfonyl chlorides **(9)** in the presence of pyridine to synthesize final compounds (**10-40).**

Synthesized compounds were screened for *in vitro* anti-inflammatory property by inhibiting the amounts of NO generation caused by lipopolysaccharide (LPS) in the RAW264.7 cells by taking indomethacin as the standard drug and it was observed that **(13)** was found to be most potent anti-inflammatory agent which reduces the formation of pro-inflammatory cytokines TNF-α, IL-1β and NO having IC_{50} values of 23.48 ± 0.46, 18.98 ± 0.21 and 20.40 ± 0.94 μM respectively. Two inflammatory mediators, namely iNOS and COX-2, generated by LPS may be inhibited by this derivative. Synthesized compounds were also subjected to molecular docking studies and it was observed that derivative **(13)** shows inhibitory activity against PDE4B enzyme with IC_{50} value of 0.94± 0.36μM by taking Rolipram (IC_{50}=1.04± 0.28μM) as standard drug protein. To test anti-inflammatory drugs AIA rat model was used and *in vivo* studies showed that in adjuvant-induced arthritic rats, compound **(13)** was found to be effective in reducing the severity of foot swelling and knee joint pathology and lowered serum levels of the inflammatory proteins TNF- and IL-1 (Scheme **2**) [19].

CHAPTER 10

Coumarins and Their Derivatives as Anti-Inflammatory Agents

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Abstract: Coumarins are a diverse class of phytochemicals found in many human diets and have been shown to have various pharmacological actions. The chapter discusses the role of coumarins in disease prevention and treatment and their classification based on structure. It also highlights that the various schemes of coumarin possess anti-inflammatory properties, making them a promising scaffold for the synthesis of a new class of anti-inflammatory drugs. Overall, this chapter provides valuable information on the potential use of coumarins as anti-inflammatory agents and their synthetic aspects. This book chapter focuses on the development of various possible potential anti-inflammatory molecules having a coumarin core.

Keywords: Anti-inflammatory agents, Coumarins, heterocycle, organic compounds, organic synthesis.

INTRODUCTION

Heterocyclic chemistry is a significant field of organic chemistry, containing nearly two-thirds of all organic compounds. Among a range of heterocycles, coumarins are versatile heterocyclic nuclei that are important structural motifs in natural products and drug molecules. Coumarin molecules have also been identified to inhibit inflammation *by* inhibiting LOX (lipoxygenase), COX (cyclooxygenase), and other similar mechanisms related to arachidonic acid metabolism routes. Various contributions by coumarins support their role in the development of anti-inflammatory molecules. Both natural and synthetic coumarin compounds have a unique ability to scavenge ROS (Reactive oxygen species) and regulate stress-related chronic diseases [1].

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OVERVIEW OF COUMARIN AND SOME COMMON DRUGS POSSESS ANTI-INFLAMMATORY PROPERTY

The control of inflammation is becoming relevant in all pathological processes. Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin **1**, naproxen **2,** and ibuprofen **4** are commonly used in the first-line treatment of a broad spectrum of chronic inflammatory conditions (Fig. **1**) [2]. The most significant drawback of NSAIDs is gastric intolerance, manifested as bleeding, dyspepsia, and ulcers. It occurs because of the inhibition of prostaglandin synthesis caused by the inhibition of COX (cytooxygenase) by NSAIDs and the acidic nature of the NSAIDs themselves. NSAID users develop three times more gastrointestinal side effects than non-users [3].

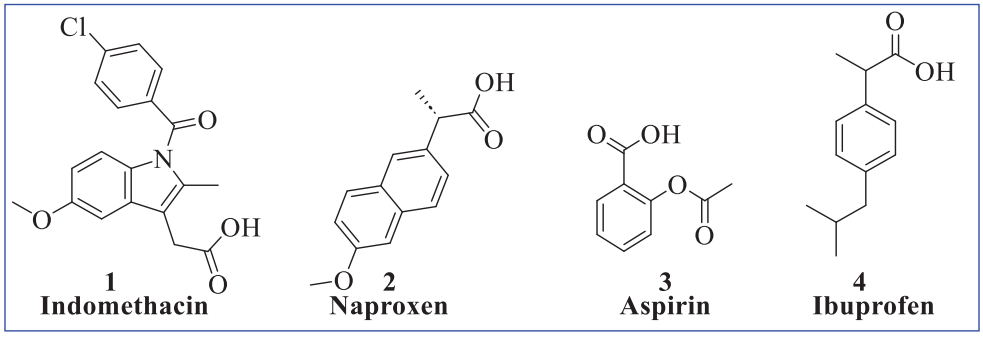

Fig. (1). Some common anti-inflammatory drugs.

Each fact points to the need to enhance the safety profile of available NSAIDs or find better alternatives. Various COX-2 depend on the significant anti-inflammatory action while being safe for GIT. Rofecoxib, MK-0966, and celecoxib are COX-2 inhibitors with potent anti-inflammatory activity but fewer adverse effects on the GIT than aspirin **3** and ibuprofen [4].

Coumarins are an elite class of compounds with a broad range of therapeutic properties, such as anti-tuberculosis, anti-tumor, anti-inflammatory, and anti-microbial activity [5]. The anti-inflammatory activity of coumarin-based molecules has been extensively studied and a significant structural-activity relationship has been established [6].

Coumarin-3-carboxylic acid is a crucial synthon in the formation of a wide range of natural & synthetic pharmacologies. Many studies have discovered that an amide bond linker between different coumarins and a variety of heterocyclic molecules refers to a broad range of compounds with biological activity. Many

experimental studies have found that different derivatives of coumarin inhibit inflammation at various levels [7].

CLASSIFICATION OF COUMARIN

Coumarin derivatives can be structurally classified into the following groups: dihydrofurocoumarins, simple coumarins, phenylcoumarins, pyranocoumarins (linear and angular), biscoumarins, and furocoumarins (Fig. **2**).

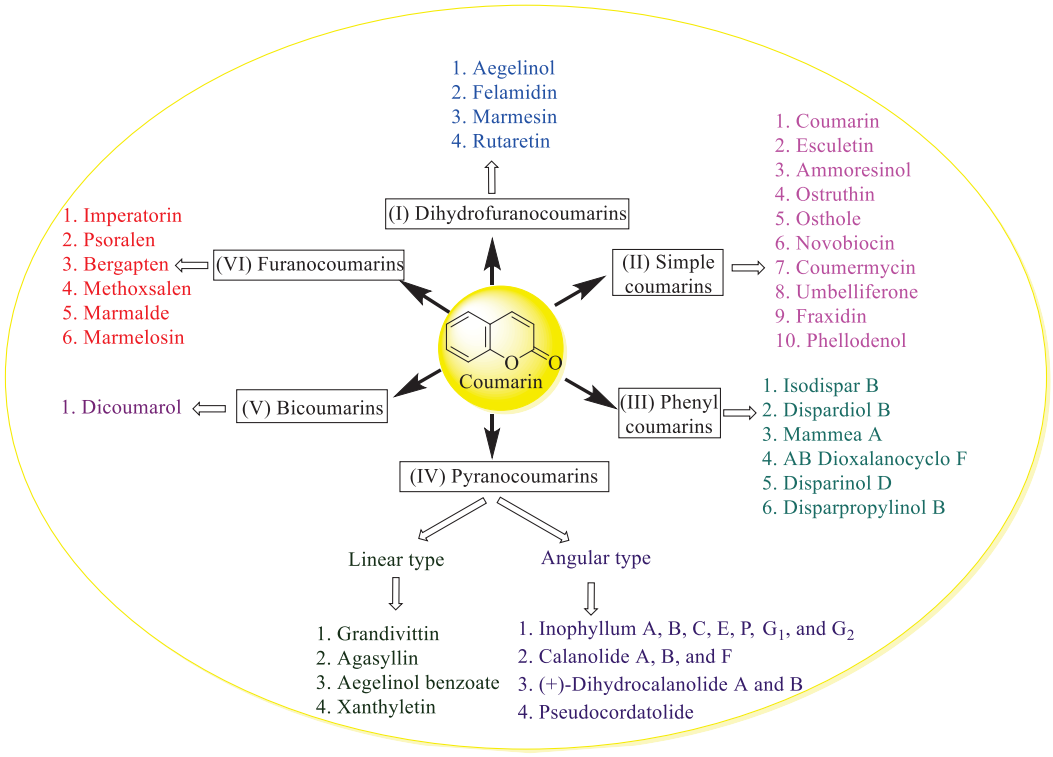

Fig. (2). Classification of coumarin derivatives.

I. Dihydro Furanocoumarins: Several dihydro furanocoumarins derivatives are given below (Fig. **3**):

Aegelinol: Aegelinol is a natural supplement and a potent antioxidant that aids in the reduction of free radicals in the human body. Aegelinol promotes the health of the skin, hair, and nails, as well as the health of the tendon, collagen formation, and connective tissue. This drug helps protect against free radical-mediated skin inflammation and hydrate the skin [8].

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M. P. Kaushik

Prof. M. P. Kaushik has been working as pro-vice chancellor & dean (research) at Amity University, Gwalior, M.P. He served as former- outstanding scientist (Sc 'H') & director, DRDO-DRDE, Gwalior, M.P & programme director (NBC), DRDO, New Delhi, India. During his tenure at DRDE, Prof. Kaushik has travelled extensively with delegations to different parts of the world, including the USA, Finland, Sweden, Germany, France, UK, Tunisia, Czech Republic, and Switzerland (Geneva). He has been awarded several prestigious awards and honors. He has more than 181 research publications in national and international journals of high repute, 20 Patents, and 09 technology transfers.

Neera Raghav

Prof. Neera Raghav is presently working as chairperson of the Department of Chemistry, Kurukshetra University, Kurukshetra, Haryana, India. She is an expert in organic chemistry and enzyme chemistry. She has contributed a lot to the scientific community in the fields of purification and characterization of enzymes, development of anti-cathepsin agents having potential use as anti-inflammatory, anti-Alzheimer's and anti-cancer agents, enzyme immobilization, development of sustained release drug delivery systems, preparation of biodegradable polymers using bio waste and validation of Ayurveda formulations. Prof. Neera has over 100 research publications in national and international journals of high repute and has recently filed 08 patent applications.