Chapter 1

Introduction

The thesis comprises of crystal and molecular structure studies on compounds of biological interest; viz., derivatives of pyrazole, isoxazole and pyridine.

1.1 Review of literature

1.1.1 Pyrazole derivatives

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic diazole series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole,
1-pyrazolyl-alanine, was isolated from seeds of watermelons. The term pyrazole was given to this class of compounds by Ludwig Knorr in 1883.

The molecular formula is $\text{C}_3\text{H}_4\text{N}_2$, and the structure of pyrazole is as shown in figure 1.1.

![Figure 1.1: Structure of pyrazole](image)

The aromatic nature arises from the four $\pi$ electrons and the unshared pair of electrons on the -NH- nitrogen. Pyrazole ring is widely found as the core structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities.\textsuperscript{1,2} Pyrazole derivatives are well known for analgesic, and antidiabetic activities.\textsuperscript{3–5} Numerous compounds containing pyrazole moiety exhibit wide range of biological activities, such as anti-inflammatory,\textsuperscript{6–8} antipyretic,\textsuperscript{9} antimicrobial,\textsuperscript{10,11} antiviral,\textsuperscript{12,13} antitumour,\textsuperscript{14–19} antidepressant,\textsuperscript{20} insecticidal,\textsuperscript{21} fungicidal,\textsuperscript{21} pesticidal,\textsuperscript{22} herbicidal,\textsuperscript{23} antibacterial,\textsuperscript{24} cytotoxic,\textsuperscript{25} antifungal,\textsuperscript{26,27} hypoglycemic,\textsuperscript{28} antihemostatic,\textsuperscript{29} antagonistic,\textsuperscript{30} inhibiting of Hsp 90,\textsuperscript{31} antiarrhythmic, sedative,\textsuperscript{32} antihyperglycemic,\textsuperscript{33} antibesic,\textsuperscript{34} molluscicidal activity,\textsuperscript{35} and cardiac hypertrophy suppression.\textsuperscript{36}

Inflammation is the result of concerted participation of a large number of vasoactive, chemostatic and proliferates at different stages. The mechanism of anti-inflammatory drugs is considered to be inhibition of prostaglandin synthesis at the site of injury. The anti-inflammatory potency of different compounds roughly corresponds with their ability to inhibit COX. The 1-phenylpyrazole motif is present in several drug candidates for treatment of various diseases, such as cyclooxygenase-2 (cox-2) inhibitors, IL-1 synthesis inhibitors, and protein kinase inhibitors etc.\textsuperscript{37} Similarly a few of the 1,5-
diarylpyrazole derivatives have been shown to exhibit non nucleoside HIV-1 reverse transcriptase inhibitory activities along with Cox-2 inhibitor. The corresponding 1,3,5- triaryl pyrazoles have been recently identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficacy for ERα subtype. Therefore continuous efforts have been devoted to the synthesis of this class of compounds. Pyrazole can be found in many marked drugs such as lonazolac (anti-inflammatory), fezolamine (anti-depressant), celecoxib (anti-inflammatory), allopurinol, betaazole, apazone, pyrazolac (non steroidal anti-inflammatory drug) etc. Dipyrone compound being a well documented and commercially available nonsteroidal anti-inflammatory drug (NSAID) used with success in the treatment of fever and pain showing a relatively weak anti-inflammatory effect.
Figure 1.3: Celecoxib

Figure 1.4: Fezolamine
Considering the important biological properties of pyrazole compounds, numerous methods toward synthesis of pyrazoles have been developed over the past decades, and the methods for the synthesis of pyrazoles have been reported in the literature. They include the reaction of α, β-unsaturated aldehydes or ketones with hydrazines, treatment of alkynes with aryl hydrazine in the presence of zinc triflate, the reaction of chalcones and heterochalcones with hydrazines under conventional heating as well as microwave irradiation, intra molecular Michael addition of α, β-unsaturated hydrazine with carbonyl compounds.

In a classical method developed by H. Pechmann in 1898, pyrazole can be synthesized from acetylene and diazomethane. Pyrazoles are produced synthetically through the reaction of α, β-unsaturated aldehydes with hy-
drazine and subsequent dehydrogenation:

\[
\text{H}_2\text{O} \quad \text{H}_2\text{N} \quad \text{NH}_2
\]

\[
\text{N} \quad \text{N} \quad \text{N} \quad \text{H}
\]

**Figure 1.7:** Synthesis of Pyrazole

Pyrazoles react with potassium borohydride to form a class of ligands known as scorpionates. Pyrazole itself reacts with potassium borohydride to form a tridentate ligand known as Tp ligand.

Therefore, continuous efforts have been devoted to the development of more general, efficient, and regioselective methods for the synthesis pyrazole derivatives. In view of their importance as discussed above, pyrazole derivatives were taken for their conformational studies to get better structural–activity correlation and are discussed in chapter 3.

Molecular and crystal structures of the following pyrazole derivatives have been reported in this thesis:

1. 4-(1,3-diphenyl-1H-pyrazol-5-yl)pyridine
2. 4-(1,5-diphenyl-1H-pyrazol-3-yl)pyridine
3. 1,3-diphenyl-5(3-pyridine)pyrazole
4. 3-(3-methylthiophen-2-yl)-1, 5-diphenyl-1H-pyrazole
5. 3-(2,5-dimethylphenyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1Hpyrazole
6. 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarbonitrile
7. Ethyl 3-methyl-5-(methylthio)-1H-pyrazole-4-carboxylate
1.1.2 Isoxazole derivative

Heterocycles are abundant in nature and are of great significance to life. They have attracted considerable attention towards the design of biologically active molecules and advanced organic materials. Among a wide variety of heterocycles that have been explored for developing pharmacologically important molecules, isoxazole unit constitutes an important group due to a wide variety of biological activities.

Isoxazole is an azole with an oxygen atom next to the nitrogen. Isoxazole rings are found in some natural products, such as ibotenic acid. Isoxazoles also form the basis for a number of drugs, including the COX-2 inhibitor valdecoxib (Bextra). A derivative, furoxan, is a nitric oxide donor. The molecular formula of isoxazole is $\text{C}_3\text{H}_3\text{NO}$ and its structure is shown in figure 1.8.

![Isoxazole](image)

Figure 1.8: Isoxazole

The chemistry of isoxazoles was first investigated in the last century. There are several naturally occurring isoxazoles with important pharmacological activities. Muscimol, (figure 1.9), from the mushroom Amanita muscaria (fly agaric), has powerful psychotropic effects. Muscimol shows activity in brain nerve cells, which use $\gamma$-aminobutyric acid as a neurotransmitter. Some of the synthetic isoxazoles, such as 4,5,6,7-(tetrahydroisoxazolo 5,4-c pyridin-6-im-3-yl)amide (figure 1.10), is a potential analgesics; cycloserine, (figure 1.11), is a naturally occurring antituberculosis–antibiotic and isoxazoline (figure 1.12), is a natural anti tumor–antibiotic. Some commercial semi synthetic penicillins have isoxazolyl side chain. 4-Hydroxyisoxazole is a seed-germination inhibitor which also occurs naturally.
Figure 1.9: 5-(ammoniomethyl)isoxazol-3-olate
1.1 Review of literature

Figure 1.10: 4,5,6,7-(tetrahydroisoxazolo5,4–cpyridin-6-ium-3-y1)amide

Figure 1.11: (R)-4-ammonio-4,5-dihydroisoxazol-3-olate
Synthesis of novel isoxazoline derivatives still retains its importance due to their diverse pharmacological activities and versatile chemotherapeutic importance.

The two most important general methods for constructing the isoxazole ring are

- The reaction of hydroxylamine with a three-carbon atom component, such as 1,3-diketone or an alkyne. This is a versatile route to isoxazoles since the substituents on both components can be varied widely.

- The cycloaddition reactions of nitrones also lead to the formation of the isoxazole ring system. Isoxazoles are formed by warming the monoximes of 1,3-diketones, e.g., 3,5-dimethylisoxazole from acetylacetonemonoxime.

The isoxazole nucleus is well known for its medicinal properties and a number of related compounds are known to exhibit antitumor and anti-HIV activities and as cestoidal agents. Diaryl isoxazole derivatives have a wide range of biological properties and commercial applications in various realms of therapy, and as cytotoxic agents. Isoxazole derivatives are also employed in the treatment of leprosy and diabetes.

Isoxazole derivatives are reported to possess antibacterial, anti-inflammatory, anti-tumor, analgesic, insecticidal, antioxidant and antidepressant properties.
1.1 Review of literature

ssant\textsuperscript{57} activities. In addition, isoxazoline derivatives have played a crucial role as intermediates in the organic synthesis of a number of heterocyclic pharmacologically active compounds. Some of the marketed drugs of isoxazole are acetylsulfisoxazole, cycloserine, drazoxol on, sulfisoxazole and zonisamide. These drugs show tuberculostatic,\textsuperscript{58} anticonvulsant,\textsuperscript{59} and neurotoxic\textsuperscript{60} activities.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{zonisamide.png}
\caption{Zonisamide}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{acetylsulfisoxazole.png}
\caption{Acetylsulfisoxazole}
\end{figure}

The crystal and molecular structure study was undertaken on isoxazole derivative

1. 5-(3-Dimethyl-P-tolylsulfonyl)-propyl-3-(4-fluo-phenyl)-isoxazole.

The structural studies have been reported in chapter 4.
1.1.3 Pyridine derivative

Functionalized nitrogen-heterocycles play a predominant role in medicinal chemistry. Pyridine is a basic heterocyclic organic compound with the chemical formula C₅H₅N. It is structurally related to benzene, with one C–H group replaced by a nitrogen atom. The structure of pyridine is as shown below.

![Figure 1.15: Structure of pyridine](image)

Pyridine was discovered in 1849 by the Scottish chemist Thomas Anderson as one of the constituents of bone oil. Two years later, Anderson isolated pure pyridine through fractional distillation of the oil. Pyridine is a colorless liquid that boils at 115.2°C and freezes at -41.6°C. Its density, 0.9819 g/cm³, is close to that of water, and its refractive index is 1.5093 at a wavelength of 589 nm and temperature of 20 °C. Historically, pyridine was produced from coal tar as a by-product of the coalgasification. However, increased demand for pyridine resulted in the development of more economical methods of synthesis from acetaldehyde and ammonia, and more than 20,000 tonnes per year are manufactured worldwide. Pyridine is not abundant in nature, except for the leaves and roots of belladonna (Atropabelladonna),⁶¹ and in marshmallow (Althaea officinalis).⁶² Pyridine derivatives, however, are often part of biomolecules such as the eponymous pyridine nucleotides and alkaloids. In daily life, trace amounts of pyridine are components of the volatile organic compounds that are produced during roasting and canning processes, e.g. in sukiyaki,⁶³ fried bacon,⁶⁴ Beaufort cheese.⁶⁵

Pyridine is used in the synthesis of sulfapyridine (a drug against bacterial and viral infections), antihistaminic drugs tripelenamine and meparamine, as well as water repellents, bactericides and herbicides. Some chemical compounds, although not synthesized from pyridine, contain its ring struc-
ture. They include B vitamins niacin and pyridoxol, an anti–tuberculosis drug isoniazid, nicotine and other nitrogen–containing plant products. The pyridine nucleus is prevalent in numerous natural products and is extremely important in chemistry of biological systems. Pyridine is used as a precursor to agrochemicals and pharmaceutical material and is also an important solvent and reagent. Similarly, 2,5-di-substituted pyridines which appear to be important in many biologically active compounds have also been reported. The chemistry and applications of N–oxides have recently received much attention due to their usefulness as synthetic intermediates and their biological importance. Heterocyclic N–oxides are also useful as protecting groups, auxiliary groups, oxidants, ligands in metal complexes and catalysts. And also pyridine derivatives represent a peculiar class of antiviral compounds that qualify as promising novel drug for exploration as potential anti–HIV agents. They have an entirely new mechanism of antiviral action and the capacity to retain antiviral activity against virus stains that have gained resistance to clinically used drugs such as nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitorism (NNRTIs) depending on the particular structure of the pyridine N-oxide derivatives. Several members of this class of compounds, functionally interact with HIV-1 RT as NNTRIs, and other distinct members inhibit HIV-replication. They do so by interacting, additionally or alternatively, with a target in the HIV-replication cycle.

The derivatives are used in treatment of alzheimer’s decease, and mycobacterium tuberculosis H37Rv, and as agonists atr 5-HT1a receptors, as calcium channel agonist-antagonist modulation activities, as inhibitors of caspase-3, as mGlu receptor antagonist, as sodium channel inhibitors, as neuronal nicotinic acetylcholine receptors, as C-Jun NH2 terminal kinases inhibitors, and so on. Molecular structure of the following pyridine derivative has been reported in this thesis

1. 4-[2-(Methyl-pyridin-2-ylamino)ethoxy]benzaldoxime

Its structural studies have been reported in chapter 5.
1.2 Outline of the thesis

Chapter 1 comprises of a brief introduction to the pyrazole, isoxazole and pyridine derivatives and their biological and pharmacological importance. It also gives review of the literature for the compounds reported in the thesis. Chapter 2 provides fundamental aspects of crystallography which includes basic X-ray diffraction phenomena and the theory of X-ray crystallography. It describes the instrument used for data collection, data acquisition, data reduction and various correction factors to be applied for the data. Also the procedure adopted for solving the structure is included. Chapter 3, 4, and 5 describe the molecular structures of pyrazoles, isoxazole and pyridine derivatives and their derived geometrical results, respectively. Chapter 6 encompasses comparative analysis of molecular conformations. The molecular structures of similar compounds are compared.


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