Paving the Path to Discoveries and Unlocking the Secrets of N-Heterocycles

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Edited by

Prashant Tiwari and Popat Mohite

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CHAPTER 1

INTRODUCTION TO N-HETEROCYCLES

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Abstract

During last few decades, nitrogen-based heterocycles had occupied an important place into the pharmaceutical field due to its wider applications. As per reports, more than 80 percent of approved drugs in the market are belonging to nitrogen-based heterocyclic compounds. It is expected that much more new compounds are yet in pipelines to be discovered in near future. This compound plays a valuable role in drug discovery and designing of modern dosage forms in pharmaceutical and biotechnological sectors. In this review article it was emphasized to highlight the significant chemical, biological, therapeutic properties and other possible applications of novel N-heterocyclic compounds. These heterocycles are reported for its vital therapeutic applications in the field of pharmaceuticals and biotechnology sectors includes antibacterial, antiviral, anticancer, antiinflammatory, anti-tumor, antidiabetic, etc. Other applications were included as corrosion inhibitors, polymers, agrochemicals, dyes, developers, etc. In the present review chapters, we tried to highlight more on few 3-, 4-, 5- and 6-ring membered N-heterocyclic compounds that would be beneficial for both scientific pharmaceutical journals and patent literatures.

Keywords: Nitrogen based heterocycles, current trends; anticancer and antiinflammatory activities; structure-activity relationship, pharmaceuticals, etc.

Introduction

In the field of medicinal chemistry, analogs of nitrogen-based heterocycles hold a unique and significant position as a valuable resource of therapeutic agents. Among the applied branches of organic chemistry, nitrogen-based heterocyclic chemistry is a class that is both significant and distinctive importance. A considerable amount of research was carried out by researchers in this specific class for creation of novel and composite molecules. Over the last two decades, these molecules have attracted an increasing amount of interest into the field of heterocyclic chemistry. They have made significant contributions to the development of a large number of protocols for organic synthesis and then discovered a wide range of applications into the field of chemical sciences (Santos, Freitas, and Fernandes, 2018, 1460-1479; Li et al., 2013, 3636-3646; Kalaria, Karad, and Raval, 2018, 917-936; Kerru et al., 2019, 2437-2459; 2017, 179-212). Nitrogen containing heterocyclic moieties was present in more than seventy-five percent of the therapeutic products that have been duly authorized by the Food and Drug Administration (US-FDA) and are now accessible in the global market (Mermer et al. 2019, 279-287; Das et al. 2019, 4265–4311). Several unique heterocycles that are based on nitrogen have been developed over the past several years. Furthermore, it is likely to be expected that a much larger proportion of novel medications based on N-heterocycles will be developed in near future. There is a growing number of novel N-heterocyclic moieties that are being discovered in the field of medicinal chemistry. These moieties exhibit noteworthy contribution and imparts applications for development of novel pharmaceutical products (Li et al. 2013, 3636-3646; Santos, Freitas, and Fernandes 2018, 1460-1479; Kalaria, Karad, and Raval 2018, 917-936; Kerru et al. 2019, 2437-2459; 2017, 179-212).

N-heterocycles are essential due to their wide range of applications in context with biomedical and pharmacological activities. They have shown promising results of varying degrees, because of their unique characteristics such as substitution in heterocyclic systems and attached pharmacologically active functional groups in the parent molecules. These features make them suitable for structure-activity relationship (SAR) studies and biological evaluations (Lang et al., 2020, 2150-2168; Akhtar et al., 2017, 143-189). The primary advantage of these heterocycles lies in their adaptable characteristics that are the result of their compact molecular structures and abundant functional variety. Carbon atoms are providing stability to these rings due to their aromaticity, while the presence of nitrogen imparts distinctive features to these heterocycles due

to their substantial electron density. The physicochemical characteristics of these heterocycles are significant in developing many innovative materials, specifically organic conductors. The process of identifying and modifying nitrogen heterocycles with various substituents might result into a wide range of applications for these compounds (Henary et al., 2020, 14170-14197).

Historical aspects of N-heterocyclic containing compounds

Three-membered N-heterocyclic compounds

The compounds that consisted of three-membered saturated heterocyclic having two carbon atoms and one nitrogen atom are known as aziridine respectively (Murphree, 2011, 11-162). Aziridines are those ring systems that are synthesized by the reduction of azirines (unsaturated double bond containing heterocycle). Aziridines are a class of compounds that are remarkable for their biological alkylating and anti-cancer properties. In addition to its pharmaceutical applications, aziridine and its derivatives are used for manufacturing in large-scale production of plastics, coatings materials, textiles etc (Silva, Elguero, and Silva, 2018, 394-429). As per current reports from a few researchers, the chemical properties of these compounds have been thoroughly examined during the past few decades. Aziridine is frequently referred to as aza cyclopropane or, more commonly, as a derivative of the parent alkene, ethylenimine. The derivatives are referred to as N-methylpropylenimine and cyclopentenimine, respectively. Aziridines and their derivatives are reported to exhibit few significant pharmacological activities viz., antimicrobial, antiparasitic, antiviral, anticancer, anti-inflammatory, analgesic, neuroprotective and cardiovascular. In addition to this the Aziridine itself exhibits toxic properties that result in eye and skin irritation, as well as internal inflammation (Weber, 2015, 9-112). The alkylating property of aziridine is highly significant for both pharmaceutical and biotechnological applications. The aziridine ring is found to be one of the specific moieties in both antibiotics and anti-cancer compounds. In the year 1959, Schmitz successfully synthesized diaziridine for the first time as per reports. Diaziridine is a fully saturated compound belonging to the three-membered N-heterocyclic class consisting of two nitrogen atoms (Singh, Sudheesh, and Keroletswe, 2017, 50-113).

Four-membered N- heterocyclic compounds

The compounds with four-membered heterocyclic rings are analogous to cyclobutane and that heterocycle having Nitrogen is referred to as azetidine. These rings are less stressed compared to three-membered heterocyclic rings, but they are challenging to synthesize using direct intramolecular cyclization methods (Kaur, 2019, 1141-1167). This challenge to some extent originates from the alteration in the location of the atoms involved in the specific reactions. Direct cyclization occurs exclusively when those combining atoms are in their suitable orientation or position and that inclination for ring closure is due to their proximity. However, as the length of the chain increases, the total number of conformations that prevents easy ring closure also increases on other hand. Azacyclobutadiene is properly referred to as azete, whereas the partly unsaturated ring is known as azetine, or more precisely, 1-azetine. The alternative structure that has a double bond at second position from the nitrogen atom is called as 2-azetine. Azetidine is fully saturated molecules that were having one nitrogen atoms in its structure and is also known as trimethyleneimine (Jursic, 2001, 143-154). Azete exhibits anti-aromaticity and is characterized by its inherent instability property. Phenyl benzazete and other benzazetes are known for their enhanced stability and have been successfully synthesized by researchers. Only a few compounds include the azetidine ring structure are found naturally. Pharmacological investigation of synthetic azetidine derivatives has not been produced with any beneficial outcomes. Nevertheless, L-azetidine-2-carboxylic acid, which is a naturally occurring antimetabolite of proline has been extracted from the plant belonging to Liliaceae family. As per the report, few researchers have successfully synthesized its 3-isomer derivative (Nayl et al., 2022, 3716; Malarney, KC, and Schmidt, 2021, 8425-8441).

Five membered N-heterocyclic compounds

There are a significant number of bioactive compounds consisted of N-heterocycles that were consisted of five-membered pyrrolidine moiety. In this context, those nicotine, tryptamine, and vinblastine are few examples of pyrrolidine ring structures that were having five-membered N-heterocycles. These compounds have crucial roles into the fields of biochemistry, medicine and agriculture sectors. Natural compounds can assume various conformations, including diphenyl prolinol rings, streptopyrrolidine and 2-pyrrolidine (Hamzah, Shaameri, and Goksu, 2013, 1-2). These ring systems can serve as flexible intermediates in the

synthesis of highly complex medically significant compounds viz., aniracetam, doxapram, cotinine, clausenamide, lactacystin, detoxime and codonopsinine respectively. Additionally, they also possess structural characteristics that are found in numerous naturally occurring bioactive natural products.

In 1834, Runge discovered that when that coal tar, bone oil and other protein derived products were getting distilled there then an unidentified substance was obtained into the ammonia fraction. The pine splint, which had been previously immersed in hydrochloric acid were transformed into a vibrant red colour substances. There then, one of the scientist Anderson had successfully obtained the compound in 1857 that was named as pyrrole in a pure form obtained from the bone oil distillates (Sims, O'Loughlin, and Crawford 1989a, 309-340). There after three years, synthesis of the compound was achieved through the process of pyrolysis of ammonium mucate. Despite of the commercial availability of pyrrole, this laboratory method also remains valuable on other hand. The pyrrole ring system gained significant attention due to its presence in numerous compounds that are widely distributed in nature. The presence of this substance was also been identified into the dye indigo, haemin derived blood product and chlorophyll respectively. Proline (pyrrolidine-2-carboxylic acid) and 4-hydroxyproline that were both derived from pyrrole are present in numerous protein substrates. Several alkaloids also contain a pyrrole ring as reported by various researchers. Two tautological formulations can be written for pyrroles containing two compounds are referred as 2H-pyrrolenine or alpha pyrrolenine and 3H-pyrrolenine or Beta-pyrrolenine respectively. There are three possible dihydropyrroles or pyrrolines in theoretical terms, and the tetrahydropyrrole is referred to as pyrrolidine. When the pyrrole ring is substituted with another moiety then it is identified as pyrryl (Bhardwaj et al., 2015, 15233-15266).

In the year 1884, Knorr discovered that a pyrazole derivative can reduce body temperature in humans, due to its antipyretic action (Varghese et al., 2017, 46999-47016). The said compound was termed as antipyrine by the scientists Domiati (Domiati et al., 2016, 163-172). This initiated interest into the field of pyrazole chemistry later on. Although antipyrine is currently not widely used but several pharmaceuticals and dyestuffs incorporate the pyrazole ring system into their products. Yet another class of five-membered compounds is well known as Imidazole that was initially synthesized in the year 1858 by combining glyoxal and ammonia, and it was also coined as glyoxaline. The term "obsolete" was used to describe its name, but later on, it was highly recommended to use the

terms “imidazole” or “iminazole” instead of the previous name. Unlike pyrazoles that are rarely found in nature, but specific imidazoles plays a crucial role in our living organisms. Examples of those Imidazole including the pilocarpine alkaloids, vitamin B12, biotin, 5-aminoimidazole-4-carboxyamide, and essential amino acid histidine and its related compounds. As reported by scientists, those few imidazoles have proven to be valuable chemotherapeutic agents for treatment of cancer diseases (Mermer, Keles, and Sirin, 2021, 105076; Li et al., 2021, 38060-38078).

Six-membered N-heterocyclic compounds

Nitrogen-containing heterocyclic compounds with six-membered rings are abundant in nature and that are playing crucial roles in several biological processes. These compounds serve as building blocks in numerous natural products including vitamins, hormones, antibiotics, alkaloids, medicines, agrochemicals, dyes, and other compounds (Amin et al., 2022, 1-27). Anderson discovered pyridine in 1849 and then successfully isolated this alkaline compound in its pure form from bone oil respectively. Anderson also obtained separated picoline (methylpyridine) and lutidine (dimethylpyridine) from identical sources (Sims, Loughlin, and Crawford, 1989b, 309-340). These pyridines are not naturally present in bones but are produced through thermal processes during distillation process. The structural correlation between pyridine and benzene was initially identified separately by Korner in 1869 and Dewar in 1971. Natural occurrences of compounds containing the pyridine ring are widespread and easily available to us. Some of them, such as vitamin B6 and nicotinamide adenine dinucleotide phosphates (NADP) are highly significant in the biochemistry field. Similar to other heterocyclic ring systems, the nitrogen atom in pyridine is designated as position-1. Pyridine is a compound with aromatic properties that closely resembles with benzene in its overall structure (Henary et al., 2020, 14170-14197). In contrast to the benzene series, the ring's asymmetry significantly increases the number of structural isomers that are possible; there is only one monomethylbenzene found as a benzene isomer but there are three monomethylpyridines found as pyridine isomer. The Pyridine has a sum of 19 potential methyl substitution products, while benzene only has only 12 potential methyl substitutions respectively. Pyridine is classified as a tertiary base and exhibits various properties that are typical of compounds in this category. Due to the challenges of incorporating substituent into the pyridine ring using electrophilic reagents and despite of the abundance of pyridine itself, numerous synthetic methods have been devised for constructing the ring.

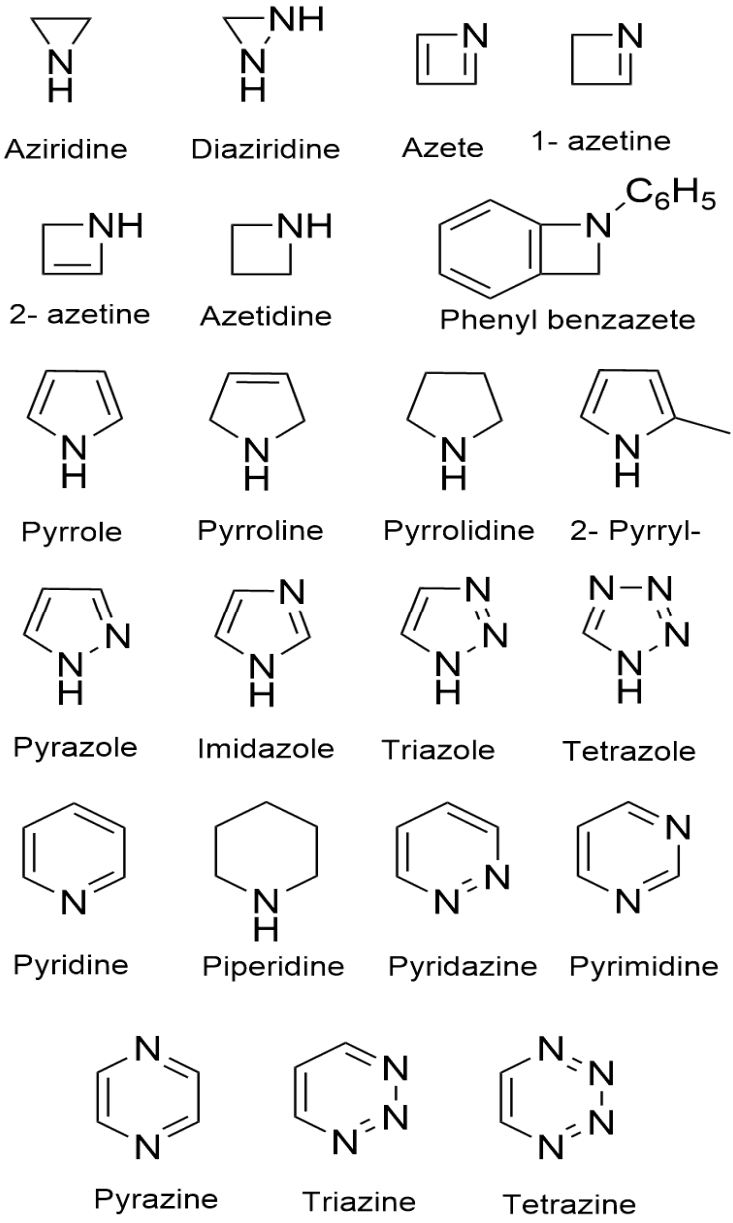


Figure 1: The basic structures of few common nitrogen containing heterocycles

The current scenario is completely different from that of the benzene series as there has been a lack of interest in synthesizing the ring due to the ease of substituting and transforming existing substituents (Mermer, Keles, and Sirin, 2021, 105076).

Heterocyclic compounds containing nitrogen and its utilizations for therapeutic activities

Four membered compounds

While synthesizing heterocyclic compounds with four members, β-lactams were useful in the development of several antibiotics. In addition to antibiotics, the β-lactam structure is an essential component in the production of other bioactive heterocyclic compounds (Newman and Cragg, 2016, 629-661; Robb and Moore, 2015, 10946-10949; Baiula et al., 2016, 9721-9742; Majewski et al., 2017, 737-744; Cele et al., 2015, 638-646). Such bioactive heterocyclic compounds include those clinical medications include ezetimibe, beta-lactamase inhibitors, clavulanic acids, and cholesterol absorption inhibitors etc. (Hosseyni and Jarrahpour, 2018, 6840-6852; Han et al., 1995, 1123-1143).

Chemists are fascinated by the different applications of nitrogen-containing four-membered heterocycles, such as β-lactams and thereafter had developed various synthesis techniques simultaneously. Bacterial resistance to commonly used β-lactam antibiotics has increased researchers' curiosity. Chromene-tagged β-lactam molecular hybrids were tested for anticancer and anti-inflammatory effects as per reports. They demonstrated strong anti-cancerous action against the colon cancer (SW1116) cell line. Adding a hydroxy group to the third position of a β-lactam and a fluorophenyl compound resulted into significant antiproliferative action against colon HT-29 and breast cancer cells. That β-lactam-anthraquinone hybrids are found to be potent antibacterial and antifungal agents (Borazjani et al., 2019, 389-403; Malebari et al., 2020, 112050).

Antibiotics containing β-lactams are classified into four distinct categories. These antibiotics are carbapenems, monobactams, cephalosporins, and penicillins respectively. Each of them has a β-lactam ring with four members, which is necessary for them to exhibit its possible antibacterial properties. One of the scientist Sir Alexander Fleming discovered penicillin in 1929 after finding that his experimental culture of staphylococcus had been contaminated by fungus, causing the bacterium to lyse into the culture medium. He named this antibacterial chemical as

penicillin because the fungus belonged to the penicillium family. Ten years later, a research team belonging to Oxford University had discovered a simple compound that was composed of several low-molecular compounds known as penicillins (F, G, K, O, V, X). Penicillin G (benzylpenicillin) was discovered to be the most efficacious of the penicillins (F, G, K, O, V, and X). Since then, several bacterial infections have been treated with penicillin G as per reports of researchers (Vellar and Hugh, 2002, 52-53; Cruickshank, 1955, 663; János and Robin, 2010, 12-15).

Likewise, Amoxicillin is an antibiotic used to treat a variety of bacterial diseases, such as urinary tract infections, middle ear infections, pneumonia, strep throat, and skin infections respectively. One of the most utilized β-lactam and best-selling antibiotics is amoxicillin itself. It was discovered in the year 1958 and was used as medicine since 1972 onwards. Compared to its precedents, it has numerous advantages, such as a higher potency spectrum, high solubility, and a high absorption rate in comparison to other antibiotics as reported (Bruggink, Roos, and de Vroom, 1998, 128-133; Wegman et al., 2001, 559-576).

An antibiotic called cefalexin is used to treat a variety of bacterial diseases in human beings. It is used to treat specific bacterial infections, such as those that grow in the body parts viz., skin, joints, middle ear, strep throat, pneumonia, and urinary tract respectively. It also helps us in the preventing of infection from bacterial endocarditis in human beings. Cefalexin was discovered in 1967 that were initially promoted under the brands Kefex and Ceporex in the year 1969 and 1970. Cefalexin is available in the market at a reasonable price in both generic and branded forms. As per reports, the first-generation cephalosporin antibiotic Cephalexin was chosen as the model drug candidate to provide dose with improved palatability, stability and simple for usages (Davis, Salmon, and Papich, 2005, 425-431; Tack et al., 1997, 739-742; Jacobs, Jones, and Giordano, 2007, 55-65; Disney, 1992, 1324-1327; Perry and Brogden, 1996, 125-158; Ehrnebo, Nilsson, and Boréus, 1979, 429-451; Jones, 1977, 232-233).

In addition to antibiotics that β-lactam structure plays a vital role as a fundamental component for the synthesis of many bioactive heterocycles. Examples of clinical drugs are clavulanic acids, which are β-lactamase inhibitors and ezetimibe, which is a cholesterol absorption inhibitor. Ezetimibe is an antibiotic used for the treatment of excessive blood cholesterol and other lipid disorders. In the United States, ezetimibe

received FDA approval for medical uses on the market in 2002. A strong inhibitor of β-lactamase-induced cholesterol absorption that lowers plasma (LDL-C), ezetimibe has two extra chiral centres at the 2-azetidinone skeleton, a stereogenic benzylic hydroxyl, and three para-substituted phenyl rings, according to structural analysis studies (Arya et al., 2014, 619-656).

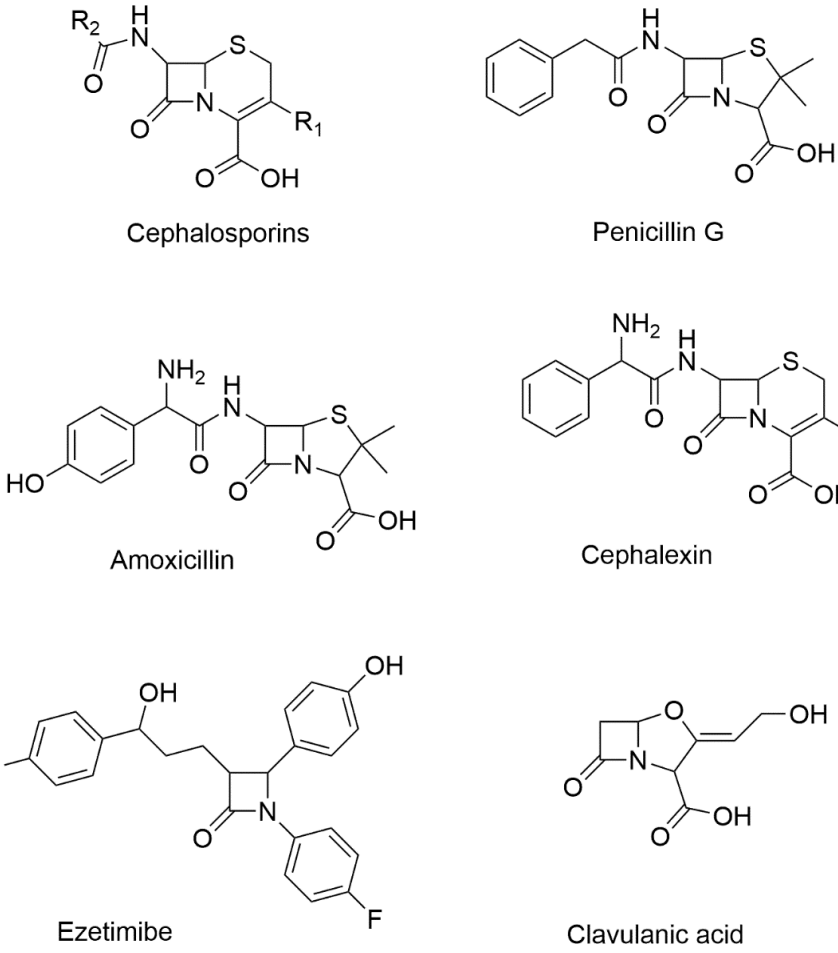


Figure 2: Chemical structures of drugs containing four membered N-heterocyclic compounds

Five membered compounds

Lisinopril that was chemically referred as N2-[(1S)-1-carboxy- 3-phenylpropyl]-L-lysyl-L-proline, is an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension, heart failure, and commonly used after a heart attack conditions. It was granted US patent in the year 1978 and approved for medicinal uses in cardiac disease thereafter in 1987 as per reports (Raghava, 2016, 269-278; Wu et al., 1985, 352-354). Enalapril, also known as Vasotec (brand name), is a medicine used to treat high blood pressure, diabetes related renal disease and congestive heart failure conditions. It is commonly used along with a diuretic such as furosemide for the management of said diseased conditions. Enalapril was developed in the year 1978 and thereafter introduced in the market in the year 1984 were approved as a prescription medicine into the market. Enalapril, (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline is prepared by treating the benzyl ester of L-alanyl-L-proline with the ethyl ester of 3-benzoylacrylic acid. In this reaction the obtained product in which the protective benzyl moiety is eliminated via hydrogenation in the presence of a RANEY® as a catalyst, achieving the desired prescribed drug enalapril. Some more methods for obtaining enalapril have also been proposed by few researchers from time to time (Wyvratt et al., 1984, 2816-2819; Patchett et al., 1980, 280-283).

Atorvastatin, known by the brand name Lipitor, is one of the often-prescribed oral statin medicines. It is known to prevent cardiovascular disease by lowering low density lipoprotein (LDL) cholesterol levels in the bloodstream. Atorvastatin was invented in 198 that were approved for prescription in the United States in 1996, and is now available as a generic medicine. Sumatriptan is available under the brand name Imitrex was got invented in the year 1982, and approved for therapeutic usage in the year 1991. Sumatriptan is a very effective and selective serotonin (5-HT1d) receptor agonist used to treat migraine attacks.

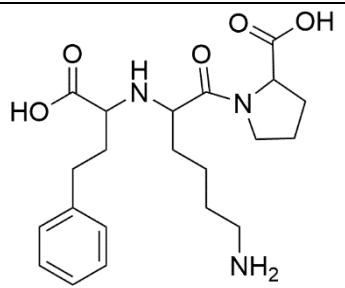
The further class of five-member compounds having 1,2,3-Triazoles serves as a crucial pharmacophore system for nitrogen-based drugs. These pentagonal heterocyclic structures which consist of three nitrogen heteroatoms can be readily synthesized via “click” chemistry or copper-catalyzed azide-alkyne cycloaddition [CuAAC] reactions. They exhibit resistance to hydrolysis in both acidic and basic conditions, as well as resistance to metabolic degradation. They establish hydrogen bonds, noncovalent and van der Waals connections, as well as dipole-dipole bonding interactions with many biological targets. In addition, triazoles

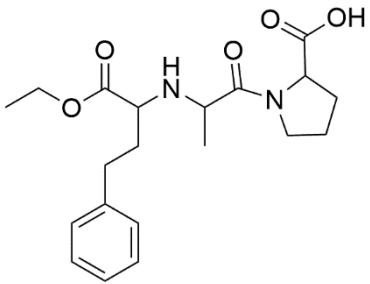
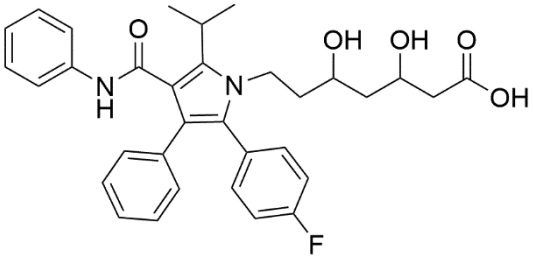
are highly vulnerable to reducing agents due to their weakly basic and acidic nature. Furthermore, the drug carboxyamidotriazole, which is based on the 1,2,3 triazole compound has been effectively assessed in clinical trials for its potential in treating cancer (Xu, Zhao, and Liu, 2019, 111700; Bozorov, Zhao, and Aisa, 2019, 3511-3531; Dheer, Singh, and Shankar, 2017, 30-54; Qian et al., 2018, 137-147).

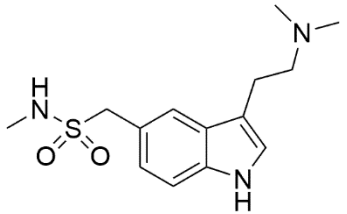
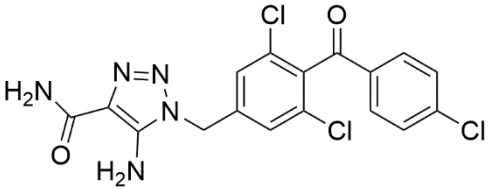
The imidazole and benzimidazole moieties are unique nitrogen-containing heterocycles consisting of five-membered rings, each with its own peculiar structural features. Imidazole derivatives possess an electron-rich character that enables them to effectively bind with various receptors and enzymes in the biological context, hence exhibiting a diverse array of biological activities. Oxiconazole, dacarbazine, and clotrimazole are examples of imidazole-based therapeutic medicines that possess strong antifungal and anticancer effects (Liu et al., 2018, 2454-2458; Zhang et al., 2014, 340-437; Adib et al., 2019, 713-718; Bolous et al., 2019, 2059-2063).

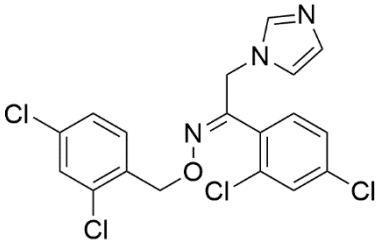
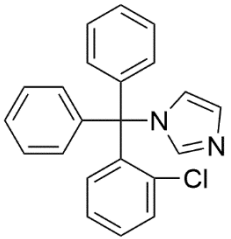
Pyrazole is a well-known nitrogen-based heterocycle that consists of five members and has a considerable number of uses in both the synthetic and biological fields. While, as per reports that of Celecoxib, rimonabant, difenamizole, and fezolamine, are examples of clinical medicines that include pyrazole moiety and exhibit anti-inflammatory, anti-obesity, analgesic, and/or antidepressant properties respectively (Baumann et al., 2011, 442-495; Karrouchi et al., 2018, 134; Silva, Elguero, and Silva, 2018, 394-429; Ansari et al., 2017, 16-41).

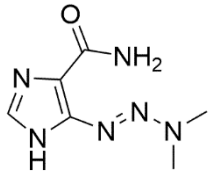
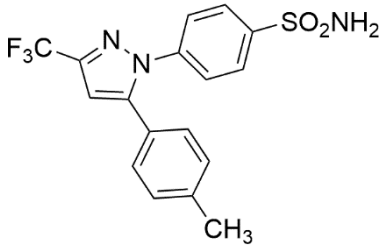
Table 1: List of five and six-member N-heterocycle-containing drugs with their biological activities

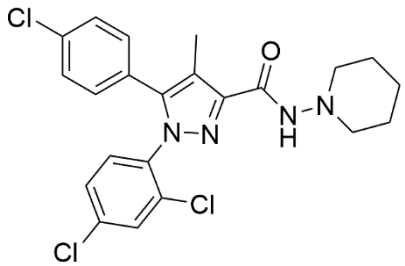
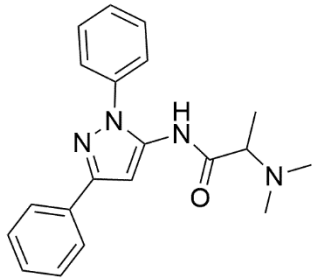
S. No.	Compound	Activity	Reference
Five-membered N-heterocycles			
1.	 Lisinopril	Antihyper-tensive	(Weber, Brilla, and Janicki 1991, 62-73)

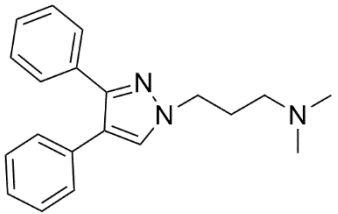
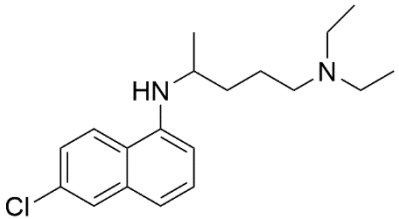
2.	 Enalapril	ANTIHYPERTENSIVE	(VERBEECK ET AL. 2017, 1933-1943)
3.	 Atorvastatine	ANTILIPEMIC	(VAN AND KASTELEIN 2005, 1191-1203)

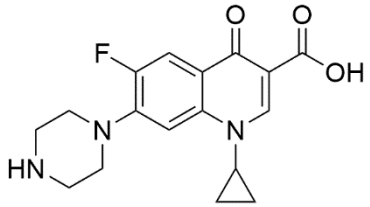
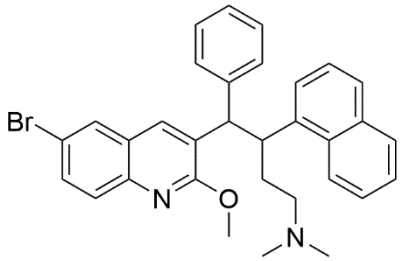
4.	 Sumatriptan	SELECTIVE SEROTONIN RECEPTOR AGONIST.	(FULLERTON AND GENGO 1992, 800-808)
5.	 Carboxyamidotriazole	ANTICANCER	(XU, ZHAO, AND LIU 2019, 111700)

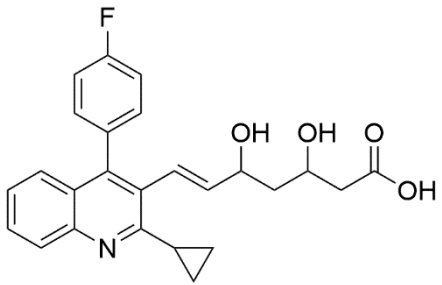
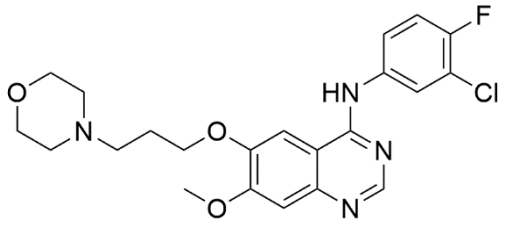
6.	 Oxiconazole	ANTIFUNGAL	(LIU ET AL. 2018, 2454-2458)
7.	 Clotrimazole	ANTIFUNGAL	(ZHANG ET AL. 2014, 340-437)

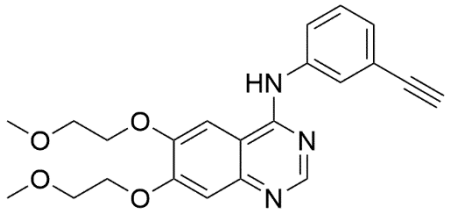
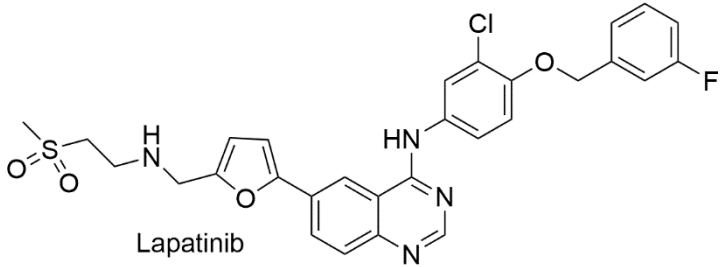
8.	 Dacarbazine	ANTICANCER	(ZHANG ET AL. 2014, 340-437)
9.	 Celecoxib	ANTI-INFLAMMATORY	(BAUMANN ET AL. 2011, 442-495)

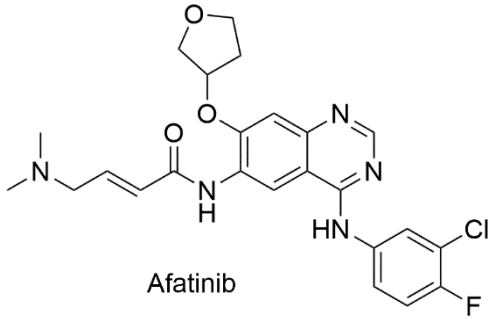
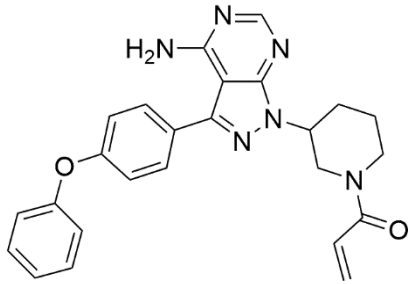
10.	 Rimonabant	ANTI-OBESITY	(KARROUCHI ET AL. 2018, 134)
11.	 Difenamizole	ANTI-INFLAMMATORY	(SILVA, ELGUERO, AND SILVA 2018, 394-429)

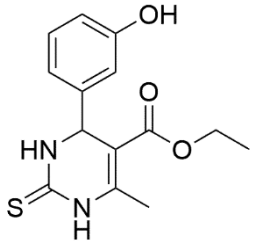
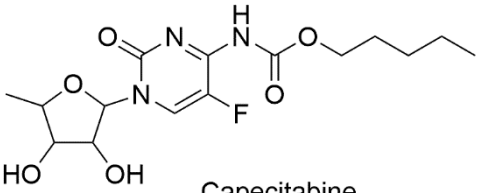
12.	 Fezolamine	ANTI-DEPRESSANT	(ANSARI ET AL. 2017, 16-41)
SIX-MEMBERED N- HETEROCYCLE			
1.	 Chloroquine	ANTI-MALARIAL	(JAIN ET AL. 2019, 4920-4946)

2.	 Ciprofloxacin	ANTI-INFECTIVE	(JAIN ET AL. 2019, 4920-4946)
3.	 Bedaquiline	ANTI-BACTERIAL	(ZHANG ET AL. 2019, 1-8)

4.	 Pitavastatine	ANTI-HYPERLIPIDAEMIC	(ZHANG ET AL. 2019, 1-8)
5.	 Gefitinib	ANTICANCER	(YANG ET AL. 2017, 2805-2819)

6.	 Erlotinib	ANTICANCER	(YANG ET AL. 2017), 2805-2819
7.	 Lapatinib	ANTICANCER	(ALAGARSAMY ET AL. 2018, 628-685)

8.	 Afatinib	ANTICANCER	(ALAGARSAMY ET AL. 2018, 628-685)
9.	 Ibrutinib	ANTICANCER	(KAUR ET AL. 2017, 108-134)

10.	 Monastrol	ANTICANCER	(VENDRUSCULO ET AL. 2018, 1553-1564)
11.	 Capecitabine	ANTICANCER	(KAUR ET AL. 2017, 108-134)