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Review on different five-membered heterocyclic aromatic compounds and their pharmaceutical applications.

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Abstract:

During the past decades and years of scientific research in the field of chemistry and pharmaceutical chemistry, many chemical compounds with various therapeutic applications have been prepared and studied, which contain heterocyclic aromatic in their chemical structure, whether they are six-membered, five-membered and four-membered rings. Among the most important of these heterocyclic compounds are the organic compounds that contain five-membered heterocyclic that containing one, two, or three heteroatoms. Because of the great importance of these heterogeneous aromatic rings in the field of chemistry and because of their great therapeutic activities for various diseases, many methods and techniques have been developed to synthesize many of these compounds and market them as compounds that have many therapeutic applications. In this research, a brief overview of the most important five-membered heterocyclic aromatic was provided, along with a summary of the most notable pharmaceutically potent compounds that have these rings in their chemical structure.

Keywords: Heterocyclic compounds, five-membered heterocyclic, therapeutic compounds, thiophene, furan, pyrrole, imidazole, thiazole, oxazole, triazole, oxadiazole, and thiadiazole.

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1- Introduction

Heterocycles are a significant class of natural compounds that are found in vitamins, hormones, alkaloids, and a variety of other natural products. In addition, they can be found in a wide range of biologically active substances. Most heterocycles are also used in combinatorial and supramolecular chemistry, as well as in medicine, agriculture, and industry [1]. In general, there are three categories of heterocyclic compounds: those based on nitrogen, such as pyrazole, indole, imidazole, piperidine, and pyridine; those based on sulfur, such as thiazole, thiadiazole, and thiophene; and those based on oxygen, such as benzofuran, oxazolidine, and pyran [2-4]. In addition to being a common component of many natural products, functional materials, ligands, and catalysts, heterocyclic compounds with nitrogen, oxygen, and sulfur atoms are also used as versatile building blocks in the synthesis of organic compounds [5,6]. They are utilized at practically every stage of the numerous metabolic processes required to maintain life, playing a crucial role in the metabolism of all living things. Their popularity can be attributed in part to the wide variety of interactions that these structures are involved in, which are made possible by the physicochemical characteristics of their heteroatoms, which can behave as either acids or bases depending on the pH of their surroundings [7,8]. These molecules are necessary for the synthesis of chlorophyll in plants, and the chemicals in hemoglobin, which consist of four pyrrole rings, are found in nature commonly [9]. The area of science known as heterocyclic chemistry is concerned with the synthesis, characteristics, and uses of heterocycles.When considered as a group, heterocyclic derivatives fall into two categories: aromatic and non-aromatic [10]. The majority of medicines fall within the category of heterogeneous substances. All live cells' metabolism depends heavily on heterocyclic compounds, many of which are five- and six-membered molecules with one to three heteroatoms in the nucleus. The compounds may be the pyrimidine and

purine bases of DNA, and these heterocyclic compounds may be isolated or fused heterocyclic systems [11]. The amino acids proline, histidine, and tryptophan, as well as the vitamins and coenzymes precursors thiamine, riboflavin, pyridoxine, folic acid, biotin, B12, and E families of the vitamins, are some of the common heterocyclic compounds used in pharmaceuticals [12].

2- five-membered heterocyclic compounds

Five-membered heterocyclic compounds have drawn a lot of attention over the past decades due to their important role in biological processes and widespread application in pharmaceutics, medicine, materials science, and the synthesis of natural products. These compounds are well recognized for being widely employed as precursors in the development of dyes, pesticides, herbicides, and other agrochemicals [13]. Over the past few decades, there has been a tremendous increase in the amount of literature on five-membered heteroaromatic rings (fig. 1)[14].

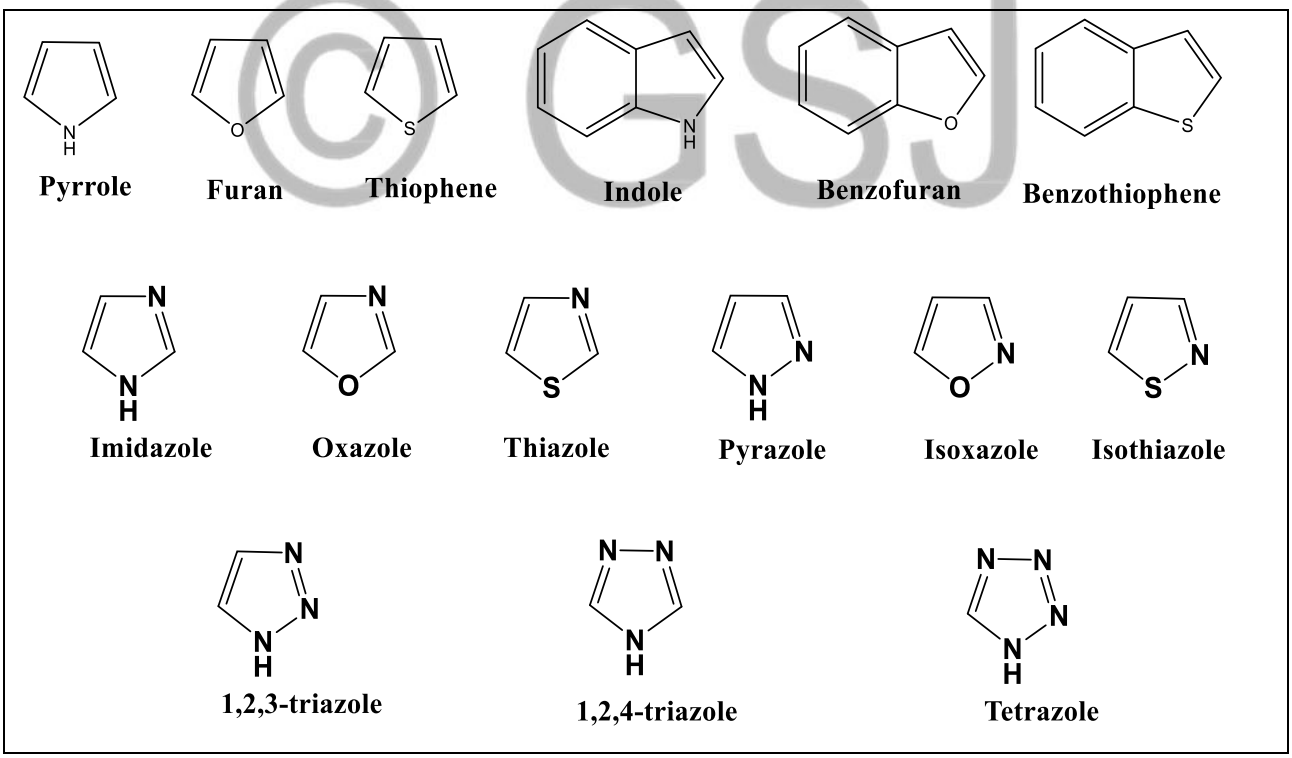

Figure 1: Chemical Structures of Five-Membered Aromatic Heterocyclic.

2.1- Five-membered heterocycles containing one heteroatom

This category includes the compounds pyrrole, furan, thiophene, and their benzo-fused derivatives such as indoles, benzofurans, and benzothiophenes. These rings make up an important class of aromatic heterocycles with five members, which are the building blocks of numerous medicinal compounds. As there are an excess of -electrons in these heteroaromatic rings (six electrons are distributed among five atoms), they are regarded as electron rich systems [15].

2.1.1- Pyrroles

Pyrroles are significant heterocycles that are widely employed in material science1 and are present in naturally occurring and crucial compounds for human life [16,17]. Many different bioactive substances and natural compounds, such as the widely used medicine atrovastatin calcium and significant anti-inflammatory, anti-tumor, and immunosuppressive medications, contain pyrroles [18,19]. Numerous natural compounds, including vitamin B12, chlorophyll heme, bile pigments, and pyrrole alkaloids generated from marine sources, have pyrrole derivatives in their structural makeup. The structures of vitamin B12 and chlorophyll heme both contain four pyrrole rings [20]. Additionally, pyrrole derivatives can be found in the majority of pharmacological structures. Biological functions of pyrrole derivatives include antibacterial [21], cholesterol reduction [22], antidiabetic [23], antiviral [24], fungicidal [25], antiasthmatic [26], antioxidant [27], antitubercular [28], and tyrosine kinas inhibiting agents [29]. Examples of pyrrole compounds with biological activity are shown in (fig. 2). Atorvastatin, an inhibitor of HMG-CoA reductase, lowers cholesterol, whereas Lamellarin O, Q, and R have anticancer properties. Pyrrolnitrin has antifungal properties [30,31].

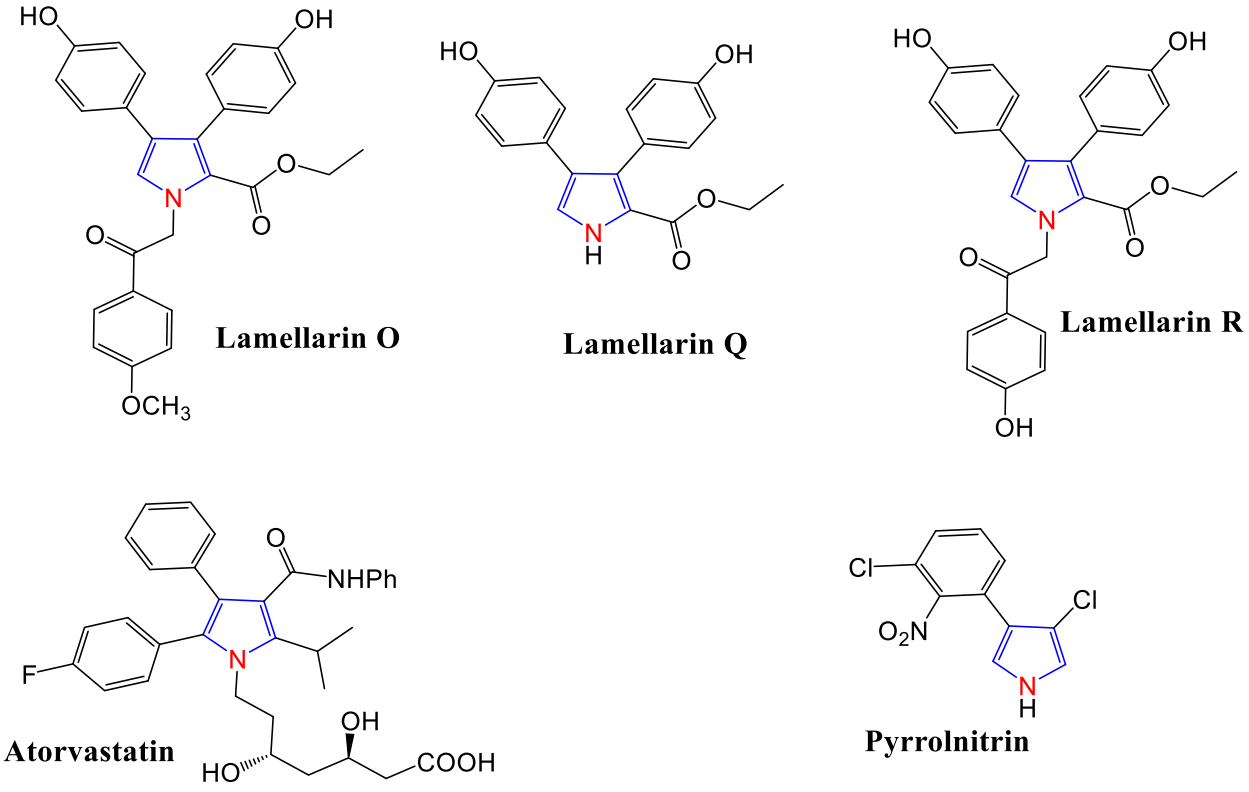

Figure 2: Structure of some pyrroles with biological activities.

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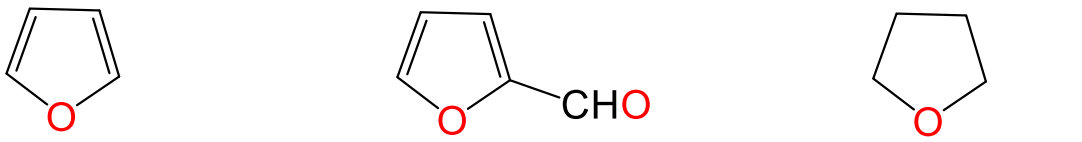
2.1.2- Furanes

Furan is an unsaturated, 5-membered heterocyclic ring molecule. From a chemical standpoint, it is the fundamental ring structure present in a vast variety of important commercial products [32]. Several other materials that are biologically active have the furan nucleus. Furans are typically used to refer to substances that include the furan ring as well as the tetrahydrofuran ring. Decarbonylation is a commercial method of making furan from furfural; the removal of carbon monoxide from furfural results in the production of furan. The equivalent that is saturated and devoid of double bonds is tetrahydrofuran[33].



Furan's electrophilic substitution reactions preferentially occur at the 2-position. In comparison to other compounds, its strong reactivity necessitates the use of extremely weak reagents [34]. In general, compounds with the furan ring make excellent solvents. Some substances are mixable with hexane and water. The ether oxygen adds polarity and increases the possibility of hydrogen bonding. The ether oxygen adds polarity and increases the possibility of hydrogen bonding [35]. Furan and its derivatives are naturally occurring substances that are generated in a variety of heated meals and beverages. Despite having a low threshold for odor, these substances considerably add to the sensory qualities of heated foods and beverages [36]. On the other hand, several furan-containing substances, like furosemide and ipomeanol (fig. 3), cause hepatic and renal necrosis in mouse and people as well as the development of potentially fatal pulmonary lesions in rats [37,38].

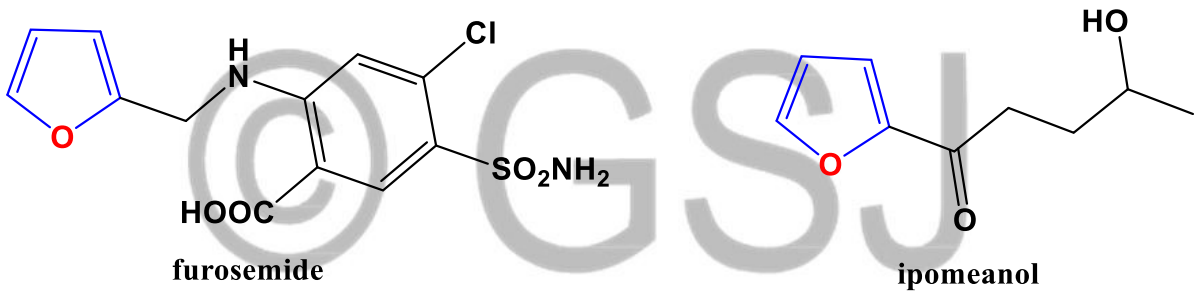


Figure 3: Chemical structure of compounds containing furan core.

2.1.3- Thiophene

Thiophene has a wide spectrum of biological and pharmacological properties, making it an essential pharmacophore. With a five-membered ring and sulfur as a heteroatom, thiophene belongs to a class of heterocyclic compounds, which having the formula C_4H_4S (fig.4). Petroleum and coal both contain thiophene and its compounds. Victor Meyer identified thiophene as a contaminant in benzene in 1882 [39,40]. He was the first to identify the ring system of thiophene, which he named from the Greek words

"theion," which means sulfur, and "phaino," which means brilliant. He isolated thiophene using its sulfonic acid derivative [41]. The stable liquid simple thiophenes have a boiling point that is the same as the corresponding benzene and a similar odor [42].

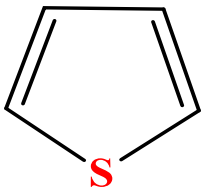
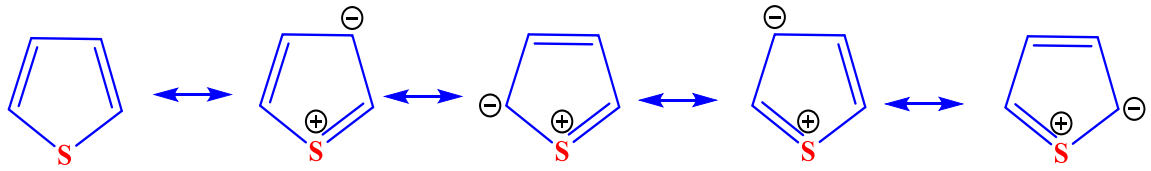


Figure 4: Structure of thiophene ring.

The liquid thiophene is hazardous, flammable, colorless, and has a benzene-like odor when it is at room temperature. The majority of organic solvents, including ether and alcohol, are soluble in it, but water is insoluble. Many agrochemicals utilize thiophenes as building blocks [41]. Thiophene's structure is similar to that of pyrrole, and because it contains a pi electron cloud, it behaves like a highly reactive benzene derivative. Organosulfur compounds found in petroleum and other products made from fossil fuels are largely covered by thiophene derivatives [43].

Thiophene is classified as an aromatic compound since it complies with the Huckel rule for 4n + 2 electrons. In the thiophene structure, the sulfur atom serves as an electron-donating heteroatom by giving the aromatic sextet two extra electrons. Thiophene is therefore regarded as an electron-rich heterocycle (Scheme 1)[44].



Scheme 1: Resonance structures of thiophene ring.

A monocyclic substance thiophene can be fused with other heterocyclic systems to create new heterocyclic systems with intriguing biological properties [45]. Several pharmacologically active chemicals and certain natural items include thiophene nuclei. Thiophene derivatives are important in medicinal chemistry because of the therapeutic uses they have [46]. It is a crucial part of several commercially marketed medications,

including Tipepidine, Timepidium bromide, Dorzolamide, Ketoconazole, Etizolam, Sertaconazole, and others[47].

2.2- Five-membered heterocycles containing two heteroatom

This is a large and structurally diverse group consisting of two heteroatoms in a five-membered aromatic heterocycle. The bulk of these ring configurations can be produced from pyrrole, furan, and thiophene by substituting one of the methine (-CH group) atoms with a sp2-hybridized nitrogen atom [48]. The structural variety of this set of heterocycles is caused by the variation in the position of extra nitrogen. The characteristics of the resultant rings are significantly altered when a nitrogen atom replaces an extra methine in pyrrole, thiophene, and furan [49]. The biotransformation pathways of the heteroaromatic rings can also be influenced by the second heteroatom's location and its electronegativity. Imidazole, oxazole, and thiazole rings, for instance, are vulnerable to oxidation processes, whereas isoxazole or isothiazole rings undergo reduction [50].

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2.2.1- Imidazoles

Imidazoles, which have nitrogen atoms at positions 1 and 3 in the ring, have been studied for more than 160 years. Henrich Debus first described it in 1858 (fig. 6) through the reaction of glyoxal, formaldehyde, and ammonia, which produced lower yields [51]. Radziszewski's group reported trisubstituted imidazoles from a mixture of a-diketones, aldehyde, and two equivalents of ammonia in alcohol in 1882, further developing the concept. Weidenhagen and Herrmann also reported producing imidazoles in 1935 with good yields via condensation of a-hydroxy ketones, ammonia, and aldehydes in the presence of hydrogen sulfide, followed by cupric acetate as an oxidant. A high yield of tetrasubstituted imidazoles was also produced by substituting amine for one equivalent of ammonia [52].

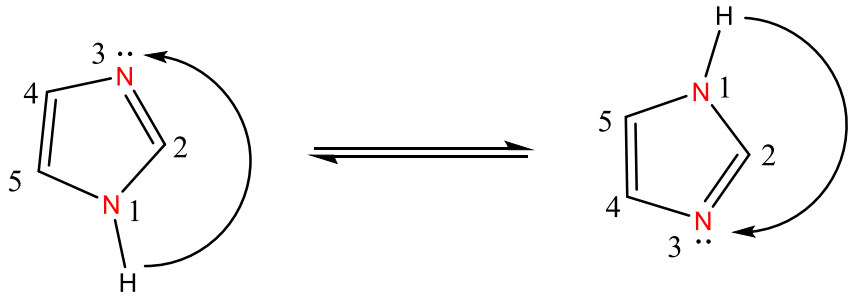

Figure 6: Tautomeric forms of imidazoles.

The heteroaromatic imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar, five-membered molecule containing 3C and 2N atoms in the 1 and 3 positions. Attacks with electrophilic and nucleophilic chemistry might damage amorphous nature. High thermal, acid, base, oxidation, and reduction stability. Because of the sextet of π-electrons in the compound—two from the protonated nitrogen atom and one from each of the other four atoms in the ring—it is categorized as aromatic [53]. The broad biological actions of imidazole and its derivatives, as well as their usage in synthetic chemistry, have given them a tremendous amount of significance. Imidazole compounds exhibit a wide range of pharmacological effects, including anti-inflammatory [54], analgesic, anti-convulsant [55], and antitubercular [56] activities. Due to the significant functions that imidazole and its derivatives play in biological systems, particularly in enzymes as proton donors and/or acceptors, coordination system ligands, and the building blocks of charge-transfer processes, they are of tremendous significance. The amino acids histidine and purines, which make up many of the most significant bases in nucleic acids, are among the naturally occurring compounds that include the imidazole nucleus [57]. Many commercially available therapeutic drugs (fig. 7) contain an imidazole ring in their chemical structure, such as: clemizole, etonitazene, enviroxime, irtemazole, astemizole, omeprazole, pantoprazole, thiabendazole, nocodazole [58], metronidazole, nitrosoimidazole, and megazol [59].

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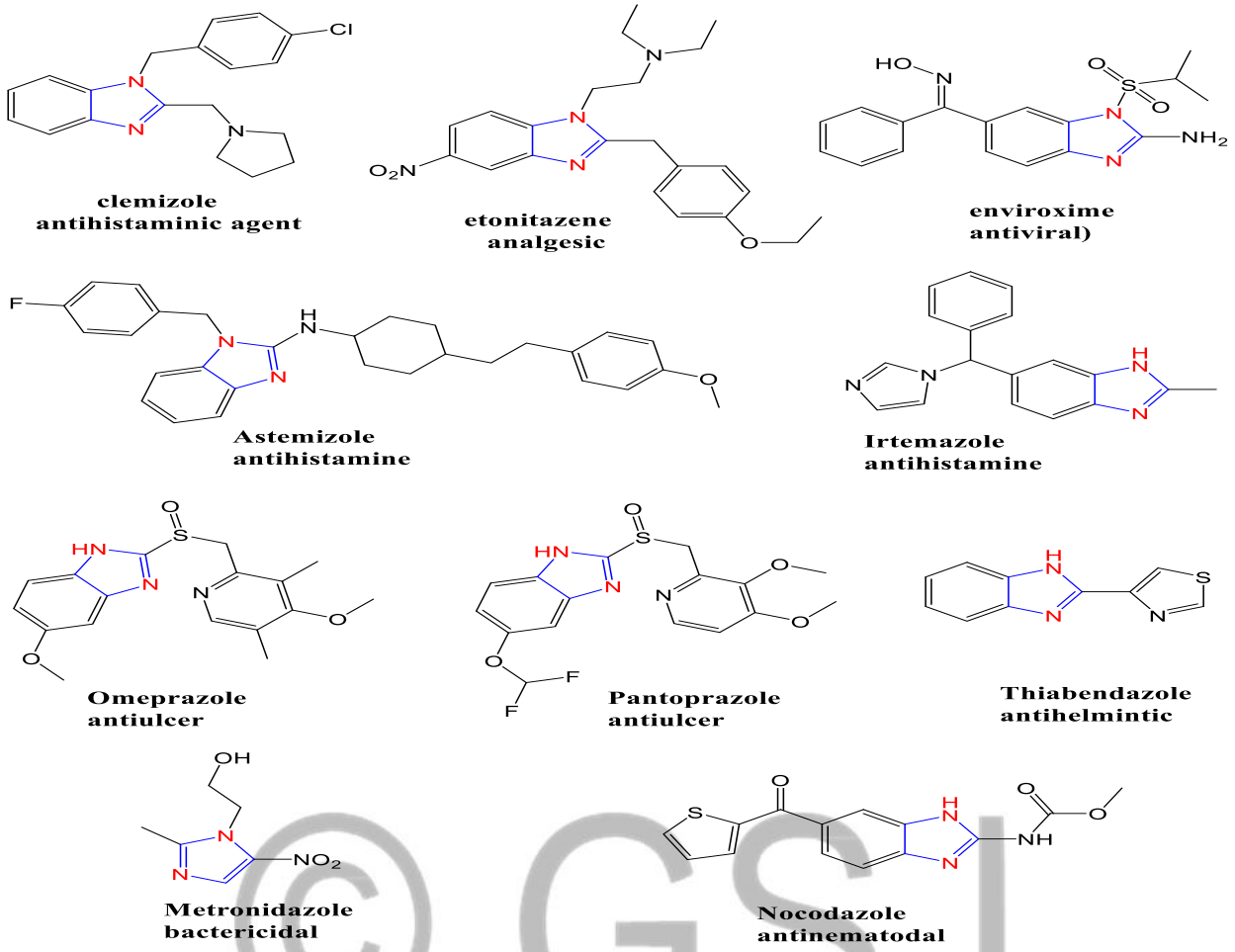
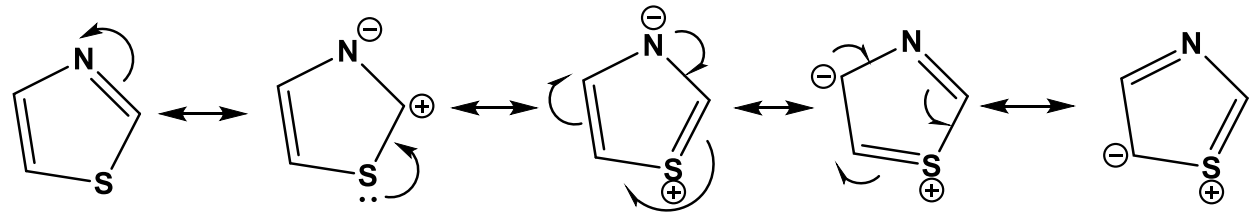


Figure 7: Many therapeutic drugs contain an imidazole ring.

2.2.2- Thiazoles

One of the classes of 5-membered aromatic heterocycles that has undergone the most thorough examination is thiazoles [60]. A thiazole scaffold has been extensively studied over the last two to three decades and has been shown to have a variety of biologically active properties, including antioxidant, antibacterial, antiviral, diuretic, anticancer, and anti-convulsant capabilities [61,62]. Both an electron-donating group (-S-) and an electron-accepting group (-N-) are present in thiazole. Thiazole's aromaticity was only achieved by delocalizing a non-bonding pair of electrons from the sulfur atom to fill the empty 6p electrons required by Hackle's rule (scheme 2) [60].



Scheme 1. Resonance structures of thiazole.

A variety of new compounds with a broad range of biological properties were produced by diversely moderating the thiazole ring in various locations. Heterocyclic thiazole compounds serve a crucial function in the clinical area to treat various bacterial illnesses in the human body because of their biological activity and availability in nature [63,64]. Thiazole-containing drugs have a wide range of pharmacological applications, making the thiazole nucleus an active nucleus. these pharmacological agents have been first described it in 1887 by Hantzsch and weber, such as Ceftriaxone, Cefotaxime, sulfathiazole , Ethaboxam, Abafungin, Ravuconazole, and Myxothiazole (fig. 8)[65-67].

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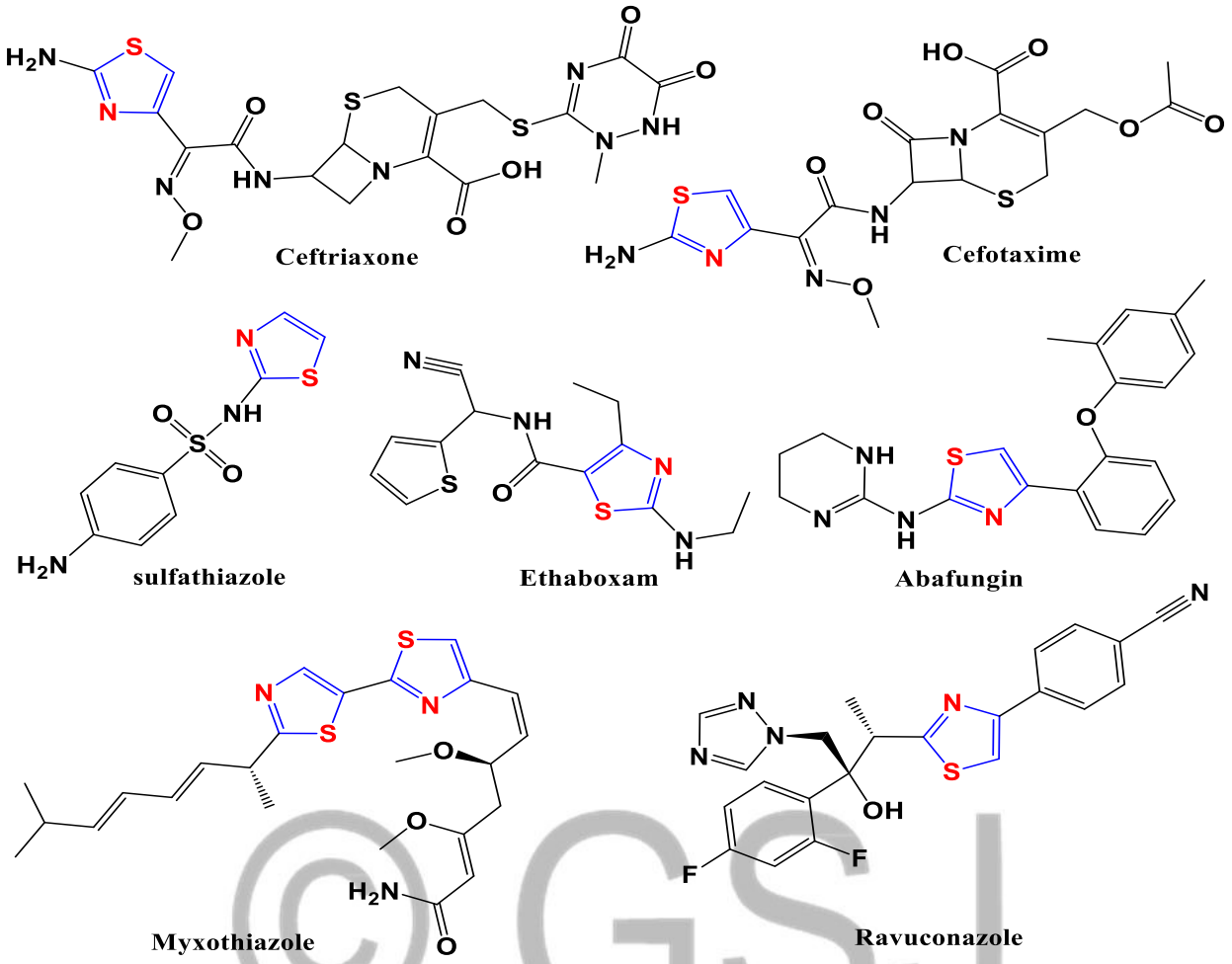

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Figure 8: pharmacological agents containing thiazole ring

2.2.3- Oxazoles

A well-known and significant heterocyclic motif called oxazole is characterized by having oxygen and nitrogen atoms in the 1,3 position of a five-membered ring. Hantzsch first described thiazole in 1887, and it was first synthesized in 1947. The oxazole ring was first seen in nature in the compound annuloline (fig. 9)[68]. Oxazolines are the name for partially reduced oxazoles and go by the names 2-, 3-, or 4-oxazoline, depending on where the double bond is located, whereas oxazolidine is the name for the fully saturated equivalent [69].

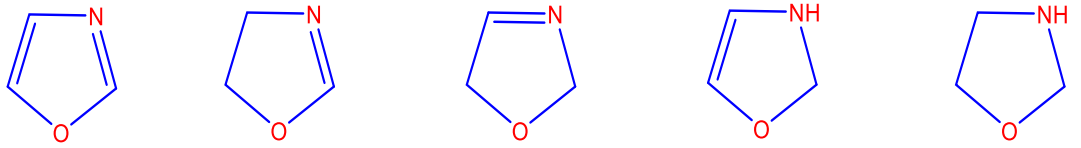

Figure 9: Chemical Structures of oxazole, oxazoline isomers, and oxazolidine

Oxazole has a dipole moment of 1.5D, is a less basic liquid, and is miscible with both water and organic solvents. Even though the oxazole ring contains a sextet of -electrons, its characteristics show insufficient delocalization of -electrons, which contributes to its low aromaticity and increased dienic character. It is incorrect to link this decreased aromaticity with instability [70]. Oxazole and its natural product-related derivatives, particularly those from marine environments, have been demonstrated to contain important biological actions, such as anti-tumor, anti-bacterial, anti-viral, antimalaria, and anthelmintic effects [71]. .Additionally, a number of oxazole-based pharmaceuticals, including linezolid [72] and virginiamycin [73], are undergoing clinical studies for the treatment and prevention of infectious illnesses. For a long time, the chemistry and biology of heterocyclic compounds have been interesting to research, and oxazole is one such moiety that has recently attracted attention due to its growing significance in the field of medicinal chemistry [74]. The pharmaceutical substances aleglitazar (antidiabetic), ditazole (platelet aggregation inhibitor), mubritinib (tyrosine kinase inhibitor), and oxaprozin (COX-2 inhibitor) all contain oxyazoles and their derivatives, (fig. 10)[75]

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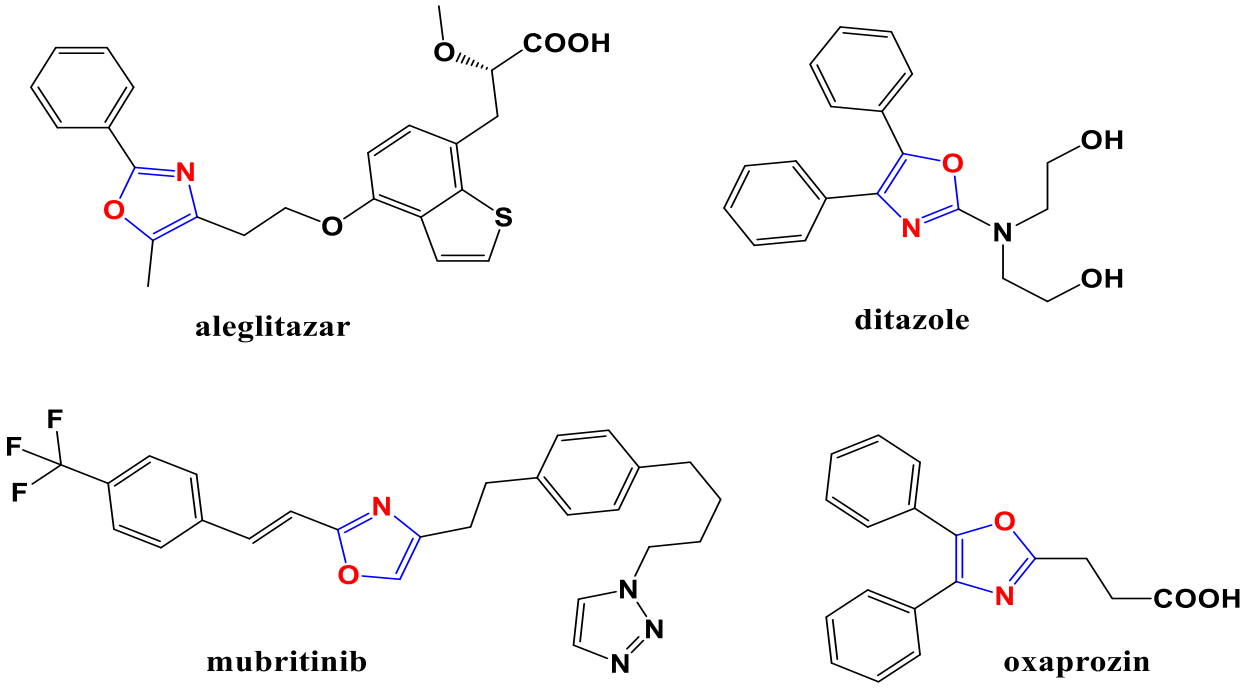

Figure 10: Some pharmaceutical compounds containing an oxazole ring.

2.3- Five-membered heterocycles containing three heteroatom

2.3.1- Triazoles

Triazoles are heterocyclic molecules with a five-membered aromatic ring made up of two carbon atoms and three nitrogen atoms. With the molecular formula $C_2H_3N_3$, the term "triazole" denotes any of a pair of isomeric chemical compounds (fig. 11)[76].

Figure 11: Structures of triazoles

The structural unit of the triazole, which is easily produced, can function as an amide, ester, carboxylic acid, and other heterocycles like pyrazole isosteres[77]. Triazole derivatives have a wide range of pharmacological properties, including antibacterial[78,79], anti-tubercular[80,81], anti-cancer[82,83], and anti-malarial activities[84,85]. This is likely due to their capacity to exert a variety of non-covalent

interactions that can increase their solubility and capacity to bind to bimolecular targets[86].

1,2,3-triazole products colorless, sweet-tasting, hygroscopic crystals with a melting point of 24 °C and a boiling point of 209 °C that are soluble in water. The 1,2,4-triazole compound has a melting point of 121 °C, a boiling point of 260 °C, and is water soluble[87].

1,2,3-triazoles are essential compounds in the pharmaceutical industry because of their characteristics. They exhibit strong aromatic stability because they are resistant to reduction, oxidation, and hydrolysis in both acidic and basic environments. The 1,2,3-triazoles have a large dipole moment (approximately 5 D)[88], and can actively engage in the creation of hydrogen bonds as well as dipole-dipole and π stacking interactions[89], which makes them more soluble and facilitates their binding to biological targets[90]. Sharpless developed the click chemistry method[91] that uses copper (I)-catalyzed azidealkyne cycloaddition (CuAAC) to produce a significant amount of 1, 4-disubstituted 1, 2, 3-triazoles in extremely high yields[92]. Potential drugs (fig. 12) derived from 1,2,3-triazoles include the anticancer drug carboxyamidotriazole(CAI)[93], the non-nucleosidereverse transcriptase inhibitor tertbutyldimethylsilylspiroaminooxathioledioxide (TSAO), the -lactum antibiotic Tazobactum, and Cefatrizine[94].

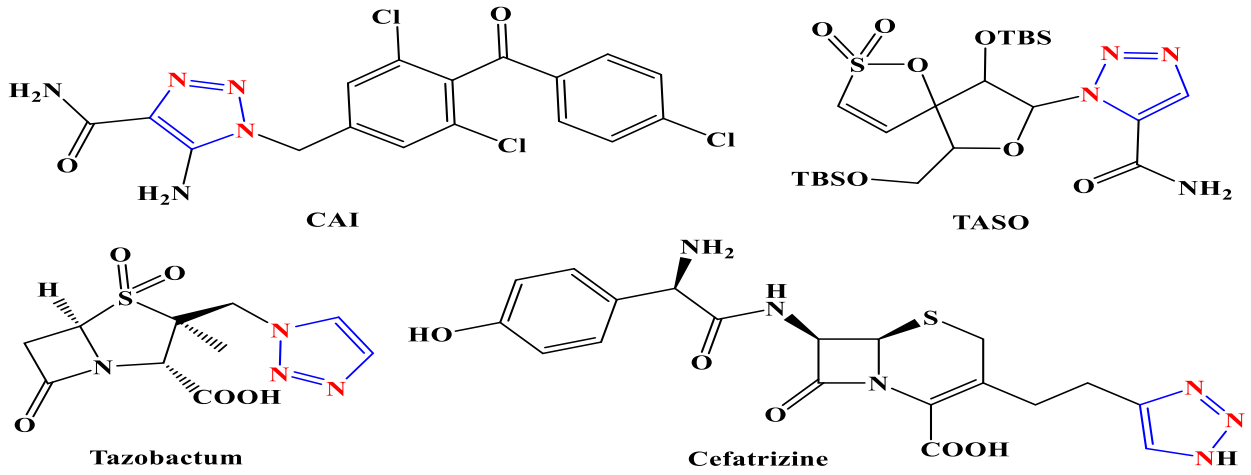

Figure 12: Potential drugs containing 1,2,3-triazole core.

On the other hand, the 1,2,4-triazole ring may be in equilibrium between the 1H-form and the 4H-form. The computed energy disparities between azole tautomers show preference for the 1H over (fig. 13)[95].

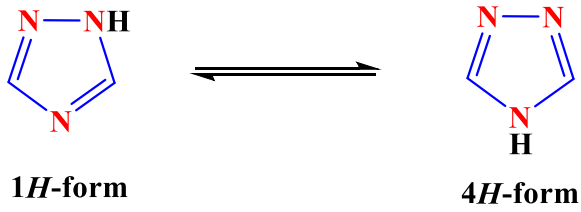

Figure 13: tautomeric forms of 1,2,4-triazole

A wide range of biological actions are displayed by 1,2,4-triazoles and their fused heterocyclic derivatives. Numerous therapeutically significant drugs used in medical treatment, including ltraconazole, alprazolam, ribavirin, trazodone, and letrozole which all contain the 1,2,4-triazole core (fig. 14)[96].

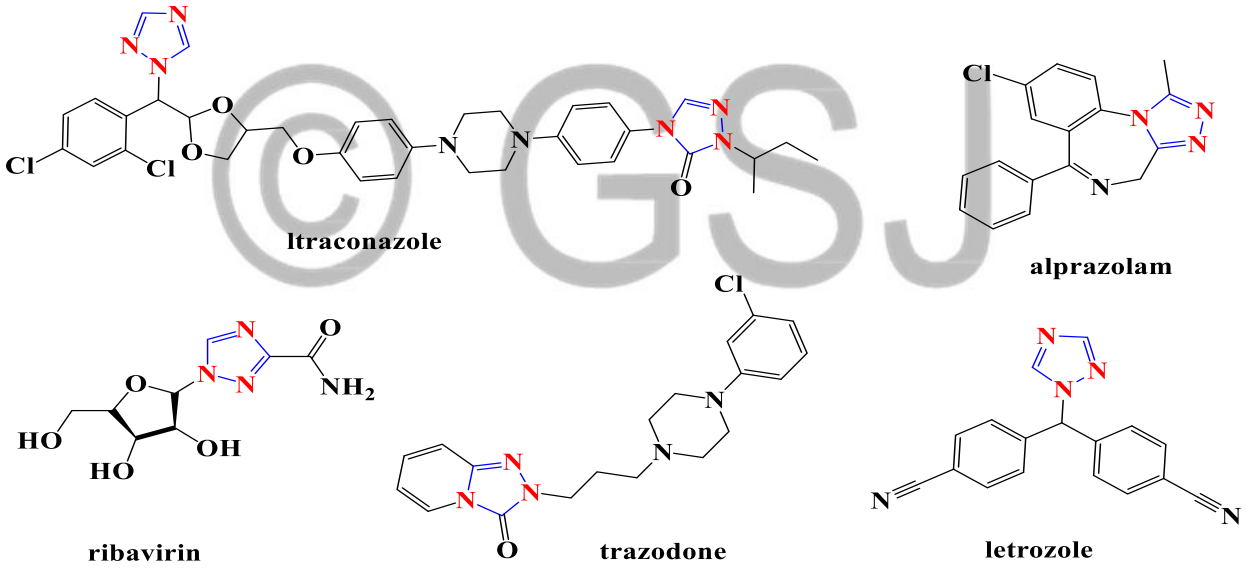

Figure 14: Some drugs containing 1,2,4-triazole ring

It is known that 1,2,4-triazole moieties interact strongly with heme iron, and aromatic substituents on the triazoles are very effective for interacting with the active site of aromatase. Other laboratories reported the same biological activity of the triazole family[97].

2.3.2- Oxadiazole

Oxadiazole is a five-membered heterocycle having two carbon atoms, two nitrogen atoms, one oxygen atom, and two double bonds[98]. By substituting two -CH= groups with two pyridine-typed nitrogens (-N=), the oxyadiazole moiety can be produced from furan. As a result, depending on where the nitrogen atom is located in the ring, there should be a potential for four different oxadiazole isomers (fig. 15)[99].

Figure 15: Isomers of oxadiazole

Due to the additional heteroatom's inductive impact, oxadiazole is a relatively weak base. Oxadiazole, as we are aware, contains two pyridine-type nitrogen atoms (-N=), which results in a decrease in the aromaticity of the oxadiazole ring and, as a result, causes the oxadiazole ring to exhibit the conjugated diene property[99]. An essential heterocyclic ring called oxadiazole is found in many biologically active compounds, including those with fungicidal, bactericidal, anticancer, and antitubercular properties[100]. Clinically, a variety of medicinally effective therapeutic compounds that containing oxadiazole moiety are utilized to treat a variety of disease states (fig. 16)[101,102].

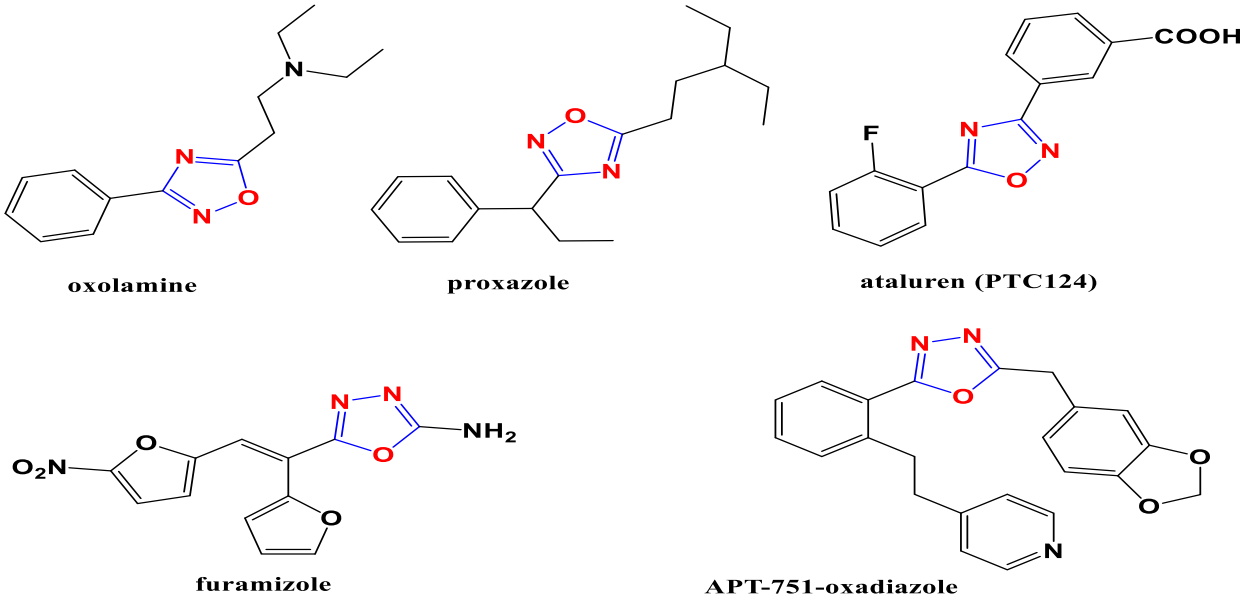

Figure 16: Chemical structure of some therapeutic drugs containing the oxadiazole ring.

2.3.3-Thiadiazole

Thiadiazole is one of the most important a five-membered heterocyclic compound that containing one sulfur and two nitrogen atoms. It occurs in nature in four isoforms: 1,2,3-thiadiazole, 1,2,4-thiadizaole, 1,2,5-thiadiazole and 1,3,4-thiadiazole (fig. 17)[103]. Given that thiadiazole is the bioisostere of pyrimidine and oxadiazole, it is not surprising that substances containing this moiety have a wide range of pharmacological properties, such as antiviral, antibacterial, antifungal, antiparasitic, anti-inflammatory, and anticancer activities [104].

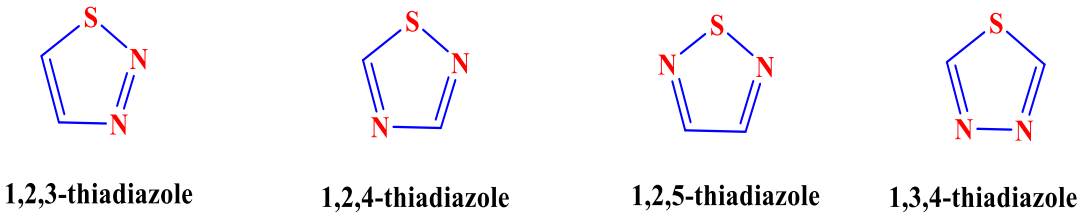

Figure 17: structures of thiadiazole isoforms.

The most significant component of a variety of natural products, a wide range of medications, and medical agents is thiadiazole. Since the identification of strong sulfa medicines containing this nucleus, the rate of advancement in the field of thiadiazole

has significantly increased [105]. Thiadiazole and its derivatives play a very well-established role as important scaffolds in pharmacology. Among the four thiadiazole isomers, 1,3,4-thiadiazoles exhibit a wide range of inhibitory actions in pharmaceutical applications. Commercially accessible medications made from 1,3,4-thiadiazole are listed in (fig. 18) along with their names and structural details. These 1,3,4-thiadiazole-based medications include Acetazolamide and Methazolamide, which are both used to treat glaucoma[106]. In addition, 1,2,3-Thiadiazoles are important heterocyclic compounds, both present a wide spectrum of biological activities[107]. Furthermore, the features of the 1,2,3-thiadiazole ring's simple breakdown into low molecular weight compounds by the release of N_2 encourage the use of its derivatives as possibilities for non-toxic, ecologically friendly pesticides[108]. There are numerous therapeutically effective commercially available medications containing 1,2,3-thiadiazole ring in their chemical structure (Fig. 18)[109]. On the other hand, A significant group of heterocycles known as 1,2,4-thiadazoles have garnered a lot of attention for their biological activity. 1,2,4-thiadiazole system has been found to have several extremely intriguing medicinal potential. Cefozopram[110], an antibiotic, is currently the only form of 1,2,4-thiadiazole medication that is used commercially, but there are other synthetic compounds related to this system that have a variety of biological properties[111], such as, thiadiazole SCH-202676 and KC 1229, (fig. 18)[112,113].

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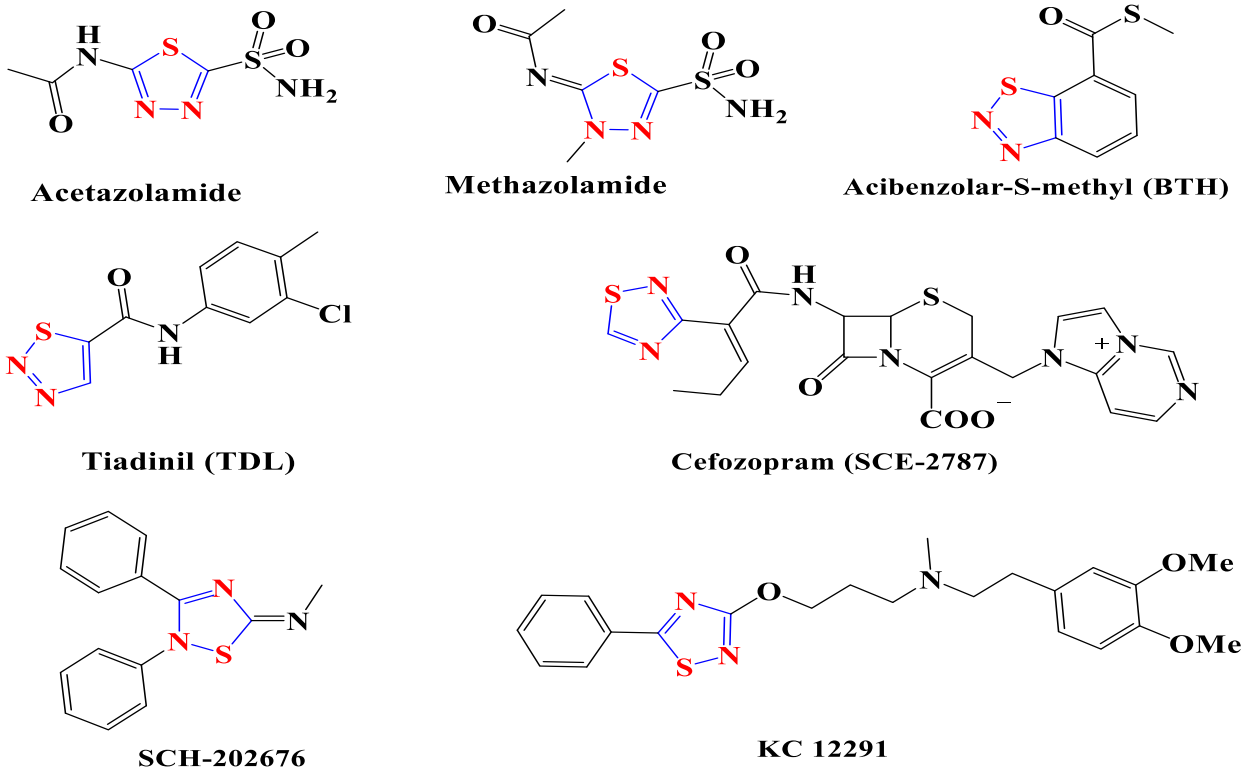

Figure 18: Some therapeutic medications that contain 1,2,3-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole moiety in their chemical structures.

Conclusion

During the past decades of the history of organic and pharmaceutical chemistry, heterocyclic compounds have proven their great importance in the medical and therapeutic field for treating many different diseases. Among the most important of these pharmaceutical compounds that were discussed in this brief review are those that contain five-membered heterocyclic aromatic in their chemical structure, due to their possession of many therapeutic and biological activities, such as: anticancer, antitubercular, antimicrobial, antidiabetic, antiinflammatory, anticonvulsant, antioxidant activities. This review gives an overview of the wide spectrum of pharmacological activities exhibited by five-membered heterocyclic aromatic. The importance of these core can be magnified by carrying out further studies on its possible substitution and thus to synthesize better agents that can have strong future commitments.

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