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A Study Of Synthesis Of Bioactive Heterocycles

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ABSTRACT

Many areas rely on heterocyclic compounds, which are essential in areas including materials science, agrochemicals, and medicines. These compounds have rings that include at least one element other than carbon. Heteroatoms like nitrogen, oxygen, or sulfur provide these compounds, which are the building blocks of many pharmaceuticals, their distinctive characteristics. Bioactive heterocycles play an essential part in contemporary organic chemistry, and this paper delves into their synthesis and importance. The study investigates their biological activity in relation to heteroatoms, as well as their uses and techniques of production. The search for new therapeutic agents is heavily focused on the development of efficient synthetic techniques for heterocyclic frameworks, which are present in over 90% of new medications.

Keyword: Bioactive heterocycles, Synthesis

INTRODUCTION

A large number of biological systems rely on heterocycles, which are organic molecules having rings that include an element other than carbon. Heterocycles are present everywhere in nature. Because of their versatility, bioactive heterocycle synthesis is an important part of contemporary organic chemistry. These compounds find use in many fields, including medicine, agriculture, and materials research. Research into these chemicals is essential for the creation of novel medicinal agents since they are the building blocks of many different types of medications. Heteroatoms like sulfur, nitrogen, or oxygen may coordinate to metal centers, undergo a variety of electrical interactions, or form hydrogen bonds, giving bioactive heterocycles their distinctive characteristics. Heterocyclic compounds' biological activity is heavily reliant on these interactions, which also affect the pharmacokinetic and pharmacodynamic profiles of the compounds and their binding to biological targets. Cyclocyclic compounds are defined as those in which all of the carbon atoms form a ring, whereas heterocyclic compounds are those in which at least one non-carbon element forms a ring. Heterocyclic rings containing heteroatoms other than nitrogen, oxygen, and sulfur are very rare.

Selenium, tellurium, and phosphorus are among the most uncommon. Conventional organic synthesis relies heavily on heterocyclic chemistry, which accounts for half of all organic chemistry research globally. Furthermore, they are crucial to a wide range of activities and businesses. It is well-known that the heterocyclic framework, an important link between biology and chemistry, is present in over 90% of newly-developed pharmaceuticals. When it comes to innovative scientific methods and innovations, heterocyclic compounds are king. **(Hussein & Khairou, 2014a)**

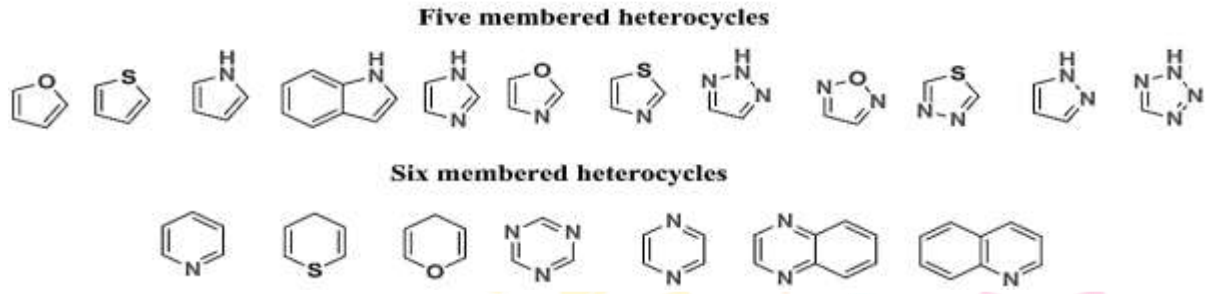


Figure I: heterocyclic skeleton

Heterocyclic moieties are now crucial to the functioning of any urbanized human civilization, in addition to their obvious biological and industrial importance. Heterocycles constitute the vast majority of pharmaceuticals that possess biological activity similar to that of natural compounds. So, scientists are always looking for new ways to mimic nature in an effort to create more effective medicines, insecticides, rodenticides, and weed killers. Biochemical reactions rely heavily on heterocyclic molecules, which are also necessary for cell survival. Cosmetics, reprography, data storage, plastics, solvents, antioxidants, and vulcanization accelerators are just a few of the many sectors that make use of these substances as additives and modifiers. In addition to this, they are strong building blocks for other naturally occurring physiologically active chemicals, such as glycosides, amino acids, heterocyclic compounds, etc. The manufacture of several transition metal catalysts, which are used in the synthesis of many organic molecules, including heterocyclic compounds, has also made considerable use of these ligands. **(Pérez-Mayoral & López-Peinado, 2021)**

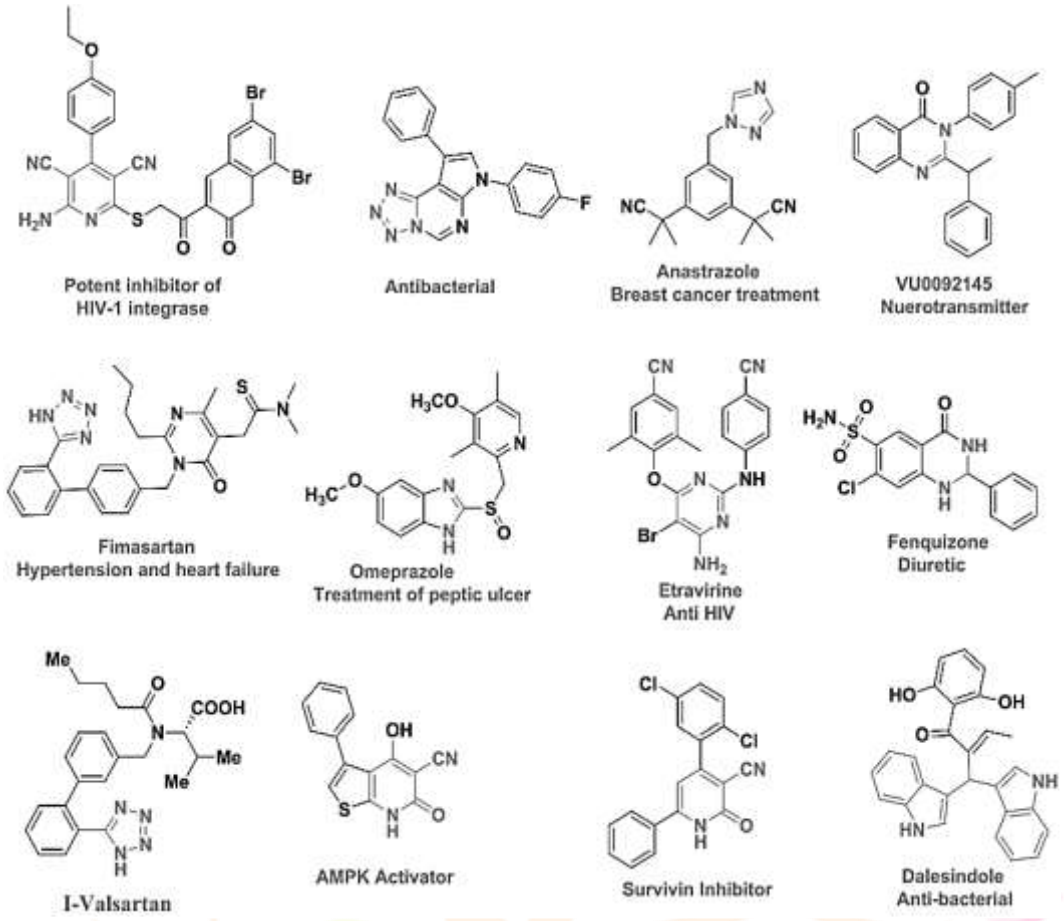


Figure I.2. Biologically active molecules having heterocyclic moiety

Many different drugs have their structural basis in heterocyclic compounds, which the pharmaceutical industry has used extensively. Any method that can successfully synthesise a new heterocyclic moiety is worth looking into. A literature analysis revealed that between 85 to 95% of newly produced medications are heterocyclic, which provides exciting new information about how the biological system functions. By mixing hetero atoms with carbon, hydrogen, and an endless number of other elements, molecules with a broad spectrum of physical, chemical, and biological properties may be constructed. Nearly half of the twenty million chemical compounds found at the turn of the century are heteroaromatic, and more than two-thirds are aromatic in some capacity. The development of new approaches and the strategic use of old ones to synthesize complex heterocyclic compounds continue to be the driving forces in synthetic organic chemistry. This is really clear. A great deal of effort and time has been devoted by organic chemists to developing more efficient methods of synthesizing these heterocyclic compounds. **(Hussein & Khairou, 2014b)**

IMPORTANCE OF HETEROCYCLES IN ORGANIC CHEMISTRY

The organic chemistry toolbox relies heavily on heterocycles, which are molecules having rings that include an element other than carbon. A wide variety of materials, medicines, agrochemicals, and natural products rely on these components. The distinctive characteristics brought about by the presence of heteroatoms, such as sulfur, nitrogen, and oxygen, are the source of their importance. Heterocycles may take part in many different chemical and biological processes because of the unique chemical reactivity and electrical characteristics introduced by these atoms. The medicinal effectiveness and specificity of many medications are enhanced by their heterocyclic compounds, which serve as their structural basis in the pharmaceutical industry. Heterocycles impact the design and development of pharmaceuticals by interacting with biological targets including enzymes and receptors; they are often found in antibiotics, antiviral agents, and anticancer treatments. **(Chinchilla et al., 2004)**

BIOACTIVE HETEROCYCLES IN PHARMACEUTICALS

Because of their structural variety and substantial biological activity, bioactive heterocycles play a crucial role in the pharmaceutical industry. Utilizing the distinct characteristics of heteroatoms like sulfur, nitrogen, or oxygen, these compounds—characterized by rings with at least one atom other than carbon—form an essential part of several medicinal substances. Hydrogen bonding and electrical effects are two of the many interactions that these heteroatoms contribute to, and they both improve the molecule's binding affinity for certain biological targets. The pharmacokinetic and pharmacodynamic profiles of a molecule are affected by its heterocyclic structure, which is present in medicines and includes pyridines, pyrimidines, indoles, and quinolines. For medication molecules to be selective and effective in therapy, heterocycles must be present. An example of this is how pyridines and pyrimidines may improve the binding affinity and specificity of drugs via hydrogen bonding with enzyme active sites. When developing compounds that inhibit enzymes or modulate receptors, this quality is crucial. The bioavailability and metabolism of the medicine are greatly affected by heterocycles, which impact the absorption, distribution, metabolism, and excretion of the drug. The creation of complex biologics and treatments generated from natural products relies heavily on heterocycles, in addition to their involvement in small molecule medications. Heterocyclic cores are the active components of many antimicrobial, antiviral, antifungal, and anticancer drugs. One example is the four-membered heterocycle known as the β-lactam ring, which is essential for the antibacterial action of medicines like penicillin and cephalosporin. **(Adhikari et al., 2022)**

HETEROCYCLIC COMPOUNDS

An important branch of organic chemistry, heterocyclic chemistry studies heterocycles and their synthesis, characteristics, and applications. A derivative of the Greek word "heteros," meaning "different," the word "heterocyclic" means "different." Organic cyclic structures containing at least one heteroatom are the basic building blocks of these molecules. Heteroatoms include sulfur, nitrogen, and oxygen; other elements that

contribute to heterocyclic compounds include selenium, phosphorus, silicon, and boron. It is well-known in this area of research that heteroatoms are essential parts of these formations. Heterocycles with sulfur (S), nitrogen (N), or oxygen (O) as heteroatoms are the most common kind, and they typically have five or six members. Famous examples of simple heterocyclic compounds include pyrrole, thiophene, furan, and pyridine. A ring of six atoms makes up pyridine; five of those atoms are carbon and one is nitrogen. The three compounds pyrrole, furan, and thiophene each have five carbon atoms, with four carbons and one-nitrogen, oxygen, or sulfur atom each. In the pharmaceutical sector, heterocyclic compounds play a crucial role. Essential to cellular metabolism are heterocyclic molecules, which typically consist of five or six carbon atoms with one to three heteroatoms located within the nucleus. These chemicals are crucial for DNA, namely for the building components purine and pyrimidine. Both free and bound forms of these heterocyclic compounds may be found in living things. Among the many amino acids and frequent heterocyclic compounds with medicinal use are proline, histidine, and tryptophan. The vitamin E family of compounds, as well as thiamine, riboflavin, pyridoxine, folic acid, biotin, and vitamin B12, are precursors of vitamins and coenzymes. Heterocyclic compounds are significant in drug research and therapy due to their wide diversity and numerous clinically employed molecules with pharmacological action. **(Qadir et al., 2022)**

BIOACTIVE HETEROCYCLES IN DRUG DISCOVERY

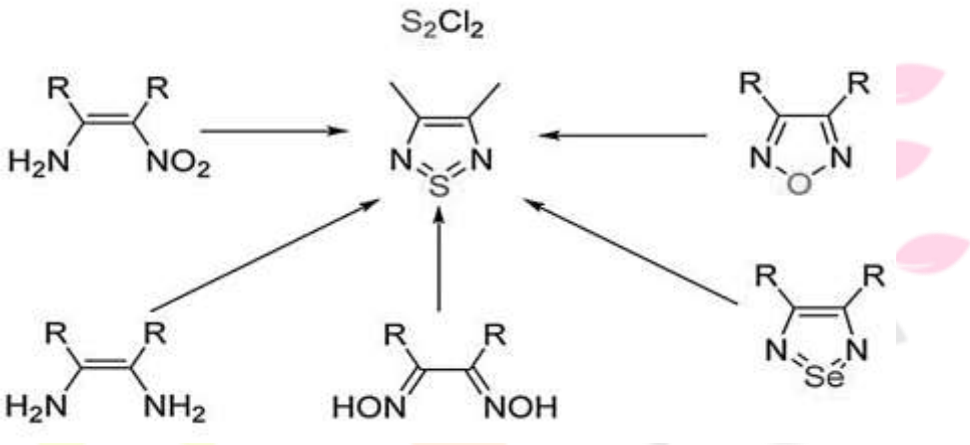
The pharmaceutical and agrochemical industries have shown a great deal of interest in bioactive heterocycles because of their powerful biological effects and availability in nature. These heterocyclic structures are present in many natural substances, including antibiotics, vitamins, and alkaloids. These molecules have strong pharmacological or pesticidal characteristics, which are particularly useful in the fields of drug development and crop protection. Their vital relevance in medicinal chemistry is shown by the fact that over 90% of newly discovered medicines include heterocyclic motifs. With a wide range of biological potentials, including antifungal and anti-inflammatory actions, these chemicals are great resources for research into biological processes and the development of new treatments. **(Banerjee, 2023)** Proline, histidine, and tryptophan are just a few amino acids that fall into the category of bioactive heterocyclic compounds used in pharmaceuticals. Thiamine, riboflavin, pyridoxine, biotin, folic acid, vitamin B12, and the E family of vitamins are some more examples. In contrast to indole-based medicines' strong anti-inflammatory properties, imidazole derivatives work well against fungal infections. Through their interactions with biological targets, which regulate their activities, these substances significantly influence our understanding of biology and the creation of therapeutic treatments. Pyrimidines and chemicals formed from them are essential for several biological properties. Some chemicals, such 2-Sulphanilamide Pyrimidines like sulphadiazine and sulphamethoxydiazine, are known to have antibacterial properties. Sulfurated 1,3,4-oxadiazoles exhibit a wide range of biological activities; for example, 2-acetamide-5-phenyl-1,3,4-oxadiazole is antiemetic, diuretic, antimitotic, and analgesic. An example of a bioactive heterocyclic molecule is an NSAID, which includes aspirin, ibuprofen, and naproxen, and has anti-inflammatory effects. **(Sharma et al., 2020)**

METHODS OF SYNTHESIS

A SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM CHEMICAL ELEMENTS

SYNTHESIS OF HETEROCYCLIC COMPOUNDS WITH FIVE MEMBERS

Sulfur monochloride's (S2Cl2) hitherto unknown reactivity has guided the development of several 1,2,5-thiadiazole syntheses in recent years. A number of molecules may be converted into 1,2,5-thiadiazoles using this reagent. These include 1,2-diamines and their synthetic analogues, such as 1,2,5-oxa/Selena diazoles, 1,2-nitrosamines, and 1,2-dioximes. This technique is becoming more important in chalcogen-nitrogen heterocyclic chemistry, and it is especially important with 1,2,5-oxa/Selena diazoles since it includes chalcogen exchange. **(A. Al-Mulla, 2017)**



There is a strong dependence on reaction conditions for the synthesis of 1,2,5-thiadiazoles from 1,2-diamines and similar synthetic chemicals including 1,2,5-oxa/Selena diazoles, 1,2-nitrosamines, and 1,2-dioximes. At 5°C, the reaction produces 2-oxides of the target thiadiazoles when dioximes are treated with S2Cl2 in MeCN; however, the same reaction, when carried out at ambient temperature, directly produces the thiadiazoles. At room temperature, thiadiazoles are formed by treating oxides with S2Cl2 and pyridine in MeCN.

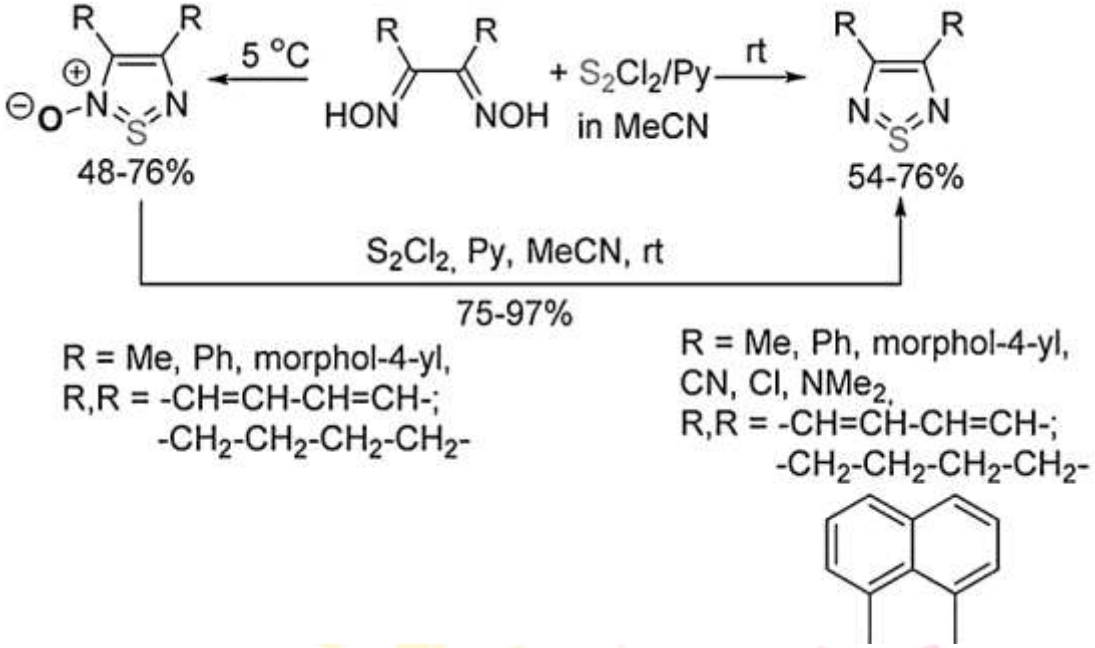


Fig.1 The Production of 1,2,5-Thiadiazoles

A BICYCLIC SYSTEM FOR THE SYNTHESIS OF PYRAZOLE

There are two nitrogen atoms and five carbon atoms in each ring of the famous aromatic heterocycle pyrazoles. The pyrrolo[2,3-c] pyrazole, a fused [5-5] system containing three heteroatoms, may be synthesized by reflux heating a combination of 3-aryl-1-phenyl-1Hpyrazol-4-carbaldehydes and ethyl azido acetate in ethanol.pyrazole, a medicine.

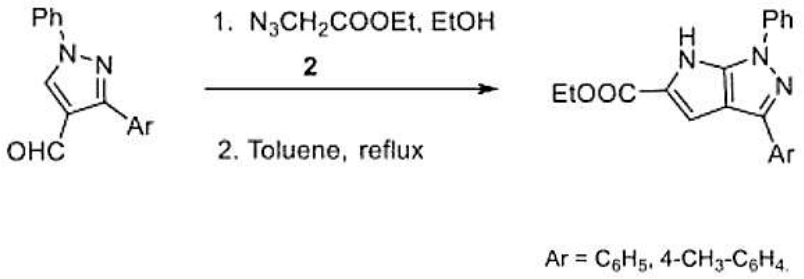


Fig.3 Synthesis of pyrrolo[2,3-c] pyrazole

COMPUTATIONAL METHODS IN DESIGNING HETEROCYCLES

The Gaussian 09W Package was used for all computational and theoretical calculations. Initially, we conducted some early conformational experiments and using Guess view to construct 3D chemical models. Geometric optimization was performed without symmetry constraints using density-functional theory (DFT) using B3LYP and a 6-31G (d, p) basis set. We used this computational model to determine the energy disparities between the lowest unoccupied molecular orbitals, or HOMO and LUMO. All calculations were carried out using the IEF PCM solvation model to replicate the real-life conditions, since dimethyl sulfoxide (DMSO) was used in the tests.

ABSORPTION, FRONT MOLECULAR ORBITALS (FMOS), AND OTHER GEOMETRIC PROPERTIES

There is a close relationship between electronic properties, such as band gap, absorption characteristics, and the HOMO and LUMO, and the excited states of molecules. Density Functional Theory (DFT) optimization led to the production of structures with lower interior energies. All computations were based on stationary points. We used the energy of the optimized structures to determine the internal energy of the system. The lower-energy excited states of triazine-based chemical species were subjected to the visual representation of Kohn-Sham orbitals generated from the resultant output files. Chemical hardness, electrophilicity, electronic energy, molecule chemical potential, and the Fermi level (FL) were among the many molecular properties examined in computational study.

DISC DIFFUSION METHOD

The disc diffusion technique was used to measure the antibacterial activity. Sterile Petri dishes were filled with autoclaved Whatman filter paper discs (6 mm diameter). The synthetic chemicals were dissolved in DMSO (20 mg/mL) in a sterile environment to reach minimal concentrations, and then, using a micropipette, these solutions were put onto the paper discs. Streptomycin, an antifungal medication, Fluconazole, and the precursor chemicals Sulfanilamide and Sulfadiazine were also used to create similar discs. The microbial strains were cultured for 24 hours in nutritional broth. Each plate of agar medium was then covered with the resultant suspensions. Next, the discs containing the chemicals and standards were placed onto the appropriate microbe plates, and after 24 hours, they were incubated at 37°C. To evaluate their antifungal and antibacterial capabilities, the inhibitory zones around the discs were measured. To find the minimal inhibitory concentration (MIC), we reduced solutions of the compounds to various concentrations ranging from 50 to 1000 µg/mL (50 µg/mL, 100 µg/mL, 150 µg/mL, 250 µg/mL, 500 µg/mL, and 1000 µg/mL). Standard compounds such as streptomycin and fluconazole were used to determine the minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC), respectively.

CYTOTOXIC STUDY

The hemolytic test required many steps, the first of which was the careful transfer of 3 mL of non-clotting human blood treated with EDTA into 15 mL of sterile falcon tubes. Using 5 mL of cooled phosphate-buffered saline (PBS) and centrifuging for 5 minutes each time, the blood samples were processed three times to eliminate any residual blood cells. After that, a 2 mL Eppendorf tube was used to mix 20 µL of the red blood cell suspension with 100 µg/mL of each chemical solution, for a total volume of 180 µL. A dilution was made by mixing 100 µL of the supernatants, which were obtained after spinning the mixtures in the tubes for 5 minutes, with 900 µL of cold PBS. A solution of 0.1% Triton X-100 served as the positive control, while PBS was used as the negative control. At 576 nm, the absorbance was measured using an ELISA plate reader.

METHOD FOR ATOMS IN MOLECULES (AIM)

Research into weak interactions, especially hydrogen bonding, has lately received interest due to the application of the theory of atoms in molecules (AIM). This research combines theoretical and experimental estimates of electron concentrations to better understand hydrogen bonding and other types of weak interactions. The topological characteristics of electron density distribution in molecular systems are investigated by means of the gradient vector field of electron density (r(r)) and the Laplacian distribution of electron density P2 r(r). We have found three rank three critical points (CPs) in the AIM framework for various experimental and theoretical electron densities: bond (BCP), ring (RCP), and cage (CCP). In order to form a bond, it is essential that the equilibrium geometry of a molecule have a BCP between the two atoms. The line that maximizes electron dispersion with respect to lateral displacement, r(r), is defined by gradient routes that start at a BCP and go to nearby nuclei. The researchers in this work used AIMPAC and AIM98PC to get the BCP characteristics, and AIM2000 to make the molecular graphs. Utilizing all-electron wave functions is crucial for AIM computations to provide useful results, which means that computationally demanding DZVP basis sets must be used instead of ECP, which are more efficient.

BIOACTIVE HETEROCYCLE STRUCTURAL DIVERSITY

A compound is considered heterocyclic if it has two hetero atoms within its ring structure; this is the reason for the compound's name. Heterocycles apply to these rings in particular. The most common types of heterocycles are those with five or six atoms in the ring, however there is no hard limit on the size of rings that have more than that. There are two main groups of heterocyclic compounds, identified by their electronic and structural configurations: aliphatic and aromatic. Cycles of amines, amides, ethers, and thioethers make up the class of aliphatic heterocyclic compounds. Saturated heterocycles are aliphatic compounds that lack double bonds and have characteristics mostly determined by ring strain. The structural and behavioral parallels between benzene and aromatic heterocyclic molecules are striking. Aromatic compounds must conform to Huckel's rule, which states that they must be cyclic, Its planar structure is the result of conjugated double bonds, and their total number of electrons is $(4n + 2)\ \pi$. **(Afridha et al., 2023)**

Examples of Heterocyclic Compounds:

Heterocycles with five, six, or fused members

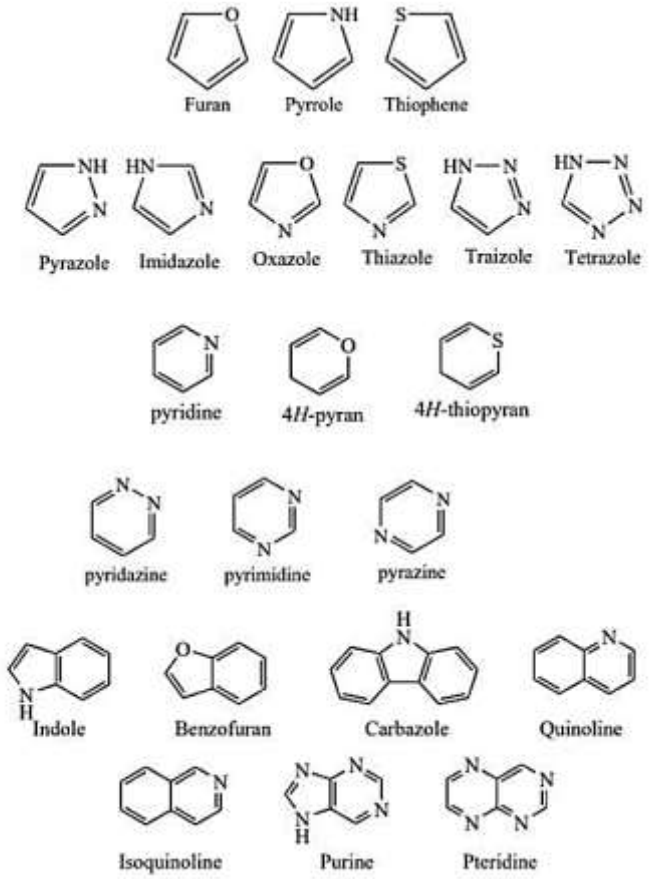


Figure: Heterocyclic Compounds

Common Heterocyclic Compounds in Pharmaceuticals

Because of their diverse biological activity and distinctive characteristics, heterocyclic compounds—which are shown in the picture—form the basis of numerous medications. A few of these chemicals are summarized below:

Pyridine: Pyridine has a strong, unpleasant odor and appears as a transparent, colorless to pale yellow liquid. Gases have a lower density than air and a flash point of 68 degrees Fahrenheit. Many various items are made from pyridine, including vitamins, paints, dyes, rubber goods, adhesives, food flavorings, insecticides, and waterproofing for textiles. Pyridine is also used as a solvent. The environmental degradation of several natural elements may also produce pyridine. The molecular formula for pyridine is C5H5N, and it is a fundamental heterocyclic organic molecule. There is a structural relationship to benzene, however instead of a methene group (=CH−), a nitrogen atom is used. It has a strong odor reminiscent of fish and is a water-miscible, somewhat acidic, and very combustible liquid. Although most pyridine is colorless, some older or less pure samples may have a yellowish hue. Vitamins, agrochemicals, and medicines are just a few of the several essential molecules that contain the pyridine ring. Pyridine was originally made from coal tar. Nowadays, its annual global synthesizer output is around to 20,000 tons.

Furan: Liquid cyclic ether furan has an ethereal aroma and is colorless and transparent. It is also combustible. Tetrahydrofuran, pyrrole, and thiophene are all derived from furan via its use as a precursor. This chemical irritates the eyes and skin and depresses the central nervous system when inhaled. Although several furan syntheses have been developed, the Feist-Benary synthesis stands out as a classic. The Paal-Knorr synthesis, which involves reacting 1,4-diketones with phosphorus pentoxide (P2O5), is one of the most straightforward ways to synthesize furans. In addition to thiophene, furans are byproducts of the 1,4-diketone reaction using Lawesson's reagent. A wide variety of synthetic methods for substituted furans are available.

Indole: Indole, having the molecular formula C8H7N, is an aromatic heterocyclic molecule. The chemical formula is a bicyclic ring with six carbon atoms fused to a pyrrole ring with five carbon atoms. A wide variety of bacteria are capable of producing indole, which is widely distributed in nature. Among the vegetables that contain indole-3-carbinol are rutabagas, mustard greens, kale, cabbage, Brussels sprouts, kale, collards, cauliflower, and kale. Another option is to have it made in a laboratory. Using Indole-3-carbinol may reduce the risk of developing cancer, including breast and colon cancers.

Pyrrole: It is common practice to distill pyrrole just before use since the colorless volatile liquid becomes black quickly when exposed to air. The aroma of pyrrole is nutty. Pyrrole is an aromatic heterocycle with five carbon atoms. Tetramethyl pyrrole is an example of a more basic compound that results from substituting an alkyl group onto pyrrole.

Synthesis: Industrial pyrrole production involves reacting furan with ammonia using solid acid catalysts such as SiO2 and Al2O3. Another way to make pyrrole is to catalytically dehydrate pyrrolidine.

Pyrrolidine : An organic molecule having the chemical formula $(CH_2)_4NH$ is pyrrolidine, which is another name for tetrahydropyrrole. To a maximum of organic solvents and water, this colorless liquid may be mixed. Some have compared its smell to that of shellfish, while others have characterized it as "ammoniacal, fishy, and distinctive.

Synthesis: To produce pyrrolidine in a controlled environment, the reaction of 1,4-butanediol and ammonia is carried out at pressures ranging from 17 to 21 MPa and temperatures between 165 and 200°C. Cobalt and nickel oxide catalysts backed by alumina facilitate the process. The reaction takes place in the liquid state in a continuous tube-or tube bundle reactor that is operated using the cycle gas approach.

ROLE OF AROMATICITY IN BIOACTIVITY

The role of aromaticity in the bioactivity of heterocyclic compounds has been the subject of much research in medicinal chemistry and medication development. Aromaticity is a fundamental concept in organic chemistry that describes the stability and unique electrical properties of cyclic compounds with conjugated π-electron systems. The aromaticity of heterocyclic compounds has a significant impact on their biological activity. Part of the reason these compounds are more stable, reactive, and attached to biological targets is

because they include aromatic rings. Enzymes, receptors, or DNA are among the biomolecular substrates that aromatic systems may interact with via π-π stacking, hydrogen bonding, or hydrophobic interactions. Solubility, lipophilicity, and membrane permeability are three physicochemical traits that may be impacted by the aromaticity of heterocyclic compounds. The compound's capacity to cross biological membranes and arrive at its intended location depends on these properties. Anticancer, antibacterial, antifungal, antiinflammatory, and antioxidant are just a few of the powerful biological effects that aromatic heterocycles often display. These compounds show great promise as therapeutic treatments due to their aromatic character, which enables them to influence biological processes and interact with particular molecular targets.

CONCLUSION

Since bioactive heterocycles have so many uses in fields as diverse as materials science, agriculture, and medicines, their synthesis has become an important focus of contemporary organic chemistry. Essential for pharmaceutical research and other commercial uses, heteroatoms like nitrogen, oxygen, and sulfur provide distinctive characteristics to these compounds that greatly enhance their biological activity. Modern computational methods and synthetic approaches have greatly increased the utility of heterocyclic compounds, opening the door to the synthesis of new molecules with intriguing and powerful biological functions. Research and development efforts in this area have the potential to provide novel medicinal medicines and enhance several scientific and industrial fields.

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