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Chapter 11: Synthesis, physical properties, and biological behaviour of synthetic aromatic heterocyclic compounds and their derivatives

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Abstract: Aromatic heterocyclic compounds are a versatile class of organic compounds that are categorized by incorporating one or heteroatoms such as nitrogen, oxygen, or sulphur. The presence of non-carbonaceous exhibits the unique electronic configurations, structural versatility, and chemical and thermal stability. These heterocyclic compounds play a vital role in various areas of chemistry, particularly in the areas of biological applications. This chapter provides an overview of the heterocyclic compounds such as pyrrole, pyridine, quinoline, imidazole, and azole derivatives with their significant properties and their application in biological applications.

Keywords: Heterocyclic compounds, ring structure, biological applications, physical properties.

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1 Introduction

Aromatic compounds are a class of compounds that are widely used in various areas of chemistry. Nowadays, the heterocyclic compounds, such as nitrogen (Mallappa et al., 2025), oxygen (Dai et al., 2025), and sulfur (García-Valverde & Torroba, 2005) etc. plays a vital role due to its unique structure, improved electronic and chemical properties differ from the other aromatic compounds. These enhanced properties make the heterocyclic compounds a superior material in the area of biological applications. These heterocyclic compounds are both naturally derived and synthesized via chemical-derived compounds. There were versatile, naturally available heterocyclic compounds such as Alkaloids, Flavonoids, Coumarins, Terpenoids, Xanthones, Lignans, etc. Similarly, the synthesized heterocyclic compound derivatives such as Pyrrole, Furan, thiophene, azoles, quinolines, etc.,

The naturally derived heterocyclic compounds not only play a vital role in all the medicinal and biological activities. Apart from the naturally derived heterocyclic compounds, some synthetic and modified compounds from natural sources are available. These heterocyclic frameworks are central to the development of numerous pharmaceutical agents, including anticancer drugs, antimalarials, antivirals, and antihypertensives. Apart from the pharmaceuticals, heterocyclic compounds are also instrumental in the formulation of agrochemicals such as herbicides, fungicides, and insecticides, as well as in diagnostic imaging agents, dyes, and functional materials in electronics and optoelectronics. Even though many heterocyclic organic compounds are employed in various fields, this chapter mainly focuses on the synthetic methods, characterization techniques, and their application in medicinal and organic chemistry of the heterocyclic compounds.

2 Literature review

The heterocyclic compounds, integrating various materials, gained the attention of the researchers. Thanh-Dao Tran et.al. have synthesized a novel heterocyclic chalcone via Claisen-Schmidt condensation in the presence of substituted benzaldehydes and heteroaryl methyl ketones, evaluated for their antibacterial activity (Tran et al., 2012). Anastasiya S. Sokolova et.al., have synthesized the camphor-based a series of camphor-based nitrogen-sulfur containing heterocycles like 1,3-thiazolidin-4-one and thiazoles containing a 1,7,7-trimethylbicyclo[2.2.1]heptan scaffold, which was used to treat the smallpox, cowpox, monkeypox virus, and vaccinia virus belonging to the Poxviridae family, and Orthopoxvirus genus. The results indicate that the synthesized thiazole derivative inhibits the reproduction of vaccina virus with the IC50 value of 2.4-3.7 micromolar range, possessing minimal cytotoxicity (Sokolova et al., 2018). Mabrouk Horchani et.al., developed a new class of compounds known as pyrazolo[3,4-

d]pyrimidin-4(5H)-one derivatives through a condensation reaction involving pyrazolopyrimidinone-hydrazide. These synthesized molecules were subjected to computational studies, including molecular docking and ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictions, to assess their potential as inhibitors of the main protease (Mpro) associated with the Omicron variant of SARS-CoV-2. The theoretical analysis suggested that the structural modification involving the attachment of a 2,5-pyrrolidinedione unit and a free carboxylic acid group to the pyrazolopyrimidinone scaffold may enhance antiviral activity. (Horchani et al., 2022).

3 Methods and materials

This experimental section signifies the various synthesis methods employed for the preparation of aromatic heterocyclic compounds.

3.1. Synthesis of nitrogen-containing aromatic heterocyclic compounds

3.1.1. Synthesis of pyrrole

In the pyrrole synthesis, it was prepared by treating furan and ammonia in the presence of Al2O3, and also, the pyrrole derivatives are synthesized using the Hantzsch synthesis. Fiest et.al., used β-ketoesters, α-haloketones, and primary amines for the synthesis of pyrrole derivatives (Feist, 1902). Paal-Knorr pyrrole synthesis 1,4 dicarbonyl compound reacts with a primary amine to yield a substituted pyrrole, and Knorr pyrrole synthesis involves the reaction of α-amino ketone with activated methylene to yield a pyrrole derivative (Paal, 1884).

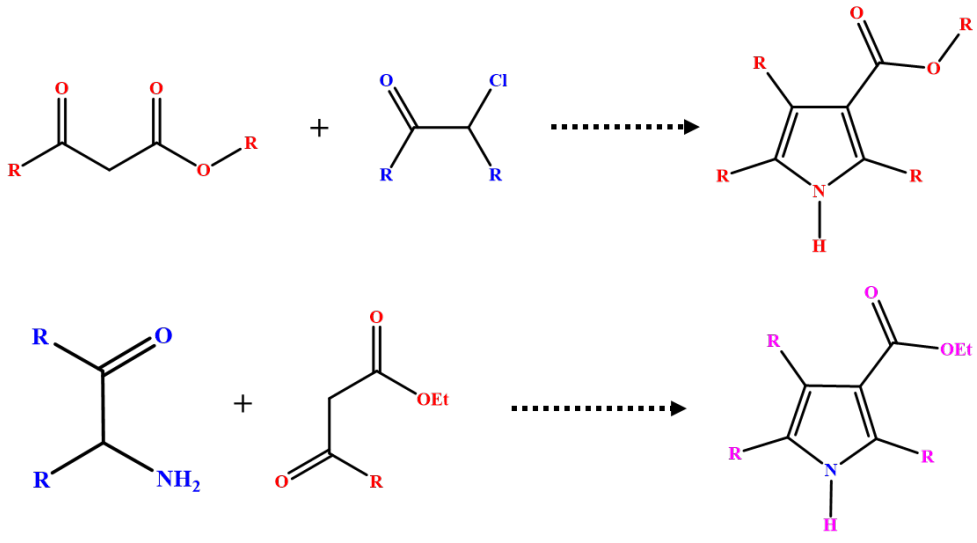

Fig. 3.1. Synthesis of pyrrole

3.1.2. Synthesis of pyridine

Commonly, the Pyridine was synthesized using Chichibabin synthesis involves in condensation of aldehyde, ketone, α, β-unsaturated carbonyl compounds, with ammonia, yielding pyridine with a yield % of 30 (Frank & Seven, 1949). Similarly, in Hantzsch pyridine synthesis, the aldehyde reacts with 2 equivalents of β-keto ester in the presence of a nitrogen donor, yielding dihydropyridine on further oxidation, yields pyridine (Hantzsch, 1881).

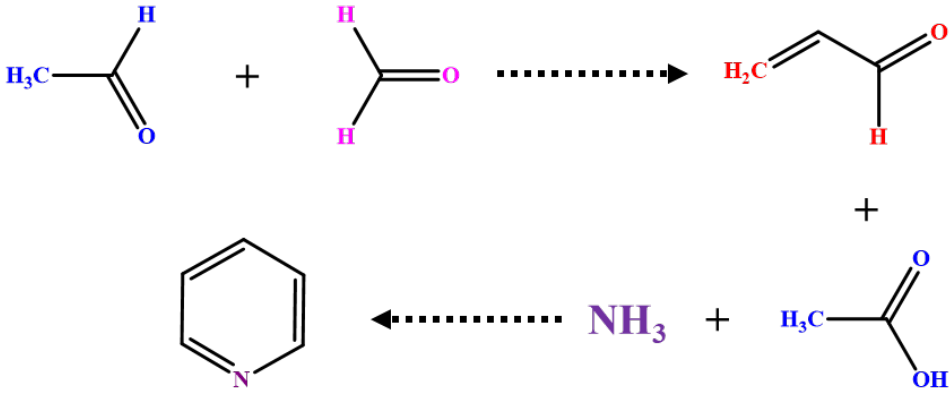

Fig. 3.2. Synthesis of pyridine

3.1.3. Synthesis of quinoline

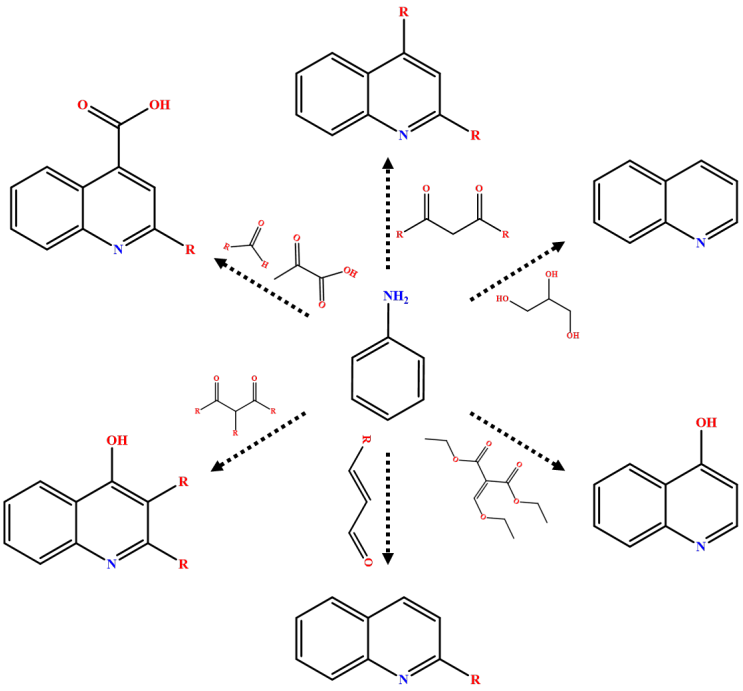

Fig. 3.3. Synthesis of quinoline

Aniline serves as a crucial starting material in the synthesis of quinoline and its derivatives through various established methods. In the Skraup synthesis, quinoline is obtained by heating aniline with glycerol, sulfuric acid, and an oxidizing agent like nitrobenzene. For comb-shaped quinoline compounds, aniline reacts with β-diketones. The Conrad-Limpach synthesis involves its reaction with β-ketoesters to form quinoline cores. Quinoline carboxylic acid derivatives are produced via the Doebner reaction, where aniline reacts with pyruvic acid. In the Doebner-Miller method, aniline reacts with α,β-unsaturated carbonyl compounds to yield methyl-substituted quinolines. Additionally, in the Gould-Jacobs reaction, aniline combines with ethyl ethoxymethylenemalonate to generate quinoline-based structures.

3.1.4. Synthesis of imidazole

At first, the imidazole was synthesized by Heinrich Debus, so the reaction was named the Debus Radziszewski reaction. in this reaction, glyoxal, in the presence of aldehyde and ammonia, condenses to form glyoxaline, commonly called imidazole.

3.1.5. Synthesis of azole

Thiazole can be synthesized by the reaction of 1,3-dipoles, with a positive and negative charge separated by three atoms, and dipolarophiles, which are unsaturated molecules that can participate in cycloaddition. the reaction of a nitrile imine (a 1,3-dipole) with a

thiazole-2(3H)-thione (a dipolarophile), leading to the formation of a spiro compound (Budarina et al., 2007). Triazoles can be synthesized by [3+2] cycloaddition between azides and alkynes in the presence of Copper (Cu) or nitriles (El Malah et al., 2025). And for the tetrazole synthesis, S. Vorona et.al., employed Thiocyanates that react with nitriles in the presence of zinc (Zn) and sodium azide, yielding 5-substituted 1*H*-tetrazoles (Vorona et al., 2014).

3.2. Synthesis of oxygen-containing aromatic heterocyclic compounds

3.2.1. Synthesis of furan

Industrial synthesis of furans occurs by reaction, decarboxylation of furfural and the reaction catalyzed by palladium (Pd), or by the oxidation of 1,3-butadiene and the reaction catalyzed by copper (Cu) (Hoydonckx et al., 2007). For the synthetic preparation of furan Feist–Benary synthesis involves in alkylation of 1,3-diketones with α-bromoketones, and followed by the dehydration of a hydroxydihydrofuran (Hou et al., 1998). The most common and efficient method for the synthesis of furan is the Paal-Knorr synthesis, where the 1,4-diketones are protonated with a hydroxy group, followed by dehydration, resulting in the synthesis of furan.

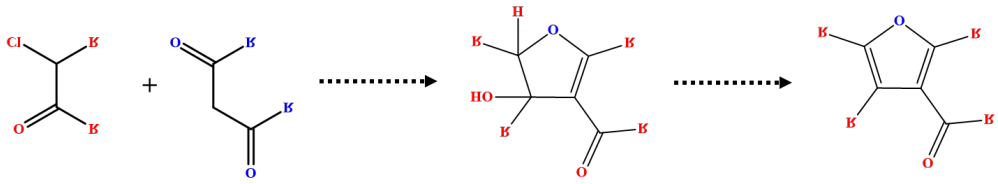

Fig. 3.4. Synthesis of furan

3.2.2. Synthesis of oxazole

The reaction between aldehyde and cyanohydrin in the presence of hydrochloric acid and ether yields an aliphatic substituted oxazole. This method was discovered by Emil Fischer, so it is named after Fischer oxazole synthesis (Palmer & Venkatraman, 2003). In 1910, Sir Robert Robinson and Siegmund Gabriel discovered that the intramolecular reaction between the 2-acylamino-ketone, followed by a dehydration to give an oxazole.

3.3. Synthesis of sulphur and other heteroatom-containing aromatic heterocyclic compounds

3.3.1. Synthesis of thiophene

The first and foremost method for the synthesis of thiophene and derivatives involves Paal–Knorr synthesis, where the 1,4-diketones react with phosphorus pentasulfide, yielding thiophene. This mechanism involves the initial formation of thioketone, the

protonation, followed by dehydration yields thiophene (Campaigne & Foye, 1952). The Gewald reaction is also employed especially for the synthesis of amino thiophenes. It involves the condensation of an aldehyde or ketone with α-cyanoester in the presence of sulphur, yielding amino thiophene.

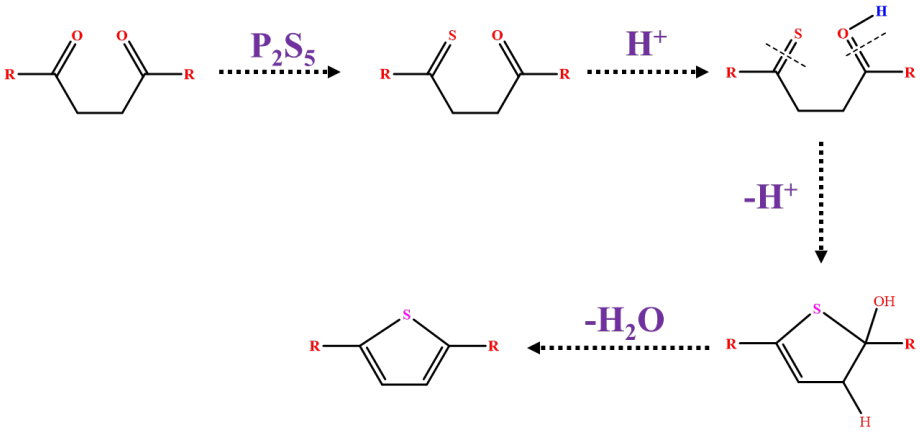

Fig. 3.5. Synthesis of thiophene

4 Results and discussion

This section explains the properties of the aromatic heterocyclic compounds.

4.1. Pyrrole

Pyrrole (C_4H_4NH) is a Nitrogen-containing heterocyclic compound (Ledade et al., 2023), and it was detected by F.F. Runge in coal tar and later isolated from bone pyrolysate (Ono & Erhard, 2011). Pyrrole is not a naturally occurring compound, but its derivatives are found in many natural products. It is a colourless, volatile liquid. in the presence of air, it is unstable and becomes dark (Armarego, 2017). Yuri G. Kappenberg et.al., have synthesized a pyrrole-hybridised spiro [chromeno[4,3-b]cycloalka [4,5]thieno [3,2-e]pyridin] cycloalkanes. Before proceeding with each step, proton and carbon NMR analyses were performed to assess the purity of the synthesized compounds. Later, the photophysical studies and the DFT analysis were performed, evidencing its physical properties (Kappenberg et al., 2025). Zhenpeng Cui et.al., synthesized a Polypyrrole using gamma rays (radiolytic method) (Cui et al., 2014). The UV spectrum reveals that the pure Pyrrole shows the absorption peak of 203 nm, and the FT-IR spectra shows the N-H vibrations around 3396 cm^{-1}, the peaks at 1571 cm^{-1} and 1467 cm^{-1} are attributed to the C-C ring stretching (Zhong et al., 2006), whereas the peak at 1047 cm^{-1} represents the deformation of C-C out of plane (Hazarika & Kumar, 2013). The peak at 726 cm^{-1} is owing to the C-H wagging

vibration. Yuehan Chen et al. have prepared a pyrrole cobalt composite. The XPS spectrum reveals that the nitrogen (N1s) spectrum of the pyrrole arises at ~400 eV.

4.2. Furan

Furan is an oxygen-containing five-membered aromatic heterocyclic compound (Xu et al., 2016), which is toxic and can induce carcinogenic effects in humans. It exhibits a chloroform-like odour, and it is a highly volatile, colourless, flammable liquid at room temperature. In 1708, Carl Wilhelm Scheele synthesized the first furan derivative from 2-furoic acid. And Furan itself, prepared by Heinrich Limpricht, is called tetraphenol (C_6H_5OH) (Limpricht, 1870). Gary Schulte et.al., synthesized five different types of furans with chlorine, Methoxy, nitrobenzene substituted, and amino functionalized furan and employed them for hypoglycemic activity, anti-inflammatory, and antidepressant activities (Schulte et al., 1980). There were more significant activities of the furan in the area of antimicrobial activities are employed so far. Kalyaev MV et.al., have synthesized 3-Aryl-3-(Furan-2-yl) Propanoic Acid, a furan derivative, with the Friedel-Crafts alkylation reaction. The prepared derivatives exhibit potent antifungal activity towards yeast-like fungi, *Candida albicans* at a concentration of 64 µg/mL, and inhibit the growth of *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) (Kalyaev et al., 2022) and Elif Logˇogˇlu et.al., successfully synthesized a range of organic compounds. Using the disc diffusion method, the antimicrobial activity was tested against various gram-positive bacteria, such as *S. aureus* (ATCC 25923), Staphylococcus enteritidis (ATCC 1376), *Pseudomonas aeruginosa* (ATCC 29212), *Bacillus subtilis* (RSKK 244), and *Bacillus megaterium*, as well as gram-negative bacteria, including *E. coli* (ATCC 27853) and *Listeria monocytogenes* (ATCC 7644). Additionally, antifungal activity was assessed against the fungal strain *Micrococcus luteus* (NRRLB), all these furan derivatives possess significant activity towards all pathogens (Loğoğlu et al., 2010).

4.3. Thiophene

Thiophene is a five-membered sulfur-containing aromatic heterocyclic compound with the chemical formula of (C_4H_4S), with a chemical name of thiacyclopentadiene (Chaudhary et al., 2012), which exists in petroleum and coal, as a contaminant in Benzene (JA, 1972). The UV spectral studies of the thiophene derivative were investigated by Mujeeb Khan et al., revealing that the thiophene has an absorption band at 260 nm and 436 nm, corresponding to molecular transitions, respectively (Khan et al., 2017). Mazimba et.al., synthesized thiophene-based chalcone analogues through a condensation reaction between 2-acetylthiophene and various salicylaldehydes. The 1,5-diketone intermediates were obtained via a solvent-free Michael addition reaction involving cyclohexanone and 2-thienylchalcones that lacked hydroxyl substituents. These diketone derivatives served as crucial synthons for the

subsequent construction of diazepine scaffolds. In Michael addition, the nucleophile present in the cyclohexanone attacks the electron-deficient carbon present in the unsaturated chalcones, leading to the formation of an aliphatic carbon, resulting in the formation of a diketone. The biological activity was performed using the serial dilution method against a panel of microbial strains, including (*S. aureus)*,(*E. coli), Bacillus subtilis* (*B. subtilis), Pseudomonas aeruginosa* (*P. aeruginosa*), and Candida albicans. The results indicate that varying degrees of antimicrobial efficacy and the potential of thiophene-derived diazepines as bioactive agents (Mazimba, 2015).

4.4. Pyridine

Pyridine is a nitrogen-containing heterocyclic compound with the chemical formula (C_5H_5N), and its structure is similar to that of benzene, where the methine group was replaced by the Nitrogen heteroatom (=C-H-). It is an immiscible, weakly alkaline, highly flammable, and pungent fish smell (Vaganova et al., 2021) . The UV absorption spectra of pyridine reveal peaks at 250 nm and 262 nm, corresponding to the π-π* and n-π* transitions, with respect to the presence of different substituents in the moiety, such as electron donors or acceptors responsible for the bathochromic and hypsochromic shift in the spectra, respectively. The FT-IR spectrum shows that the pyridine derivatives possess the functional groups C=N, which display the vibration bands at 1582-1660 cm^{-1}, whereas the C=C appears around 1589-1599 cm^{-1} respectively (Jamale et al., 2018). Mark S. Veselov et.al., have synthesized as series of series of 5-oxo-4H-pyrrolo[3,2-b]pyridine derivatives, and the antibacterial activity of the compound was evaluated using the high-throughput screening (HTS) approach using a dual-reporter system, pDualrep2, enabling rapid screening while offering insights into the mechanism of action by detecting translation inhibition and SOS response induction. The most active compound demonstrated a MIC of 3.35 μg/mL against *E. coli*, with signs of translation inhibition and no activation of the SOS pathway, suggesting selective antibacterial action. Structural optimization led to several analogues with improved activity and favorable toxicity profiles.

4.5. Quinoline

Quinoline is a nitrogen-containing aromatic heterocyclic compound with the chemical formula (C_9H_7N), and it was first isolated from coal tar in an impure form by Runge. In 1842 Gergardt obtained it as a degradation product from quinine and colchicine (Matada et al., 2021) . It is a colourless liquid on exposure to light, becomes yellow, followed by brown, and it is highly soluble in hot water and organic solvents, but rather slightly soluble in cold water; it possesses moderate solubility. The absorption studies of the quinone show two different, distinct peaks at π-π* transition at 278 nm and 389 nm, and thus correspond to the presence of quinone moiety and the intramolecular charge transfer, respectively. The quinone exhibits the redox behavior

in the by (quinhydrone ⇔ hydroquinone) (Ravichandiran & Vasanthkumar, 2015). Duan et.al., synthesized two different 1,2-naphthoquinone derivatives, which were examined for their antibacterial activity towards positive and negative pathogens. As a result, both pathogens possess potent antibacterial activity towards both pathogens (Wang et al., 2015). Yennam et al. designed and synthesized a novel series of diaziridinyl quinone–isoxazole hybrid molecules, intending to explore their antibacterial properties. The biological evaluation involved screening all the synthesized derivatives for antibacterial activity against various microbial strains, as well as assessing their cytotoxic effects on human cancer cell lines A549 (lung carcinoma) and PC3 (prostate carcinoma). Among the tested compounds, 13h stood out due to its superior antibacterial performance. It demonstrated strong inhibitory activity against multiple clinically relevant pathogens, including *Staphylococcus aureus* MTCC 96, *S. aureus* MLS-16 MTCC 2940 (a methicillin-resistant strain), *Bacillus subtilis* MTCC 121, and *Klebsiella planticola* MTCC 530.

4.6. Imidazole

Imidazole is a naturally occurring five-membered aromatic compound with two hydrogen atoms in the moiety $(CH)_3(NH)N$. Generally, most of the alkaloids, namely Pilocarpine, Naamines, etc. Imidazole exists in two tautomeric forms, resulting from the ability of a hydrogen atom to shift between the two nitrogen atoms in the ring. This compound exhibits strong polarity, as indicated by its calculated dipole moment of 3.61 Debye, as aromatic due to the presence of delocalized pi-electrons and lone pairs present in the nitrogen atom. The imidazole possesses an amphoteric nature, which can act as both a proton donor and acceptor (Hossain, 2018). Smitha et.al., have synthesized the 2-chloroimidazole derivative and studied its reactivity using molecular dynamics and theoretical density functional theory, in which the compound exhibits potential antibacterial activity against Gram-positive and negative bacterial agents. Moreover, the molecular docking studies assess the binding interaction of the synthesized derivatives, indicating they act as inhibitors against the APO-Liver alcohol dehydrogenase enzyme. This evidence supports the 2-chloroimidazole derivatives as a suitable material for antibacterial agents. (Smitha et al., 2018). Renjith Thomas et.al., synthesized imidazole derivatives using solvent-free imidazole derivatives, confirmed by the NMR, FT-IR, and various spectroscopic techniques, along with the theoretical calculations using the density functional theory using the B3LYP basic set. The Molecular docking revealed strong binding of both compounds with Aspulvinone dimethylallyl transferase, indicating potential enzyme inhibition. Biologically, CLMPDI displayed broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, whereas BPCLDI was active only against *Staphylococcus aureus*.

4.7. Oxazole

Oxazole is an oxygen and nitrogen-containing aromatic heterocyclic compound at the first and third positions, respectively. It exhibits high thermal stability owing to the presence of pyridine-like nitrogen in the compound, and it was stable at room temperature (Turchi & Dewar, 1975). Wei Zhang et.al., have synthesized a novel Chiral 2-(substituted-hydroxyl) -3-(benzo[d]oxazol-5-yl) propanoic acid derivative and tested it against fungi, Gram-negative and Gram-positive bacteria. Thus, the synthesized compound delivers a good activity with a lower MIC in the *Candida albicans*, whereas the hydrophobic substitutes, para-tert-butyl, para-phenyl and para-benzyloxy on the phenoxyl side chain possess the remarkable activities against all Gram-negative and Gram-positive bacteria with MIC values between 1.56 and 6.25 mg/mL. Ram Prasad et.al., have prepared an oxazole derivative. The synthesized compounds were subjected to antimicrobial activity at the concentrations of 10µg, 20µg, and 30µg per ml. The synthesized compounds were tested at different concentrations, and 30 µg/mL showed the best antimicrobial effect. At this level, the compounds were able to stop the growth of both Gram-positive bacteria like *S. aureus* and *Bacillus cereus*, and Gram-negative bacteria such as *Pseudomonas aeruginosa* and *E. coli*. They also worked well against fungal strains like *Aspergillus niger* and *Aspergillus fumigatus*. The strong activity of the compounds damages the outer structure of microbes and they also block important functions inside the cells, such as protein or DNA production. In fungi, the compounds might cause stress by releasing harmful oxygen-based particles, which can damage cell parts. These combined effects stop the microbes from growing or kill them. Since the compounds work against different types of microbes, they may act in more than one way. This makes them good candidates for developing new antimicrobial medicines (Prasad et al., 2012).

Conclusions

Heterocyclic compounds have high demand in the field of biological applications owing to their significant physical and chemical properties. So, researchers try to separate and produce natural and synthetic heterocyclic compounds. A clear and in-depth discussion of the heterocyclic compounds is summarized in this chapter. Moreover, the synthetic methods are explained in detail. The physical properties of the nitrogen, oxygen, and sulfur-based compounds are discussed. Based on the properties, the biological applications of the heterocyclic compounds have been discussed in this chapter.

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