Chapter 1

Introduction

This chapter gives a brief introduction to the Pyrazole, Benzimidazopyrimidine and Isoxazole derivatives. The biological and therapeutical importance of these compounds with their applications have been discussed.

1.1 Background

1.1.1 Pyrazole derivatives

The term pyrazole was given by German chemist Ludwig Knörr in 1883. Pyrazole is a five-membered heterocyclic ring structure composed of three carbon atoms and two nitrogen atoms in adjacent position as shown in Figure 1.1. Among the two nitrogen atoms, one is basic and the other is neutral in nature; arises from the four $\pi$ electrons and the unshared pair of electrons on the $\text{-NH}$ nitrogen. In 1959, the first natural pyrazole, ’1-pyrazolyl-alanine’ was isolated from the seeds of water melon [1]. In 1898, a classical method was developed by H. V. Pechmann to synthesize the pyrazole from acetylene and diazomethane [2].

Pyrazole is a colorless solid, with high boiling point of $187^\circ\text{C}$ and low melting point of $70^\circ\text{C}$. Pyrazole is soluble in water and insoluble in petroleum ether. Pyrazole is very
Pyrazole and its derivatives have drawn more attention in the field of current medicinal and pharmacological research; and reported to have a broad spectrum of biological activities including anti-inflammatory [3], antitumor [4], analgesic [5], antimicrobial [6], anticancer, radioprotective [7], antiamoebic [8], antioxidant [9], anti-hypertensive [10], anticonvulsant [11], antiviral [12] and antidepressant [13]. Pyrazole derivatives have a long history of application in agrochemicals such as herbicidal [14] and insecticidal [15]. Some commercial pesticides like Fripronil [16] and Pyrazolate [17] are well known in agricultural industry. Compounds containing the pyrazole ring with organophosphate and carbamoyl functionalities have been used in agriculture, which imparts insecticidal activity through linkage to many organic molecules. These compounds also act by interfering with acetyl cholinesterase in the cholinergic synapses [18].

Fused pyrazole with other heterocyclic derivatives possess various biological properties. For instance, a series of fused pyrazole with isoxazole derivatives showed antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Corynebacterium diphtheriae* and *Staphylococcus aureus* [19]. Substituent pyrazole derivatives like, 3, 5-dimethyl pyrazoles and 3-methyl pyrazol-5-one compounds showed ulcerogenic and lipid peroxidation activities [20]. Various pyrazole derivatives are developed by linking pyrimidine, carboxyhydrazide as well as ferrocenyl molecules with the pyrazole
cap; all are effective against lung cell carcinoma (A549 cell). Particularly, a series of novel 1-(20-hydroxy- 30-aroxypropyl)-3-aryl-1H-pyrazole-5-carbohydrazide derivatives inhibited the growth of A549 cells [21].

Polydentate pyrazolic compounds are regarded as good agents not only for their affinity to complex alkaline cations [22], but also to form the stable complexes with the ions of metals of transition [23]. Pyrazole containing donor-acceptor chromophores are applicable in materials science for their property study; such as non-linear optical (NLO), optical limiting [24], electrochemical sensing [25] and langmuir film [26].

Pyrazoles have played a crucial role in the development of the theory in heterocyclic chemistry and have been used extensively in organic synthesis [27-31]. The recent success of pyrazole COX-2 inhibitor, has further highlighted the importance of these heterocyclic moieties in medicinal field [32]. Hence, a systematic investigation of this class of heterocyclic lead containing pharmacoactive agents, may play an important role in medicinal and pharmaceutical chemistry.

The literature survey revealed that many pyrazole derivatives have been used for clinical application as non-steroidal anti-inflammatory drugs (NSAIDS). Among the available COX-2 inhibitors, Celecoxib (4-[5-(4-methylphenyl)-3-(trifluromethyl)-1H-pyrazol-1-yl]benzenesulfonamide), is the potent anti-inflammatory and analgesic agent [33]. Among the various pyrazoline derivatives known, antipyrine is the first reported pyrazoline derivative being used as an antipyrine agent [34-35]; however their use is restrictive due to their gastrointestinal (GI) side effects.

Pyrazole derivatives are used as chelating agents and inhibitors for the corrosion of the steel [36-37]. Some pyrazole derivatives have been implemented as antileukemic [38-40] and anti-proliferative [41-42] agents; beside their capability to exert remarkable anticancer effects by inhibiting different types of enzymes that play important roles in cell division [43-45]. Recently, some aryl pyrazoles are reported to have non nucleoside HIV-1 reverse transcriptase inhibitor activities [46]. Several pyrazole derivatives have exhibited potent anticancer action by the inhibition of the cyclin-dependent kinases
(CDKs), which are responsible for eukaryotic cell cycle regulation and are intensively studied for their cancer implication [47]. Particularly, Tozasertib (VX-680), a 3-aminopyrazole derivative inhibits Aurora kinases by inducing apoptosis in tumor cells and was later developed by structural optimization of an aminopyrazole quinazoline derivative [48].

In view of the therapeutical and pharmaceutical importance of the pyrazole derivatives, we have reported the crystal and molecular structures of the following pyrazole derivatives:

1. \((E)\)-\(N\)-hydroxy-1,3-diphenyl-4,5-dihydro-1\(H\)-pyrazole-5-carboximidamide

2. Ethyl 5-methyl-1,3-diphenyl-1\(H\)-pyrazole-4-carboxylate

3. 5-methyl-1,3-diphenyl-\(N\)-(5-phenyl-1,3,4-thiadiazol-2-yl)-1\(H\)-pyrazole-4-carboxamide

4. \(N\)'-benzoyl-5-methyl-1,3-diphenyl-1\(H\)-pyrazole-4-carboxyhydrazide

In addition, due to its important role in therapeutics and pharmaceutical activities of pyrazole derivatives, we herein undertake molecular docking studies of some selected pyrazole derivatives with Aurora A, Cyclin-dependent kinases (CDKs) and Vascular Endothelial Growth Factor Receptor (VEGFR-2) protein targets.
1.1.2 Benzimidazopyrimidine derivatives

Benzimidazopyrimidine, a fused heterocyclic system of benzimidazole and pyrimidine moieties having three nitrogen atoms (Figure 1.2). The most prominent benzimidazole moiety in nature is N-ribosyl -dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$ [49].

![Figure 1.2: Schematic diagram of benzimidazopyrimidine](image)

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Benzimidazole derivatives serve as highly potent diverse biological and therapeutic agents, including antimicrobial [50], antitumor [51], anti inflammatory [52], antiviral [53], antiparasitic [54], antiprotozoal [55], antihelminthic [56] and protein kinase inhibitor [57] activities. Also, heterocycles containing an imidazolone moiety exhibits various biological activities, such as antibacterial and antifungal [58-60].

Coumarin substituted benzimidazole derivatives are important class of widely distributed heterocyclic natural products exhibiting several biological properties. 4-amino-3-(2-methylbenzyl)coumarin derivatives [61] exhibited potent estrogenic activity on the estrogen receptor positive ($ER^+$) human Michigan cancer foundation-7 (MCF-7) breast cancer cell line. Benzothiazolyl coumarin acetamide derivatives [62] exhibited strong in vitro anti-HIV effect against the wild-type HIV-1 cell line. The in vitro antioxidant activities of 4-schiff bases-7-benzylxoy coumarin derivatives [63] revealed that 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2’-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$) radical scavenging activities were better than that of the commercial antioxidant butylhydroxytoluene (BHT). Also, cou-
marin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones showed antimicrobial and anticancer activities [64].

Fused heterocyles having benzimidazole and pyrimidine cores are frequently used in the development of new drugs. For instance, pyrimidine moiety is a structural constituent of some important anticancer drugs like Fluorouracil, Tegafur, Tethotrexate and Cytosine [65]. Compounds based on the 1,2-dihydropyrimido[1,2-a]benzimidazole core have demonstrated antiproliferative activity [66]. These derivatives differ in the mechanism of action based on the substitution pattern in the dihydropyrimidine ring. Some of them act as Topoisomerase I and Topoisomerase II inhibitors [67-68], while others act as dual kinesin spindle protein (KSP) and Aurora-A kinase inhibitors [69]. Benzimidazolo pyrimidine conjugates [70] and 1,2,5-Trisubstituted benzimidazoles [71] were found to be antitumor agents against Melanoma cell lines. In fact, imidazopyridines are the major class of non-benzodiazepines, acting upon various central nervous systems (CNS) disorders. Interestingly, several imidazopyridine based drugs such as Zolpidem, Alpidem and Saripidem exhibit potency against pentylenetetrazole (PTZ) induced seizures [72].

Extensive biochemical and pharmacological studies have confirmed that benzimidazole and its derivatives are highly effective against various strains of microorganism [73]. The earliest report of antibacterial activity of benzimidazole appeared in 1964 [74], and more recently two groups of substituted benzimidazoles, namely, the 5,6-dinitro and 2-trifluoromethyl derivatives are found to be promising candidates for antimicrobial drugs [75]. Some benzimidazole nucleosides, particularly 5,6-dichlorobenzimidazole-1-β-D-ribofuranoside (DRB) and its 2-substituted derivatives showed activity against human cytomegalovirus [76]. They are also inhibitors of photosynthesis and exhibits appreciable herbicidal activity [77]. Most recently, antiprotozoal activity of substituted 2-trifluorobenzimidazoles has been reported [78] and is consistent with several earlier studies on the antigiardial activity of various benzimidazole derivatives [79-80].

The benzimidazole ring system and its related compounds play an important role in agricultural field [81-82]. Benzimidazoles are useful insecticides, acaricides, nemato-
cides, herbicides and other plant protective agents in the field of pest control [83]. Also, substituted benzimidazole derivatives have found commercial application in veterinarian medicine as anthelmintic agent and in human therapeutic areas; such as treatment of ulcers and antihistaminic [84]. In addition, benzimidazole derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are extensively used in organic synthesis.

Some derivatives of benzimidazole act as an important pharmacophore and as a privileged structure in medicinal chemistry. Literature survey revealed that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically potent and hence the design and synthesis of 2-substituted benzimidazoles have become a subject of potential area of research [85]. Benzimidazole drugs are widely used in the prevention and treatment of parasitic infections. Thiabendazole (TBZ) was the first benzimidazole to be marketed over 40 years. It has been widely used for the control of gastrointestinal nematodes, lungworms and as a fungicidal agent. After its introduction, a number of alternative benzimidazoles offering similar activity came into the market, such as Parbendazole (PAR), Cambendazole (CAM), Mebendazole (MBZ) and Oxibendazole (OXI). Benzimidazoles possessing sulphide and sulphone functional groups were subsequently introduced, thereby offering a wider spectrum of activity with improved efficacy. Albendazole (ABZ), Fenbendazole (FBZ) and Oxfendazole (OFZ) were the first benzimidazoles, which are successfully used in the treatment of all growth stages of gastrointestinal nematodes. They may be also used in the treatment of lungworms, tapeworms and adult stages of liver fluke.

From past two decades, benzimidazole and its analogues have received much attention due to their chemotherapeutic potentials. 1H-benzimidazole ring possess basic nature due to nitrogen content and is the pharmacophore model of several drugs such as Carbenadazim, Droperidol, Albendazole, Pimozide and Omeprazole. This ring system was proved to be most significant, as it is involved in numerous antioxidant [86] and antiallergic [87] agents. Because of their significant medicinal importance, the synthesis of substituted benzimidazoles have become a focus for synthetic organic
chemist. The most important classical synthetic method for preparation of a wide range of benzimidazoles, is the condensation reaction of o-phenylenediamine with carboxylic acid.

Recently, benzimidazoles have been reported as selective neuropeptides YY1 receptor antagonists [88], potent inhibitors of TIE-2 and vascular endothelial growth factor (VEGF-2) tyrosine kinase receptors [89], gamma-amino butyric acid agonists and 5-HT3 antagonists [90], respectively. In addition to this, bisbenzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity [91] and can act as ligands for modeling biological systems [92].

In view of this extensive background of these derivatives crystal and molecular structures of the following benzimidazopyridimine derivatives have been reported here:

1. Trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one

2. 10-(6-Fluro-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5] imidazo[1,2-a]pyrimidin-4-one

3. 10-(6,8-Dimethyl-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one

4. 10-((3-oxo-3H-benzo[f]chromen-1-yl)methyl)-2-(trifluoromethyl)-9a, 10-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4(5aH)-one

In addition, owing to various interesting biological activities of above said derivatives, we herein undertake molecular docking studies of some selected benzimidazopyrimidine and coumarin substituted benzimidazopyrimidine derivatives with human Aurora A kinase target.
1.1.3 Isoxazole derivatives

Isoxazole is a five-membered heterocyclic ring structure composed of three carbon atoms, a nitrogen and an oxygen atom in its adjacent positions (Figure 1.3). In a variety of heterocycles explored for developing biologically important molecules, isoxazole and its derivatives forms an important group owing to a lot of pharmacological activities.

![Figure 1.3: Schematic diagram of isoxazole](image)

Synthesis of isoxazole derivatives still retains its importance due to their versatile role as chemotherapeutic agents. The general method for constructing the isoxazole ring system, is the reaction of hydroxylamine with a three-carbon atom component, such as 1,3-diketone or an alkyne. This is a versatile route of isoxazoles; since the substituents on both components can be varied. Secondly, the cycloaddition reactions of nitrones lead to the formation of the isoxazole ring system. Generally, isoxazoles are formed by warming the monoximes of 1,3-diketones, such as 3,5-dimethylisoxazole from acetylacetonemonoxime.

Isoxazole and its derivatives act as intermediates in the synthesis of natural products and as building blocks for construction of new molecular systems [93]. Isoxazoles are largely employed in the area of pharmaceuticals and therapeutics, such as antitumor [94], antiviral [95], anti-mycobacterial [96], antibacterial [97] and cyclooxygenase (COX-2) inhibitory [98-99] activities. Some of these isoxazole acting as COX-2 inhibitors exhibited anti-inflammatory activity with reduced gastrointestinal side effects. Also, few isoxazoles have been reported as potential agrochemical agents including herbicidal and soil fungicidal activities; thus they have been used as pesticides and insecticides [100].
1.1 Background

Some of the available marketed isoxazole drugs such as Drazoxolon, Acetylsulfisoxazole, Sulfoisoxazole, Zonisamide and Cycloserine showed tuberculostatic, anticonvulsant and neurotoxic activities [101-103]. Diaryl isoxazole derivatives have exhibited a wide range of biological properties and commercial applications in various realms of therapy, such as cytotoxic agents [104] and are employed in the treatment of leprosy [105] and diabetes [106].

Nitrogen-containing heterocycles exhibit diverse useful bioactivities and are widely used as key intermediates in the preparation of natural products such as lbotenic acid [107] and its related structures [107-109]. Some isoxazoles are selectively potent agonists for human cloned dopamine D4 receptors [110] and exhibit $GABA_A$ receptor ($\gamma$-aminobutyric acid) antagonist [111], analgesic [112] and antinociceptive [113] activities. Also, few isoxazole rings are present in the structural skeleton of the anabolic steroids and possess metastatic activity [114-115].

Some of the isoxazole moieties represented a class of unique pharmacophores, which are constituent units of diverse therapeutic agents. Therefore, they have become interesting targets in the development of new drug leads in solid-phase combinatorial chemistry [116]. Substituted isoxazole and its isothiazolylureas analogs showed cytotoxic effects having the ability to enhance the effect of antitumor agents in drugs like Cisplatin and Carboplatin, thereby making it possible to reduce therapeutic dose of these toxic drugs [117]. In addition, 4,5-dihydroisoxazoles are recognized as useful intermediates in organic synthesis. For example, they can be converted into various important synthetic units such as $\beta$-hydroxy ketones [118], $\gamma$-amino alcohols [119], $\beta,\gamma$-unsaturated ketones [120] and $\beta$-hydroxy nitriles [121].

With this background of isoxazoles, crystal and molecular structures of the following isoxazole derivatives have been reported:

1. 5-Methyl-3-phenylisoxazole-4-carboxylic acid

2. Ethyl 5-methyl-3-phenylisoxazole-4-carboxylate
3. 3-(4-Methoxyphenyl)-5-methylisoxazole-4-carboxylic acid

In continuation, owing to importance of biological activities of isoxazole derivatives, we herein proposed molecular docking studies of some isoxazole derivatives with Cyclooxygenase-2 inhibitor.
References


